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U.F.R. Santé Médecine Biologie Humaine
Ecole doctorale Galilée
et
ALMA MATER STUDIORUM - UNIVERSITA' DI BOLOGNA
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TITRE

NOUVELLES APPROCHES DU RISQUE CARDIOVASCULAIRE ET METABOLIQUE

(NUOVI APPROCCI AL RISCHIO CARDIOVASCOLARE E METABOLICO)

Présentée et soutenue publiquement le 9 Octobre 2013 par :

Davide Agnoletti

Directeur de thèse : Signature :

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J'ai donc commencé mes études et tous les matins j'allais le voir pour discuter de mes avancements. Il prenait tout le temps qu'il fallait pour me donner des explications en anglais. Dans son bureau on parlait d'histoire, du cinéma italien, de philosophie, et bien sûr de médecine.

J'ai bientôt compris que quand je lui montrais tout fièrement ce que j'avais fait ou pensé il n'était souvent pas d'accord, mais quand dans mon écriture ou dans mes commentaires transparaissait un air d'incertitude sur les résultats ou une attitude « trop » humble, c'était alors qu'il m'encourageait à être sûr des mes résultats et à les montrer franchement, comme si on était les meilleurs.

En général, lorsque je pensais avoir compris un nouveau facteur, la discussion avec lui me révélait toutes autres choses auxquelles je n'avais pas pensé.

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Je pense avoir compris ce qui fait qu'il est un « grand » Professeur.

Résumé

Notre travail de recherche de ces dernières années a été caractérisé par deux thématiques principales : l'étude de la mécanique vasculaire et des problématiques associées à la mesure des paramètres hémodynamiques centraux ; l'intérêt de l'hémodynamique pour les maladies métaboliques. Le système cardiovasculaire est caractérisé, d'une part, par les ondes de pression et de flux qui représentent la propagation de l'énergie pulsatile du cœur aux tissus ; et d'autre part par la relation complexe entre les deux (pression et flux), qui est le dialogue permanent entre le ventricule gauche et les vaisseaux. Les ondes de pression peuvent être mesurées par différentes techniques, mais la calibration des ondes, permettant d'obtenir les valeurs précises de pression artérielle, comporte des approximations et des contraintes qui ne sont pas encore résolues. Notamment, des calibrations différentes peuvent aboutir à des valeurs de pression très différentes. Notre travail montre que l'étude de l'amplification de la pression pulsée permet de dépasser les problèmes liés à la calibration, et aurait une importance non négligeable en matière de stratégies d'évaluation et de réduction du risque cardiovasculaire. Nos résultats suggèrent que l'hémodynamique centrale est un outil permettant d'étudier les modifications physiopathologiques artérielles occasionnées par les maladies cardiovasculaires et métaboliques. Chez les patients porteurs de ces maladies, la mesure de la rigidité aortique semble être capable de quantifier le degré de l'atteinte artérielle et donc le sur-risque cardiovasculaire, indépendamment et au-delà de l'hypertension artérielle.

Mots clés

Gros troncs artériels – Rigidité artérielle – Vitesse de l'onde de pouls – Amplification – Pression pulsée – Calibration – Risque cardiovasculaire – Maladies métaboliques – Diabète.

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1. Centre de Diagnostic et de Thérapeutique, Hôpital Hôtel-Dieu, Paris, France.
2. Medicina Interna, Ospedale Sant'Orsola-Malpighi, Bologna, Italia.

A few observation and much reasoning lead to error;

many observations and little reasoning to truth.

(Alexis Carrel)

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Introduction générale

L'intérêt de l'hémodynamique centrale

Dans la pratique clinique, la modalité courante pour analyser l'hypertension artérielle est de mesurer les valeurs systolique et diastolique de la pression artérielle, qui représentent le pic et le nadir de la courbe de pression artérielle. Cependant, durant les dernières années la courbe de pression artérielle a été de plus en plus étudiée, chez les sujets hypertendus, âgés, et dans différentes conditions cliniques, pour de nombreuses raisons. Tout d'abord, alors que la pression artérielle diastolique (PAD) était considérée jadis comme le meilleur guide pour déterminer le degré de sévérité de la maladie, des études épidémiologiques ont recentré l'attention sur la pression artérielle systolique (PAS) comme étant un facteur de risque cardiovasculaire plus puissant, en particulier chez des sujets de plus de 50 ans, et il a été montré que la pression pulsée (PP) était un marqueur indépendant du risque cardiovasculaire.[1] Ensuite, chez des sujets âgés de plus de 50 ans, l'éjection ventriculaire a tendance à se réduire, et donc ce sont la rigidité artérielle et l'amplitude/timing des ondes de réflexion qui jouent le rôle le plus important dans l'incrément de la PAS et de la PP chez le sujet âgé. Enfin, tandis que le contrôle médicamenteux de la PAD est atteint chez la plupart des sujets hypertendus, il n'en est pas de même pour le contrôle de la PAS qui représente souvent un véritable défi.[2]

En effet, avec la survenue de l'hypertension artérielle on observe des modifications progressives de la structure des artères qui amènent à une rigidification des parois artérielles et à l'augmentation concomitante des pressions systolique et pulsée. Les propriétés viscoélastiques des gros troncs artériels jouent donc un rôle essentiel dans l'hémodynamique cardiovasculaire, surtout dans la

détermination de la pression artérielle systolique[3,4]. L'étude des propriétés viscoélastique des gros troncs artériels est appelée hémodynamique centrale ; elle se base sur la détermination de la rigidité artérielle, de la pression artérielle aortique et sur l'étude des phénomènes de réflexion et d'amplification des ondes de pression.

La valeur ajoutée de l'hémodynamique centrale a été démontrée grâce à des études qui ont montré que les paramètres centraux sont des prédicteurs indépendants de morbidité et mortalité cardiovasculaires, en particulier chez les patients en insuffisance rénale terminale,[5–7] chez les patients hypertendus,[8,9] chez les sujets ayant une maladie coronarienne[10,11] et chez les sujets âgés.[12,13]

Insuffisance rénale terminale

Les patients présentant une maladie rénale avancée ont été les premiers à être étudiés, en 1999, par Blacher et al. Une cohorte de 241 patients avec insuffisance rénale terminale, dialisés, a été suivie pendant 72 mois en moyenne.[7]Dans cette population, après la survenue de 48 événements cardiovasculaires et 25 évènements non cardiovasculaires, la mesure de la rigidité aortique (vitesse de l'onde de pouls > 12 m/s) était associée à la mortalité globale (odds ratio, OR, intervalle de confiance au 95 %, 95 % CI, 5,4 [2,4-11,9]) ainsi qu'à la mortalité cardiovasculaire (OR [95 % CI] 5,9 [2,3-15,5]).

En outre, Safar et al., en 2002, ont suivi 180 patients hémodialysés pendant 52 mois en moyenne, et ont montré que la pression pulsée carotidienne (risque relatif pour augmentation d'une déviation standard = 1,4 [1,1-1,8]) et l'amplification de la pression pulsée (risque relatif pour augmentation d'une déviation standard = 0,5 [0,3-0,8]) étaient de puissants prédicteurs de la mortalité globale.[6]

D'autres résultats intéressants viennent d'une étude de Guérin et al. en 2001,[14] où les auteurs ont suivi 150 patients avec maladie rénale avancée pendant en moyenne 51 mois, soumis à une stratégie thérapeutique antihypertensive. Depuis l'entrée dans l'étude jusqu'à la fin du suivi, ont été mesurées les modifications de rigidité artérielle en réponse aux diminutions de pression artérielle. Après le follow-up, 40 événements cardiovasculaires et 19 évènements non cardiovasculaires sont survenus. Les résultats montrent donc que l'absence de réduction de rigidité artérielle en réponse à la baisse de la pression artérielle était un puissant prédicteur de mortalité globale et cardiovasculaire.

Hypertension artérielle

En 2001, Laurent et al. publièrent les résultats d'une étude portant sur 1980 patients avec hypertension essentielle[8] chez qui la rigidité artérielle était associée à la mortalité globale et cardiovasculaire, indépendamment des maladies cardiovasculaires sous-jacentes, de l'âge et de la présence du diabète.

De même, Blacher et al. ont montré que, chez 710 patients hypertendus, la rigidité artérielle était associée à l'extension de la maladie athérosclérotique ainsi qu'au risque cardiovasculaire.[9]

Coronaropathie

En 2005, deux études ont porté sur les paramètres hémodynamiques centraux chez des patients soumis à une coronarographie. Dans la première, chez 262 patients, après un follow-up moyen de deux ans, les ondes de réflexion ont montré une association indépendante de la survenue des événements

cardiovasculaires,[10] tandis que la deuxième a suivi 297 hommes pendant trois ans en moyenne, et a montré que les ondes de réflexion étaient associées à un sur-risque de mortalité.[11]

Sujets âgés

Le vieillissement de l'arbre artériel s'accompagne de changements structurels, comme la fragmentation et la dégénérescence de l'élastine, l'augmentation du collagène, l'épaississement de la paroi artérielle et la dilatation progressive des artères. De ces modifications résulte une rigidification progressive des vaisseaux sanguins. Avec l'âge, on observe un passage graduel de la pression diastolique à la systolique et enfin à la pulsée comme puissance de prédiction du risque cardiovasculaire. En effet, après 60 ans, la pression pulsée devient supérieure à la systolique et à la diastolique dans la prédiction de l'infarctus du myocarde.[15] En outre, la rigidité aortique, étant liée à la pression pulsée, se comporterait comme un prédicteur indépendant du risque cardiovasculaire chez le sujet âgé.[12,16]

En effet, Meaume et al. ont montré que, chez 141 sujets hospitalisés, d'âge moyen 87 ans, la rigidité aortique était un prédicteur indépendant de mortalité cardiovasculaire (OR [95 % CI] 1,19 [1,03-1,37] pour un incrément de 1 m/s de vitesse de l'onde de pouls).[12] De même, dans une étude portant sur 2488 sujets âgés principalement sains, la rigidité aortique a montré une relation avec la mortalité globale et cardiovasculaire ainsi qu'avec la maladie coronaire et cérébrovasculaire.[16]

Maladie métabolique

L'étude de l'hémodynamique centrale a également prouvé son intérêt dans les maladies métaboliques.

Plusieurs études ont mis en évidence des anomalies hémodynamiques chez les patients diabétiques,[17–23] et le diabète est considéré un facteur de risque cardiovasculaire (RCV) bien établi. Les altérations métaboliques, et notamment la résistance à l'insuline, les produits de glycation avancée (advanced glycation endproduts, AGEs), la dysfonction endothéliale et l'inflammation chronique sont de possibles contributeurs à la pathogenèse de la maladie cardiovasculaire associée au diabète.[24] Ces altérations compromettent les propriétés fonctionnelles/structurelles de l'arbre artériel, qui sont strictement liées au RCV.[25,26] En outre, la valeur prédictive sur le RCV des paramètres hémodynamiques centraux chez des patients diabétiques a été mise en évidence dans la littérature. Par exemple, l'étude de Cruickshank a montré que la rigidité aortique était corrélée à la mortalité chez les patients diabétiques.[23] Un grand nombre d'études épidémiologiques indique que dans le diabète de type 1[27–36] et de type 2[18–23,37–49] la rigidité aortique est augmentée. Phénomène précoce, survenant avant l'apparition des complications vasculaires,[27,28,32,34,36,50–52] la rigidité aortique est majorée en présence de microangiopathie (p.e. néphropathie, microalbuminurie, rétinopathie).[27,35,53] Ce phénomène se produit aussi en présence d'une altération du métabolisme glycémique (altération de la glycémie à jeun et tolérance glycémique altérée) (résistance à l'insuline et intolérance au glucose),[41,43,47,49,54] avant la survenue du diabète, suggérant que la maladie cardiovasculaire associée au diabète de type 2 pourrait débuter à l'état pré-diabètique.[55,56]

Au-delà de l'hémodynamique centrale ?

Dans le diagnostic et le traitement de l'hypertension artérielle, la multiplication des mesures au cabinet et/ou à domicile (mesure ambulatoire sur 24 heures ou automesures) permet de limiter le bruit de fond et de cibler au mieux ce niveau de PA systolique moyen, tant pour l'indication d'un traitement que pour son suivi.

Récemment, l'équipe de Peter M. Rothwell (Centre de Recherche sur la Prévention des AVC, Neurologie, Hôpital de Radcliffe, Oxford) a publié plusieurs articles dans le Lancet et le Lancet Neurology suggérant l'existence d'un nouveau marqueur de risque vasculaire, à savoir la variabilité tensionnelle intervisites.[57–59] Cette variabilité serait non seulement un puissant marqueur de risque cardiovasculaire, mais expliquerait également la différence d'efficacité entre l'amlodipine et l'aténolol que l'on avait observée dans l'essai thérapeutique ASCOT.[60] L'amlodipine était plus efficace car « stabilisait » mieux la pression artérielle dans le temps que l'aténolol.[59]

Les travaux de Rothwell et al. ont mis en évidence de nouveaux marqueurs de risque cardiovasculaire originaux et innovants : la variabilité intervisite, la variabilité résiduelle sous traitement, l'importance de l'HTA épisodique, l'importance des valeurs maximales de la PA systolique.

L'hypertension artérielle en France

L'hypertension artérielle est considérée comme étant un facteur de risque majeur et la cause principale de maints événements cérébro-cardiovasculaires,[61–63] comme les cardiopathies ischémiques, les accidents vasculaires cérébraux, l'insuffisance cardiaque, les artériopathies des membres inférieurs et l'insuffisance rénale terminale. Il semble donc important de dépister et traiter l'hypertension artérielle mais, même si l'hypertension artérielle est théoriquement traitable, la réalité montre que le contrôle tensionnel dans le monde entier est loin d'être atteint.[63,64]

En France, plusieurs enquêtes ont été menées sur des échantillons représentatifs de la population générale. En 2008, l'Etude Nationale Nutrition Santé (ENNS) a publié une enquête avec mesure de la pression artérielle sur un échantillon national de sujets âgés de 18 à 74 ans résidant en métropole. [65] L'objectif principal était de décrire la prévalence de l'hypertension artérielle dans la population adulte résidant en France métropolitaine entre 2006 et 2007. Les valeurs moyennes de PAS et de PAD étaient respectivement à 123 mmHg et 77,7 mmHg, tandis que la prévalence de l'hypertension artérielle était de 31 % (34,2 % chez les hommes et 27,8 % chez les femmes). 82 % des hypertendus étaient traités, parmi lesquels 50,9 % avaient atteint un contrôle tensionnel.

Dans la pratique clinique, il peut arriver très souvent que le médecin généraliste éprouve des difficultés à contrôler le niveau de pression artérielle avec les médicaments antihypertenseurs, ce qui amène à modifier le traitement une ou plusieurs fois. Aussi, pour cette raison, en France, les dernières recommandations de la Société d'Hypertension Artérielle[66] suggèrent aux médecins généralistes d'adresser au spécialiste tout cas d'hypertension difficile où le contrôle tensionnel ne

peut être obtenu. Même si plusieurs études ont analysé le problème de l'hypertension résistante, qui comporte la nécessité de trois agents antihypertenseurs ou plus, dont un diurétique, il existe très peu d'informations épidémiologiques sur l'hypertension non contrôlée et, notamment, sur les caractéristiques de ces patients ainsi que sur les causes du non contrôle tensionnel.

L'étude Age Vasculaire et risque résiduel chez l'hyperteNdu TrAité vu en médecine GénélalE (AVANT'AGE) est un essai clinique *open label* chez des patients ayant une pression artérielle non contrôlée dans le cadre de la médecine générale en France.[67] 710 médecins généralistes, représentatifs de médecins généralistes français actifs, ont inclus les 10 premiers patients hypertendus ayant un mauvais contrôle tensionnel (dans 91 % des cas) ou une faible tolérance et/ou compliance au traitement (46 %), et chez lesquels ils avaient décidé de modifier le traitement antihypertenseur en cours. Le nombre des patients inclus était de 7032 (58 % d'hommes), âgés de 21 à 98 ans, âge moyen 62,4 ± 11,5 ans. 6256 patients (93 %) avaient reçu comme traitement additif une combinaison fixe de perindopril et d'amlodipine : 5/5 mg chez 46,4 %, 5/10 mg chez 11,7 %, 10/5 mg chez 24,6 % et 10/10 mg chez 17,3 %. Les analyses ont porté sur les 6256 patients ayant reçu cette combinaison. Des mesures de la pression artérielle ont été effectuées à l'inclusion et après 3 mois. A la fin de l'étude on a observé une réduction moyenne de la PAS de 20,3 mmHg et de la PAD de 11,3 mmHg. 62,3 % des patients ont obtenu le contrôle tensionnel. Les réductions de pression systolique et diastolique étaient déterminées principalement par le tour de taille et l'index de masse corporelle, qui était aussi le seul déterminant du contrôle systolique et diastolique. La conclusion de l'étude était que la combinaison fixe de perindopril et d'amlodipine surajoutée au traitement était efficace sur le contrôle tensionnel chez 62,3 % des patients avec hypertension non

contrôlée. En outre, le niveau tensionnel à l'inclusion et l'obésité étaient des facteurs principaux capables d'influencer le contrôle tensionnel.

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Research Article

Effect of a fixed combination of Perindopril and Amlodipine on blood pressure control in 6256 patients with not-at-goal hypertension: the AVANT'AGE study

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Abstract

In clinical practice, general practitioners are likely to face hypertensives with uncontrolled blood pressure (BP), whose antihypertensive treatment need to be modified. In the present study, 710 general practitioners have each included the first 10 patients with not-at-goal hypertension, for whom they decided to modify their antihypertensive treatment with addition of a fixed combination of Perindopril and Amlodipine at either of its four dosages: 5/5, 5/10, 10/5, or 10/10 mg. In total, 6256 patients were included, with BP measured both at baseline and after 3 months. At the end of follow-up, a mean reduction of 20.3 ± 12.4 mm Hg in systolic BP and 11.3 ± 9.6 mm Hg in diastolic BP were observed, and 62.3% achieved successful BP control. Body mass index and waist circumference were significant determinants of both systolic and diastolic BP reductions ($P \leq .04$). Moreover, in addition to baseline BP level, body mass index was the only significant determinant of BP control of systolic, diastolic BP, and of both ($P \leq .04$). Addition of a fixed combination of Perindopril and Amlodipine to BP regimen was efficient, in terms of BP control, for 62.3% of those patients with not-at-goal hypertension. Furthermore, baseline BP level and obesity were important influential factors of BP control. J Am Soc Hypertens 2013;7(2):163–169.

Keywords: Hypertension; blood pressure control; cardiovascular risk factor.

Introduction

Arterial hypertension is a prevalent condition and the leading cause of various cerebrovascular and cardiovascular (CV) events and mortality.[1–3] Although this common CV risk factor is theoretically treatable, the reality of worldwide blood pressure (BP) control is far from perfect.[3,4] Furthermore, in routine clinical practice, it is very common for general practitioners (GPs) to find difficulty in patients' BP control with antihypertensive agents, even according to the most current guideline.[5] In this respect, a decision on the modification of chronic antihypertensive treatment needs to be made by the GPs, because of patients' uncontrolled BP or poor compliance and/or tolerance. Many studies have focussed on patients with resistant hypertension, but few studies have focused on patients with not-at-goal hypertension, especially in a nationwide survey in "real-life" clinical practice. Furthermore, characteristics of these patients, as well as the cause of their resistant condition, were largely unknown.

In literature, many studies have documented that angiotensin enzyme-converting inhibitor (ACEI) and calcium channel blocker (CCB) were beneficial in BP control in patients with resistant hypertension,[6–9] but the combined effect of these two agents on not-at-goal hypertension remained unclear.

We therefore conducted the AVANT'AGE study in 6256 patients with not-at-goal hypertension, for whom their GPs

Conflict of Interest: Jacques Blacher, principal investigator of the AVANT'AGE study, received honoraria from Servier. Servier was the unique sponsor of the AVANT'AGE study.

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decided to modify their chronic antihypertensive treatments with addition of a fixed combination of Perindopril and Amlodipine. Our goal was to investigate the combined effect of ACEI and CCB on BP control, as well as its influential factors, in these hypertensives.

Methods

Study Design

The Age Vasculaire et risqué résiduel chez I'hyperteNdu TrAité vu en médicine GénéralE (AVANT'AGE) study was an open-label clinical trial, which has focused on the BP control in patients with not-at-goal hypertension in general practice. 710 GPs, representative of the French active GPs, have each included the first 10 hypertensives with uncontrolled BP or poor compliance and/or tolerance (ie, the hypertensive patients for whom they decided to modify the chronic antihypertensive treatment). The decision of treatment modification was based on uncontrolled BP (91%) and/or poor compliance/tolerance (46%). Included in the present study were 7032 patients (58% males), with mean age ± standard deviation (SD) of 62.4 ± 11.5 years, ranged from 21 to 98 years, whose antihypertensive treatments were modified by their GPs, of whom 6256 participants (93%) were given the same modification with addition of COVERAM (a fixed combination of Perindopril and Amlodipine). Specifically, the dosages of the fixed combination of Perindopril and Amlodipine were 5/5 mg (46.4%), 5/10 mg (11.7%), 10/5 mg (24.6%), 10/10 mg (17.3%), and the specific dosage of the combination for each patient was decided by his or her GP according to the patient's BP. Written informed consent was obtained from each study participant.

Anthropometric, Clinical, and Biological Parameters

Body height, body weight and waist circumference were measured, and body mass index (BMI) was calculated as body weight in kg divided by the square of body height in meters. Overweight and obesity were defined as BMI >25 kg/m^2 and >30 kg/m^2, respectively, and abdominal obesity were defined as waist circumference >102 cm in men and >88 cm in women. Clinical data was collected from patient's medical document by GP for each participant, including smoking habit, the presence of diabetes mellitus, dyslipidemia, left ventricular hypertrophy, coronary heart disease, microalbuminuria, and renal insufficiency, as well as the use of medications, especially the use of antihypertensive agents. Biological tests were not performed in the context of our study, but data obtained previously were used for characterizing each subject.

Blood Pressure Measurement

Each participant's BP was measured by his or her GP by the electronic device currently used by the physician, after at least 5 minutes rest in the sitting position, both at baseline and at the end of the follow-up.

Follow-up Procedure

Follow-up started from the baseline examination of each individual and lasted for 3 months. Of all 6256 participants in the present study, 304 (4.9%) were lost to follow up. BP measurements were repeated during the following visit that took place 3 months later. After reviewing medical history and use of medication, target BP was set for each participant by his or her GP according to the current guideline (ie, 130/80 mm Hg for hypertensives with diabetes mellitus, renal dysfunction or established CV diseases)[5]. Controlled BP was defined as patient's BP below the target BP. However, since a small number of patients' medical documents were not complete, and their target BPs could not be set accurately, only 5677 patients had successful evaluation of systolic and diastolic BP control.

Statistical Analysis

Anthropometric, clinical, and biological parameters were compared between men and women by student's t test and Fisher's exact test for quantitative and qualitative variables, respectively. Student's t test was also applied to compare BP properties between at baseline and after treatment, and to compare the magnitude of BP reductions between patients with and without related abnormalities. Determinants of the magnitude of BP reduction and of BP control were assessed by multivariate linear and logistic regression models, respectively, with taking age, male gender, BMI, waist circumference, current smoking, plasma glucose, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, number of previous antihypertensive agents, and baseline BP level as potential confounders. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). $P < .05$ was considered statistically significant.

Results

Characteristics of participants by gender were presented in Table 1, including conventional CV risk factors, BP properties, biochemical parameters, related disorders and treatments. Men, compared with women, had significantly higher BMI (27.9 ± 4.1 vs 27.0 ± 5.4 kg/m^2; $P < .001$) and waist circumference (100.4 ± 11.9 vs 91.3 ± 13.7 cm; $P < .001$), higher diastolic BP (90.4 ± 8.7 vs 89.8 ± 8.8 mm Hg; $P < .007$), plasma glucose (7.08 ± 1.55 vs 6.86 ± 1.59 mmol/L; $P < .001$), and triglyceride (1.22 ± 0.27 vs 1.18 ± 0.27 mmol/L; $P < .001$), more frequently

Table 1
Characteristics of participants by gender

	Total (n = 6256)	Men (n = 3645)	Women (n = 2611)	*P*
Age, years	62.4 ± 11.5	61.4 ± 10.9	63.8 ± 12.0	**<.001**
Body mass index, kg/m^2	27.6 ± 4.7	27.9 ± 4.1	27.0 ± 5.4	**<.001**
Waist circumference, cm	96.7 ± 13.4	100.4 ± 11.9	91.3 ± 13.7	**<.001**
Current smoke, n (%)	950 (15.4)	686 (19.1)	264 (10.3)	**<.001**
Systolic blood pressure, mm Hg	154.9 ± 11.8	154.7 ± 11.7	155.1 ± 11.9	.16
Diastolic blood pressure, mm Hg	90.2 ± 8.8	90.4 ± 8.7	89.8 ± 8.8	**.007**
Heart rate, beats/second	75.8 ± 8.8	75.7 ± 8.9	76.0 ± 8.6	.18
Plasma glucose, mmol/L	6.99 ± 1.57	7.08 ± 1.55	6.86 ± 1.59	**<.001**
HbA1c, %	6.74 ± 1.06	6.72 ± 1.03	6.77 ± 1.09	.37
Total cholesterol, mmol/L	5.40 ± 1.04	5.37 ± 1.07	5.44 ± 1.00	**.01**
Low-density lipoprotein cholesterol, mmol/L	3.31 ± 0.95	3.30 ± 0.97	3.33 ± 0.91	.22
High-density lipoprotein cholesterol, mmol/L	1.39 ± 0.42	1.33 ± 0.41	1.46 ± 0.43	**<.001**
Triglyceride, mmol/L	1.20 ± 0.27	1.22 ± 0.27	1.18 ± 0.27	**<.001**
Diabetes mellitus, n (%)	1408 (22.9)	860 (24.0)	548 (21.3)	**.01**
Dyslipidemia, n (%)	1786 (35.1)	1113 (37.8)	673 (31.4)	**<.001**
Left ventricular hypertrophy, n (%)	687 (12.3)	429 (13.1)	258 (11.2)	**.03**
Coronary heart disease, n (%)	455 (7.7)	348 (10.1)	107 (4.3)	**<.001**
Microalbuminuria, n (%)	358 (7.1)	230 (7.7)	128 (6.2)	**.03**
Renal insufficiency, n (%)	281 (4.7)	140 (4.0)	141 (5.7)	**.002**
Antidiabetic therapy, n (%)	1377 (22.3)	848 (23.5)	529 (20.5)	**.004**
Antihyperlipidemic therapy, n (%)	2778 (44.9)	1733 (48.0)	1045 (40.5)	**<.001**
Antiplatelet therapy, n (%)	1747 (28.3)	1117 (31.1)	630 (24.5)	**<.001**

Values are means ± standard deviation or numbers in parenthesis. Diseases and treatments were defined by reading patients' medical document by general practitioners. Biochemical parameters were the last measurements of patients' medical document.

reported smoking (19.1% vs 10.3%; $P < .001$), and higher prevalence of related disorders, including diabetes mellitus, dyslipidemia, left ventricular hypertrophy, coronary heart disease, microalbuminuria, and renal insufficiency ($P \leq .03$) and the corresponding treatments, such as antidiabetic, antihyperlipidemic, and antiplatelet therapies ($P \leq .004$). Women, on the contrary, were significantly older (age, 63.8 ± 12.0 years vs 61.4 ± 10.9 years; $P < .001$), and had significantly higher total (5.44 ± 1.00 vs 5.37 ± 1.07 mmol/L; $P = .01$) and HDL cholesterol (1.46 ± 0.43 vs 1.33 ± 0.41 mmol/L; $P < .001$).

At baseline, antihypertensive monotherapy concerned 74.4%, bitherapy 19.9%, tritherapy 4.8%, and quartherapy or more 0.9% of all participants. Use of antihypertensive agents was prevalence in the present population, namely 38.6% for ACEI, 20.8% for ARB, 30.2% for CCB, 16.8% for β-blocker, 29.1% for diuretics, 3.0% for central-acting agent, and 0.8% for renin inhibitor, respectively. After 6256 patients took Perindopril and Amlodipine, in addition, there are still 627 patients (10.0%) having two antihypertensive agents, 97 (1.6%) having three antihypertensive agents, and 11 (0.2%) having four or more antihypertensive agents, with 562 patients (75.3%) taking β-blocker, 227 (30.4%) taking diuretics, and 64 (8.6%) taking central-acting agent.

At the end of follow-up, after addition of a fixed combination of Perindopril and Amlodipine, systolic BP, diastolic BP, and pulse pressure changed by -20.3 ± 12.4, -11.3 ± 9.6, and -9.0 ± 12.3 mm Hg, respectively ($P < .001$, Table 2). Of all patients, 4342 (76.4%) had successful BP

Table 2
Modifications in blood pressure after addition of a fixed combination of Perindopril and Amlodipine

	Baseline	After Treatment with COVERAM	*P**	Difference	*P*†
Systolic blood pressure, mm Hg	154.9 ± 11.8	134.6 ± 9.7	**<.001**	-20.3 ± 12.4	**<.001**
Diastolic blood pressure, mm Hg	90.2 ± 8.8	78.9 ± 7.8	**<.001**	-11.3 ± 9.6	**<.001**
Pulse pressure, mm Hg	64.7 ± 11.8	55.7 ± 9.1	**<.001**	-9.0 ± 12.3	**<.001**

COVERAM is the brand name of the fixed combination of Perindopril and Amlodipine.
* Indicates *P* value for interclass comparison.
† Indicates *P* value for comparison between absolute difference and zero.

control in either systolic or diastolic BP, with 3537 (62.3%) in both, 606 (10.7%) only in systolic BP, and 199 (3.5%) only in diastolic BP.

In Figure 1, the magnitude of BP reductions were compared between patients with and without related disorders, such as obesity, abdominal obesity, diabetes, and dyslipidemia. As compared with non-obese patients, patients with obesity and overweight had significantly lower BP reductions (20.6 ± 11.9 and 20.5 ± 11.3 vs 21.7 ± 11.9 mm Hg in systolic BP; 11.7 ± 8.9 and 11.9 ± 8.7 vs 12.9 ± 9.0 mm Hg in diastolic BP; $P = .003$ and $P < .001$). Similarly, patients with abdominal obesity had lower BP reductions than non-abdominal-obese patients, with a reduction of 20.6 ± 11.5 vs 21.1 ± 11.6 mm Hg and 11.7 ± 8.6 vs 12.5 ± 8.9 mm Hg in systolic and diastolic BP, respectively, but only the difference in diastolic BP reached statistical significance ($P = .001$). On the other hand, patients with diabetes had significant lower BP reductions than the normal (19.9 ± 11.6 vs. 21.1 ± 11.7 mm Hg in systolic BP and 11.4 ± 8.6 vs 12.4 ± 8.9 mm Hg in diastolic BP; both $P < .001$).

As shown in Table 3, determinants of the magnitude of BP reduction were investigated in multivariate linear regression models, with taking age, male gender, BMI, waist circumference, current smoking, plasma glucose, LDL and HDL cholesterol, number of previous antihypertensive agents,

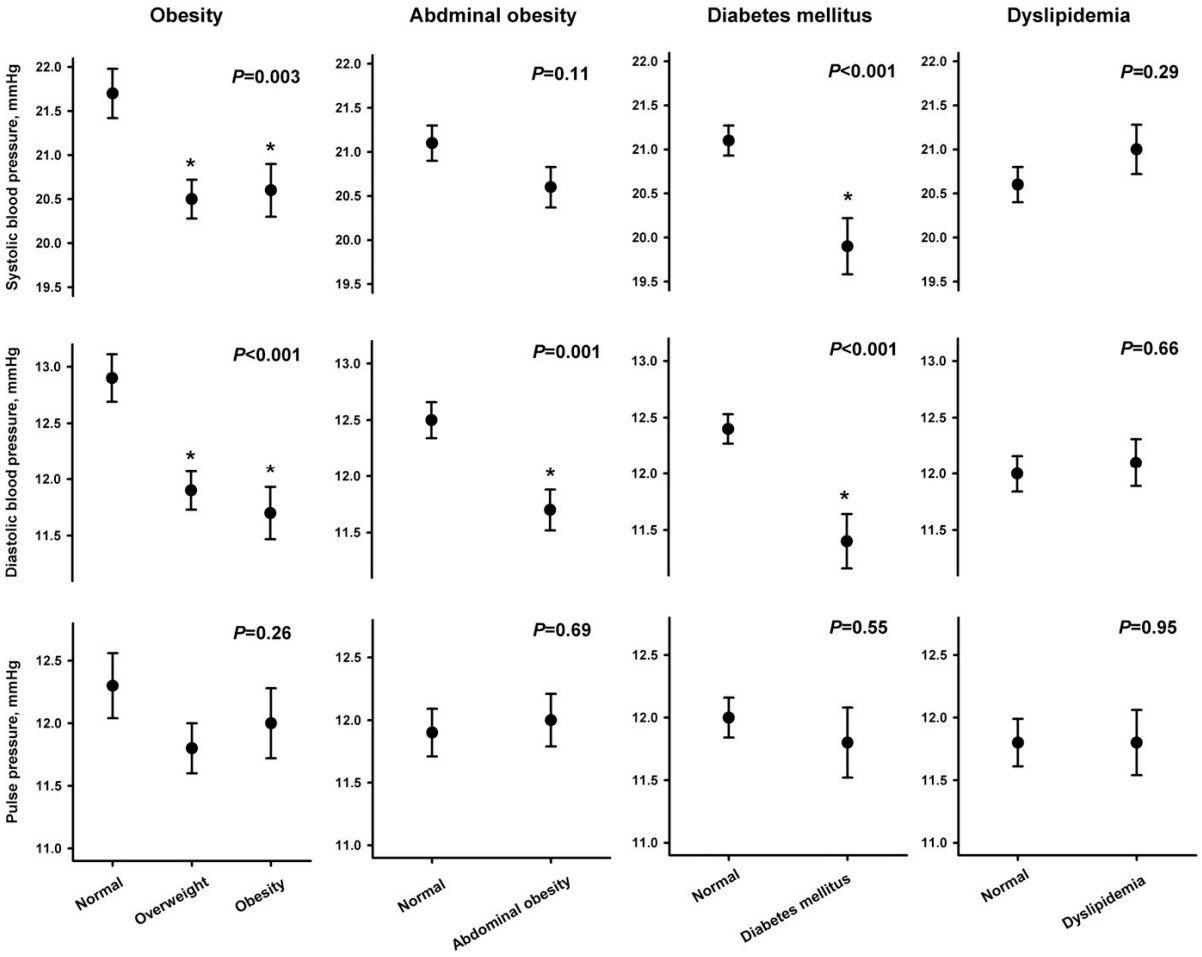

Figure 1. Comparison of the magnitude of blood pressure reduction between patients with and without related abnormalities. The magnitude of reductions in systolic and diastolic blood pressure and pulse pressure (mean and standard errors) were shown in patients with and without related abnormalities, such as obesity, abdominal obesity, diabetes mellitus, and dyslipidemia. Normal weight, overweight, and obesity were defined as body mass index <25 kg/m^2, 25 to 30 kg/m^2, and >30 kg/m^2, respectively. Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women, respectively. Diabetes mellitus and dyslipidemia were defined by reviewing patients' medical document. *Indicates the difference in blood pressure reduction reached statistical significance between patients with and without related abnormalities.

Table 3
Determinants of the magnitude of blood pressure reduction

	Systolic Blood Pressure		Diastolic Blood Pressure		Pulse Pressure	
	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*
Corresponding blood pressure, +10 mm Hg*	7.15 ± 0.11	<.001	6.52 ± 0.13	<.001	6.28 ± 0.11	<.001
Age, +10 years	-0.54 ± 0.11	<.001	-0.21 ± 0.10	.03	-0.29 ± 0.11	.007
Male gender, (1 = men, 0 = women)	–	–	–	–	–	–
Body mass index, kg/m^2	-0.08 ± 0.04	.04	-0.07 ± 0.03	.03	–	–
Waist circumference, +10 cm	-0.37 ± 0.14	.009	-0.51 ± 0.12	<.001	–	–
Current smoker, (1 = smoker, 0 = non-smoker)	–	–	–	–	–	–
Plasma glucose, mmol/L	–	–	–	–	–	–
Low-density lipoprotein cholesterol, mmol/L	-0.37 ± 0.13	.006	-0.31 ± 0.11	.006	–	–
High-density lipoprotein cholesterol, mmol/L	–	–	0.61 ± 0.25	.01	–	–
Number of previous antihypertensive agents	-0.62 ± 0.21	.004	–	–	-0.48 ± 0.20	.02

β, Estimated parameter; SE, standard error.
Multivariate linear regression models were applied to define the determinants of the magnitude of blood pressure reduction.
–Indicates non-significant.
* Indicates the corresponding blood pressure components at baseline.

and baseline BP level as potential confounders. Age and baseline BP level were the most pronounced determinants of the magnitude of BP reduction, and explained 47%, 36%, and 46% of the variation of BP reductions in systolic and diastolic BP and pulse pressure, respectively. In addition, only BMI, waist circumference, and LDL cholesterol stayed in the models accounting for the magnitude of BP reduction in systolic and diastolic BP ($P \leq .04$), while the impact of plasma glucose on the BP reduction became nonsignificant ($P \geq .08$).

With similar adjustment, determinants of BP control were investigated by multivariate logistic regression models. Older age, increased BMI, waist circumference, plasma glucose and baseline systolic BP, decreased HDL cholesterol, and more previous antihypertensive agents were in favor of not-at-goal systolic BP, with hazard ratios of 0.93 (0.87-0.99), 0.91 (0.83-1.00), 0.85 (0.77-0.93), 0.88 (0.82-0.94), 0.77 (0.73-0.83), 1.08 (1.02-1.16), and 0.81 (0.73-0.90), respectively (Figure 2). Increased BMI and baseline diastolic BP, and more frequently current smoking were in favor of not-at-goal diastolic BP, with hazard ratios of 0.89 (0.81-0.98), 0.74 (0.69-0.79), and 0.82 (0.68-0.98), respectively. Increased BMI and baseline diastolic BP were in favor of unsuccessful BP control in both systolic and diastolic BP, with hazard ratios of 0.90 (0.82-0.98) and 0.80 (0.55-0.86), respectively. Of note, in addition to baseline

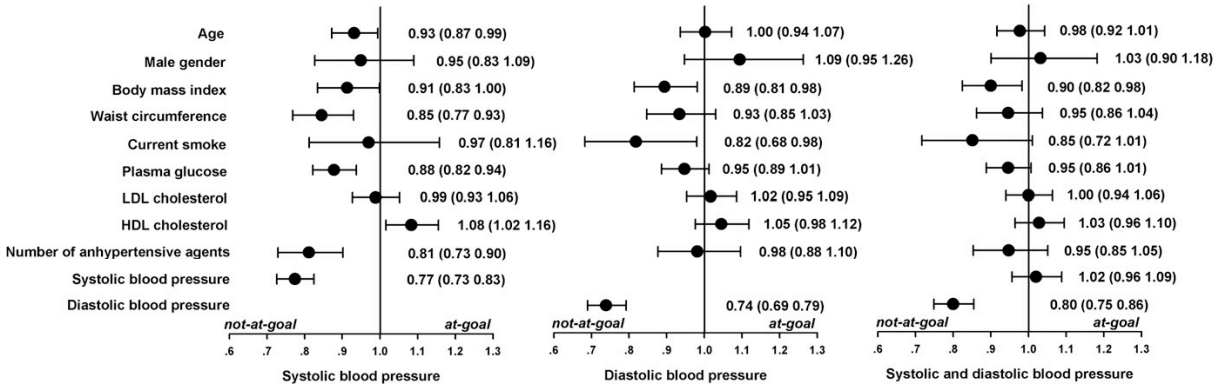

Figure 2. Determinants of blood pressure control of systolic and diastolic blood pressure and of both. Multivariate logistic regression models were applied to define the determinants of blood pressure control of systolic and diastolic blood pressure. Multivariate ordinal logistic regression model was applied to define the determinants of blood pressure control of both systolic and diastolic blood pressure, with 0 = blood pressure control of neither systolic nor diastolic blood pressure, 1 = blood pressure control of either systolic or diastolic blood pressure, and 2 = blood pressure control of both systolic and diastolic blood pressure. Odds ratio and 95% confidential interval were present on the right side of each plot, and calculated per 1-SD unit in quantitative variables and presence versus absence in qualitative variables.

BP level, BMI was the only factor in three models to influence successful BP control of either systolic or diastolic BP, and of both ($P \leq .04$).

Discussion

Major Findings

The present study contains two major findings: 1) after addition of a fixed combination of Perindopril and Amlodipine, 4342 (76.4%) patients had successful BP control of either systolic or diastolic BP, and 3537 (62.3%) of both; 2) in addition to baseline BP level, obesity was an independent determinant of BP reduction and of BP control.

Aggregation of Cardiovascular Risk in Patients With not-at-Goal Hypertension

Patients with not-at-goal hypertension, as observed in the present study, had quite high prevalence of many CV risk factors, namely 15.3% were current smokers, 25.6% were obese, 39.3% of men and 53.5% of women had abdominal obesity, 22.8% were diabetic, 35.1% had dyslipidemia, 12.0% had left ventricular hypertrophy, and 7.1% had microalbuminuria. Cuspidi et al also reported that, compared with patients with controlled BP, patients with resistant hypertension had a significant higher prevalence of left ventricular hypertrophy, increased carotid intima-media thickness, and microalbuminuria.[10] Similar findings could also be observed in other studies.[11,12] All these findings indicated that, no matter in patients with resistant or not-at-goal hypertension, the aggregation of CV risk factors was frequently reported, which indicated that the resistant condition of BP control in these patients was partly attributable to the risk aggregation.

Effect of Perindopril and Amlodipine on Blood Pressure Reduction

After addition of a fixed combination of Perindopril and Amlodipine, a reduction of about 20 mm Hg in systolic BP and 11 mm Hg in diastolic BP were observed, and about three-quarters of these patients had achieved successful BP control of either systolic or diastolic BP. This remarkable reduction in BP level, as well as a significant improvement in BP control, indicated that addition of a fixed combination of Perindopril and Amlodipine was efficient in most patients with not-at-goal hypertension.

Influential Factors for Blood Pressure Reduction

We found that, in the present study, patients with either obesity (overall or abdominal) or diabetes had significant lower BP reduction, as compared with patients without related abnormalities, but the similar finding was absent in patients with dyslipidemia, which indicated that obesity and diabetes, but not dyslipidemia, would have a negative impact on BP reduction. However, in multivariate analysis, we noted that, in addition to baseline BP level and age, only BMI and waist circumference, as well as LDL cholesterol, stayed in the models influencing the magnitude of BP reduction in systolic and diastolic BP, but the impact from plasma glucose was non-significant. Similarly, in multivariate analysis of BP control, in addition to baseline BP level, BMI was the only influential factor staying three models to affect BP control of systolic and diastolic BP, and of both, which highlighted the importance of obesity in the risk reduction strategy for successful BP control. In consistence with our finding, in the Framingham study, it was reported that the strongest predictor of lack of BP control was obesity, baseline BP level, and age.[13,14] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, the predictors of resistant BP included obesity, older age, high baseline BP, and left ventricular hypertrophy.[15] In this respect, from a practical point of view, strengthened strategy for body weight reduction would be strongly recommended for a better BP control in patients with not-at-goal hypertension and obesity.

On the other hand, we also noted that, in the present study, the impact of diabetes on BP reduction was significant in univariate analysis, but became neglectable after full adjustment. This finding raised a question about whether patients with diabetes had poorer BP control only because of their obese stature. In order to test this hypothesis, we compared the magnitude of BP reductions after treatment in patients without obesity or diabetes ($n = 1661$), with obesity but no diabetes ($n = 3268$), and with both obesity and diabetes ($n = 1205$), and found that the reductions were 21.8 ± 12.1, 20.8 ± 11.4, and 19.8 ± 11.8 mm Hg in systolic BP ($P < .001$), and 12.9 ± 9.0, 11.9 ± 8.7, and 11.7 ± 8.9 mm Hg in diastolic BP (both $P < .001$), respectively. Furthermore, after adjustment for age and gender, the above-mentioned trend remained significant (both $P < .001$). This finding indicated that, even with a remarkable weight reduction, a better management of plasma glucose would remain beneficial for a better BP control. However, this hypothesis needs to be further confirmed by prospective interventional studies.

Strength and Limitations

A strength of the present study is its nationwide survey in patients with not-at-goal hypertension. On the other hand, as an open-label study without a control group, findings in the present study need to be carefully interpreted. The magnitude of BP control could be partly attributed to regression to the mean effect or to improved compliance in relation to participation to a clinical research protocol.

In summary, we found that addition of a fixed combination of Perindopril and Amlodipine to BP regimen was efficient, in terms of BP control, for 62.3% of those patients with not-at-goal hypertension. Furthermore, in addition to baseline BP level, obesity was an independent and significant influential factor of BP control.

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Une deuxième analyse de cette population a porté sur l'étude du risque cardiovasculaire des patients ayant une hypertension artérielle non contrôlée.[68] Parmi les 7032 patients inclus (58 % hommes, âge moyen 62,4 ± 11,5 ans), les facteurs de risque cardiovasculaire représentaient une prévalence élevée : tabagisme 15,1 % , obésité 26,1 %, diabète 22,8 % , dyslipidémie 35,1 % , hypertrophie ventriculaire gauche 12 % et insuffisance rénale 4,9 %. Dans le sous-groupe des patients âgés de 30 à 74 ans et en prévention primaire (n = 4697), l'âge vasculaire, estimé par les lipoprotéines, était supérieur à l'âge chronologique ; chez ces patients, le risque cardiovasculaire a été calculé selon les équations de Framingham. Le risque cardiovasculaire global à 10 ans a été estimé à 25,3 ± 13,6 %, avec un risque de maladie coronaire de 16,0 ± 10,5 %, d'infarctus du myocarde de 8,7 ± 6,8 %, d'événement cérébrovasculaire de 5,8 ± 4,5 %, et de mortalité cardiovasculaire de 6,8 ± 6,6 %.

Ces résultats indiquent que les patients avec hypertension artérielle non contrôlée ont une association de plusieurs facteurs de risque cardiovasculaire qui pourrait être en partie la cause de l'échec thérapeutique même. En d'autres termes, la clef pour un contrôle optimal du niveau tensionnel chez ces patients résiderait probablement dans la mise en place de mesures visant au contrôle du fardeau des facteurs de risque.

Par rapport à une population similaire, ayant un pattern favorable de risque cardiovasculaire, on a observé que le risque cardiovasculaire absolu estimé chez nos patients augmentait d'une façon significative avec l'âge, mais que le risque relatif diminuait. Par conséquent, les patients plus jeunes ayant un mauvais contrôle tensionnel auraient un risque relatif plus élevé que leur contrepartie saine, tandis que les patients plus âgés non contrôlés présenteraient un risque relatif comparable aux

patients sains de même âge. Ce résultat est probablement attribuable au fait que les patients plus jeunes ont moins de facteurs de risque que les patients plus âgés, et le mauvais contrôle tensionnel représenterait leur seule anormalité, en compétition avec peu d'autres facteurs de risque.

En particulier, comme l'on a dit, même si les patients ont été recrutés à cause des valeurs élevées de pression artérielle, ils présentaient d'autres facteurs de risque, notamment la glycémie à jeun et le tour de taille étaient en moyenne respectivement de 7,08 ± 1,56 mmol/L et 100,4 ± 11,9 mm pour les hommes et de 6,85 ± 1,59 mmol/L et 91,2 ± 13,7 mm chez les femmes. Ces valeurs sont en effet élevées ou à la limite de la normalité, ce qui aide à quantifier l'apport des autres facteurs de risque en dehors de l'hypertension artérielle.

ORIGINAL PAPER

Characteristics and Future Cardiovascular Risk of Patients With Not-At-Goal Hypertension in General Practice in France: The AVANT'AGE Study

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Although many studies focus on patients with resistant hypertension, general practitioners (GPs) are more likely to face patients in clinical practice with not-at-goal hypertension, whose antihypertensive treatment needs to be modified. However, information regarding such patients is limited. In the present study, 710 GPs in France each included their first 10 not-at-goal hypertensive patients, ie, the patients for whom they decided to modify antihypertensive treatment. The study population was composed of 7032 patients (58% men, mean age 62.4±11.5 years). Anthropometric and biologic measurements and clinical data were collected, and vascular age and 10-year cardiovascular risk were estimated by standard formula. Of 7032 participants, cardiovascular risk factors were prevalent, with 15.1% current smokers, 26.1% obese, 22.8% with diabetes mellitus, 35.1% with dyslipidemia, 12.0% with left ventricular hypertrophy, and 4.9% with renal insufficiency. In the subgroup (n=4697) of patients aged between 30 and 74 years and undergoing primary cardiovascular prevention, vascular age was superior (13 to 28 years) when compared with chronological age in different subgroups. The patients' estimated 10-year cardiovascular global risk was 25.3±13.6%, with 16.0±10.5% for coronary heart disease, 8.7±6.8% for myocardial infarction, 5.8±4.5% for stroke, and 6.8±6.6% for cardiovascular mortality. Patients with not-at-goal hypertension in primary care bear a heavy burden of cardiovascular diseases. *J Clin Hypertenas (Greenwich)* 2013;15:291–295. ©2013 Wiley Periodicals, Inc.

Arterial hypertension is a prevalent condition and the leading cause of various cerebrovascular and cardiovascular (CV) events and mortality.[1–3] In a recent report on worldwide blood pressure (BP) control, with 786 country-years and 5.4 million participants, Danaei and colleagues[4] documented that from 1980 to 2008, the global mean reductions in systolic BP (SBP) were only 0.8 mm Hg and 1.0 mm Hg per decade for men and women, respectively. The situation is partly attributable to resistant and not-at-goal hypertension. In routine clinical practice, it is common for a general practitioner (GP) to have difficulty in controlling patients' BP with antihypertensive agents. In this case, a decision on the modification of chronic antihypertensive treatments needs to be made. The key for the GP to make an effective decision is to know the characteristics of their patients, as well as their future CV risk. Many studies have focused on patients with resistant hypertension, but few studies have focused on patients with not-at-goal hypertension, especially in a nationwide scan in general practice. We therefore conducted a cross-sectional study of 7032 patients with not-at-goal hypertension, for whom their GPs decided to modify their chronic antihypertensive treatments. Our goal was to investigate the charac-teristics and future CV risk of these patients.

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METHODS

Study Design

The Age Vasculaire et Risqué Résiduel Chez l'Hypertendu Traité vu en Médicine Générale (AVANT'AGE) study was an epidemiological observational study that focused on patients with not-at-goal hypertension in general practice. A total of 710 GPs, representative of currently active GPs in France, each included the first 10 not-at-goal hypertensives, ie, the hypertensive patients for whom they decided to modify the chronic antihypertensive treatment. The decision of treatment modification was based on uncontrolled BP (91%) and/or poor compliance/tolerance (46%). A BP goal was set at 130/80 mm Hg for patients with diabetes, renal dysfunction, or established CV diseases, and at 140/90 mm Hg for those without these conditions. The definition of resistant hypertension and not-at-goal hypertension are summarized in Table I. In total, 7032 patients (58% men) were included in the present study, with a mean age±standard deviation (SD) of 62.4±11.5 years (range, 21 to 98 years). Written informed consent was obtained from each study participant.

Anthropometric, Clinical, and Biological Parameters

Body height, body weight, and waist circumference were measured and body mass index (BMI) was

TABLE I. Definition of Resistant Hypertension and Not-At-Goal Hypertension

Resistant Hypertension	Not-At-Goal Hypertension
BP remains above goal in spite of the concurrent use of ≥3 antihypertensive agents of different classes at optimal dosages, with one of the agents a diuretic	Patients' chronic antihypertensive treatment needs to be modified by their GPs because of uncontrolled BP and/or poor compliance/tolerance

Abbreviations: BP, blood pressure; GP, general practitioner.

calculated as body weight in kilogram divided by the square of body height in meters. Clinical information was collected from the patient's medical document by the GPs for each participant, including smoking habit and the presence of diabetes mellitus, dyslipidemia, coronary heart disease, microalbuminuria, or renal insufficiency, as well as the use of medications. Left ventricular hypertrophy (LVH) was previously defined by echocardiography with the criteria of left ventricular mass index >125 g/m^2 (men) and >110 g/m^2 (women), and reviewed by the GPs in patients' medical records. Biochemical tests were not performed in the context of our study, but previously obtained biological data were used for characterizing each patient.

Antihypertensive Treatment

Use of antihypertensive agents was recorded for each patient by his or her GP, including number of antihypertensive agents and their categories. Antihypertensive agents were then categorized into 4 classes, namely diuretics, anti–renin-angiotensin-aldosteronism (RAS) system agents (including angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, and renin inhibitors), calcium channel blockers (CCBs), and antiadrenergic agents (including β-blockers and central-acting agents).

BP Measurement

Each participant's BP was measured with the electronic device currently used by his or her GP after at least 5 minutes of rest in the sitting position.

Estimation of 10-Year CV Risk by the Framingham Formula and Vascular Age

Patients' absolute risk for 10-year CV diseases were estimated by the Framingham formula proposed by Anderson and colleagues[5] based on conventional CV risk factors (age, total and high-density lipoprotein [HDL] cholesterol, BP, diabetes, and smoking status). The relative risk was estimated as the calculated risk of the present population divided by the risk of a similar population in terms of nonmodifiable risk factors (age and sex) but optimal modifiable risk factors (SBP=120 mm Hg, no diabetes, no LVH, no smoking, total/HDL cholesterol=4). Risk excess was estimated as the calculated risk of the present population minus the risk of the above-mentioned optimal population. Vascular age was estimated based on lipoprotein, according to the formula proposed by D'Agostino and colleagues.[6]

Statistics

Anthropometric, clinical, and biological parameters were compared between men and women by Student's *t* test and Fisher's exact test for quantitative and qualitative variables, respectively. Percentages of the use of each antihypertensive agent were calculated in patients with 1, 2, 3, and ≥4 antihypertensive therapies, and were compared by chi-square test. Differences between chronological age and vascular age were compared with 0 by the Student's *t* test. Analysis of variance was applied to test the associations of estimated 10-year CV diseases and mortality with age. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). $P<.05$ was considered statistically significant.

RESULTS

In the 7032 participants, mean SBP and diastolic BP (DBP) were 154.2±12.5/89.6±9.1 mm Hg; mean total and low-density lipoprotein (LDL) cholesterol were 5.38±1.04 and 3.31±0.91 mmol/L, respectively; and mean plasma glucose was 6.98±1.57 mmol/L. In addition, other CV risk factors were also prevalent in this population, with 15.1% current smokers, 26.1% obese, 22.8% with diabetes mellitus, 35.1% with dyslipidemia, 12.0% with LVH, and 4.9% with renal insufficiency. Table II shows characteristics of participants by sex. Specifically, men, compared with women, had significantly higher BMI (27.9±4.2 vs 27.0±5.4 kg/m^2, $P<.001$) and waist circumference values (100.4±11.9 vs 91.2±13.7 cm, $P<.001$); higher DBP (89.8±9.0 vs 89.3±9.1 mm Hg, $P=.03$), plasma glucose (7.05±1.56 vs 6.85±1.59 mmol/L, $P<.001$), and triglycerides (1.22±0.27 vs 1.18±0.27 mmol/L, $P<.001$); more frequently reported smoking (18.9% vs 10.3%, $P<.001$); and a higher prevalence of related disorders ($P\leq.048$) and corresponding treatments ($P\leq.004$). Women, on the contrary, were significantly older (age, 63.8±12.0 vs 61.4±11.0 years, $P<.001$) and had significantly higher SBP (154.6±12.7 vs 154.0±12.4 mm Hg, $P=.04$), pulse pressure (65.3±12.3 vs 64.2±11.8 mm Hg, $P<.001$), and total (5.44±1.00 vs 5.35±1.06 mmol/L, $P<.001$) and high-density lipoprotein (HDL) cholesterol (1.46±0.43 vs 1.33±0.41 mmol/L, $P<.001$).

As shown in Table III, 1 antihypertensive treatment was used in 74.4% of patients, 2 treatments in 19.9%, 3 treatments in 4.8%, and ≥4 in 0.9% of participants. The trend of antihypertensive agent use was investigated in patients with increasing number of antihypertensive therapy. Specifically, the use of diuretics and CCBs were

TABLE II. Characteristics of Participants by Sex

	Total (N=7032)	Men (n=4073)	Women (n=2959)	*P* Value
Age, y	62.4±11.5	61.4±11.0	63.8±12.0	<.001
Body mass index, kg/m^2	27.6±4.8	27.9±4.2	27.0±5.4	<.001
Waist circumference, cm	96.5±13.5	100.4±11.9	91.2±13.7	<.001
Current smoke, No. (%)	1058 (15.3)	760 (18.9)	298 (10.3)	<.001
Systolic BP, mm Hg	154.2±12.5	154.0±12.4	154.6±12.7	.04
Diastolic BP, mm Hg	89.6±9.1	89.8±9.0	89.3±9.1	.03
Mean BP, mm Hg	111.1±8.6	111.2±8.6	111.1±8.7	.58
Pulse pressure, mm Hg	64.6±12.0	64.2±11.8	65.3±12.3	<.001
Heart rate, beats per s	75.6±8.8	75.5±8.9	75.8±8.7	.16
Plasma glucose, mmol/L	6.98±1.57	7.08±1.56	6.85±1.59	<.001
Hemoglobin A_{1c}, %	6.74±1.08	6.71±1.04	6.77±1.13	.29
Total cholesterol, mmol/L	5.38±1.04	5.35±1.06	5.44±1.00	<.001
LDL cholesterol, mmol/L	3.31±0.94	3.29±0.97	3.33±0.91	.11
HDL cholesterol, mmol/L	1.39±0.42	1.33±0.41	1.46±0.43	<.001
Triglyceride, mmol/L	1.20±0.27	1.22±0.27	1.18±0.27	<.001
Diabetes mellitus, No. (%)	1572 (22.8)	955 (23.9)	617 (21.2)	.008
Dyslipidemia, No. (%)	2007 (35.1)	1246 (37.8)	761 (31.4)	<.001
Left ventricular hypertrophy, No. (%)	753 (12.0)	289 (12.7)	298 (11.1)	.048
Coronary heart disease, No. (%)	519 (7.8)	387 (10.1)	132 (4.7)	<.001
Microalbuminuria, No. (%)	399 (7.1)	257 (7.8)	142 (6.1)	.01
Renal insufficiency, No. (%)	328 (4.9)	166 (4.3)	162 (5.8)	.004
Antidiabetic therapy, No. (%)	1537 (22.1)	938 (23.3)	599 (20.5)	.004
Antihyperlipidemic therapy, No. (%)	3110 (44.7)	1932 (47.9)	1178 (40.3)	<.001
Antiplatelet therapy, No. (%)	1947 (28.1)	1247 (31.0)	700 (24.0)	<.001

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Values are presented as mean±standard deviation or numbers (percentages). Disorders and therapy were defined by reading patients' medical document.

TABLE III. Use of Antihypertensive Agents in Patients With Not-At-Goal Hypertension

	Overall (N=7032)	One Agent (n=5232)	Two Agents (n=1397)	Three Agents (n=340)	Four or More Agents (n=63)	*P* Value
Diuretics, No. (%)	2048 (29.1)	1134 (21.7)	624 (22.3)	233 (23.8)	57 (22.6)	.81
Anti-RAS system agents, No. (%)	4232 (60.2)	3013 (57.6)	979 (70.1)	277 (81.5)	53 (84.1)	<.001
Calcium channel blocker, No. (%)	2120 (30.2)	1102 (21.1)	724 (25.9)	243 (23.8)	51 (20.3)	<.001
Antiadrenergic agents, No. (%)	1385 (19.7)	441 (8.4)	627 (44.9)	254 (74.7)	63 (100.0)	<.001

Values are presented as numbers (percentage). Anti–renin-angiotensin-aldosteronism (RAS) system agents include angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, and renin inhibitors. Antiadrenergic agents include β-blockers and central-acting agents.

similar in patients with different numbers of antihypertensive agents, but a progressively decreasing use of anti-RAS system agents, as well as a progressively increasing use of antiadrenergic agents, were detected in patients with increasing number of antihypertensive therapy (*P*<.001).

In the subgroup (n=4697) aged between 30 and 74 years and in primary CV prevention, patients' vascular age estimated by lipoprotein was compared with patents' chronological age. Vascular age was significantly greater (13 to 28 years) than the chronological age in the different age subgroups (Table IV, *P*<.001).

Finally, in the subgroup aged between 30 and 74 years and in primary CV prevention (n=4697), patients' estimated 10-year CV global risk was 25.3%±13.6%. Specifically, the 10-year risk for coronary heart disease, myocardial infarction, stroke, and CV mortality were 16.0%±10.5%, 8.7%±6.8%, 5.8%±4.5%, and 6.8%±6.6%, respectively. In comparison with patients with optimal modifiable CV risk factors, relative risk was 2.2±1.4 for coronary heart disease, 3.9±4.2 for myocardial infarction, 3.8±2.2 for stroke, and 4.1±4.5 for CV mortality, and the corresponding risk excess were 8.7%±6.8%, 6.0%±4.5%, 4.3%±4.1%, and 4.6%±5.5%, respectively. Furthermore, as shown in

TABLE IV. Comparison of Patients' Chronological Age and Vascular Age Estimated by Lipoprotein

Age Groups	Chronological Age	Vascular Age by Lipoprotein	Difference	*P* Value
Overall (N=4697)	59.0±9.1	81.2±8.0	22.2±8.1	<.001
30–39 y (n=124)	36.5±2.5	61.3±13.4	24.9±12.9	<.001
40–49 y (n=619)	43.6±2.8	73.9±11.4	28.3±10.8	<.001
50–59 y (n=1491)	54.8±2.9	81.1±6.8	26.3±6.6	<.001
60–69 y (n=1808)	64.0±2.8	84.0±3.5	20.0±4.1	<.001
70–74 y (n=655)	71.8±1.4	84.6±2.0	12.8±2.4	<.001

Vascular age was estimated based on lipoprotein according to the formula proposed by D'Agostino and colleagues. Values are presented as means±standard deviation of patients' age.

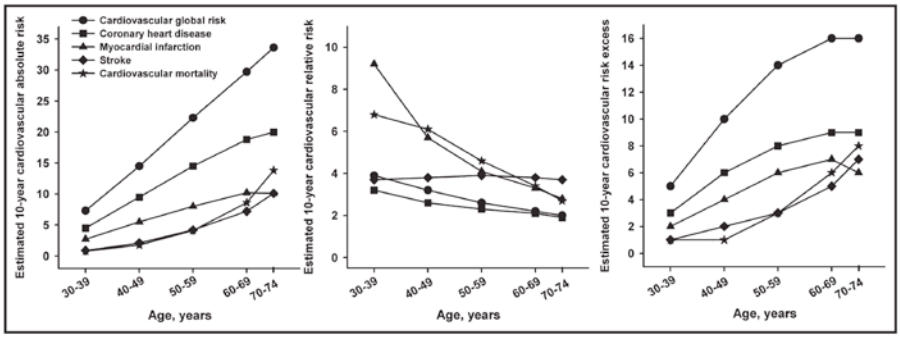

FIGURE. Estimated 10-year cardiovascular absolute risk, relative risk, and risk excess in patients with not-at-goal hypertension by age. All trends of estimated 10-year cardiovascular risk with age were statistically significant (*P*<.001) except for the relative risk for stroke (*P*=.34). Ten-year cardiovascular absolute risk was estimated by the Framingham formula; relative risk was estimated as the calculated risk of the present population divided by the risk of a similar populations in terms of nonmodifiable risk factors (age and sex) but optimal modifiable risk factors (systolic blood pressure=120 mm Hg, no diabetes, no left ventricular hypertrophy, no smoking, total/high-density lipoprotein cholesterol=4). Risk excess was estimated as the calculated risk of the present population minus the risk of the above-mentioned optimal population.

the Figure, with advancing age, the estimated 10-year CV risk and risk excess as compared with optimal group increased progressively and significantly (*P*<.001), whereas relative risk as compared with optimal group decreased (*P*<.001), except for the relative risk for stroke (*P*=.34).

DISCUSSIONS

The present study contains two major findings: (1) patients with not-at-goal hypertension in primary care were characterized with aggregation of CV risk factors, as well as high estimated 10-year CV risk; and (2) the absolute and excess risk of estimated 10-year CV diseases increased with advancing age, but the relative risk decreased.

Patients with not-at-goal hypertension, as shown in the present study, had a high prevalence of many CV risk factors, namely 15.1% were current smokers, 26.1% were obese, 39.3% of men and 53.5% of women had abdominal obesity, 22.8% were diabetic, 35.1% had dyslipidemia, 12.0% had LVH, and 4.9% had renal insufficiency. Cuspidi and colleagues[7] also documented that, compared with patients with controlled BP, patients with resistant hypertension had a significant higher prevalence of LVH, increased carotid intima–media thickness, and microalbuminuria. Similar findings could also be observed in other studies.[8,9] Those findings and ours showed that in patients with not-at-goal or resistant hypertension, the aggregation of CV risk factors was frequently reported, indicating that the resistant condition of BP control in these patients was partly attributable to the observed risk aggregation. In other words, the key to successful BP control in these patients probably lies in the effective countermeasures to those risk factors.

In the present study, we also noted that use of diuretics and CCBs were similar in patients with not-at-goal hypertension, with almost 30% for each, whereas patients taking more antihypertensive agents were less likely to take anti-RAS system agents but more antiadrenergic agents. This trend in antihypertensive therapy of not-at-goal hypertensive patients was in accordance with current guideline.[10]

It is not surprising that in patients with not-at-goal hypertension, vascular age was superior of 13 to 28 years than the chronological age in the different age subgroups. Moreover, patients' estimated 10-year CV risk increased with advancing age and reached about 1 out of 3 for CV global risk, about 1 out of 5 for CHD, and about 1 out of 10 for myocardial infarction

and stroke. Compared with a similar population with optimal modifiable risk factors, the excess risk in patients with not-at-goal hypertension also increased with age, but the relative risk decreased. In other words, the young patients with not-at-goal hypertension, compared with older patients, would have higher relative CV risk than their healthy counterparts. This finding was likely attributed to the fact that younger patients have fewer CV risk factors than older patients, so uncontrolled hypertension would be the only abnormality, with fewer other competing risk factors in term of risk assessment. Other reports also mentioned a decreasing relative risk of cardiovascular disease with increasing age in hypertensive patients. Antihypertensive treatment benefit was less efficient in the elderly in terms of relative risk reduction but more efficient in terms of absolute risk reduction.[11]

It is also interesting to note that, in the present study, these patients were recruited mainly because of their high BP, but high BP is obviously not the only uncontrolled risk factor. For instance, mean plasma glucose and waist circumference in the present population were 7.08±1.56 mmol/L and 100.4±11.9 mm in men and 6.85±1.59 mmol/L and 91.2±13.7 mm in women, respectively, which were all higher or around the normal range. This finding indicated that in patients with not-at-goal hypertension, although high BP was apparently the major problem, other risk factors, especially obesity and high plasma glucose, also need to be considered.

LIMITATIONS

It is important to note that our study has some limitations. First, the 710 GPs were not randomly chosen from all French GPs; nevertheless, they were representative of the French GP population in terms of age, sex, and geographic location. Second, the concept of "not-at-goal hypertension" is not a well-accepted concept, such as resistant hypertension or severe hypertension, but we wanted to assess a "real hypertensive" population in which the GP decided to modify the antihypertensive treatment. Third, no specific complementary examinations were performed in the setting of our study, and therefore the prevalence of some complications such as LVH or coronary heart disease was probably underestimated. Finally, antihypertensive drugs were not randomly allocated and the cause-and-effect relationship cannot be assessed, but again, our goal was to be in the real hypertensive life in the setting of primary care.

CONCLUSIONS

In summary, patients with not-at-goal hypertension in primary care bear a heavy burden of CV diseases, with the aggregation of many CV risk factors and high estimated 10-year CV risk. Moreover, CV burden grows with advancing age, but the relative risk decreases. Medical attention is needed in order to decrease the elevated CV risk in this specific population.

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OBJET ET BUT DE LA THESE

A la lumière de ce qui a été dit jusque-là, nous pouvons désormais considérer l'hémodynamique centrale comme un outil nous permettant d'investiguer les modifications physiopathologiques artérielles qui participent au développement de la maladie cardiovasculaire sous plusieurs conditions cliniques apparemment différentes.

De même, les données épidémiologiques sur la situation du contrôle tensionnel en France indiquent la nécessité d'une vision globale du patient hypertendu, en révélant premièrement que ce sont justement les patients dont l'ensemble des facteurs de risque ne sont pas contrôlés qui souffrent le plus d'une difficulté thérapeutique. Deuxièmement, même en présence d'un traitement hypotenseur optimal, comportant l'association d'un inhibiteur du système rénine angiotensine et d'un inhibiteur calcique, l'obtention des valeurs optimales de pression artérielle était associé de manière importante à des paramètres anthropo/métaboliques comme la circonférence abdominale et l'index de masse corporelle.

Nous avons vu comment, dans la maladie cardiovasculaire, rénale et métabolique, ainsi que dans le processus de vieillissement, les enjeux vis-à-vis de la morbi-mortalité cardiovasculaire et globale sont très importants et surtout liés profondément aux modifications hémodynamiques.

De plus, une évaluation dynamique de la pression artérielle, qui échappe en quelque sorte aux mesures conventionnelles et statiques, a montré son intérêt. L'étude de la variabilité tensionnelle s'impose aujourd'hui sinon comme une alternative, certainement comme un paramètre complémentaire capable d'investiguer dans la temporalité les modifications de la pression artérielle, et donc la capacité adaptative du système cardiovasculaire. La découverte qu'une évaluation

dynamique de la pression artérielle pourrait aussi bien s'ajouter aux facteurs pronostiques de mortalité cardiovasculaire et globale, fait de cette mesure un domaine de recherche encore plus intéressant.

Au final, les facteurs de risque cardiovasculaire classiques, l'hypertension artérielle et son traitement, la coronaropathie, la maladie rénale, le diabète, le vieillissement, la variabilité tensionnelle… auraient-ils, certes, des implications pathologiques communes, pourraient-ils se superposer et aggraver la situation clinique de nos patients, nous sommes néanmoins portés à nous demander s'il existe un mécanisme qui les lierait, une altération commune qui les amènerait sur la voie de la maladie cardiovasculaire.

C'est justement dans cet esprit qu'a pris forme notre travail de recherche. Dans la première partie de la thèse nous allons montrer tout d'abord le rôle et le fonctionnement du système cardiovasculaire, et les modèles utilisés pour sa compréhension ; ensuite nous analyserons les fondamentaux de l'analyse des ondes de pression et les issues concernant la propagation et la réflexion des ondes ; ensuite nous nous focaliserons sur la mesure tonométrique des ondes de pression et ses applications cliniques.

Dans la deuxième partie, nous allons investiguer le lien entre l'hypertension (et la maladie cardiovasculaire) et les maladies métaboliques, en particulier le diabète sucré.

Nous allons enfin donner des perspectives et des hypothèses pour un travail futur.

Première Partie

BASES MÉTHODOLOGIQUES :

PRINCIPES D'HÉMODYNAMIQUE VASCULAIRE

Depuis le commencement

L'histoire de la mécanique des ondes de pression artérielle est longue et dense. Le mot « artère », qui vient du grec « ἀρτηρία », composé de « ἀήρ » (air) et « τηρέω » (garder), était utilisé originellement pour désigner la trachée, puis pour désigner les artères car on pensait qu'elles étaient remplies d'air ou de quelques esprits. Ce fut Galien (129-210) qui découvrit le premier que les artères contenaient du sang. Dans la médecine traditionnelle chinoise, la palpation du pouls radial a été utilisée pendant plus que 3000 ans, et l'un des premiers livres consacrés à l'analyse du pouls artériel date de 220.[69] Evidemment, les textes anciens ne rapportent que des informations sur le pouls, sans étudier les mécanismes sous-jacents. Ce fut beaucoup plus tard, avec William Harvey (1578-1657) et Giovanni Borelli (1608-1679), que l'on découvrit d'abord que le pouls des artères est envoyé simultanément le long de l'arbre artériel, et ensuite que les artères élastiques ont la capacité d'accumuler le sang pendant la systole et de le renvoyer en diastole. La première détermination intra-artérielle de la pression artérielle est attribuée à l'abbé Stephen Hales. En 1733, il publia une série de travaux dans le journal de la Royal Society. Au cours de ses expériences il incisa l'artère crurale d'une jument et y glissa un tube métallique fixé dans un tube de verre. Quand il ouvrit l'artère, le sang arriva environ à 300 centimètres de hauteur dans le tube. Puis il mesura la vitesse du flux sanguin à l'entrée de l'aorte (calculée à 0,44 m/s), en décrivant *a curious artifice of nature* (un curieux artifice de la nature) : le sang pouvait circuler jusqu'à la périphérie de l'arbre artériel grâce aux propriétés élastiques des artères qui fonctionneraient en réservoir, tout comme l'air dans les pompes utilisées par les pompiers d'autrefois. Cela fut la première description de l'effet *Windkessel* (de l'allemand : chambre à air).

L'analyse mécanique quantitative du système cardiovasculaire doit ses origines à Leonhard Euler (1707-1783), qui a établi les équations générales du mouvement des fluides, théoriquement semblables à celles utilisées aujourd'hui. Parallèlement, Daniel Bernoulli, qui était un compagnon de Euler, décrivit la relation entre la pression artérielle et la vitesse du flux sanguin dans les artères.

Les propriétés élastiques des artères ainsi que leur relation avec la vitesse de propagation du pouls artériel furent étudiées par Thomas Young (1773-1829), dont le travail sur l'élasticité amena au concept de module élastique qui porte son nom.

Depuis, l'histoire passe à travers les études de Fourier sur les fonctions périodiques (d'où les transformées de Fourier) et de Poiseuille sur la relation entre le flux, le gradient de pression et les dimensions du tube capillaire ; le travail des frères Weber sur la propagation des ondes de pression ; les contributions de Rienmann, Moens et Korteweg. Le français E.J. Marey (1830-1904) ajouta des connaissances importantes sur la mesure non invasive des ondes de pression, et, avec Akbar Mahomed, fut le premier à mesurer avec précision le pouls artériel chez l'homme avec le sphygmographe (Figure 1).

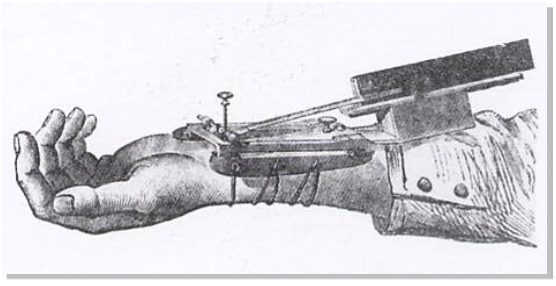
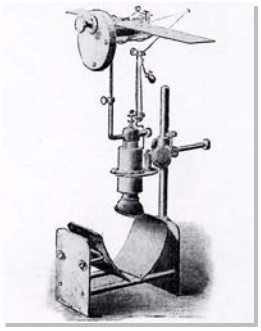
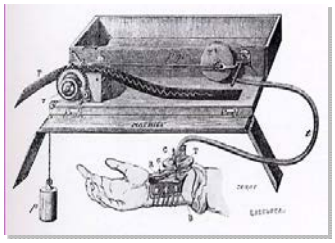


Figure 1. Sphygmographe de Marey (1860).

Avec l'introduction du sphygmographe et des mesures de pouls et de pression artérielle démarra l'hémodynamique artérielle *sensu proprio* (Figure 2).



Pound, 1878



Meurisse et Mathieu, 1879

Figure 2. Sphygmographes.

L'introduction du système Riva-Rocci avec le sphygmomanomètre brachial en 1896 et de la méthode de Korotkoff en 1905 a permis la mesure des valeurs maximales et minimales de la pression artérielle brachiale, qui a été largement diffusée dans la pratique clinique. Cependant, on a assisté à la disparition presque totale de l'analyse des courbes de pression.

Au début du 20ème siècle, la vitesse de transmission des ondes a été appliquée dans l'étude de l'élasticité artérielle grâce aux travaux de Bramwell et Hill (1922), de Bazett (1922), Beyerholm (1922), Steele (1937), etc. Cependant, ce fut le travail de Otto Frank qui domina le monde de la physiologie quantitative. Au-delà de ses études sur la contraction cardiaque (d'où la loi de Frank et Starling), en s'inspirant du travail de Hales et à l'aide des premiers manomètres, il arriva à une formulation mathématique de l'effet *Windkessel*. Il considéra les artères comme un compartiment compliant unique et décrivit le changement de la pression et du volume pendant la diastole, en dérivant l'équation exponentielle de la chute de pression diastolique. Ensuite, il introduisit une théorie des ondes dans les artères, par laquelle il prit en compte la propagation des ondes de pression et leur réflexion aux bifurcations artérielles, à travers l'analyse de Fourier.

Depuis l'introduction des premiers ordinateurs, avec la possibilité d'appliquer largement les transformées de Fourier, l'hémodynamique « en fréquentiel » a connu une véritable explosion d'expériences réalisées par différents scientifiques : MacKenzie, Womersely, Morgan, Kiely, McDonald, Nichols, Apéria, Taylor, O'Rourke, Noordergraaf, Westerhof, Milnor.

Ce regard historique du monde de l'hémodynamique nous permet de prendre conscience du fait que notre petite contribution à la science repose sur un travail qui dure depuis des centaines d'années, et qui a été accompli par de grandes personnalités scientifiques ; ceci nous incite à garder une position humble par rapport à notre travail.

Nous pouvons donc entrer sur la pointe des pieds dans le vif du sujet.

I Le système cardiovasculaire

Afin d'assurer l'apport en oxygène et en nutriments aux tissus périphériques et aux organes vitaux et leur permettre de fonctionner, le système cœur-vaisseaux est chargé de faire circuler le sang comme dans un réseau hydraulique. Le cœur a donc la fonction d'une pompe, et les artères celle de connecter la pompe à la périphérie.

En observant le système cardiovasculaire, on s'est donc aperçu qu'il présente tout d'abord une pulsatilité, déterminée par les contractions cardiaques et propagée par les artères. Néanmoins, le flux sanguin est continu en périphérie, d'où l'on peut déduire que les artères présentent, outre la fonction de transporter le sang, celle de transformer le flux de pulsatile en continu. La deuxième caractéristique du système cardiovasculaire est donc la distensibilité, qui peut expliquer justement cette transformation du flux, comme Hales en avait déjà émis l'hypothèse.

La pulsatilité du système est associée à la production des ondes de pression et de flux, qui, comme toute onde mécanique, se propagent dans un milieu à une vitesse qui dépend des caractéristiques de celui-ci, et génèrent des ondes de réflexion. L'interaction harmonique entre ces ondes est gouvernée par les lois de la physique et peut aboutir à des interférences constructives ou destructives.

D'autre part, la distensibilité du système (artériel) implique que la propagation de la pulsatilité engendrée par le cœur soit « acceptée » par les vaisseaux, de façon à ce que la pression, le flux, et leur propagation centrifuge ou centripète soient intrinsèquement liés à la fois à la fréquence de pulsatilité (fréquence cardiaque), au débit cardiaque, à la composition/structure de la paroi artérielle et à la taille du système. Toutes ces composantes, cardiaques et artérielles, sont connectées entre elles, réalisant ainsi le couplage cœur-vaisseaux. Il semble donc

évident qu'il existe une double interaction entre le cœur et les artères, où chaque participant peut influencer l'autre.

D'un point de vue théorique, comme la plupart des systèmes naturels, le système cardiovasculaire est pensé et a évolué afin d'obtenir la meilleure prestation avec le moindre effort. Laissons donc parler O'Rourke qui décrit l'interaction cœur-vaisseaux :

« Dans le règne animal il semble que le cœur ait évolué afin d'obtenir une fréquence cardiaque au repos pour laquelle la plupart de l'énergie de l'éjection ventriculaire est dépensée à une fréquence où l'impédance est plus faible. D'une part, la longueur du corps détermine la plage de fréquence où l'impédance est faible, d'autre part le cœur présente des fréquences plus élevées chez les petits animaux et plus basses chez les grands. Cette relation favorable est maintenue même quand la fréquence cardiaque augmente, du fait que la durée de la systole est très peu modifiée par rapport à celle de la diastole.

Il semble donc raisonnable de penser que le système artériel et le cœur soient favorablement et réciproquement adaptés. Le couplage optimal nous est montré par la relation parfaite entre l'impédance et le flux. En fait, le flux est plus élevé là où l'impédance est plus basse, ce qui engendre une fluctuation de pression assez modeste. De cela découle aussi l'observation que si le cœur devait produire le même travail d'une façon continue plutôt que pulsatile, il devrait dépenser huit fois plus d'énergie ….. ».[70]

«….. Il semblerait souhaitable d'avoir une distensibilité la plus grande possible, parce que cela réduirait la quantité des fluctuations de la pression pulsée générées par le flux pulsatile à l'entrée. Toutefois, dans ce cas on serait face à des contraintes. Si la distensibilité était très grande le système artériel nécessiterait d'être

très large et de contenir un grand volume de sang. Dans le cas de la nécessité d'augmenter la pression moyenne, comme dans l'exercice physique, le volume artériel devrait augmenter considérablement par un remplissage ultérieur de sang. L'augmentation du flux vers les tissus serait donc très retardée pendant que le volume de sang augmenterait, et le retour veineux vers le cœur serait compromis, limitant la capacité du cœur même d'augmenter le débit. Un fonctionnement idéal/optimal au repos serait donc associé à un dysfonctionnement dans des conditions de stress. Taylor a montré comment le fait que l'on ait dans l'arbre artériel des artères non uniformément élastiques comporte les bénéfices et pas les inconvénients d'un tube très distensible. En effet, le système artériel présente cette propriété : il est très élastique dans sa partie proximale (aorte ascendante) et devient plus rigide au fur et à mesure qu'il s'approche de sa partie finale (les artérioles) ».[70]

I.1. Modélisation du système cardiovasculaire

A partir de ces observations sur la nature du système cardiovasculaire, on peut facilement imaginer les raisons pour lesquelles il est intéressant d'en étudier le fonctionnement si complexe.

Les deux modèles qui ont joué et jouent toujours le rôle le plus important dans l'analyse du système cardiovasculaire sont le modèle de *Windkessel* et celui de propagation des ondes.

I.1.1. Elasticité, distensibilité, compliance

Avant de présenter ces modèles, il nous semble nécessaire de nous familiariser avec la nature élastique des artères.

La paroi des artères est formée de trois tuniques : l'intima (à l'intérieur), la média, et l'adventice (à l'extérieur). L'intima est constituée principalement d'une couche unique de cellules endothéliales, recouverte par une couche fine de tissu conjonctif fibroélastique et par la membrane limitante élastique interne, formée de fibres d'élastine. La média est la tunique moyenne, et la plus épaisse, formée de cellules musculaires lisses, d'une matrice extracellulaire de collagène, d'élastine, de mucopolysaccharides, et d'une limitante élastique externe. L'adventice est constituée par des fibres de collagène et d'élastine, et par une enveloppe qui assure l'ancrage des artères aux structures avoisinantes.

Du centre à la périphérie, le diamètre artériel diminue, le nombre des fibres élastiques diminue tandis que celui des fibres de collagène augmente, et l'épaisseur de la paroi augmente progressivement par rapport au diamètre.

La composition de la paroi artérielle a une influence sur son élasticité qui peut être évaluée à partir de la compliance et de la distensibilité.

La compliance (C) correspond à la capacité de l'artère d'augmenter son volume (V) par rapport à une variation de pression (P), selon la formule :

$$C = \Delta V / \Delta P \text{ (ml/mmHg)} \qquad (1)$$

La distensibilité (Ds) met en relation la compliance avec les paramètres géométriques propres à l'artère, comme le volume (V0), l'aire (A0) ou le diamètre (D0) initiaux, selon les formules :

$$Ds = (\Delta V / V0) / \Delta P \text{ ou } (\Delta A / A0) / \Delta P \text{ ou } 2(\Delta D / D0) / \Delta P \qquad (2)$$

I.1.2. Le modèle de *Windkessel*

Même si l'hypothèse d'un modèle de *Windkessel* a été formulée au début du 18ème siècle, il a fallu attendre le début du 20ème pour en avoir une formulation mathématique qui, depuis, a dominé l'histoire de l'hémodynamique. Ce modèle considère l'arbre artériel comme un compartiment unique (sans prendre en compte les bifurcations), et se base sur le fait qu'après l'éjection ventriculaire gauche et la fermeture des valvules aortiques, la plupart du sang est « stocké » dans l'aorte et dans les gros troncs artériels. Pendant la phase diastolique suivante, grâce à leurs propriétés viscoélastiques, les grosses artères retournent à la condition de repos et poussent le sang vers la périphérie, en garantissant à la fois de bons niveaux de pression artérielle en diastole et un amortissement de la pulsatilité (Figure 3).

Figure 3. Le modèle de Windkessel.

Le modèle conçu par Frank est capable d'analyser la relation entre les résistances périphériques (R) et la compliance artérielle totale (C), et prédit qu'en diastole, quand les valves aortiques sont fermées, la pression diminue de façon exponentielle avec une constante de temps, selon la formule suivante (Figure 4) :

$$\tau = R * C \quad (3)$$

où τ est la constante de temps, *i.e*. le temps nécessaire pour que la pression baisse de 37 % par rapport à sa valeur au début de la diastole. Plus grande est la résistance, plus lentement le sang « stocké » dans les grosses artères quitte le système et plus longue sera la constante de temps (τ). Mais aussi, plus grande est la compliance, plus grand est le volume de sang « stocké », et plus longue sera la constante de temps.

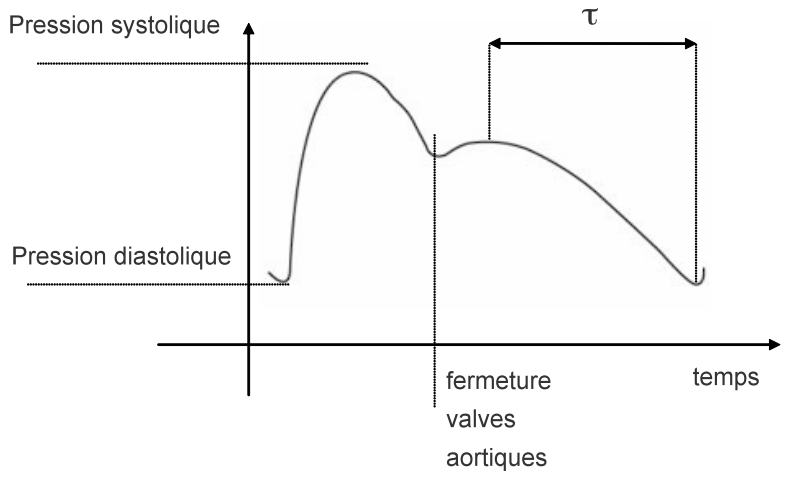


Figure 4. Onde de pression.

Pour mieux comprendre le travail de Frank, nous recourrons au modèle électrique de la loi de Ohms où la résistance est égale à la différence de potentiel divisée par l'intensité de courant électrique. En effet, grâce à une dérivation de la loi de Poiseuille, on peut décrire la relation entre la chute de pression (ΔP), le flux (Q) et les résistances (R) d'une façon très semblable :

$$\Delta P / Q = R \quad (4)$$

A l'époque où on pouvait mesurer la pression mais pas encore le flux, l'objectif de Frank était de calculer le débit cardiaque à partir de la pression dans l'aorte ascendante. Grâce aux formules (1) et (2), en calculant les résistances à partir de la compliance et de la constante de temps diastolique, il calcula le débit cardiaque (Q) :

$$Q = \Delta P * C * 1/\tau \qquad (5)$$

Etant donné qu'à proximité du cœur la pression veineuse est considérée comme négligeable, nous pouvons considérer la valeur ΔP comme étant la valeur de la pression artérielle moyenne (PAM) au niveau de l'aorte ascendante :

$$Q = PAM * C * 1/\tau \qquad (6)$$

Grâce à ces équations, on comprend comment il est possible d'évaluer la relation entre la pression, le flux et la compliance.

Cependant, ce modèle présente des limitations importantes :

1. si l'on considère l'arbre artériel comme un compartiment unique, le phénomène de réflexion des ondes ne peut être pris en compte ;
2. la relation entre la pression et le volume ne peut être correctement étudiée que dans la phase diastolique ;
3. l'assimilation de la compliance totale à la compliance aortique, sans considérer le rôle, petit mais significatif, de la compliance des petites artères, introduit une erreur.[71]

Ce modèle de Windkessel est dit modèle à deux éléments, parce qu'il ne considère dans l'analyse de la relation entre le flux et la pression que la résistance et la compliance.

I.1.3. Le modèle de la propagation des ondes (la vitesse de l'onde de pouls)

Comme nous l'avons dit, le cœur génère des ondes de pression et de flux qui, du fait de l'élasticité des artères de gros calibre, sont transmises en périphérie avec une certaine vitesse, appelée vitesse de l'onde de pouls. La transmission des ondes est caractérisée par le temps qu'il faut à la perturbation (onde) pour parcourir une certaine distance. Il faut bien préciser que la vitesse de propagation de l'onde n'est pas de même nature que la vitesse du flux. En effet, la transmission de l'onde survient même en l'absence de flux, comme on peut l'observer en plongeant un caillou dans un pot. En présence d'un flux, l'onde se propage à une vitesse plus grande que celle du flux et théoriquement les deux s'ajoutent. Dans le cas du système cardiovasculaire, le sang voyage à une vitesse de l'ordre de quelques centimètres par seconde, alors que la vitesse de l'onde est de l'ordre de mètres par seconde.

Les équations de Moens-Korteweg relient la vitesse des ondes à l'élasticité du matériel qui constitue la paroi artérielle, selon cette relation :

$$c^2 = (h * E_{inc}) / (2 * r * \rho) \qquad (7)$$

où c est la vitesse, E_{inc} le module de Young, ρ la densité du sang, h l'épaisseur de la paroi, r le rayon du vaisseau.

Au début du 20ème siècle, Frank en dériva une autre expression, liant la vitesse de l'onde à la compliance :

$$c^2 = V/\rho * 1/C \quad (8)$$

où V est le volume et C la compliance.

Une caractéristique fondamentale des ondes dans un système de tubes comme le système cardiovasculaire est la production d'ondes de réflexion suite à des changements de la composition du moyen de transmission (qui, dans le cas de l'onde de pression, est représenté par la paroi des artères), ou de son calibre, ainsi qu'en présence de bifurcations (cf page 110). En tout point de l'arbre artériel, les ondes de pression et de flux qu'on peut mesurer sont la somme des ondes antérogrades (transmises vers la périphérie) et des ondes rétrogrades (réfléchies vers le centre). On peut remarquer que les ondes de pression et de flux antérogrades présentent la même forme, alors que les ondes de flux réfléchies sont inversées par rapport aux ondes de pression réfléchies. Ainsi, la somme des ondes antérogrades et réfléchies donne lieu à des formes différentes des ondes de pression et de flux (Figure 5).

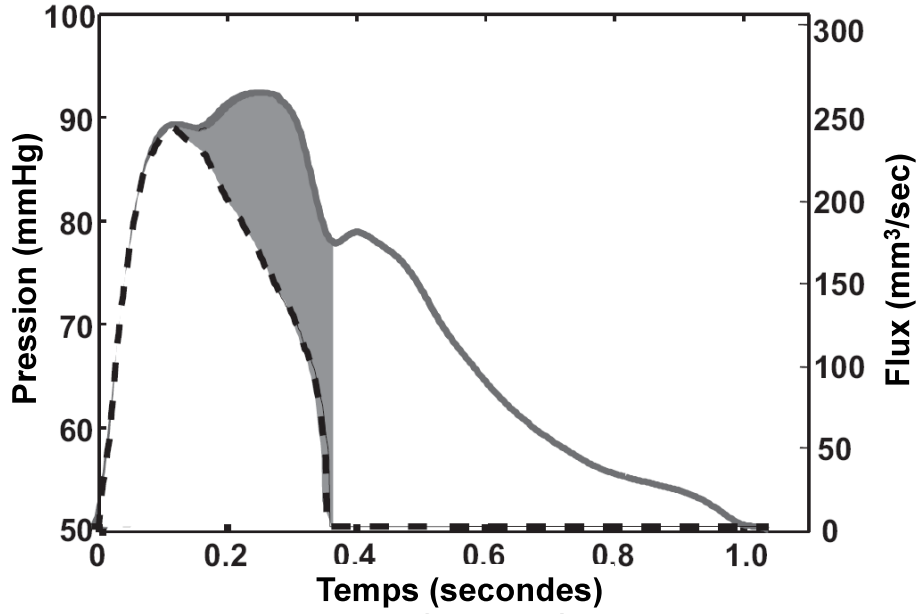


Figure 5. Ondes de pression (ligne continue) et de flux (ligne pointillée).

A partir de ce modèle, on peut donc déduire 5 notions principales :

1. l'élasticité et la compliance artérielles peuvent être estimées par la vitesse de l'onde de pouls, si la géométrie (diamètre et épaisseur de la paroi artérielle) est connue ;
2. la vitesse de l'onde de pouls dépend du niveau de pression : en effet, la distension de la paroi artérielle répond de façon non linéaire aux variations de pression du fait de la nature visco-élastique de la paroi ;
3. étant donné qu'avec le vieillissement les artères perdent progressivement leur composante élastique, la vitesse de l'onde de pouls dépend de l'âge ;
4. il est possible d'étudier la relation entre les ondes antérogrades et rétrogrades, qui détermine la forme finale de l'onde mesurée ;

5. du point de vue de la propagation des ondes, il est intéressant d'analyser la relation entre les ondes de pression et de flux, étant donné qu'elle dépend des ondes réfléchies.

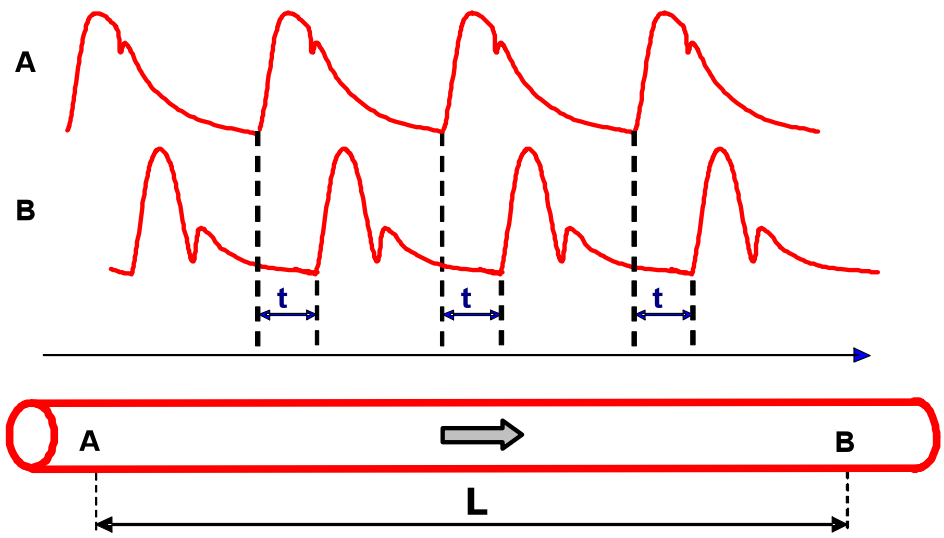
Le grand avantage de ce modèle de propagation et de réflexion des ondes de pouls est que, pour mesurer la vitesse de propagation des ondes, il n'est pas nécessaire d'analyser la relation entre la pression et le flux qui, comme on le verra par la suite, requiert des mesures précises de pression et de flux et n'est pas d'interprétation facile (cf page 103).

I.2. ARTICLE 1 : Différentes méthodologies pour estimer la vitesse de l'onde de pouls[72]

I.2.1. Introduction de l'ARTICLE 1

En pratique, plusieurs méthodologies existent pour évaluer la vitesse de l'onde de pouls. Durant mon internat à l'Hôpital de Cesena, Italie, nous avons comparé et publié trois méthodes pour la détermination de la vitesse de l'onde de pouls.

Première méthode

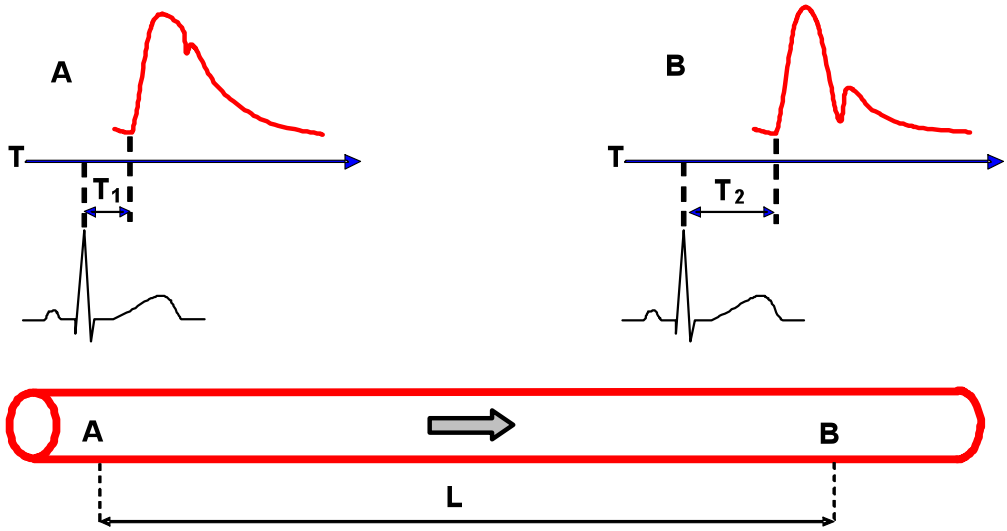


La vitesse de l'onde de pouls (VOP) est calculée comme étant la distance entre les deux sites d'enregistrement de la courbe de pression artérielle divisée par le décalage de temps entre les deux courbes enregistrées simultanément.

VOP = L / t

Cette méthode, utilisée par le Complior® (Alam Medical, France), emploie deux mécanocepteurs pour enregistrer l'onde de pouls.

Deuxième méthode

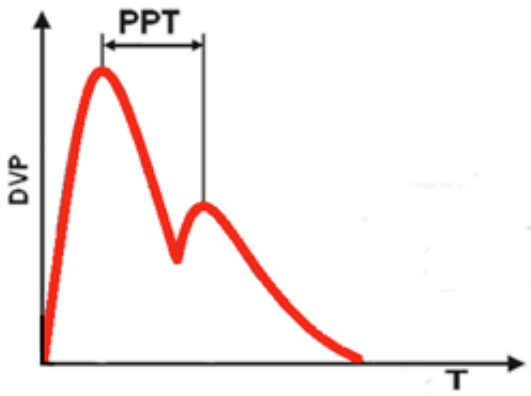


La VOP est calculée comme étant la distance (L) entre les deux sites d'enregistrement divisée par le décalage de temps entre les deux courbes. Ce décalage est obtenu par la soustraction du décalage entre l'onde R du complexe qRs de l'ECG et le pied de la courbe enregistrée au niveau de la carotide, au décalage entre l'onde R du complexe qRs de l'ECG et le pied de la courbe enregistrée au niveau de l'artère fémorale.

VOP = L / (T2-T1)

Cette méthode, utilisée par le PulsePen® (DiaTecne, Milan, Italie) et SphygmoCor® (AtCor, Sydney, Australie), emploie un tonomètre pour enregistrer l'onde de la pression artérielle.

Troisième méthode



L'index de rigidité artérielle (*stiffness index*). Dans cette méthode, la VOP est calculée sur la base de la taille divisée par le décalage de temps entre le premier pic systolique et le pic diastolique de la courbe d'enregistrement de la variation systolodiastolique du volume au niveau du doigt, obtenue par un système de photoplethysmographie.

Index de rigidité artérielle = Taille / PPT

Cette méthode est utilisée par le PulseTrace® PCA (Micro Medical Ltd, Rochester, UK). Elle est beaucoup plus facile à employer que les autres méthodes : il suffit de poser un doigt de la main à l'intérieur d'un capteur à infrarouge capable de capter le signal photopléthysmographique. Toutefois, son principe de fonctionnement n'est pas confirmé par des bases physiologiques solides.

Une population de 50 sujets (25 hommes et 25 femmes) a été recrutée pour cette étude. Pour garantir une bonne distribution par rapport à l'âge, on a inclus quatre sujets pour chaque tranche de cinq ans d'âge. Vingt-sept sujets travaillaient à

l'hôpital et 23 étaient hospitalisés ; 11 étaient hypertendus sous traitement, deux diabétiques et huit fumeurs.

Les trois méthodes analysées dans cette étude ont été comparées à une méthode de référence. Les mesures de la VOP ont été faites après 15 minutes de repos, dans une salle climatisée à 20°C, selon l'ordre suivant : Complior® → PulseTrace PCA® → méthode de référence → PulsePen®. Afin de déterminer aussi la reproductibilité des mesures, toutes les déterminations de la VOP ont été répétées une deuxième fois, dans le même ordre. Les temps d'exécution des examens étaient eux aussi déterminés.

Méthode de référence

La méthode de référence était la mesure de la VOP à l'aide de deux tonomètres, fournis par la société DiaTecne (Milan, Italie), pour l'enregistrement simultané de la pression artérielle carotidienne et fémorale. La distance était calculée par la méthode de soustraction : la distance entre la fourchette sternale et le site d'acquisition de la courbe fémorale moins la distance entre la fourchette sternale et le site d'acquisition de la courbe carotidienne. Le décalage entre la courbe fémorale et la courbe carotidienne était calculé par deux opérateurs n'ayant pas participé directement à la première phase de l'étude. Les courbes de pression artérielle étaient enregistrées sur papier, avec une définition de 10 ms/mm et une échelle variant entre 7 et 10 mmHg/mm. Les opérateurs ont déterminé sur papier le décalage de temps entre les deux courbes par la méthode *foot-to-foot*, considérée aujourd'hui comme la méthode de référence dans la détermination de la VOP.[73] La VOP a été donc calculée comme la distance entre les deux sites d'enregistrement de

la courbe de pression artérielle (carotide et fémorale), divisée par le décalage de temps entre les deux courbes enregistrées simultanément.

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ORIGINAL ARTICLE

Comparative study of methodologies for pulse wave velocity estimation

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Arterial stiffness, estimated by pulse wave velocity (PWV), is an independent predictor of cardiovascular mortality and morbidity. However, the clinical applicability of these measurements and the elaboration of reference PWV values are difficult due to differences between the various devices used. In a population of 50 subjects aged 20–84 years, we compared PWV measurements with three frequently used devices: the Complior and the PulsePen, both of which determine aortic PWV as the delay between carotid and femoral pressure wave and the PulseTrace, which estimates the Stiffness Index (SI) by analyzing photoplethysmographic waves acquired on the fingertip. PWV was measured twice by each device. Coefficient of variation of PWV was 12.3, 12.4 and 14.5% for PulsePen, Complior and PulseTrace, respectively. These measurements were compared with the reference method, that is, a simultaneous acquisition of pressure waves using two tonometers. High correlation coefficients with the reference method were observed for PulsePen ($r=0.99$) and Complior ($r=0.83$), whereas for PulseTrace correlation with the reference method was much lower ($r=0.55$). Upon Bland–Altman analysis, mean differences of values ± 2s.d. versus the reference method were -0.15 ± 0.62 m/s, 2.09 ± 2.68 m/s and -1.12 ± 4.92 m/s, for PulsePen, Complior and PulseTrace, respectively. This study confirms the reliability of Complior and PulsePen devices in estimating PWV, while the SI determined by the PulseTrace device was found to be inappropriate as a surrogate of PWV. The present results indicate the urgent need for evaluation and comparison of the different devices to standardize PWV measurements and establish reference values.
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Keywords: pulse wave velocity; PWV; arterial stiffness; aortic stiffness; stiffness index; tonometry

Introduction

Viscoelastic properties of large arteries play an essential role in cardiovascular hemodynamics, especially in systolic blood pressure (SBP) determination.[1,2] Certain physiological and pathological conditions such as age, hypertension and diabetes are responsible for a loss in arterial compliance.[3] Arterial stiffness, estimated by pulse wave velocity (PWV), has been shown to be an independent predictor of cardiovascular mortality and morbidity.[4,5] The measurement of PWV is generally accepted as the simplest as well the most noninvasive, rapid and reproducible method for assessing large artery stiffness.[6–9] Assessment of PWV may therefore play an important role in cardiovascular prevention and the evaluation of treatment efficacy[10–12] in addition to the fact that recent ESH–ESC recommendations indicate PWV measurement as a suitable exploration venue for use in clinical practice.[13]

Pulse wave (PW) travels along the arteries at a velocity rate, which varies according to wall elasticity: the less elastic the wall, the higher the velocity of PW propagation. PWV measures the time of travel of the pressure wave over a known distance and is calculated as the distance between the two positions of the pulse transducer divided by the time delay measured between pressure upstroke at each site. Most commonly, PWV is recorded between carotid and femoral artery sites to provide a measure of aortic stiffness. The pressure wave can be recorded directly by means of force recorders, such as high-fidelity applanation tonometers[14–17] or by detecting arterial wall motion secondary to pulse pressure by means of mechanotransducers or ultrasonographic systems.[18–22] A surrogate of PWV, the stiffness index (SI), has also been proposed by assessing capillary consequences of arterial stiffness using photoplethysmography, although some studies have showed a feeble correlation between SI and carotid–femoral PWV ($PWV_{c\ f}$).[23–25] The calculation of propagation time can be measured by various means, including analyzing the foot of the pulse wave, the points of maximum upslope or peak-to-peak time.

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The existence of several devices for the determination of PWV, using very different methods, renders the use of this parameter difficult in clinical practice, especially in the elaboration of proper reference values. To our knowledge, no comparison has been made yet between major assessment methods to evaluate the correspondence of obtained values, when one or another of these devices are used. In this study, three major noninvasive methods for assessing large artery stiffness were used and compared to a reference method.

Materials and methods

A population of 50 subjects (25 men and 25 women) aged 20–84 years (mean age: 49.3 ± 19.6 years) were recruited. To constitute homogeneously aged groups, subjects were evenly distributed according to age (from 20 to 79 years), with four individuals per each 5-year period being included. Two subjects older than 80 years of age were also included. Among the subjects recruited, 27 worked at the hospital and 23 were inpatients in our hospital. These inpatients were admitted for cardiovascular diseases (3), gastrointestinal disease (18), respiratory infection (1) and systemic disease (1). Eight subjects were smokers; 11 subjects were hypertensive (BP >140/90 in antihypertensive treatment); two inpatients were diabetic and seven subjects had dyslipidemia. Patients with cardiac arrhythmia were excluded from the study. The study protocol was approved by the Local Ethics Committee and conducted in accordance with the Helsinki Declaration.[26] Participants provided informed consent. Medical history, clinical examination and automatic BP assessment in supine position (Dinamap 1846 SX Critikon, JJM Inc. Arlington, TX, USA) were performed in all subjects. PWV was assessed in all 50 subjects using each of the four tested devices: Complior II, PulsePen, Pulse Trace PCA and the reference method. All testing was conducted in a quiet, temperature-controlled room. Subjects were asked to fast after having omitted any morning medication. Tests were initiated after a 15-min supine rest period. Estimation of PWV was performed in the following order: Complior II, PulseTrace PCA, reference method and PulsePen. Acquisition time was determined for all the tests. Testing was then repeated a second time in the same order. The four individual measurements obtained from each of the tested devices were carried out over different days at the same hour.

Reference method

The PWV_{c-f} is determined by the simultaneous acquisition of pressure waves using two high-fidelity tonometers (Figure 1, upper panel), considered as a 'reference method' test of arterial stiffness.[19] In this study, the time delay between the pulse waves was calculated using the 'foot-to-foot' method, determined as the mean of measured values on paper by two operators not directly involved in the acquisition phase. To this end, the carotid and femoral pressure waveforms were simultaneously recorded; the peripheral wave delay to the central wave was considered as the pressure wave progression time. Two tonometers provided by DiaTecne s.r.l., Milan were used. For assessment of the PW delay, the waves were printed on paper with a regular definition of 10 ms/mm for the time scale and a variable scale from 7 to 10 mm Hg/mm for pressure values. The units for the pressure value scale were dependent on the amplitude of the PW and were variable to record the pressure waveform on the entire height of the paper. The 'foot' of the pressure pulse waveform was determined by the intersection of the horizontal line tangent to the lowest point of the pressure waveform following the electrocardiogram complex with the extension of the line resulting from the initial protosystolic

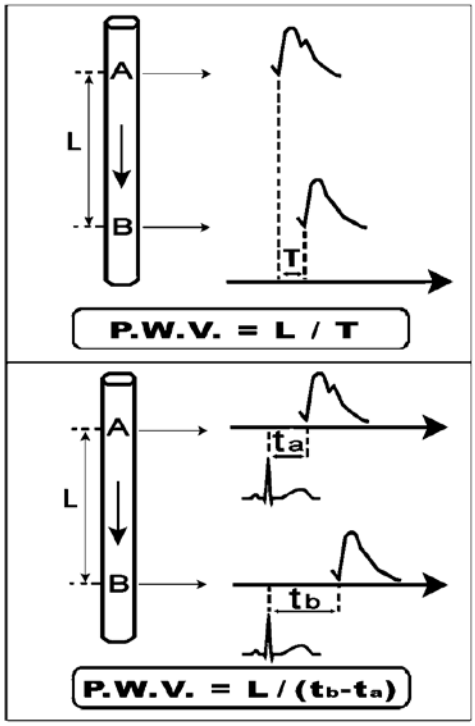

Figure 1 The two methods used to measure pulse wave velocity (PWV). Upper panel: PWV is calculated as the distance (L) between the two recording sites divided by the time delay (T) between the feet of the two waveforms at each site. This method has been used for the reference method and for the measurements with the Complior device. Lower panel: PWV is calculated as the distance (L) between the two recording sites divided by the pulse transit time, obtained by the time delay between the electrocardiogram and the carotid pulse (Ta) subtracted from the time delay between electrocardiogram and the femoral pulse (Tb). This method was used for the measurements of PWV with the PulsePen device.

rapid ascending phase of the pressure waveform. For the reference method as well as for Complior and PulsePen, the distance between the arterial points was assessed in a straight line, with a flexible meter, as the distance between the recording site at the femoral artery to the suprasternal notch minus the distance from the recording site at the carotid artery to the suprasternal notch, using a tape-measure located at the same location as the probe. The $PWV_{c\ f}$ obtained with the reference method was compared with the respective $PWV_{c\ f}$ values obtained with the three different devices:

Complior II *(Artec-medical, Pantin, France)*. This device, characterized by the simultaneous measurement of pressure pulses, employs dedicated mechanotransducers directly applied to the skin. The first operator begins positioning the probe at the common carotid artery, the central detection site, while a second operator places a second probe at the femoral artery site (Figure 1, upper panel). The sensor used to detect the pulse produces a signal, which is related to the derivative of the pressure pulse. A proprietary algorithm is then used to identify the waveform in the proximal and the peripheral artery to measure the time difference between the two sites and thereby to calculate the PWV from the distance between the two sites.[18]

PulsePen *(DiaTecne s.r.l., Milan Italy)*. With this device, the delay between pressure wave is determined by a single high-fidelity applanation tonometer to obtain the carotid and femoral pulse recorded sequentially in highly rapid succession, using the electrocardiogram trace as reference (Figure 1, lower panel). The PulsePen device has been previously described in details.[27,28] Herein, when the difference between heart rate recorded during the carotid measurement and that recorded during the femoral measurement was equal or greater than 10%, the PWV measurement was repeated (the difference in heart rate is indicated in the PulsePen software). According to this procedure, measurement of PWV had to be repeated in seven subjects.

PulseTrace PCA *(Micro Medical Ltd, Rochester, UK)*. This device estimates the SI by analyzing the photoplethysmographic waves (digital volume pulse) acquired on the fingertip of the subject.[23] The determining form of SI is shown in Figure 2.

All statistical analyses were performed using the NCSS Statistical software. Values are presented as the mean ± s.d. For each method, we first assessed variability and repeatability of PWV and PW transit time delay. The lack of agreement between the two measurements was estimated by the mean difference and the s.d. of the differences. Repeatability was assessed by calculating coefficient of variation (CV) for repeated measurements[29] and defined as the ratio of the s.d. of the between-measure difference to the overall mean expressed as percentage. Coefficient of repeatability, expressed as 2s.d. of differences, was also calculated.

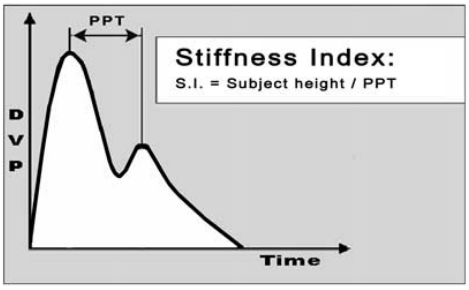

Figure 2 The digital volume pulse obtained from an infrared sensor (photoplethysmography). Stiffness index is calculated as the height divided by the time delay between the first systolic peak and the early diastolic peak in the waveform.

Comparisons between the different methods were then realized. For that, mean values of the two measurements for each method were used. The results were analyzed in two steps according to the recommendations of Bland and Altman.[30] In the first step, the correlation between measurement values (equation of the linear relationship, correlation coefficient and *P*-value) was investigated. Secondly, the relative (positive or negative) differences within each pair of measurements were plotted against the mean of the pair to ensure that no obvious relationship appeared between the estimated value (mean) and the difference.

Results

Table 1 summarizes the characteristics of Complior, PulsePen and PulseTrace, mean values of PWV and the duration of the PWV measurements with each device.

Figure 3 shows the reproducibility of the values of PWV obtained by each method, according to Bland–Altman analysis. The coefficient of repeatability of PWV measurements with the reference method was 1.44 m/s, with the Complior device was 1.51 m/s, with the PulsePen device was 2.03 m/s and with the PulseTrace device was 2.64 m/s. The repeatability of PW transit time delay with the reference method was 9.0 ms, with the Complior device was 15.3 ms, with the PulsePen device was 13.4 ms. PulseTrace device does not use the PW transit time delay for the measurements of SI. Coefficient of variation (s.d. of differences/means of values) of PWV was 12.4, 12.3 and 14.5% and of PW transit time delay was 9.6, 11.3 and 13.8% for Complior, PulsePen and PulseTrace, respectively.

Measurements obtained by the two operators for the reference method (two tonometers), analyzing the same waves printed on paper were very similar: the mean difference in the carotid–femoral time

Table 1 Device characteristics and mean PWV values of Complior, PulsePen, PulseTrace PCA and reference method

	Reference method	*Complior*	*PulsePen*	*PulseTrace PCA*
Probes	Two tonometers	Two mechanotransducers	One tonometer	Photoplethysmograph
Carotid–femoral pulse recording	Simultaneous	Simultaneous	Sequential, in two times	No
Arterial BP waveform analysis (augmentation index)		No	Yes	No
Total time to measure PWV		3′34″ ± 33″	6′06″ ± 77″	2′39″ ± 38″
Time to prepare the test		1′59″ ± 36″	2′43″ ± 39″	1′02″ ± 07″
Time to measure		1′35″ ± 29″	3′23″ ± 76″	1′37″ ± 35″
Weight (g)		1000	121	630
PWV (m/s)	8.07 ± 2.18	5.98 ± 1.38	8.22 ± 2.22	9.19 ± 2.60[a]
PWTT delay (ms)	60.0 ± 14.2	79.5 ± 15.4	59.2 ± 14.3	20.0 ± 5.9[a]

Abbreviations: BP, blood pressure; PPT, peak-to-peak time; PWTT, Pulse wave transit time; PWV, pulse wave velocity; SI, stiffness index.
[a]In PulseTrace SI and PPT was determined instead of PWV and PWTT delay, respectively. Data presented as mean ± s.d.

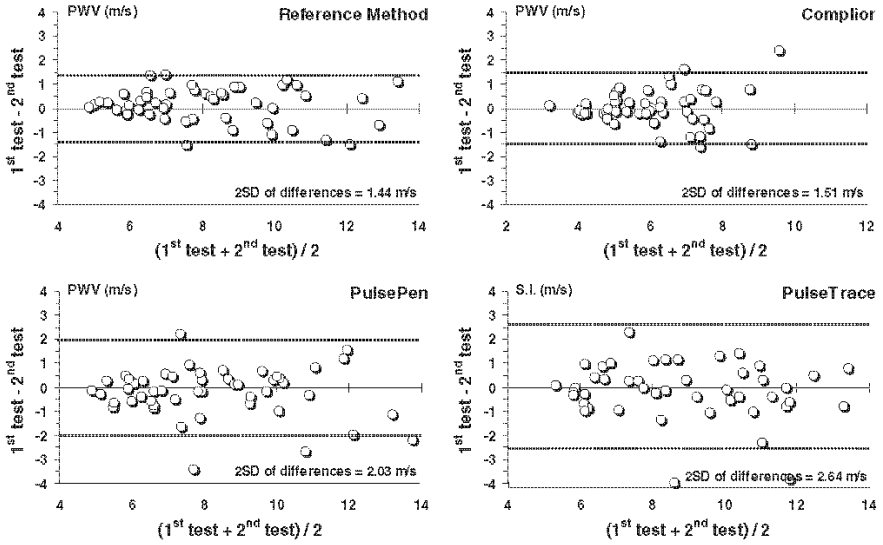

Figure 3 Bland–Altman analysis shows repeatability of pulse wave velocity (PWV) values obtained by the two measurements with the reference method (upper left), Complior (upper right), PulsePen (lower left) and PulseTrace (lower right).

delay (± s.d.) was 1.0 ± 1.9 ms, whereas the maximum difference between the two measurements was 4 ms. PWV mean difference was 0.18 ± 0.68 m/s.

All of the assessed methods were significantly correlated with age ($P<0.001$; Table 2). The correlations between PWV measured by the Complior and SBP and pulse pressure (PP = SBP-DBP) were statistically significant ($P<0.01$); no significant correlation was shown between SBP and PP versus values obtained with either the PulseTrace, PulsePen or reference method.

In Figure 4, PWV measurements with the reference method are compared against the Complior (upper panel), PulsePen (middle panel) and PulseTrace (lower panel) devices. On the left, the scatter plot shows linear correlation between PWV values measured by the reference method versus PWV measured by the other devices. All of the devices were significantly correlated with the reference method ($P<0.001$) with correlation coefficients (r) of $r=0.99$ for the PulsePen, $r=0.83$ for the Complior

Table 2 Spearman correlation coefficient between PWV measurements and anthropometric and clinical characteristics

	Reference method	*Complior*	*PulsePen*	*PulseTrace PCA*
Age	0.76**	0.58**	0.75**	0.62**
SBP	0.19	0.40 *	0.19	−0.02
DBP	0.16	0.11	0.17	0.15
PP	0.12	0.41*	0.12	−0.14
HR	0.21	0.14	0.21	−0.10
Height	−0.39*	−0.04	−0.39*	−0.23

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
*$P<0.01$; **$P<0.001$.

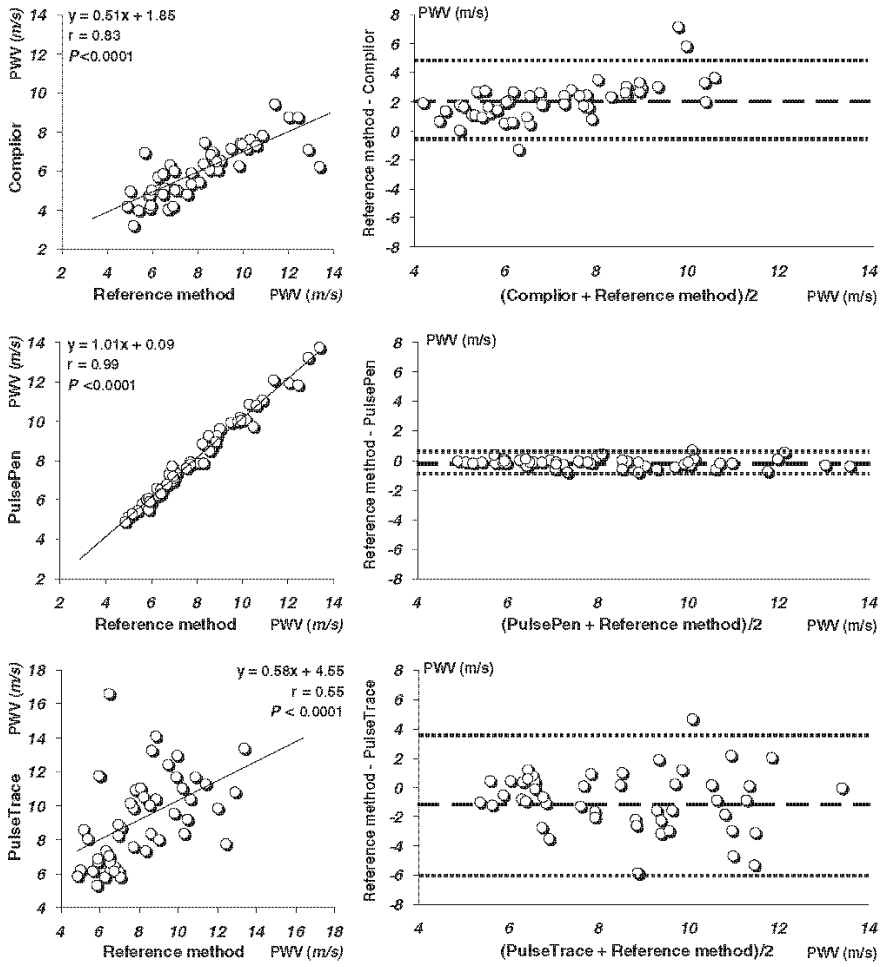

Figure 4 Pulse wave velocity (PWV) measurements with the reference method (simultaneous measurements with two tonometers) versus Complior (upper panel), PulsePen (middle panel) and PulseTrace (lower panel) devices. On the left, the scatter plot shows a linear correlation between PWV values measured by the reference method versus PWV measured by the other devices. On the right, Bland–Altman analyses show differences in PWV between reference method and the three other methods.

and $r = 0.55$ for the PulseTrace. The Bland–Altman analysis (Figure 4, right panels) revealed a mean difference of values ± 2s.d. versus the reference method of 2.09 ± 2.68 m/s, -0.15 ± 0.62 m/s and -1.12 ± 4.92 m/s for Complior, PulsePen and PulseTrace, respectively. Thus, with the PulseTrace, 66% of the measurements differed from the reference method by more than 1.0 m/s and 26% by more than 2.0 m/s. With the Complior, 26% of the measurements differed from the reference method by more than 1.0 m/s and 8% by more than 2.0 m/s. As for the PulsePen, no value was different by more than 1 m/s as compared to the reference method (95% of the measurements differed from the reference method by less than 0.6 m/s.).

In Figure 5, PW transit time delay measurements with the reference method are compared against the Complior (upper panel) and PulsePen (lower panel) devices. On the left, the scatter plot shows linear correlation between transit time values measured by the reference method versus PW transit time measured by Complior and PulsePen. Values from both devices were significantly correlated with the reference method ($P < 0.001$) with correlation coefficients (r) of $r = 0.99$ for the PulsePen and $r = 0.78$ for the Complior. The Bland–Altman analysis (Figure 5, right panels) revealed a mean difference of values ± 2s.d. versus the reference method of 19.5 ± 20.2 ms and 0.8 ± 3.9 ms for Complior and PulsePen, respectively.

Figure 6 shows linear correlation between PWV values measured by the three devices: PulsePen versus PulseTrace (upper panel), Complior versus PulseTrace (middle panel) and PulsePen versus Complior (lower panel). PWV values obtained with the Complior and PulsePen were well correlated ($r = 0.83$). Relationships were weaker when SI determined by the PulseTrace device was compared with the PulsePen or the Complior devices.

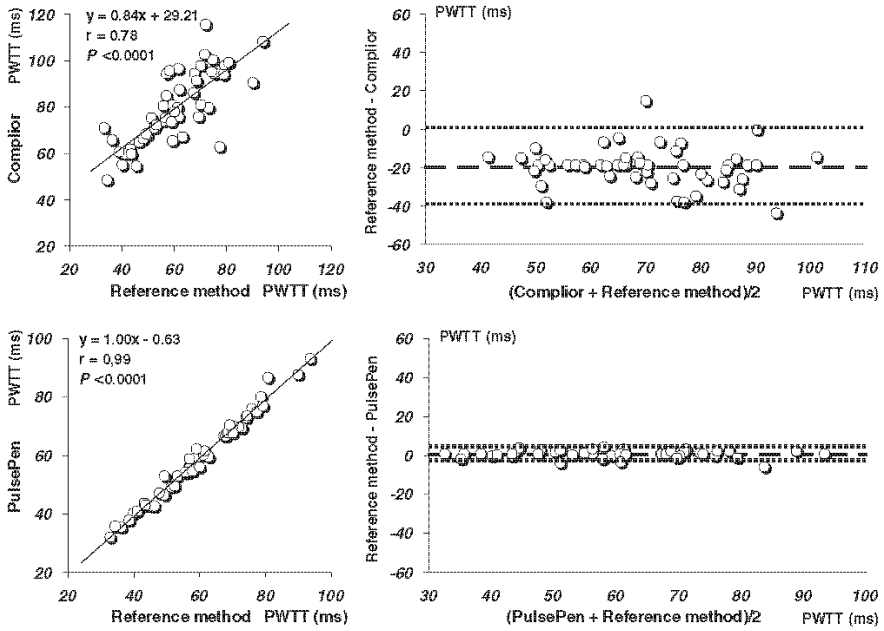

Figure 5 Pulse wave transit time (PWTT) delay measurements with the reference method (simultaneous measurements with two tonometers) versus Complior (upper panel) and PulsePen (lower panel) devices. On the left, the scatter plot shows a linear correlation between transit time values measured by the reference method versus transit time measured by the other devices. On the right, Bland–Altman analyses show differences in PWTT delay between reference method and the two other methods.

Discussion

In this study, a good correlation was found between aortic PWV values obtained with the devices based on measurements of the delay between carotid and femoral pressure pulse waves (PulsePen and Complior) and the reference method measured manually by the simultaneous use of two tonometers.

The PWV measured by the Complior device was significantly lower than the PWV measured by either PulsePen or reference method. PulsePen measures the carotid–femoral propagation time using the intersecting tangent algorithm to identify the foot of the waveform, while the Complior measures the propagation time from the point of maximum upstroke of the signal. In a previous report, Millasseau *et al.*[31] noted a significant difference between the Complior system and the intersecting tangent foot-to-foot algorithm used by the SphygmoCor (AtCor, Sydney, Australia) device. In their study, the PWV with the SphygmoCor was significantly greater than that of the Complior (mean difference ± s.d.; 0.91 ± 1.07 m/s; $P<0.001$), with the difference increasing with increasing PWV, that is, at a mean PWV of 12 m/s, the difference was 1.7 ± 0.75 m/s (mean ± s.d.). However, this difference was almost nullified when the intersecting tangent method was used to calculate the propagation time from the Complior waveforms. The PulsePen device tested herein utilizes the same method as the SphygmoCor. In the current study, we found similar results when comparing the Complior with the PulsePen as well as the Complior with the reference method. The difference was more pronounced in subject with higher PWV values. These results are in agreement with the conclusion of Millasseau *et al.*[31] that computation of PWV is critically dependent on the algorithm used to determine wave time delay in each device.

As we have shown in Figure 5, the PW transit time delay is constantly higher with Complior as compared to the PW transit time delay measured by the reference method. The absolute value of this difference is about 20 ms and not influenced by the level of the transit time. This difference of 20 ms leads to an underestimation of PWV, which in relative value is more pronounced when the PWV is high, that is, when the transit time is lower. For example, in a subject with a PW transit time delay of 100 ms measured by the reference method and a distance between the two probes of 500 mm, PWV is calculated at 5 m/s. In this case, the time delay with Complior will be at 100 + 20 = 120 mms and the PWV is 4.1 m/s, that is, lower by 0.9 m/s. If now a patient with the same distance between the two probes has a PW transit time delay of 50 ms measured by the reference method, his PWV is calculated at 10 m/s. For this patient, adding 20 ms in the transit delay time (that is, from 50 to 70 ms) will lead to a PWV of 7.1 m/s, that is, a decrease in PWV by 2.9 m/s, which represents an almost 30% in PWV. These considerations can explain the

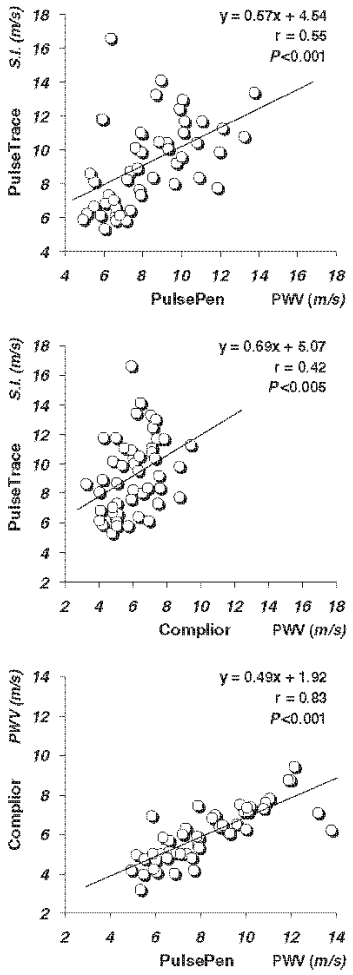

Figure 6 Scatter plots show linear correlation between pulse wave velocity (PWV) values measured by the three devices: PulsePen versus PulseTrace (upper panel), Complior versus PulseTrace (middle panel) and PulsePen versus Complior (lower panel).

results observed in Figure 4 (upper, right panel) showing more pronounced underestimation of PWV measured by Complior in subjects with higher PWV.

In this study, we found a strong correlation between the reference method and the PulsePen ($r=0.99$) than between the reference method and the Complior ($r=0.83$). This difference can be explained by the fact that a tonometer was used for both the reference method and the PulsePen, whereas mechanotransducers were used for Complior measurements. In addition, the algorithm used by the PulsePen software to determine the foot of the pressure wave closely follows the method used by the two operators to detect the waveform foot printed on the paper. The strong relationship between the PulsePen and the reference method confirms that the use of a single tonometer measurement with the PulsePen provides almost identical values to that obtained with the manual reference method using two tonometers.

The time needed to perform the test with the PulsePen device was almost twice as long as with the PulseTrace and Complior devices. As the PWV is influenced by heart rate, the two-step measurement of aortic PWV with the PulsePen device always forces the operator to verify the heart rate difference during carotid and femoral measurements, and to repeat these measurements if the difference in heart rate between the two are elevated.

PulseTrace device is very easy to use and does not require specific training for the operators. This method is not dependent on adeptness or ability of operators, contrary to the PulsePen and Complior devices where specific training is necessary.

No significant correlation was found between PulseTrace SI and the reference method. Previously, Millasseau *et al.*[24] demonstrated a significant correlation between PWV determined by SphygmoCor and SI based on digital volume pulse waves ($r=0.65$, $P<0.001$) in a study performed on 84 seemingly healthy subjects under 68 years of age. In the Millasseau study, results from the Bland–Altman analysis revealed that the difference in observed measurements between the two methods was upwards of 1 m/s in 44 subjects (51%) and upwards of 2 m/s in 20 subjects (23%). Similar data are also shown herein where 26% of the measurements by PulseTrace differed from the reference method by more than 2.0 m/s and 66% by more than 1.0 m/s. Therefore, our study confirms that the use of a method based on digital volume pulse waves (such as the PulseTrace device) is not appropriate for measuring aortic PWV in clinical practice. The SI derived from the PulseTrace measurement is believed to be dependent on wave reflection, which in turn is a function of not only PWV, but also vascular tone and ventricular ejection.

In conclusion, this study confirms the reliability of methods based on the delay between carotid and femoral pressure pulses in estimating aortic PWV (PulsePen and Complior devices). On the contrary, the SI determined by the PulseTrace device cannot be successfully employed for the same purpose. The significant data dispersion and the very weak correlation of PulseTrace data versus the reference method as well as the Complior and PulsePen data, together with the uncertain physiological and hemodynamic principles, suggest against the use of PulseTrace as an analogous system to carotid–femoral PWV.

This study also shows that it is not possible to define absolute reference values for PWV and, therefore, it is necessary to define reference values for each device. More importantly, it would appear imperative in the future to homogenize the algorithms for these different devices to obtain similar PWV values.

What is known about this topic

- Carotid–femoral PWV is considered as the 'gold standard' measurement of noninvasive determination of arterial stiffness, which is now recognized as an independent risk factor for cardiovascular disease.
- Several devices are used to measure PWV. Values of PWV obtained with these devices may considerably vary from one device to the other depending on the technique, the type of probes and the algorithms used to define PWV.
- There is an urgent need for the evaluation and the comparison of the different devices to standardize PWV measurements and establish reference values

What this study adds

- There is a good correlation between PWV values obtained with two devices (PulsePen and Complior) both based on measurements of the delay between carotid and femoral pressure pulse waves. Values obtained with these two devices are well correlated with the reference (manual) method using tonometers.
- PWV values measured by the Complior device are significantly lower than the PWV measured by either PulsePen or reference method due to different algorithms for the calculation of the foot-to-foot time delay. This difference should taken into account in the definition of reference values.
- Stiffness Index determined by the PulseTrace device is not well correlated with values obtained by PulsePen, Complior or the reference method.

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I.2.2. Conclusion de l'ARTICLE 1

Une corrélation très significative a été démontrée entre les valeurs de VOP obtenues avec le PulsePen®, le Complior® et la méthode de référence. Cette étude a donc confirmé la fiabilité de ces appareils dans l'étude des propriétés viscoélastiques de l'aorte.

Les valeurs de VOP déterminées avec le Complior® sont toujours plus basses que celles mesurées avec le PulsePen® ou le système de référence.

Pour rendre comparables les valeurs de VOP du Complior® et du PulsePen®, dans la formule de détermination de la VOP il est nécessaire d'ajouter 20 ms à l'intervalle de temps carotidofémoral calculé par le PulsePen® (ou bien de soustraire 20 ms à l'intervalle défini par le Complior®).

L'index de rigidité (*stiffness index*) déterminé avec le PulseTrace® ne peut pas être considéré comme substitutif de la détermination de la vitesse de l'onde de pouls carotidofémorale dans l'étude de la rigidité aortique.

I.3. ARTICLE 2 : Les caractéristiques de la vitesse de l'onde de pouls dans les artères élastiques et musculaires[74]

I.3.1. Introduction de l'ARTICLE 2

La vitesse de l'onde de pouls dans les artères élastiques (comme l'aorte) a été acceptée en tant que gold standard de la mesure de rigidité artérielle dans la pratique clinique, et constitue un marqueur de risque cardiovasculaire.[7–9,75–78]

Néanmoins, quelques études ont suggéré que la rigidité des artères musculaires (périphériques), évaluée par système d'échotracking ou par photoplethysmographie, serait stationnaire tout au long de la vie, contrairement à la rigidité des artères centrales qui augmente avec l'âge.

Dans cette étude, nous nous proposons d'évaluer par tonométrie d'applanation l'association entre la rigidité artérielle des artères musculaires et élastiques et l'âge, ainsi que leur relation avec les paramètres anthropométriques, la pression artérielle, l'épaisseur intima-media et des paramètres biologiques.

Nous avons donc mesuré les vitesses de l'onde de pouls carotido-fémorale, carotidopédieuse, carotidoradiale et fémoropédieuse par le tonomètre PulsePen chez 198 patients bénéficiant d'une hospitalisation de jour (Centre de Diagnostic, hôpital Hôtel-Dieu, Paris).

Les vitesses de l'onde de pouls carotidofémorale et carotidopédieuse augmentaient avec l'âge chez les hommes et les femmes. Avec l'âge, nous avons observé, uniquement chez les hommes, une petite augmentation de la vitesse de l'onde de pouls carotidoradiale et une réduction modeste de la vitesse de l'onde de pouls fémoropédieuse.

Original Article

Characteristics of pulse wave velocity in elastic and muscular arteries: a mismatch beyond age

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Background: Although aortic pulse wave velocity (PWV) has been accepted as gold standard of arterial stiffness, characteristics of PWVs in other arteries have never been reported.

Methods: We measured carotid-femoral, carotid-pedis, carotid-radial, and femoral-pedis PWVs by a validated tonometry PulsePen, and assessed body fat percentage by bioelectrical impedance analyzer, carotid intima–media thickness (IMT) by ultrasonograph, and other cardiovascular risk factors, in 198 patients from our ambulatory cardiovascular department.

Results: Carotid-femoral and carotid-pedis PWVs increased significantly and progressively with age in both men and women ($P \leq 0.03$), whereas only in men, a slight increase and decrease in carotid-radial and femoral-pedis PWVs, respectively, were detected with aging ($P \leq 0.006$). Carotid-femoral and carotid-pedis PWVs, but not carotid-radial and femoral-pedis PWVs, were significantly associated with age, body height and body fat percentage, brachial mean blood pressure (MBP), and pulse pressure (PP), carotid PP, PP amplification, carotid IMT, plasma glucose and taking antihypertensive agent ($P \leq 0.047$). In full adjustment models, carotid-femoral PWV increased by 0.89 ± 0.21, 0.38 ± 0.13, 0.74 ± 0.26, 0.40 ± 0.16, 0.51 ± 0.23 m/s, with an increase of 10 years in age, of 1 mmol/l in plasma glucose, of 10 mmHg in brachial PP, of 100 μm in IMT, and of 10 mmHg in brachial MBP, respectively, whereas carotid-pedis PWV increased by 0.31 ± 0.11 and 0.33 ± 0.12 m/s with an increase of 10 years in age and of 10 mmHg in brachial MBP, respectively.

Conclusion: Arterial stiffness in elastic arteries, but not in muscular arteries, increased significantly and progressively with age, and was more closely correlated to BP, plasma glucose and arterial thickness.

Keywords: arterial stiffness, cardiovascular risk factors, pulse wave velocity, PulsePen, tonometry

Abbreviations: AUC, area under curve; PWV, pulse wave velocity

INTRODUCTION

Pulse wave velocity (PWV) in elastic artery, such as carotid-femoral PWV, has been well accepted as a gold standard of arterial stiffness in clinical practice, and widely applied as a cardiovascular risk factor in various population-based studies [1–6]. Furthermore, carotid-femoral PWV has been recommended by the European Society of Hypertension and the European Society of Cardiology as a clinical marker for cardiovascular risk stratification in hypertensives [7]. Nevertheless, some studies have demonstrated that arterial stiffness in muscular arteries, but not in elastic arteries, evaluated by echo-track system and photoplethysmograph, would remain unaltered with advancing age or increasing blood pressure (BP) [8–10], but characteristics of PWV in muscular arteries and its association with age and other cardiovascular risk factors have never been studied. In recent years, with development of applanation tonometry, we were able to measure not only the classical carotid-femoral PWV in elastic artery, but also carotid-radial and femoral-pedis PWVs in the upper-limb or lower-limb muscular arteries, as well as in carotid-pedis PWV in the elastic and muscular artery. Herein, in the present study, we aimed to investigate the association of arterial stiffness in elastic and muscular arteries with advancing age, and their relationship with body size, body components, central and peripheral BP, arterial wall thickness and biological markers, in 198 consecutive patients from our ambulatory cardiovascular department.

METHODS

Patients

One hundred and ninety-eight consecutive inpatients, aged from 20 to 84 years, were recruited from the ambulatory cardiovascular department of Hotel-Dieu Hospital, Paris,

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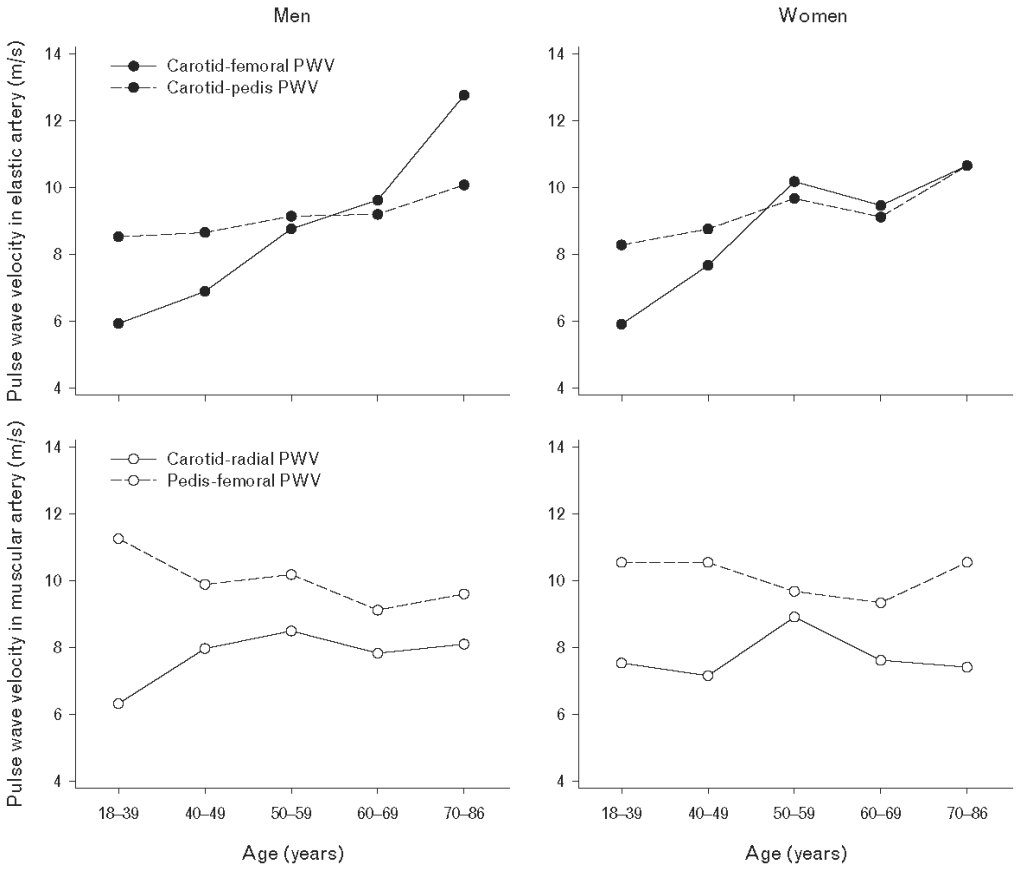

FIGURE 1 Association of pulse wave velocities in elastic and muscular arteries with age by sex. Carotid-femoral (filled circles with solid line), carotid-pedis (filled circles with spotted line), carotid-radial (unfilled circles with solid line), and pedis-femoral (unfilled circles with spotted line) pulse wave velocities were presented in different age groups, in men and women, respectively. In both men and women, carotid-femoral and carotid-pedis PWVs increased significantly and progressively with advancing age ($P \leq 0.03$), whereas only in men, carotid-radial PWV decreased and femoral-pedis PWV increased with aging ($P = 0.006$ and $P < 0.001$, respectively). PWV, pulse wave velocity.

France. All patients were referred for a cardiovascular evaluation in the context of presence of at least one cardiovascular risk factor. Inclusion criteria contained age more than 18 years and willingness to participate in this study. Exclusion criteria involved atrial fibrillation, and severe heart failure (New York Heart Association III-IV). Informed consent was obtained from all participants. Clinical documents were reviewed to define the cardiovascular diseases and antihypertensive treatment. The Ethics Committee of Hotel-Dieu Hospital approved the study protocol.

Anthropometric, biological and blood pressure measurements

Body height and body weight were measured, and body fat percentage was detected for each participant by a validated bioelectrical impedance analyzer TANITA TPF-300 (Omron, Japan). Biological markers, including plasma glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, were assessed by the standard methods in laboratory. Brachial BP was recorded twice by a validated oscillometric device (SCVL, Paris, France) after at least 5 min rest in the supine position, and averaged for further analysis.

Tonometry-based measurements on carotid blood pressure

After brachial BP was recorded twice and averaged, mean SBP and DBP were used to calibrate the radial pressure waveform, which was directly recorded by a high-fidelity applanation tonometer with a validated PulsePen device (DiaTecne s.r.l., Milan, Italy). Then, the radial DBP and mean BP were automatically calculated by the inbuilt PulsePen software with the area under curve method. Finally, carotid SBP and DBP were obtained with the carotid pressure waveform, recorded with the same method as radial pressure waveform, calibrated by the radial DBP and mean BP. More details regarding PulsePen device and the recording procedure are available in a previous publication [11]. Pulse pressure (PP) amplification was defined as brachial/carotid PP.

Tonometry-based measurements on pulse wave velocities in elastic and muscular arteries

Pressure waveforms in the carotid, femoral, pedis and radial arteries were recorded for each participant by the PulsePen device, and transit time for each artery were automatically calculated by the 'foot-to-foot' method with

TABLE 1. Characteristics of participants by sex

Variables	Total ($n=198$)	Men ($n=119$)	Women ($n=79$)	P
Age (years)	57.9 ± 14.2	58.4 ± 13.1	57.1 ± 15.9	0.51
Body height (cm)	170.0 ± 10.1	173.5 ± 7.6	159.7 ± 7.4	<0.001
Body weight (kg)	77.1 ± 14.4	81.0 ± 12.8	71.3 ± 14.9	<0.001
Body fat percentage (%)	29.3 ± 9.7	24.1 ± 6.5	37.2 ± 8.3	<0.001
Smoke, *n* (%)	59 (38.6)	36 (39.6)	32 (37.1)	0.76
Hypertension, *n* (%)	116 (60.4)	74 (63.3)	42 (56.0)	0.32
Diabetes, *n* (%)	36 (19.0)	26 (22.8)	10 (13.2)	0.10
Dyslipidemia, *n* (%)	62 (33.9)	40 (36.4)	22 (30.1)	0.38
Brachial SBP (mmHg)	133.3 ± 17.7	133.7 ± 17.7	129.9 ± 17.7	0.76
Brachial DBP (mmHg)	80.5 ± 10.1	81.5 ± 9.6	79.1 ± 10.6	0.10
Brachial mean BP (mmHg)	100.2 ± 12.4	100.8 ± 12.5	99.3 ± 12.1	0.41
Brachial PP (mmHg)	52.8 ± 13.2	52.2 ± 13.4	53.8 ± 12.9	0.40
Carotid PP (mmHg)	48.2 ± 12.8	46.9 ± 13.4	50.2 ± 11.6	0.07
PP amplification	1.08 ± 0.15	1.10 ± 0.14	1.05 ± 0.15	0.009
Plasma glucose (mmol/l)	6.27 ± 1.97	6.54 ± 2.32	5.87 ± 1.17	0.02
Triglycerides (mmol/l)	1.17 ± 0.71	1.28 ± 0.80	0.98 ± 0.49	0.005
Total cholesterol (mmol/L)	4.83 ± 1.04	4.75 ± 1.06	4.95 ± 1.00	0.24
High-density lipoprotein cholesterol (mmol/l)	1.42 ± 0.47	1.32 ± 0.46	1.57 ± 0.45	0.74
Low-density lipoprotein cholesterol (mmol/l)	2.85 ± 0.89	2.83 ± 0.95	2.88 ± 0.79	0.002
Carotid IMT (μm)	755.8 ± 158.2	776.1 ± 171.9	726.9 ± 129.9	0.04
Carotid-femoral PWV (m/s)	9.26 ± 3.67	9.40 ± 4.02	9.05 ± 3.08	0.50
Carotid-pedis PWV (m/s)	9.27 ± 1.35	9.20 ± 1.31	9.37 ± 1.42	0.49
Carotid-radial PWV (m/s)	7.88 ± 1.28	8.02 ± 1.34	7.67 ± 1.15	0.07
Femoral-pedis PWV (m/s)	9.95 ± 1.54	9.85 ± 1.39	10.11 ± 1.74	0.34

BP, blood pressure; PP, pulse pressure; PWV, pulse wave velocity. Values are means ± SD or numbers with percentage in parenthesis. The presence of hypertension, diabetes and dyslipidemia were defined as SBP at least 140 mmHg or DBP at least 90 mmHg or taking antihypertensive agents, fasting blood glucose level at least 7.0 mmol/l or taking insulin or oral hypoglycemic agent, and total cholesterol more than 5.69 mmol/l or triglyceride more than 1.69 mmol/l or high-density lipoprotein cholesterol less than 1.03 mmol/l or taking hypolipidemic agent. Brachial mean BP was calculated with the area under curve method. PP amplification was calculated as brachial/carotid PP. PWV was calculated as subtracted distance over the corresponding difference in transit time of the two measured points.

the inbuilt software, as the time interval from the beginning of the QRS wave in electrocardiogram to the beginning of the pressure waveform in each artery. Then, the distance from suprasternal notch to each artery site was measured by a caliper. Finally, as the definition of carotid-femoral PWV, carotid-pedis PWV was defined as (notch-pedis distance – notch-carotid distance)/(pedis transit time – carotid transit time); femoral-pedis PWV as (notch-pedis distance – notch-femoral distance)/(pedis transit time – femoral transit time); and carotid-radial PWV as (notch-radial distance – notch-carotid distance)/(radial transit time – carotid transit time), respectively. In previous report, the interobserver and intraobserver coefficients of variation in PWV measurement by PulsePen were 7.94 and 7.20%, respectively [11].

Ultrasonography

The common carotid artery intima–media thickness (IMT) was measured by an ultrasound system Sigma 440 (Kontron, Paris, France) with a 7.5-MHz transducer. Measurements were taken on the left common carotid artery, 2 cm from the bifurcation, and always performed on plaque-free arterial segments. IMT was automatically determined from changes of density on the section perpendicular to the vessel wall using specific software [12,13]. In our previous publication, the correlation coefficients for interobserver and intraobserver variability in IMT measurement by the Kontron ultrasound system were 0.71 and 0.77, respectively [12].

Statistics

Quantitative and qualitative parameters were presented as means ± SD and numbers with percentages in parenthesis, and compared between men and women by student's *t*-test and χ^2 test, respectively. Univariate Pearson's correlations were applied to investigate the association of PWVs in different arteries with conventional cardiovascular risk factors, and multivariate linear regressions were used to detect the independent influential factors, with covariables as age, sex, smoke, body height, body fat percentage, brachial mean and PP, carotid PP, carotid IMT, plasma glucose, total/HDL cholesterol and taking antihypertensive agent. Associations of PWVs in different arteries with age in both sexes were tested by the analysis of variance test. Statistical analysis was performed using SAS software, version 9.1 (SAS institute, Cary, North Carolina, USA). *P* value less than 0.05 was considered as statistically significant.

RESULTS

The 198 participants included 119 (60.1%) men, 116 (58.6%) patients with hypertension, 36 (19.0%) with diabetes, 62 (33.9%) with dyslipidemia, 13 (6.6%) with renal dysfunction, one (0.5%) with a history of stroke and one (0.5%) with a history of heart failure. As shown in Table 1, men compared with women, had significantly higher body height (173.5 ± 7.6 vs. 159.7 ± 7.2 cm, $P<0.001$), body weight (81.0 ± 12.8 vs. 71.3 ± 14.9 kg, $P<0.001$), PP amplification (1.10 ± 0.14 vs. 1.05 ± 0.15, $P=0.009$), plasma glucose (6.54 ± 2.32 vs. 5.87 ± 1.17 mmol/l, $P=0.02$),

TABLE 2. Univariate correlation between different pulse wave velocities and cardiovascular risk factors

Variables	Carotid-femoral PWV		Carotid-pedis PWV		Carotid-radial PWV		Femoral-pedis PWV	
	R	P	R	P	R	P	R	P
Age (years)	0.51	<0.001	0.44	<0.001	0.11	0.16	−0.17	0.052
Sex, (1 = men, 0 = women)	0.05	0.52	−0.06	0.49	0.13	0.07	−0.08	0.34
Smoke, (1 = yes, 0 = no)	0.10	0.20	−0.01	0.99	0.05	0.55	0.02	0.87
Body height (cm)	−0.14	0.044	−0.24	0.006	0.02	0.77	−0.07	0.43
Body fat percentage (%)	0.14	0.047	0.20	0.02	−0.01	0.99	−0.08	0.38
Brachial mean BP (mmHg)	0.34	<0.001	0.42	<0.001	0.37	<0.001	0.09	0.29
Brachial PP (mmHg)	0.37	<0.001	0.29	<0.001	0.04	0.63	−0.01	0.95
Carotid PP (mmHg)	0.38	<0.001	0.35	<0.001	0.13	0.08	0.01	0.89
PP amplification	−0.05	0.52	−0.23	0.008	−0.11	0.15	−0.08	0.38
Carotid IMT (μm)	0.41	<0.001	0.31	<0.001	0.13	0.11	−0.07	0.48
Plasma glucose (mmol/l)	0.33	<0.001	0.12	0.24	0.18	0.03	−0.06	0.59
Total/HDL cholesterol	0.01	0.99	−0.06	0.58	0.12	0.18	−0.07	0.49
Taking antihypertensive agent, (1 = yes, 0 = no)	0.21	0.003	0.11	0.23	0.12	0.11	−0.10	0.24

Univariate Pearson's correlation analyses were applied between different pulse wave velocities and cardiovascular risk factors, and correlation coefficients (*R*) and the corresponding *P* values were shown. BP, blood pressure; PP, pulse pressure; PWV, pulse wave velocity; HDL, high-density lipoprotein.

triglyceride (1.28 ± 0.30 vs. 0.98 ± 0.49 mmol/l, $P = 0.005$) and carotid IMT (776.1 ± 171.9 vs. 726.9 ± 129.9 μm, $P = 0.04$). Women, on the contrary, had significantly higher body fat percentage (37.2 ± 8.3 vs. $24.1 \pm 6.5\%$, $P < 0.001$), and LDL cholesterol (2.88 ± 0.79 vs. 2.83 ± 0.95 mmol/l, $P = 0.002$). Of note, there was no significant sex difference in carotid and brachial BPs and PWVs in different arteries ($P \geq 0.07$).

Associations of PWVs in elastic and muscular arteries with age were investigated, as patients were categorized into five age groups (Fig. 1). In both men and women, carotid-femoral and carotid-pedis PWVs increased significantly and progressively with advancing age ($P \leq 0.03$), whereas only in men, carotid-radial PWV decreased and femoral-pedis PWV increased significantly with aging ($P = 0.006$ and $P < 0.001$, respectively).

As shown in Table 2, PWVs in elastic arteries were significantly associated with cardiovascular risk factors, including age, body height, body fat percentage, brachial mean BP and PP, carotid PP, PP amplification, carotid IMT, plasma glucose and taking antihypertensive agent ($P \leq 0.047$). However, only significant associations of carotid-radial PWV with brachial mean BP and plasma glucose were detected in PWVs in muscular arteries ($P \leq 0.03$).

In Table 3, multivariate linear regression models were applied to investigate determinants of PWVs in elastic and muscular arteries. Age, plasma glucose, brachial mean BP and PP and carotid IMT were significant and independent determinants of carotid-femoral PWV ($P \leq 0.03$), wheras age and brachial mean BP were significantly and independently associated with carotid-pedis PWV ($P \leq 0.009$). Of note, there was no significant association of carotid-radial and femoral-pedis PWVs with any cardiovascular risk factor.

DISCUSSION

There were two major findings in the present study. First, arterial stiffness, assessed by PWV, significantly and progressively increased with age in elastic arteries in both men and women, whereas in muscular arteries, only slight age-related modifications in PWVs were detected in men. Second, only PWVs in elastic arteries, but not in muscular arteries, were significantly and independently associated with age, plasma glucose, brachial BPs and carotid IMT.

In consistence with previous publications [14–16], we found that, in the present studies, there was a significant and progressive age-related increase in arterial stiffness of

TABLE 3. Determinants of different pulse wave velocities by multivariate regression analyses

Variables	Regression coefficients	P
Carotid-femoral PWV (m/s)		
Age, per 10 years	0.89 ± 0.21	<0.001
Plasma glucose, per 1 mmol/l	0.38 ± 0.13	0.003
Brachial PP, per 10 mmHg	0.74 ± 0.26	0.006
Carotid IMT, per 100 μm	0.40 ± 0.16	0.01
Brachial mean BP, per 10 mmHg	0.51 ± 0.23	0.03
Carotid-pedis PWV (m/s)		
Age, per 10 years	0.31 ± 0.11	0.007
Brachial mean BP, per 10 mmHg	0.33 ± 0.12	0.009

BP, blood pressure; IMT, intima–media thickness; PP, pulse pressure; PWV, pulse wave velocity. Multivariate regression analyses were applied to investigate the determinants of different pulse wave velocities, with age, gender, smoke, body height, body fat percentage, brachial mean and PP, carotid PP, carotid IMT, plasma glucose, total/HDL cholesterol, and taking antihypertensive agent considered as potential confounders in models.

elastic arteries. This was commonly attributable to the elastin depletion and collagen deposition in elastic arteries with advancing age [17]. On the contrary, we also found that arterial stiffness in the upper-limb or lower-limb muscular artery almost remained stable with aging. A similar finding was also observed in the upper-limb muscular artery in the Framingham Heart Study [16] and in other previous studies, in which arterial stiffness was assessed by the echo-track system and photoplethysmograph [8–10]. As muscular artery, compared with elastic artery, contains less elastin, but much more smooth muscle cell, the observed slight age-related modification in arterial stiffness was probably attributed to the atherosclerosis and regional muscular atrophy.

From a physiological point of view, with advancing age, the increased arterial stiffness in elastic arteries and unchanged arterial stiffness in muscular arteries would contribute to an attenuated mismatch between central aorta and periphery arteries, and consequently lead to an increase in pulsatile energy transmitted from the aorta to the microcirculation [18]. In the present study, we found that arterial stiffness in elastic arteries were significantly and independently associated with age, plasma glucose, brachial BPs, and arterial thickness. On the contrary, no influential factor was detected for arterial stiffness in muscular arteries. In other words, compared with elastic arterial stiffness, the stiffness in muscular arteries seems to be 'invulnerable' to conventional cardiovascular risk factors, including age, smoking, plasma glucose and cholesterol, BP levels and arterial thickness. The vulnerable and invulnerable state of elastic and muscular arteries, respectively, would inevitably lead to an impairment in the protective impedance of arterial stiffness, with presence of not only old age, but also the conventional cardiovascular risk factors, such as high plasma glucose and high brachial BP. As a result, this would cause a decreased magnitude of reflected wave, more pulsatile energy from central to microcirculation, and more associated end-organ damage. In this respect, the present study, from a pathophysiological point of view, provides a novel explanation for microvasculature-related complication in patients with hypertension and diabetes. However, as a tentative theory, the hypothesis should be further tested by future prospective studies and laboratory researches.

The strength of the present study was no other than the systematic evaluation of arterial stiffness in four large elastic and muscular arteries, as well as conventional cardiovascular risk factors, in 198 consecutive patients. However, findings in our study need to be carefully interpreted within the context of its limitations. First, as almost every hemodynamic measurement was conducted in the supine position, including carotid ultrasonography, PWV, and central BP, we only measured patients' BP in the supine position and characterized patients with it. Second, it was of note that, the SD of carotid-femoral PWV in the present study was almost twice as reported in the Framingham Heart Study [19]. We believe that the discrepancy was mostly attributable to three factors: Participants from the present study were mainly composed of cardiovascular inpatients with a relatively high prevalence of hypertension, diabetes and dyslipidemia, whereas the Framingham Heart Study was conducted in a general population; Sample size in the present study was only about 200 patients and much smaller than that in the Framingham Heart Study; PulsePen was used for the PWV measurement in our study, whereas SPT-301 was applied in the Framingham Heart Study. Lastly, due to technical reason, PWV in the pedis artery was not measured in 63 patients.

In summary, arterial stiffness in elastic arteries, but not in muscular arteries, increased significantly with advancing age and the presence of high plasma glucose and high BP. This discrepancy in arterial stiffness would probably lead to an attenuated impedance match between aorta and peripheral arteries and future microcirculation-related end-organ damage.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

In this cross-sectional study, carried out in a group of adults of both genders, the authors have compared the relationships to age and various cardiovascular risk factors of pulse wave velocities (PWV) in elastic (carotid-femoral PWV) versus muscular arteries (carotid-radial and femoral-pedis PWV). The data confirm two well known facts: (1) that carotid-femoral PWV increases with age, blood pressure, plasma glucose, and abnormalities of lipid profile, (2) that age and cardiovascular risk factors have far less influence on carotid-radial PWV. The new finding is that femoral-pedis PWV behaves in this respect as does the carotid-radial. Thus, the stronger influence of age and cardiovascular risk factors on the mechanical behavior of human elastic versus muscular arteries seems to be a general phenomenon.

Reviewer 2

Few studies in the past suggested that hypertension affects elastic and muscle arteries differently.

Elastic arteries become stiffer while muscle arteries are less sensible to increased blood pressure. The authors of this study extend this concept to age. They use a gold standard parameter, namely pulse wave velocity, and conclude affirming that peripheral muscle arteries are less sensible to age than central elastic arteries, and that a difference can also be seen between man and woman. The strength of this manuscript is the use of a stable and reproducible method. The weaknesses are related to the relatively small number of enrolled subjects and the presence of both healthy and pathologic subjects in the group.

I.3.2. Conclusion de l'ARTICLE 2

Notre étude a donc confirmé que la rigidité des artères élastiques augmente avec l'âge, la pression artérielle, le glucose plasmatique et les altérations du profil lipidique, tandis que le vieillissement et les facteurs de risque cardiovasculaire ont un effet modeste sur la rigidité des artères musculaires. En particulier, nous avons montré que l'artère du membre inférieur se comporte de la même façon de l'artère du membre supérieur.

II Principes d'analyse de la forme des ondes

Après avoir présenté les deux modèles nous permettant d'analyser le système cardiovasculaire et avoir donné un exemple de l'utilisation pratique d'un modèle théorique, nous aborderons les principes de l'analyse des ondes sur laquelle se base toute la structure de l'hémodynamique moderne.

A la suite de Landois (1874), qui a enregistré sur une bande de papier roulant le jet du sang sorti de l'artère coupée d'un chien (hématographie), l'histoire nous a proposé plusieurs méthodes de mesure des ondes.

Nous présentons dans ce paragraphe deux façons complémentaires d'étudier la morphologie des ondes : la première, dite du *time domain (*domaine temporel*)*, nécessite que les valeurs de pression soient calculées instant par instant au cours du cycle cardiaque ; la deuxième, dite analyse en fréquentiel (ou *frequency domain*), considère les ondes de pression comme des ondes sinusoïdales et analyse la pression par rapport aux fréquences des ondes.

II.1. Analyse en temporel (*time domain*)

L'onde de pression au niveau de l'aorte ascendante (Figure 6, ligne rouge) est composée d'une phase ascendante rapide qui atteint un pic (le sommet de la courbe, qui représente le pic systolique), d'une phase descendante rapide qui amène à un creux correspondant à la fermeture des valves aortiques, d'une courte phase ascendante qui amène au pic de pression diastolique, et d'une phase descendante lente qui amène au niveau de la pression diastolique.

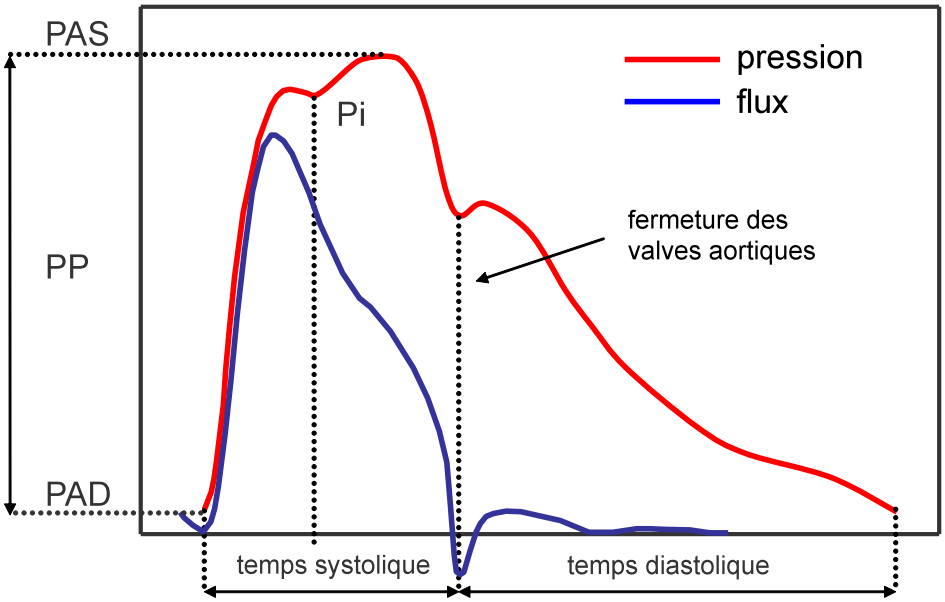


Figure 6. Ondes de pression et de flux et paramètres analysés.

La courbe de flux (Figure 6, ligne bleue) comporte une phase ascendante qui se termine au pic du flux, une phase descendante (normalement avant le pic de pression systolique), une phase de flux négatif qui correspond à la fermeture des valves aortiques, et enfin un retour à zéro.

A partir de ces figures on peut visualiser la différence entre les formes des ondes de pression et de flux. Notamment, le flux commence à diminuer quand la pression est encore en train d'augmenter, et il présente aussi une phase négative. Cela, comme nous l'avons dit, est dû principalement à l'effet des réflexions (page 113).

De l'onde de pression on peut dériver la pression systolique (PAS, le pic maximal de pression), la pression diastolique (PAD, la valeur la plus basse de pression), la pression pulsée (PP, la différence mathématique entre les deux), et la pression moyenne (obtenue par intégration de la courbe de pression sur le temps).

Après avoir analysé les propriétés de la propagation des ondes, nous verrons en détail les composantes de la courbe de pression (cf page 131).

De l'analyse en temporel, on peut aussi dériver la constante de temps de chute de pression diastolique (formule (3)), les temps systolique et diastolique, la pression moyenne systolique (l'aire sous la courbe pendant la systole) et diastolique (l'aire sous la courbe pendant la diastole). Le paramètre qui caractérise la phase systolique de l'onde de pression aortique est l'inflexion de la courbe (Pi) correspondant au point où l'on peut imaginer que l'onde de pression antérograde rencontre l'onde de pression réfléchie. Ce dernier point sera analysé en détail dans le paragraphe III.3, page 115.

II.2. Analyse en fréquentiel (Frequency domain)

Depuis la découverte de l'analyse des harmoniques par Fourier, il est possible de représenter une onde cyclique par la superposition d'une série d'ondes sinusoïdales (Figure 7).

Pour mieux comprendre cette analyse, imaginons le son produit par une corde de guitare. Une fois pincée, la corde produit une vibration sonore qui correspond à une note ; si on la bloque soudain, on s'aperçoit que d'autres cordes (qui donnent des notes différentes) sont en train de vibrer, alors qu'elles étaient en état de repos : pourquoi ? Parce que le son de la corde qui a été pincée n'est pas un son pur, mais le résultat de la superposition de différentes harmoniques ; ainsi, les cordes voisines « sentent » certaines harmoniques (certaines fréquences) qui leur ressemblent, et entrent en résonance.

Avec des précautions d'interprétation, il en est de même pour les ondes de pression et de flux, et avec la décomposition de Fourier il est possible d'obtenir plusieurs harmoniques qui constituent l'onde originaire, comme montré dans la Figure 8.

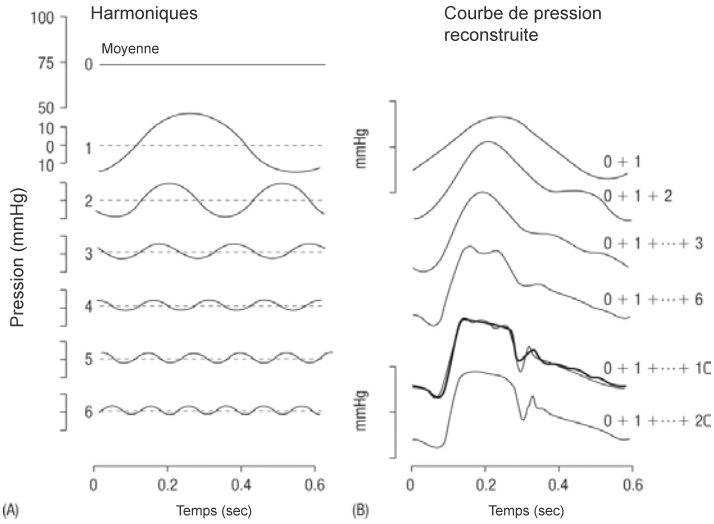


Figure 7. Reconstruction d'une courbe de pression à partir des harmoniques (de [79]).

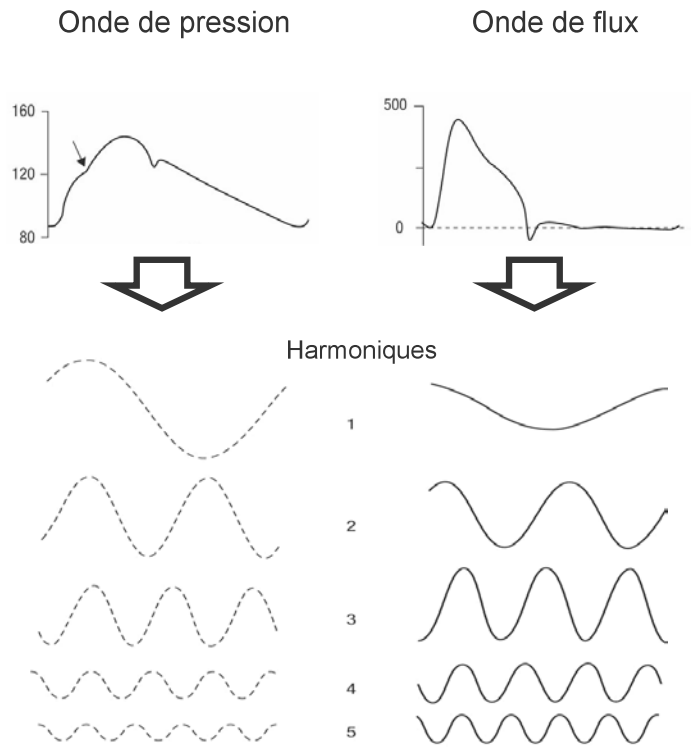


Figure 8. Décomposition de Fourier (adapte de [80])

A partir de l'analyse de Fourier on peut donc « voir » une onde du point de vue de la fréquence en dessinant un graphique ayant pour abscisse les différentes harmoniques et pour ordonnée l'amplitude de chaque harmonique (Figure 9).

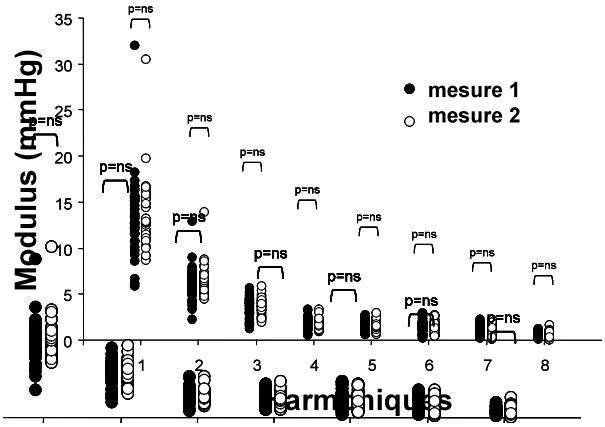


Figure 9. Deux mesures d'une onde de pression carotidienne en fréquence.

On remarque que l'information principale de l'onde de pression est contenue dans les huit premières harmoniques. En effet, la fréquence augmentant, la contribution des harmoniques est de plus en plus faible.

Un des intérêts de l'étude en fréquence consiste à pouvoir mettre en relation les ondes de pression et de flux à partir de leurs harmoniques, comme nous allons le voir ci-dessous.

II.3. La relation entre la pression et le flux : l'impédance

La modélisation du système cardiovasculaire, basée sur la mesure de la pression artérielle réalisée par Frank, et d'autres après lui, a évolué à partir des années 1960 grâce à la mesure des ondes de flux.

Cet événement a été une étape fondamentale dans la compréhension de la mécanique cardiovasculaire et du couplage cœur/vaisseaux. C'est pourquoi, bien que ces études aient été partiellement abandonnées à cause de leur difficulté d'application et d'interprétation, il nous semble opportun d'en citer les fondamentaux.

Lorsqu'on a commencé à mesurer le flux, on s'est vite rendu compte que cette relation pression/flux pouvait être décrite à partir d'un paramètre appelé « impédance ». On peut définir l'impédance comme la modalité, typique pour chaque artère dans un système artériel donné, selon laquelle la paroi artérielle « accueille » la pulsatilité cardiaque, en transformant la relation entre pression et flux.

Dans la Figure 10, l'impédance (Zc) est représentée par la dérivée de la courbe flux/pression. En fréquentiel on peut étudier l'impédance, qui est représentée par la courbe dessinée en fonction de la fréquence (Figure 11).

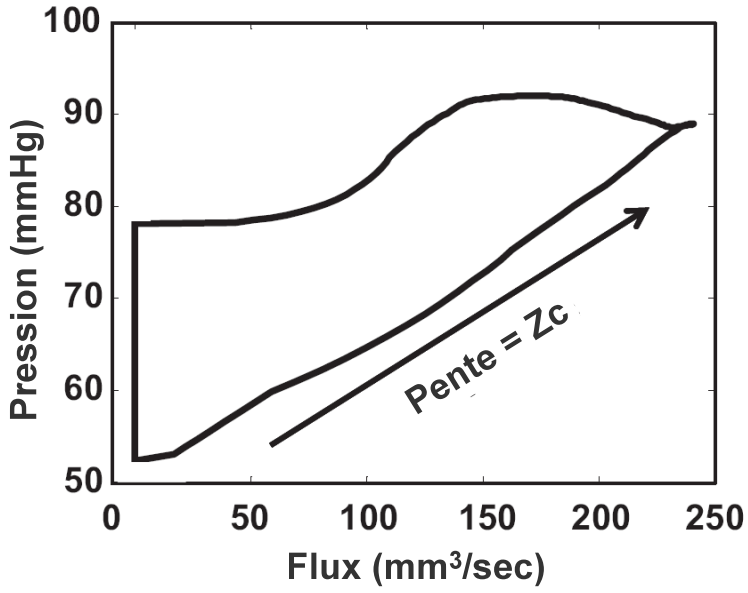


Figure 10. Impédance dans le *time domain* (adaptée de [81]).

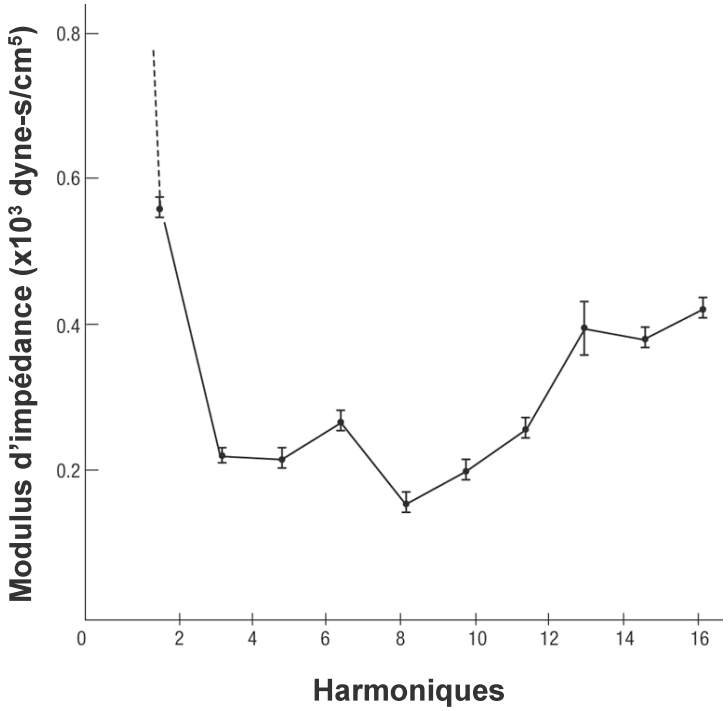


Figure 11. Impédance dans le *frequency domain* (adaptée de [82]).

Comme on peut le constater sur ces deux modèles, l'impédance varie en fonction du cycle cardiaque (*time domain*, Figure 10) ou de la fréquence analysée (*frequency domain*, Figure 11). Ces variations d'impédance dépendent du fait que, comme on l'a vu, la relation flux/pression est modifiée par les ondes de réflexion. Si on pouvait imaginer un système sans ondes de réflexion, les ondes de pression et de flux auraient la même forme et leur relation serait constante : dans ce cas l'impédance mesurée (qu'on appelle impédance caractéristique) ne correspondrait qu'aux caractéristiques de la paroi de l'artère. On peut mesurer l'impédance caractéristique comme la pente de la courbe flux/pression après l'ouverture des valves aortiques dans la première phase de la systole (Figure 10), ou comme la valeur d'impédance autour de laquelle varie le module d'impédance pour des fréquences élevées (Figure 11).

III Propagation des ondes et ondes de réflexion

Dans les paragraphes précédents, nous avons montré comment le système cardiovasculaire est un système pulsatile qui peut être étudié par l'analyse des phénomènes ondulatoires. Ceux-ci peuvent être associés à des variations considérables des valeurs de pression artérielle qui suivent la superposition des ondes de flux et de pression et des ondes de réflexion. L'analyse des ondes est donc fascinante, car elle nous permet, au moins en partie, d'évaluer la compliance artérielle et les modifications de pression artérielle (dans l'arbre artériel ou aux différents âges de la vie). Dans ce paragraphe nous nous proposons d'analyser en détail le phénomène de réflexion des ondes de pression.

Pour bien comprendre ce qu'est une onde de réflexion, prenons l'exemple d'une pierre qui tombe dans une cuvette remplie d'eau, créant des ondes allant vers la périphérie. Arrivées à la périphérie, elles ne disparaissent pas mais produisent des ondes qui reviennent au centre de la cuvette, appelées «ondes de réflexion» (Figure 12). Si une deuxième pierre tombe quelques secondes après la première, l'onde qui va vers la périphérie se superpose à l'onde de la première pierre réfléchie par le bord de la cuvette. Le résultat est une onde plus élevée, qui est la somme des deux ondes. Dans le système cardiovasculaire, les ondes voyageant à une vitesse supérieure à celle de l'exemple, l'onde directe et l'onde réfléchie sont issues de la même contraction cardiaque.

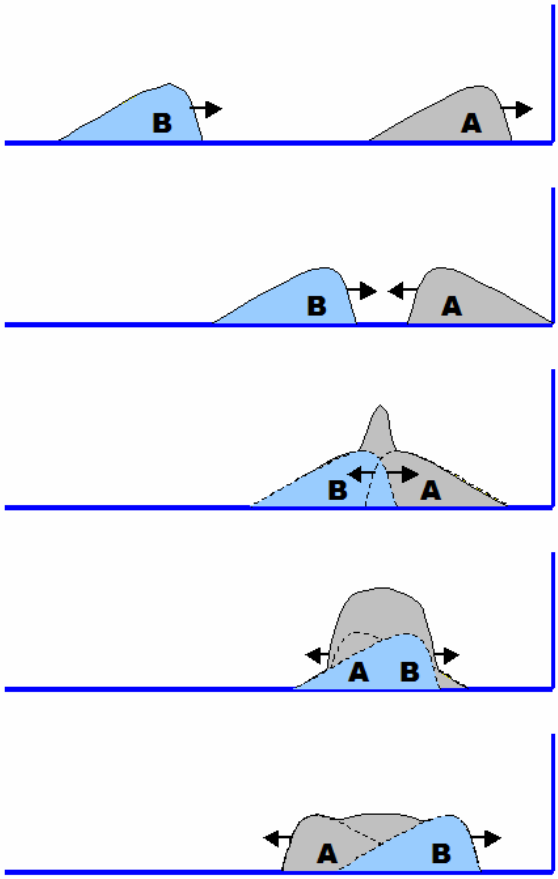


Figure 12. Le phénomène de réflexion.

III.1. Les sites de réflexion

Comme nous l'avons dit précédemment, dans le système cardiovasculaire les ondes de réflexion (ou centripètes, ou indirectes) sont engendrées à chaque fois que l'onde incidente (ou centrifuge, ou directe) rencontre des modifications du milieu de propagation, notamment :

1. toutes les variations de calibre (diamètre), d'épaisseur ou de composition de la paroi artérielle (il faut rappeler que les propriétés de la paroi aortique se modifient dès l'aorte ascendante jusqu'à la bifurcation iliaque, avec une élasticité moindre en s'éloignant vers la périphérie) ;
2. les petites artérioles qui constituent les résistances vasculaires périphériques ;

3. les bifurcations artérielles et les plaques d'athérosclérose.

L'onde résultante sera donc la somme de l'onde directe et des ondes réfléchies. Cependant, tandis que l'onde directe a une morphologie bien définie – elle est produite en effet par l'éjection ventriculaire gauche et modifiée sur la base des propriétés viscoélastiques de l'aorte et des gros troncs artériels –, les ondes réfléchies, au contraire, représentent le résultat de millions et millions de sites de réflexion particuliers. Par conséquent, l'onde de réflexion n'est pas un élément hémodynamique unique et bien défini.

III.1.1. Les résistances vasculaires périphériques

Tout au long de l'arbre artériel, de l'aorte ascendante aux petites artères de résistance, on observe une augmentation du nombre de vaisseaux et de leur section totale, ce qui va de pair avec la diminution de leur rayon et de leur longueur

Tableau 1).

Tableau 1. Dimensions moyennes de l'arbre vasculaire (d'après McDonald 1974).

Nom	Niveau	Diamètre entrée mm	Diamètre sortie mm	Diamètre moyen entrée	Surface totale (cm^2)	Nombre
Aorte	1	20	7	20	3,2	1
Grandes artères	2	10-1,8	1,8	3,2	3,4	20
Branches principales	3	4,0-1,0	1	3,4	3,4	260
Branches secondaires	4	2,0-0,4	0,4	0,8	4,0	800
	5	0,8-0,2	0,2	0,31	5	7 103
Branches tertiaires	6	0,4-0,1	0,1	0,16	6	$3\ 10^4$
Artères terminales	7	0,2-0,04	0,04	0,08	10	$2\ 10^5$
Branches terminales	8	0,1-0,025	0,025	0,032	16	$2\ 10^6$
Artérioles	9	0,06-0,015	0,015	0,02	25	$8\ 10^6$
	10	0,03-0,008	0,008	0,012	35	$3\ 10^7$
Capillaires	11	0,01-0,008	0,008	0,008	80	$2\ 10^8$

Cependant, d'un point de vue hémodynamique, le fait le plus important est qu'on observe au niveau des artérioles une chute très significative de la pression artérielle. Ceci est dû à la fois à une réduction du diamètre, à une augmentation de l'épaisseur et à un changement de la composition de la paroi artérielle (la composante musculaire prévaut sur la composante élastique). Le comportement de la pression artérielle au niveau des artérioles est montré dans la Figure 13 ; c'est donc là le site le plus important de réflexion des ondes.

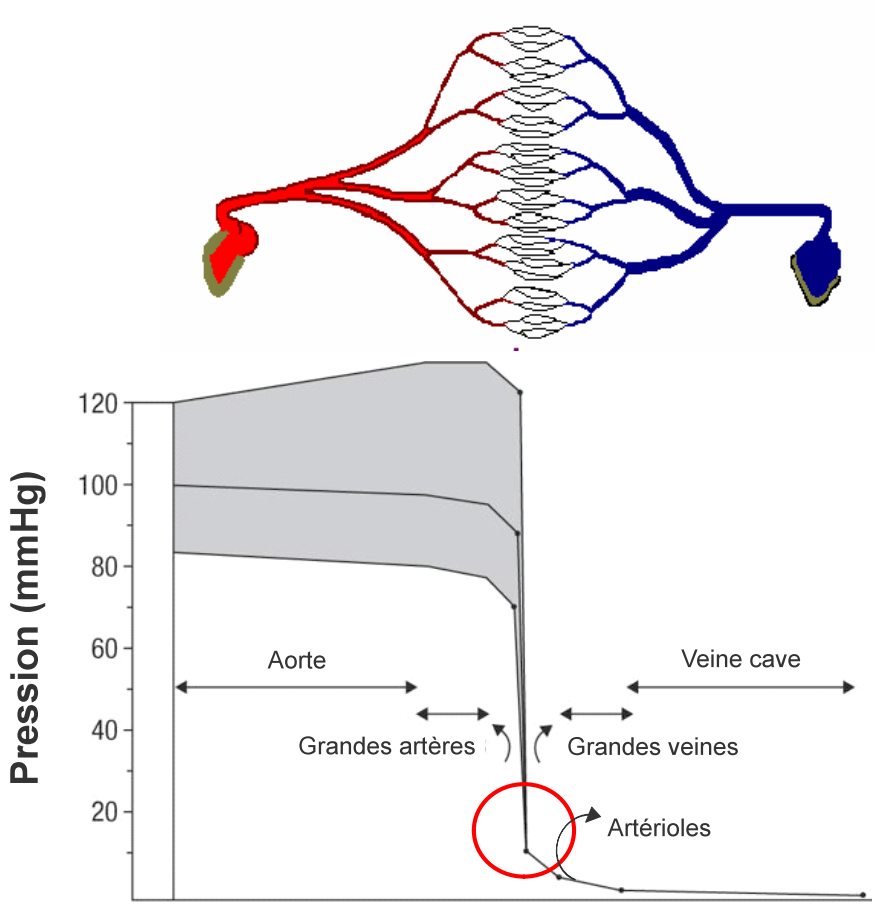


Figure 13. Comportement de la pression artérielle dans différentes sections de l'arbre artéro-veineux (adaptée de [80]).

III.1.2. Les points de bifurcation des artères et les plaques athéromateuses

Les bifurcations des artères représentent d'autres sites de réflexion : au niveau d'une bifurcation, l'onde directe se divise en deux ondes centrifuges continuant leur progression vers la périphérie et produit une onde réfléchie, centripète. L'ampleur de cette onde dépend de l'angle de bifurcation et du calibre des branches secondaires qui naissent de l'artère principale.

Les plaques d'athérosclérose et les autres zones segmentaires de rigidité artérielle représentent un site de réflexion particulièrement important dans des conditions de polyangiosclérose. Au niveau d'une plaque athéromateuse, l'onde directe se scinde en deux composantes : une composante directe et une composante réfléchie.

III.2. Le rôle de la réflexion sur la pression et le flux : un modèle simplifié

Pour commencer, imaginons un tube élastique fermé à une extrémité, à travers lequel se propagent une onde de pression et une onde de flux. Les lois de l'hémodynamique nous apprennent que les deux ondes vont être réfléchies, et que les ondes réfléchies reviennent vers le centre à la même vitesse que les ondes incidentes ; les ondes de pression et de flux que l'on peut mesurer ne sont donc que la somme des ondes directes et indirectes. Dans un tube fermé à une extrémité, l'onde de pression réfléchie sera positive (Figure 14) tandis que l'onde de flux réfléchie sera négative, et donc inversée par rapport à l'onde incidente (Figure 15) ; ceci implique aussi que l'onde de pression mesurée est le résultat de la somme de

deux ondes positives, tandis que l'onde de flux mesurée est la somme d'une onde positive et d'une onde négative. La raison pour laquelle les ondes de pression et de flux mesurées n'ont pas la même forme vient donc du phénomène de réflexion.

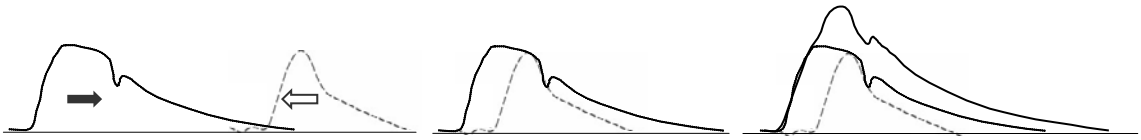


Figure 14. Ondes de pression, de gauche à droite : directe, réfléchie, superposition des ondes directe et réfléchie, résultante de la superposition (onde mesurée, ligne continue).

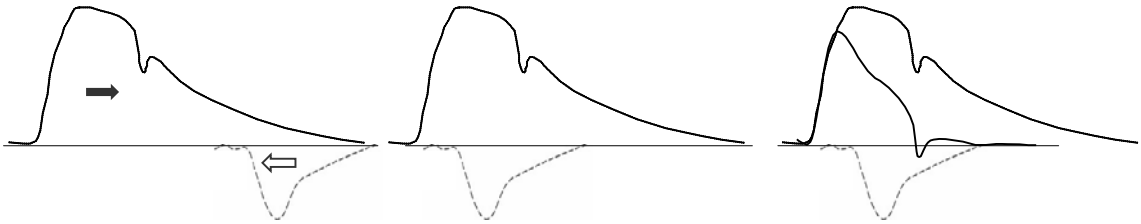


Figure 15. Ondes de flux, de gauche à droite : directe, réfléchie, superposition des ondes directe et réfléchie, résultante de la superposition (onde mesurée, ligne continue).

Par ce modèle on peut aussi étudier la séparation des ondes directes et indirectes. En effet, si (et seulement si) la relation entre la pression et le flux est connue pour un segment donné de l'artère (impédance), selon les formules suivantes on peut calculer les deux composantes (incidente et réfléchie) de l'onde de pression et de flux :

$$Pd = Zc * Fd = (Pm + Zc * Fm) / 2 \quad (9)$$

$$Pr = - Zc * Fr = (Pm – Zc * Fm) / 2 \quad (10)$$

où P est la pression, F le flux, d directe, r réfléchie, m mesurée, et Zc est l'impédance caractéristique. Les formules sont appliquées aux harmoniques, selon la décomposition de Fourier (page 101).

Or ce modèle suppose que le système artériel soit assimilable à un seul tube, ce qui n'est évidement pas le cas. Comme nous l'avons dit ci-dessus, à cause des bifurcations et des multiples site de réflexion, il est difficile d'imaginer une onde réfléchie unique ; en effet on pourrait plutôt penser à une multitude d'ondes réfléchies qui se superposent et reviennent vers le centre du système. Le modèle d'un tube singulier fermé à l'extrémité et la méthode de séparation des ondes contiennent donc des approximations, et il n'existe pas encore de consensus dans le monde de l'hémodynamique vasculaire sur les mécanismes concernant la réflexion des ondes.[83,84]

Cependant, sans entrer en détail dans le débat, nous nous permettons de simplifier notre discours et d'utiliser ce modèle, qui semble être très intéressant d'un point de vue didactique. Nous allons nous concentrer sur l'étude des ondes de pression.

III.3. Une caractéristique des ondes de réflexion : le point d'inflexion

Comme nous avons vu dans le chapitre II, page 97, l'analyse de l'onde de pression dans le domaine temporel nous permet d'en étudier les caractéristiques. Murgo et al. a décrit quatre typologies des ondes de pression.[80,85]

Type A : le pic systolique tombe dans la partie finale de la systole, après le point d'inflexion ; l'index d'augmentation est supérieur à 12 %.

Type B : le pic systolique tombe dans la partie finale de la systole, après le point d'inflexion, mais l'index d'augmentation est compris entre 0 % et 12 %.

Type C : le point d'inflexion tombe après le pic systolique, et l'index d'augmentation est négatif (< 0 %). Les ondes du type C peuvent être divisées en type Cs si le pic de l'onde réfléchie tombe en systole et type Cd s'il tombe en diastole.

Type D : le point d'inflexion ne peut être repéré dans la courbe de pression, du fait que l'onde de réflexion arrive très tôt en systole et se superpose entièrement à l'onde incidente.

Ce qui caractérise une onde de pression est donc : 1/ la présence et l'emplacement du point d'inflexion qui représente idéalement le moment où l'onde réfléchie rencontre l'onde incidente ; 2/ l'amplitude de l'onde de réflexion, capable de modifier la forme de l'onde de pression.

Analysons l'onde de pression mesurée, dans le cas d'une artère élastique, comme l'aorte (Figure 16A, gauche).

Si on prend comme repère le point d'inflexion, on peut reconstruire idéalement l'onde réfléchie et l'onde incidente. Dans ce cas, étant donné que le point d'inflexion se trouve dans la phase descendante de la systole, après le pic systolique (type C), toute la contribution de l'onde réfléchie aura lieu pendant la dernière phase de la systole et pendant la diastole. Ainsi le pic systolique n'est pas influencé par la réflexion, alors que pendant la phase diastolique on observe une augmentation de la pression due à la réflexion. Ceci aura deux effets fondamentaux : 1/ la post-charge du ventricule gauche (la pression systolique aortique) n'est pas influencée par les

réflexions, et 2/ la pression coronaire pendant la diastole sera augmentée grâce aux réflexions.

Prenons maintenant l'exemple d'une artère plus périphérique, comme l'artère fémorale (Figure 16A, droite). Dans ce cas, on ne peut plus observer le point d'inflexion dans la forme de l'onde de pression, mais simplement un pic systolique, qui d'ailleurs est plus élevé que le pic aortique, et un pic diastolique. Que s'est-il passé ? Si l'on s'éloigne du centre du système vasculaire, deux événements contribuent aux modifications de l'onde de pression : d'une part, l'artère périphérique est plus proche des sites de réflexion représentés par les petites artérioles, et, d'autre part, l'élasticité pariétale régionale est diminuée. Par conséquent, les ondes de réflexion arrivent beaucoup plus tôt à la rencontre de l'onde directe, l'amplitude des ondes de réflexion est plus importante, et la superposition entre l'onde directe et réfléchie survient très tôt pendant la phase systolique ascendante. Ainsi, le pic systolique est dominé par la contribution des ondes de réflexion, tandis que la phase diastolique n'est presque pas concernée.

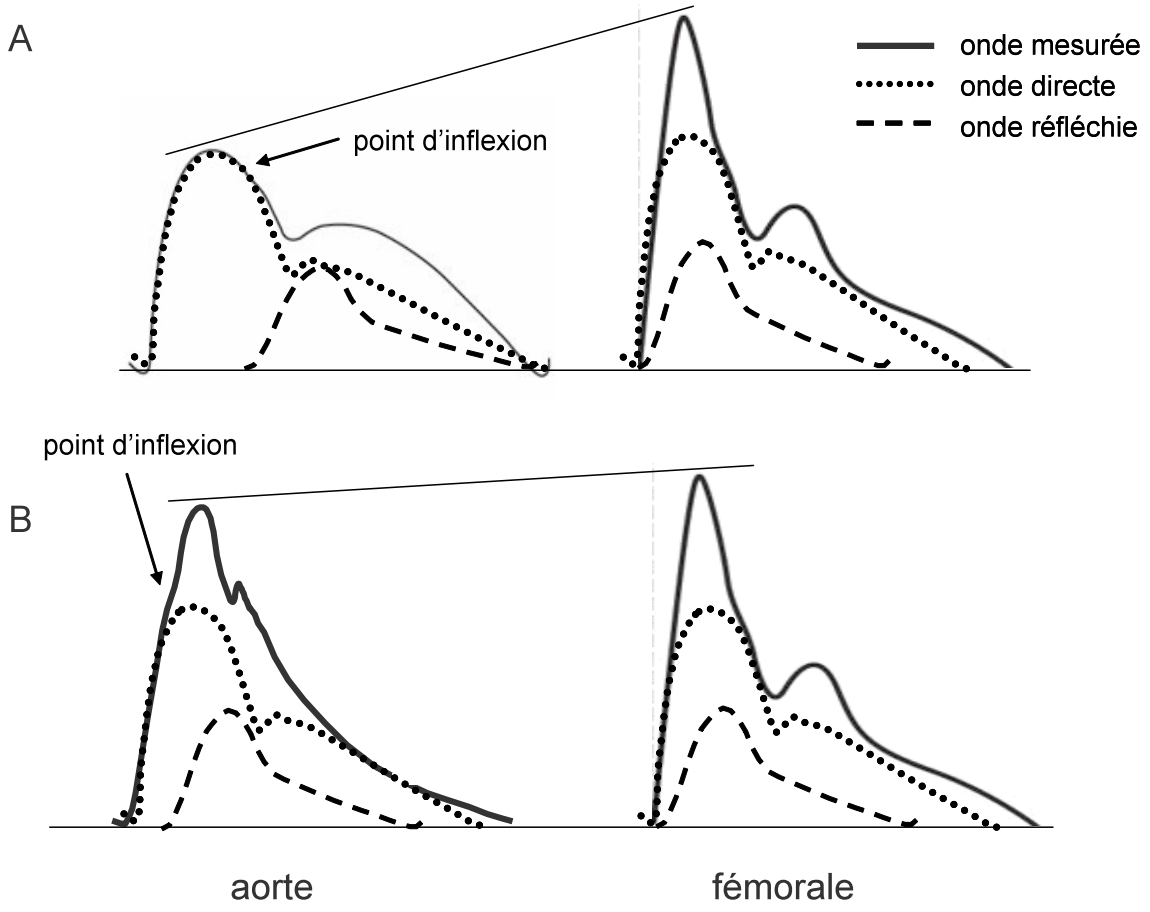


Figure 16. Courbes de pression aortiques et fémorales dans le cas d'élasticité aortique (A), et de rigidité aortique (B).

Avec ces exemples, nous avons montré que la réflexion joue un rôle dans la forme de la courbe de pression, à la fois au niveau du temps (le moment où survient la superposition) et au niveau de l'amplitude des ondes réfléchies.

III.3.1. Le cas de rigidité aortique

Une altération des propriétés viscoélastiques des grosses artères détermine la rigidité artérielle et l'augmentation de la vitesse de transmission de l'onde de pouls.

Si l'onde directe est transmise vers la périphérie du système cardiovasculaire plus rapidement à cause de la rigidité vasculaire, les ondes réfléchies retournent elles aussi plus rapidement vers le cœur. Donc, s'il y a une rigidité vasculaire, les ondes réfléchies dans l'aorte ascendante se superposent à l'onde directe dès le début et pendant toute la phase systolique (Figure 16B, gauche). Il en découle que : 1/ le pic de la pression artérielle systolique est défini par les ondes réfléchies superposées à une onde directe déjà altérée du fait des propriétés réduites d'amortissement de l'aorte ; 2/ les ondes de réflexion n'influencent pas beaucoup la phase diastolique de la courbe tensionnelle, ainsi la pression artérielle diastolique est réduite. Cette situation est presque la même qu'au niveau périphérique, et fait que la différence entre la pression artérielle centrale et la pression périphérique sera très réduite chez les sujets âgés ou hypertendus, ou dans une situation de rigidité vasculaire.

III.3.2. La longueur de l'aorte (taille du sujet)

Un autre facteur pouvant influencer un retour précoce des ondes réfléchies est la distance entre les sites de réflexion et l'aorte ascendante. Ceci est tout à fait logique : avec la même distensibilité vasculaire, plus l'aorte ascendante est proche de la périphérie du système vasculaire, plus les ondes de réflexion arriveront de façon précoce au centre, et la différence entre les pressions systoliques périphérique et centrale sera réduite.

La taille du sujet est le paramètre directement en relation avec la longueur de l'aorte et la distance des sites de réflexion.

III.3.3. La fréquence cardiaque

Les modalités selon lesquelles la fréquence cardiaque agit sur les valeurs de pression et sur la morphologie de l'onde de pression au niveau de l'aorte ascendante sont complexes et contrastées.

La fréquence cardiaque influence la vitesse de transmission de l'onde de pouls : plus elle est élevée, plus la vitesse de l'onde de pouls est élevée, d'environ 0,5 m/s tous les 10 bpm.[86,87] Nous avons vu que l'accélération de la vitesse de l'onde de pouls s'accompagne d'une augmentation de la pression artérielle systolique et d'une réduction de l'amplification de la pression artérielle. Par conséquent, une accélération de la fréquence cardiaque devrait théoriquement causer une réduction de l'amplification.

Cependant, la fréquence cardiaque a aussi une action qui n'est pas en relation avec la précocité du retour des ondes réfléchies, mais plutôt avec le rapport entre la morphologie de l'onde directe et le retour de l'onde réfléchie.

Une augmentation de la fréquence cardiaque s'accompagne d'une réduction de la phase diastolique du cycle cardiaque et d'une réduction du temps d'éjection ventriculaire gauche. La conséquence principale de la réduction du temps diastolique est la réduction du remplissage diastolique du ventricule gauche ; ceci détermine une modification de la morphologie de l'onde de pression artérielle centrale, qui sera caractérisée par un pic systolique plus précoce suivi d'une chute rapide des valeurs de pression artérielle. Quand l'onde réfléchie revient au centre, elle se superpose à l'onde directe en correspondance de la « phase descendante » de la courbe directe. Le résultat de ces phénomènes à fréquence cardiaque élevée est que l'onde réfléchie participe moins à la détermination de la pression artérielle systolique

aortique ; la conséquence est l'augmentation de l'amplification de la pression artérielle (cf page 124).

Vice versa, en situation de bradycardie, l'onde réfléchie se superpose au pic de l'onde directe et le résultat est une réduction du phénomène d'amplification. Pour résumer : plus la fréquence cardiaque est élevée, plus l'amplification est élevée.

Il ne faut pas oublier que la réduction de la fréquence cardiaque représente probablement la circonstance principale qui permet d'obtenir une réduction du travail cardiaque et une amélioration de la perfusion coronarienne. Il faut donc que les deux phénomènes, c'est-à-dire l'amplification de la pression artérielle et les changements de la fréquence cardiaque, soient considérés dans le contexte général pour l'évaluation du travail cardiaque global.

III.4. Une mesure de réflexion : l'index d'augmentation

L'index d'augmentation est un paramètre qui donne des indications sur la précocité et l'amplitude des ondes de réflexion. Il s'agit du rapport entre l'augmentation de la pression artérielle due à l'onde de réflexion (AP) et la pression pulsée (PP) :

$$\text{Index d'augmentation} = AP / PP * 100 \qquad (11)$$

Par convention, l'index d'augmentation est négatif si la rencontre entre l'onde réfléchie et l'onde directe se vérifie après le pic systolique, et il est positif si la rencontre entre l'onde réfléchie et l'onde directe se vérifie avant le pic systolique.

Les facteurs qui influencent le plus l'index d'augmentation sont : les propriétés viscoélastiques de l'aorte et des gros troncs artériels ; la longueur de l'aorte (la taille du sujet) ; la fréquence cardiaque ; le débit cardiaque ; le sexe.

Les modifications de la courbe de pression avec l'âge sont tout à fait évidentes. L'inflexion de la courbe (Pi), qui correspond au point où l'onde de pression directe rencontre l'onde de pression réfléchie est toujours plus anticipée avec l'âge :

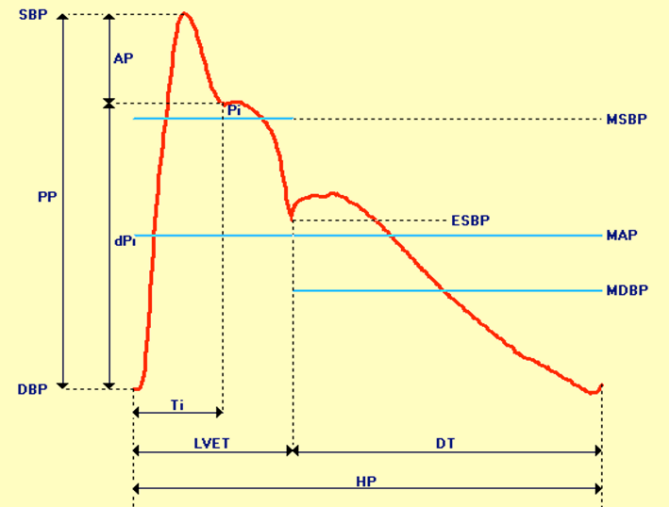


Figure 17. Type C

chez les sujets jeunes, Pi tombe après le pic systolique de la courbe, par conséquent :

- l'index d'augmentation est négatif,
- les ondes de réflexion n'influencent pas les valeurs de la pression artérielle systolique,
- la phase diastolique de la courbe a une morphologie pleine, convexe.

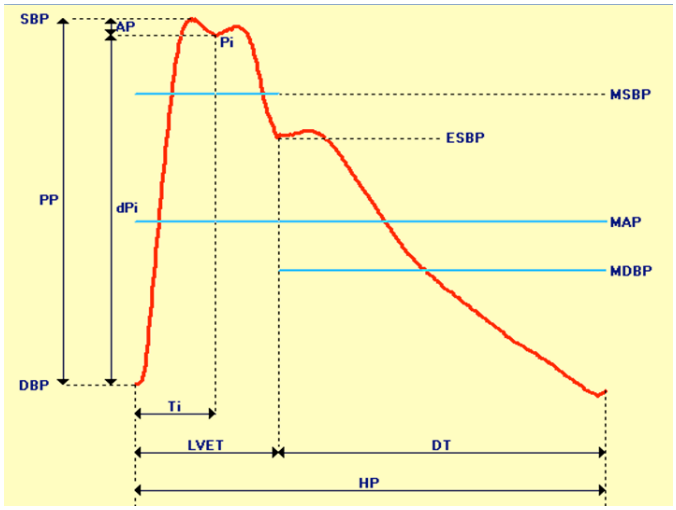


Figure 18. Type B.

Chez les sujets adultes, Pi tombe à proximité du pic systolique de la courbe (tout de suite avant ou tout de suite après le pic), par conséquent :

- l'index d'augmentation est inférieur à 15-20 %,
- la courbe a souvent une morphologie « en bosse de chameau »,
- l'influence des ondes de réflexion sur la pression artérielle systolique est faible,
- la phase diastolique de la courbe a une morphologie pleine, convexe.

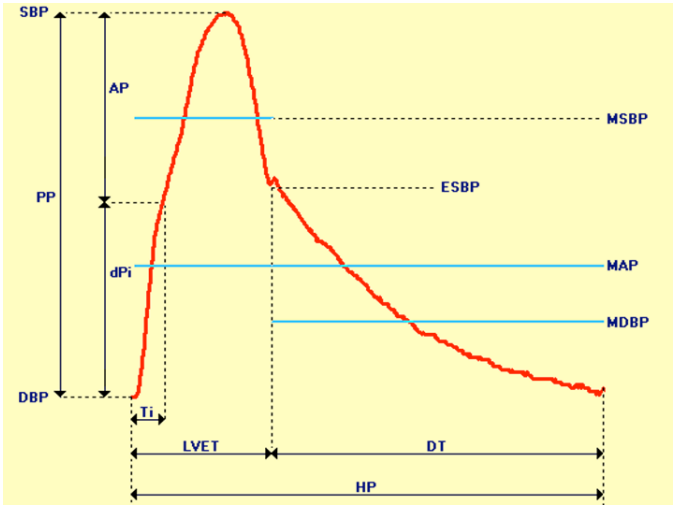


Figure 19. Type A.

Chez les sujets âgés, Pi tombe très précocement par rapport au pic systolique de la courbe, par conséquent :

- l'index d'augmentation est forcément positif (> 20 %),
- la pression artérielle systolique est déterminée par la présence des ondes de réflexion,
- la phase diastolique de la courbe a une morphologie infléchie, concave.

III.5. De l'aorte ascendante à la périphérie : le phénomène d'amplification

L'observation du système cardiovasculaire a conduit à la notion que la pression artérielle change dans l'arbre artériel du centre vers la périphérie (Figure 20). Les éléments dont nous avons jusqu'ici montré l'intérêt peuvent aider dans la compréhension des modifications de la pression.

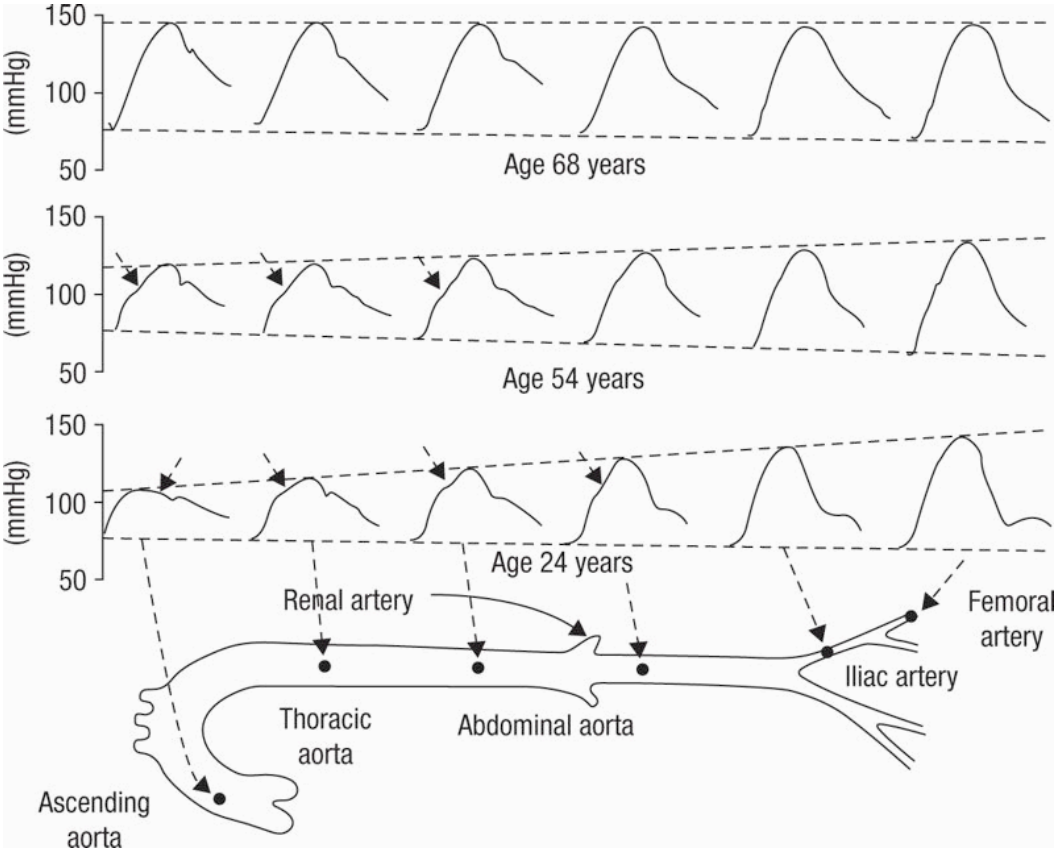


Figure 20. Amplification de l'onde de pression le long de l'aorte et selon l'âge (de [88]).

III.5.1. L'amplification le long de l'aorte

Reprenons l'exemple de l'aorte (en condition d'élasticité) en comparaison à celui de l'artère fémorale. Tandis qu'au niveau de l'aorte ascendante, chez le patient jeune avec une aorte élastique, le pic de la PA systolique est défini par la seule onde directe, au niveau de l'artère fémorale le pic de la PA systolique se définit, par contre, par l'onde directe plus l'onde réfléchie.

Au niveau des artères périphériques des membres inférieurs, les ondes de réflexion amplifient l'onde de pression artérielle parce que l'onde réfléchie est très précoce. La superposition de l'onde réfléchie à l'onde directe a lieu au début de la phase systolique ; donc le pic systolique est défini par l'addition des ondes directes

et réfléchies. Le résultat est que l'amplitude de l'onde de la pression artérielle est plus élevée au niveau des artères périphériques qu'au niveau des artères centrales. Ce phénomène s'appelle « phénomène d'amplification ».

Outre la contribution de la réflexion, le phénomène d'amplification est également dû aux modifications des propriétés de la paroi des artères. En effet, comme nous l'avons déjà expliqué, plus l'on s'éloigne du cœur, plus le module élastique diminue ; ceci cause une augmentation progressive de la vitesse de l'onde de pouls ainsi que de l'impédance. Il a été démontré que les oscillations de la pression augmentent du centre à la périphérie, même en l'absence de réflexion, justement à cause de ces modifications.[80]

Le phénomène d'amplification est un phénomène très astucieux. Il est étonnant de constater que dans un système mécanique, hydraulique, comme le système cardiovasculaire, la pression est plus élevée à la périphérie qu'au centre. Habituellement, le but des systèmes mécaniques conçus par l'homme est de réduire le plus possible la dispersion d'énergie au fur et à mesure que l'on va vers la périphérie ; au contraire, dans le système cardiovasculaire, la pression périphérique est franchement supérieure à la pression au niveau de la pompe-cœur.

On revient donc à la citation de O'Rourke (page 58), où l'on avait pu constater que la pulsatilité cardiaque, la compliance artérielle et les ondes de réflexion présentent une relation optimale pour que la pompe-cœur puisse assurer une activité continue ininterrompue pendant de longues années, quelquefois 100 ans et plus. C'est pour cette raison que ce système utilise tous les moyens possibles pouvant réduire le travail du cœur au minimum indispensable.

Le phénomène d'amplification doit être situé dans ce contexte : pour des valeurs de pression artérielle périphérique égales, là où l'amplification est élevée la

pression artérielle centrale est plus basse et il y a une réduction de la post-charge et du travail cardiaque.

III.5.2. L'amplification dans le membre supérieur

L'arbre artériel de l'être humain est asymétrique, présentant une partie plus « courte » (la circulation dans la partie supérieure du corps, ou système brachiocéphalique), et une partie plus « longue » (la partie inférieure du corps, ou système fémorosaphène). Le mécanisme d'amplification est donc différent entre les deux parties. Si l'on se place à la racine du membre inférieur (dans l'aorte descendante abdominale ou l'artère fémorale), on observe une grande quantité d'ondes réfléchies provenant des multiples bifurcations et des sites de résistance de tout le membre inférieur. Le résultat sera donc celui déjà décrit ci-dessus. Par contre, au niveau du membre supérieur (dans l'artère brachiale ou radiale), la quantité de réflexion provenant de la périphérie (de la main) sera beaucoup moins importante qu'au niveau du membre inférieur. L'amplification observée au niveau du membre supérieur dérive donc simplement du changement d'élasticité et d'impédance de la paroi artérielle, et non des ondes de réflexion.[80]

Donc, le mécanisme d'amplification entre les deux parties du système cardiovasculaire est différent, mais quel est le rôle de la réflexion au niveau du membre supérieur ?

On constate que la forme de l'onde de pression radiale est différente de celle de l'onde fémorale (Figure 21). En particulier, l'onde radiale présente normalement une inflexion dans la partie tardive de la systole, appellée « deuxième pic systolique radial ». Cette inflexion sur la courbe radiale représente en effet

l'arrivée des ondes de réflexion provenant de la partie inférieure du corps (des membres inférieurs) qui, après avoir atteint l'aorte ascendante, continuent leur parcours jusqu'aux membres supérieurs.[89]

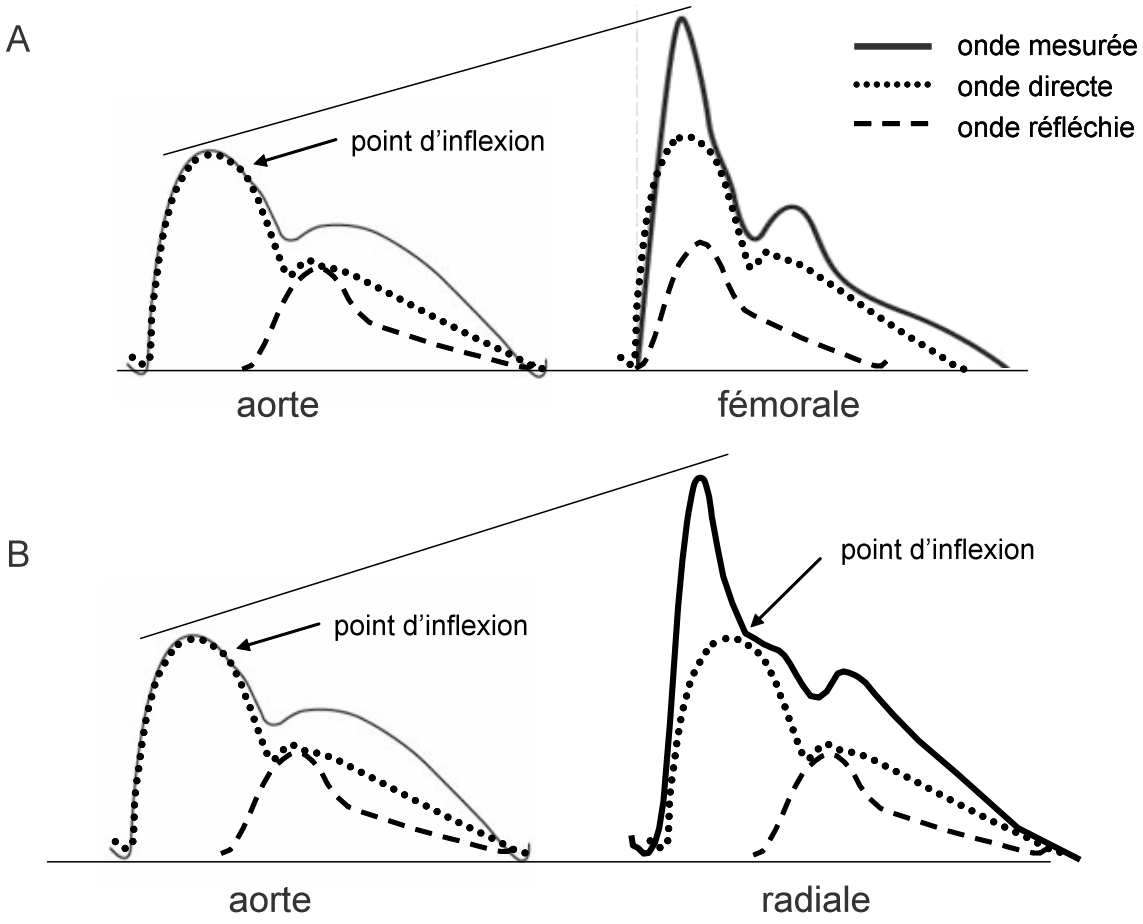


Figure 21. Courbes de pression aortique, fémorale et radiale, dans le cas d'élasticité aortique.

L'amplification de l'onde de pression dans le membre supérieur a une importance clinique fondamentale, car elle met en relation la pression périphérique que l'on peut mesurer au niveau de l'artère brachiale avec la pression dans les artères centrales. Au contraire de ce qu'on pourrait penser, deux patients différents avec des valeurs de pression brachiale similaires peuvent ne pas avoir la même pression centrale et donc la même condition hémodynamique. L'étude CAFE (sous-

étude de ASCOT) a montré clairement que deux traitements capables de réduire la pression brachiale de la même entité avaient des effets très différents dans la modification de la pression centrale (Figure 22). Notamment, les patients traités par amlodipine présentait une baisse significative de la pression centrale, par rapport aux patients traités par atenolol.[90]

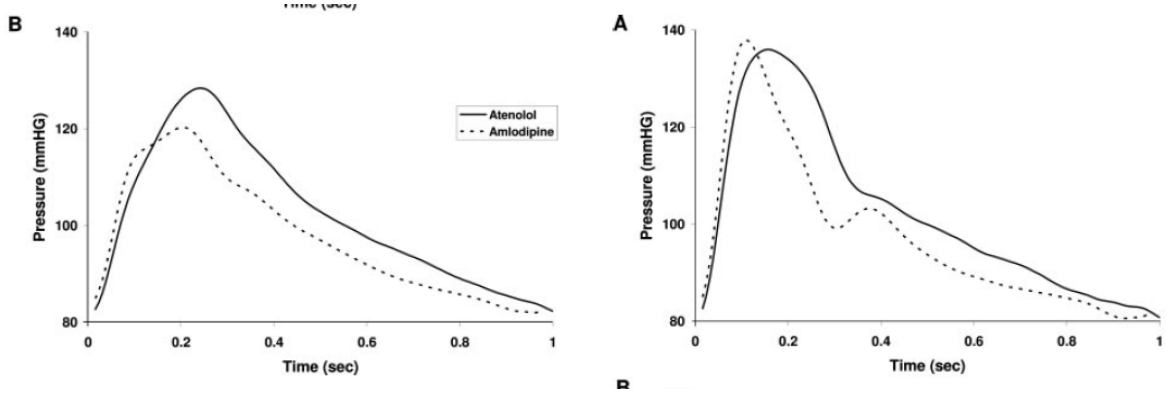


Figure 22. Effet antihypertenseur sur la pression centrale (gauche) et périphérique (droite) (adaptée de [90]).

De plus, dans l'étude de base ASCOT, le groupe de patients traités par amlodipine était associé avec une moindre survenue d'événements cardiovasculaires.[60] Plusieurs études ont aussi montré que la pression centrale et l'amplification sont de puissants prédicteurs de mortalité cardiovasculaire et toute cause.[5–12,91]

Une autre caractéristique de l'hémodynamique du membre supérieur est que, avec le vieillissement, les artères ne perdent pas de leur élasticité et la vitesse de l'onde de pouls est presque conservée tout au long de la vie.[80,92] Au niveau du membre inférieur, la réduction de l'amplification avec le vieillissement est due à l'incrément de la vitesse de l'onde de pouls aortique qui provoque un retour précoce des ondes de réflexion vers le centre. Au contraire, l'effet du vieillissement sur

l'amplification du membre supérieur est entièrement dû aux modifications de la forme de la courbe de pression aortique et non pas aux modifications structurelles des artères du membre supérieur. L'importance de cette observation est que, au niveau du bras, il est possible d'utiliser des fonctions dites de « transfert ». Ces fonctions se basent sur l'analyse en harmonique de Fourier et sont capables de calculer la courbe de pression centrale à partir de la courbe de pression périphérique. Etant donné que des modifications de vitesse de l'onde de pouls sont capables d'altérer certaines harmoniques, il va de soi que les fonctions de transfert peuvent donner des résultats faux si la rigidité artérielle n'est pas prise en considération. Afin d'appliquer une fonction de transfert de façon généralisée, il convient donc d'utiliser le membre supérieur, où la rigidité ne change pas au cours du vieillissement.

IV La pression artérielle et ses composantes

Dans le paragraphe précédent nous avons montré comment on peut comprendre l'hémodynamique vasculaire à partir de l'analyse de la courbe de l'onde de pression ; et nous avons vu comment la pulsatilité est transmise du centre à la périphérie. Il semble important maintenant de se focaliser sur la courbe de pression afin d'en comprendre ses deux composantes, pulsatile et statique.

IV.1. La pression pulsée

Au niveau de la courbe de pression, comme nous l'avons vu dans le chapitre II (page 99), la pulsatilité est représentée par l'amplitude de l'onde de pression, c'est-à-dire la pression pulsée. D'un point de vue pragmatique, quand nous parlons de l'amplification des oscillations de la pression artérielle du centre vers la périphérie, il s'agit avant tout de modifications de la pression pulsée, comme représenté sur la Figure 20. Or, avec l'analyse des mécanismes responsables de l'amplification, nous avons aussi montré que le changement de pulsatilité, et donc de pression pulsée, est d'abord dû aux variations du pic systolique et donc de la pression systolique. Qu'en est-il de la pression diastolique et de la pression moyenne ?

IV.2. La pression diastolique

La pression diastolique est la valeur de pression artérielle minimale enregistrée pendant le cycle cardiaque. Elle est influencée par différents facteurs cardiaques et artériels, mais la caractéristique la plus importante, de notre point de vue, est qu'elle diminue avec le processus de rigidité artérielle. Ceci fait que, dans l'aorte ascendante, la pression pulsée (calculée comme pression systolique moins

diastolique) augmente en relation avec le degré de compliance artérielle, du fait à la fois de l'augmentation de la pression systolique et de la diminution de la pression diastolique. Par contre, le niveau de pression diastolique est très peu modifié dans l'arbre artériel, et du centre à la périphérie on observe de petites diminutions de pression diastolique (de l'ordre de quelques millimètre de mercure pour un sujet allongé).

IV.3. La pression moyenne

Si jusqu'à présent nous nous sommes focalisés sur la pulsatilité et avons décrit son comportement le long de l'arbre artériel, il faut introduire le concept de pression moyenne, qui est assez compliqué à visualiser puisque la pression moyenne n'existe pas réellement.

Nous avons montré (paragraphe I.1.2, page 61) que le système cardiovasculaire peut être étudié selon un modèle électrique où la différence de pression est comparable à la différence de potentiel, le flux à l'intensité du courant électrique, et les résistances périphériques aux résistances électriques. Par ce modèle on peut facilement mettre en relation la pression, le flux et les résistances. Nous avons aussi montré que la différence de pression entre l'aorte ascendante et la veine cave peut être assimilée à la pression moyenne dans l'aorte ascendante, parce que la pression veineuse est beaucoup plus faible. Comment définir la pression moyenne ? Pour répondre, imaginons le cœur comme une pompe continue, comme dans le modèle électrique. Dans ce cas, la pression moyenne (PAM) peut être dérivée du flux ou débit cardiaque (Q), et des résistances périphériques (R) selon la formule :

$$PAM = Q * R \quad (12)$$

Le débit cardiaque (Q) étant le produit du volume d'éjection systolique (Vs) multiplié par la fréquence cardiaque (Fc), nous pouvons passer à la formule :

$$PAM = Vs * Fc * Rp \quad (13)$$

Sur la base de (13), les valeurs de pression artérielle moyenne sont explicables par trois facteurs : le volume d'éjection systolique, la fréquence cardiaque et les résistances vasculaires périphériques.

Une façon différente de considérer la pression moyenne est d'imaginer les instants qui suivent l'arrêt du cœur. Une fois que le pouls a cessé et avant le passage du sang dans le circuit veineux, les artères sont immobiles et remplies d'une certaine quantité de sang ; à ce moment la pression intra-artérielle équivaut à la pression moyenne.

On comprend donc que cette pression moyenne n'est pas une entité mesurable *in vivo* (comme la longueur ou le poids d'un objet), mais qu'elle peut être estimée à partir d'autres mesures.

Néanmoins, l'importance de la pression moyenne réside dans le fait qu'il s'agit de la « pression de distension » basale des artères. Imaginons deux systèmes cardiovasculaires, tout à fait semblables, soumis à la même pulsatilité mais avec des pressions moyennes différentes. La paroi de l'aorte (avec prédominance de fibres élastiques) sera plus « détendue » dans le système à pression moyenne élevée. La distension de la paroi aortique détermine également le degré de distension des fibres élastiques et par conséquent la rigidité de la paroi elle-même. Or, il semble clair que

la transmission de la pulsatilité, qui dépend de la rigidité vasculaire, sera plus rapide dans le système à forte pression de distension et donc à pression moyenne élevée. Nous venons donc de décrire un des aspects fondamentaux du système cardiovasculaire : la dépendance directe de la propagation des ondes à la pression moyenne.

Une deuxième caractéristique importante de la pression moyenne est qu'elle est relativement constante dans tout l'arbre artériel, jusqu'aux artérioles pour un sujet allongé.[93–95] Ceci a un impact pratique dans la mesure de la pression, comme on va le voir dans les paragraphes suivants.

En résumé, nous avons montré que la pulsatilité augmente du centre à la périphérie, principalement par l'augmentation de la pression systolique, tandis que la pression diastolique présente une diminution négligeable et que la pression moyenne est constante.

Mais comment peut-on en réalité mesurer la pression moyenne dans un système pulsatile ?

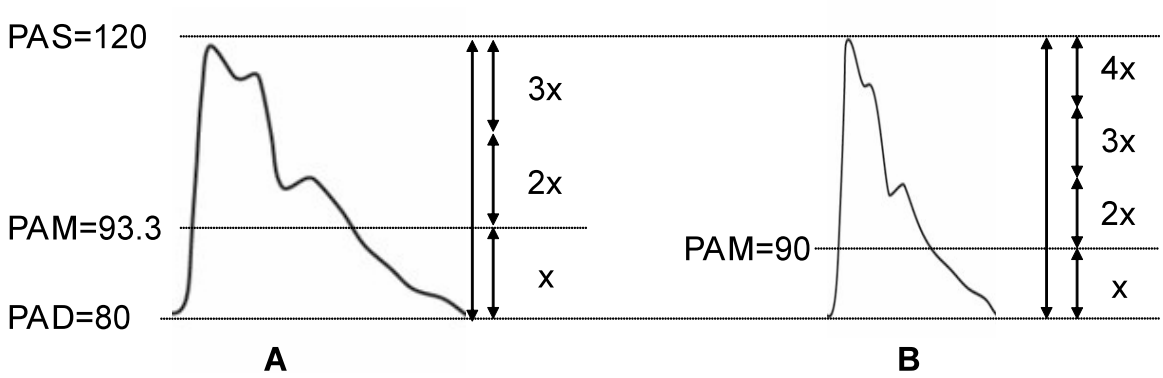
IV.3.1. Le *form factor*

Le *form factor* (FF) est un index en relation avec la forme de la courbe de pression. Il est défini comme le pourcentage de la pression pulsée (PP) qui doit être additionné à la pression diastolique (PAD) pour obtenir la pression moyenne (PAM).

En formule on pourrait écrire :

$$FF = (PAM - PAD) / PP \qquad (14)$$

Pour en comprendre le sens pratique, considérons deux courbes de pression :



Dans les deux courbes, avec même niveau de pression systolique et diastolique, le *form factor* est représenté par le « x », qui est la valeur à rajouter à la pression diastolique pour obtenir la pression moyenne. Dans la courbe A, le « x » sera un tiers de la pression pulsée (x = 13.3), alors que dans la courbe B le « x » sera un quart de la pression pulsée (x = 10). En connaissant la valeur de « x » il est donc possible de calculer la pression moyenne à partir de la pression systolique et diastolique ; par contre, en connaissant la pression moyenne, la diastolique et le *form factor* il est possible de calculer la pression systolique.

Dans la littérature, le *form factor* utilisé est de 33 % même si récemment certains auteurs conseillent plutôt 40 %.

Ceci est donc une première méthodologie pour calculer la pression moyenne.

IV.3.2. L'intégration de l'onde de pression

Une autre méthode pour calculer la pression moyenne se base sur l'intégration de l'onde de pression. Si on considère que le temps entre le début et la fin de l'onde de pression correspond au cycle cardiaque, et qu'à chaque instant du cycle cardiaque on peut mesurer une certaine valeur de pression artérielle, la

pression moyenne peut être calculée comme l'intégrale de la pression sur le temps, ce qui donne l'aire sous la courbe de pression.

IV.3.3. La méthode oscillométrique

La pression moyenne peut aussi être mesurée par un brassard oscillométrique (cf chapitre suivant).

V La mesure non invasive de la pression artérielle

V.1. La pression brachiale (ou périphérique)

En pratique clinique mais aussi en recherche, pour des raisons évidentes il est important de pouvoir mesurer les valeurs de pression artérielle de façon simple et non invasive. Pour cela, la méthode auscultatoire qui découle des travaux de Riva-Rocci et Korotkov est encore aujourd'hui la plus utilisée dans le domaine clinique. Il est intéressant de remarquer que la validation des nouveaux appareils automatiques est jusqu'à présent comparée à la méthode auscultatoire considérée comme mesure de référence.[96]

La mesure de la pression artérielle a connu une révolution avec la méthode oscillométrique qui utilise un principe étudié naguère par Marey,[97] et qui consiste en la possibilité de détecter les oscillations de la pression artérielle grâce à un brassard gonflé puis dégonflé avec de l'air. Le flux pulsatile à travers les artères produit des oscillations de la paroi artérielle qui sont transmises au brassard. Au début, le brassard est gonflé au-delà de la pression systolique, où les oscillations sont minimes ; ensuite, il est progressivement dégonflé et les oscillations se font plus importantes. Quand l'amplitude des oscillations atteint sa valeur maximale, la pression dans le brassard correspond à la pression moyenne. Quand la pression dans le brassard est réduite aux valeurs inférieures à la pression diastolique, les oscillations diminuent fortement. La pression dans le brassard au moment où les oscillations commencent à augmenter correspond à la pression systolique ; la pression la plus basse dans le brassard juste avant que l'amplitude des oscillations arrête de diminuer correspond à la pression diastolique.[80] La méthode oscillométrique est montrée dans la Figure 23.

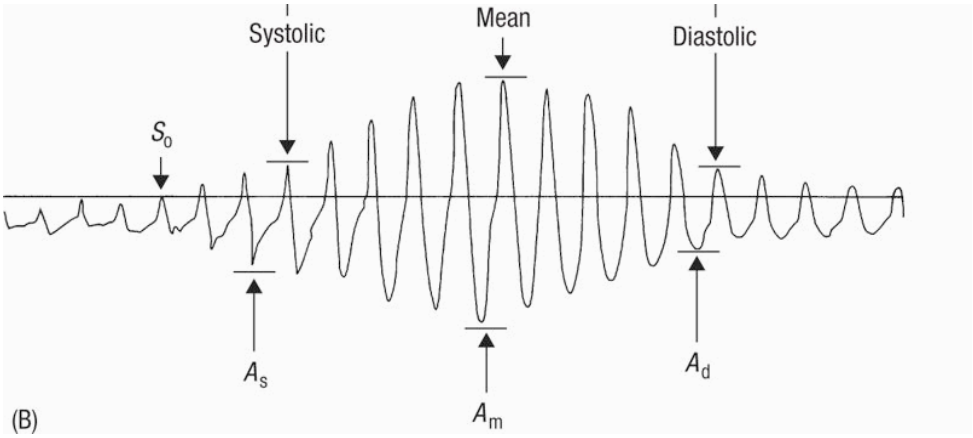


Figure 23. La méthode oscillométrique (adaptée de [80]).

Les appareils électroniques détectent automatiquement l'apparition, la disparition et le maximum des oscillations. Cependant, pour s'assurer de leur précision, plusieurs protocoles internationaux ont été développés, le plus reconnu étant le protocole de la société Européenne d'hypertension : ESH-IP2010.[96]

Un exemple de validation d'un appareil oscillométrique selon ce protocole est donné dans l'Annexe 1.

V.2. La pression aortique (ou centrale)

La pression centrale est définie comme la pression au niveau de l'aorte ascendante. L'intérêt de la mesure de la pression centrale ayant déjà été démontré, il n'est pas surprenant que, dans les dernières années, différents appareils aient été mis sur le marché pour l'estimer.

Les méthodes utilisées le plus fréquemment sont :

- la tonométrie artérielle d'applanation :

- tonométrie carotidienne ;
- tonométrie radiale : application d'une fonction de transfert ; utilisation du deuxième pic systolique ;

– l'oscillométrie et l'application d'une fonction de transfert.

V.3. ARTICLE 3 : Validation de l'appareil CENTRON cBP-301 pour la mesure la pression centrale et de l'amplification de la pression pulsée

V.3.1. Introduction de l'ARTICLE 3

De nombreux d'appareils utilisent la méthode oscillométrique brachiale pour dériver la pression centrale, du fait que les tracés oscillométriques sont faciles à obtenir et sont indépendants de l'opérateur. Pour calculer la pression centrale à partir de l'oscillométrie, on peut utiliser une fonction de transfert spécifique (qui applique l'analyse de Fourier, page 101) ou l'analyse de l'onde.

Les publications concernant l'évaluation des appareils oscillométriques pour la mesure de la pression centrale sont présentées dans le Tableau 2.

Tableau 2. Publications sur PubMed des articles de validation des appareils oscillométriques qui mesurent la pression centrale.

Journal	Appareil	Registration à	méthode	calibration	comparé avec	Nbr de sujets	erreur en cSBP en mmHg (m±sd)
Chen, 2003 [29]	Prototype using Microlife WatchBP	40 mmHg	WA	bSBP & bDBP	Dual filled catheter	85	-4.3 ± 3.5
Pauca 2005 [24]	Vicorder	Around g	TF	Invasive MAP & DBP	Dual filled catheter	90	-4.9 ± 7.4
				bSBP & bDBP			-4.4 ± 7.4
				NSBP & bDBP	SphygmoCor calibrated to SBP & DBP	89	-6.2 ± 4.6
				bMAP & bDBP	SphygmoCor calibrated to MAP & DBP		-8.5 ± 3.3
Bratt 2012 [19]	Custom dBP301	6mmHg	TF	Invasive MAP & DBP	Invasive pressure tip	29	0.0 ± 5.0
		(SBP+MAP)/2		bMAP & bDBP	SphygmoCor calibrated to bMAP & bDBP	100	-0.6 ± 3.9
				bSBP & bDBP	SphygmoCor calibrated to bSBP & bDBP		1.6 ± 4.5
Sidhu 2012 [25]	SphygmoCor XCEL	2?	TF	Device own calibration	SphygmoCor (calibration not specified)	30	0.5 ± 1.8
Chasse 2012 [23]	PulseCor R65	Should g above SBP	PM	Device own calibration	SphygmoCor calibrated to bMAP & bDBP	47	1.2 ± 2.2
Gallagher 2012 [22]	Arteriograph	Should g above SBP	WA	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	102	8.8 ± 7.3
Lu 2012 [30]	PulseCor R65	Should g above SBP	PM	Invasive MAP & DBP	Dual filled catheter	37	2.8 ± 3.9
				Device own calibration			0.5 ± 4.3
Lacolley 2012 [21]	Mobil-o-graph (ATCardiovi)	DBP level	TF	Device own calibration	SphygmoCor (calibration not specified)	35	-1.2 ± 5.1
Weiss 2012 [31]	Mobil-o-graph (ATCardiovi)	DBP level	TF	Device own calibration	SphygmoCor (calibration not specified)	100	0.5 ± 4.5
Nürnberger 2011 [17]	Arteriograph	Should g above SBP	WA	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	44	3.7 ± ?? (supine) 10.0 ± ?? (sitting)
Weber 2011 [18]	Mobil-o-graph (ATCardiovi)	DBP level	TF	Invasive MAP & DBP	Invasive pressure tip	38	3.0 ± 6.0
				bMAP & bDBP			5.8 ± 8.5
				bSBP & bDBP			14.4 ± 8.7
Chong 2010 [28]	Prototype from Colin VP2000	6mmHg	WA	bSBP & bDBP	Dual filled catheter	96	-0.3 ± 7.4 (baseline) 0.2 ± 7.7 (after GTN)
Horváth 2010 [27]	Arteriograph	Should g above SBP	WA	Device own calibration	Dual filled catheter	52	0.90 ± 8.5
Wassertheurer 2010 [16]	Mobil-o-graph (ATCardiovi)	DBP level	TF	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	300	-0.1 ± 5.1
Lass 2009 [26]	PulseCor R65	2mmHg above SBP	PM	Device own calibration	Dual filled catheter	16	-1.0 ± 4.7

On relève 15 publications pour huit appareils et aucune étude n'utilise le même protocole de validation. Il est surprenant de remarquer que, malgré l'intérêt toujours grandissant pour la mesure rapide, non invasive et économique de la pression centrale, il n'existe pas aujourd'hui un protocole standardisé pour la validation de ces appareils. Dans la moitié des articles présentés, les auteurs ont comparé les résultats avec une mesure invasive de la pression artérielle. Cependant, réaliser des validations invasives requiert une certaine expertise, se limite aux sujets soumis à angiographie, et risque donc de ne pas avoir une bonne validité externe. De plus, avec le nombre toujours grandissant de nouveaux appareils, leur validation invasive poserait problème du point de vue éthique. Il nous semble donc qu'un protocole de validation non invasif et standardisé est nécessaire.

Le protocole ESH-IP 2010 est très utilisé pour la validation des appareils automatiques au bras.[96] Il prévoit que des mesures auscultatoires (avec le système à colonne de mercure) soient alternées avec des mesures oscillométriques par l'appareil automatique à tester. Les mesures doivent être réalisées chez des sujets ayant une plage de pression artérielle relativement large. Les erreurs relevées entre l'appareil testé et la méthode de référence sont quantifiées et évaluées par rapport aux erreurs cliniquement acceptables. Nous avons donc proposé un protocole standardisé pour la validation non invasive de la mesure de la pression centrale par un appareil oscillométrique, le Centron cBP301 (Centron diagnostics, UK), en nous basant sur le protocole ESH-IP 2010.[96]

Validation of the Centron CBP301 device for central blood pressure and pulse pressure amplification based on the international protocol of the European Society of Hypertension

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Conflicts of interest: Sandrine Millasseau works as a freelance specialist on pulse wave analysis and receives revenues from several medical devices companies including AtCor Medical and Centron Diagnostics whose devices have been used in this study.
Davide Agnoletti has received funding from AtCor to attend a workshop.
The study was sponsored by Centron Diagnostics Ltd and the Hotel Dieu Diagnosis and Therapeutic center received financial compensation for this study.

Keywords: central pressure, pulse pressure, pressure amplification, validation protocole

Abstract

Central pressure (cBP) and pulse pressure amplification (PPratio) are receiving renewed interest with the rise of non-invasive techniques which enable to measure it. However to date, there is no standardised protocol to validate their accuracy. While invasive comparison seems intellectually ideal, it will soon raise technical and ethic issues with the growing number of devices to be validated. We proposed a protocol based on the ESH-IP2010 protocol for electronic brachial devices to validate non-invasively systolic cBP and PPratio. We then applied it on the newly commercialised Centron cBP301 device. We used radial tonometry SphygmoCor (AtCor, Australia) as reference.

Radial tonometric SphygmoCor measurements were done 4 times alternated with 3 Centron cBP301 measurements. Each Centron recordings were compared with the most favorable SphygmoCor recordings done immediately before or after and calibrated with Centron peripheral SBP and DBP measurements. Following protocol requirements, 33 subjects (21men and 12 women) were recruited in the low, medium and high peripheral BP range. Systolic cBP varied from 88 to 188 and the difference between the devices was -0.33 ± 3.28 mmHg (m±sd). It falls within the pass ESH-IP2010 requirements for the number of measurements within 5, 10 and 15mmHg. PPratio varied from 1.13 to 2.09 and the difference between devices was -0.03 ± 0.11 which show good agreement for PPratio.

Centron cBP301 fulfils the pass criteria of the modified ESH-IP2010 protocol. It provides accurate measurement of systolic cBP and PPratio when compared to similarly calibrated SphygmoCor.

Abstract: 240 words

Introduction:

Central blood pressure differs from peripheral blood pressure due to arterial wave propagation and reflection[1;2]. Several studies have shown the importance of central blood pressure (cBP) to predict cardiovascular mortality with results exceeding standard peripheral cuff measurements[3-9]. Up to recently it was only possible to assess cBP with an invasive line. The first non-invasive technology was to apply applanation tonometry on the carotid artery[3;5;7]. However some authors raised issues about the limited quality of carotid pressure traces[10]. The commercially available SphygmoCor device (AtCor, Australia) proposed a solution based on calibrated radial tonometry and a transfer function to transform radial waveforms into cBP waveforms. In its standard use, a high fidelity tonometer is hand-held over the radial artery. The radial pressure waveform is then calibrated to cuff systolic (SBP) and diastolic pressure (DBP) previously measured with a standard cuff blood pressure device. Then a transfer function is mathematically applied to obtain central pressure. This technology has been extensively validated in invasive studies[10-15] and is now often used as reference for non-invasive central pressure assessment (table 1) [16-24].

In the last couple of year, several new devices arrived on the market estimating cBP. Many use brachial oscillometric approach to estimate systolic cBP as oscillometric traces are easy to obtain with a standard cuff and are operator independent. Some use device specific transfer function applied to the brachial oscillometric tracing [16;18-21;24;25], other apply wave analysis to derive cBP[17;22;23;26-30]. On table 1 are listed publications referenced in PubMed regarding the evaluation of oscillometric devices to assess systolic cBP. There are 15 studies concerning 8 devices, all published in the last 5 years with half of them in 2012, and already 2 on the first quarter of 2013. However, none of these studies uses the same protocol. Indeed, despite this growing interest to provide widely clinically usable devices to assess cBP non-invasively, there is no standardised protocol to validate non invasive cBP devices[31]. In the review of the literature presented in table 1, half of the articles (8 out of 15) compared their results to invasively recorded pressure. However performing invasive validations requires expertise. It is limited to subjects undergoing angiography and hence potentially restricts their validity to this specific cohort. What is more, with the increasing number of non invasive cBP devices on the market, invasive validation studies will raise ethics and regulatory issues. A non-invasive standardised protocol is urgently required[31].

The ESH-IP 2010 protocol is widely used to validate upper arm automatic device[32]. Several successive manual auscultatory blood pressure measurements with a mercury column are used as gold standard and compared to the tested automatic device in a cohort with a wide range of blood pressure values. Errors between

the tested device and reference method are quantified and evaluated against clinically acceptable errors. We proposed a standardised protocol for the validation of non-invasive cBP device based on the ESH-IP 2010 protocol and applied it to test a newly commercially available device, the Centron cBP301 (Centron diagnostics, UK).

Methods:

Protocol to validate non invasive cBP devices:

The study should be performed in a quiet room at comfortable temperature. Subjects' selection should be done following the ESH-IP 2010 protocol. Thirty three subjects from the general population should be recruited fulfilling the age (≥25years), gender (at least 10men and 10 women) and both peripheral SBP and DBP requirements (between 10 and 12 subjects per blood pressure ranges which are 90-129 mmHg, 130-160mmHg and 161-180 for SBP and 40-79 mmHg, 80-100 mmHg, 101-130 mmHg for DBP). In order to avoid a high number of exclusion because of their blood pressure range, subjects can be pre-selected before screening.

The operator must be experienced to the use of both reference and tested device. The reference device should be extensively invasively validated and recognised as such. At the present time, despite his high dependence on calibration only the radial tonometric SphygmoCor device have been validated extensively by different independent groups [10-15]. In this study, it will be considered as the reference device. As calibration is crucial for the evaluation of cBP[33-35], both devices should be calibrated to the same peripheral blood pressure values. Measurements from the tested and reference devices should be performed on the same arm. The variability observed between the 2 devices will hence be due to intrinsic variability and not on calibration errors.

If the peripheral blood pressure calibration is external to both reference and tested devices, a third validated cuff BP device should be used. If the tested device has an integrated brachial cuff measure, its values should be used to calibrate the reference device.

The validation procedure includes 4 measurements with device 1 alternated with 3 measurements with device 2 as explained on figure 1. Device 1 should be the device with integrated brachial cuff measure as device 2 can hence be calibrated with previous and next cuff BP values. In our study, as the reference device will be radial tonometry from the SphygmoCor system and the tested device the Centron cBP301 which provides brachial BP values, device 1 will be the Centron cBP301 and device 2 is the SphygmoCor device.

Data analysis:

As central DBP is considered equivalent to the peripheral DBP, only accuracy of systolic central pressure is studied[36;37]. Pass/fail criteria will be identical to the ESH-IP 2010 protocol. Differences are calculated between successive tested and reference devices measurements giving 6 differences values. The most favourable error for each device 2 recording is used to give a total of 3 error values per subjects. These errors are then classified according to whether they fall within 5, 10 or 15mmHg. The number of measurements falling in each error range is compared with the required number in the ESH-IP 2010 protocol[32] (table 3). Bland-Altman plot of the difference between tested and reference device systolic cBP values is also performed to check for any bias across the pressure range.

The ESH-IP 2010 protocol does not provide pass/fail criteria for pulse pressure. Pulse Pressure Amplification (PPratio) is calculated as the ratio of brachial pulse pressure over central pulse pressure (Ppratio = brachial PP / central PP). This parameter is free of calibration error when calculated from brachial and central PP measured with the same method and several studies have shown its clinical importance[3;33;38;39]. The ESH-IP 2010 protocol accepts that 93% (=2SD) of the measures fall within 15mmHg [32] (table 3). This corresponds to a standard deviation of the error of 7.5mmHg. As Ppratio in the overall general population is 1.38 [39], a similar criteria applied to Ppratio requires that the error on Ppratio is not different from 0 with a maximum SD of 0.28.

Study to validate the cuff based Centron cBP301 device:

The above protocol was applied to validate the cBP 301 device (Centron Diagnostics).

cBP301 has been previously compared to invasively recorded waveforms and to SphygmoCor in an unselected group of patients undergoing blood pressure check [19]. The Centron cBP301 device includes a validated brachial blood pressure unit (SunTech Advantage A+, SunTech Medical, USA) assorted to 2 cuff sizes (normal:22-32 cm and large:32-42 cm). After the assessment of brachial pressure, the device inflates to the arithmetic mean blood pressure [(SPB+DBP)/2] to record oscillometric traces. These waveforms are calibrated to brachial SBP and DBP and then a built-in proprietary transfer function is used to obtain central systolic pressure as explained elsewhere[19]. All measurements were done on the right arm of the patient. Arm circumferences were measured in each patient to ensure the use of the adequate cuff size and were distributed by chance. Diastolic pressures are assumed to be similar at central and peripheral level.

The reference device used was the radial tonometry Sphygmocor system. It has been extensively validated invasively[10-15] and is often used as the reference for non-invasive central pressure measurement (table 1). Ten

seconds of radial waveforms are recorded by applanation tonometry on the right wrist by a single operator (D.A.) with high data quality (built-in operator index >80) and used to estimate central blood pressure with the commercial SphygmoCor software (SphygmoCor v8.2, AtCor, Australia). However radial tonometric waveforms require calibration and were calibrated to Centron brachial SBP and DBP values.

Participants were installed on a comfortable chair in a quiet room. Centron cBP301 cuff was installed on their right arm and the subject positioned his arm, radial artery upward on the side of a table. A first brachial measurement was done after at least 5 minutes rest to classify subjects in the right blood pressure group or to discard him/her if the blood pressure group was complete. Then 4 measurements with the Centron device were alternated with 3 measurements done with SphygmoCor devices as explained on figure 1.

Each SphygmoCor measurements were calibrated with systolic and diastolic pressures done immediately before (S1, S2 and S3 measurements) and immediately after (S1b, S2b, S3b) waveform acquisition.

Results:

Participants were recruited from patients and family members attending the diagnosis and therapeutics centre from Hotel Dieu Paris between the December 2011 and September 2012. A pre-selection before screening was performed to include subjects within the correct BP ranges especially at the end of the recruitment period when only high ranges were missing. In total 44 subjects were screened and 33 subjects (21 men, 12 women) were included. Their repartition according to blood pressure groups is shown on table 1 and fulfils the blood ranges of ESH-IP 2010 criteria. Their characteristics are presented on table 2. Seven subjects were free of any known cardiovascular risk, 24 were treated for hypertension, 9 for diabetes, 5 for renal diseases, 2 had documented heart failure, 2 had history of myocardial infract and 9 of coronary heart diseases.

The numbers of Centron measurements differing from the reference SphygmoCor by 5, 10 and 15mmHg or less are shown in table 3. The Bland-Altman plot comparing the central SBP readings from the 2 devices are shown on figure 2 with a mean error of -1.33 ± 3.28 mmHg (non significantly different from 0). Ppratio varies from 1.13 to 2.09. Figure 3 shows the Bland-Altman plot the difference between Ppratio assess by SphygmoCor and Centron cBP301. Mean error was -0.05 ± 0.15. The highest values which seems to bring a bias across the Ppratio range are due to assessments done a single patient (patient #24, male, 44yrs old, BP: 165/98, HR: 102 bpm). If this patient is removed from the analysis, the mean difference does not changed significantly (0.03 ± 0.11, p=ns from the whole cohort).

Discussion:

This study is the first to propose a non-invasive protocol to validate cBP device based on the ESH-IP 2010 protocol. The ESH-IP 2010 protocol is internationally recognised to validate brachial electronic oscillometric devices against the century old blood pressure cuff reference: manual ausculatory measurements[32]. Subject recruitment has to follow specific rules to insure a cohort with wide pressure range and accuracy thresholds are defined to determine if a device pass or fail the validation study. Up to now, there is no standardized protocol to validate cBP[31]. We adapted the ESH-IP 2010 with as little changes as possible to fit specificities of cBP measurement. We kept the cohort recruitment requirements. As the reference device, we use the most widely available and extensively invasively validated radial tonometry SphygmoCor device. Some might argue that the SphygmoCor device is not ideal to be used as a reference[29;40]. Indeed the precision of systolic cBP estimation with the SphygmoCor device reaches -2.4 ± 3.4 mmHg when invasive calibration is used but soars to -8.2 ± 11.6 mmHg when using standard cuff calibration (pulled results from 10 studies – Cheng's meta-analysis[40]). This discrepancy is due to the imprecision of cuff blood pressure measurements (manual or electronic)[41;42] and is difficult to overcome with present non-invasive technologies which have to be compatible with brachial auscultatory pressure values, a century of epidemiological data and clinical habit[32]. To overcome the calibration limitation and to compare techniques per se with no influence of calibration, both devices were calibrated to the same blood pressure. Hence the observed error between devices is only due to the recorded signals and their respective transfer functions.

The mean error between SphygmoCor and Centron cBP301 was -1.33 ± 3.28 mmHg (figure 2). These results are in agreement with Brett's paper which validated the early prototype of Centron cBP301 and where the error was -1.6 ± 4.5 mmHg when calibrating to peripheral SBP and DBP (table1) [19]. It falls well within the AAMI criteria[42].

However with the ESH-IP protocol, the mean error is not as important as the absolute error distribution[32]. Centron cBP301 fulfils the pass requirement in terms of the number of measurement within 5, 10 and 15mmHg (see table 3) confirming that Centron cBP301 is accurate to assess central systolic blood pressure.

Some have found solutions to overcome the calibration issue when estimating central pressure[13;29;43]. This is in the detriment of pressure amplification expressed as the difference or the ratio between central and peripheral pressure. Several authors have shown than Ppratio might be as useful, if not more valuable, than the absolute value of central pulse or systolic pressure [3;38;44]. It might hence be better to accept the century old absolute

error with invasive pressure due to the calibration and to conserve the information regarding the relative difference between peripheral and central pressure. In our proposed protocol, validation criteria are also issue for Ppratio. Between SphygmoCor and Centron cBP301, we found overall a negligible difference between Ppratio (-0.05 ± 0.15). To our knowledge, these are the first data studying the difference on Ppratio. This is a rather recent index and its definition varies from ratio to substraction of brachial and central PP. We choose the definition used in the Avolio et al. expert opinion and review of data [38;39] as it is independent of calibration is measured with the same technique. Compared to the variations of Ppratio versus age (figure 3a of Avolio et al.[38]), the standard deviation of the difference between the 2 devices is rather small. What is more, if we translate the ESH-IP 2010 or the AAMI criteria on SBP to the Ppratio, a standard deviation lower than 0.28 is considered as a pass. This confirms that Ppratio measured with Centron cBP301 is similar to the one measured with SphygmoCor.

Limitations:

SphygmoCor was used as the non-invasive reference despite its weakness regarding calibration[33;35]. Some could argue that only invasive measurement should be used as gold standard. However the ESH-IP protocol to validate electronic cuff devices is not based on accurate invasive brachial pressure measurement but on the methodology used in routine practice: the mercury column despite its limited accuracy. Performing invasive studies to validate all new devices raise ethics issues which encourage the definition of a non-invasive standardise protocol. Despite its need of external calibration, we (and other) have felt that the radial tonometric SphygmoCor is the device with most validations and could be used as the reference technology while a better non-invasive technology emerges. Among the 15 studies evaluating the performance of oscillometric cBP, 10 of them compare their results to radial SphygmoCor tonometry. This is the only non-invasive technique used for this type of comparison in the literature.

Our study only included 33 subjects which can be seen as rather small. However one should point out it is not a randomly recruited cohort but a group of subjects which fit into the ESH-IP 2010 BP categories. The BP repartition insures that a large spectrum of systolic, diastolic and pulse pressure are met. We however can not exclude that our results concerning the close fitting between Centron cBP301 and SphygmoCor only apply to our general cohort. The 2 devices might not be in agreement in a different context or on a more specific cohort.

Conclusion: We introduced a modified ESH-IP 2010 protocol to validate cBP devices. According to this protocol, Centron cBP301 fulfils the pass criteria and provides accurate measurement of central systolic pressure and pulse pressure amplification.

Table 1: Review of studies comparing oscillometric based estimation of central pressure

paper	Apparatus	Oscillometric recording at	method	calibration	Compared to	Nb of subjects	Reported error on cSBP in mmHg (m±sd)
Cheng 2013 [29]	Prototype using Microlife WatchBP	60 mmHg	WA	bSBP & bDBP	Fluid filled catheter	85	-4.3 ± 3.5
Pucci 2013 [24]	Vicorder	70mmHg	TF	Invasive MAP & DBP	Fluid filled catheter	50	-4.0 ± 7.4
				bSBP & bDBP			-6.4 ± 7.4
				bSBP & bDBP	SphygmoCor calibrated to SBP & DBP	90	-6.2 ± 4.6
				bMAP & bDBP	SphygmoCor calibrated to MAP & DBP		-0.5 ± 3.3
Brett 2012 [19]	Centron cBP301	65mmHg	TF	Invasive MAP & DBP	Invasive pressure tip	29	0.0 ± 5.9
		(SBP+MAP)/2		bMAP & bDBP	Sphygmocor calibrated to bMAP & bDBP	100	-0.6 ± 3.9
				bSBP & bDBP	SphygmoCor calibrated to bSBP & bDBP		1.6 ± 4.5
Butlin 2012 [25]	SphygmoCor XCEL	??	TF	Device own calibration	SphygmoCor (calibration not specified)	30	0.5 ± 1.8
Climie 2012 [23]	PulseCor R6.5	30mmHg above SBP	PM	Device own calibration	SphygmoCor calibrated to bMAP & bDBP	47	1.2 ± 2.2
Gunjaca 2012 [22]	Arteriograph	35mmHg above SBP	WA	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	1012	8.8 ± 7.3
Lin 2012 [30]	PulseCor R6.5	30mmHg above SBP	PM	Invasive MAP & DBP	Fluid filled catheter	37	2.8 ± 3.9
				Device own calibration			0.25 ± 6.3
Luzardo 2012 [21]	Mobil-o-graph (ARCsolver)	DBP level	TF	Device own calibration	SphygmoCor (calibration not specified)	35	-1.2 ± 3.1
Weiss 2012 [21]	Mobil-o-graph (ARCsolver)	DBP level	TF	Device own calibration	SphygmoCor (calibration not specified)	100	0.5 ± 4.5
Nurnberger 2011 [17]	Arteriograph	35mmHg above SBP	WA	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	44	3.7 ± np (supine) 10.0 ± np (sitting)
Weber 2011 [18]	Mobil-o-graph (ARCsolver)	DBP level	TF	Invasive MAP & DBP	Invasive pressure tip	30	3.0 ± 6.0
				bMAP & bDBP			-3.0 ± 9.5
				bSBP & bDBP			14.4 ± 9.7
				bMAP & bDBP	SphygmoCor calibrated to bMAP & bDBP	111	-0.5 ± 4.7
				bSBP & bDBP	SphygmoCor calibrated to bSBP & bDBP		0.3 ± 4.2
Cheng 2010 [28]	Prototype from Colin VP2000	60mmHg	WA	bSBP & bDBP	Fluid filled catheter	50	-0.3 ± 7.4 (baseline) 0.2 ± 7.7 (after GTN)
Horvath 2010 [27]	Arteriograph	35mmHg above SBP	WA	Device own calibration	Fluid filled catheter	55	0.56 ± 8.5
Wassertheurer 2010 [16]	Mobil-o-graph (ARCsolver)	DBP level	TF	Device own calibration	SphygmoCor calibrated to bSBP & bDBP	302	-0.1 ± 3.1
Lowe 2009 [26]	PulseCor R6.5	25mmHg above SBP	PM	Device own calibration	Fluid filled catheter	16	-1.0 ±14.7

TF = transfer function WA = wave analysis PM = Physics model
np = not provided
Total 15 articles (referenced in Pubmed) with 8 devices. 8 compared to invasive pressure, 10 to radial tonometry SphygmoCor (including 3 using both)

Table 2: Subject repartition according to their blood pressure ranges

		SBP			
		≤129	**130-160**	**≥161**	**total**
DBP	≤ 79	8	2	2	**n=12**
	80-100	2	6	4	**n=11**
	≥ 101	0	3	7	**n=10**
	total	**n=10**	**n=11**	**n=12**	

4 patients had SBP > 180 (this is the maximum allowed)
None had SBP <90mmHg, nor DBP outside the 40-130mmHg range.

Table 3: Subjects characteristics

	Mean ± sd	range
Age (years)	61 ± 15	31 – 81
Height (cm)	171 ± 9	150 – 189
Weight (kg)	77 ± 13	48-108
Arm circumference (cm)	29 ± 3	23- 38
SBP (mmHg)	148 ± 30	103 – 209
DBP (mmHg)	84 ± 18	57 – 122
Systolic cBP (mmHg)	128 ± 26	88 - 188
PPratio	1.30 ± 0.16	1.10 – 1.64
HR (mmHg)	73 ± 13	52 - 105

Table 4: Results for the Centron cBP301 according to the ESH-IP criteria

		ESH-IP2010 criteria			
Part 1		≤ 5 mmHg	≤ 10 mmHg	≤ 15 mmHg	
Pass requirement	Two of	73	87	96	
	All of	65	81	93	
Achieved		**93**	**98**	**99**	**PASS**
Part 2		2 or 3 ≤5mmHg	0 out of 3 ≤5mmHg		
Pass requirement		≥ 24	≤ 3		
Achieved		**29**	**1**		**PASS**

Figure 1:

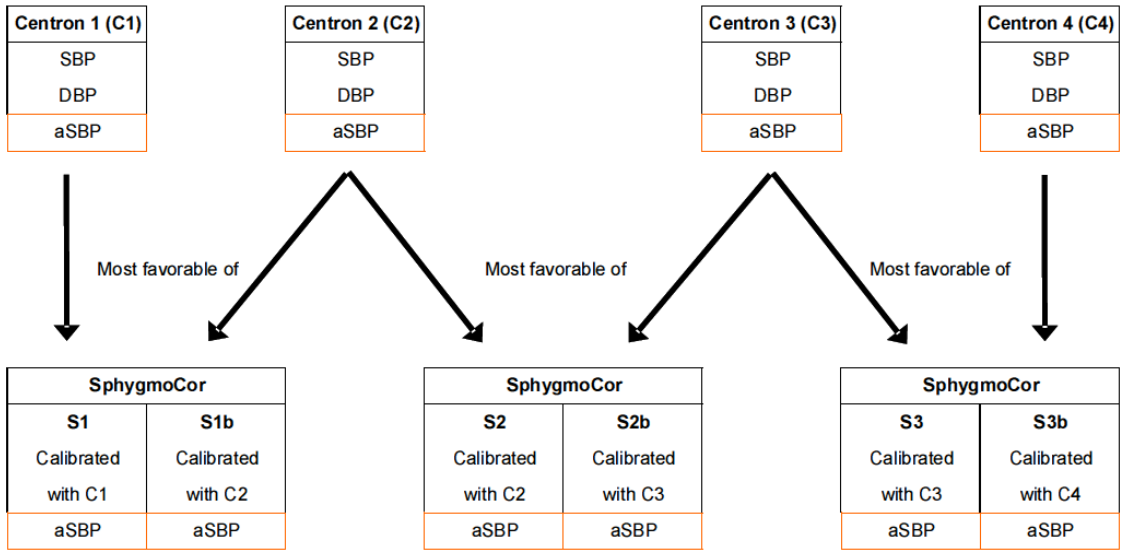

Centron 1 (C1)
SBP
DBP
aSBP
Centron 2 (C2)
SBP
DBP
aSBP
Centron 3 (C3)
SBP
DBP
aSBP
Centron 4 (C4)
SBP
DBP
aSBP
Most favorable of
Most favorable of
Most favorable of
SphygmoCor
S1
Calibrated
with C1
aSBP
S1b
Calibrated
with C2
aSBP
SphygmoCor
S2
Calibrated
with C2
aSBP
S2b
Calibrated
with C3
aSBP
SphygmoCor
S3
Calibrated
with C3
aSBP
S3b
Calibrated
with C4
aSBP

Figure 2:

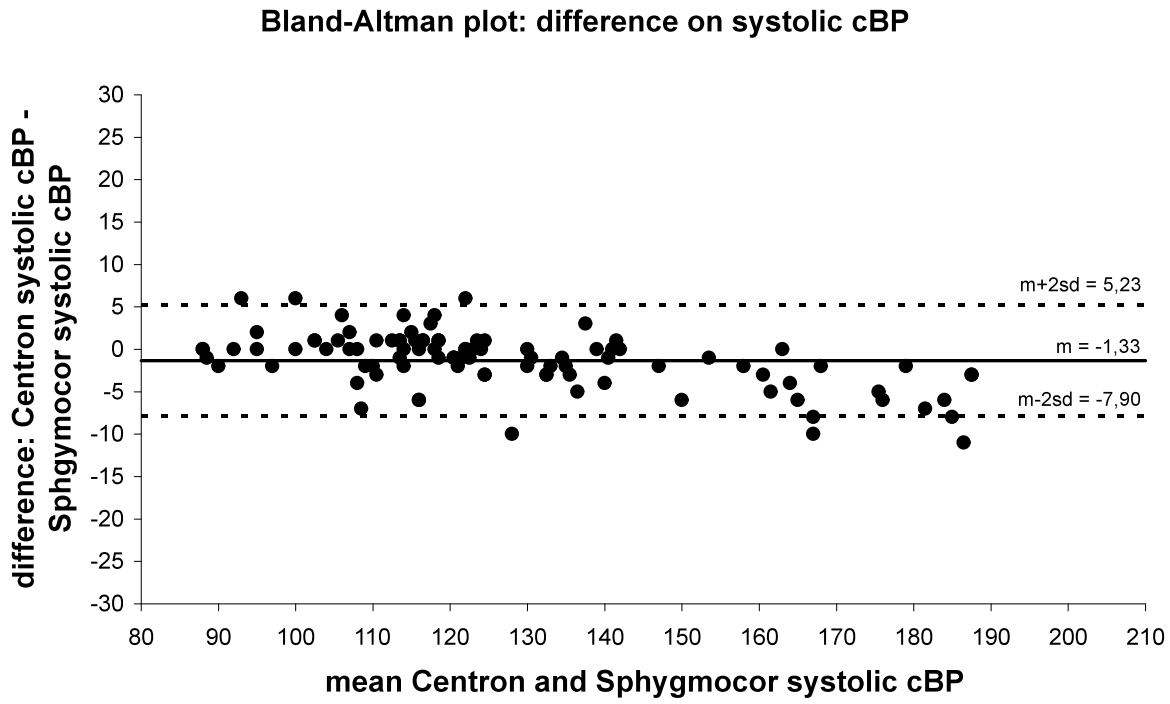
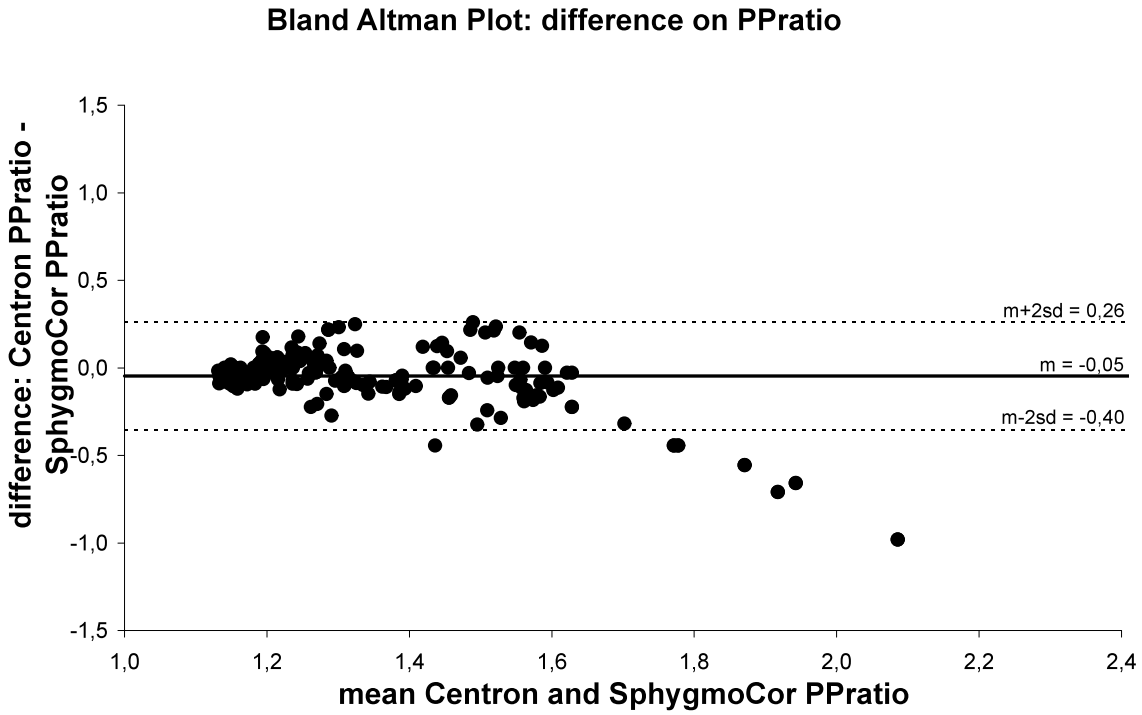

Bland-Altman plot: difference on systolic cBP
difference: Centron systolic cBP - Sphgymocor systolic cBP
mean Centron and Sphygmocor systolic cBP
m+2sd = 5,23
m = -1,33
m-2sd = -7,90
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
80
90
100
110
120
130
140
150
160
170
180
190
200
210

Figure 3:


Bland Altman Plot: difference on PPratio
difference: Centron PPratio - SphygmoCor PPratio
1,5
1,0
0,5
0,0
-0,5
-1,0
-1,5
m+2sd = 0,26
m = -0,05
m-2sd = -0,40
1,0
1,2
1,4
1,6
1,8
2,0
2,2
2,4
mean Centron and SphygmoCor PPratio

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V.3.2. Conclusion de l'ARTICLE 3

Nous avons donc mis en place un protocole ESH-IP 2010 modifié pour la validation non invasive des appareils de mesure de la pression artérielle centrale.

Selon ce protocole l'appareil Centron cBP301 a satisfait les critères de validation et est capable de donner des mesures précises de pression artérielle systolique et d'amplification de la pression pulsée.

VI La tonométrie artérielle d'applanation et la calibration de l'onde de pression

La vraie révolution dans les études hémodynamiques non invasives s'est produite pendant les années soixante avec l'introduction de la tonométrie artérielle d'applanation. Cette méthode découle de la tonométrie utilisée en ophtalmologie pour définir la pression intra-oculaire ; elle permet de déterminer la pression intra-artérielle et d'étudier sa morphologie de façon non invasive.

La sonde est placée sur l'artère (Figure 24), là où la pulsation est la plus forte, et où l'on peut comprimer l'artère contre les tissus osseux ou musculaires sous-jacents (au niveau des artères carotide, humérale, radiale, fémorale, pédieuse et tibiale postérieure).

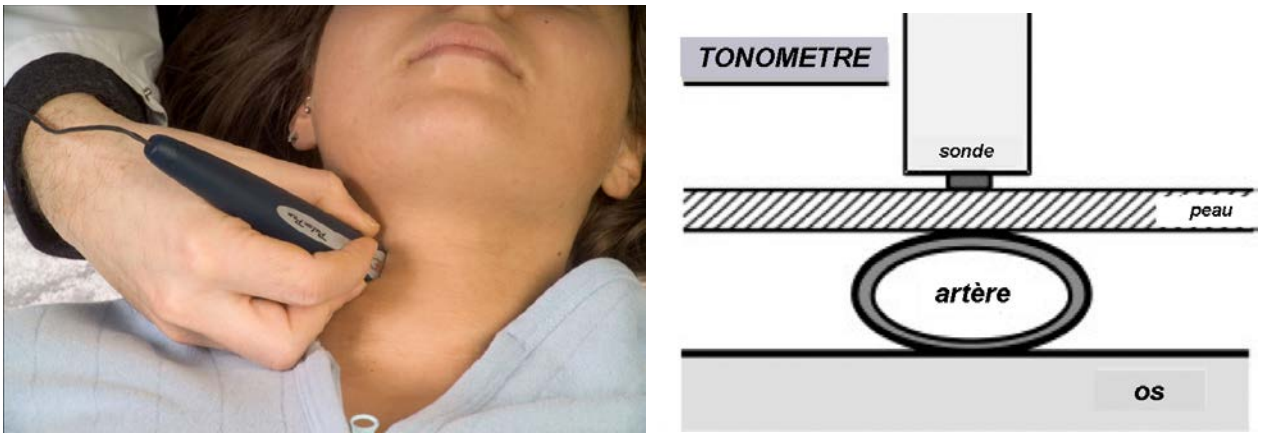

Figure 24. La tonométrie d'applanation.

Grâce à la loi de La Place on peut considérer que la pression dans le centre de l'artère est égale à la pression transmise sur chaque point de la paroi de l'artère. En comprimant donc l'artère, le tonomètre est capable de détecter des variations de pression artérielle qu'il transforme en variations de courant électrique. Le signal électrique est ensuite envoyé au logiciel capable de le traiter et de visualiser la courbe de pression. Mais, afin de passer d'un signal en millivolts à un signal en mmHg, il est nécessaire d'effectuer une calibration de la courbe qui nous permette

de « positionner » correctement l'onde de pouls au bon niveau de pression, pour en dériver les pressions systolique, diastolique et/ou moyenne en mmHg. Cela peut se faire par deux méthodes différentes : 1/ la voie invasive, qui consiste à mesurer la pression intra-artérielle par cathétérisme ; 2/ la voie non invasive, qui se base sur la mesure de la pression brachiale par tensiomètre.

Comment calibre-t-on la courbe de pression artérielle carotidienne ? Plusieurs méthodes de calibration non invasive des ondes de pression existent, toutes basées sur le même principe.

En supposant que les pressions moyenne et diastolique sont relativement constantes le long de l'arbre artériel, il suffirait de les mesurer et de calibrer ensuite la courbe de pression carotidienne par ces valeurs, obtenant ainsi la pression systolique carotidienne.

Un des problèmes les plus importants est donc la mesure des pressions moyenne et diastolique.

Pour la mesure non invasive de la pression diastolique, tout cardiologue connaît bien les problèmes de la méthode auscultatoire et des appareils automatiques par rapport à leur précision dans cette mesure. Néanmoins, il n'existe pas aujourd'hui d'alternative non invasive correctement validée.

En ce qui concerne la pression moyenne (PAM), on peut utiliser une des cinq méthodes de mesure non invasives déjà mentionnées :

1. des formules mathématiques, et notamment les deux formules suivantes, en utilisant par convention un *form factor* de 3 (ou méthode de 33 %) pour la première et de 2,5 (méthode de 40 %) pour la deuxième :

1a. PAM = pression diastolique + pression pulsée / 3 (15)

1b. PAM = pression diastolique + pression pulsée / 2,5 (16)

Selon cette méthode il suffirait de mesurer les pressions systolique et diastolique brachiales et d'en dériver la pression moyenne.

2. La méthode « oscillométrique ».

3. La méthode de l'aire sous la courbe : 3a. brachiale ; 3b. radiale.

Le vrai problème des méthodes de calibration est qu'elles donnent des valeurs différentes de pression.

Par exemple, si nous voulons calibrer un signal tonométrique carotidien, nous avons à disposition la pression brachiale par tensiomètre oscillométrique (PAS / PAD [PAM] = 120 / 80 [94]), la courbe de pression brachiale, la courbe de pression radiale.

Selon les cinq méthodes non invasives :

1a. PAM = 80 + 40 / 3 = 93.33

1b. PAM = 80 + 40 / 2,5 = 96

2. PAM = PAM oscillométrique = 94

3a. PAM = aire sous la courbe brachiale : pour calculer l'aire sous la courbe brachiale on utilise la courbe tonométrique brachiale que l'on calibre par les valeurs de pression systolique et diastolique du tensiomètre brachial et on obtient PAM = PAM brachiale ;

3b. PAM = aire sous la courbe radiale : pour calculer l'aire sous la courbe radiale on utilise la courbe tonométrique radiale que l'on calibre par les valeurs de pression systolique et diastolique du tensiomètre brachial et on obtient PAM = PAM radiale.

Nous allons alors calibrer notre courbe de pression carotidienne par une des PAM et par la pression diastolique brachiale du tensiomètre : on peut imaginer que les valeurs de pression systolique carotidienne seront différentes selon la méthode utilisée.

VI.1. L'amplification de la pression et la calibration : un problème de cohérence ?

Dans le paragraphe sur les ondes de pression, nous avons pu constater que la pulsatilité du système cardiovasculaire ainsi que le phénomène d'amplification des ondes de pression représentent une caractéristique fondamentale du système cardiovasculaire. De même, notre équipe a déjà montré en 2002 le rôle pronostique de l'amplification ;[6] depuis, de nombreuses études ont confirmé que l'amplification est capable de rajouter des informations sur le risque cardiovasculaire.[91,98–102]

En considérant l'intérêt actuel et/ou potentiel de l'amplification, il nous semble important d'en analyser les coulisses.

Pour calculer l'amplification nous avons besoin d'une pression artérielle à la fois périphérique et centrale. Une fois obtenues les valeurs de pression, on peut choisir de calculer l'amplification de la pression systolique ou l'amplification de la pression pulsée. En général, l'amplification de la pression pulsée prenant en considération aussi les petites variations de pression diastolique, elle nous semble

plus informative. A ce point, trois formules peuvent être utilisées, où l'amplification de la pression pulsée = APP, la pression pulsée périphérique = PPp et la pression pulsée centrale = PPc :

$$APP = PPp - PPc \quad (17)$$

$$APP = PPp / PPc \quad (18)$$

$$APP = (PPp - PPc) / PPc \quad (19)$$

Nous verrons plus tard que la formule utilisée peut influencer les résultats, mais pour le moment nous choisirons la formule (18), le rapport direct entre les pressions pulsées périphérique et centrale.

Pour bien comprendre la problématique de la calibration par rapport à l'amplification, il faut distinguer les mesures de pression n'ayant pas besoin d'une calibration de celles qui en ont besoin. Les pressions artérielles déterminées par la méthode auscultatoire et par l'oscillométrie n'ont pas besoin d'être calibrées car ces deux méthodes mesurent directement la pression artérielle dans une artère donnée. Par contre, les pressions artérielles mesurées par tonométrie et par oscillométrie « indirecte » (en appliquant une fonction de transfert au signal oscillométrique pour en dériver la pression centrale) nécessitent forcément une calibration.

Pour des raisons mathématiques, si les deux pressions pulsées sont calculées par la même calibration, quand l'amplification est obtenue par le rapport entre les pressions pulsées, le résultat est indépendant de la calibration utilisée. Par contre, si une des deux pressions est obtenue par calibration et l'autre par mesure directe (par exemple par tensiomètre), l'amplification calculée sera dépendante de la

méthode de calibration choisie. De même, si l'amplification est calculée comme différence des pressions (formule (17)), le résultat sera dépendant de la calibration.

VI.2. ARTICLE 4 : L'amplification de la pression pulsée, la calibration des ondes de pression, les applications cliniques[103]

VI.2.1. Introduction de l'ARTICLE 4

Afin d'analyser en détail la problématique de la calibration des ondes de pression et l'application pratique de l'amplification, nous avons mené une étude portant sur 108 sujets chez qui nous avons mesuré la courbe de pression par tonométrie dans les artères carotide, fémorale, brachiale, radiale et pédieuse. Nous avons recruté des patients bénéficiant d'une hospitalisation de jour au Centre de Diagnostic, Hôpital Hôtel-Dieu, Paris.

Nous avons inclus consécutivement 115 sujets présentant le critère d'inclusion principal suivant : un enregistrement de haute qualité des ondes de pression au moins aux niveaux carotidien, radial et brachial. Les critères d'exclusion étaient la présence d'une fibrillation auriculaire et une insuffisance cardiaque sévère. Après exclusion de 7 sujets à cause d'un signal carotidien (6 sujets) ou radial (1 sujet) de qualité non conforme, nous avons donc analysé 108 patients.

Nous avons recueilli les informations cliniques, anamnestiques, et des données anthropométriques. La pression brachiale a été mesurée par un tensiomètre validé (SCVL , Paris, France), après 5 minutes de repos en position allongée. Les valeurs de pression systolique et diastolique brachiales ont été mesurées juste avant l'enregistrement de chaque onde de pression par tonométrie d'applanation (tonomètre PulsePen).

Les quatre méthodes utilisées pour la mesure de la pression moyenne sont présentées dans la Figure 25 : la méthode du 33 % (où la pression pulsée est divisée

par 3, comme dans la formule (15)), du 40 % (pression pulsée divisée par 2,5, formule (16)), la méthode de l'aire sous la courbe brachiale et la méthode de l'aire sous la courbe radiale.

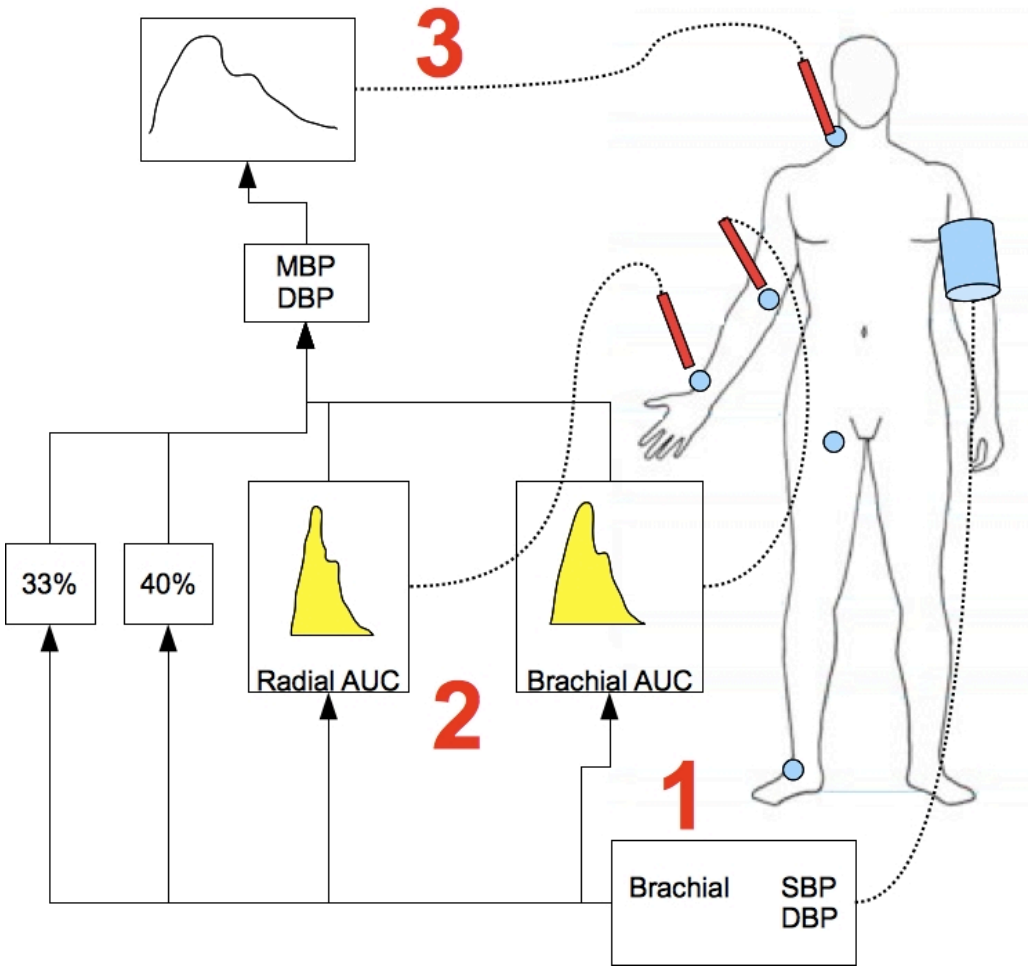

Figure 25. Procédure pour la calibration des ondes de pression.

Ensuite, avec les valeurs de pression moyenne et la pression diastolique brachiale, nous avons recalibré toutes les ondes de pression et calculé la pression pulsée dans les cinq artères : carotide, fémorale, brachiale, radiale, pédieuse.

Les résultats sont présentés dans la Figure 26.

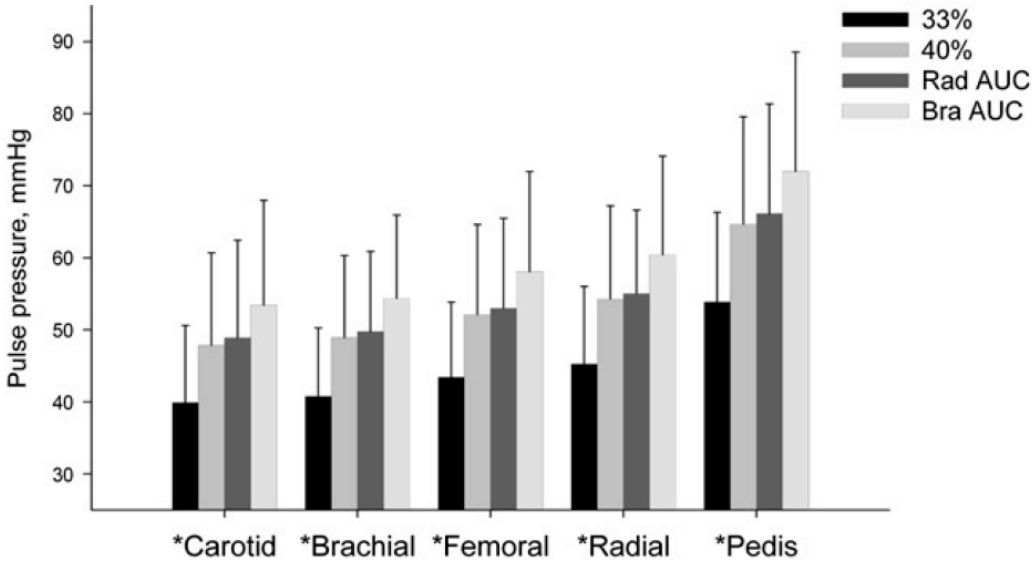

Figure 26. Valeurs de pression pulsée dans cinq artères, selon les quatre méthodes de calibration.

Comme on peut le constater, la calibration influence les valeurs de pression pulsée, avec des différences pouvant aller jusqu'à 14-18 mmHg.

Nous avons ensuite calculé l'amplification à partir des courbes tonométriques dans cinq territoires : carotidobrachial, carotidofémoral, carotidoradial, fémoropédieux et carotidopédieux.

L'amplification étant calculée comme rapport entre deux courbes de pression calibrées, le résultat est indépendant de la méthode de calibration utilisée.

Les résultats sont présentés dans la Figure 27.

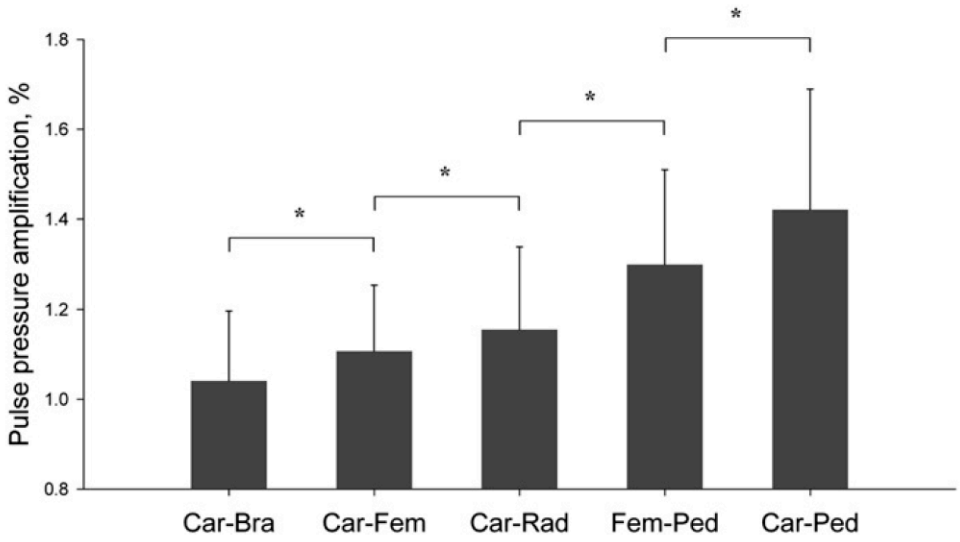

Figure 27. Amplification de la pression pulsée dans cinq territoires. * p < 0,05.

On voit dans cette figure que l'amplification augmente avec la distance entre les artères, notamment entre la carotide (artère centrale) et les artères plus périphériques.

Puis nous avons analysé les paramètres cliniques associés à l'amplification dans les cinq territoires, par des modèles de régression multiple présentés dans le Tableau 3.

Tableau 3. Modèles de régression analysant les facteurs associés avec l'amplification de la pression pulsée dans les cinq territoires.

	Carotid-brachial		Carotid-radial		Carotid-femoral		Carotid-pedis		Femoral-pedis	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Intercept	−0.651	0.244	1.046	<0.001	−0.062	0.894	2.191	<0.001	1.276	<0.001
Sex	0.058	0.234	−0.061	0.112	−0.004	0.930	−0.149	0.002	−0.027	0.471
Age	0.000	0.795	−0.002	0.091	0.000	0.918	−0.005	0.006	−0.001	0.617
MAP	−0.002	0.200	−0.004	0.005	0.000	0.988	−0.003	0.150	−0.002	0.401
Body height	0.007	0.005			0.006	0.005				
Body weight	−0.004	0.003								
HR	0.004	0.003	0.005	0.002	0.003	0.034				
WHR	0.771	0.001	0.438	0.035						
Diabetes	−0.099	0.011								
CF-PWV									−0.023	0.001
CR-PWV									0.057	0.002
R-square	0.26*		0.22*		0.21*		0.24*		0.27*	

Comme on peut le remarquer, le *pattern* des déterminants diffère selon le territoire considéré. En particulier, l'amplification carotidobrachiale était associée positivement à la taille et à la fréquence cardiaque et négativement au poids et à la présence d'un diabète ; l'amplification carotidoradiale était associée négativement à la pression moyenne et positivement à la fréquence cardiaque ; l'amplification carotidopédieuse était la seule à être associée à la vitesse de l'onde de pouls carotidofémorale (négativement) et carotidoradiale (positivement).

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Pulse pressure amplification, pressure waveform calibration and clinical applications

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ABSTRACT

Obtaining pulse pressure non-invasively from applanation tonometry requires the calibration of pressure waveform with brachial systolic and diastolic blood pressure. In the literature, several calibration methodologies are applied, and clinical studies disagree about the predictive value of central hemodynamic parameters. Our aim was to compare 4 calibration methodologies and assess the usefulness of pulse pressure amplification as an index independent of calibration. We investigated 108 subjects with tonometry in carotid, femoral, brachial, radial and dorsalis-pedis arteries; pulse pressure amplification between arterial waveforms was calculated. Four methods to calibrate the waveforms were compared: the 1/3 rule, the 40% rule, the integral of radial and brachial waveforms. Pulse pressure amplification in 5 arterial territories (carotid-femoral, carotid-brachial, carotid-radial and carotid-pedis amplifications; femoral-pedis amplification) was studied. Pulse pressure was successfully measured non-invasively at the 5 arterial sites. Pulse pressure was markedly dependent on calibration, with differences up to 18 mmHg between methods. Calculation of pulse pressure amplification eliminated effects of calibration method. Furthermore, pulse pressure amplifications in the 5 arterial sites presented a distinct pattern of clinical/biological determinants: heart rate and body height were common determinants of carotid to brachial, radial and femoral amplifications; diabetes was related to carotid to brachial amplification and pulse wave velocity to femoral to pedis amplification. In conclusion, the calibration of pulse pressure will influence results of clinical trials, but calculation of pulse pressure amplification can avoid this. We also suggest that the alteration of amplification in each arterial territory might be considered as a signal of clinical/subclinical damage.

1. Introduction

In recent years, many devices enabling non-invasive study of peripheral and central blood pressure (BP) have been developed. The arterial systolic blood pressure (SBP) and pulse pressure (PP) can be non-invasively determined through applanation tonometry and, once the pressure waveform (PW) is obtained, a calibration procedure is used to get absolute values of arterial BP. Generally, PWs are calibrated by mean arterial pressure (MAP) and diastolic blood pressure (DBP), assuming that they remain constant along the arterial tree [1].

One of the main problems of the calibration procedure is MAP estimation, because the only precise way to measure MAP is by using an intra-arterial catheter. However, several arithmetic and integration methodologies can be applied [2–7] in order to non-invasively estimate MAP, calibrate PWs, and measure local arterial BP.

At the same time, the finding that a difference exists in the SBPs and the PPs between central and peripheral arteries led to the concept of pressure amplification (PA). In fact, central BP is physiologically lower than peripheral BP [2,8]. This parameter has been poorly evaluated in clinical studies, but PA is considered to be correlated to cardiovascular risk, and it has shown a predictive prognostic value in some population studies [8–10]. Notably, in literature there exist several formula to calculate PA, like the

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subtraction of central to peripheral BP, or the ratio between brachial over central BP. Furthermore, either sphygmomanometric or tonometric brachial BP can be used in the PA formula. This can lead to a situation in which central BP is obtained by PW calibration, while brachial BP is derived from a sphygmomanometric device, not requiring calibration. When calculating PA as a ratio of brachial over central BP, we will obtain a calibration-dependent value. This may contribute to the different prognostic power of PA as various clinical trials and population studies have shown through different calibration methods.

On the other hand, calculating PA as the ratio between two calibrated tonometric PWs contributes to reduce errors related to the different calibration procedures [9].

In this setting, we examined the tonometric PP in five arteries, for the first time: carotid, femoral, brachial, radial, and dorsalis pedis arteries. Then we compared 4 common calibration methods: the 33% and 40% methods, and the brachial and radial PWs integration method. Finally, we studied the PP amplification and its clinical role in 5 arterial sites (district PA): carotid-femoral, carotid-brachial, carotid-radial, carotid-pedis and femoral-pedis.

We will show that: (1) tonometric BP strictly depends on PW calibration; (2) the PA is correlated to organ damage.

2. Methods

2.1. Study participants

In the present study, 115 consecutive outpatient subjects, aged from 20 to 84 years, were recruited from the Department of the Diagnosis and Therapeutic Center of Hôtel-Dieu Hospital, Paris, France, for the evaluation of one or more cardio-vascular (CV) risk factors, including high BP, smoking, dyslipidemia, diabetes mellitus, and/or family history of premature CV disease, with or without clinical events previously identified. The inclusion criteria were the presence of an adequate quality of PW recording of at least carotid, radial and brachial arteries. Exclusion criteria involved atrial fibrillation and severe heart failure (NYHA III-IV). Informed consent was obtained from all participants. Seven subjects did not have a good quality tonometric signal (6 for the carotid tonometry and 1 for radial tonometry) and were therefore excluded. The final number of patients was 108.

2.2. Anthropometric measurements and clinical information

Clinical characteristics concerning family history diseases, smoking habits and pharmacological treatment were obtained from patients' documents. Smoking was defined as a history of smoking and/or current smoking. Body height (BH) and weight (BW), waist and hip circumferences (WC, HC) were measured. Body mass index (BMI) was calculated by routine formula. Hypertension was defined as systolic BP (SBP) >140 mmHg and/or diastolic BP (DBP) above 90 mmHg, with a minimum of three casual measurements during the previous month, or when antihypertensive therapy was present.

Brachial BP was determined using a validated oscillometric device (SCVL, Paris, France), after at least 5 min rest in supine position. Brachial sphygmomanometer SBP and DBP was then recorded just before each tonometric PW recording; brachial MAP was automatically calculated by the oscillometric device with the formula: DBP + (0.412 × (SBP-DBP)) [5].

2.3. Tonometric analysis and estimation methods

Applanation tonometry provides accurate profile of intra-arterial BP curves through the application of a piezoresistive sensor -the tonometer- over an artery through the skin. PulsePen (DiaTecne s.r.l., Milan, Italy) is a light and compact device for transcutaneous applanation tonometry that provides pulse wave velocity (PWV) and pulse wave analysis (PWA) assessments [11]. A PW registration of at least 12 s is considered acceptable for the subsequent analysis. Therefore, PWs of five artery sites (carotid, brachial, radial, femoral and dorsalis pedis arteries) were obtained with PulsePen by a skilled physician with the following methodology.

Firstly, brachial artery SBP and DBP were achieved using the sphygmomanometer. Secondly, MAP is calculated with four different methods. Methods 1 and 2 are the 33% and the 40% rules: MAP = PP/3 + DBP and MAP = PP/2.5 + DBP respectively. As far as the other two methods are concerned, sphygmomanometric SBP and DBP are used to calibrate radial (Method 3) and brachial (Method 4) tonometric PWs; the area under the curve (AUC) of the tonometric radial and brachial PWs is then automatically calculated and represents MAP. Finally, we utilized MAP obtained from the 4 estimation methods to recalibrate each PW, and calculate PP in mmHg in each of the 5 arteries, assuming MAP as constant along the arterial tree [1].

In order to calculate PWV, simultaneously ECG recordings were achieved and the foot-to-foot method was applied to the waveform as described elsewhere [11]. The distal and proximal distances were measured with a caliper from carotid to suprasternal notch, and then from suprasternal notch to peripheral artery. Carotid-peripheral artery distances were calculated as distal distance subtracted by proximal distance. We calculated carotid-femoral and femoral-pedis PWV.

2.4. Definitions of amplification of each particular site

Carotid artery PW was considered as a surrogate of the central BP [12–14], and the tonometric PP amplification between the 2 arterial sites was calculated according to the following formula: peripheral PP/central PP. We obtained PA as a dimensionless number, without any unit in 5 different sites: carotid to femoral, brachial, radial and pedis amplifications, and femoral to pedis amplification.

2.5. Statistical analysis

Statistics were performed with NCSS 2000 software (Kaysville, Utah, USA). A $P < 0.05$ was considered as statistically significant. We represent data as mean ± standard deviation. We compared the differences in PP and PP amplification between the 4 methods and between the 5 arteries with ANOVA. We also investigated the possible determinants of PA in different sites with multiple regression analysis. We compared the determinants in a regression model for each arterial district, forcing age, gender and MAP in all the models, and choosing only the 3rd estimation method (Radial AUC), as frequently used in literature.

Furthermore, we studied the factors influencing PA independently of each particular site. For this purpose, we built a single multiple-regression model with PA as the dependent variable and sex, age quartiles, heart rate (HR), BMI, waist to hip ratio (WHR), distance, mean arterial pressure, diabetes, ankle-brachial index (ABI), LDL-cholesterol, proteinuria, hypertension, smoking as the independent variables.

3. Results

The final number of patients was 108. Table 1 shows the characteristics of the study participants. Compared to women, we found in men higher BH, BW and DBP, and lower HR (data not shown).

Table 1
Anthropometric and clinical characteristics of patients.

Variables	Male ($n = 60$)	Female ($n = 48$)	All ($n = 108$)	P value[a]
Age, years	58 ± 13	57 ± 16	58 ± 14	0.702
Body height, cm	174 ± 8	159 ± 7	167 ± 10	< 0.0001
Body weight, kg	81 ± 13	71 ± 16	77 ± 15	< 0.001
BMI, kg/m2	27 ± 4	28 ± 6	27 ± 5	0.154
Heart rate, bpm	65 ± 10	70 ± 12	67 ± 11	0.015
Brachial CUFF SBP, mmHg	133 ± 17	130 ± 14	132 ± 16	0.363
Brachial CUFF DBP, mmHg	82 ± 8	77 ± 11	80 ± 10	0.023
Brachial CUFF MAP, mmHg	103 ± 11	99 ± 11	101 ± 11	0.082
Hypertension, n(%)	45 (80)	26 (68)	71 (75.5)	0.225
Diabetes, n(%)	14 (26)	6 (15)	29 (21.5)	0.308
Dyslipidemia, n(%)	23 (46)	15 (42)	38 (44.2)	0.826
CHD, n(%)	8 (16)	1 (3)	9 (10.8)	0.08
Smoking, n(%)	17 (39)	12 (40)	29 (39.2)	0.99

Data except percentage are presented as mean value ± standard deviation (SD). BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, automatically calculated by the oscillometric device with the formula: DBP + (0.412 × (SBP-DBP)); CHD, coronary heart disease; CUFF, sphygmomanometer det × rmination during carotid tonometry.

[a] Two sample T-Test for normal variables, Wilkoxon test for non-normal variables, Fisher exact test for categorical variables.

The Fig. 1 shows the values of tonometric PP in mmHg, in each artery. Pulse pressure values increase from the left to the right, i.e. from central to peripheral arteries. Looking at each particular artery, we see that the PP was different ($P < 0.01$) depending on the MAP estimation method. The 33% method (the first small column) gave the lower values and the Brachial AUC method (the last little column) the higher ones.

District PA was independent from the 4 estimation methods (data not shown); therefore we arbitrarily chose the third calibration method (Radial AUC) and showed that district PA (Fig. 2) changes moving through the different arterial sites.

Factors influencing PA independently from each particular site were the distance of each particular site, HR, age quartiles, BMI, WHR, MAP (data not shown). This regression model explains up to 50% of PA variability, with the greatest role played by the distance ($R^2 = 0.44$) and HR ($R^2 = 0.07$). Remaining parameters are negligible (age quartiles, BMI, WHR, MAP, with $R^2 < 0.06$).

3.1. Clinical applications

Thereafter, we considered the clinical role of regional PA (Table 2). We found that HR was a common determinant of carotid

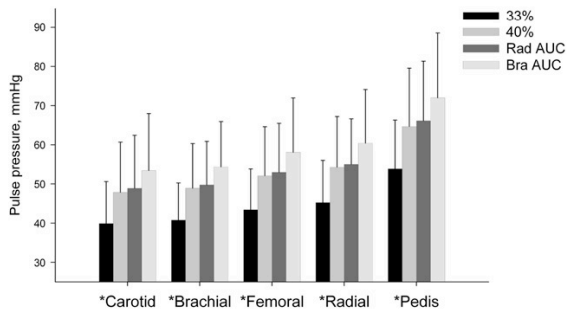

Fig. 1. Pulse pressure (mmHg) in 5 artery sites obtained with 4 calibration methodologies: 33% = 33% of pulse pressure + diastolic blood pressure (DBP); 40% = 40% of pulse pressure + DBP; Rad AUC = integral of the radial pressure waveform; Bra AUC = integral of the brachial pressure waveform. *P for trend < 0.001.

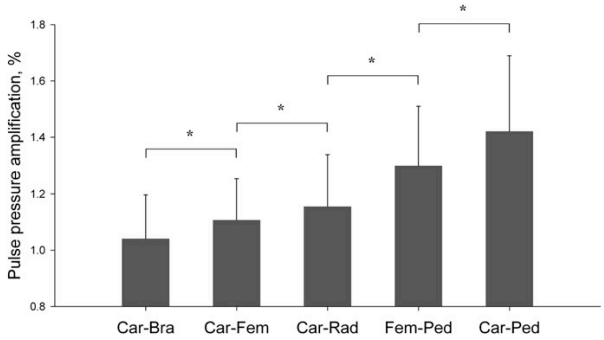

Fig. 2. Pulse pressure amplification calculated as a ratio of peripheral tonometric PP over central tonometric PP. Radial AUC calibration was used. *P for difference < 0.05.

to brachial, radial and femoral amplifications ($P < 0.05$). Then, only carotid to radial amplification was influenced by the MAP (obtained with the Radial AUC method). Carotid to brachial amplification presented a characteristic metabolic pattern of determinants: BW, WHR and diabetes ($P < 0.05$). Carotid to femoral amplification was related to BH, while age and gender were significantly and inversely associated to carotid to pedis amplification. Finally, carotid-femoral (negatively) and carotid-radial (positively) pulse wave velocities were correlated to femoral to pedis amplification ($P < 0.03$).

4. Discussion

In this study, we measured arterial PP in men and women, from 20 to 87 years old, by a tonometry essay taken in 5 arteries (carotid, femoral, brachial, radial, dorsalis pedis). Our findings show that, firstly, PP absolute values in each artery depend on the MAP estimation method; secondly, calculating the PA as a ratio of peripheral over central tonometric PWs leads to values independent from calibration method. Finally, the determinants of PA change through different arterial sites.

4.1. Calibration procedure

The major interest of our study is related to the PW calibration. Our findings show that a non-invasive measurement of PP can lead to contrasting results depending on PW calibration. Notably, we found a difference of 14–18 mmHg in PP measured with 4 estimation methods, which is incompatible with an authenticity in BP measurement. In addition, each method for MAP estimation carries an intrinsic inaccuracy [15].

Calculating the integral of the radial PW, scaled with cuff systolic and DBP, assumes that brachial BP is equivalent to radial BP. Other investigators and us found a significant brachial to radial amplification, which is variable and may bring to a considerable inaccuracy [6,16,17]. We remind that most tonometry devices apply this kind of procedure in order to obtain local and central BP measurements.

The feasibility of recording brachial tonometry has also been discussed [18,19]. In fact, the anatomy of brachial region is not apt for a correct compression of the artery under the probe. Nevertheless, no final evidence has been shown yet of the validity/weakness of this technique. Concerning our data, no patients with brachial tonometry essay were excluded from our analysis because of unstable or poor quality tonometric signal, and brachial measurements standard deviations were comparable to the other ones.

Table 2
Pulse pressure amplifications in specific territories and their determinants in multiple regression analysis.

	Carotid-brachial		Carotid-radial		Carotid-femoral		Carotid-pedis		Femoral-pedis	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Intercept	−0.651	0.244	1.046	<0.001	−0.062	0.894	2.191	<0.001	1.276	<0.001
Sex	0.058	0.234	−0.061	0.112	−0.004	0.930	−0.149	0.002	−0.027	0.471
Age	0.000	0.795	−0.002	0.091	0.000	0.918	−0.005	0.006	−0.001	0.617
MAP	−0.002	0.200	−0.004	0.005	0.000	0.988	−0.003	0.150	−0.002	0.401
Body height	0.007	0.005			0.006	0.005				
Body weight	−0.004	0.003								
HR	0.004	0.003	0.005	0.002	0.003	0.034				
WHR	0.771	0.001	0.438	0.035						
Diabetes	−0.099	0.011								
CF-PWV									−0.023	0.001
CR-PWV									0.057	0.002
R-square	0.26*		0.22*		0.21*		0.24*		0.27*	

Sex, age and mean arterial pressure were forced in all models.
MAP indicates mean arterial pressure; HR, heart rate; WHR, waist to hip ratio; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity.
*$P < 0.001$.

In literature, one study focused in the role of the radial PW calibration [7]. In this study, Mahieu et al. proposed and discussed three calibration methods: the first was a simple application of cuff systolic and DBP measurements to the radial waveform, considering no amplification between the brachial and radial arteries; the latter two estimated the MAP by either the 33% or the 40% rules. Then, central BP was calculated through a transfer function. Interestingly, they found that non-invasive central BP measurement depends on PW calibration. They also provided information on the weakness of the 1/3rd rule as compared to 40%. In any case, taking into account the inter/intra-individual variability of the waveform shape, not even the value of 40% can assure a correct estimation of MAP in the whole the population.

We have shown that the non-invasive tonometric BP determination is strictly linked to the waveform calibration methods that produce different absolute values. Therefore, correctly calculating the PA is instrumental to overcome this issue.

4.2. PP amplification

PA has been proved to be a useful marker of cardiovascular risk [9,10,20]. The original concept of PA was to divide peripheral by central BP, obtained with a waveform analysis [2]. Therefore, mathematically, calculating PA as a non-calibrated BP divided by a calibrated PW leads to a calibration dependent value. On the other hand, our findings support the application of the ratio between two tonometrically obtained PPs as the only method of measuring PP amplification independently of calibration.

4.3. Clinical implications

In addition, we found that determining PA between several arterial sites along human body might be a method of great interest. Firstly, PA increases together with the distance between arteries; and secondly, the PA between two particular arteries is correlated to a specific organ impairment. Previous studies report that PA values are influenced by the gender, age and anthropometric/cardiovascular parameters [16,21]. For the same MAP level, pressure pulsatility changes in different arterial sites. In fact, the modification of arterial visco-elasticity properties between center and periphery is considered to influence the elastic modulus and, as a consequence, the arterial wall rigidity. So, physiologically, pressure waves will travel from large central elastic arteries to small peripheral stiffer arteries, producing two main consequences: first, in a peripheral artery the reflected wave travels more rapidly towards the center and meets the forward wave in the early phase of the systole, increasing the systolic peak. Second, in a central young artery, the reflected wave travels slower to the center and meets the forward wave in the late systolic phase. Whether reflected waves arrive during late systolic or diastolic phases, is still a matter of debate [2,22,23]. This produces little or no effect on the systolic peak, as well as an augmentation of the mean diastolic pressure.

Clearly, this reflected wave behavior produces a lower central systolic pressure load and, consequently, a lower cardiac workload, while contributing to an increase in the diastolic coronary perfusion. At the same time, the systolic pressure in periphery is kept at higher values assuring an adequate perfusion level to the organs [2,8].

Nonetheless, no investigation evaluated PA all along the human body. As a secondary finding, focusing on the regional PA (Table 2), we found that factors influencing PA differ markedly from those linked to PWV and classical end-organ damage manifestations such as left ventricular hypertrophy, proteinuria, and creatininemia. In fact, different patterns of determinants seem to belong to specific PA sites. In particular, HR was a common determinant of carotid to brachial, radial and femoral amplifications. This implies that HR is linked to aorta and upper limb PA, suggesting a role of autonomic nervous system activity [24]. Besides, determining the relationship of PA and HR/BP variability might represent an interesting goal for a clinical prospective investigation.

Another important determinant of PA is the presence of diabetes, which contributes to carotid to brachial amplification. When considering the physiopathology and the clinical history of diabetes, one would expect that the muscular arteries' damage involve the arterial network of the lower limb more than the upper limb's one. A study measuring arterial diameter, distensibility and compliance showed that neither carotid nor brachial arterial properties were different between insulin-dependent diabetics and controls; at the contrary, the femoral artery presented a lower distensibility in diabetic subjects [25]. Anyway, in our analysis, we did not investigate the same arterial properties, but a combination of wave reflection and arterial stiffness parameters. Therefore, two possible explanations to our result have to be considered. Firstly, a low statistical power could have masked determinants' significance in our regression models, as reported below. Secondly, the carotid-brachial and carotid-radial PAs are the only amplifications directly relating a central to a peripheral artery; in fact, carotid-femoral represents aortic PA, carotid-pedis PA includes the aorta, and femoral-pedis PA does not include a central artery. We can so argue that diabetes may change the relationship between central/elastic and peripheral/muscular arteries. Why this affects only carotid-brachial and not carotid-radial PA remains uncertain, and possibly linked to the statistical power.

4.4. Limitations

The main limitation of our study is the lack of intra-arterial measurement as a gold standard for the arterial pressure measurement. Nonetheless, validations of these procedures with invasive measurement have already been done [11,26,27].

Together with MAP estimation errors, the measurement of DBP by routine brachial sphygmomanometer carries also an intrinsic inaccuracy [28]. Therefore, it should be emphasized that the determination of BP from PW analysis, which is calibrated with MAP and DBP, represents an estimation of actual arterial pressure values. In this setting, the measurement of PA may overcome this issue. Other limitations are found in all the 4 calibration procedures (see calibration procedure paragraph).

A further limitation is the small number of population sample, which could have affected the power of our multiple regression statistical analysis.

5. Conclusion

Our findings confirm that the most reliable non-invasive procedure to calibrate the PW is not well established, and, more importantly, that it is very difficult to compare the results from studies applying different MAP estimation methods. From our results it appears that using different calibration produces different absolute values of central/peripheral BP parameters, and that calculating the PA as a ratio between two tonometric PWs permits to study central and peripheral hemodynamic better, whatever MAP estimation method is used. Consequently, we propose firstly that PA should be calculated by the PW analysis and, secondly, that investigations studying central BP and PA should be compared considering the particular estimation method employed. Moreover, our results, within the statistical power limits, suggest that taking into account the alterations of each particular site of the arterial tree may give information about the risks of having or developing specific organ damage. This suggestion and its usefulness in clinical practice should be verified by large prospective studies. The PA between men and women should also be compared in order to understand better the particular role of this simple hemodynamic parameter.

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Conflict of interest

Paolo Salvi is a consultant for PulsePen (DiaTecne s.r.l., Milan, Italy).

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VI.2.2. Conclusion de l'ARTICLE 4

L'intérêt principal de cette étude réside dans la calibration des ondes de pression. Nos résultats montrent que la mesure non invasive de la pression pulsée peut donner des valeurs très différentes selon la méthode de calibration employée. En particulier, nous avons trouvé une différence de 14 à 18 mmHg dans la mesure de la pression pulsée, qui est assez incompatible avec ce qu'on peut appeler une mesure authentique de la pression artérielle.

De plus, chacune des méthodes pour l'estimation de la pression moyenne présente des inconvénients.

Le candidat idéal à la méthode de l'aire sous la courbe est l'artère brachiale, parce qu'il est possible de mesurer à la fois la pression systolique et la pression diastolique à l'aide un tensiomètre, et la courbe de pression par tonométrie. La même procédure peut être appliquée à l'artère radiale, en supposant que la pression systolique mesurée par le brassard brachial soit égale à la pression systolique radiale. Cependant, des études ont montré qu'il existe une certaine amplification entre la pression brachiale et radiale, ce qui engendrerait une erreur.[104–106] Il faut aussi rappeler que la plupart des appareils tonométriques appliquent cette méthode.

Dans le cas de la pression brachiale, il existe un problème de faisabilité, étant donné que la compression de l'artère ne peut être réalisée de façon optimale. En effet les tissus sous-jacents à l'artère sont des tendons et des muscles, et donc par nature assez mobiles et plus souples qu'un os. D'autre part, l'assertion que les pressions systoliques brachiale et radiale sont comparables n'est pas étayée par des preuves scientifiques. Ceci fait que, dans la littérature, il existe encore aujourd'hui un débat à la fois sur la faisabilité de la tonométrie brachiale et sur la validité d'une mesure radiale.[107] Dans notre expérience, nous n'avons exclus aucun patient à

cause de la mauvaise qualité des courbes brachiales, et les écarts types des mesures brachiales étaient comparables à ceux des autres artères.

La mesure de la pression moyenne par formule mathématique, formules (15) et (16), contient un problème intrinsèque : on suppose que le *form factor*, et donc la forme de la courbe de pression, est fixé à 3 pour la (15) et à 2,5 pour la (16). En considérant la variabilité inter et intra individuelle de la forme de l'onde de pression, cette approximation a été sérieusement remise en question.[108]

Nos résultats ont montré que la mesure tonométrique de la pression artérielle dépend strictement de la méthode de calibration de l'onde de pression : c'est pourquoi le calcul de l'amplification de la pression pulsée, comme un rapport entre deux ondes de pression calibrées, pourrait dépasser cet obstacle parce qu'il donne une valeur indépendante de la calibration.

Enfin, nous avons montré que l'évaluation de l'amplification dans plusieurs territoires du corps humain pourrait avoir un grand intérêt. Premièrement, l'amplification augmente avec la distance entre les artères et, deuxièmement, l'amplification d'un territoire spécifique est corrélée à des facteurs cliniques particuliers. Notamment, la fréquence cardiaque était un déterminant commun à l'amplification carotidobrachiale et carotidoradiale. Cela semble indiquer que la fréquence cardiaque est associée à l'amplification du membre supérieur, en suggérant un rôle du système nerveux autonome, comme nous l'avons aussi montré.[109] Un autre facteur important est la présence d'un diabète, qui n'est associée qu'à l'amplification carotidobrachiale. Dans la pathologie diabétique on observe plus fréquemment une atteinte artérielle au niveau du membre inférieur qu'au niveau du membre supérieur ; de plus une étude, où la compliance artérielle a été mesurée chez des sujets diabétiques et des sujets contrôles, a montré que la compliance

fémorale, et non pas carotidienne ou brachiale, était réduite chez les diabétiques. Toutefois, l'amplification est un paramètre qui ne mesure pas directement la compliance, mais les effet combinés des ondes de réflexion et de la rigidité artérielle. On pourrait donc penser qu'en mesurant l'amplification carotidobrachiale et carotidoradiale on met en relation une artère centrale avec une artère périphérique, alors qu'avec l'amplification carotidofémorale et carotidopédieuse on analyse en effet l'aorte, et avec l'amplification fémoropédieuse on ne prend en considération que deux artères relativement périphériques. La raison pour laquelle l'amplification carotidobrachiale et l'amplification carotidoradiale se comportent différemment par rapport au diabète reste obscure, mais elle pourrait être due à la faible puissance statistique de nos analyses.

Au final, nous avons donc montré que dans la pratique clinique la procédure la plus exacte pour calibrer l'onde de pression n'a pas encore été découverte, et qu'il est très difficile de comparer des études cliniques qui utilisent différentes méthodes de calibration. En effet, nos résultats montrent que ces méthodes donnent des valeurs absolues de pression artérielle très différentes. L'application de l'amplification pourrait permettre d'étudier correctement le système hémodynamique, indépendamment de la méthode d'estimation de la pression moyenne. Par conséquent nous proposons : 1/ que l'amplification soit calculée par l'analyse des ondes de pression et non pas à l'aide d'un tensiomètre ; 2/ que les résultats des études cliniques qui analysent la pression centrale et l'amplification soient comparés en prenant en compte la méthode de calibration utilisée. Enfin, nous suggérons que l'évaluation de l'amplification dans différents territoires pourrait donner des

informations sur l'atteinte d'organes spécifiques. Ce dernier point devrait être confirmé par de plus larges études prospectives.

VII La mesure de la pression centrale par tonométrie d'applanation

Comme nous l'avons dit précédemment, la tonométrie d'applanation permet d'estimer la pression centrale selon trois modalités :

- tonométrie carotidienne directe ;
- tonométrie radiale :
    - indirecte, par fonction de transfert ;
    - directe, par analyse du deuxième pic systolique.

La tonométrie carotidienne permet d'obtenir la courbe de pression carotidienne et, après calibration, la pression systolique carotidienne. Or il est reconnu que : 1/ la carotide est considérée comme une artère centrale élastique ; 2/ les courbes de pression carotidiennes et aortiques sont superposables ; 3/ les valeurs de pression systolique sont semblables, avec des différences d'environ 2 mmHg.[110,111]

L'application d'une fonction de transfert à la courbe de pression radiale, calibrée par les pressions systolique et diastolique brachiales, a été validée depuis 1993.[112] La décomposition des ondes de pression radiales par l'analyse de Fourier, grâce à la conservation des propriétés d'élasticité des artères du membre supérieur, permet de dériver une onde de pression centrale. Cette méthode est appliquée principalement par le tonomètre SphygmoCor.

Sur les différentes figures que nous avons montrées, et en particulier la Figure 28, on peut constater que le début de la deuxième inflexion systolique de la courbe radiale est approximativement au même niveau de pression que le pic systolique central, comme rapporté par différentes études.[113–115]

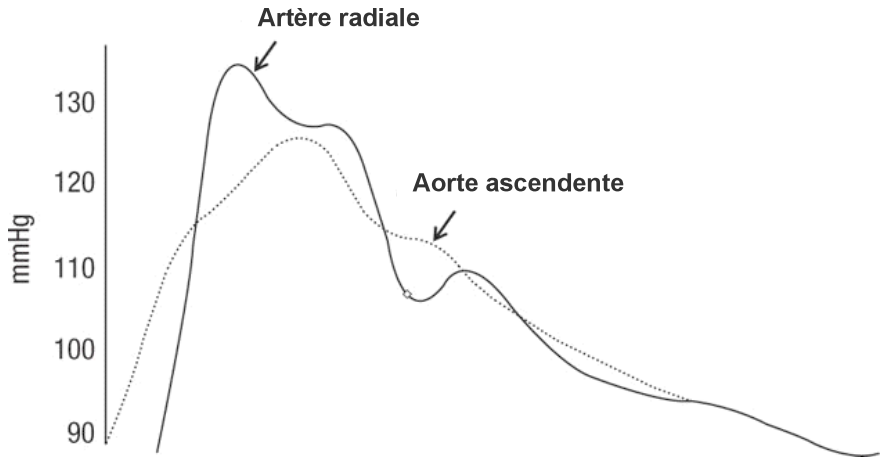

Figure 28. Courbes de pression radiale (ligne continue) et aortique (ligne pointilleé), d'après [80].

Une raison de cette association pourrait être que, comme on l'a vu à la page 127, le point d'inflexion dans la partie finale de la systole de la courbe radiale est dû aux réflexions provenant des membres inférieurs ; cette composante du pouls, une fois arrivée dans l'aorte, serait transmise ensuite dans le bras.[80] La méthode du deuxième pic systolique radial ne peut être appliquée que quand l'inflexion est effectivement visible sur la courbe radiale, ce qui n'arrive pas toujours. Dans le paragraphe suivant nous donnerons un exemple de l'application pratique de cette méthode.

VII.1. ARTICLE 5 : Le deuxième pic systolique radial : un succédané de la pression centrale ?[116]

VII.1.1. Introduction de l'ARTICLE 5

Cette étude porte sur 139 sujets recrutés consécutivement dans le Centre de Diagnostic, Hôpital Hôtel-Dieu, Paris. Les patients étaient âgés de 20 à 84 ans. Les critères d'exclusion étaient la présence d'une fibrillation auriculaire et une insuffisance cardiaque sévère.

Nous avons mesuré les paramètres anthropométriques (taille, poids, tour de taille et de hanche), et obtenu la pression brachiale par tensiomètre (SCVL, Paris, France).

Pour mesurer les courbes de pression aortiques, carotidiennes et radiales, nous avons utilisé deux appareils tonométriques, le SphygmoCor et le PulsePen, pour chaque patient.

La séquence des mesures avec les deux appareils a été randomisée, et deux opérateurs (un pour chaque appareil) ont réalisé la totalité des mesures.

Nous avons appliqué la même méthode de calibration de la courbe carotidienne : l'intégrale de la courbe radiale (pag.137). A partir des courbes radiales, nous avons calculé la pression au niveau du deuxième pic systolique. La pression aortique n'a été calculée qu'avec le SphygmoCor, à partir de la courbe radiale, par une fonction de transfert.

Sur les 139 patients inclus, 20 ont été exclus à cause d'une impossibilité à déterminer le deuxième pic systolique radial (6 pour le SphygmoCor et 14 pour le PulsePen), et 13 à cause d'une qualité médiocre des signaux carotidiens (10 pour le

SphygmoCor et 3 pour le PulsePen). Le nombre de patients analysés était donc de 106.

Le Tableau 4 présente les résultats de comparaison et les Figure 29 et Figure 30, les corrélations entre les différents paramètres.

Tableau 4. Comparaison entre les pressions systoliques centrales carotidiennes (cSBP), aortiques (aSBP), et calculées par le deuxième pic systolique radial (rSBP2), à partir du SphygmoCor (Sphy) et du PulsePen (PPen).

cSBP	rSBP2	Difference (aSBP or cSBP – rSBP2)	*P*-value
15.0	119.0 ± 17.4	1.2 ± 5.1	0.016
16.5	119.0 ± 17.4	2.6 ± 7.8	<0.001
17.2	115.8 ± 15.0	13.9 ± 8.5	<0.001
15.0	115.8 ± 15.0	4.4 ± 7.9	<0.001
16.5	115.8 ± 15.0	5.8 ± 9.4	<0.001
17.2	119.0 ± 17.4	10.7 ± 10.9	<0.001
²2	rSBP2	Difference	*P*-value
17.4	115.8 ± 15.0	3.2 ± 9.7	<0.001

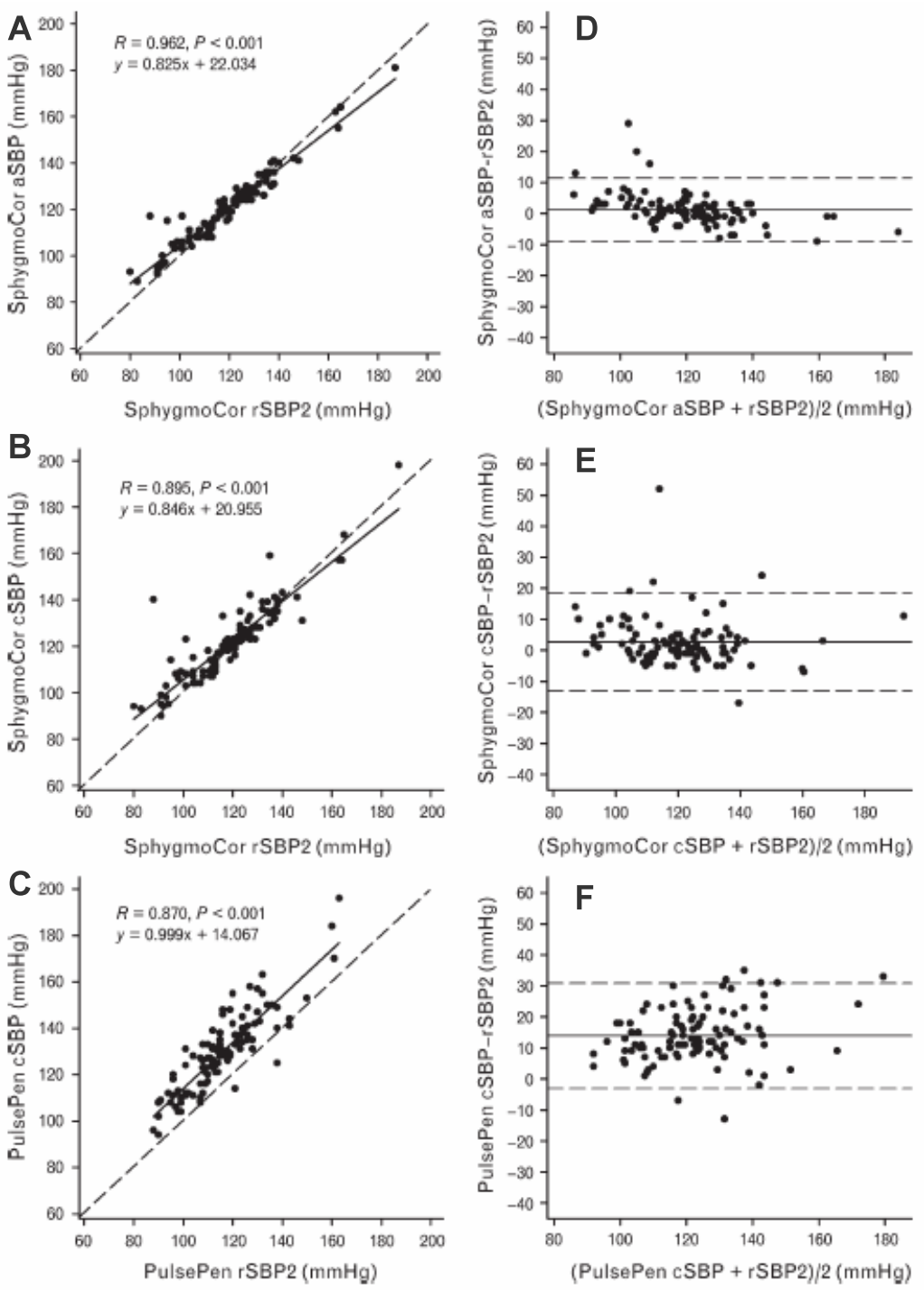

Figure 29. Graphiques de correlation entre les pressions systoliques aortiques (aSBP), carotidiennes (cSBP), et calculées par le deuxième pic systolique radial (rSBP2), mesurées par le SphygmoCor (A et B) et par le PulsePen (C) ; analyse de Bland Altman sur la droite (D, E, et F).

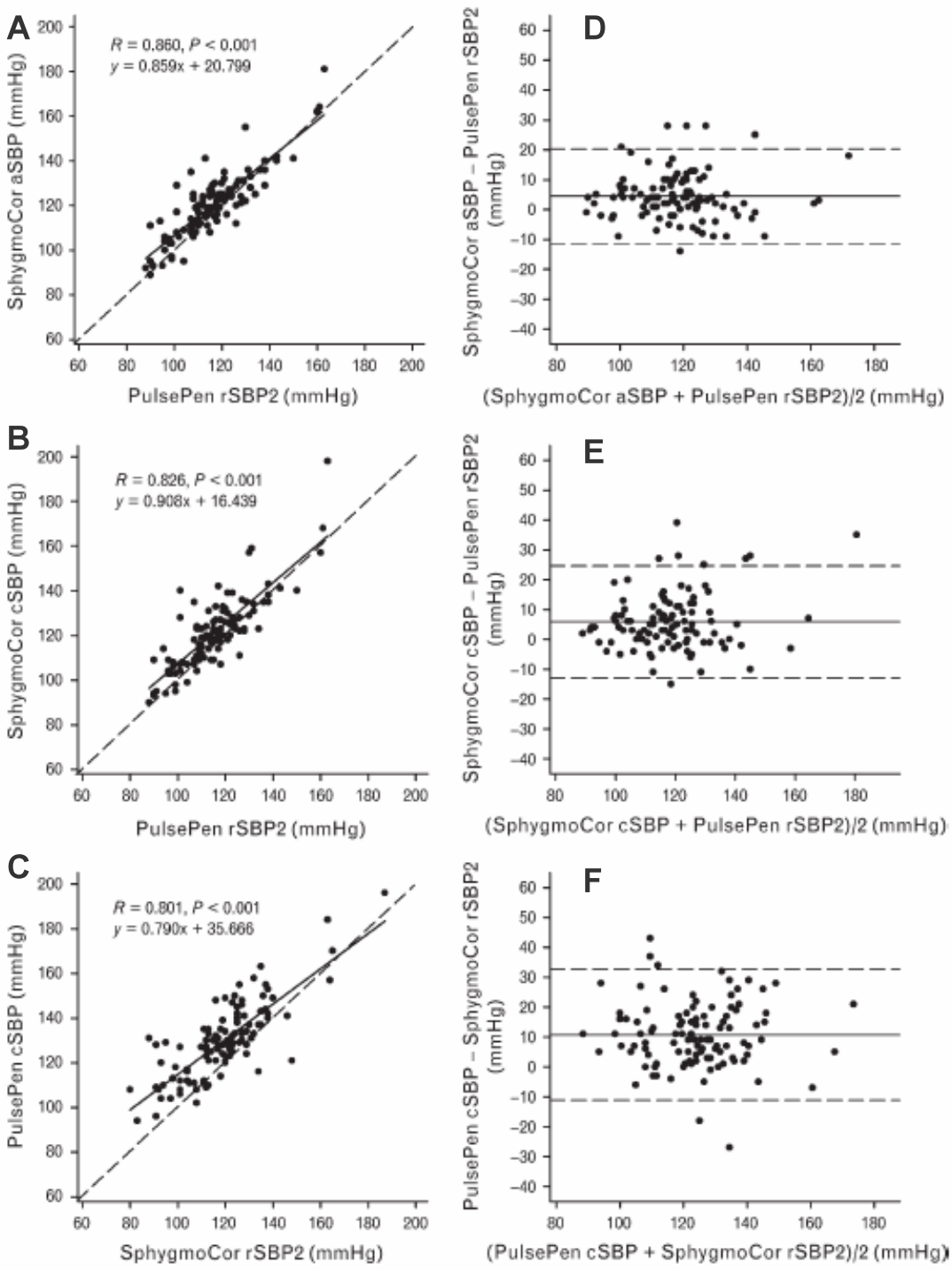

Figure 30. Graphiques de corrélation entre les résultats de SphygmoCor et de PulsePen sur les pressions systoliques aortiques (aSBP), carotidiennes (cSBP), et calculées par le deuxième pic systolique radial (rSBP2) (A, B, et C) ; analyse de Blant Altman sur la droite (D, E, et F).

Radial late-SBP as a surrogate for central SBP

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Background **Recent studies indicated that central SBP could be estimated by radial late-SBP (rSBP2) with a small disparity. However, most of these studies were conducted by SphygmoCor with a transfer function. The agreement between rSBP2 and central SBP was also tested in several invasive studies, but with inconsistent results. The objective of the present study was, therefore, to investigate whether rSBP2, from commercially available noninvasive devices, could practically indicate central SBP in current clinical care.**

Methods **We assessed carotid SPB (cSBP) and aortic SBP (aSBP) and rSBP2 by two broadly used tonometry-based devices, SphygmoCor and PulsePen, in 106 patients (57.5 ± 14.1 years) from our cardiovascular department.**

Results **In SphygmoCor and PulsePen, rSBP2 correlated well with aSBP and cSBP ($R>0.80$, $P<0.001$), but significantly underestimated them with a discrepancy ranging from 1.2 ± 5.1 to 13.9 ± 10.9 mmHg. The slopes of regression line in the correlation plots between the PulsePen rSBP2 and cSBPs from SphygmoCor and PulsePen were 0.91 and 0.99, respectively, and did not significantly differ from 1.**

Conclusion **PulsePen rSBP2 underestimated cSBP with a systematical but clinically substantial discrepancy, whereas SphygmoCor rSBP2 underestimated aSBP and cSBP with a nonsystematical but much smaller disparity. From a practical point of view, neither of these noninvasive devices can be applied for the precise estimation of central SBP with rSBP2 in clinical practice.** ***J Hypertens*** **29:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: central SBP, PulsePen, radial late-SBP, SphygmoCor, validation

Abbreviations: aSBP, aortic SBP; cSBP, carotid SBP; rSBP2, radial late-SBP

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Introduction

It is well accepted that, compared with brachial blood pressure (BP), aortic BP is a better predictor of cardiovascular events and mortality [1–3]. However, direct invasive BP measurement in the aorta cannot be widely used in routine risk assessment in clinical practice. Therefore, noninvasive devices, such as tonometry and oscillometry, were broadly used to estimate aortic SBP (aSBP) in most epidemiological studies and clinical trials. Generally, two principal methodologies were applied in these devices. As carotid SBP (cSBP) is only 1–2 mmHg higher than aSBP [4], one methodology is to measure carotid waveform directly, instead of aortic waveform. Another methodology is to derive the aortic waveform from the radial waveform recording by means of a generalized transfer function. However, carotid waveform recording requires technical expertise and operation training. Therefore, several investigators proposed a third methodology, which is to estimate aSBP with radial late-SPB (rSBP2) [5]. They also indicated the proximity of aSBP to rSBP2, with a disparity of about 1 mmHg in some population studies [6–9]. However, most of these studies were conducted by the SphygmoCor system (AtCor Medical, Sydney, Australia) with the transfer function. Other investigators applied the Omron HEM-9000AI system, but still used the SphygmoCor system as a reference [10].

Several invasive studies were conducted to test the agreement between rSBP2 and aSBP [8,9,11–13], but produced inconsistent results. For instance, Takazawa *et al.* [13] reported that rSBP2 from Omron device underestimated invasively measured aSBP by 11.7 ± 7.1 mmHg in 18 patients, whereas Hickson *et al.* [9] stated that, when rSBP2 from SphygmorCor and aSBP from a catheter were compared in 31 patients, only a discrepancy of 1 mmHg was observed. This disparity may be attributed to the different tonometry devices applied in these studies, or simply the application of the transfer function.

For that reason, we conducted the present study to investigate the agreement between rSBP2 and central SBP by two broadly used tonometry-based devices, SphygmoCor and PulsePen (DiaTecne s.r.l., Milan, Italy), in consecutive patients from our cardiovascular department. Our goal was to investigate whether rSBP2, from the commercially available noninvasive devices, can practically be a surrogate for central SBP in routine clinical care.

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Methods

Patients

A total number of 139 consecutive outpatients, aged from 20 to 84 years, were recruited (January–June 2010) from the cardiovascular department of Hotel-Dieu Hospital, Paris, France. Exclusion criteria included atrial fibrillation and severe heart failure [New York Heart Association (NYHA) class III–IV]. Informed consent was obtained from all participants.

Anthropometric and brachial blood pressure measurements

Body height, body weight and waist and hip circumferences were measured. BMI was calculated as body weight in kg divided by the square of body height in meters. Brachial BP was recorded twice by a validated oscillometric device (SCVL, Paris, France) after at least 5 min rest in the supine position, and averaged for further analysis.

Tonometry devices and determination of radial late-SBP

SphygmoCor v8.1 is a tonometry-based device, in which rSBP2 is determined automatically by the inbuilt software with the help of multidimensional derivatives. The aortic waveform is derived from the radial waveform with the application of a generalized transfer function. Additionally, in the present study, the carotid waveform was recorded directly by the applanation tonometry without any transfer function.

PulsePen is another high-fidelity applanation tonometer, in which no transfer function is applied and, therefore, no aSBP measurement is available. In the present study, the rSBP2 was determined manually in PulsePen and was defined as the third zero crossing point of the fourth derivative from the bottom to the top, as recommended by Takazawa *et al.* [11]. More details regarding PulsePen device are available in a previous publication [14]. The PulsePen software version 1.1.8d was used in this study.

Comparison procedure

The sequence of devices was randomized for each patient, and tonometric measurements were performed by two experienced physicians, with one specific for one device, at a single visit. Before measurement, brachial BP was obtained as mentioned above, and SBP and DBP were further used to calibrate the radial waveform. Carotid pressure waveform was then recorded and calibrated by radial DBP and mean BP, with the latter calculated by the radial area under curve method. aSBP was derived directly from radial waveform with the generalized transfer function (only available in SphygmoCor).

Table 1 Characteristics of participants ($n = 106$)

Variables	Mean ± SD
Age (years)	57.5 ± 14.1
Male sex, *n* (%)	60 (56.6)
Body height (cm)	167.5 ± 10.2
Body weight (kg)	76.5 ± 15.1
BMI (kg/m^2)	27.3 ± 4.9
SBP (mmHg)	134.7 ± 16.7
DBP (mmHg)	80.7 ± 9.2
Hypertension, *n* (%)	70 (66.0)
Coronary heart disease, *n* (%)	9 (8.5)
Diabetes, *n* (%)	19 (17.9)
Dyslipidemia, *n* (%)	37 (34.9)
Renal dysfunction, *n* (%)	9 (8.5)

The cardiovascular and metabolic diseases were defined by reviewing patients' medical history in documents.

Statistics

Quantitative and qualitative parameters were presented as mean value ± SD and absolute number with percentage in parenthesis, respectively. *T*-test was used to compare the absolute differences of hemodynamic parameters measured by SphygmoCor and PulsePen. Correlations of hemodynamic parameters and their mean value and differences were studied with Pearson's method and Bland–Altman plot. *Z*-test was applied to compare the slopes of correlation plots with 1. Statistical analysis was performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina, USA). *P*-value less than 0.05 was considered as statistically significant.

Results

We recruited 139 consecutive patients, and excluded 33 patients from analysis because of the failure to determine rSBP2 ($n = 6$ for SphygmoCor and $n = 14$ for PulsePen, respectively) and the failure to record carotid pulse

Table 2 Comparison between radial late-SPB and aortic SBP or carotid SBP from SphygmoCor and PulsePen

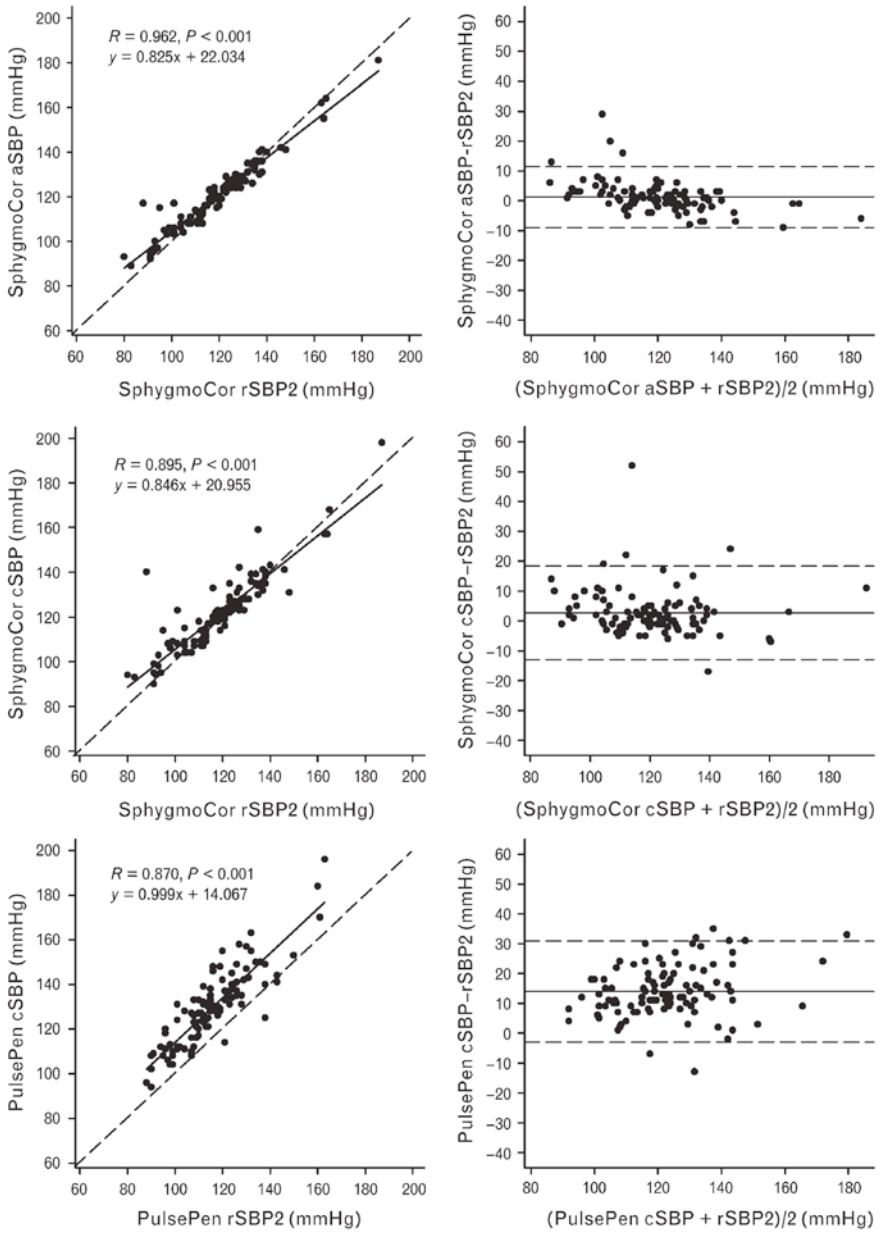
	aSBP or cSBP	rSBP2	Difference (aSBP or cSBP – rSBP2)	*P*-value
Sphy				
aSBP vs. rSBP2	120.2 ± 15.0	119.0 ± 17.4	1.2 ± 5.1	0.016
cSBP vs. rSBP2	121.6 ± 16.5	119.0 ± 17.4	2.6 ± 7.8	<0.001
PPen				
cSBP vs. rSBP2	129.7 ± 17.2	115.8 ± 15.0	13.9 ± 8.5	<0.001
Two devices				
Sphy aSBP vs. PPen rSBP2	120.2 ± 15.0	115.8 ± 15.0	4.4 ± 7.9	<0.001
Sphy cSBP vs. PPen rSBP2	121.6 ± 16.5	115.8 ± 15.0	5.8 ± 9.4	<0.001
PPen cSBP vs. Sphy rSBP2	129.7 ± 17.2	119.0 ± 17.4	10.7 ± 10.9	<0.001
	rSBP2	rSBP2	Difference	*P*-value
Sphy rSBP2 vs. PPen rSBP2	119.0 ± 17.4	115.8 ± 15.0	3.2 ± 9.7	<0.001

aSBP, aortic SBP; cSBP, carotid SBP; PPen, PulsePen; rSBP2, radial late-SBP; Sphy, SphygmoCor.

waveform ($n = 10$ for SphygmoCor and $n = 3$ for PulsePen, respectively). Therefore, the final number of participants was 106 in the present analysis. There was no significant difference in characteristics between the included patients ($n = 106$) and those excluded from analysis ($n = 33$). The characteristics of the analyzed participants are shown in Table 1.

In Table 2, absolute differences between rSBP2 and central SBP were compared in SphygmoCor and PulsePen in the normal and crosscheck modes. Generally, rSBP2 from both SphygmoCor and PulsePen consistently and significantly underestimated aSBP and cSBP ($P < 0.016$). The discrepancies varied from 1.2 ± 5.1 to 13.9 ± 10.9 mmHg, with the smallest disparity within the SphygmoCor system and

Fig. 1

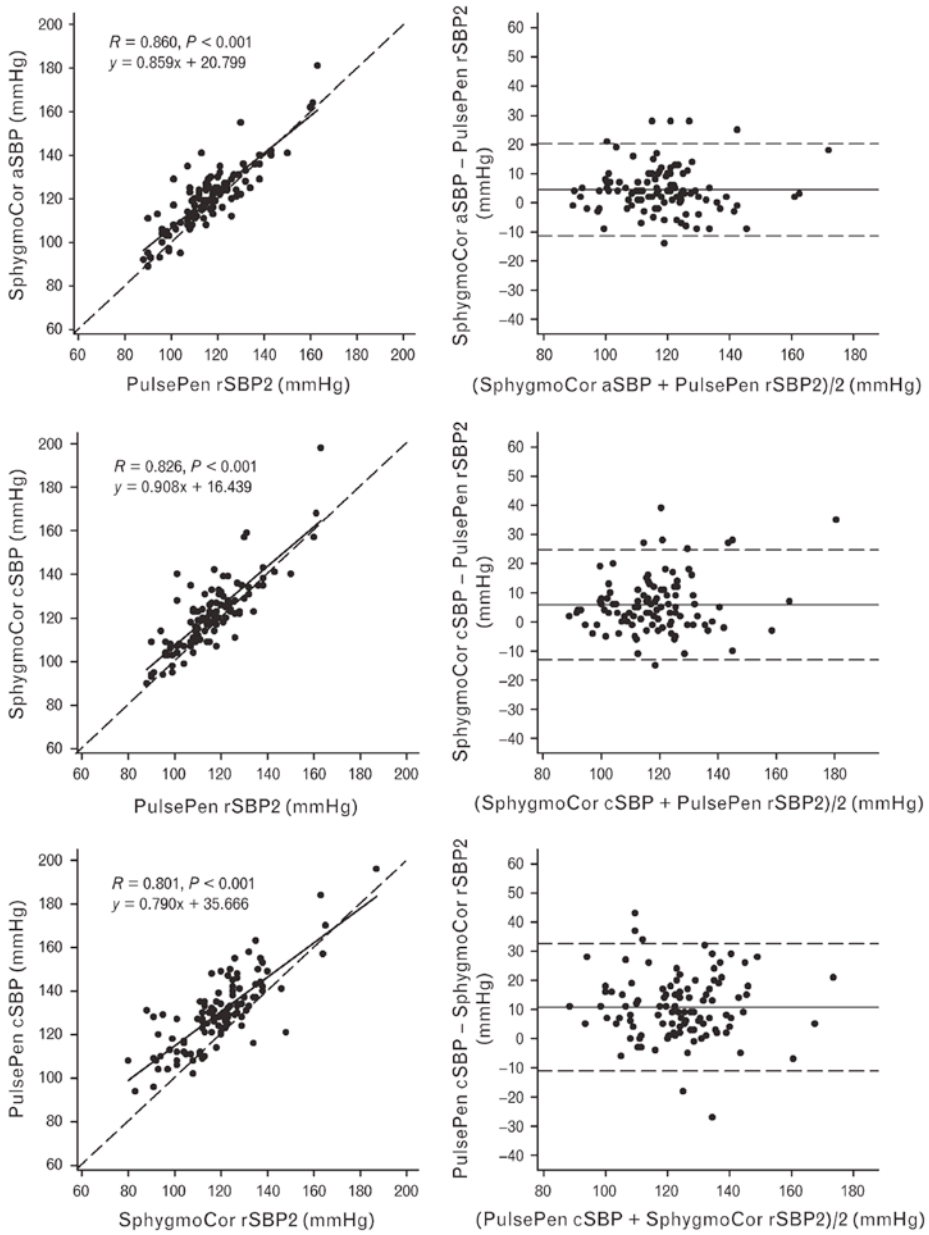


Correlation and Bland–Altman plots between radial late-SPB (rSBP2) and aortic SPB (aSBP) or carotid SBP (cSBP) from SphygmoCor and PulsePen. Correlations indexes in Bland–Altman plots for the SphygmoCor aSBP, the SphygmoCor cSBP, and the PulsePen cSBP are −0.491 ($P < 0.001$), −0.127 ($P = 0.196$), and 0.271 ($P = 0.005$), respectively.

the largest within the PulsePen system. The discrepancy of rSBP2 measured by the two devices also reached statistical significance (3.2 ± 9.7 mmHg, $P < 0.001$).

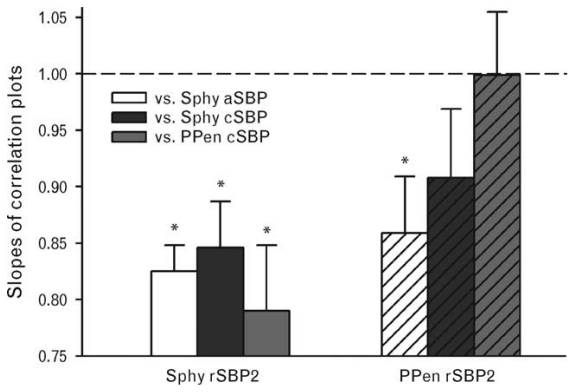
As shown in Figs 1 and 2, rSBP2 correlated well with central SBP within both SphygmoCor and PulsePen system, as well as in crosscheck modes ($R > 0.80$, $P < 0.001$). However, the slopes of the regression line in the correlation analysis between SphygmoCor rSBP2 and aSBP or cSBP were significantly different from 1 ($P < 0.001$), and ranging from 0.790 to 0.846. The corresponding values for PulsePen rSBP2 ranged from 0.86 to

Fig. 2



Crosscheck correlation and Bland–Altman plots between radial late-SPB (rSBP2) and aortic SPB (aSBP) or carotid SBP (cSBP) from SphygmoCor and PulsePen. Correlations indexes in Bland–Altman plots for the SphygmoCor aSBP, the SphygmoCor cSBP, and the PulsePen cSBP are −0.002 ($P = 0.981$), 0.167 ($P = 0.087$), and −0.023 ($P = 0.813$), respectively.

Fig. 3



Slopes of the correlation plots between radial late-SPB (rSBP2) and aortic SPB (aSBP) or carotid SBP (cSBP) from SphygmoCor (Sphy) and PulsePen (PPen). *Significant difference exists between 1 and slopes of correlation plots between rSBP2 and aSBP or cSBP derived from Sphy or PPen.

0.99, and the slopes between PulsePen rSBP2 and cSBPs from SphygmoCor and PulsePen were not significantly different from 1 ($P > 0.13$), but for SphygmoCor aSBP, the slope reached statistical significance ($P = 0.005$, Fig. 3).

Discussion

The main findings of the present study included the following observation: first, both in SphygmoCor and PulsePen, rSBP2 correlated well with aSBP and cSBP, but with a significant absolute underestimation of central SBP, especially in PulsePen; second, the slopes of regression line in the correlation plots between the PulsePen rSBP2 and cSBPs from SphygmoCor and PulsePen were nonsignificantly different from 1, indicating that only systematical underestimation existed when cSBP was estimated by PulsePen rSBP2. On the contrary, the estimation of central SBP by SphygmoCor rSBP2 had a nonsystematical underestimation.

In the present study, although close correlations were observed between rSBP2 and central SBP, both SphygmoCor and PulsePen had their own shortcomings. Specifically, the PulsePen rSBP2 significantly but systematically underestimated cSBP, indicating that the PulsePen rSBP2 is a good indicator of the change of cSBP, but with a clinically substantial discrepancy. On the contrary, in SphygmoCor, although with much smaller but significant disparity, a nonsystematical underestimation was detected, indicating that the SphygmoCor rSBP2 can not simultaneously reflect the change of central SBP. The differences between the two devices are mainly attributable to two factors. First, although tonometry was the only technique, and validated in both devices with the invasive method [4,14], the contours of recorded pressure waveform at radial and carotid sites were not exactly the same. Significant differences were observed between the two devices in radial and carotid form factors, as an indicator of the morphology of pressure waveform, with 33.4 ± 3.6 vs. $38.4 \pm 3.7\%$ ($P < 0.001$) and 41.0 ± 3.8 vs. $44.0 \pm 3.6\%$ ($P < 0.001$) for radial and carotid sites, respectively (data not shown). The determination of rSBP2 was based on multidimensional derivatives in both devices, but specifically, SphygmoCor rSBP2 was automatically determined by the second or third derivative with the help of the inbuilt software, whereas in PulsePen, this process was performed manually by the fourth derivative with the Takazawa's method [11].

There were several other epidemiological studies concerning the surrogate role of rSBP2 in central SBP estimation [5–10], most of which were conducted by SphygmoCor system with the transfer function. For instance, Munir *et al.* [8] reported that rSBP2 overestimated aSBP by 0.5 ± 5.0 mmHg in SphygmoCor in 391 patients. On the other hand, with Omron HEM-9000AI system, Richardson *et al.* [10] reported that, although no significant difference was observed between rSBP2 from Omron and SphygmoCor in 33 patients (104.6 ± 13.1 vs. 105.5 ± 13.5 mmHg, $P = 0.36$), the Omron rSBP2 significantly underestimated aSBP from Omron and SphygmoCor by 1.8 ± 4.3 and 13.9 ± 0.8 mmHg, respectively ($P = 0.02$, $P < 0.001$), which was in line with our findings. In literature, we noted that the close agreement between rSBP2 and aSBP was mainly observed in the SphygmoCor system, when the transfer function was applied. This cast some doubts upon the critical role of transfer function in the close association between aSBP and rSBP2. Recently, Matsumoto *et al.* [15] reported that the prognostic significance of the Omron rSBP2 was very limited in a middle-age Japanese population. Considering all these considerations we can hypothesize that the application of rSBP2 as a surrogate for central SBP is finally questionable, not only for technical feasibility, but also for clinical significance. Further study are undoubtedly warranted.

The lack of gold standard is the principal limitation of our investigation. However, the purpose of the present study is to investigate the application of rSBP2 as a surrogate for central SBP in current clinical care with commercially available devices, and not to test the accuracy of the rSBP2 in the hemodynamic laboratory, which has already been studied in several invasive investigations [8,9,13].

In summary, rSBP2 from SphygmoCor and PulsePen were closely correlated with central SBP, but with a significant discrepancy, especially in PulsePen. However, in PulsePen, a systematical underestimation of cSBP by rSBP2 was observed, whereas in SphygmoCor, this underestimation was not systematical. According to our findings and others, we concluded that, from a practical

point of view, neither of these noninvasive devices can be applied for the precise estimation of central SBP with rSBP2 in clinical practice.

Acknowledgement

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VII.1.2. Conclusion de l'ARTICLE 5

Dans cette étude, nous avons montré que les deuxièmes pics systoliques radiaux de SphygmoCor et de PulsePen sont strictement corrélés mais présentent des différences significatives. En particulier, le deuxième pic systolique donné par le PulsePen est fortement corrélé à la pression centrale avec une pente de corrélation très près de 1, mais avec une différence absolue remarquable. Par contre, le deuxième pic systolique radial obtenu par le SphygmoCor est corrélé à la pression systolique centrale, avec une différence absolue mineure mais avec une pente de corrélation plus basse.

Notamment, les deux appareils donnent des valeurs de *form factor* différentes à la fois pour l'artère radiale (33,4 ± 3,6 % PulsePen vs. 38,4 ± 3,7 % SphygmoCor, $p < 0.001$) et pour l'artère carotide (41,0 ± 3,8 % PulsePen vs. 44,0 ± 3,6 % SphygmoCor, $p < 0.001$).

VII.2. ARTICLE 6 : La comparaison de la mesure des ondes de pression par deux tonomètres (soumis à Am J Physiol Heart Circ Physiol)

VII.2.1. Introduction de l'ARTICLE 6

Dans l'étude précédente, nous avons observé des différences du deuxième pic systolique radial (*radial second systolic peak*, rSBP2) et du *form factor* (FF) entre les courbes de pression radiale obtenues par les deux tonomètres SphygmoCor (SCor) et PulsePen (PPen). Les sondes tonométriques des deux appareils ont été validées avec des signaux invasifs : le tonomètre Millar, utilisé par SphygmoCor, a été validé par Kelly et al. en 1989,[117] et celui de PulsePen par Salvi et al. en 2004.[118] Des différences de rSBP2 pourraient avoir des conséquences dans l'interprétation et la comparaison des études cliniques qui mesurent la pression centrale, en particulier quand ces valeurs sont utilisées pour calibrer les signaux carotidiens.

Puisque de nombreux appareils pour la mesure non invasive de la pression centrale (comme des sphygmomanomètres oscillométriques) sont de plus en plus validés avec la tonométrie d'applanation, et du fait de l'intérêt toujours grandissant pour les paramètres hémodynamique centraux, notre but est d'étudier en profondeur et de quantifier les différences potentielles entre les courbes de pression obtenues par SCor et PPen, ainsi que leurs conséquences sur les paramètres hémodynamiques centraux.

Les enregistrements des courbes de pression ont été réalisés sur les artères radiale et carotide par les deux appareils en succession aléatoire, après une mesure de pression brachiale par sphygmomanomètre pour chaque appareil, vu

l'impossibilité d'avoir deux mesures tonométriques contemporaines sur la même artère (Figure 31). Ensuite, afin de pouvoir comparer des courbes de pression avec des variations hémodynamiques minimes, on n'a utilisé que les mesures pour lesquelles il existait une variation de pression brachiale inférieure à 3 mmHg, et de fréquence cardiaque inférieure à 5 % entre les mesures des deux appareils. Parmi 178 patients consécutifs reçus au Centre de Diagnostic de l'Hôtel-dieu de Paris, seulement 40 remplissaient les critères hémodynamiques d'inclusion. Après 10 minutes de repos en position allongée, la pression brachiale a été mesurée par brassard oscillométrique (SCVL), suivie par 10 secondes d'enregistrement de signal tonométrique radial et carotidien avec le même appareil. La même procédure a été répétée avec l'autre appareil, après une deuxième mesure de pression brachiale. Afin de minimiser les biais potentiels dus au traitement du signal par les logiciels de SCor ou PPen, les courbes de pression ont été extraites sous format numérique et analysées par le logiciel MathLab (MathWorks, US). On a ensuite fait la moyenne des courbes de pression enregistrées pendant les 10 secondes, pour chaque artère et chaque appareil (Figure 31).

La courbe de pression radiale moyenne a été calibrée en amplitude par les valeurs moyennes de pression brachiale systolique et diastolique obtenues avant la tonométrie. Même si les variations de FC étaient inférieures à 5 %, les courbes de pression ont été aussi calibrées en temps par la FC moyenne afin d'obtenir une meilleure comparaison. Les pressions artérielles moyennes radiales (*radial mean arterial pressures*, rMAPs) de SCor et PPen ont ensuite été calculées comme l'intégrale sous la courbe de pression moyenne calibrée. Enfin, les deux courbes de pression de SCor et PPen ont été superposées selon le temps (Figure 31) et selon la fréquence (Figure 33A). Dans l'analyse selon le temps, la différence absolue entre

les deux aires sous la courbe a été calculée par l'erreur *mean root square* (RMS).[119] Le FF radial (rFF) a été calculé à partir des pressions systoliques, diastoliques et rMAPs, et le rSBP2 a été aussi calculé. Dans l'analyse en fréquence, les transformées de Fourier ont été utilisées pour comparer les modules des huit premières harmoniques.

Pour l'analyse carotidienne, les courbes moyennes carotidiennes de SCor et PPen ont été soumises à deux calibrations différentes. Le premier se base sur l'observation que la pression moyenne et la pression diastolique ne varient pas le long de l'arbre artériel en position allongée, et consiste à utiliser la rMAP d'un appareil et la pression diastolique brachiale pour calibrer la courbe carotidienne du même appareil, dans le but de comparer les pics systoliques (cSBP_scor et cSBP_ppen) et les index d'augmentation (AIx_scor et AIx_ppen) carotidiens des deux appareils.

La deuxième calibration a permis de quantifier les différences de forme des courbes de pression. On a donc forcé les courbes carotidiennes de SCor et de PPen à avoir la même amplitude en les calibrant avec la pression systolique, obtenue par la moyenne de c_SBP_scor et cSBP_ppen, et avec la pression diastolique brachiale. Les ondes de pression des deux appareils ont donc été superposées afin de calculer l'erreur RMS et le FF. On a fait ensuite une analyse en fréquentiel.

Quarante sujets ont rempli les critères hémodynamiques d'inclusion. Chez deux patients il n'a pas été possible d'obtenir des courbes carotidiennes de bonne qualité.

Un exemple de superposition des courbes radiales est montré dans la Figure 32A. Les résultats de la comparaison des ondes radiales montrent que l'erreur RMS était 2,7 ± 1,4 mmHg, quand la différence entre le rMAPs était de 1,5 ±

1,7 mmHg ($p < 0,001$), la courbe de SCor se trouvant au-dessous de celle de PPen chez 33 patients sur 38. Cette discordance s'accompagnait de différences d'autres paramètres hémodynamiques : le FF et le rSBP2 (tout $p < 0,01$).

Dans l'analyse en fréquentiel (Figure 33A), il n'existait une différence qu'entre les amplitudes de la première harmonique (0,38 mmHg, $p = 0,028$), de la troisième (0,17 mmHg, $p= 0,04$) et de la septième (0,16 mmHg, $p = 0,0001$).

Dans les Figure 32B et Figure 32C on retrouve un exemple de superposition des courbes carotidiennes de SCor et PPen avec les deux calibrations.

Avec la première calibration, l'erreur RMS était de 2,9 ± 1,5 mmHg, tandis que la différence entre les pics systoliques était de 2,7 ± 4,4 mmHg ($p < 0,001$), le pic de SCor étant inférieur au pic de PPen chez 31 patients sur 38. Par contre, il n'y avait pas de différence significative en cAIx et en FF.

Avec la deuxième calibration, l'erreur RMS était de 1,8 ± 1,3 mmHg. Etant donné que le FF et l'AIx sont des paramètres indépendants de la calibration, on ne retrouve pas de différences dans la deuxième calibration.

L'analyse en fréquentiel (Figure 33B) n'a montré de différence significative qu'entre les amplitudes de la première (0,87 mmHg, $p = 0,003$) et de la deuxième harmonique (0,45 mmHg, $p = 0,002$).

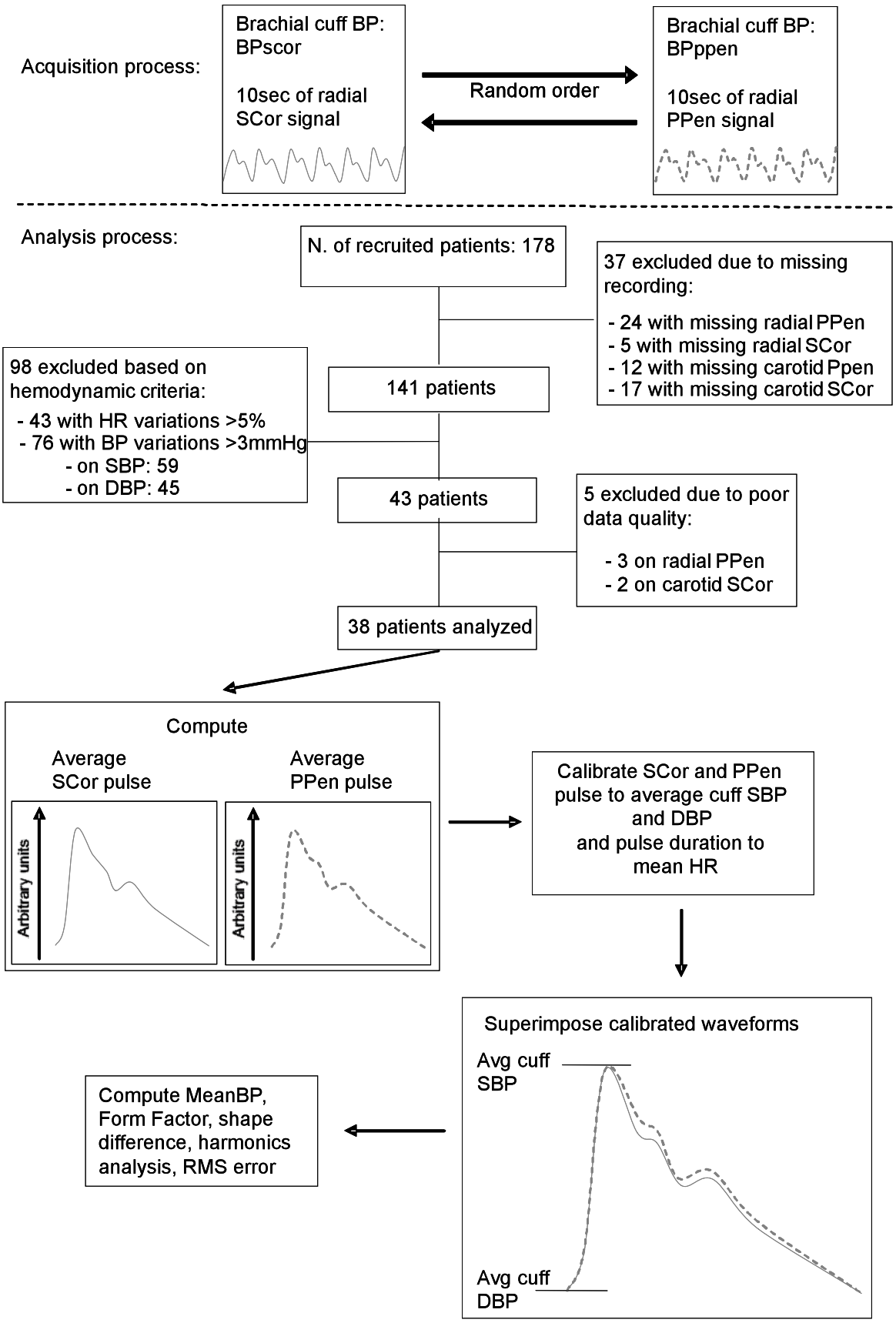

Figure 31. Processus d'analyse des courbes de pression radiales.

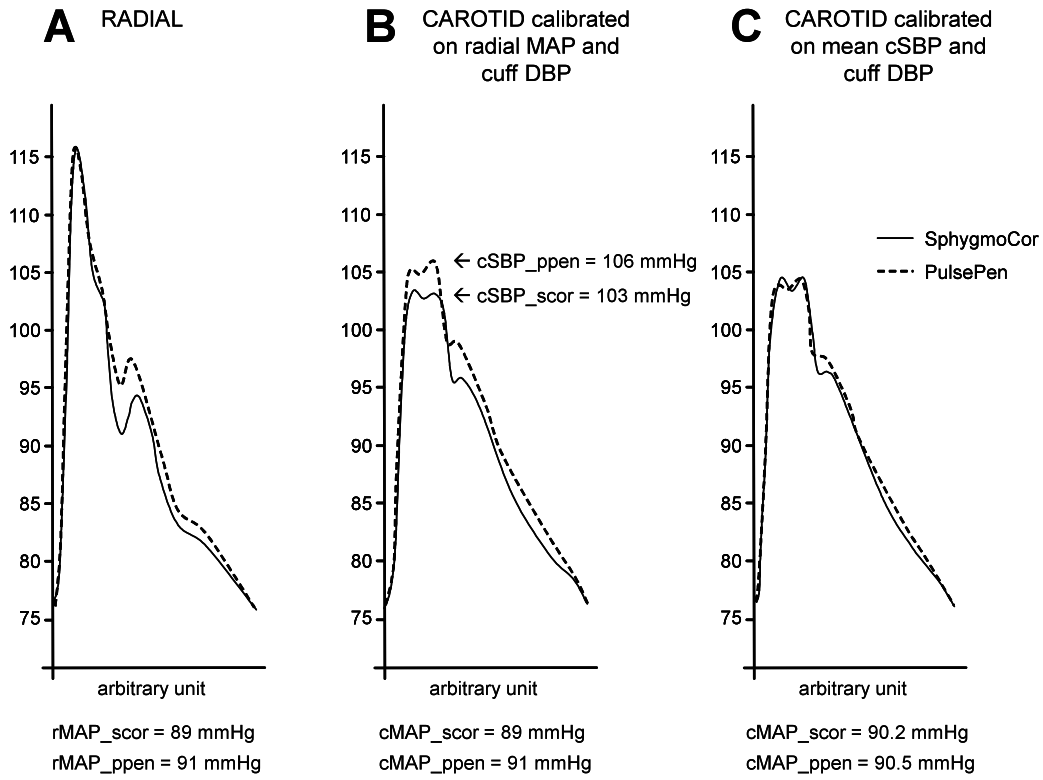

Figure 32. Exemple de courbes de pression du patient ID 64 (homme, 49 ans). Lignes continues : SphygmoCor (SCor) ; lignes pointillées : PulsePen (PPen). rMAP : pression artérielle moyenne radiale ; cMAP : pression artérielle moyenne carotidienne. cSBP : pression artérielle systolique carotidienne.

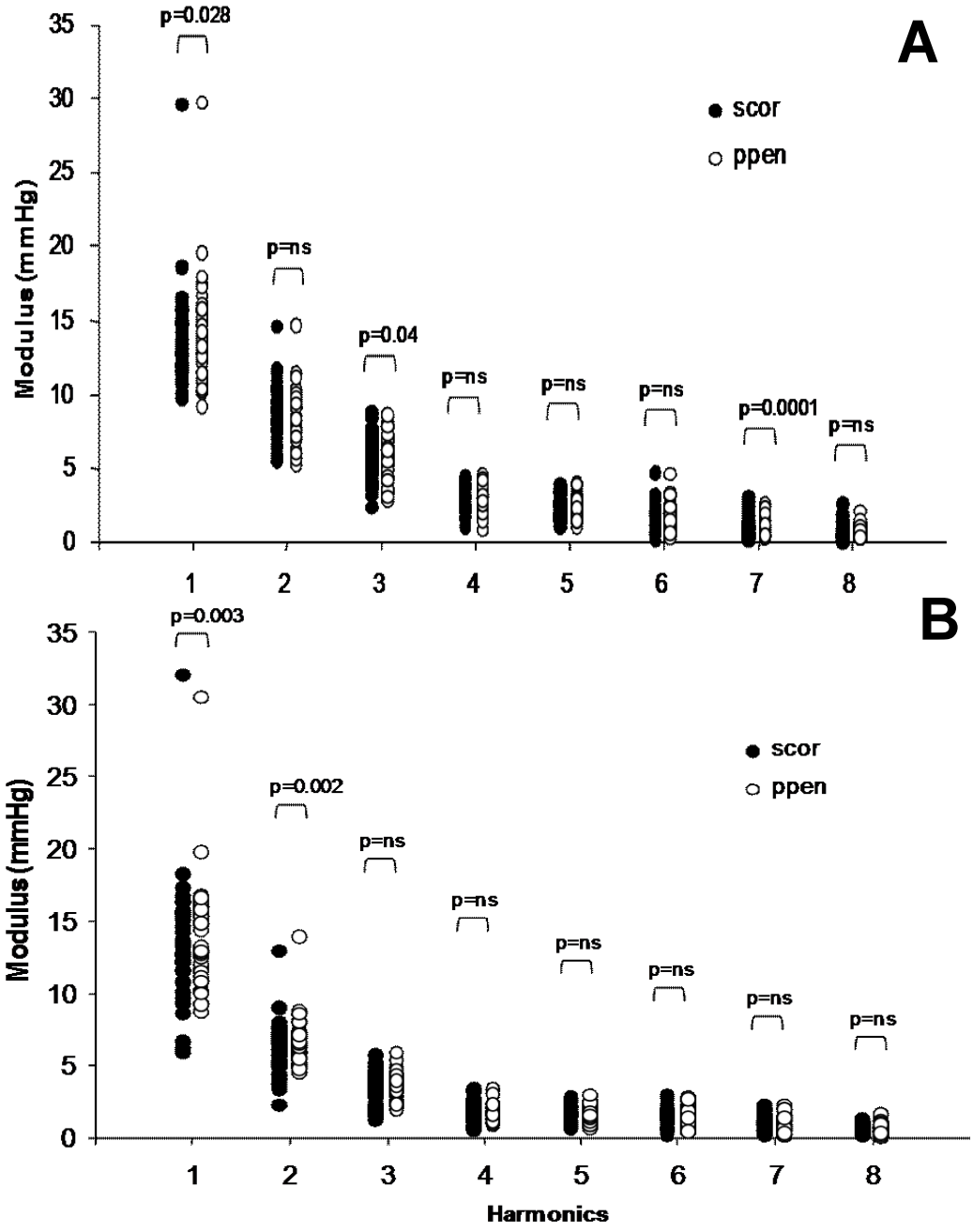

Figure 33. Décomposition de Fourier des courbes de pression radiales (A) et carotidiennes (B) de SphygmoCor (scor, points noirs) et de PulsePen (ppen, point blancs).

Pulse wave analysis with two tonometric devices: a comparison study

Short title: Pulse wave analysis comparison

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Conflicts of interest: Sandrine Millasseau works as a freelance specialist on pulse wave analysis and receives revenues from several medical devices companies including AtCor Medical whose device has been used in this study.
Davide Agnoletti has received funding from AtCor to attend a workshop.

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Abstract

Background and aim: Pulse wave analysis is a pivotal tool to estimate central hemodynamic parameters. Radial and/or carotid applanation tonometry is usually used to detect pressure waveforms. Available commercial devices have been validated against invasive catheterism, showing good agreement of harmonics pattern. In a previous investigation, we observed differences on radial second systolic peak (rSPB2) between two commonly used devices: SphygmoCor (AtCor, Australia) and PulsePen (DiaTecne, Italy). The aim of our study was to further quantify differences on radial and carotid signals from the two devices.

Methods: we measured radial and carotid pressure waveforms in 38 patients where systolic, diastolic blood pressure and heart rate presented minimal changes between measurements. Waveforms were digitally extracted for off-line analysis.

Results: rSBP2, mean arterial pressure, form factor and augmentation index were different with SphygmoCor providing lower values (mean differences: 2.2±3.8mmHg; 1.5±1.7mmHg; 3.2±3.5%; 4.2±8.4%, respectively). Carotid augmentation index and form factor were similar. However carotid systolic pressure (cSBP) from PulsePen was higher than cSBP from SphygmoCor (2.7±4.4mmHg, $p<0.001$). For both carotid and radial signals, harmonics moduli were similar across the spectrum with the exception of the 1st harmonic.

Conclusion: PulsePen and SphygmoCor sensors are not equivalent and provide different wave shape despite similar harmonics content. These differences on wave shape have important consequences on parameters computed from these waveforms with more discrepancy on radial derived parameters such as rSBP2 and mean arterial pressure than on carotid derived parameters. Further studies are required to compare invasive pressure parameters to indices derived from these 2 devices.

Short abstract

Pulse wave analysis (PWA) is usually performed by tonometry. In a previous study we observed differences in raw radial signals recorded by 2 commercial tonometric devices. This study aimed to further quantify these differences and evaluate their impact on carotid PWA.

Radial and carotid signals were recorded in 38 subjects in a strict stable hemodynamic state with the 2 devices. Radial mean pressure, late second systolic peak, augmentation index, and form factor were statistically different. On carotid traces, carotid systolic pressure and form factor were statistically different. Despite similar frequency content, commercial tonometric devices are not equivalent for PWA.

Introduction:

Recently, several technologies have been proposed to record non-invasive pressure waveforms (PWs) and apply signal processing to derive arterial parameters. High fidelity recording of pressure waveforms by arterial applanation tonometry has been widely validated. It allows estimation of systolic and diastolic blood pressures (BPs), of form factor (FF), an indicator of PW shape, and of the augmentation index (AIx), an index of reflected waves. Consequently, it has been possible to perform pulse wave analysis on large cohorts of patients. Particularly, central BP and aortic AIx have shown their clinical importance beyond standard cuff pressure measurements[1-5]. In order to obtain central systolic BP (SBP) by arterial tonometry, several methodologies can be applied. Pulse wave analysis can be performed directly on carotid PWs, as they are a good estimate of aortic PWs, with a mean difference of only 3 mmHg between aortic and carotid SBP[6, 7]. This methodology has been used in 3 of the 6 studies showing that central BP is a better predictor of mortality than standard cuff BP measurement [1, 3, 4]. Another technique consists in directly analyzing radial PWs after calibration and deriving central SBP from the late second systolic radial shoulder (rSBP2)[8-14]. A validated transfer function can also be applied on calibrated radial PWs to estimate central pressure curve[15-19].

In a previous publication[20], we observed differences in rSBP2 and FF between radial PWs obtained from the two commercially available tonometry devices SphygmoCor (AtCor, Australia) and PulsePen (Diatecne, Italy). Sensors from both devices have however been validated against invasive signals. The Millar tonometer used by SphygmoCor (SCor) has been validated by Kelly et al. in 1989[21], and PulsePen (PPen) system by Salvi et al. in 2004[22]. Discrepancies in radial rSBP2 and FF may be due to differences in PW between the two devices. This could have consequences on the interpretation and comparison of studies assessing central BP especially when these values are used to calibrate carotid signals.

Since many new non-invasive devices estimating central BP (like oscillometric cuff sphygmomanometers) are usually validated against non-invasive applanation tonometry, and in consideration of the growing clinical interest for central hemodynamic parameters, we aimed to investigate deeper the potential differences in PW recordings between SCor and PPen and their subsequent consequences on derived hemodynamic parameters.

Methods:

In 2010, 178 consecutive patients were recruited for a hemodynamic study in the setting of cardiovascular prevention of HIV infected patients. Eligible subjects were prospectively examined in the ambulatory department of cardiovascular prevention of Hotel-Dieu Hospital (Paris, France). Clinical information were obtained from patients, involving age, sex, weight, height, family and personal history of diseases, smoking habits, and pharmacological treatments.

Applanation tonometry was performed on radial and carotid arteries by PPen and SCor with the following methodology, also described elsewhere[23]. Firstly, brachial BP was obtained with a validated oscillometric cuff device (SCLV-2007 Cardio-Vascular Lab, HealthWorks, France) after 10-minute rest in supine position. Then, 10 seconds recording of radial and carotid PWs were obtained with one tonometric device, followed by a second brachial cuff BP measurement, radial and carotid recordings with the second tonometric device. PPen and SCor measurements cannot be performed simultaneously on the same artery, hence measurements were done successively and in random order.

To compare PWs with minimal hemodynamic differences, only data where brachial systolic and diastolic BP varied by less than 3mmHg between measurements done prior to both devices were used. Similar criteria were applied on heart rate (HR), for which a variation no greater than 5% was accepted. Eventually, to discard any analysis bias potentially introduced by PPen or SCor softwares, PWs were digitally extracted for further off-line analysis with MatLab (Mathworks, US).

Radial waveforms analysis:

For each subjects, and for each device, the average radial PW was computed from the 10 seconds recording. Then the average PW was calibrated in amplitude with SBP and diastolic BP (DBP) obtained from the mean of the two brachial cuff BP measurements. Despite HR variation smaller than 5%, PWs were also calibrated in time to the mean HR, in order to be better compared. Both SCor and PPen radial mean arterial pressures (rMAP) were calculated from the integration of the calibrated radial PWs. PPen and SCor radial PWs were superimposed in both time and frequency domain to assess wave shape agreement as explained on figure 1.

The time domain, superposition allowed to quantify the area between the 2 PWs with the root mean square (RMS) error [24]. The form factor (FF), which evaluates how "peaked" is the PW, was also calculated from rMAP, SBP and DBP, with the formula: rFF = (rMAP – DBP) / (SBP-DBP)*100 [24, 25]. rSBP2 and radial AIx (rAIx) were also calculated.

In the frequency domain, Fourier transforms were used to compare moduli of the first 8 harmonics.

Carotid waveforms analysis:

Similarly, averaged SCor and PPen carotid PWs were computed and calibrated in time to mean HR. Two calibrations methods were then used to further study the difference between the PWs.

The first calibration method corresponded the standard methodology generally used, based on the observation that mean and diastolic BPs are similar along the arterial tree in supine position [26-28]. Radial MAP and cuff DBP of SCor measurements were used to calibrate the carotid SCor PWs and rMAP and cuff DBP of PPen measurement to calibrate the carotid PPen PWs. Carotid SBP (cSBP_scor and cSBP_ppen) and carotid AIx (cAIx_scor and cAIx_ppen) were then measured and compared.

A second calibration methodology was used in order to quantify wave shape differences: in order to compare PWs without the influence of the calibration, we forced carotid PWs to have the same amplitude. PPen and SCor PWs were calibrated to the same amplitude with mean cSBP (= (cSBP_scor + cSBP_ppen)/2) and DBP. Carotid PWs were then superimposed to calculate the RMS error and the FF. Frequency analysis was also performed.

Statistics:

Statistical analysis was performed with MatLab (Mathworks, US). All variables were normally distributed. Paired t-tests were used to compare values obtained from SCor and PPen waveforms and on moduli from the frequency analysis. $P<0.05$ was taken as significant.

Results:

Out of the 178 consecutive patients, only 43 subjects fulfilled our strict hemodynamic inclusion criteria (figure 1): 37 patients were excluded due to the absence of one or more of the 4 tonometric measurements (radial or carotid with PPen or SCor). Of the remaining patients, 43 patients were excluded due to high HR variation, and 76 patients due to BP variation (figure 1).

Finally 5 patients were further excluded due to poor tonometric data quality (operator index lower than 80): 3 due to poor radial PPen and 2 due to poor carotid SCor PWs. Characteristics of the remaining 38 subjects are presented in table 1.

Radial artery

An example of superimposed radial PWs is shown in figure 2a. Results on the comparison of radial PWs (table 2) showed that the RMS error was 2.7 ± 1.4 mmHg ($p<0.001$ from zero), while the difference between the arithmetic mean radial pressures was 1.5 ± 1.7 mmHg ($p<0.001$), with radial SCor PWs being under PPen PWs in 33 out of 38 subjects. This discrepancy induced statistical differences between pulse wave analysis parameters: FF, rSBP2 and rAIx (all p value < 0.01; table 2).

In the frequency domain, only amplitude of the 1^{st}, 3^{rd} and 7^{th} harmonics were slightly different (0.38, 0.17 and 0.16mmHg for the difference on 1^{st}, 3^{rd} and 7^{th} harmonics moduli respectively, $p<0.05$, figure 3a). No difference was observed for the other harmonics ($p>0.05$).

Carotid artery

On figure 2b and 2c, an example of superimposed carotid PWs with the 2 calibration methodologies is presented. As expected, because carotid PWs were less “peaky” than radial PWs, cFF was higher

than rFF. The difference between cFF_scor and cFF_ppen was small and did not reach statistical significance (p=0.07, table 2).

With the first calibration method the RMS error was 2.9 ± 1.5 mmHg (p<0.001), and the error on cSBP reached 2.7 ± 4.4 mmHg (p<0.001), with cSBP_scor being lower than cSBP_ppen in 31 out 38 patients. The difference in cAIx was however not significant with a relatively large spread (-1.2 ± 5.9, p=0.22).

With the second calibration method, the RMS error was 1.8 ± 1.3 mmHg (p<0.001). As expected, we found the same results on FF and cAIx, because they are ratios, and hence are independent of calibration.

Figure 3b shows the frequency analysis of the carotid PWs with small difference on the 1st and 2nd harmonics (0.87 and 0.45 mmHg respectively, p<0.05) and no statistical difference for higher harmonics (p>0.05).

Discussion:

Our investigation on potential differences between SCor and PPen PWs showed that SCor tended to give lower value for integration of the carotid and radial curves than PPen, with significant differences in MAP, central SBP and FF between the two devices.

Carotid SBP

As standard carotid PW calibration is based on cuff diastolic and radial calculated mean pressures[24, 27], differences on rMAP could have a big impact on carotid BP [28, 29].

Indeed, we found that carotid PWs calibrated from their respective rMAP provided different cSBP (115 vs 118mmHg). This difference is significant even if relatively small and it fulfills the AAMI criteria for peripheral device validation [24]. However it could have impacts when comparing results or merging data from different studies. While central BP showed its superior predicting value compare to brachial cuff BP, no data are available to quantify the necessary central BP reduction required to have a benefit on cardiovascular risk. Hypertension trials have shown that small reduction of brachial BP of only a few mmHg can have a positive impact on cardiovascular risk. These results are likely to be

similar on central BP but as the size of this reduction is of the same order of the inter device variability great caution should be taken on the device used.

Augmentation index

After central SBP, the most used hemodynamic parameter is the AIx. Despite PW differences (difference in cFF), we found no difference in cAIx between the 2 devices. This is a rather surprising result which could be explained by the fact that carotid PW difference is smaller than the difference on radial PW (difference in FF 3.2 ± 3.5 for radial and 0.8 ± 2.8 for carotid, p=0.002)

Radial second systolic peak

rSBP2 has been used in several studies as an estimation of aortic SBP[8-14]. We found that using 2 different commercially available devices leads to small but significant differences on rSBP2 values (Δ=2.2 ± 3.8 mmHg) in selected patients with strict hemodynamic stability. This confirms our previous results[20] that rSBP2_scor and rSBP2_ppen are different. The difference in rSBP2 can be explained from the different wave shape because SCor radial PW is more “peaky” (lower FF) and usually lies under the PPen PW, giving lower calculated rMAP.

Both devices have been invasively validated. The Millar tonometer used in the SCor system has been compared to invasive radial pressure in 62 patients [21]. Good correlation was found between the moduli of the first 8 harmonics, even if the tonometer had a tendency to overestimate the 1st harmonic by 0.6 mmHg (p<0.0.2). Our results on radial PWs show as well good agreement in the frequency domain. There was statistically small discrepancy the 1st, 3rd and 7th harmonic (all <1mmHg).

The PPen sensor was tested in 10 patients undergoing coronography[22]. Non invasive PPen carotid traces were compared to invasive signals obtained at the initial tract of the same common carotid artery. They found no difference in the amplitude on the harmonics. We found a small (<1mmHg) but statistically significant difference for the 1st and 2nd harmonics only.

The SCor sensor validation study was performed in 1989 and only involved the tonometer. It is unknown if the manufacture and the characteristics of today commercialized SCor tonometer and whole system correspond exactly to what have been used in Kelly's study.

One could points out that Kelly and Salvi did not use the same arterial site to validate their sensor. Because radial and carotid PWs do not have the same shape and hence the same frequency content, this could influence the results. However, from our results, small apparently negligible differences on the frequency content, can lead to important wave shape differences. Despite similar harmonics content between the 2 devices on radial or carotid PWs, the shape and pulse wave analysis parameters were different, especially on the radial artery. Hence, our results suggest as mentioned previously[30] that harmonics analysis may not be sufficient to guaranty correct validation and superimposition of PWs. Errors on rSBP2 or cSBP were not negligible even when compared to its physiological range and on individual basis.

The reason why SCor traces tend to be lower than PPen traces is a bit difficult to understand. To obtain good quality signal, manufacturers needs to filter signals to remove 50Hz noise and also to reduce slow variations due to breathing or holding pressure. Differences in low frequency filtering, as suggested by the small difference on the amplitude of the low order harmonics, might contribute to explain the difference between the 2 devices.

Limitations and strengths

The most important limitation of our study is the absence of invasive PW as gold standard to compare to tonometric curves. Consequently, we cannot argue on which device provide the most accurate PWs, and this was not the aim of our work. The difference on central SBP between devices falls within the limits proposed by the AAMI for peripheral BP. Nonetheless, these criteria were not established for validating central BP measurements. Our results suggest that new criteria to validate central BP measurements are required. Taking into consideration the growing number of new devices, which are often validated against arterial tonometry, a protocol and fail/pass criteria to validate central BP is urgently needed [31].

The major strength of our investigation was that we selected only high quality pressure wave recordings with strict hemodynamic stability, guarantied from the limited allowed variations in BP and HR between measurements of the two devices.

Furthermore, the order of devices measurements was randomized. With these criteria, we were able to compare differences due to devices with no effect of physiological variations.

Further studies with invasive signals recorded simultaneously or, at least with strictly stable hemodynamic state, are required to conclude which device provides the correct PW. From our results we suggest that comparison between devices should not be performed in the frequency content only, but pressure analysis parameters should also be used to assess the between-device agreement.

Conclusion: PPen and SCor sensors are not equivalent and provide differences in wave shape despite similar harmonics content. These differences on wave shape have important consequences on pressure analysis parameters computed from these PWs with more discrepancy on radial derived parameters such as rSBP2 than on carotid derived parameters. Invasive studies, looking not only at central SBP, but also on the whole PW are required to validate devices measuring central BP. While waiting for these validations, comparisons or merging data from these 2 devices should be performed with great caution.

Table 1. Patients' characteristics (n=38).

Variables	Mean ± SD
Age, years	48 ± 8
Male gender, n(%)	34 (90)
Body Mass Index, kg/m^2	23 ± 3
Metabolic syndrome, n(%)	15 (43)
Systolic BP, mmHg	125 ± 18
Diastolic BP, mmHg	80 ± 13
Heart rate, bpm	72 ± 13

Table 2. Comparison of pulse wave analysis parameters.

		SphygmoCor	PulsePen	difference	p
RADIAL	rMAP (mmHg)	94.9 ± 14.9	96.4 ± 15.1	-1.5 ± 1.7	<0.001
	rFF (%)	33.9 ± 4.0	37.2 ± 4.6	-3.2 ± 3.5	<0.001
	rSBP2 (mmHg)*	110.2 ± 20.0	111.7 ± 20.9	-2.2 ± 3.8	0.001
	rAIx (%)	67.4 ± 17.8	70.9 ± 17.2	-4.2 ± 8.4	0.006
CAROTID calibrated on radial MAP and cuff DBP	cSBP (mmHg)	114.8 ± 19.1	117.5 ± 19.7	-2.7 ± 4.4	<0.001
	Form Factor (%)	43,6 ± 3.6	44.5 ± 4.0	-0.8 ± 2.8	0.07
	cAIx (%)	-4.1 ± 17.1	-2.9 ± 17.8	-1.2 ± 5.9	0.22
CAROTID calibrated on cSBP and cuff DBP	cMAP (mmHg)	95.5 ± 14.9	95.8 ± 15.0	-0.3 ± 1.1	0.08
	Form Factor (%)	43,6 ± 3.6	44.5 ± 4.0	-0.8 ± 2.8	0.07
	cAIx (%)	-4.1 ± 17.1	-2.9 ± 17.8	-1.2 ± 5.9	0.22

rMAP indicates radial mean arterial pressure; rFF, radial form factor; rSBP2, radial second systolic peak; rAIx, radial augmentation index; cSBP, carotid systolic blood pressure; cAIx, carotid augmentation index; cMAP, carotid mean arterial pressure; RMS, root means square (indicating the difference between the SCor and PPen waveform areas)
* SBP2 was not detectable in 3 subjects in one or both device.

Figure 1. Analysis process for radial traces.

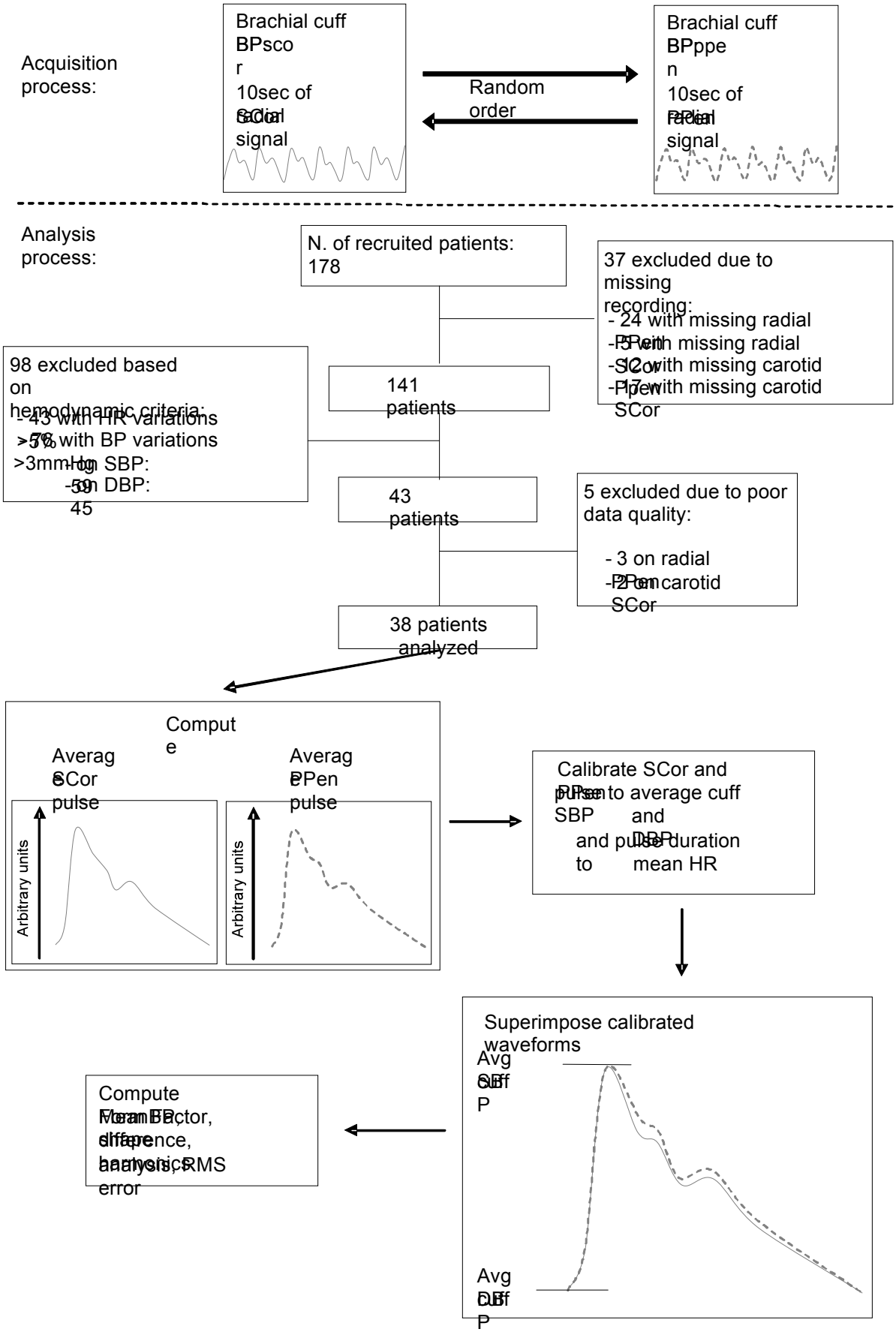
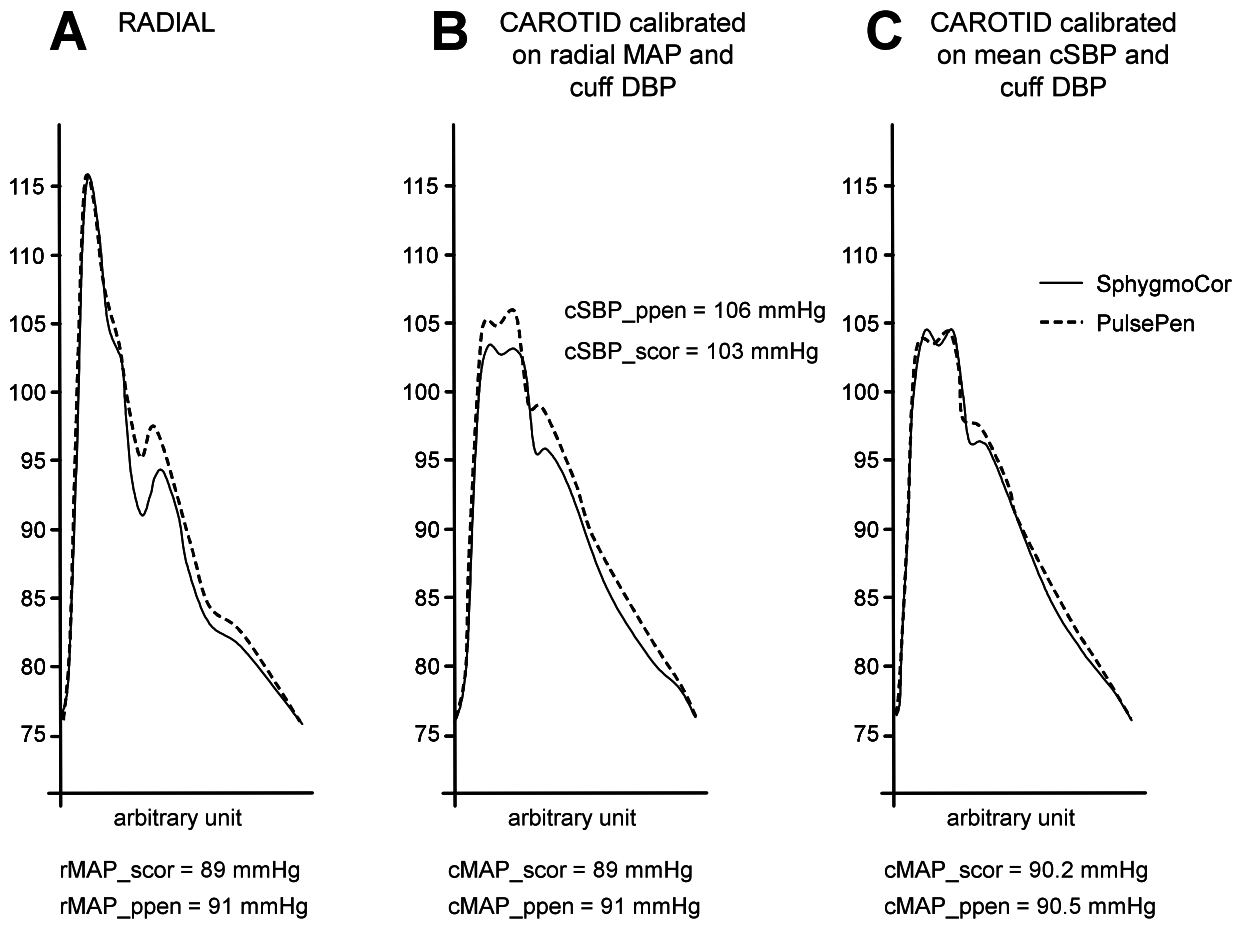


Figure 2. Example of waveforms from patient ID 64 (male, 49 years old).



Solid lines: waveforms from SphygmoCor device
Dash lines: waveforms from PulsePen device

Figure 3a. Fourier decomposition of radial waveforms.

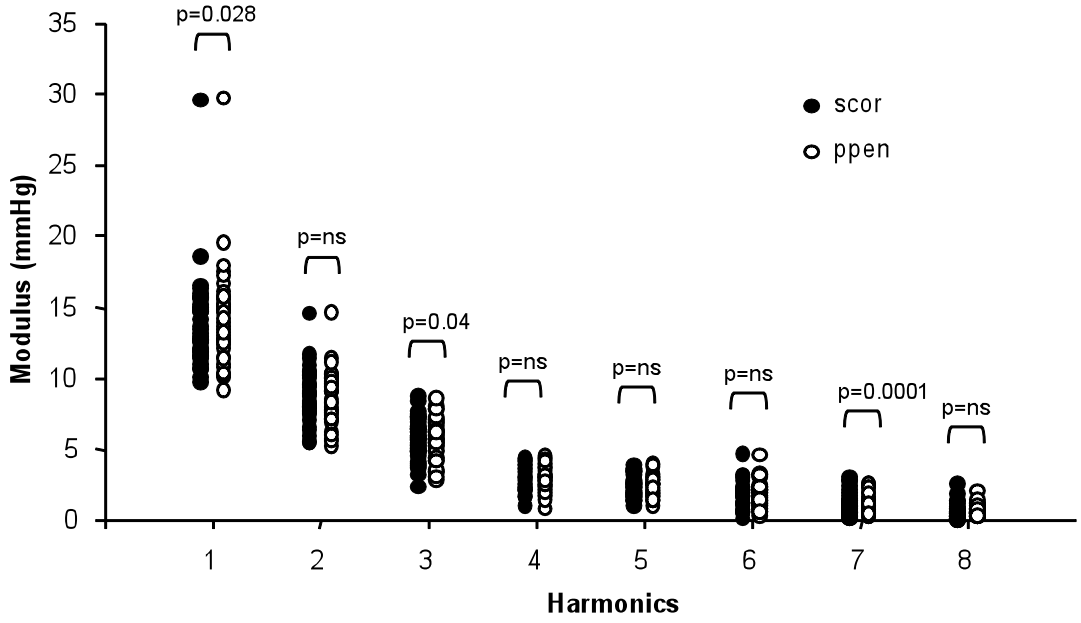
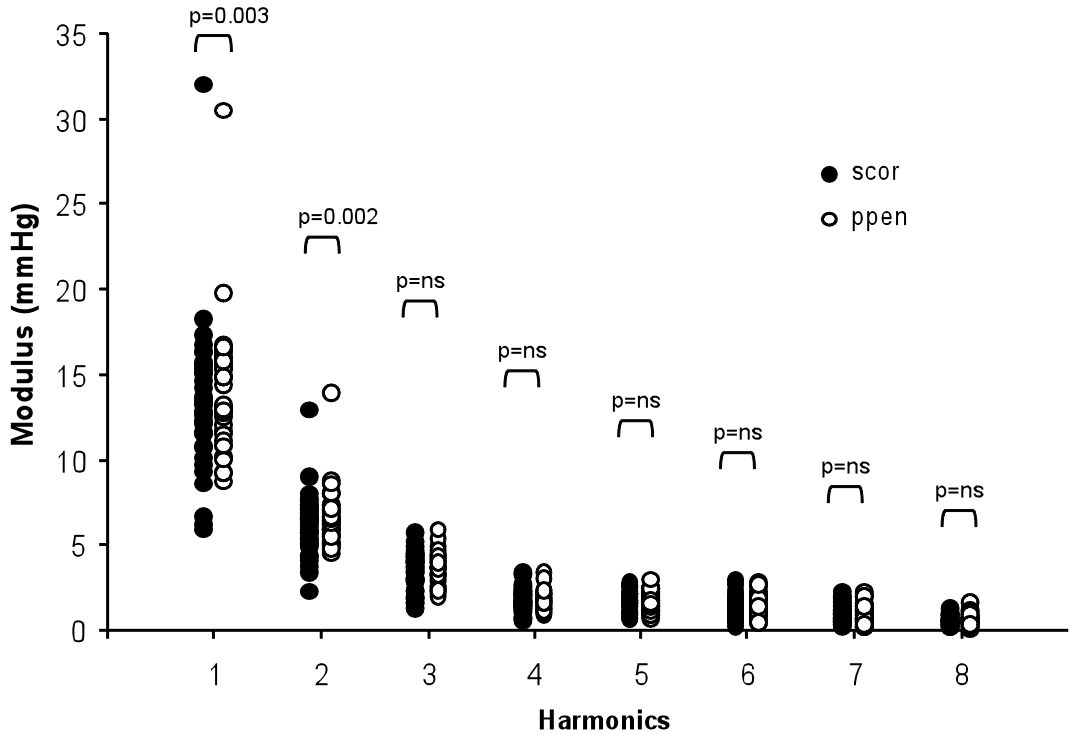


Figure 3b. Fourier decomposition of carotid waveforms.



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VII.2.2. Conclusion de l'ARTICLE 6

Notre étude sur les différences potentielles entre SCor et PPen en termes de courbes de pression a montré que le SCor a tendance à donner des valeurs de pression inférieures à celles du PPen, avec des différences significatives de pression moyenne, de pression systolique carotidienne et de *form factor* entre les deux appareils.

La calibration standard de la courbe carotidienne est basée sur la pression diastolique brachiale et la pression artérielle moyenne calculée à partir de l'intégrale de la courbe radiale. De ce fait, des différences de rMAP pourraient avoir une importance sur la détermination de la pression carotidienne. En effet, nos résultats montrent que les courbes de pression carotidienne calibrées par les rMAP correspondantes engendrent des valeurs différentes de pression systolique carotidienne (115 *vs* 118 mmHg). Cette différence, même si elle est relativement faible, en rentrant dans les critères de l'Association pour l'Avancement de l'Instrumentation Médicale (AAMI) pour la validation des sphygmomanomètres, est significative et pourrait avoir un impact si l'on compare les résultats ou regroupe les données des différentes études. De plus, des essais thérapeutiques interventionnels et observationnels sur l'hypertension ont trouvé qu'une réduction de pression systolique de quelques millimètres de mercure induite par les médicaments peut être considéré cliniquement significative. Ces résultats et les nôtres montrent qu'il existe une variabilité des mesures entre les appareils, cela pouvant présenter un intérêt clinique.

Après la pression systolique centrale, le paramètre hémodynamique le plus utilisé est l'index d'augmentation. Même s'il existe des différences de *form factor* radial, nous n'en avons pas retrouvé dans l'index d'augmentation carotidien entre les

deux appareils. Ceci est un résultat assez surprenant qui peut être expliqué par le fait que la différence entre les courbes de pression carotidienne des deux appareils n'était pas aussi prononcée que pour l'artère radiale.

Le rSBP2 a été utilisé dans de nombreuses études comme succédané de la pression systolique aortique. Nos résultats montrent qu'en utilisant deux appareils différents disponibles sur le marché, on retrouve des différences faibles mais significatives en rSBP2 (2,2 ± 3,8 mmHg) chez des patients très sélectionnés, avec une stabilité hémodynamique stricte. Cela confirme nos résultats précédents où les rSBP2 du SCor et du PPen étaient différents, cette différence pouvant être expliquée par la forme différente de l'onde de pression, la courbe de pression radiale de SCor étant plus « piquée » et se trouvant normalement au-dessous de la courbe du PPen, donnant des valeurs inférieures de rMAP.

Les deux appareils ont été validés par voie invasive. Le tonomètre Millar utilisé par SCor a été comparé avec un cathéter intra artériel chez 62 patients. De bonnes corrélations ont été retrouvées entre les modules des huit premières harmoniques, même si le tonomètre avait tendance à surestimer la première harmonique de 0,6 mmHg ($p < 0,02$). Nos résultats montrent aussi une bonne concordance au niveau de l'analyse en fréquentiel sur les courbes radiales : il y avait des petites différences (< 1 mmHg) sur la première la troisième et la septième harmonique.

La sonde du PPen a été testée chez 10 patients soumis à une coronarographie. Les tracés carotidiens non invasifs du PPen ont été comparés aux signaux invasifs obtenus au niveau du segment initial de la même artère carotide commune. Les auteurs n'ont pas retrouvé de différence dans l'amplitude des

harmoniques. Nous avons retrouvé une petite différence (< 1 mmHg) entre les premières et les deuxièmes harmoniques carotidiennes des deux appareils.

Le système du SCor a été validé en 1989 et seule la sonde tonométrique a été concernée par la validation. Or, on ne sait pas si la fabrication et les caractéristiques du tonomètre aujourd'hui sur le marché correspondent exactement à celles du tonomètre utilisé dans l'étude de Kelly.

On pourrait souligner que Kelly et Salvi n'ont pas utilisé le même site artériel pour la validation des sondes tonométriques. Le fait que les courbes de pression carotidienne et radiale ne présentent pas la même forme ni le même contenu en harmonique pourrait influencer les résultats. De toute manière, depuis nos résultats, les petites différences entre les harmoniques des appareils, apparemment négligeables, peuvent entraîner des différences importantes de forme de courbe de pression. Même si le contenu en harmonique était similaire entre les deux appareils, la forme de la courbe de pression et les paramètres hémodynamiques étaient différents, surtout dans l'artère radiale. Par conséquent, nos résultats suggèrent que l'analyse des harmoniques ne suffit pas à garantir une validation et une superposition correctes des courbes de pression.

Le fait que les courbes du SCor tendent à être inférieures à celles du PPen est compliqué à comprendre. Afin d'obtenir des signaux de bonne qualité, les fabricants ont besoin de filtrer les signaux. Cela permet, en effet, d'éliminer le bruit de fond causé par les fréquences de 50 Hz et de réduire les variations lentes de la courbe de base dues à la respiration ou à la pression manuelle. Des différences du filtrage des basses fréquences pourraient donc contribuer à l'explication des différences entre les deux appareils.

Finalement, nous avons montré que les sondes tonométriques du PPen et du SCor ne sont pas équivalentes et donnent des formes d'onde de pression différentes, en présence du même contenu en harmoniques. Ces différences ont des conséquences importantes sur les paramètres hémodynamiques calculés à partir de ces courbes, surtout en ce qui concerne l'artère radiale. D'autres études de comparaison invasive de courbes de pression semblent être importantes pour définir quel appareil produit des ondes de pression valides. L'analyse de comparaison devrait concerner la forme des ondes de pression et les paramètres hémodynamiques qui en résultent, au lieu de la seule analyse en fréquentiel.

Dans l'attente de validations ultérieures, il faut être prudent dans la comparaison ou le regroupement des données obtenues avec ces deux appareils.

VII.3. ARTICLE 7 : L'amplification et le traitement antihypertenseur : une application clinique[120]

VII.3.1. Introduction de l'ARTICLE 7

L'hypertension artérielle est un facteur de risque cardiovasculaire bien établi, et la pression artérielle brachiale le paramètre couramment utilisé pour sa définition et son traitement. Ces dernières années, la pression centrale a été aussi reconnue comme un paramètre très important dans le pronostic cardiovasculaire ; des études ont notamment montré sa supériorité par rapport à la pression brachiale.[121–123] De plus, depuis l'étude CAFE,[90] plusieurs études ont essayé d'évaluer le rôle des médicaments antihypertenseurs sur les modifications de la pression centrale par rapport à la pression périphérique.[124,125] L'amplification de la pression pulsée entre le bras et l'aorte ascendante est un paramètre qui pourrait permettre d'atteindre ce but.

Dans ce cadre, un médicament capable de réduire plus la pression centrale que la pression périphérique pourrait augmenter l'amplification, signe d'une action à la fois sur la rigidité artérielle et sur les ondes de réflexion, et être ainsi associé à un pronostic plus favorable.

L'étude Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT)[126] est une large étude randomisée, contrôlée, en double aveugle, comparant l'effet de trois médicaments antihypertenseurs *versus* placebo, après 12 semaines de traitement. Les molécules actives étaient : l'indapamide à libération prolongée (1,5 mg), le candesartan (8 mg) et l'amlodipine (5 mg). Cette étude a montré une plus grande réduction de la pression pulsée brachiale avec l'indapamide qu'avec les autres

molécules.[126] Cela nous a amenés à conduire une analyse sur l'effet de ces médicaments sur les paramètres hémodynamiques centraux.

L'étude X-CELLENT a recruté 1762 patients âgés de 40 à 80 ans présentant une hypertension essentielle. Tous les patients présentant une maladie coronaire, une insuffisance cardiaque, un accident vasculaire cérébral, une hypertrophie ventriculaire gauche, un diabète sucré ou une insuffisance rénale n'ont pas été inclus. Le traitement antihypertenseur en cours a été interrompu quatre semaines avant le début de l'étude.

Pour notre analyse nous avons sélectionné 76 hommes et 69 femmes (âge moyen 58,2 ± 10,7 ans) dont les mesures tonométriques carotidiennes et radiales étaient disponibles à la fois au baseline et après le follow-up.

Les courbes de pression ont été obtenues par le tonomètre Millar (SPT-301, Millar Instruments, Houston, TX), enregistré sur papier à 100 mm/s par l'appareil Gould 8188 (Gould Electronic, Boulanvilliers, France), et calibré par la méthode de l'intégrale de la courbe radiale. La vitesse de l'onde de pouls carotidofémorale a été obtenue par le tonomètre SphygmoCor.

Parmi les 155 patients inclus au baseline, un n'a pas terminé l'étude, neuf ont été retirés du fait de données manquantes ou de signaux tonométriques de mauvaise qualité. Les 145 patients restants ont été analysés.

Les trois médicaments actifs ont baissé la pression centrale par rapport au placebo, tandis que leur effet sur la pression brachiale n'était évident qu'au niveau de la pression diastolique, et, seulement pour l'amlodipine et l'indapamide, au niveau de la pression systolique. (Figure 34)

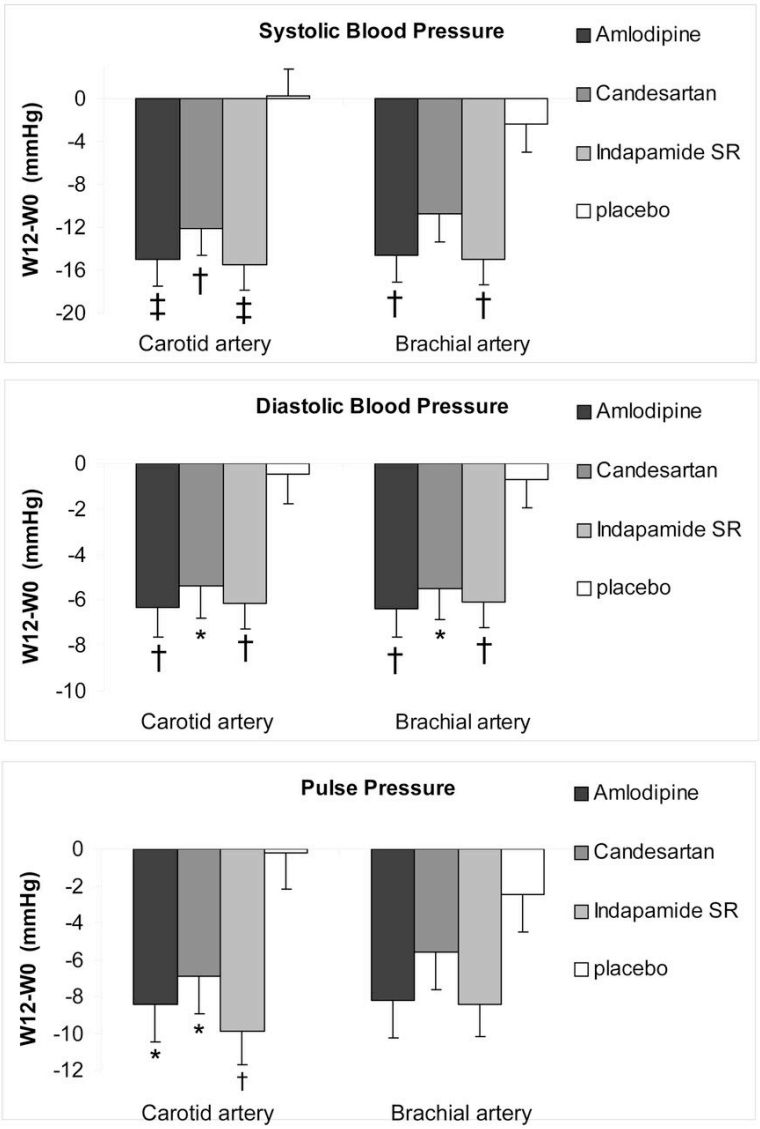

Figure 34. Représentation des modifications des pressions systolique (panneau supérieur), diastolique (panneau du milieu) et pulsée (panneau inférieur), par les trois médicament actifs et par le placebo.

La Figure 35 montre l'effet des médicaments sur l'amplification de la pression pulsée. Les trois médicaments actifs ont augmenté l'amplification : l'indapamide de façon significative par rapport au placebo (p = 0,02) ; le candesartan à la limite de la significativité (p = 0,07) ; l'amplodipine de façon non significative (p = 0,14).

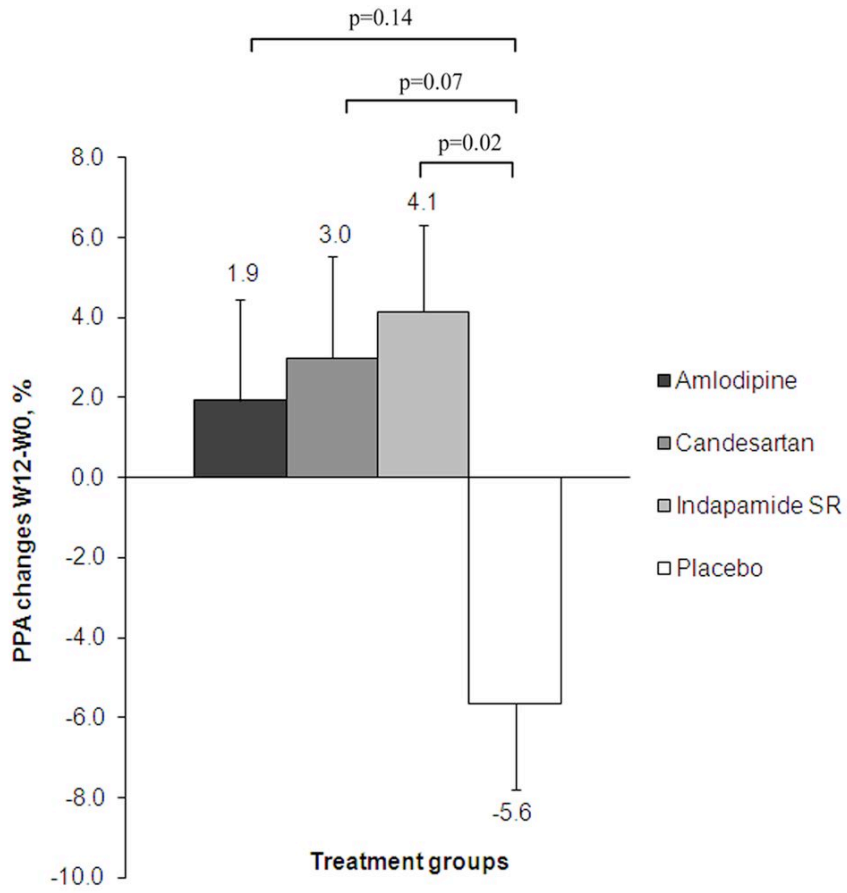

Figure 35. Modification de l'amplification de la pression pulsée par les trois médicaments actifs et par le placebo.

ORIGINAL ARTICLE

Effects of Antihypertensive Drugs on Central Blood Pressure in Humans: A Preliminary Observation

Davide Agnoletti,[1,2] Yi Zhang,[3] Claudio Borghi,[2] Jacques Blacher,[1] and Michel E. Safar[1]

BACKGROUND
Central blood pressure (BP) is considered a better predictor of cardiovascular events than brachial BP. Modifications of central, beyond brachial BP, can be assessed by pressure amplification, a potential new cardiovascular risk factor. Comparison between drugs' effect on central hemodynamics has been poorly studied. Our aim was to assess the hemodynamic effect of a 12-week treatment with amlodipine 5 mg, or candesartan 8 mg, or indapamide sustained-release 1.5 mg, in comparison with placebo.

METHODS
We analyzed 145 out-patients with essential hypertension in primary prevention enrolled in the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) study, a multicenter, randomized, double-blinded, placebo-controlled trial. Arterial stiffness, central BP, pressure amplification, and wave reflection were measured by applanation tonometry.

RESULTS
Baseline characteristics of patients were homogeneous between groups. After treatment, we found that active drugs produced similar reduction of both central and peripheral BPs, with no significant interdrug differences (all $P < 0.05$; excluded peripheral pulse pressure, compared with placebo). Second, amlodipine (1.9% ± 15.3%), candesartan (3.0% ± 14.6%) and indapamide (4.1% ± 14.4%) all increased pulse pressure amplification, but only indapamide was statistically different from placebo ($P = 0.02$). Finally, no significant changes were observed on pulse wave velocity, heart rate, and augmentation index.

CONCLUSIONS
The 3 antihypertensive drugs similarly reduced peripheral and central BP, as compared with placebo, but a significant increase in pulse pressure amplification was obtained only with indapamide, independently of arterial stiffness modifications.

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Keywords: antihypertensive agents; arterial stiffness; blood pressure; central blood pressure; hypertension; pressure amplification; wave reflection.

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Because hypertension is a well-known reversible cardiovascular (CV) risk factor, systolic blood pressure (SBP), and particularly brachial SBP, is considered the best guide for antihypertensive treatment.[1] More recently, central SBP has become a more important objective for CV risk assessment than brachial SBP.[2] It has been shown that central (aortic or carotid) blood pressure (BP) is normally lower than peripheral (e.g., brachial) BP, and many studies have shown a consistent relationship between central SBP and CV mortality, as well as the potential for some drugs to lower central SBP beyond brachial SBP.[3]

Whereas mean arterial pressure and diastolic BP (DBP) remain almost constant along the arterial tree, SBP and pulse pressure (PP) markedly increase from the central thoracic aorta to the peripheral arteries. This phenomenon, called SBP or PP amplification (PPA),[4] can be calculated as a ratio of peripheral to central SBP or PP[5] and is due to the transit of the reflected waves along the arterial tree, together with the progressive increase in vessel stiffness and the corresponding reduction of arterial diameter. PPA is important to be considered because it is an independent CV risk factor,[6,7] and there is growing interest in its pharmacologic modification. Thus, many drug classes have been studied to establish their role in reducing central SBP and PP and in modifying systolic and PPA.[3]

The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) study[8] is a large, randomized, controlled, double–blind investigation that compared the effect of placebo vs. 3 different antihypertensive agents: indapamide sustained-release (SR) 1.5 mg, a thiazide-type diuretic; candesartan 8 mg, an angiotensin II receptor blocker; and amlodipine 5 mg, a long-acting calcium channel blocker. This study showed a lesser reduction of brachial ambulatory 24-hour DBP under indapamide SR than under the 2 other agents and hence a greater reduction of PP. The effect of indapamide SR

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on PP reduction suggested a particular modification of the mechanical arterial properties, leading to this analysis.

The aims of this study were, first, to assess by arterial applanation tonometry the differential effects of the 3 antihypertensive drugs (amlodipine, candesartan, indapamide SR) on peripheral and central BP; second, to focalize on the drug contribution to PPA modification; and, third, to focalize on the mechanisms leading to these effects, in particular investigating the respective roles of arterial stiffness and wave reflection.

METHODS

Study design and patients population

The X-CELLENT study, which has been described in a previous publication,[8] was a multicenter study that included 1,762 patients (50.7% men) aged 40–80 years. All patients had essential hypertension, with either SBP of ≥150 to <180 mm Hg and DBP of ≥95 to <110 mm Hg or SBP of ≥160 to <180 mm Hg and DBP of <90 mm Hg according to the presence of isolated systolic or systolic–diastolic hypertension. Patients with a history of coronary artery disease, heart failure, stroke or transient ischemic attack, left ventricular hypertrophy, diabetes mellitus (type 1 or type 2), and renal failure were not included in this study. Lipid- or uric acid–lowering agents as well as low-dose (<350 mg/d) aspirin were permitted; other treatments that might affect BP were not allowed. Previous antihypertensive treatment (prevalence of 34%) was interrupted for 4 weeks before randomization. For our investigation, we selected 76 male and 69 female patients of mean age of 58.2 years (SD = 10.7), who presented the following 3 main conditions: they underwent 2 tonometric analyses, one before (W0) and one after (W12) drug administration; each tonometric examination included both radial and carotid measurements; and a single antihypertensive agent (indapamide SR or candesartan or amlodipine or placebo) was given after randomization. The study protocol was approved by the responsible ethic committees in each country, and all patients willing to participate gave their written informed consent.

Hemodynamic measurements

Tonometry. Radial and carotid artery applanation tonometry by a high-fidelity Millar probe (SPT–301; Millar Instruments, Houston, TX) was performed as described elsewhere in detail.[9] Briefly, the derived pressure waveforms were recorded on a Gould 8,188 recorder (Gould Electronic, Boulainvilliers, France) at a paper speed of 100 mm/s. Radial pressure waveform calibrated from brachial SBP and DBP was used for determination of the mean BP via application of an integration method. Mean and diastolic BPs were used to calibrate carotid pressure waveform and calculate PP and SBP, which are known to be close surrogates for aortic PP and SBP. Carotid augmented pressure (AP) was measured by locating the shoulder of the carotid curve in its upward part (corresponding to the crossing point of the reflected wave) and then taking the pressure value at this level and subtracting it from the SBP value.[10,11] Augmentation index (AIx) is AP divided by carotid PP, expressed in percent. PP amplification was calculated as brachial PP didvided by carotid PP (arbitrary unit).[10,11]

Pulse wave velocity. Carotid–femoral (aortic) pulse wave velocity (PWV) was determined using the SphygmoCor device (AtCor Medical, Sydney, Australia) using the foot-to-foot method. Analysis of reproducibility can be found in previous publications.[12]

Safety and acceptability. Safety and acceptability were assessed in terms of adverse events reported at each visit and by using clinical signs and examinations, including body weight, heart rate (HR), and laboratory tests. Adherence to treatment was evaluated by direct questioning and tablet and capsule count at each visit.

Validation and reproducibility. To assure high-quality hemodynamic measurements and to reduce between-center variability, each recruitment center passed a certification procedure before including patients. This consisted of performing high-quality radial and arterial tonometry measurements in at least 90% of 20 patients. Then, for each included patient, a real-time validation of tonometric measurement was done by the reference center (Fleury-Merogis, France). Reproducibility data in the reference center were interobserver and intraobserver correlation for carotid pulse wave contour (r = 0.96 and 0.97, respectively; 5.3% ± 3.6% for PWV; and difference on carotid AIx of 4.1% ± 2.5%).[13,14]

Statistical analysis

Statistics were performed with SAS software version 9.0 (SAS Institute, Cary, NC). $P \leq 0.05$ was considered statistically significant. Mean values (SDs) are presented. We compared the 4 groups of patient at W0 and W12 (or last value obtained) with respect to the difference in quantitative variables by analysis of variance and qualitative variables by the χ^2 test. P values for trend across treatment groups were generated by the analysis of covariance (ANCOVA) for the change from baseline values (W12 – W0). This analysis is adjusted for W0 values and recruitment center. This method is well described in literature and provides solid results even if imbalance at baseline is present.[15]

When significant trends across groups were found for W12 – W0 by the ANCOVA, a test to investigate differences between groups was done. The priority analysis was the Dunnett multiple comparison test, performed to investigate differences between each active drug and placebo. A secondary analysis was the Bonferroni test to compare each treatment group vs. each other. Analyses on PPA W12 – W0 were also adjusted for changes in mean arterial pressure and HR between W0 and W12.

RESULTS

Of the 155 subjects studied at baseline, 1 did not reach the end of the trial and 9 were withdrawn from statistical evaluation because of missing or poor-quality

pressure measurements at W12 (Figure 1). The remaining 145 patients were divided into 4 groups according to drug treatment (Table 1). Age, sex, body weight and height, and distribution of previous antihypertensive therapy did not differ significantly across the 4 groups (P_{trend} for all > 0.1) (Table 1).

Brachial and carotid BP measurements

Concerning the ANCOVA test across treatment groups for brachial BP (Table 2), we found that at W0 only SBP presented a significant trend among the groups ($P = 0.02$), whereas DBP, PP, and HR were similar (all $P > 0.12$). At W12, a significant trend is shown for SBP and DBP (all $P < 0.01$) but not for PP and HR ($P > 0.5$). For W12 – W0, we found a significant trend for SBP and DBP ($P = 0.005$ and $P = 0.001$, respectively).

ANCOVA tests for carotid BPs are also shown in Table 2. At W0, no significant trends were found across treatment groups for SBP ($P = 0.06$), DBP ($P = 0.06$), and PP ($P = 0.45$). At W12 and for W12 – W0, there were significant trends for SBP, DBP, and PP (all $P < 0.01$).

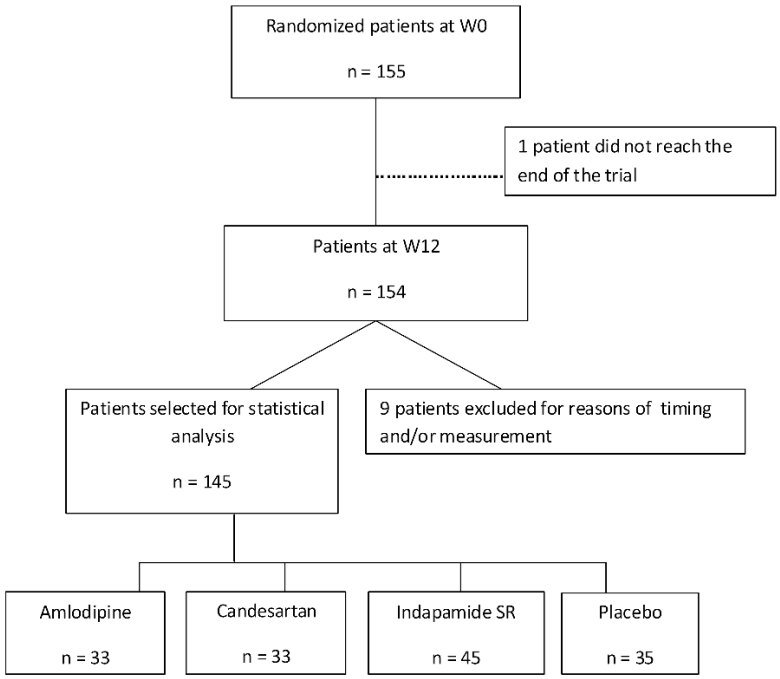

Figure 1. Flow diagram of X-CELLENT study participants. Abbreviations: W0, baseline assessment; W12, assessment after a 12-week treatment.

Table 1. Characteristics of patients by treatment group

	Amlodipine (n = 33)	Candesartan (n = 33)	Indapamide (n = 44)	Placebo (n = 35)	Total (n = 145)	P_{trend}
Age, years	59.5 (11.6)	57.2 (8.6)	59.2 (10.6)	56.6 (11.7)	58.2 (10.7)	0.59
Male, No. (%)	17 (52)	18 (55)	25 (57)	16 (46)	76 (52)	0.79
Weight, kg	74.9 (14.6)	76.6 (13.5)	74.0 (12.1)	71.8 (10.8)	74.3 (12.7)	0.47
Height, cm	165.9 (11.1)	167.9 (8.4)	166.5 (9.0)	162.9 (8.9)	165.8 (9.4)	0.16
Smoking, No. (%)	7 (21)	5 (15)	8 (18)	8 (23)	28 (19)	0.67
Hypertension, mo.	64.1 (60.2)	44.5 (60.9)	57.8 (90.2)	51.9 (66.4)	54.5 (72.0)	0.77
Previous antihypertensive drugs, No. (%)	14 (47)	11 (37)	12 (29)	8 (25)	45 (34)	0.27

Data are presented as mean values (SD) or number (percent) for continuous or discrete variables, respectively.
P values were generated by the analysis of variance test across groups.

Table 2. Brachial and carotid arteries measurements

	Amlodipine (n = 33)	Candesartan (n = 33)	Indapamide (n = 44)	Placebo (n = 35)	P_{trend}
HR, bpm					
W0	70 (15)	69 (14)	68 (10)	67 (10)	0.80
W12	69 (12)	66 (11)	66 (10)	66 (9)	0.58
W12 − W0	0.5 (9)	4.0 (12)	2.9 (12)	0.3 (10)	0.28[a]
Brachial artery					
SBP, mm Hg					
W0	165 (8)	164 (5)	160 (7)	162 (9)	**0.02**
W12	148 (13)	145 (13)	142 (13)	153 (13)	**0.005**
W12 − W0	−17 (15)	−20 (14)	−18 (15)	−9 (13)	**0.005**[a]
DBP, mm Hg					
W0	94 (8)	94 (6)	94 (6)	95 (8)	0.71
W12	87 (8)	84 (8)	84 (8)	92 (10)	**<0.001**
W12 − W0	−7 (8)	−10 (8)	−10 (9)	−3 (8)	**0.001**[a]
PP, mm Hg					
W0	71 (11)	70 (9)	66 (10)	67 (14)	0.12
W12	61 (13)	60 (11)	58 (12)	61 (10)	0.60
W12 − W0	−10 (11)	−10 (12)	−9 (15)	−6 (11)	0.63[a]
Carotid artery					
SBP, mm Hg					
W0	155 (27)	150 (17)	147 (13)	157 (19)	0.06
W12	139 (21)	138 (19)	133 (16)	155 (19)	**<0.001**
W12 − W0	−16 (17)	−12 (16)	−14 (15)	−2 (17)	**<0.001**[a]
DBP, mm Hg					
W0	95 (12)	90 (6)	91 (10)	96 (12)	0.06
W12	88 (10)	86 (10)	85 (10)	95 (12)	**0.001**
W12 − W0	−7 (9)	−5 (9)	−6 (7)	−1 (7)	**0.001**[a]
PP, mm Hg					
W0	60 (23)	59 (16)	56 (14)	62 (16)	0.45
W12	51 (18)	52 (14)	48 (14)	61 (18)	**0.005**
W12 − W0	−9 (11)	−7 (12)	−8 (15)	−1 (14)	**0.005**[a]

Data are presented as mean (SD). *P* values were generated by the analysis of covariance test across groups, adjusted for recruitment center.
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; W0, baseline value; W12, outcome value after 12-week treatment; W12 − W0, change between after and before treatment values.
[a]*P* values adjusted for center and W0 value.
Significant *P* values are presented in bold.

In Figure 2, Dunnett comparison tests between each active drug and placebo effects on central and peripheral BPs are shown. Each active drug caused a more pronounced reduction than the placebo in carotid SBP (all $P < 0.01$), DBP (all $P < 0.05$), and PP (all $P < 0.05$). For brachial pressure, SBP was significantly lowered more than placebo by amlodipine ($P < 0.01$) and indapamide SR ($P < 0.01$), whereas candesartan did not reach statistical significance ($P = 0.07$). Brachial DBP was similarly reduced by the 3 active drugs (all $P < 0.05$). Brachial PP was reduced in all treatment groups, but with no significant difference between active drugs and placebo.

Tests for differences in all BP parameters between active drugs groups were not statistically significant (data not shown).

Pulse pressure amplification, wave reflection, and arterial stiffness

In Table 3 the drugs' effect on modification of hemodynamic parameters (PPA, arterial stiffness, and wave reflection) is shown. The ANCOVA test showed no significant trend across treatment groups at W0 for each parameter (all $P > 0.28$). The effect on PPA and AP reached significant trend at W12 ($P = 0.05$ and $P = 0.01$, respectively), and for

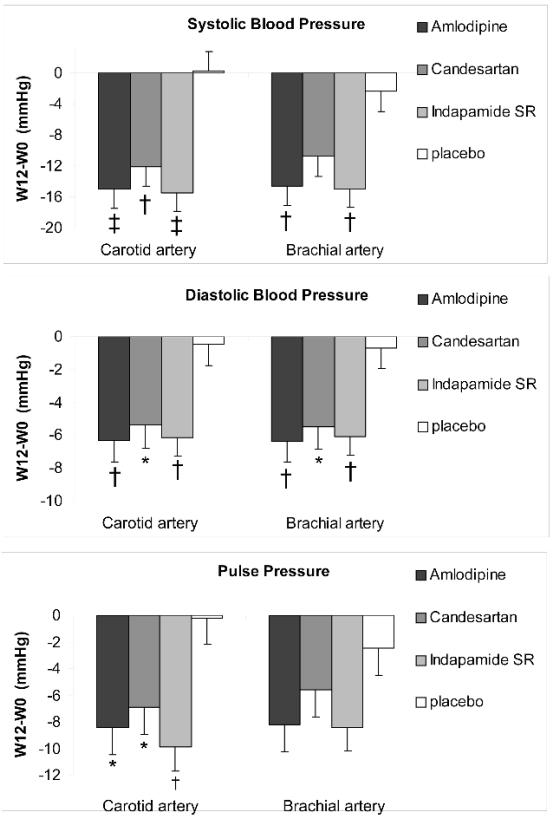

Figure 2. Changes from baseline (W12 (assessment after 12-week treatment) – W0 (baseline assessment)) of carotid and brachial systolic and diastolic blood pressure, and pulse pressure. *P* values were generated by the Dunnett test for comparison between each active drug and placebo. The analysis was adjusted for baseline value and recruitment center. **P* < 0.05, ***P* < 0.01, ****P* < 0.0001. Adjusted means and SEs are presented. *P* values for trend across groups can be found in Table 2. No statistical difference between active drugs was found.

W12 – W0 ($P = 0.03$ and $P = 0.01$, respectively). No significant trends were found at W12 and W12 – W0 for AIx and PWV.

The Dunnett multiple comparison test between each active drug and placebo for change in PPA from baseline is shown in Figure 3. Amlodipine (1.9% ± 15.3 %) and candesartan (3.0% ± 14.6 %) effects did not reach statistical significance versus placebo ($P = 0.14$ and $P = 0.07$ respectively), whereas indapamide SR did (4.1% ± 14.4 %; $P = 0.02$).

Each active drug had a greater effect than placebo in reducing AP (data not shown; $P = 0.02$, $P = 0.04$, $P = 0.01$, for amlodipine, candesartan, and indapamide SR, respectively).

Tests for differences in all hemodynamic parameters between active drug groups were not statistically significant (data not shown).

DISCUSSION

In our study, which compared the therapeutic effect of 3 antihypertensive agents (amlodipine, candesartan, and indapamide SR) vs. placebo in 145 subjects, after a 12-week treatment, we found that active drugs produced a similar reduction in both central and peripheral BPs, and this effect was statistically different from placebo. Furthermore, all active drugs improved PPA, but only indapamide SR reached statistical significance vs. placebo. Finally, no significant changes were observed in arterial stiffness and AIx by active treatments.

Central BP was lowered to a similar extent by amlodipine, candesartan, and indapamide SR; particularly, whereas little or no effect was observed on peripheral PP, the active drugs reduced central PP, and this may be associated with a better CV outcome, as previously suggested by some investigators.[16]

Dihydropyridine calcium channel blockers and angiotensin II receptor blockers are expected to reduce both central and peripheral BP,[17–23] and our results confirm this finding. Diuretic compounds were considered to have little or no effect on central BP,[24,25] particularly when thiazide agents were used, in small clinical trials. This apparent poor central action might be because of the lack of large-scale, long-term follow-up and placebo-controlled studies applying central BP analysis. More recently, the central effect of thiazide diuretic agents has been proposed by a small trial on 13 subjects with isolated systolic hypertension.[18] To our knowledge, no randomized, controlled clinical trial has analyzed the effect of indapamide on central BP and PPA.

PPA is a physiological phenomenon caused by the change in the arterial viscoelastic properties from central to peripheral arteries and to the return of the reflected waves. Beyond its physiological role, PPA is known to be correlated to cardiovascular risk and mortality, even in very old patients,[6,7,26] thus pharmacological treatments are more and more investigated for their ability to improve amplification.

Even if limited by the relative small sample size, our results suggest for the first time that indapamide SR might exert an early beneficial effect in treatment of hypertensive patients.

Indapamide is considered a thiazide-like molecule, but it presents some differences: in fact, besides its diuretic properties, indapamide presents some effects on vascular/organ damage protection in animal and human investigations. It was effective in reducing left-ventricular mass index in hypertensive patients and microalbuminuria in diabetic hypertensives, without significant metabolic modifications.[27] Furthermore, the HYVET study demonstrated a reduction of cardiovascular risk in very old patients treated with indapamide.[28] Recently, a survey cohort study in very old subjects showed that PPA, but not central/peripheral BP or aortic stiffness, was associated with prognosis.[26] The mechanism of indapamide on central hemodynamic effect is yet to be established, but it seems related to modification of the relationship between forward and reflected waves.

A reduction of central beyond peripheral BP can be due to a decrease in arterial stiffness, a modification of amplitude/timing of wave reflections, or both. This study indicates that reflected waves modification was the principal driving event, whereas aortic stiffness had little or no short-term impact. The importance of the change in wave reflections is highlighted by the observation that AP, which is a direct marker of altered wave reflections in the absence of AIx

Table 3. Central hemodynamic measurements

	Amlodipine (n = 33)	Candesartan (n = 33)	Indapamide (n = 44)	Placebo (n = 35)	P_{trend}
Pulse pressure amplification, %					
W0	113 (19)	111 (13)	114 (14)	112 (18)	0.91
W12	115 (19)	115 (15)	118 (17)	107 (12)	**0.05**
W12 − W0	1.9 (15)	3.0 (14)	4.1 (14)	−5.6 (17)	**0.02**[a]
Augmented pressure, mm Hg					
W0	16.6 (14.1)	17.0 (11.4)	14.6 (7.7)	19.7 (11.9)	0.29
W12	11.7 (10.3)	12.7 (11.1)	10.5 (7.1)	18.1 (9.6)	**0.006**
W12 − W0	−4.9 (7.2)	−4.6 (10.5)	−4.1 (6.8)	−1.4 (8.3)	**0.01**[b]
Augmentation index, %					
W0	24.7 (15.4)	26.5 (16.0)	25.2 (10.9)	30.5 (12.3)	0.32
W12	20.5 (14.7)	23.2 (16.5)	21.1 (12.8)	28.8 (9.7)	0.06
W12 − W0	−4.2 (10.3)	−4 .0 (12.6)	−4.1 (10.5)	−1.6 (10.5)	0.23[b]
Pulse wave velocity, m/s					
W0	10.3 (3.2)	9.6 (2.2)	9.7 (2.7)	9.7 (3.1)	0.78
W12	9.8 (2.8)	9.7 (2.2)	9.8 (2.6)	9.6 (2.7)	0.95
W12 − W0	−0.5 (2.4)	−0.01 (1.2)	0.1 (1.7)	−0.02 (2.0)	0.89[b]

Data are presented as mean (SD). *P* values were generated by the analysis of covariance test across groups, adjusted for recruitment center.
Abbreviations: W0, baseline value; W12, outcome value after 12-week treatment; W12 − W0 between before and after treatment values.
[a]*P* values adjusted for center, W0 value, and changes in mean arterial pressure and heart rate from W12.
[b]*P* values adjusted for center and W0 value.
Significant *P* values are presented in bold.

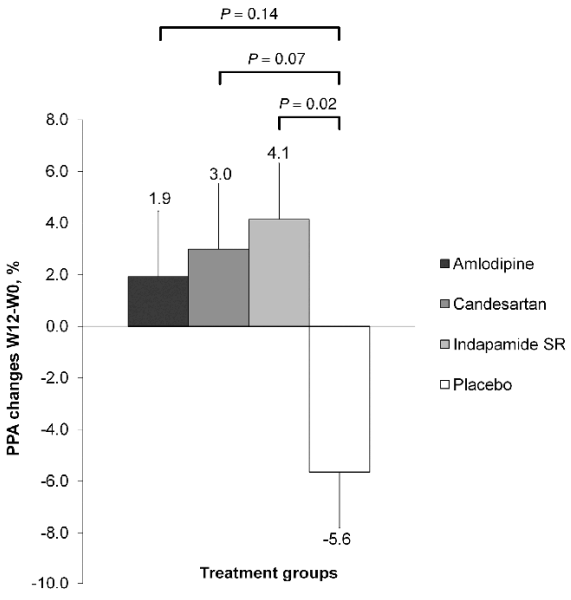

Figure 3. Changes from baseline (W12 (assessment after 12-week treatment) – W0 (baseline assessment)) of carotid to brachial pulse pressure amplification (PPA). *P* values were generated by the Dunnett test for comparison between each active drug and placebo. The analysis was adjusted for baseline PPA, change in mean arterial pressure and heart rate from baseline, and recruitment center. Adjusted means and SEs are presented. *P* value for trend across groups can be found in Table 3. No statistical difference between active drugs was found.

modifications, was reduced by the active drugs. Even if little nonsignificant imbalance was observed in HR changes between groups, analyses on AP and AIx were adjusted for HR, with no significance modification. This softens the possible bias of HR imbalance between groups.

In this study, a minimal drug role on PWV was observed. Calcium channel blockers, angiotensin II receptor blockers, and diuretics like indapamide SR are known to modify PWV, depending primarily on the dose of each agent and on the treatment duration.[18,19,29–33] This factor may play an important role, particularly regarding candesartan and its effect on angiotensin blockade. Besides, the Reason study has shown that during a pharmacological treatment the drug's effect on large arteries is initiated by wave reflections; thereafter during the first year of treatment the effect on PWV comes out, owing to modifications of arterial wall mechanical properties.[34] Of note, in our study, the treatment duration did not exceed 12 weeks, and the drugs were administered at fixed dosage.

For this analysis, an inclusion criteria was the presence of both carotid and radial measurements. In this study, only 9 patients were excluded, and there was no statistical difference between the characteristics of the examined (n = 145) and the excluded (n = 9) subjects at baseline or under treatment.

This study represents a subgroup analysis of a randomized, double-blinded, placebo-controlled clinical trial. For this reason, every result has to be considered within the limitation of this secondary analysis.

The relative small population sample and the 4-arm setting are major limitations of our study, which could have

contributed to the low statistical power for detecting differences between groups. Any lack of difference should therefore be interpreted with caution, but, at the same time, the finding of significant differences between drugs is less likely to be driven by chance. In particular, the comparison test between candesartan and placebo for PPA, which is not far from statistical significance ($P = 0.07$), could have been significant in the presence of bigger sample size. Moreover, the elevated SDs of means documented that measurements with great variation exist.

The short duration of the trial (12 weeks) and the fixed-dose therapeutic scheme are also important limitations that could have masked therapeutic effects on BP parameters and arterial stiffness. Each therapeutic agent was given at the low/medium dose, as recommended for the start of antihypertensive treatment.[8]

We found a certain degree of imbalance in baseline outcome variables that could attenuate analysis power; as reported in literature, the ANCOVA with adjustment for baseline value is unbiased, more efficient, and controls α level.[15]

The major finding of our study was that amlodipine, candesartan, and indapamide SR reduced both steady and pulsatile central BP after a 12-week treatment. Within the limits of the study, the central PP lowering effect was not or only slightly due to changes in PWV but was instead related to changes in wave reflections, particularly regarding indapamide SR, which was the only drug able to significantly improve PPA. Thus, considering the preliminary nature of our results, it seems interesting to establish whether the improvement of the arterial properties is involved in CV risk modification by long-term interventional trials.

ACKNOWLEDGMENTS

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DISCLOSURE

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VII.3.2. Conclusion de l'ARTICLE 7

Dans cette étude, nous avons donc comparé l'effet de trois médicaments antihypertenseurs *versus* placebo chez 145 patients hypertendus après 12 semaines de traitement.

La pression centrale a été réduite de façon similaire par l'amlodipine, le candesartan et l'indapamide ; nous n'avons pas noté d'effet sur la pression pulsée périphérique, alors que les trois médicaments ont réduit la pression pulsée centrale, ce qui pourrait être associé à un meilleur pronostic cardiovasculaire.

L'amlodipine est un inhibiteur calcique dihydropyridine et le candesartan un inhibiteur du récepteur de l'angiotensine II : ces deux classes thérapeutiques ont déjà montré leur capacité à réduire à la fois la pression centrale et la pression périphérique, et nos résultats sont confirmatifs.[127–129] Les études réalisées jusqu'à maintenant n'ont pas mis en évidence d'effet des diurétiques sur la pression centrale, surtout les diurétiques thiazidiques.[130] Ces résultats sont peut-être dus au manque d'études sur une large échelle, avec un long follow-up. Cependant, à notre connaissance, il n'y a pas d'étude randomisée et contrôlée évaluant l'effet de l'indapamide sur la pression centrale et l'amplification.

Même si notre étude est limitée par la taille de l'échantillon, nos résultats suggèrent que l'indapamide à libération prolongée pourrait avoir un effet bénéfique précoce dans le traitement des patients hypertendus. L'indapamide est considéré comme un diurétique de la famille des thiazidiques, mais avec des différences : en effet, outre l'effet diurétique, il a démontré des effets protecteurs sur l'atteinte vasculaire et d'organe cible, ainsi que sur le risque cardiovasculaire, dans des études sur les animaux et les humains.[131,132] Nous avons récemment publié une étude où nous avons montré que l'amplification de la pression pulsée, et non pas la

pression centrale ni périphérique, ni la vitesse de l'onde de pouls, était associée au pronostic des patients très âgés.[91] Les mécanismes par lesquels l'indapamide a un effet sur la pression centrale sont encore à découvrir, mais il se peut qu'ils concernent des modifications de la relation entre les ondes directes et les ondes réfléchies.

Au final, le résultat principal de notre étude est que l'amlodipine, le candesartan et l'indapamide à libération prolongée ont réduit toutes les composantes de la pression centrale par rapport au placebo, après 12 semaines de traitement. Dans les limites de l'étude, l'effet sur la baisse de la pression centrale n'était pas dû aux modifications de la rigidité artérielle mais plutôt à celles des ondes de réflexion, en particulier pour l'indapamide qui, seul, a montré un effet positif significatif sur l'amplification.

Conclusion

Dans cette première partie, nous avons amorcé les bases physiopathologiques de l'hémodynamique cardiovasculaire, en partant de l'histoire des découvertes scientifiques qui nous ont permis d'arriver là où nous nous trouvons. L'observation du système cardiovasculaire nous a aussi permis d'en analyser les composantes et le fonctionnement, dont les modèles mathématiques ne constituent qu'une modeste tentative d'explication d'un système en réalité très complexe.

La pulsatilité cardiaque et la compliance artérielle semblent donc être les deux caractéristiques de départ qui ont fasciné une multitude de scientifiques et constitué un véritable défi jusqu'à aujourd'hui.

Si la pulsatilité, qui est principalement énergie, veut dire, avant tout, système ondulatoire, résonance et réflexion, la compliance est la manière dont la matière physique accueille et modifie la pulsatilité ; si les ondes de pression et de flux représentent la propagation de l'énergie pulsatile du cœur aux tissus, la relation complexe entre les deux (pression et flux) est le dialogue entre le ventricule gauche et les vaisseaux. Ce dialogue permet aux artères de répondre aux sollicitations cardiaques et de modifier la propagation de l'énergie le plus convenablement possible.

La possibilité de mesurer plus ou moins objectivement les caractéristiques des ondes de pression du centre à la périphérie du système cardiovasculaire trouve sa justification dans la tentative, premièrement, de compréhension du système même, surtout en présence de conditions pathologiques comme l'hypertension artérielle, et, deuxièmement, de traitement actif de l'atteinte artérielle.

Dans la deuxième partie de notre travail, nous allons donc aborder la manière dont l'étude de l'hémodynamique nous permet d'investiguer l'atteinte

artérielle et le risque cardiovasculaire, associés aux maladies non premièrement cardiovasculaires, comme les maladies du métabolisme.

Deuxième partie

RIGIDITE ARTERIELLE ET ALTERATIONS METABOLIQUES

Après avoir étudié les principes de fonctionnement de l'hémodynamique vasculaire, après avoir compris la problématique de l'analyse de l'onde de pression ainsi que de la mesure de propagation de l'onde, après avoir reconnu les contraintes liées à la validation des mesures hémodynamiques, nous avons montré l'intérêt de ces mesures dans la maladie cardiovasculaire.

Toutefois, nous avons pu aussi constater, dans notre étude sur le calibrage de l'onde de pression et sur l'amplification de la pression pulsée (cf ARTICLE 4, page 177), que cette dernière pouvait être aussi négativement associée à la présence d'un diabète, ceci pouvant ainsi expliquer, au moins en partie, des mécanismes qui relient le diabète au risque cardiovasculaire.

Ainsi même si la maladie artérielle est habituellement considérée dans le cadre de l'hypertension, il faut aussi se rendre compte que des maladies à genèse non cardiovasculaire présentent un risque de mortalité cardiovasculaire et, de plus, peuvent entraîner des modifications artérielles propres à la maladie cardiovasculaire.

Les maladies métaboliques (intolérance glycémique, insulino-résistance, syndrome métabolique et le diabète sucré) , en sont parmi les exemples les plus évidents.

Dans ce chapitre, nous allons donc proposer une approche cardiovasculaire aux maladies métaboliques, dans le but de montrer que l'expression du risque cardiovasculaire associé au syndrome métabolique et au diabète sucré passe par des altérations de la mécanique vasculaire, indépendamment de la présence d'hypertension ou du niveau tensionnel seul.

Nous étudierons d'abord le rôle du syndrome métabolique et de la stéatose hépatique non alcoolique dans le processus de rigidité artérielle, puis les différences entre les sujets diabétiques et non diabétiques, de même niveau de pression

artérielle, par rapport aux modifications de la rigidité artérielle ; enfin, nous analyserons la relation entre l'ancienneté du diabète, le risque cardiovasculaire et la rigidité aortique.

I Le syndrome métabolique

De nombreux patients présentent plusieurs facteurs de risque majeurs, tels une obésité abdominale, une dyslipidémie athérogène (avec élévation des petites lipoprotéines à basse densité (cholestérol LDL) et des triglycérides, et bas niveau de lipoprotéines à densité élevée), une élévation de la pression artérielle, un état d'insulinorésistence (avec ou sans intolérance glucidique) et un état prothrombotique et proinflammatoire. Tous ces facteurs constituent le syndrome métabolique,[133] qui est reconnu par l'ATP III comme une cible secondaire pour la thérapie de réduction du risque cardiovasculaire, après la cible primaire qui est le le cholestérol LDL.[133]

Le diagnostic du syndrome métabolique repose sur la présence d'au moins trois des cinq critères suivants :[133]

- périmètre abdominal > 102 cm chez l'homme et > 88 cm chez la femme ;
- triglycérides > 1,5 g/l ;
- HDL cholestérol < 0,40 g/l chez l'homme et < 0,50 g/l chez la femme ;
- pression artérielle > 130/85 mmHg ;
- glycémie à jeun > 1,1 g/l.

Les travaux qui ont étudié l'association entre les maladies métaboliques et l'hémodynamique artérielle ont montré une augmentation de la rigidité artérielle chez les sujets avec syndrome métabolique.[134]

Ces altérations délétères des propriétés artérielles sont également présentes chez le sujet jeune (adolescents[135] et jeunes adultes obèses[136]). La rigidification observée dans le syndrome métabolique serait provoquée par des petites altérations métaboliques survenant avant le diabète, étayant ainsi l'hypothèse que l'atteinte macrovasculaire due au diabète de type 2 débuterait précocement à l'état de pré-diabète. Des études prospectives ont aussi montré que l'incrément de la

rigidité artérielle associé au vieillissement est plus élevé chez les sujets avec syndrome métabolique que chez les sujets sans syndrome métabolique.[137,138] De plus, chez ces sujets où le syndrome métabolique régresse au long des années, on observe une progression mineure de la rigidification artérielle.[139]

I.1. ARTICLE 8 : La stéatose hépatique non alcoolique est associée à la rigidité artérielle

I.1.1. Introduction de l'ARTICLE 8

La stéatose hépatique représente l'un des diagnostics les plus fréquents parmi les maladies chroniques du foie. Même si la stéatose a été initialement considérée comme une maladie bénigne, elle a montré sa capacité à se transformer en affections plus sévères telles que la cirrhose et le carcinome hépatocellulaire. La stéatose hépatique non-alcoolique, « non alcoholic fatty liver disease » (NAFLD), est une forme de stéatose dont la prévalence a beaucoup augmenté dans les pays occidentaux où elle est estimée à environ 14-40 % dans la population générale et jusqu'à 50-90 % chez les personnes obèses. En outre, la NAFLD représente le facteur étiologique dans 80 % des cas de cirrhose cryptogénétique, tandis que 50 à 80 % de NAFLD sont associés au syndrome métabolique. Couramment, beaucoup d'auteurs considèrent la NAFLD et sa forme avancée, la stéatohépatite non alcoolique, comme des manifestations hépatiques avancées du syndrome métabolique. En effet, la NAFLD partage avec le syndrome métabolique des facteurs étiologiques comme l'obésité, le diabète et la dyslipidémie, qui eux-mêmes sont des facteurs de risque cardiovasculaire majeurs. Pour cela, on s'attend à ce que la présence de la NAFLD soit significativement associée à une surmortalité par rapport à la population générale. Des études épidémiologiques ont montré une forte relation positive entre la NAFLD et la prévalence de la maladie cardiovasculaire, indépendamment des facteurs de risque classiques. Les études cliniques actuellement disponibles suggèrent que la NAFLD semblerait être associée à une

augmentation du risque cardiovasculaire et qu'elle pourrait être non seulement un marqueur, mais aussi un médiateur d'athérosclérose.

L'étude Gambettola ObservatOry liver Steatosis Estimation (GOOSE) est une étude de cohorte conçue dans l'objectif d'évaluer la prévalence de la stéatose hépatique et des facteurs associés dans la population générale. Grâce à son étude ancillaire Cardio-GOOSE, il a été possible de déterminer la relation entre le syndrome métabolique, la NAFLD et l'atteinte vasculaire infra clinique, estimée par l'épaisseur intima-média carotidienne (IMT) et par la rigidité aortique.

La population étudiée était constituée de 220 participants à l'étude GOOSE, âgés de 30 à 70 ans, dont 123 femmes. La rigidité aortique a été déterminée par la vitesse de l'onde de pouls carotido-fémorale, par tonométrie d'applanation.

Le diagnostic de NAFLD était associé à la présence du syndrome métabolique dans 48 % des cas, et l'épaisseur intima-media était significativement corrélée aux facteurs du syndrome métabolique. La vitesse de l'onde de pouls était significativement plus basse chez les patients sans NAFLD (7,40 ± 1,47 m/s) que chez les patients avec NAFLD isolée (7,98 ± 1,51 m/s, $p<0,05$) et les patients avec NAFLD plus syndrome métabolique (8,29 ± 2,2, $p<0,001$). De même, la prévalence de NAFLD était augmentée chez les patients ayant les valeurs les plus élevées de vitesse de l'onde de pouls, même après ajustement.

Increased arterial stiffness in nonalcoholic fatty liver disease: the Cardio-GOOSE study

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Objective **Nonalcoholic fatty liver disease (NAFLD) is a very frequent disease in Western countries. NAFLD shares with metabolic syndrome the same etiologic factors, such as obesity, diabetes, and dyslipidemia, which are also major cardiovascular risk factors. Cardio-GOOSE (Cardio-Gambettola ObservatOry liver Steatosis Estimation) is a population-based cohort study finalized to evaluate the relationship between NAFLD, subclinical vascular damage, and arterial stiffness.**

Methods **The study population consisted of 220 participants (123 women), aged between 30 and 70 years, who participated in the GOOSE study. Arterial stiffness was determined by measuring the carotid-femoral pulse wave velocity (PWV) by means of the PulsePen device. Preclinical atherosclerosis was detected by carotid intima–media thickness (IMT) measurement.**

Results **NAFLD was associated with metabolic syndrome in 48% of cases. IMT values were strongly related to metabolic syndrome factors. No significant differences in IMT were found between controls and patients with isolated NAFLD (0.77 ± 0.15 mm versus 0.76 ± 0.14 mm). Conversely, in patients with NAFLD associated with metabolic syndrome, IMT values were significantly higher than in patients with NAFLD alone (0.85 ± 0.16 mm, $P<0.005$). PWV values were significantly lower in controls compared to patients with isolated NAFLD (7.40 ± 1.47 versus 7.98 ± 1.51 m/s, $P<0.05$) as well as patients with both NAFLD and metabolic syndrome (8.29 ± 2.2 m/s, $P<0.001$). The prevalence in NAFLD was increased in patients with the highest PWV values, and persisted after adjustment for factors determining metabolic syndrome ($P<0.05$).**

Conclusions **This study has shown a possible independent role of NAFLD in determining arterial stiffness.** ***J Hypertens*** **28:1699–1707 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: arterial stiffness, intima–media thickness, metabolic syndrome, nonalcoholic fatty liver disease, pulse wave analysis

Abbreviations: AIx, augmentation index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CVD, cardiovascular diseases; GGT, γ-glutamyltransferase; GOOSE, Gambettola ObservatOry liver Steatosis Estimation; HDL-chol, high-density lipoprotein cholesterol; HR, heart rate; IDF, International Diabetes Federation Epidemiology Task Force Consensus Group; IMT, intima–media thickness; LDL-chol, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; NCEP-ATPIII, Third Report of the National Cholesterol Education Program, Adult Treatment Panel III; PP, pulse pressure; PPA, pulse pressure amplification; PWV, pulse wave velocity

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Introduction

Liver steatosis is one of the more frequent diagnoses of chronic liver disease. Initially regarded as a benign disease, liver steatosis has shown the possibility of developing into a more serious disease, such as cirrhosis [1–4] and hepatocellular carcinoma (HCC) [4,5]. NAFLD (nonalcoholic fatty liver disease) is the nonalcoholic form of liver steatosis, and has become increasingly more frequent in Western countries, where its global prevalence is estimated from 14 to 40%, and from 50 to 90% in the obese population [6,7]. Moreover, NAFLD represents the etiologic factor in 80% of cases of cryptogenetic cirrhosis [8] while 50–80% of NAFLD cases are associated with metabolic syndrome [9,10]. Currently, many authors consider NALFD and its progressive subtype, nonalcoholic steatohepatitis (NASH), as a hepatic manifestation of metabolic syndrome [11,12]. NAFLD shares with metabolic syndrome the same etiologic factors, such as obesity, diabetes, dyslipidemia. These factors also represent the main cardiovascular risk factors, and thus NAFLD would be expected to have an increased risk of cardiovascular diseases (CVD). Indeed, NAFLD is associated with a significantly greater overall mortality than in the general population [1,7,13], and epidemiological studies have shown a strong associations between NAFLD and increased CVD prevalence [11,14–16], independently of classical risk factors and other prognostic factors [11,17,18]. The current body of evidence strongly suggests that NAFLD is likely to be associated with increased CVD risk, and raises the possibility that NAFLD may be not only a marker but also an early mediator of atherosclerosis.

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The GOOSE Study (Gambettola ObservatOry liver Steatosis Estimation) is a population-based cohort study conceived with the purpose of detecting the prevalence of liver steatosis and associated factors in the general population [19]. Cardio-GOOSE, an ancillary study of the GOOSE Study, is the first clinical study finalized to evaluate the relationship between metabolic syndrome, NAFLD and subclinical vascular disease, determined by intima–media thickness (IMT), and arterial stiffness, detected by carotid-femoral pulse wave velocity (PWV).

Research design and methods

Participants

In the GOOSE Study, a population sample comprised of 426 patients was recruited from drawn lots from the electoral register of the municipal district of Gambettola in north Italy. The total population of Gambettola is approximately 10 000 inhabitants. Draws were stratified according to age (30–70 years) and participants were invited by letter to take part in the study. Participants who accepted to participate in the study filled in a standardized questionnaire, which included life habits, physical activity, personal and family medical history, any therapy as well as data relative to socioeconomic and educational level. Smoking, eating habits, and alcohol intake by means of visual analogs were also assessed with this questionnaire. Only individuals with a daily intake of alcohol less than 20 g were considered eligible for the Cardio-GOOSE study. All individuals of the GOOSE cohort suitable for the Cardio-GOOSE study were invited by telephone to participate at this second phase of the study.

This study was approved by the local ethics committee (Comitato Etico AUSL Cesena) and conducted in accordance with the Helsinki Declaration. All participants provided written informed consent prior to the study.

Diagnostic criteria of metabolic syndrome

Metabolic syndrome was diagnosed according to the unified criteria of a recent Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity [20]. The presence of three or more of the following risk factors constituted a diagnosis of metabolic syndrome: elevated triglycerides ($\geq$150 mg/dl); low high-density lipoprotein (HDL) cholesterol ($<$40 mg/dl in males, $<$50 mg/dl in females); hypertension (BP $\geq$ 130/$\geq$85 mmHg); impaired fasting glucose ($\geq$100 mg/dl); increased waist circumference (for Europids: $\geq$94 cm for men, $\geq$80 cm for women). In order to compare these criteria with other less recent criteria, metabolic syndrome was also determined according to the International Diabetes Federation Epidemiology Task Force Consensus Group (IDF) [21] and the Third Report of the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATPIII) [22] criteria.

Clinical and anthropometric parameters

Anthropometric measurements were performed by the medical staff. Weight and height were measured with precision electronic scales and fixed stadiometers. All participants were measured without shoes and with light clothes. The body mass index (BMI) was calculated as weight divided by the height squared (kg/m^2). The waist circumference was measured at the midway level between the lowest rib margin and the iliac crest. The hip circumference was measured at the widest level over the great trochanters. Waist-to-hip ratio was calculated as waist circumference divided by hip circumference.

Blood pressure (BP) and heart rate (HR) were measured in the morning (from 0800 to 1200 h), after 10 min rest in a quiet and tempered room (20 ± 1°C). All measurements were performed using a validated automated oscillometric device (Omron 705IT, Omron Co., Kyoto, Japan) [23]. Measurements were repeated three times, with intervals of 3 min on the left arm in a sitting position without replacing the cuff between the three measurements. If intra measurement differences were greater than 8%, measurements were repeated until stabilization of BP values. Moreover BP measurements were assessed twice using the same method: in concomitance with the liver ultrasound study and in concomitance with PWV and IMT measurements. Pulse pressure (PP) was calculated as systolic BP – diastolic BP while mean BP was calculated as diastolic BP + PP/3. All participants were subjected to an ECG to identify any persistent alterations in cardiac rhythm.

Blood samples were drawn after an 8 h overnight fast. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-chol), low-density lipoprotein cholesterol (LDL-chol), uric acid, and glucose were evaluated by standard techniques. All participants with elevated AST and ALT values, or AST/ALT ratio greater than 1 were subjected to further analysis, in order to exclude other etiologies as the cause of liver disease, including hepatitis C and hepatitis B virus and autoimmune liver diseases as well as possible drug-related hepatic disorders.

Abdominal ultrasonography

The diagnosis of fatty liver was based on the results of abdominal ultrasonography performed by the same expert gastroenterologist. Four known criteria [24] were used to attribute a diagnosis of NAFLD: hepatorenal echo contrast (sonographic contrast between the liver and right renal cortex); liver brightness; deep attenuation (clear attenuation of echo penetration into the deep

portion of the liver and impaired visualization of the diaphragm); and vessel blurring (reduced definition of the borders of the intrahepatic vessel).

Arterial stiffness

Arterial stiffness was determined by measurement of PWV. PWV is considered as the 'gold-standard' measurement of arterial stiffness [25]. Both carotid-femoral PWV (aortic PWV) and carotid-radial PWV (upper limb PWV) were determined by means of a PulsePen device (DiaTecne srl, Milan, Italy), a validated [26,27], easy to use and high-fidelity tonometer. The procedure has been detailed previously [26]. Briefly, the PulsePen is comprised of one tonometer and an integrated ECG unit. The PulsePen determines the PWV at two intervals in highly rapid succession and is defined as the distance divided by the difference between the rise delay of the distal pulse wave to the R wave belonging to the ECG qRs complex and the rise delay of the proximal pulse wave to R wave belonging to the ECG qRs complex. The pulse wave delay can be determined by calculating the time elapsed from the peak of the R wave and the 'foot' of the pressure pulse contour. In carotid-femoral measurements, the distance of the pulse wave transit represents the difference between the distance from the supra-sternal notch to the femoral point of application of the tonometer and the distance from the carotid point of tonometer application and the supra-sternal notch. The PulsePen did not validate measurements if differences between BP and HR in carotid and femoral were greater than 10% during assessment. The inter-/intra-observer reliabilities have previously been published, with a coefficient of variation reaching 7.94 and 7.20% respectively [26].

Pulse wave analysis and central blood pressure measurement

The PulsePen applanation tonometer was also used also to record central arterial waveform and central BP values [26]. Augmentation Index (AIx) was defined as the difference between the second and first systolic peaks and expressed as a percentage of central PP [28]. Amplification phenomenon [29] was expressed as pulse pressure amplification (PPA) that is, the percentage of increase of PP in the brachial artery (PP_B) relative to central PP (PP_C), according to the formula: $PPA = 100 \cdot (PP_B - PP_C)/PP_C$.

Intima–media thickness

Carotid IMT measurement obtained with a B-mode ultrasound is currently recommended to directly identify preclinical atherosclerosis in human arteries [30,31]. IMT was measured in supine position in the left and right common carotid arteries in anterolateral, posterolateral, and mediolateral directions. The extracranial carotid arteries were bilaterally examined with a high-resolution B-mode ultrasound Philips iU22 (Philips Ultrasound, Bothell, WA, USA), equipped with a 9–3 MHz linear array transducer. Reference point for measurement of the IMT was the onset of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave-triggered optimal longitudinal image of the far wall was frozen and stored on video-tape. On this image, the leading edges corresponding to the transition zone between lumen–intima and media–adventitia were traced, over a length of 1 cm proximal to the reference point and the total intimamedia surface of this selected area was calculated. For each participant, three measurements on both sides were performed. A mean IMT of these six measurements was calculated. Carotid plaques were evaluated in all participants. Carotid plaque was defined as a focal thickening of at least 1.3 mm at the level of carotid artery.

Statistical analysis

Descriptive values are expressed as means ± standard deviation (SD) or number and percentages. Univariate regression analyses and two-factor analysis of variance were performed using PWV, IMT, and carotid plaques as the dependent outcome, with NAFLD and metabolic syndrome as independent predictors. The association of PWV and IMT on NAFLD was assessed by dividing the population into tertiles, according to the level of PWV and IMT respectively. Differences in frequency were tested by ANOVA. Multiple ascending stepwise regression analysis was used to determine independent predictors of PWV, IMT, and carotid plaques. Age, sex, NAFLD, and metabolic syndrome were candidates to the model. A *P*-value less than 0.05 was regarded as statistically significant. Statistical analyses were performed using the NCSS 2000 statistical software package (Kaysville, Utah, USA).

Results

The overall participation rate in the GOOSE Study was 82.9%: 353 of the 426 drawn participants responded to the invitation to participate in the study. Forty-three participants were excluded because of an admitted intake of alcohol 20 g/day or more of those eligible, 70.1% of the participants agreed to participate in this Cardio-GOOSE Study: 92 participants/119 with a diagnosis of NAFLD in the GOOSE study (77.3%), and 128 participants/185 without NAFLD (69.2%). Hence, this study was ultimately comprised of 220 participants, 97 males (mean age: 48.5 ± 9.6) and 123 females (mean age: 49.9 ± 10.1) of which 67 participants were smokers (33 males and 34 females). Fifteen participants were considered as diabetics (seven men and eight women). All participants had type 2 diabetes and none were on insulin treatment. Five participants were in treatment with oral antidiabetics. In four participants, diabetes was first diagnosed during this study. Six participants were in treatment with only diet. Sixty-two participants were considered as hypertensives (32 males and 30 females). Thirty-eight of these had a known treated hypertension whereas in 24 participants,

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hypertension was diagnosed during the course of this study. Diagnosis of hypertension was formulated according to criteria proposed by 2007 Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology [32]. Other declared diseases included celiac disease (2), peptic ulcer (8), chronic intestinal disease (3), gallstone (18), hypothyroidism (7), previous lymphoma (1), seminoma (1), breast cancer (1), and stroke (2).

Descriptive characteristics of all participants are presented in Table 1. Of the 220 participants, NAFLD was present in 92 participants (41.8%) including 44 (47.8%) with an associated metabolic syndrome. A total of 59 participants (26.8%) exhibited the characteristics for a diagnosis of metabolic syndrome; 74.6% of these participants (44/59) had an associated NAFLD. On the other hand, metabolic syndrome was present in 11.7% of participants without NAFLD (15/128).

The more recent criteria for diagnosing metabolic syndrome [20] allowed adding four participants to the NAFLD group and five participants to the control group, compared with the NCEP-ATPIII criteria [22], and two participants to NAFLD group when compared with IDF criteria [21].

Table 1 Clinical, hemodynamic, and anthropometric parameters of all participants

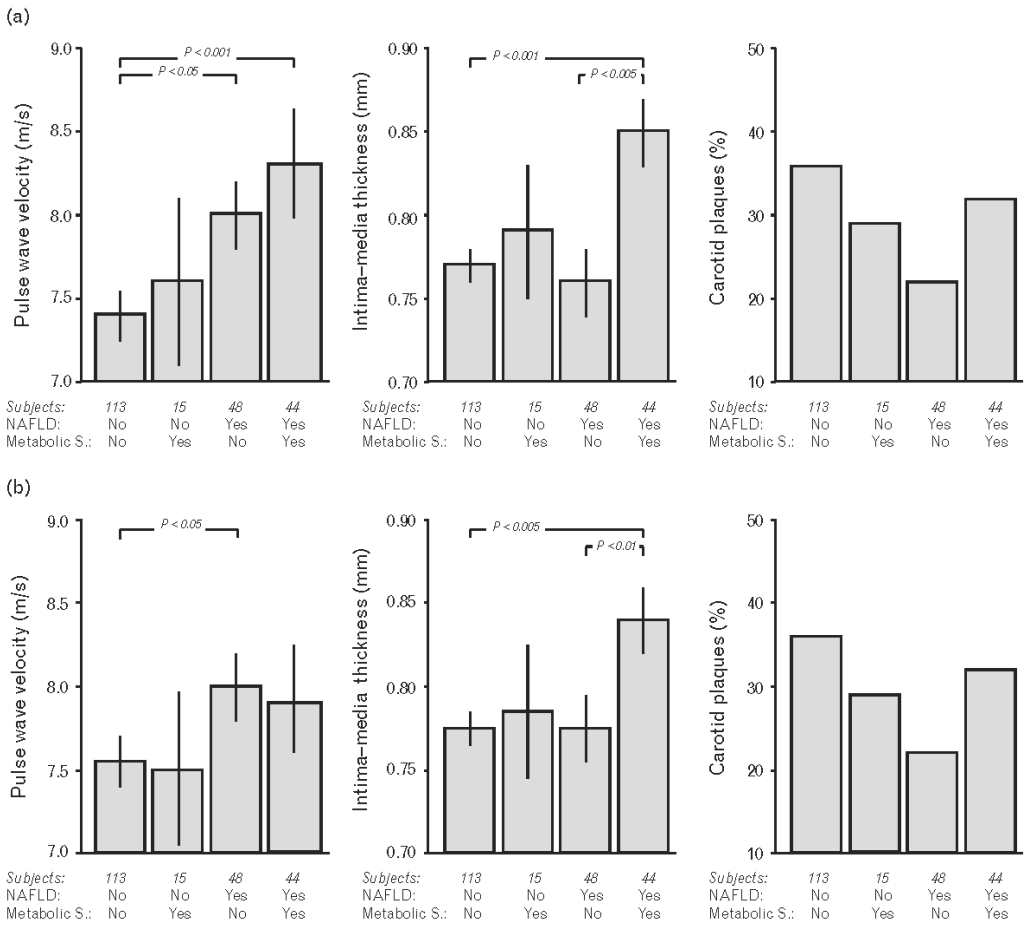
	Controls	NAFLD patients	Probability level (*P*)
Patients	128	92	
Sex (male/female)	47/81	50/42	
Age (years)	49.3 ± 9.4	50.7 ± 10.4	n.s.
Weight (kg)	66.4 ± 11.6	84.5 ± 15.2	<0.001
Height (cm)	167.1 ± 9.1	169.0 ± 9.5	n.s.
BMI (kg/m^2)	23.7 ± 3.3	29.5 ± 4.8	<0.001
Overweight (BMI 25–30)	34/128 (26.6%)	41/92 (44.6%)	<0.001
Obesity (BMI > 30)	6/128 (4.7%)	40/98 (43.5%)	<0.001
Waist circumference (cm)	83.3 ± 11.5	100.3 ± 13.8	<0.001
Hip circumference (cm)	96.4 ± 8.8	107.6 ± 9.4	<0.001
Waist-to-hip ratio	0.86 ± 0.09	0.93 ± 0.11	<0.001
Smoking	30.5%	30.4%	n.s.
Hypertension	18.0%	42.4%	<0.001
Diabetes	1.6%	14.1%	<0.001
Metabolic S. (NCEP-ATPIII)	10/128 (7.8%)	40/92 (43.5%)	<0.001
Metabolic S. (IDF)	15/128 (11.7%)	42/92 (45.7%)	<0.001
Metabolic S. (2009-JIS)	15/128 (11.7%)	44/92 (47.8%)	<0.001
Uric acid (mg/dl)	3.9 ± 1.4	5.0 ± 1.4	<0.001
AST (U/L)	18.6 ± 7.9	19.8 ± 6.6	n.s.
ALT (U/L)	18.0 ± 12.3	26.3 ± 19.0	<0.001
AST/ALT ratio	1.15 ± 0.33	0.93 ± 0.34	<0.001
γ-Glutamyl transferase (U/L)	26.2 ± 37.3	36.8 ± 30.7	<0.05
Alkaline phosphatase (mg/dl)	61.5 ± 18.5	70.5 ± 19.2	<0.001
Total cholesterol (mg/dl)	202.0 ± 33.0	211.5 ± 41.7	n.s.
HDL cholesterol (mg/dl)	53.8 ± 14.3	45.4 ± 10.5	<0.001
LDL cholesterol (mg/dl)	133.0 ± 27.5	141.8 ± 39.8	n.s.
Triglycerides (mg/dl)	76.1 ± 35.6	121.8 ± 79.3	<0.001
Glucose (mg/dl)	86.8 ± 11.5	94.1 ± 18.6	<0.001
Systolic BP (mmHg)	122.8 ± 17.4	132.1 ± 17.0	<0.001
Diastolic BP (mmHg)	73.0 ± 10.1	78.5 ± 9.2	<0.001
Mean BP (mmHg)	89.6 ± 11.8	96.3 ± 11.0	<0.001
Humeral PP (mmHg)	49.8 ± 11.4	53.6 ± 12.2	<0.05
Aortic PP (mmHg)	37.4 ± 9.2	40.3 ± 10.7	<0.05
PP amplification (%)	34.2 ± 8.2	34.8 ± 10.4	n.s.
Augmentation index (%)	13.0 ± 16.3	16.6 ± 15.0	n.s.
Heart rate (bpm)	72.5 ± 12.7	72.4 ± 12.1	n.s.
Carotid-femoral PWV (m/s)	7.30 ± 1.57	8.30 ± 1.94	<0.001
Carotid-radial PWV (m/s)	8.52 ± 1.50	8.91 ± 1.75	n.s.
IMT (mm)	0.76 ± 0.15	0.82 ± 0.16	<0.01
Carotid plaques	33.6%	29.3%	n.s.
Treatment			
Diuretics	3.8%	14.0%	<0.01
β-blockers	4.6%	6.6%	n.s.
CCB (dihydropiridines)	3.1%	7.5%	n.s.
ACE inhibitors	5.4%	6.5%	n.s.
ARBs	3.1%	8.6%	n.s.
ASA	1.5%	3.2%	n.s.
Statines	4.6%	5.4%	n.s.

Data are expressed as mean ± standard deviation. 2009-JIS, 2009 Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; American Heart Association; ARBs, angiotensin II receptor blockers; ASA, acetyl salicylic acid; AST, aspartate aminotransferase; BMI, body mass index; CCB, calcium channel blockers; HDL cholesterol, high-density lipoprotein cholesterol; IDF, International Diabetes Federation Epidemiology Task Force Consensus Group; IMT, intima–media thickness; International Atherosclerosis Society; and International Association for the Study of Obesity; LDL cholesterol, low-density lipoprotein cholesterol; Metabolic S., metabolic syndrome; n.s., not significant; NAFLD, nonalcoholic fatty liver disease; National Heart, Lung, and Blood Institute; NCEP-ATPIII, Third Report of the National Cholesterol Education Program, Adult Treatment Panel III; PP, pulse pressure; BP, blood pressure; PWV, pulse wave velocity; World Heart Federation.

Carotid-femoral PWV and IMT were significantly higher in the NAFLD group compared to the non-NAFLD control group: 8.30 ± 1.94 versus 7.30 ± 1.57 m/s ($P < 0.001$) and 0.82 ± 0.16 versus 0.76 ± 0.15 mm ($P < 0.01$) respectively. Conversely, no significant difference was found in carotid-radial PWV values between controls (8.52 ± 1.50 m/s) and NAFLD patients (8.91 ± 1.75 m/s).

Figure 1 depicts aortic PWV (left panel), IMT (middle panel), and carotid plaques (right panel) in patients without NAFLD or metabolic syndrome (first column), in patients with metabolic syndrome without NAFLD (second column), in patients with isolated NAFLD only (third column) and in patients with NAFLD associated with metabolic syndrome (fourth column). In upper section of the panel (Fig. 1a) all data were adjusted for age, sex, and HR. When compared to the control group, aortic PWV was significantly increased when both NAFLD and metabolic syndrome were present (8.29 ± 2.20 versus 7.40 ± 1.47 m/s, $P < 0.001$). PWV values were also significantly higher in presence of NAFLD without associated metabolic syndrome (7.98 ± 1.51 m/s, $P < 0.05$), compared the control group. Moreover, in a further adjustment of all data for mean arterial pressure (Fig. 1b), PWV values remained significantly lower in the control group compared to the NAFLD group without associated metabolic syndrome (7.56 versus 7.98 m/s, $P < 0.05$); this difference was weaker, however, compared to the group with both NAFLD and metabolic syndrome (7.91 m/s, $P < 0.2$).

Fig. 1



Pulse wave velocity, intima–media thickness, and carotid plaques in nonalcoholic fatty liver disease and in metabolic syndrome. Metabolic S., metabolic syndrome; NAFLD, nonalcoholic fatty liver disease. Pulse wave velocity (left panel), intima–media thickness (middle panel) and prevalence of carotid plaques (right panel), in patients without NAFLD or metabolic syndrome (first column), in patients with metabolic syndrome without NAFLD (second column), in patients with NAFLD alone (third column), and in patients with NAFLD associated with metabolic syndrome (fourth column). In panel (a), data were adjusted for age, sex, and heart rate; in panel (b) data were adjusted as in panel (a) plus mean arterial pressure.

Table 2 Pulse wave velocity, intima–media thickness, and carotid plaques in nonalcoholic fatty liver disease and in metabolic syndrome: two-factor analysis of variance

	F-ratio	*P*
PWV		
NAFLD	4.75	<0.03
Metabolic S.	13.28	<0.001
Interactions	0.03	0.9
IMT		
NAFLD	1.65	0.2
Metabolic S.	19.41	<0.001
Interactions	0.98	0.4
Plaques		
NAFLD	0.54	0.5
Metabolic S.	0.84	<0.05
Interactions	1.19	0.3

IMT was significantly higher in the presence of NAFLD associated with metabolic syndrome in comparison to both the control group (0.85 ± 0.16 versus 0.77 ± 0.15 mm, $P < 0.001$), and isolated NAFLD group (0.76 ± 0.14 mm, $P < 0.005$). Both of these differences also remained statistically significant after further adjustment for mean arterial pressure ($P < 0.005$ and $P < 0.01$ respectively). Finally, no significant difference in prevalence of carotid plaques was found between the four groups considered.

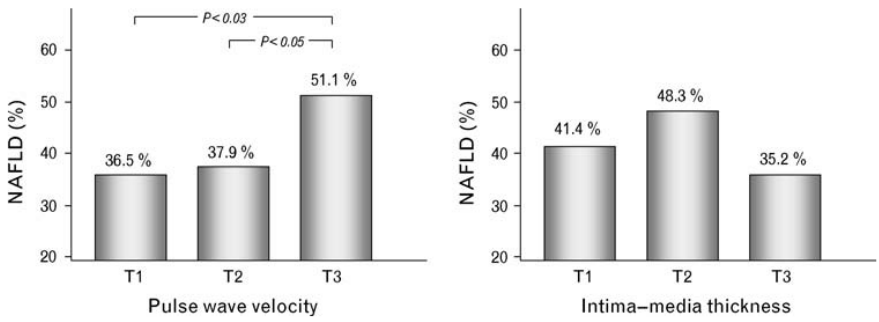
The possible role of the antihypertensive treatment in these results was assessed, by taking into account the distribution of antihypertensive medications in the four groups. No difference was observed in relation to the presence of NAFLD. Adjusting for the type of antihypertensive treatment did not modify results presented in Fig. 1.

The effects of metabolic syndrome and NAFLD and their interaction on the vascular parameters were also evaluated with a two-factor analysis of variance (Table 2). This analysis confirmed the role of metabolic syndrome on all three vascular parameters (PWV, IMT, carotid plaques) and the influence of NAFLD on PWV only. No significant interaction was found.

All participants were further subdivided into tertiles (each group comprised of 74, 73, and 73 participants respectively) after which prevalence of NAFLD was analyzed according to PWV and IMT values. Data were adjusted for age, sex, HR and the main cardiovascular risk factors as well as factors determining metabolic syndrome: diabetes, triglycerides, HDL cholesterol, BMI, and systolic BP values. As shown in Fig. 2, with regard to aortic PWV (left panel), prevalence of NAFLD was significantly lower ($P < 0.05$) in the first and second tertile compared to the third tertile. By contrast, no association was found between IMT tertiles and NAFLD prevalence (right panel) after adjustment for the above-mentioned parameters.

Table 3 summarizes the results of stepwise regression analysis with IMT and aortic PWV as dependent variables. Two models were used: in the first model (Model A, Table 2, upper panel) age, sex, and metabolic syndrome were taken as independent variables. This model accounted for 30% of the variance in PWV (higher section), with major contributors being age (19.4%) and metabolic syndrome (2.4%) and for 35% of the variance in carotid IMT (lower section), with major contributors being age (22.0%), metabolic syndrome (2.3) and sex (1.8%). In the second model (Model B, Table 2, lower panel) NAFLD was added as an independent variable. This model accounted for 32% of the variance in PWV (higher section), with major contributors being age (24.8%) and NAFLD (4.6%), while the role of metabolic syndrome was nonsignificant. For IMT (35% of the variance, lower section), major contributors were age (22.0%), metabolic syndrome (2.3%), and sex (1.8%). Stepwise regression analysis was performed also with presence of carotid plaques as dependent variable; this model accounted for 16% of the variance, with the alone contributor of age (16.0%). These data not change after add of NAFLD as independent variable.

Fig. 2



Percentage of nonalcoholic fatty liver disease (NAFLD) per pulse wave velocity tertiles (left panel) and intima–media thickness tertiles (right panel). Data were adjusted for age, sex, heart rate, diabetes, triglycerides, HDL cholesterol, body mass index, and humeral systolic blood pressure values.

Table 3 Results of stepwise regression analysis with pulse wave velocity and intima–media thickness as dependent variables in the entire study population

Variable	Standard. coefficient	R^2 change (%)	R^2 other X's	T-value	P
Model A					
Dependent variable: PWV ($R^2 - 0.30$, $P < 0.001$)					
Age	0.47	19.4	0.12	7.76	<0.0001
Metabolic S.	0.17	2.4	0.12	2.75	0.007
Sex		1.1	0.02	1.85	0.07
Dependent variable: IMT ($R^2 - 0.35$, $P < 0.001$)					
Age	0.51	22.0	0.14	8.49	<0.0001
Metabolic S.	0.16	2.3	0.14	2.76	0.007
Sex	−0.13	1.8	0.02	−2.44	0.02
Model B					
Dependent variable: PWV ($R^2 - 0.32$, $P < 0.001$)					
Age	0.50	24.8	0.01	8.92	<0.0001
NAFLD	0.22	4.6	0.01	3.86	0.0002
Sex		0.7	0.04	1.55	0.2
Metabolic S.		0.6	0.25	1.41	0.2
Dependent variable: IMT ($R^2 - 0.35$; $P < 0.001$)					
Age	0.50	22.0	0.14	8.49	<0.0001
Metabolic S.	0.16	2.3	0.14	2.76	0.007
Sex	−0.14	1.8	0.02	−2.44	0.02
NAFLD		0.3	0.17	0.97	0.4

In Model A (upper panel), age, metabolic syndrome (Metabolic S.), and sex are the independent variables. In Model B (lower panel), age, metabolic syndrome, sex, and nonalcoholic fatty liver disease (NAFLD) are the independent variables. For each model, the dependent variable is PWV in the upper section of the panel, and IMT in the lower section. P, probability level.

Discussion

The predominant result of this study is the observed strong relationship between NAFLD and arterial stiffness. The data also revealed a close relationship between NAFLD and metabolic syndrome: 48% of patients with NAFLD had an associated metabolic syndrome and 75% of patients with metabolic syndrome presented an associated NAFLD. Hence, it is not surprising that all factors determining or closely related with metabolic syndrome were significantly higher in NAFLD compared to controls, such as weight, BMI, waist circumference, hip circumference, hypertension and BP values, diabetes, uric acid, glucose, triglycerides, and GGT. However, HDL cholesterol levels were lower in patients with NAFLD. These data do not substantially differ from prevalence reported in the literature [9–10], and appear to confirm the suggested view of considering NAFLD as the hepatic expression of metabolic syndrome [11–12]. Recent studies suggest that insulin-resistance is the early metabolic disorder [33], and that NAFLD may be considered an additional feature of metabolic syndrome, with specific hepatic insulin resistance [34].

Carotid IMT values in the present study were strongly related to the presence of metabolic syndrome factors. In patients with NAFLD without metabolic syndrome, IMT values were significantly lower, when compared to the NAFLD group with associated metabolic syndrome. Moreover, the prevalence in NAFLD significantly increased in tertiles with the highest values of IMT, although this significant relationship was negated after adjustment for factors determining metabolic syndrome.

Aortic PWV values were significantly increased when NAFLD was associated with metabolic syndrome. This is not surprising considering that the presence of the single factors determining metabolic syndrome also determines an increase in PWV, that is, the greater the number of associated factors, the greater the PWV values [35]. Nevertheless, such reasoning cannot explain the increase in prevalence of NAFLD in patients with high PWV values, especially since data were adjusted for all factors determining metabolic syndrome. Moreover PWV also increased significantly when NAFLD was not associated with metabolic syndrome. Stepwise regression analysis confirmed the independent role of NAFLD in the increase in aortic PWV. When age, sex, and metabolic syndrome were used as independent variables (Table 2, Model A), the major contributors of both PWV and IMT were age and metabolic syndrome. However, when NAFLD was added as an independent variable to the above model (Table 2, Model B), NAFLD was found to be the major contributor of aortic PWV rather than metabolic syndrome, whereas the contribution of NAFLD for carotid IMT was not significant. Therefore, it can be deducted that aortic PWV is related to metabolic syndrome only if it is associated with NAFLD. Currently, carotid-femoral PWV is considered an important and independent risk factor for CVD [36,37] and the close relationship with NAFLD may contribute in explaining the higher mortality in patients with NAFLD [1,11,13–16], even after adjustment for classical risk factors and metabolic syndrome components [11,18]. The differences observed between PWV and results pertaining to IMT and carotid plaques confirm the concept of differences between stiffness and atheromatosis. The possible biological mechanisms linking NAFLD and higher risk of CVD remain little known however. Several mechanisms have been suggested, such as increased oxidative stress [38,39] and chronic subclinical inflammation [38–40] as well as decreased adiponectin concentrations [40–42] and an adipose-secreted cytokine with antiatherogenic properties [41,43]. Moreover, the presence of abnormal lipoprotein metabolism [44,45] or an increase in whole-body insulin resistance [11] and/or dyslipidemia could also lead to accelerated atherosclerosis [46]. In keeping with these hypotheses, it is not surprising that the effect of NAFLD was observed on aortic PWV and not on upper limb PWV, since our group recently demonstrated that arterial inflammation is associated with an increase in central PWV, and not peripheral PWV [47].

Some limitations of this study merit consideration. Firstly, in the present study, NAFLD diagnosis was exclusively based on ultrasound imaging, although not confirmed by liver biopsy, which is the best-known diagnostic tool for confirming NAFLD. Several studies

assessing the sensitivity and specificity of ultrasound (U/S) in detecting hepatic steatosis have related a sensitivity between 60 and 94% and a specificity between 88 and 95% [4,48–51]. Sensitivity of U/S increases with increasing degrees of fatty infiltration: U/S has a high specificity but underestimates the prevalence of hepatic steatosis when fat is less than 20% [52]. In order to attain the highest level of sensitivity and specificity and the lowest level of operator dependence in the diagnosis of NAFLD, we used the strict and rigorous criteria described above, and all abdominal U/S were performed by the same operator (A.P.), a gastroenterologist with more than 25 years of experience in U/S liver examination. Another limitation is the cross-sectional design of the study, which hampers the assessment of cause and effect. Nevertheless, the Cardio-GOOSE study being a longitudinal study, the data observed herein relative to mortality and morbidity will be very useful in gaining a better understanding of the role of NAFLD and PWV in cardiovascular damage. A further possible limitation of this study was the presence of patients receiving drugs with possible effects on arterial distensibility, especially antihypertensive treatments. This factor was taken into account in all statistical analysis, and has been verified that adjustment for the type of antihypertensive treatment did not modify results.

In conclusion, the present study demonstrates a close relationship between NAFLD and carotid IMT (the latter being considered as an index of preclinical atherosclerosis), although this relationship was strongly associated with metabolic syndrome and its determining factors.

A strong relationship was also found between NAFLD and PWV, this relationship was only partially related to the presence of metabolic syndrome. The above data likely support a specific role of NAFLD in determining arterial stiffness.

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I.1.2. Conclusion de l'ARTICLE 8

Cette étude montre une forte corrélation entre la stéatose hépatique non alcoolique et la rigidité artérielle. Les résultats confirment aussi l'association entre la NAFLD et le syndrome métabolique : 48 % des patients avec NAFLD avaient aussi un syndrome métabolique, tandis que 75 % des patients avec syndrome métabolique présentaient aussi une NAFLD. Il n'est donc pas surprenant que tous les facteurs associés au syndrome métabolique soient plus représentés chez les patients avec NAFLD que chez les sujets contrôles. Ces résultats semblent donc confirmer la notion selon laquelle la NAFLD serait l'expression hépatique du syndrome métabolique.

La rigidité aortique était aussi plus élevée chez les patients avec NAFLD avec ou sans syndrome métabolique, ce qui suggère donc que l'association entre rigidité et NAFLD est indépendante du syndrome métabolique.

II Le diabète de type 2

Après avoir étudié les modifications vasculaires dans l'état d'insulinorésistance, étudions-les maintenant dans le cadre du diabète.

Dans ce chapitre, nous aborderons d'abord l'interaction entre diabète et hypertension artérielle, deux conditions cliniques très fréquentes et souvent associées, en essayant de montrer la contribution spécifique du diabète dans la rigidité artérielle, au delà des niveaux tensionnels.

Ensuite, en nous focalisant sur des sujets diabétiques, nous tenterons d'évaluer l'intérêt théorique et pratique de la mesure de la rigidité artérielle chez ces patients, ainsi que la relation entre les complications macro et microvasculaires, l'ancienneté du diabète et le degré de rigidité artérielle.

Le diabète de type 2 est considéré comme un facteur de risque cardiovasculaire bien établi, qui concerne plusieurs millions de personnes dans le monde. Des facteurs métaboliques, les produits de glycation et l'inflammation contribuent à la pathogénèse de la maladie cardiovasculaire associée au diabète.[24] Ces altérations impliquent les propriétés fonctionnelles et structurelles de l'arbre artériel, qui sont par ailleurs étroitement liées au risque cardiovasculaire.

Il existe un certain nombre de preuves montrant une rigidité artérielle accrue dans le diabète de type 1 et de type 2. Cette rigidification artérielle est un phénomène précoce survenant avant le début clinique de la maladie macro et microvasculaire. Ensuite, la rigidité artérielle augmente en présence de ces complications. Le fait que ces modifications artérielles sont présentes aussi dans l'intolérance glucidique, avant le début du diabète, indique que la maladie macrovasculaire associée au diabète de type 2 prend ses origines à partir de l'état de pré-diabète.

Même en l'absence d'une atteinte artérielle significative, il est reconnu que la morbi-mortalité dans le diabète résulte d'une restriction du flux sanguin dans les tissus due aux altérations microvasculaires. Ceci met en exergue la maladie microvasculaire diabétique, associée à l'atteinte rétinienne et rénale. Il est surprenant que des études sur les animaux aient montré que la dysfonction des *vasa vasorum* des gros troncs artériels est associée à la rigidification artérielle, en supposant une interaction potentielle entre grandes et petites artères qui aboutirait à un processus de rigidité accéléré dans le cadre du diabète. Il existe aussi des altérations de la relaxation des capillaires et des vaisseaux de résistance survenant à la fois avant et après le début du diabète. Pour cela la question se pose de savoir où commence la maladie: dans les grosses ou dans les petites artères ou, une fois que la maladie se déclare, à chacun des deux niveaux. De plus, la rigidité artérielle dépend strictement du niveau tensionnel, ce qui complique ultérieurement la relation entre grosses et petites artères : en effet, une augmentation de la pression moyenne pourrait augmenter par elle-même la rigidité apparente des gros troncs artériels. Au final, deux scénarios semblent se dégager : le premier est la détérioration primitive de la fonction rénale du fait d'un dysfonctionnement des petites artères qui conduirait à une atteinte des gros troncs par l'augmentation de la pression artérielle ; le deuxième, *a contrario*, consiste d'abord en une rigidification des grosses artères associée à l'élévation de la pression artérielle, qui entrainerait une transmission trop élevée des ondes de flux et de pression au niveau du lit vasculaire rénal. Cela affecterait directement les artérioles afférentes, résultant en une détérioration progressive de la fonction rénale.

L'effet de l'insuline *per se*, plutôt que de l'hyperglycémie, pourrait être un médiateur important de la rigidité artérielle, mais cela n'est pas encore prouvé. Les

patients porteurs d'un diabète de type 1 ou d'un diabète de type 2 présentent une tendance à la maladie vasculaire et à une rigidité artérielle augmentée, indépendamment des niveaux plasmatiques d'insuline. D'autre part, chez des sujets âgés non diabétiques, la pression pulsée et la vitesse de l'onde de pouls sont négativement corrélées avec la sensibilité à l'insuline, sans prendre en compte la tolérance glycémique. De même, la vitesse de l'onde de pouls aortique est élevée dans l'hyperinsulinisme. Toutefois, le niveau de preuve que la résistance insulinique augmente le risque cardiovasculaire ne semble pas suffisamment élevé.

L'insuline, en concentrations physiologiques, a un effet aigu vasodilatateur qui tend à augmenter la distensibilité artérielle, mais cet effet bénéfique est réduit dans les conditions d'insulinorésistance comme l'obésité, le syndrome métabolique et le diabète. L'effet chronique de l'insulinorésistance sur la rigidité artérielle a aussi été évalué chez des sujets sains, où l'on a observé une relation positive entre l'*uptake* de glucose induit par l'insuline et la distensibilité artérielle ; toutefois cette relation n'a été trouvée que pour la distensibilité de l'artère fémorale et uniquement chez les femmes.

II.1. ARTICLE 9 : Hypertension versus diabète : au-delà de la pression artérielle ? (soumis à Atherosclerosis)

II.1.1. Introduction de l'article 9

Jusqu'à présent, le dépistage de la maladie cardiovasculaire dans le diabète était fondé principalement sur la mesure des pressions systolique et pulsée brachiales.[25,26] Toutefois, dans des essais cliniques récents la pression artérielle centrale (systolique et pulsée) a montré sa supériorité par rapport à la périphérique dans l'estimation du risque cardiovasculaire,[6] et la rigidité artérielle est proposée comme un véritable marqueur du risque.[75]

Dans la littérature, les sujets diabétiques ont présenté des altérations des paramètres hémodynamiques centraux, notamment la pression centrale et la vitesse de l'onde de pouls qui se sont révélées plus élevées que chez les populations contrôles.[37,140] La plupart des études ont comparé les patients diabétiques aux sujets sains, mais chez les patients qui présentent à la fois un diabète et une hypertension artérielle la rigidité aortique semble être plus élevée que chez les patients avec une seule des deux maladies.[21,141] Dans le processus de rigidification artérielle chez les diabétiques, des facteurs hémodynamiques et mécaniques semblent être impliqués, ces derniers dérivant d'altérations des protéines de la matrice extracellulaire de la paroi artérielle.

L'étude suivante se propose donc d'analyser les modifications de la vitesse de l'onde de pouls et les facteurs associés, l'index d'augmentation et l'amplification de la pression pulsée, chez des patients diabétiques, en comparaison avec des patients non diabétiques, la plupart étant hypertendus.

Les deux groupes de patients, diabétiques (n=126) et non diabétiques (n=203), avaient des valeurs de pression artérielle comparables, sans différence statistique (Figure 36).

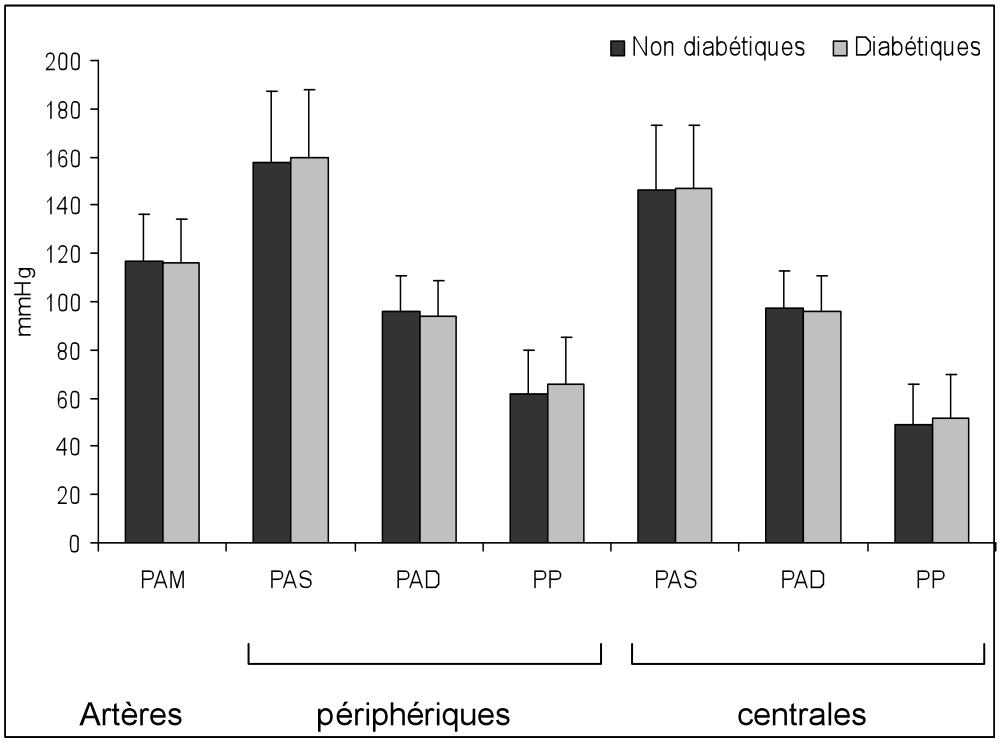

Figure 36. Pression artérielle moyenne (PAM), systolique (PAS), dsiastolique (PAD) et pulsée (PP), périphériques et centrales.

Les diabétiques présentaient une plus grande vitesse de l'onde de pouls, même après ajustement pour l'âge, le sexe, la pression artérielle moyenne, la fréquence cardiaque et le syndrome métabolique (Figure 37A).

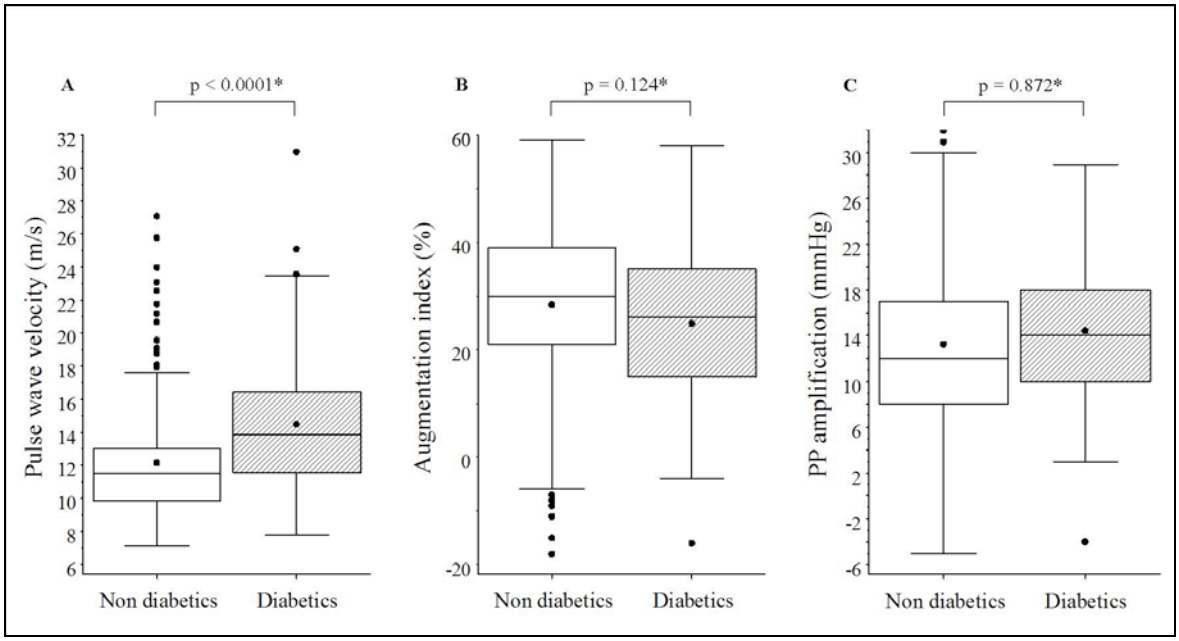

Figure 37. Modification des paramètres hémodynamiques. * valeur de p ajustée pour : âge, sexe, pression artérielle moyenne, fréquence cardiaque, et syndrome métabolique.

Ensuite, nous avons analysé les facteurs associés aux modifications de la vitesse de l'onde de pouls dans les deux groupes à travers des modèles de régression multiple (Tableau 5). Chez les patients non diabétiques, les variables indépendamment corrélées à la rigidité aortique étaient l'âge, la pression moyenne et la fréquence cardiaque ; chez les patients diabétiques nous avons retrouvé l'âge, la fréquence cardiaque et la présence d'un traitement par insuline. Il faut bien remarquer que la pression artérielle moyenne, normalement fortement corrélée à la vitesse de l'onde de pouls, n'était plus significativement corrélée à la rigidité aortique en présence des facteurs confondants.

Tableau 5. Facteurs associés aux modifications de la vitesse de l'onde de pouls*.

	Diabétiques (n=125)			Non-diabétiques (n=200)		
Variables	beta	R2	p	beta	R2	p
Age	0.463	0.221	<.0001	0.518	0.286	<.0001
Sexe			0.734			0.363
PAM			0.102	0.244	0.084	<.0001
FC*	0.241	0.073	0.003	0.211	0.063	0.000
Insuline	0.226	0.068	0.004			
R2 ajusté		0.31			0.38	

* variable transformée en logarithme. Taille, tabagisme, syndrome métabolique, traitement par sartans n'étaient pas significatifs. PAM : pression artérielle moyenne.

De plus la présence d'un diabète était associée aux valeurs les plus élevées de vitesse de l'onde de pouls, quel que soit le niveau de pression moyenne, tandis que la relation entre la vitesse de l'onde de pouls et l'âge présentait une pente plus raide chez les diabétiques, indiquant probablement un vieillissement artériel accéléré.

Par ces analyses nous avons aussi constaté que les patients diabétiques traités par insuline présentent des valeurs plus élevées de pression systolique, moyenne et pulsée, une maladie plus ancienne (durée du diabète plus élevée), plus sévère (hémoglobine glyquée augmentée), une rigidité aortique plus élevée que les patients non traités par insuline.

CENTRAL HEMODYNAMIC MODIFICATIONS IN DIABETES MELLITUS

Short title: CENTRAL HEMODYNAMICS IN DIABETES

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Abstract

Arterial stiffness in hypertension is markedly influenced by age, mean arterial pressure and heart rate, whereas factors influencing this parameter in diabetes mellitus remain partly unknown. We aimed to compare central hemodynamics in diabetics (n=126) versus non-diabetic controls (n=203), most of them being hypertensive, and at similar mean arterial pressure. Anthropometric, biological, and clinical examinations were obtained. Hemodynamic parameters (central blood pressure, aortic pulse wave velocity (PWV), augmentation index (AIx) and pulse pressure amplification (PPA)) were measured by applanation tonometry. Heart rate, PWV and augmentation index were significantly increased in diabetics, after adjustment for age, gender, mean arterial pressure, and heart rate, After further adjustment for metabolic syndrome only the difference in PWV persisted ($p<0.0001$). PPA was slightly but non-significantly altered. PWV in diabetics did not correlate with mean arterial pressure, suggesting that other structural alterations, promoted by insulin resistance may account for diabetic arterial stiffening more than, and independently of, blood pressure. Chronic treatment with insulin was associated with increased PWV, independently of blood pressure, diabetes control and duration and common confounders. In conclusion, hypertensive diabetics presented higher arterial stiffness than hypertensive control subjects. In diabetes, multiple factors affect arterial stiffening independently of hemodynamic status. Particularly, insulin therapy (IT) is associated with worse arterial stiffness,

suggesting a consistent relationship between these parameters. The question arises whether IT is a marker of diabetes severity favoring arterial stiffness, or has a direct/indirect effect on arterial wall modification.

Key words: diabetes mellitus, central hemodynamics, insulin therapy, pulse pressure amplification, pulse wave velocity, arterial stiffness.

Word count: Manuscript 4203 (without abstract, title page, and references), Abstract 225; Numbers: Tables 5; Figures 2.

Introduction

Diabetes mellitus (DM) is an established cardiovascular risk (CVR) factor, affecting several million of people in the world. Metabolic factors, glycation products, endothelial dysfunction, and inflammation are possible contributors in the pathogenesis of DM-induced cardiovascular diseases (CVD) [1]. Such alterations involve functional/structural properties of the arterial tree, which are strictly correlated to CVR. So far, the CVR assessment in DM has been based mainly on measurements of peripheral systolic blood pressure (SBP) and pulse pressure (PP) [2,3]. However, in recent population trials, central blood pressure (BP) has been found superior to peripheral BP to evaluate CVR [4], and aortic stiffness has become an established CVR marker [5]. These central hemodynamic parameters can be non-invasively studied by the arterial applanation tonometry, able to estimate central BP, aortic pulse wave velocity (PWV), a marker of aortic stiffness, augmentation index (AIx), linked to both cardiac contribution and wave reflection phenomena, and PP amplification (PPA), which implicates both aortic stiffness and wave reflection.

In literature, diabetic subjects are often compared only to control healthy subjects and alterations of central hemodynamics have been found in diabetic patients, who present increased central BP and PWV with regard to control populations [6,7]. Anyway, in patients having both diabetes and hypertension aortic stiffness seems to be higher than in those with one disease alone [8,9], but few studies compared diabetic with hypertensive patients with similar blood pressure [10] and there is little information about the implication of DM on arterial stiffness and BP modifications in hypertensive subjects. Hemodynamic and mechanical factors are implicated in the process of diabetic arterial

stiffening, the latter lying on alterations in matrix proteins within the arterial wall, where non-enzymatic crosslink between glucose and amino groups generates advanced-glycation-end-products (AGEs).

In the natural history of DM, insulin therapy (IT) is advocated in the presence of poor disease control, often associated to a long-duration disease. The physiologic acute effect of insulin on large arteries produces a decrease of aortic AIx, independently from the peripheral artery vasodilatation. At the contrary, obesity, metabolic syndrome (MetSyn), insulin resistance, and DM present an impaired response to insulin effect [11]. Anyway, the effect of a chronic insulin treatment on aortic PWV has been poorly investigated, and whether and how endogen hyperinsulinism and IT can influence large artery stiffness and central hemodynamics remains to be established.

To this respect, we aimed to investigate the levels and determinants of PWV, AIx and PPA, in diabetic subjects in comparison with non-diabetics, most of them being hypertensives, and to focus further on the role of IT in hemodynamic parameters' modification.

Methods

Patients

From November 2007 to November 2008 450 consecutive patients was prospectively examinated in the ambulatory department of cardiovascular prevention of Hotel-Dieu Hospital (Paris, France) for evaluation of one or more CVR factors including high BP, smoking, dyslipidemia, DM, and/or family history of premature CVD, with or without previously identified clinical events. Subjects with secondary hypertension, atrial fibrillation, chronic renal failure, congestive heart failure, and valvular heart disease were not included. Informed consent was obtained from all participants. For the present analysis, only subjects with both central and peripheral BP recordings, as well as PWV measurements were considered. The patients included (n = 329) were analyzed by forming two groups: non-diabetics group (n = 203), and diabetics group (n = 126). Furthermore, the diabetic group was divided into two more groups: patient treated (n = 59) and untreated (n = 67) by insulin therapy. Patients' characteristics were thus compared between groups.

Anthropometric measurements and clinical information

Clinical information were obtained from patients' filled questionnaire, involving age, sex, weight, height, family and personal history of diseases, smoking habits, and pharmacological treatment. Smoking was defined as a history of smoking and/or current smoking. Body mass index (BMI) was calculated by routine formula. MetSyn was defined according to the NCEP criteria [12]. DM was defined as fasting glucose > 7 mmol/L, or use of oral anti-diabetic agents or insulin. Laboratory and supplementary clinical information were obtained during hospitalization. Hypertension was defined as office SBP >140 mmHg and/or diastolic BP (DBP) above 90 mmHg, measured at least three times during the last two months, or when antihypertensive therapy was present. Brachial systolic and diastolic BPs were determined by OMRON 705IT (HEM-759E) [2], after at least 10 minutes rest in a supine position. A single physician performed three consecutive BP measurements and the average value was used for data analysis. Central and peripheral PPs were calculated as SBP – DBP.

Tonometric analysis

Arterial tonometry was performed by the SphygmoCor® device (AtCor Medical, Sydney, Australia) in radial, carotid and femoral arteries. Radial pressure waveform was obtained and calibrated with brachial SBP and DBP (obtained by OMRON 705IT). Mean arterial pressure (MAP) was calculated by integration of the calibrated radial pressure wave. Central pressure was determined using a transfer function starting from the radial artery pressure waveform. We previously described this methodology in detail [3]. AIx was automatically calculated by the SphygmoCor software. PPA was calculated as the ratio of brachial PP over central PP [4]. Carotid–femoral (aortic) PWV was determined using the foot-to-foot method over a 10-second period of consecutive waveforms registration [5].

Statistical analysis

Statistics were performed with SAS software version 9.0 (SAS Institute, Cary, NC). A $p \leqslant 0.05$ was considered as statistically significant. We represented quantitative variables as mean $\pm$ standard deviation. Weight, body mass index, total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL), plasma glucose, glycated hemoglobin, heart rate (HR), PWV, central PP, PPA, and DM duration had a non-normal distribution and are presented as median (interquantile range). Qualitative variables are expressed as frequency and percentage. Non-normal

variables were log transformed, except for total cholesterol and DM duration, which were root-square transformed.

Adjusted comparisons between diabetic and non-diabetic patients, and between insulin versus non-insulin treated patients, were made by ANCOVA test and logistic regression analysis for continuous and discrete variables, respectively. Multiple regression analyses were performed on PWV, AIx and PPA in total population. Correlation between PWV and age and MAP were obtained in diabetic/non-diabetic patients and in insulin/non-insulin taking patients. Interaction age/DM and MAP/DM, as well as age/insulin and MAP/insulin on the level of PWV, and adjusted correlations were investigated by general linear models procedure.

Results

Diabetics versus non-diabetics

Included subjects (n=329) were aged from 19 to 94 years. Anthropometric and laboratory parameters, CVR factors and drug treatment were compared between the two groups (table 1). No difference in gender distribution was found. Diabetic population was older, with higher weight, BMI and waist circumference than non-diabetic population. Plasma glucose and glycosylated hemoglobin were higher in diabetic subjects, while the lipid profile, expressed by total cholesterol, HDL and LDL cholesterol, but not triglycerides, was better controlled in diabetic subjects. The proportion of hypertensive patients was slightly higher in non-diabetic group, which was less treated with statins or angiotensin blockers. Treatment with beta-blockers was equally distributed between the two groups.

Hemodynamic parameters comparison between diabetic and non-diabetic patients is shown in table 2. The two groups presented similar MAP (p for difference = 0.5). No statistical difference was found in central and peripheral BPs between the two groups, while HR was significantly higher in diabetic than non-diabetic subjects (75±17 vs. 69±18 bpm, respectively, adjusted P=0.022). AIx was slightly lower in diabetic (24.9±13.4%) than non-diabetic (28.4±15%) subjects (adjusted P=0.014), but after subsequent adjustment for metabolic syndrome the significance disappeared. PPA was slightly higher in diabetics then in non-diabetics (median[interquartile range]: 1.292[1.2-1.41]% vs 1.271[1.16-1.4]%, unadjusted p=0.014), but the difference was not statistically significant after adjustment (adjusted P=0.412).

Insulin treated versus untreated

Among diabetic subjects, we compared IT versus non-IT groups. There was no difference in anthropometric characteristics between the two groups, but chronically insulin treated patients presented a longer DM duration (median 17 years, interquantile range (11-13) vs. 7 years (3-12)), higher smokers frequency, lower prevalence of hypertension, and worse controlled diabetes (glycated hemoglobin 7.8±1.5 vs. 6.9±1.3 %, adjusted P<0.0001) than diabetic without IT. AIx and PPA were similar between groups (P=n.s. for both). Anthropometric, biochemical and treatment parameters did not differ between groups; particularly, the prevalence of hypoglycemic and antihypertensive treatments (statins, beta-blockers, angiotensin blockers, calcium channel blockers, and diuretics) was similarly distributed.

Pulse wave velocity

PWV was more than 2 m/s higher in diabetic than in non-diabetic subjects (median 13.9 interquantile range (11.6-16.4) vs. 11.5 (9.9-13.0) m/s, respectively, adjusted P<0.0001), but analyzing the correlation between PWV and age (figure 1 left panel) we found a significant interaction between age and the presence of DM. In particular, in diabetics the correlation between age and PWV was steeper than in non-diabetics and the difference between PWV in diabetics versus non-diabetics was significant only for patients older than 60 years. In figure 1 right panel, we show that PWV was constantly higher (1.4 m/s, p<0.0001) in diabetics for each level of MAP with no interaction, and significant correlation between PWV and MAP independently of the presence of DM. In diabetic patients, PWV was 1 m/s significantly higher (adjusted P=0.003) in IT than non-IT group.

In figure 2, correlations are analyzed for IT versus non-IT groups between PWV and either age or MAP. Analyses were adjusted for age, gender, MAP, heart rate, body height, glycated hemoglobin, and diabetes duration. In the left panel we can observe that no interaction is present between age and IT, the correlation between PWV and age is significant independently from IT, and PWV is constantly higher (1.4 m/s, p=0.025) in IT than non-IT for each age. At the contrary, in the right panel we show that there is no significant correlation between PWV and MAP in diabetic subjects, no interaction, and that PWV was 1.4 m/s higher in IT group for each MAP level (p=0.026).

Determinants of hemodynamic parameters in total population

In table 3, we show the determinants of PWV, AIx and PPA in total population. Parameters independently correlated to PWV are age, MAP, heart rate, and height, which are also significant determinants of AIx and PPA. Gender was correlated to AIx and PPA, but not to PWV, and DM was an independent determinant of PWV and AIx, but not of PPA.

Determinants of hemodynamic parameters in diabetic and non-diabetic patients

Table 4 shows the factors associated to PWV in diabetic and non-diabetic subjects. In diabetics, age, HR and the presence of IT were major determinants of PWV, independently from gender, height and MAP. DM duration, when substituted to IT, was also a significant determinant (data not shown). In non-diabetics, independent determinants of PWV were age, MAP, HR, and body height.

Discussion

Our principal finding was that PWV, but not AIx and PPA, was altered in diabetic subject versus non diabetics, and this was not explained by altered hemodynamic status. Furthermore, we showed that mechanisms of arterial stiffening seem to differ in diabetic and non-diabetic subjects. In particular, increased PWV correlated with MAP in non-diabetics but not in diabetic subjects. Finally, in DM, IT was independently related to increase in arterial stiffness.

Aortic stiffness

It is well established that insulin resistance, MetSyn and DM are associated to arterial tree stiffening [6,10,13–22] and thus, to increased CVR. Moreover, one recent trial analyzing the role of DM duration in CVD risk and all-cause mortality [23] found that men with long DM duration and no prior myocardial infarction were at the same risk level as non-diabetics with history of myocardial infarction. The pathogenesis of increased aortic stiffness in DM is complex. Metabolic factors, like hyperglycemia, AGEs, lipoproteins alteration, as well as endothelial dysfunction and inflammation, are associated to alteration of arterial pressure, function and structure, leading to increased aortic stiffness in DM [1].

In particular, it seems likely that stiffening of the arterial tree happens in DM independently from BP level. One study focused on the determination of aortic stiffness in healthy subjects compared to patients with DM alone, hypertension alone, and both DM and hypertension [8]. The authors found

that patients with DM and hypertension had higher aortic stiffness than subjects with only hypertension. In line with these results, we found that PWV was more than 2 m/s higher in diabetic (hypertension 80%) than in non-diabetic group (hypertension 86%), and this results was independent of HR, MAP, and metabolic alterations typical of DM, like increased waist circumference and glycated hemoglobin, or MetSyn. Thus, we evaluated possible mechanisms that could lead to this difference, and we found that, in DM, determinants of PWV did not include MAP. Even if this result could be driven by a relevant sample size difference and so a lack of power, Llauradò et al found similar results when considering a group of diabetic patients compared to control healthy subjects [24]: in the group of men, the authors found that low-grade inflammation and not MAP was a determinant of PWV in DM. It is possible that, in hypertensive diabetic subjects, arteriolar damage and capillary rarefaction are enhanced, causing on one side a reduction of antihypertensive drug power to improve BP control [25]. On the other side, in the presence of structural alteration typical of DM, the role of MAP on aortic stiffness may become secondary.

Moreover, in line with literature, we found a steeper correlation between PWV and age in DM than in control, independently of MAP, gender and other confounders [26,27]. Interestingly, De Angelis et al. showed that, in women, the correlation between PWV and age was steeper in the presence of DM than in MAP matched control subjects, but this was not true for men [26].

These and our results indicate that DM contribution per se leads to accelerated arterial aging, represented by increased aortic stiffness. In particular, as DM progresses, it is likely that insulin resistance, metabolic alteration and the formation of AGEs increase aortic stiffness by a local arterial wall effect [1], independently of MAP and classical determinants of aortic stiffness. This effect may justify at least in part the increased CVR observed in diabetic individuals.

Conversely, we did not find a specific role of AIx in DM. In literature, some studies analyzed differences in AIx in DM with disaccording results [6,7,22,28], Furthermore, recently, AIx seems likely to incorporate information about both arterial vessels properties (wave reflection, Windkessel effects, compliance) and cardiac contribution [29]. In line with this literature, our findings suggest that AIx may not be a major parameter for DM assessment.

The role of insulin therapy

Westerbacka et al. showed that the physiological reduction of aortic stiffness produced by insulin infusion was impaired in insulin resistance status [11]. Furthermore, Tamminen et al. found that chronic (6 months) IT in DM was associated to an improved vascular function [30]. In our study, IT was associated with increased aortic stiffness. In our population, insulin treated diabetics present a longer duration of DM, a higher prevalence of smokers, and higher glycated hemoglobin than diabetics without IT. Anyway, IT was independently correlated with PWV, and we found a difference in PWV between IT and non-IT subjects independently of both DM metabolic control (glycated hemoglobin) and DM duration.

It is difficult to explain these results. On one hand, the study of Tamminen et al. [30] showed that IT improved vascular function as measured by the only AIx and not by PWV, then the study sample was small, and the trial was neither randomized nor placebo-controlled. On the other hand, to our knowledge, no clinical trial investigated the effect of long-lasting (years) insulin treatment on arterial stiffness.

From our findings, it seems that IT may be involved in the process of arterial stiffening in DM, suggesting a relationship between insulin, AGEs, inflammation and aortic stiffness. Thus, question arises as whether IT is a marker of metabolic status favoring aortic stiffness, or has a direct/indirect effect on arterial wall modification. Further studies investigating this relationship as well as specific therapeutic goals are warranted.

Limitations

This study presents some limitations. Firstly, our population sample has been selected from patients presenting multiple CVR factors, thus deserving a day hospital care. As results, the diabetic and hypertensive populations may not be representative of every diabetic or hypertensive subjects. Secondly, the relatively low number of patients included did not permit a separate analysis in men and women. Nonetheless, in our study, there was no difference in gender distribution between groups, and the analyses were always adjusted for gender. Thirdly, our study is limited by its cross-sectional setting. Regression analysis can only provide information on the correlations between variables, but not on the cause-effect relationship. In our analysis, we adjusted for the most important confounding factors in determining an increase of arterial stiffness, besides diabetes, trying to avoid excessive collinearity and thus making the models solid. Anyway many other factors could play a role in

increasing arterial stiffness, and the assumption of linear correlation between variables is rarely met in clinical studies. Therefore, results from regression analyses should be interpreted with caution, Finally, the analysis on insulin treatment was limited by the low number of diabetic subjects (59 insulin treated, 67 untreated). Strengths of our investigation lay in the fully adjusted analyses that have been done in order to understand better the modifications of each hemodynamic parameter in DM.

In conclusion, our results suggest that: (1) DM contribution per se lead to early arterial aging, with increased PWV, but no modifications of AIx or PPA; (2) mechanisms of arterial stiffening are different in diabetic and non-diabetic subjects, and PWV loose its tight correlation with MAP in DM; (3) in DM, IT is independently associated with worse arterial stiffness, questioning about a direct/indirect effect of insulin on arterial wall modification, versus a simple marker of DM severity. As Insulin resistance and therapy, AGEs, inflammation, and aortic stiffness seem to be intercorrelated. Clinical longitudinal studies focusing on the role of AGEs on stiffness and cardiovascular disease in diabetic patients are thus welcome.

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Table 1. Clinical and biological parameters in diabetic versus non-diabetic population.

	Non diabetics (n = 203) Mean ± SD	Diabetics (n = 126) Mean ± SD	Total (n = 329) Mean ± SD	P*
Anthropometric characteristics				
Age, years	57 ± 15	63 ± 10	59 ± 14	**<.0001**
Male gender, n (%)	106 (52)	71 (56)	177 (54)	0.565
Weight, kg	75 (64-86)	80 (72-92)	76 (68-87)	**0.0002**
Height, cm	169 ± 9	168 ± 8	168 ± 9	0.712
Body mass index, kg/m2	25.8 (23.6-29.8)	28.4 (25.8-31.1)	27.1 (24.4-30.7)	**<.0001**
Waist circumference, mm	93 ± 14	101 ± 12	96 ± 14	**<.0001**
CV risk factors and laboratory				
Metabolic syndrome, n (%)	51 (25)	88 (70)	139 (42)	**<.0001**
Total cholesterol, mmol/L	4.90 (4.26-5.65)	4.14 (3.61-4.86)	4.71 (4.64-3.95)	**<.0001**
HDL cholesterol, mmol/L	1.34 (1.10-1.60)	1.20 (1.00-1.50)	1.32 (1.30-1.00)	**0.023**
Triglycerides, mmol/L	1.06 (0.79-1.46)	1.20 (0.90-1.61)	1.32 (1.12-0.84)	0.090
LDL cholesterol, mmol/L	2.92 (2.33-3.63)	2.29 (1.75-2.92)	2.79 (2.70-2.13)	**<.0001**
Smoking, pack-year	8 ± 14	13 ± 16	9 ± 15	**0.021**
Current or previous smoker, n (%)	94 (46)	69 (55)	163 (50)	0.133
Coronary heart disease, n (%)	17 (9)	14 (11)	31 (10)	0.881
Cerebrovascular disease, n (%)	8 (4)	5 (4)	13 (4)	0.737
Hypertension, n (%)	174 (86)	101 (80)	275 (84)	**0.021**
Duration of hypertension, years	11.6 ± 10.1	11.7 ± 7.6	11.7 ± 9.2	0.313
Creatinine, mcmol/L	83.8 ± 27.6	89.2 ± 48.1	85.8 ± 36.8	0.232
Plasma glucose, mmol/L	5.4 (4.9-5.8)	7.1 (6.1-9.3)	5.7 (5.1-6.8)	**<.0001**
HbA1C, %	5.7 (5.4-6.0)	7.3 (6.7-8.2)	6.1 (5.6-7.2)	**<.0001**
Urinary protein, g/24h	0.28 ± 0.88	0.56 ± 1.07	0.38 ± 0.97	**0.009**
Drug treatment				
ACE-I	21(10.5)	20(16)	41(12.6)	0.142

	Non diabetics (n = 203) Mean ± SD	Diabetics (n = 126) Mean ± SD	Total (n = 329) Mean ± SD	P*
ARBs	59(29.2)	73(58.4)	132(40.4)	<.0001
Diuretics, n (%)	81 (40)	67 (53)	148 (45)	0.249
Calcium channel blockers, n (%)	103 (51)	52 (41)	155 (47)	0.074
Alpha blockers, n (%)	11 (6)	4 (3)	15 (5)	0.375
Beta-Blockers, n (%)	61 (30)	32 (26)	93 (28)	0.063
Statins, n (%)	60 (30)	67 (53)	127 (39)	**0.002**
Antidiabetics with insulin, n (%)		59 (47)	59 (18)	
Antidiabetics without insulin, n (%)	57 (45)	57 (17)		

Values, except percentage, are presented as mean standard deviation, or median (interquartile range for non-normal variables.

SD indicates standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, glycated haemoglobin; ACE-I, inhibitors of the angiotensin converting enzyme; ARBs, angiotensin II receptor blockers.

P values are adjusted for age, gender and mean arterial pressure.

Table 2. Hemodynamic parameters in diabetic versus non-diabetic patients.

	Non diabetics (n = 203) Mean ± SD	Diabetics (n = 126) Mean ± SD	Total (n = 329) Mean ± SD	P*	P**
Mean arterial pressure, mmHg	117 ± 19	116 ± 18	116 ± 19	0.509	
Peripheral measurements					
SBP - brachial artery, mmHg	158 ± 29	160 ± 28	159 ± 28	0.953	
DBP - brachial artery, mmHg	96 ± 15	94 ± 15	95 ± 15	0.285	
PP - brachial artery, mmHg	62 ± 18	66 ± 19	64 ± 19	0.418	
Central measurements					
SBP - aortic, mmHg	146 ± 27	147 ± 26	146 ± 27	0.507	
DBP - aortic, mmHg	97 ± 16	96 ± 15	96 ± 16	0.288	
PP - aortic, mmHg	47 (37-58)	50.5 (37-63)	48 (37-61)	0.983	
Hemodynamic parameters					
Heart rate, bpm	69 (62-80)	75 (66-83)	72 (64-81)	**0.022**	
AIx, %	28.4 ± 15.0	24.9 ± 13.4	27.1 ± 14.5	**0.014**	0.124
PP amplification, %	1.271 (1.16-1.4)	1.292 (1.2-1.41)	1.276 (1.2-1.4)	0.412	0.872

Values, except percentage, are presented as mean standard deviation, or median (interquartile range) for non normal variables.

SD indicates standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; PWV, pulse wave velocity; AIx, augmentation index.

* P values are adjusted for age and gender; AIx and PP amplification are adjusted also for mean arterial pressure and heart rate.

** P values further adjusted for metabolic syndrome.

Table 3. Determinants of pulse wave velocity (PWV), AI and PP amplification in the totality of the population.

	PWV* (n=325)			AIx (n=329)			PPA* (n=329)		
Variables	beta	R2	P value	beta	R2	P value	beta	R2	P value
Age	0.479	0.254	<0.0001	0.169	0.038	<0.001	-0.364	0.200	<0.0001
Gender	.	.	0.424	0.185	0.028	0.003	-0.250	0.068	<0.0001
Mean arterial pressure	0.200	0.062	<0.0001	0.195	0.054	<0.0001	-0.191	0.070	<0.0001
Heart rate*	0.212	0.067	<0.0001	-0.460	0.237	<0.0001	0.503	0.338	<0.0001
Height	0.140	0.018	0.016	-0.220	0.041	<0.001	0.200	0.047	<0.0001
Diabetes mellitus	0.203	0.062	<0.0001	-0.114	0.019	0.014	.	.	0.289
Adjusted R2		0.41			0.36			0.53	

* log transformed in the model.

PWV indicates pulse wave velocity; AIx, augmentation index; PPA, pulse pressure amplification.

Smoking status and treatment with sartans were not significant determinants for every model.

Table 4. Determinants of pulse wave velocity (PWV*) in diabetics and non-diabetics.

	Diabetics (n=125)			Non-diabetics (n=200)		
Variables	beta	R2	P value	beta	R2	P value
Age	0.463	0.221	<.0001	0.518	0.286	<.0001
Gender			0.734			0.363
Mean arterial pressure			0.102	0.244	0.084	<.0001
Heart rate*	0.241	0.073	0.003	0.211	0.063	0.000
Insulin therapy	0.226	0.068	0.004			
Adjusted R2		0.31			0.38	

* log transformed in the model.

Body height, smoking status, metabolic syndrome, and treatment with sartans were not significant in each model.

Table 5. Clinical and biological parameters in insulin versus non-insulin treated diabetics.

	Without insulin (n = 67) Mean ± SD	Insulin (n = 59) Mean ± SD	Tot. diabetics (n = 126) Mean ± SD	P*
Anthropometric characteristics				
Age, years	63 ± 10	63 ± 10	63 ± 10	0.967
Male gender, n (%)	40 (60)	31 (53)	71 (56)	0.415
Body mass index, kg/m2	27.9 (25.6-31.1)	29.3 (25.9-31.2)	28.4 (25.8-31.1)	0.992
CV risk factors and laboratory				
Diabetes duration, years	7 (3-12)	17 (11-23)	11 (6-20)	**<.0001**
Total cholesterol, mmol/L	4.27 (3.65-4.71)	3.97 (3.43-4.92)	4.14 (3.61-4.86)	0.409
Current or previous smoker, n (%)	32 (48)	37 (63)	69 (55)	**0.024**
Coronary heart disease, n (%)	8 (12)	6 (10)	14 (11)	0.869
Cerebrovascular disease, n (%)	3 (5)	2 (3)	5 (4)	0.716
Hypertension, n (%)	59 (88)	42 (71)	101 (80)	**0.006**
Duration of hypertension, years	12 ± 9	11 ± 6	12 ± 8	0.562
HbA1C, %	6.9 (6.4-7.7)	7.8 (7.2-8.7)	7.3 (6.7-8.2)	**<.0001**
Urinary protein, g/24h	0.32 ± 0.65	0.83 ± 1.36	0.56 ± 1.07	**0.01**
Hemodynamic parameters				
Heart rate, bpm	73 (64-80)	80 (67-85)	75 (66-83)	0.209
PWV, m/s	13.3 (11-15.9)	14.4 (12.5-18.7)	13.9 (11.6-16.4)	**0.003**
AIx, %	25.4 ± 14.1	24.5 ± 12.6	24.9 ± 13.4	0.465
PP amplification, %	1.298 (1.19-1.46)	1.276 (1.17-1.39)	1.292 (1.18-1.41)	0.243

Values, except percentage, are presented as mean standard deviation, or median (interquartile range) for non-normal variables.
SD indicates standard deviation; HbA1c, glycated haemoglobin; PWV, pulse wave velocity; AIx, augmentation index; PP, pulse pressure.
Anthropometric, biochemical and treatment parameters that are not shown in this table were not significantly different between the two groups, even after adjustment for age, gender and mean arterial pressure.
* P values are adjusted for age, gender and mean arterial pressure.

Figure Legends

Figure 1. Correlations between aortic pulse wave velocity and age (left panel) and mean arterial pressure (right panel), in diabetics (empty squares) versus non-diabetics (full circles). Analyses are adjusted for age, gender, MAP, HR, body height.

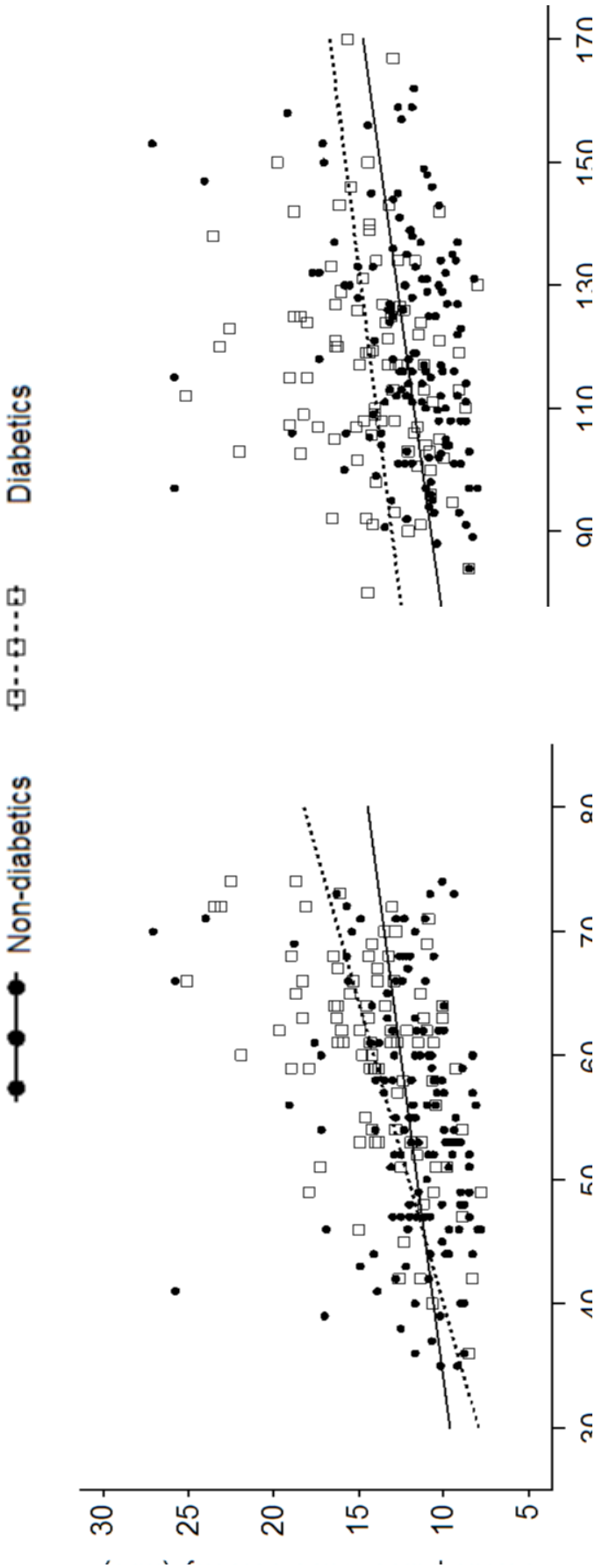
Left panel: p for interaction = 0.048 unadjusted, 0.044 adjusted. Correlations: a) Non-diabetics: beta 0.116, $p < 0.0001$; b) Diabetics: beta 0.185, $p < 0.0001$.

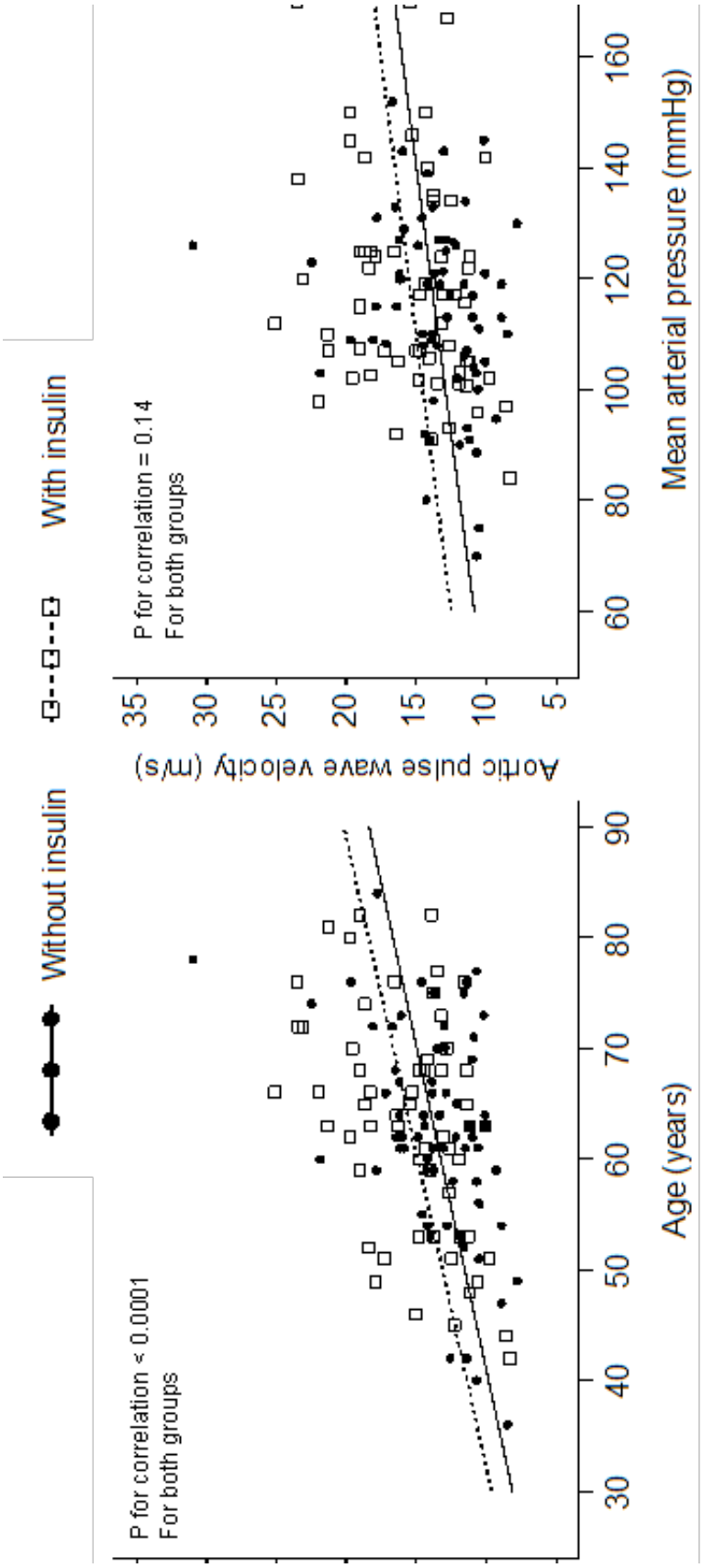
Right panel: p for interaction = 0.6. Correlation: ß = 0.20, $p<0.0001$. Analysis adjusted for gender, age, Heart rate, body height.

Figure 2. Correlations between aortic pulse wave velocity and age (left panel), and mean arterial pressure (right panel), in diabetics treated with insulin (empty squares) versus untreated (full circles). Analyses adjusted for age, gender, MAP, heart rate, body height. Adjusting for glycated hemoglobin and/or diabetes duration did not change the results.

Left panel: p for interaction = 0.9. Adjusted correlation: ß = 0.23, $p<0.0001$.

Right panel: p for interaction = 0.8. Adjusted correlation: ß = 0.12, $p=0.14$.


Non-diabetics
Diabetics
30
25
20
15
10
5
20
40
60
80
90
110
130
150
170


Without insulin
With insulin
P for correlation < 0.0001
For both groups
Age (years)
30
40
50
60
70
80
90
Aortic pulse wave velocity (m/s)
5
10
15
20
25
30
35
P for correlation = 0.14
For both groups
Mean arterial pressure (mmHg)
60
80
100
120
140
160

II.1.2. Conclusion de l'ARTICLE 9

Ces résultats montrent donc un effet du diabète sur la structure de la paroi des artères, qui est capable de se rajouter à l'hypertension indépendamment du niveau de pression artérielle moyenne. Comme on l'a vu dans la première partie, la compliance artérielle dépend en premier lieu de la composition de la paroi artérielle, et notamment du rapport entre les fibres élastiques et le collagène. Secondairement, la « pression de distension » joue un rôle fondamental : il s'agit de la pression qui se trouverait dans une artère à l'état de repos et qui correspond à la pression moyenne du système hémodynamique. Il semble donc clair que deux artères avec la même composition de paroi, mais à deux niveaux différents de pression moyenne, présentent des rigidités différentes ; et, inversement, deux artères à même niveau de pression moyenne mais avec des compositions de paroi différentes auront aussi des rigidités différentes.

Cela nous conduit à penser que les altérations métaboliques liées au diabète jouent un rôle propre dans la modification de la structure de la paroi artérielle à travers plusieurs facteurs tels que l'accumulation des produits de glycation avancée, le stress oxydatif, la dysfonction endothéliale.[24]

De plus, nous avons mis en évidence un vieillissement artériel accéléré chez les patients diabétiques ainsi qu'une relation entre le traitement par insuline et la rigidité aortique. Etant donné que les patients traités par insuline avaient aussi une maladie plus sévère et ancienne, on peut se poser la question de savoir si l'insuline est en soi liée aux modifications de la paroi artérielle ou si elle n'est qu'un marqueur de sévérité du diabète.

II.2. ARTICLE 10 : La rigidité artérielle dans le diabète : un prédicteur du risque cardiovasculaire ?[142]

II.2.1. Introduction de l'ARTICLE 10

Nous allons maintenant analyser en détail le rôle de l'ancienneté du diabète dans la maladie cardiovasculaire. Cette étude est née du constat que les patients diabétiques ne sont pas tous égaux, et notamment présentent différents niveaux de rigidité artérielle selon qu'ils soient ou non traités par insuline, comme nous l'avons montré dans l'article précédent. Nous évaluerons donc le sur-risque cardiovasculaire des patients diabétiques et son lien avec la rigidité artérielle, ainsi que la relation entre durée du diabète, rigidité artérielle et complications micro et macrovasculaires.

Les complications cardiovasculaires associées au diabète augmentent avec la progression de la maladie, et pour cette raison l'ancienneté du diabète peut être considérée comme un reflet à la fois du vieillissement et des complications cardiovasculaires. En effet, des études ont montré que l'ancienneté du diabète était corrélée à une augmentation du risque de mortalité coronaire,[143–145] de mortalité pour causes naturelles,[146] et d'altérations de la fonction du myocarde.[147]

Dans une des études les plus intéressantes, Wannamethee et al. ont examiné l'influence de l'âge au moment du diagnostic du diabète, la durée du diabète sur le risque cardiovasculaire et la mortalité toutes causes chez des hommes de 60-79 ans.[145] Quatre mille quarante-cinq hommes ont été inclus et suivis pendant neuf ans. Les patients étaient classifiés comme : sans histoire d'infarctus du myocarde ni de diabète ; avec un diagnostic de diabète après l'âge de 60 ans ; avec

un diabète précoce, diagnostiqué avant l'âge de 60 ans ; ou avec un antécédent d'infarctus du myocarde.

Les résultats de l'étude sont assez surprenants : les patients avec un diabète « précoce » (associé à une durée de 16,7 ans) présentaient un risque comparable à celui des patients avec antécédent d'infarctus du myocarde (Tableau 6).

Tableau 6. Rapport de risque pour événements coronaires et cardiovasculaires, et mortalité toutes causes. (de [145]).

Event	Study Group: No Prevalent Diabetes or Prior MI (n = 3197)	Men With Prevalent Diabetes With No Prior MI: Late Onset (n = 307)	Men With Prevalent Diabetes With No Prior MI: Early Onset (n = 107)	Men With Prior MI With No Prevalent Diabetes (n = 368)
Major CHD (n = 353)				
Rate (No. of events)	8.7 (229)	15.7 (36)	21.7 (18)	25.7 (70)
Age	1 [Reference]	1.70 (1.20-2.42)	2.93 (1.81-4.74)	2.73 (2.08-3.56)
Model 1[b]	1 [Reference]	1.69 (1.18-2.41)	2.86 (1.76-4.64)	2.62 (1.99-3.44)
Model 2[c]	1 [Reference]	1.55 (1.08-2.21)	2.63 (1.56-4.42)	2.61 (1.96-3.49)
Model 3[d]	1 [Reference]	1.54 (1.07-2.21)	2.39 (1.41-4.05)	2.51 (1.88-3.36)
Major CVD (n = 534)				
Rate (No. of events)	13.5 (361)	22.7 (53)	28.5 (24)	34.5 (96)
Age	1 [Reference]	1.59 (1.19-2.12)	2.61 (1.73-3.96)	2.35 (1.88-2.95)
Model 1[b]	1 [Reference]	1.53 (1.15-2.06)	2.52 (1.65-3.84)	2.23 (1.76-2.83)
Model 2[c]	1 [Reference]	1.42 (1.05-1.91)	2.35 (1.51-3.67)	2.27 (1.79-2.89)
Model 3[d]	1 [Reference]	1.37 (1.01-1.84)	2.08 (1.33-3.25)	2.17 (1.71-2.77)
All-Cause Mortality (n = 1080)				
Rate (No. of events)	29.3 (784)	46.2 (108)	48.7 (41)	52.8 (147)
Age	1 [Reference]	1.51 (1.23-1.84)	2.10 (1.53-2.88)	1.65 (1.38-1.97)
Model 1[b]	1 [Reference]	1.41 (1.15-1.73)	1.96 (1.42-2.72)	1.56 (1.30-1.88)
Model 2[c]	1 [Reference]	1.39 (1.13-1.91)	1.85 (1.31-2.60)	1.56 (1.29-1.87)
Model 3[d]	1 [Reference]	1.31 (1.06-1.62)	1.68 (1.19-2.38)	1.48 (1.22-1.78)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.
[a] CVD events include CVD deaths and nonfatal MI. We excluded 66 men with diabetes and MI (32 deaths and 19 major CHD events). Unless otherwise indicated, data are expressed as hazards ratio (95% confidence interval). Early and late onset of diabetes are described in Table 1.
[b] Includes age, smoking, alcohol consumption, social class, body mass index, physical activity, and previous stroke.
[c] Includes model 1 plus systolic blood pressure, high-density lipoprotein and total cholesterol levels, and low forced expiratory volume in 1 second.
[d] Includes model 2 plus C-reactive protein and von Willebrand factor levels and estimated glomerular filtration rate.

La rigidité artérielle est considérée comme un marqueur de l'effet combiné des facteurs de risque cardiovasculaire, et pourrait représenter le lien entre le diabète et la maladie cardiovasculaire.[75]

Notre équipe a déjà montré l'intérêt de la rigidité artérielle chez des patients diabétiques.[142] Dans une étude transversale, portant sur 618 sujets diabétiques algériens, la vitesse de l'onde de pouls carotido-fémorale était très corrélée à la prévalence de la maladie cardiovasculaire ; de plus la rigidité artérielle se rajoute

significativement aux autres facteurs de risque, en améliorant la prédiction de la maladie cardiovasculaire.

Original Article

Aortic stiffness and cardiovascular risk in type 2 diabetes

Abdellah Salah Mansour[a], Alexandra Yannoutsos[b], Nilla Majahalme[b], Davide Agnoletti[b], Michel E. Safar[b], Said Ouerdane[a], and Jacques Blacher[b]

Objective: Damage to large arteries is a major contributor to high cardiovascular morbi-mortality in type 2 diabetic patients. Pulse wave velocity (PWV), depending on both structural and functional characteristics of the arterial wall, has poorly been ascertained in its ability to be a marker of cardiovascular risk in diabetic patients. In order to determine the factors influencing aortic stiffness, and the potential predictor role of this measurement, a cross-sectional study on a cohort of 618 type 2 diabetic patients with or without cardiovascular events was conducted.

Methods: Aortic PWV (estimated by carotid-femoral PWV measurement) was determined using an automatic device and cardiovascular risk was determined, using Framingham equation (10-year absolute cardiovascular disease risk), in individuals without previous cardiovascular events. Multilinear regression analysis was performed to assess relationships between aortic PWV, population characteristics and the presence of cardiovascular disease. Multivariate models (with and without PWV) were compared to determine whether aortic PWV improves explicative model of presence of cardiovascular disease.

Results: Increased aortic PWV was strongly associated with presence of coronary, cerebral and peripheral vascular diseases. Increased aortic PWV was independently associated with previous cardiovascular events and improved the explicative model of presence of cardiovascular disease above the known cardiovascular risk factors.

Conclusion: This study provides evidence that aortic PWV is a forceful independent marker of cardiovascular disease in diabetic patients, as it has already been demonstrated in hypertensive individuals. Prospective trials are needed to assess the improvement in cardiovascular risk prediction for widespread use of aortic PWV in diabetic patients.

Keywords: aortic stiffness, atherosclerosis, cardiovascular disease, cardiovascular risk assessment, cardiovascular risk factors, carotid-femoral pulse wave velocity, type 2 diabetes

Abbreviations: ABPI, ankle-brachial pressure index; AUC, area under the receiver operating characteristic curve; CHD, coronary heart disease; FRS, Framingham risk score; PWV, pulse wave velocity; RIDI, relative integrated discrimination improvement

INTRODUCTION

Type 2 diabetes is a worldwide health problem and major cause of cardiovascular morbi-mortality. More than 250 million people worldwide have type 2 diabetes, and an increase of more than 50% is expected until 2025. This is an emerging health problem in Maghreb countries, as the changes in lifestyle and nutritional habits within the last few decades have led to an increase of metabolic diseases. Around 10% of the Algerian adult population suffer from type 2 diabetes, and a large number of patients have not yet been diagnosed. There is a frequent association between type 2 diabetes and hypertension, because of nutritional and epidemiological transition, especially increased salt consumption [1] and the spread of obesity, both closely related with insulin resistance. More than one-third of Algerian adult population is hypertensive, almost 7 million people and more than 40% of type 2 diabetic patients are suffering from hypertension. However, awareness, treatment and control of type 2 diabetes and hypertension in Algeria remain low and have to be improved.

The epidemiological studies highlighted increased cardiovascular risk in diabetic patients, enhanced by the frequent association with other cardiovascular risk factors, particularly hypertension and dyslipidemia [2]. Whether type 2 diabetes alone is a coronary heart disease (CHD) risk equivalent [2,3] remains controversial [4]. Heterogeneity in cardiovascular risk has been demonstrated in diabetic population, especially in younger and newly diagnosed patients without associated cardiovascular risk factor or target organ damage. Recent study highlights that, among elderly men (aged 60–79 years), only diabetes duration of a decade or more is to be considered as a CHD risk equivalent [4]. Delayed glycemic control and long

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duration of diabetes dramatically increase cardiovascular risk. There is a direct relation between the risk of developing cardiovascular complications and the increasing hyperglycemia, especially for microvascular diseases [5]. The emphasis must be on achieving optimal blood glucose levels at the time of diagnosis, because of the existence of a 'glycemic memory' [6], associated with others cardiovascular risk factors control. The past history of atherosclerotic disease, the delayed onset date of diabetic treatment, the short duration of both blood glucose control and follow-up may explain the lack of optimal treatment benefit on cardiovascular morbi-mortality in three recent interventional trials [7–9]. Moreover, elevated pulse pressure, a consequence of arterial stiffening, has to be taken into account for its strong predictive value of cardiovascular disease risk in type 2 diabetes [10]. The current strategy suggests a more intensive blood glucose, blood pressure (BP) and lipid lowering in high-risk diabetic patients. The cardiovascular risk equations do not provide at the moment reliable risk estimates in type 2 diabetes [11].

Assessment of aortic stiffness, an infraclinic atherosclerotic damage, in addition to standard cardiovascular risk factors, would distinguish poor cardiovascular prognosis arguing about a more intensive level of care. High SBP and pulse pressure, low DBP, consequences of arterial stiffening, have been identified as independent factors of cardiovascular morbi-mortality [12]. The interest of peripheral haemodynamic measurement has shifted to more direct aortic stiffness measurement, as target organs are more exposed to central haemodynamic changes than peripheral ones [13]. The carotid-femoral pulse wave velocity (PWV) is considered as the gold standard direct and noninvasive aortic stiffness assessment [14]. Central pulse pressure or wave reflection analysis gives further information about aortic stiffness. Recently, the Framingham heart study [15] highlighted the lack of association of carotid-radial (muscular artery) PWV, augmentation index, central pulse pressure and carotid brachial pulse pressure amplification with first-onset major cardiovascular event, in contrast to aortic PWV. The independent predictive value of aortic PWV has been established for all-cause and cardiovascular mortality, fatal and nonfatal coronary events and fatal stroke in hypertensive patients [16–18], in end-stage renal disease [19,20], in older adults [21,22] and in the general population [23–25]. This indicates that aortic stiffness must be considered as a tissue biomarker of early vascular ageing, allowing a cumulative measure of previous exposure to all cardiovascular risk factors. In hypertensive patients, the predictive value of Framingham Risk Score (FRS) for primary CHD is improved by aortic stiffness assessment [17]. The European Society of Hypertension/European Society of Cardiology (ESC) recommends aortic PWV measurement, in addition to other cardiovascular risk factors, to identify hypertensive patients with higher cardiovascular risk [26]. Nevertheless, clinical utility of aortic stiffness measurements in a population of diabetic patients has been poorly studied.

The goal of the present study was to test the ability for aortic PWV to act as a marker of individual cardiovascular risk, integrating the atherosclerotic vascular damage caused by the most common cardiovascular risk factors, and then to identify high-risk patients from a diabetic population never treated or even treated medically by antihypertensive agents. In order to determine the factors influencing aortic stiffness (estimated by measuring the carotid-femoral PWV), and whether aortic PWV improves explicative model of presence of cardiovascular disease over and above the traditional cardiovascular risk factors, we conducted this cross-sectional study on a cohort of 618 type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

Study cohort

From 2005 to 2009, a cross-sectional study was conducted in patients with type 2 diabetes, with or without previously identified cardiovascular diseases. Definition of type 2 diabetes was classical: patients with fasting blood glucose greater than 1.26 or 2 g/l at any time tested twice or those with antidiabetic dietary or treated with oral hypoglycemic agents alone or associated with insulin therapy. Cardiovascular events (CHD, cerebrovascular disease and peripheral vascular disease) were retrospectively assessed. All patients were recruited after consultation in the Department of Internal Medicine of Tizi Ouzou Hospital. The majority of patients were referred by their general practitioner, for a cardiovascular check-up, and the others were in-hospital source of patients, with follow-up consultation after hospital care in internal medicine service. Patients with cancer (other than basal cell carcinoma), type 1 diabetes and severe renal insufficiency (creatinine >300 μmol/l) were not included in the study. The first 693 type 2 diabetic patients seen during this consultation, with no exclusion criteria, were selected. Central haemodynamic and laboratory measurements have not been performed successfully in 32 patients (atrial fibrillation in eight patients, frequent extrasystoles or poor quality waveform) and 43 patients, respectively. The study cohort was then composed of 618 consecutive patients (260 men, 358 women), with mean age (±SD) of 59.4 ± 11.5 years. Each individual provided informed consent for the study, which was approved by our institutional review board.

Information compiled from the questionnaire filled out at inclusion included sex, age, weight and height, BMI (weight in kilograms divided by the square of the height in meters), family (first-degree relatives) history of premature cardiovascular events, personal history of dyslipidaemia, hypertension, smoking habits, previous diseases and use of medications, including antidiabetics, lipid-lowering agents and antihypertensive drugs. From the clinical questionnaire and the findings of the check-up during hospitalization, cardiovascular events were present in 127 patients and absent in 491 patients. Cardiovascular events were ascertained and validated: scan imaging documented stroke for cerebrovascular disease; past medical history of documented myocardial infarction, coronary revascularization or typical electrocardiographic modifications for CHD; ankle-brachial pressure index (ABPI) value less than 0.90 or 20% diminishing ABPI after sensitivity exercise testing (if ABPI value range from 0.9 to 1), imaging-documented arteriopathy including peripheral vascular disease and abdominal aortic aneurysm, arterial

revascularization or lower limb amputation for atherosclerotic peripheral vascular disease. Dyslipidemia was defined as a total/high-density lipoprotein (HDL) cholesterol ratio of more than 5 or the presence of a hypocholesterolemic drug. In patients without previously diagnosed hypertension, high normal BP was defined as SBP of at least 130 mmHg and/or DBP of at least 85 mmHg; high BP was defined as SBP of at least 140 mmHg and/or DBP of at least 90 mmHg, measured by sphygmomanometry, in the supine position with a minimum of three casual measurements during the last month.

Materials and methods

The measurements were performed in the morning after an overnight fast, each patient being in supine position. Brachial BP was measured at the right arm using an automatic BP monitor (OMRON 705 CP II IT; Omron Healthcare Co., Ltd, Kyoto, Japan) after 5 min of rest. Three measurements 2 min apart were performed and the average of the last two measures was considered. Mean BP (MBP) was calculated as MBP = DBP + [(SBP − DBP)/3].

After BP determination, the aortic PWV measurement was performed, before the three-lead orthogonal ECG and blood sample. Carotid-femoral PWV, the 'gold standard' noninvasive measurement for aortic stiffness, was determined using an automatic device: the Complior* (Colson, Garges les Gonesses, France), which allowed an on-line pulse wave recording and automatic calculation of PWV [27]. Details, validation and reproductibility of this procedure have been previously published [27].

Heart period, ECG left ventricular hypertrophy and waist circumference determinations have already been described [28]. Venous blood samples were obtained in individuals after an overnight fast. Plasma was separated without delay at 4°C in a refrigerated centrifuge and stored at 4°C (for the determination of routine chemistry profile by standard methods) until analysis.

Metabolic syndrome was defined when having at least three out of the five following criteria [29]: BP above 130 mmHg for systolic and/or 85 mmHg for diastolic measurement or treated hypertension; waist measurement exceeding 102 cm in men and 88 cm in women; triglycerides concentration above 150 mg/dl (1.69 mmol/l); HDL-cholesterol concentration below 40 mg/dl (1.04 mmol/l) in men and 50 mg/dl (1.29 mmol/l) in women; and fasting plasma glucose concentration above 110 mg/dl (6.1 mmol/l).

The ABPI was determined according to the consensus statement of the American Diabetes Association [30]. The normal range of ABPI was defined by 1–1.3. An ABPI value less than 0.90 defined arteriopathy. An ABPI value range from 0.9 to 1 required a sensitivity exercise testing.

Statistical analysis

The current analysis was performed on individuals who had aortic PWV data available ($n = 618$). Data are expressed as mean ± SD. Clinical, biochemical and cardiovascular parameters were compared between two groups, defined by the presence (1) or absence (0) of history of one or more prior cardiovascular events, using Student's *t*-test for comparison of continuous variables and chi-squared analysis for discrete variables. Smoking status was expressed with dummy variables (0: never, 1: former, 2: current) with the reference group being 0 in logistic regression. All other discrete data were expressed in binary, with 1 indicating presence and 0 indicating absence of a characteristic.

The primary goal of the analysis was to assess the independent factors modulating aortic PWV and to evaluate aortic stiffness as a marker of severity of cardiovascular disease in diabetic patients. Multilinear regression analysis was performed to assess relationships between aortic PWV, population characteristics and presence of cardiovascular events, using a stepwise selection method. Models displaying excessive multicollinearity were rejected. Aortic PWV was further categorized by rounding the result of division by one standard deviation to the nearest integer. Logistic regression was performed on this categorization to calculate odds ratios variables that were found to be significant in the multilinear model.

Logistic regression was also used to analyse relationships between cardiovascular events and population characteristics. To determine whether aortic PWV is a major predictor of cardiovascular events and to quantify the improvement in risk prediction, we compared two multivariate models (with and without PWV) using the area under the receiver operating characteristic curve (AUC) and relative integrated discrimination improvement (RIDI) [31]. AUC was implemented with the SAS %ROC macro [32], and RIDI calculations were performed using the UCR %NRIIDI macro [33].

Of the 491 patients without cardiovascular events, age range was from 30 to 74 years in 453 patients. In this group corresponding to the age range of the Framingham cohorts, 10-year absolute cardiovascular disease risk was calculated, based on the equation described by Anderson *et al.* [34].

Statistical analysis was performed using SAS version 9.0 (SAS Institute Inc., Cary, North Carolina, USA). A P value of less than 0.05 was considered statistically significant.

RESULTS

Overall population

The study cohort is composed of 618 patients, 260 men and 358 women. One hundred and twenty-seven patients have previously experienced cardiovascular event, involving at least one vascular site: 79 (62%) patients presented CHD, 36 (28%) patients presented peripheral vascular disease and 32 (25%) patients presented cerebrovascular disease. Clinical and haemodynamic parameters of the study participants are given in Table 1, biochemical parameters and cardiovascular risk factors are given in Table 2, according to the presence or absence of cardiovascular events. The mean age (±SD) of participants at entry was 59 ± 12 years. Compared with individuals who did not have a history of cardiovascular events, individuals with one or more cardiovascular events were mostly men and were older. Duration of type 2 diabetes and hypertension, waist circumference, systolic, mean and pulse pressure, aortic PWV and ABPI were higher in patients with cardiovascular events. HDL cholesterol was lower in this group. Metabolic syndrome, sedentarity, microalbuminuria and chronic renal insufficiency were more frequent in

TABLE 1. Clinical and haemodynamic parameters of individuals according to history of cardiovascular events

	All individuals ($n=618$)	One or more previous CV events ($n=127$)	No previous CV event ($n=491$)	p
Clinical parameters				
Age (years)	59 ± 12	66 ± 10	58 ± 11	<0.001
Male (n), Female (n)	260, 358	64, 63	196, 295	
Male (%), Female (%)	42, 58	50, 50	40, 60	
Duration of type 2 diabetes (years)[a]	7 ± 8	10 ± 8	7 ± 8	<0.001
Duration of hypertension (years)[b]	4 ± 7 (n − 494)	6 ± 9 (n − 113)	3 ± 6 ($n-381$)	0.002
Weight (kg)	73 ± 15	73 ± 13	73 ± 15	0.795
BMI (kg/m^2)	27.8 ± 5.8	27.8 ± 4.7	27.8 ± 6.0	0.974
Waist circumference (cm)	98 ± 13	100 ± 12	97 ± 13	0.018
Haemodynamic parameters				
Heart rate (bpm)	76 ± 14	76 ± 13	77 ± 14	0.128
SBP (mmHg)	148 ± 23	156 ± 25	146 ± 22	<0.001
DBP (mmHg)	81 ± 10	80 ± 11	81 ± 10	0.550
Mean BP (mmHg)	103 ± 13	106 ± 14	102 ± 12	0.013
Pulse pressure (mmHg)	67 ± 19	76 ± 20	65 ± 19	<0.001
Pulse wave velocity (m/s)	13.96 ± 3.69	15.82 ± 3.73	13.48 ± 3.53	<0.001
Ankle-brachial index	1.06 ± 0.13	0.99 ± 0.20	1.07 ± 0.11	<0.001
	($n-559$)	($n-116$)	(n − 443)	

Continuous variables are presented as mean ± standard deviation. BP, blood pressure; CV, cardiovascular.
[a]A time of 0 was used to denote 0–11 months.
[b]One hundred and eighty-eight previously undiagnosed patients were diagnosed as hypertensive at the time of inclusion (162 patients with no CV event, 26 patients with one or more CV events, $P=0.006$). A time of 0 was used to denote 0–11 months.

patients with cardiovascular events. From the 618 patients, 246 patients were on lipid-lowering medication or classified as dyslipidemic [67 patients (53%) in the group with cardiovascular events and 179 patients (37%) in the group without cardiovascular events, $P=0.001$]. From the 618 patients, 579 were treated with oral hypoglycemic agents alone (including biguanides and sulfamides) or associated with insulin therapy: 441 patients were on oral therapy exclusively, included biguanides (360 patients) and sulphamides (316 patients) either alone or in combination, and 138 patients were on oral agents associated with insulin therapy. One hundred and thirty-four patients were on statin therapy and 289 patients were receiving aspirin as antiplatelet therapy. Mean (±SD) aortic PWV

TABLE 2. Biochemical parameters and cardiovascular risk factors of individualss according to the history of cardiovascular events

	All individuals ($n=618$)	One or more previous CV events ($n=127$)	No previous CV event ($n=491$)	P
Biochemical parameters				
Plasma glucose (mmol/l)	9.99 ± 4.16	10.16 ± 4.27	9.94 ± 4.16	0.578
Glycated haemoglobin (%)	8.20 ± 2.37	8.21 ± 2.19	8.20 ± 2.42	0.943
Total cholesterol (mmol/l)	4.78 ± 1.11	4.65 ± 1.11	4.84 ± 1.11	0.096
HDL cholesterol (mmol/l)	1.24 ± 0.39	1.19 ± 0.36	1.27 ± 0.39	0.039
LDL cholesterol (mmol/l)	2.90 ± 0.91	2.77 ± 0.88	2.92 ± 0.91	0.075
Triglycerides (mmol/l)	1.59 ± 1.11	1.69 ± 1.01	1.57 ± 1.13	0.276
Total/HDL cholesterol ratio	4.20 ± 1.57	4.30 ± 1.80	4.17 ± 1.51	0.481
Plasma creatinine (μmol/l)	87.78 ± 58.96	111.91 ± 89.99	81.59 ± 45.88	0.001
eGFR: MDRD formula (ml/s)	1.37 ± 0.52	1.14 ± 0.47	1.44 ± 0.51	<0.001
CV risk factors				
Current smokers (% of males)[a]	13	14	13	0.871
Former smokers (% of males)[a]	49	58	46	0.114
Metabolic syndrome (%)	73	82	70	0.009
Sedentary lifestyle (%)	52	69	48	<0.001
Previously diagnosed HT (%)	51	71	46	<0.001
HT or high normal BP (%)	82	91	79	0.116
Dyslipidemia[b] (%)	40	53	37	0.001
Chronic renal insufficiency (%)	12	24	9	<0.001
Microalbuminuria (%)	20	30	18	0.003

Continuous variables are presented as mean ± standard deviation. BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease.
[a]Smoking was not observed in women.
[b]Patients receiving lipid-lowering medication or classified as dyslipidemic.

TABLE 3. Multivariate linear regression: determinants of aortic pulse wave velocity (odds ratios generated by SD categorization of pulse wave velocity)

	OR	95% CI	*P*
Age (years)	2.39	2.01–2.85	0.0001
Time since type 2 diabetes diagnosis (years)	1.39	1.19–1.63	0.0001
Heart rate (bpm)	1.38	1.18–1.61	0.0001
Mean BP (mmHg)	1.73	1.48–2.03	0.0001
Plasma glucose (mmol/l)	1.24	1.06–1.44	0.006

Odds ratios calculated for 1 SD unit increase in variables. BP, blood pressure; CI, confidence interval; CV, cardiovascular; OR odds ratio; SD, standard deviation.

was 15.82 ± 3.73 m/s in the group with one or more cardiovascular events and 13.48 ± 3.53 m/s in the group without cardiovascular events ($P < 0.001$). Age ($P < 0.0001$), duration of type 2 diabetes ($P < 0.0001$), MBP ($P < 0.0001$), heart rate ($P < 0.0001$) and plasma glucose ($P = 0.006$) were the only independent factors modulating aortic PWV in multivariate analysis, with a positive correlation (Table 3).

Although there is a significant association between aortic PWV and microalbuminuria, chronic renal insufficiency, plasma creatinine, estimated glomerular filtration rate (Modification of Diet in Renal Disease formula), sedentarity and weight in the univariate analysis (online supplementary table S1, http://links.lww.com/HJH/A256), these factors were not independently related to aortic PWV in the multivariate analysis.

The independent factors modulating positively the presence of cardiovascular events in multivariate analysis were age ($P = 0.001$), SBP ($P = 0.002$), smoking status ($P < 0.001$), sedentary lifestyle ($P = 0.047$) and waist circumference ($P = 0.013$), whereas DBP ($P = 0.039$) and creatinine clearance ($P < 0.001$) were modulating negatively the presence of cardiovascular events (Table 4).

Aortic PWV improves the explicative model of the presence of cardiovascular disease over and above the known cardiovascular risk factors.

The increase of aortic PWV was proportional to the FRS (12.4 m/s for low FRS, 14.9 m/s for moderate FRS, 15.7 m/s for high FRS) (data not shown). Figure 1 shows the positive and linear relation between aortic PWV and 10-year cardiovascular disease risk according to FRS ($r = 0.5126$; $P < 0.0001$).

The unadjusted odds ratio (OR) for aortic PWV as an explicative parameter for the presence of cardiovascular

TABLE 4. Multivariate logistic regression: determinants of the presence of cardiovascular disease according to cardiovascular risk factors

	OR	95% CI	*P*
Age (years)	1.61	1.24–2.11	0.001
SBP (mmHg)	1.55	1.18–2.02	0.002
DBP (mmHg)	0.76	0.58–0.99	0.039
eGFR: MDRD (ml/s)	0.55	0.42–0.73	<0.001
Former smoker	2.81	1.63–4.82	<0.001
Current smoker	5.73	2.17–15.11	<0.001
Sedentary lifestyle	1.26	1.00–1.59	0.047
Waist circumference	1.37	1.07–1.76	0.013

Odds ratios calculated for 1 SD unit increase in variables. BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; R^2: 0.1575.

events was 1.18 [95% confidence interval (CI), 1.12–1.25, $P < 0.0001$]. After introducing aortic PWV in Table 4 model, DBP was no more significantly associated with the presence of cardiovascular events, although a trend to significance, whereas there was a significant and independent association between aortic PWV and the presence of cardiovascular disease (Table 5). Aortic PWV was also significantly higher in each subgroup of patients with cardiovascular disease including cerebrovascular, coronary and peripheral artery disease (data not shown). Aortic PWV appeared as a stronger single predictor for cardiovascular events than age, elevated SBP, sedentarity or elevated waist circumference (Table 5). We demonstrated that per 1 SD increase in aortic PWV, the relative risk of a cardiovascular event was significantly increased (OR 1.47; 95% CI 1.16–1.85, $P = 0.002$).

The addition of aortic PWV to the multivariate model of cardiovascular events improved the model with a statistically significant increase of the RIDI (1.8%, standard error 0.007, $P = 0.009$). The corresponding AUCs increased from 0.7787 to 0.7877 after addition of aortic PWV (nonstatistically significant increase: $P = 0.189$).

DISCUSSION

In the present study, we tested the ability for aortic PWV to act as a marker of individual cardiovascular risk in type 2 diabetes leading to a better risk classification. We focused on the Algerian diabetic population because of the increasing health problem of metabolic disorders in this population. The salient findings of this study were that, in a population of treated and untreated individuals with type 2 diabetes, aortic PWV was strongly related to the presence of cardiovascular events and significantly improves the explicative model of presence of cardiovascular disease. This marker may therefore represent a relevant predictor of cardiovascular disease risk in type 2 diabetic patients, which has to be confirmed in further prospective studies.

Aortic stiffness as a marker of cardiovascular disease in type 2 diabetic patients

In the present population, significantly increased aortic stiffness was found in patients with a past history of cardiovascular events. Age, MBP, heart rate, duration of type 2 diabetes and plasma glucose were positively and independently correlated with aortic PWV. A significant association has already been suggested between arterial stiffness, HbA1C and duration of type 2 diabetes in patients with or without hypertension [35,36]. Elevated heart rate

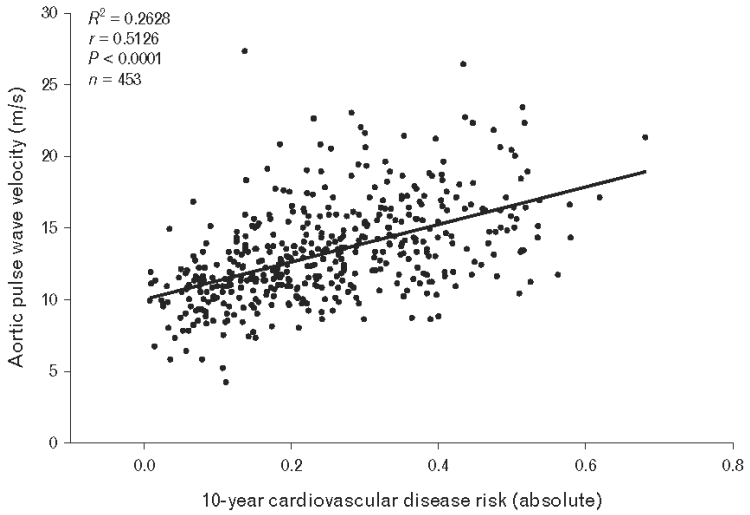

FIGURE 1 Relationship between 10-year cardiovascular disease risk and aortic pulse wave velocity.

was positively correlated with aortic PWV in our study population. Benetos *et al.* [37] have drawn the same conclusion in treated hypertensive individuals and furthermore ascertained heart rate as a determinant of arterial stiffening. A recent systematic review emphasized a dissociation of the majority cardiovascular risk factors, others than elevated BP and age, with aortic stiffness, which seems to be not driven by an atherosclerotic process [38]. Alterations of the arterial wall, such as decreased elastin content, development of extra-cellular matrix with increased collagen content and collagen cross-links from advanced glycation end products, may be the processes leading to vascular stiffness mediated by long duration of hypertension and impaired glucose tolerance [35,36,38]. Apart from the effect of ageing and hypertension, many pathophysiological conditions seem to be associated with arterial stiffness such as atherosclerotic genetic background and genetic polymorphisms, chronic inflammation disease, salt consumption or low birth weight. Finally, in the univariate analysis, there was a significant association between aortic PWV and chronic renal insufficiency, in which type 2 diabetes and hypertension are commonly present, and increased arterial stiffness has been previously described [19,20,37]. However, in the multivariate analysis, this significant association was not observed.

TABLE 5. Multivariate logistic regression: determinants of the presence of cardiovascular disease according to cardiovascular risk factors and aortic pulse wave velocity

	OR	95% CI	*P*
Age (years)	1.46	1.10–1.93	0.008
SBP (mmHg)	1.36	1.02–1.80	0.035
DBP (mmHg)	0.77	0.59–1.00	0.052
eGFR: MDRD (ml/s)	0.56	0.43–0.74	<0.001
Former smoker	3.12	1.80–5.40	<0.001
Current smoker	5.91	2.22–15.73	<0.001
Sedentary lifestyle	1.27	1.01–1.60	0.043
Waist circumference	1.40	1.09–1.80	0.009
Pulse wave velocity (m/s)	1.47	1.16–1.85	0.002

Odds ratios calculated for 1 SD unit increase in variables. BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; R^2: 0.1711.

Aortic stiffness as a potential predictor of cardiovascular risk in type 2 diabetic patients

An important result of the present study was that, in the population of diabetic individuals without cardiovascular events, aortic PWV significantly improves the explicative model of presence of cardiovascular disease over and above the traditional cardiovascular risk factors. This result suggests that increased aortic PWV might be a significant and independent predictor of cardiovascular events. A positive and linear correlation was assessed between aortic PWV and 10-year absolute cardiovascular disease risk according to FRS in patients without cardiovascular events. This result was expected, as age and SBP, both risk factors included in the Framingham equation, are strong predictors of aortic stiffness. Aortic PWV is considered as a marker of cumulative exposure to all cardiovascular risk factors (traditional and nontraditional ones), depending on the level of present and past exposure to these vascular damage factors. Therefore, this marker might be more closely related to individual cardiovascular risk than any risk scale, which gives a population risk level more than an individual one. In our study population, aortic PWV was associated more closely to the presence of cardiovascular disease than age, elevated SBP, sedentarity and elevated waist circumference. When added to the explicative model of cardiovascular events, aortic PWV significantly contributed to better stratification shown by an increase in RIDI. It has already been suggested that for a given age, aortic PWV appeared as the strongest predictor of cardiovascular mortality in hypertensive patients [28]. There is a large amount of epidemiological evidence for

its independent predictive value for cardiovascular events in several populations [15–25,39], first shown in high cardiovascular risk patients with end-stage renal disease [19]. Cruickshank *et al.* [40] suggested for the first time that aortic PWV is a strong independent predictor of all-cause and cardiovascular mortality in both type 2 diabetes and impaired glucose tolerance, displacing SBP from the list of the others independent risk factors. In a recent meta-analysis, evaluating the predictive value of aortic PWV for cardiovascular risk in several populations (general population, with risk factors or disease), Vlachopoulos *et al.* [39] demonstrated that an increase in aortic PWV by 1 SD was associated with a risk increase of 47% for cardiovascular events and cardiovascular mortality, results that are very similar to the OR (1.47) of aortic PWV in the explicative model of cardiovascular disease in our study.

Some study limitations should be underlined.

In this cross-sectional study, aortic PWV was strongly correlated with the presence of cardiovascular disease and improves the explicative model of cardiovascular disease, but we cannot conclude to its potential cardiovascular predictive value in diabetic patients, as the design of our study does not imply causality. A significant added value in predicting cardiovascular events over and above traditional risk factors in type 2 diabetic patients will have to be ascertained in further prospective cohort studies before widespread use of aortic PWV in clinical practice in this population.

We used the Framingham equations based cardiovascular scale to stratify cardiovascular risk in the Algerian population, but whether FRS is adapted to this population is not known. This risk prediction model has been assessed by the follow-up of an American population, in primary cardiovascular prevention, including a small number of diabetic patients. Actually, this risk equation cannot be generalized in subgroups of patients and lacks accuracy in young people, women, those with metabolic syndrome and in diabetic patients. Despite that, FRS has a widespread use to identify high cardiovascular risk across populations. In 2007, the ESC and the European Association for the Study of Diabetes recommended to apply cardiovascular risk assessment tools, including FRS, to both nondiabetic and diabetic individuals [41]. Considering cardiovascular risk heterogeneity in diabetic patients, accurate risk assessment tools are needed to improve medical management in primary prevention.

We used carotid-femoral PWV as the gold standard for arterial stiffness assessment. Other methods for arterial stiffness measurement, such as central pulse wave analysis, have demonstrated their predictive value in end-stage renal disease [42], hypertension [43] and CHD [44]. Whether these measurements can improve risk stratification in type 2 diabetes or metabolic syndrome remains to be shown.

The improvement of the explicative model for cardiovascular events with aortic PWV could not have been suggested only on the increase in AUC, which was not significant. The increase in RIDI, an objective indicator of reclassification improvement, was of small magnitude (of 1.8%) but statistically significant. Further prospective trials are needed to assess the net clinical benefit of this reclassification improvement.

Several pharmacological treatments and lifestyle modifications improve arterial stiffness and have also a beneficial impact on cardiovascular prognosis. It remains unknown whether the improved arterial elastic properties *per se* mediates an improvement in prognostic [45]. Only one study [46] has shown an independent benefit of arterial stiffness reduction on survival in patients with end-stage renal disease. The CAFE study [43] highlighted the benefits of central BP reduction treatment in cardiovascular mortality [47]. Further controlled trials are needed to confirm a benefit of aortic stiffness treatment on cardiovascular prognosis, especially in the diabetic population, independently of the normalization of the other cardiovascular risk factors. Finally, to help this purpose, establishment of normal values and cut-off points of PWV to assess aortic stiffness are needed.

Finally, it is reasonable to believe that some patients with a past history of cardiovascular events could have been wrongly included in the group of patients in primary prevention, as the retrospective assessment of cardiovascular events was based at first on patient declaration (e.g. past history of coronary revascularization without electrocardiographic modifications at inclusion). Although statistically significant, the difference between mean value of aortic PWV in patients with and without cardiovascular events would have been presumably higher, supporting our results.

In conclusion, the present study provides evidence, in a cohort of untreated and treated diabetic patients, that increased aortic PWV is a forceful independent marker of cardiovascular disease and significantly improves the explicative model of presence of cardiovascular disease. Prospective trials are needed to assess the potential improvement in cardiovascular risk prediction for widespread use of aortic PWV in type 2 diabetic patients in clinical practice. This marker may present ability to determine higher cardiovascular risk, which may not be detected routinely. Further large trials are needed to assess the independent effect of aortic stiffness reduction on survival improvement in diabetic patients.

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M.E.S. is the guarantor of this work, had full access to all the data and takes full responsibility for the integrity of data and the accuracy of data analysis.

S.A. and A.S.M. conducted this cross-sectional study in an Algerian diabetic population and collected the patients' data. A.Y. drafted the manuscript under the supervision of J.B. and M.E.S. N.M. performed statistical analysis under the supervision of D.A. All authors contributed to discussion, reviewed and edited the manuscript.

No previous presentations of the whole or part of the work presented in this article.

Conflicts of interest

There is no conflict of interest for any of the authors.

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Reviewer's Summary Evaluation

Reviewer 2

This paper investigated pulse wave velocity (PWV) and other cardiovascular (CV) risk factors in Algerian people with diabetes in whom CV events were ascertained. Despite its cross-sectional nature these data add to knowledge, particularly by demonstrating that higher PWV is associated with increased odds of a CV event. Another strength of the study is that it was conducted in a community at high risk of hypertension and diabetes. The findings of this study should prompt future prospective studies into the value of PWV as a predictor of cardiovascular events in people with diabetes.

II.2.2. Conclusion de l'ARTICLE 10

Dans cette étude nous avons évalué la possibilité que la rigidité aortique soit un marqueur du risque cardiovasculaire individuel dans le diabète de type 2.

Les patients avec histoire des événements cardiovasculaire présentaient des valeurs plus élevées de rigidité aortique. L'âge, la pression artérielle moyenne, la fréquence cardiaque, la durée du diabète et la glycémie étaient indépendamment corrélés à la vitesse de l'onde de pouls aortique. Des altérations de la paroi artérielle, telles que la modification du rapport élastine/collagène et la formation des produits de glycation avancée, pourraient être responsables de la ridification artérielle.

Un autre résultat important est que la rigidité artérielle améliore le modèle décrivant les facteurs associées à la maladie cardiovasculaire. Cela suggère que l'augmentation de la rigidité aortique pourrait être un prédicteur indépendant des événement cardiovascuaires. Nous avons trouvé une corrélation positive entre la vitesse de l'onde de pouls aortique et le risque absolu de maladie cardiovasculaire à 10 ans, selon le score de Framingham, chez les patients en prévention primaire. Considérant que l'âge et la pression artérielle systolique influencent fortement le niveau de rigidité aortique et qu'ils sont aussi utilisé dans les formules de Framingham, ce résultat n'est pas totalement inattendu.

La rigidité aortique est considérée un marqueur de l'exposition de l'arbre artériel aux facteurs de risque cardiovasculaire, par conséquent elle pourrait être plus corrélée au risque cardiovasculaire individuel que les échelles de risque.

II.3. ARTICLE 11 : L'ancienneté du diabète et la rigidité artérielle : une intégration possible entre maladie cardiovasculaire et diabète ? (soumis à JACC)

II.3.1. Introduction de l'ARTICLE 11

Dans la littérature, quelques études ont analysé la relation entre l'ancienneté du diabète de type 2 et la rigidité artérielle. Van Dijk et al.[148] et Wadwa et al.[149] ont étudié 81 et 60 patients respectivement, ayant un diabète relativement jeune (en moyenne 3 ans d'ancienneté), sans trouver de lien entre durée et rigidité. Une autre étude, portant sur 165 patients diabétiques de type 2 sans complication macro ou microvasculaire, avec une ancienneté du diabète de 10 ans, n'a pas non plus mis en évidence cette relation.[150] Au contraire, Cardoso et al.[151] ont analysé 482 diabétiques et montré que l'ancienneté du diabète (en moyenne 13 ans) était indépendamment associée à la rigidité artérielle (vitesse de l'onde de pouls supérieure à 12 m/s). D'autres études ont également montré une relation similaire chez des patients diabétiques avec durée moyenne de 10-11 ans.[152,153]

Ces études ne sont pas homogènes dans la sélection des patients ni dans la durée moyenne du diabète., Il nous semble, en particulier, que ce n'est pas par hasard que les études ayant inclus des sujets avec un diabète récent ne montrent pas de relation entre l'ancienneté et la rigidité, alors que celles incluant des diabétiques avec une plus longue durée sont positives.

Une étude récente de Teoh et al.[154] a montré, chez 860 sujets diabétiques, une relation indépendante entre la durée du diabète (9 ans en moyenne) et la rigidité artérielle. Cette relation était significative même après ajustement pour la pression

moyenne, l'âge, le tour de taille et l'hémoglobine glyquée, et portait sur 0,9 % de la variabilité de la vitesse de l'onde de pouls.

En poursuivant l'analyse sur ces 618 patients diabétiques algériens, nous avons donc analysé en détail la relation entre l'ancienneté du diabète et la rigidité artérielle. L'ancienneté du diabète étant distribuée d'une façon non gaussienne, les patients ont été partagés en trois groupes selon les tertiles de durée du diabète : le premier tertile avec une durée inférieure à 2 ans (médiane inférieure à 1 an), le deuxième entre 2 et 9 ans (médiane 5 ans), et le troisième avec une durée supérieure à 9 ans (médiane 15 ans). Les analyses ont montré que les pressions moyenne, systolique et pulsée étaient positivement associées à l'ancienneté du diabète, tandis que la pression diastolique était constante (Figure 38),

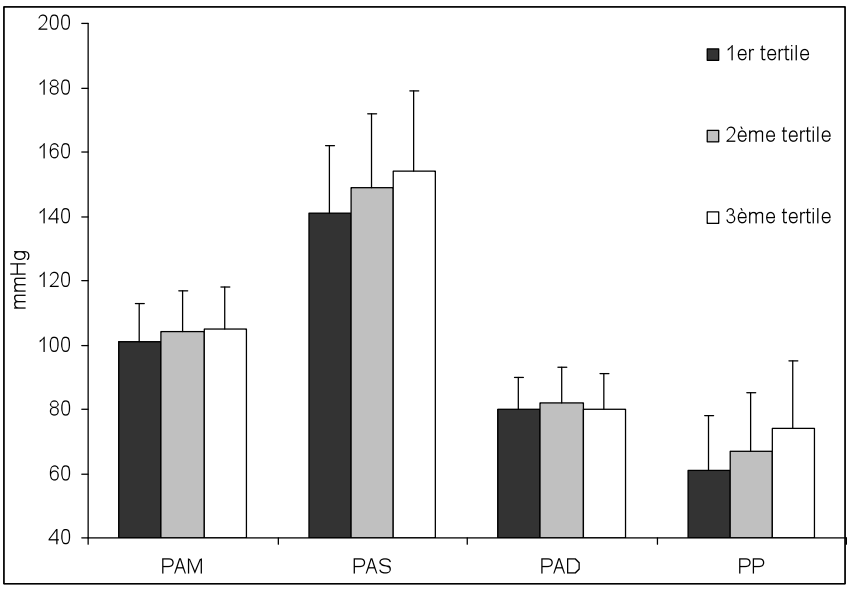


Figure 38. Modifications des pressions artérielles moyenne (PAM), systolique (PAS), diastolique (PAD) et pulsée (PP) au long de tertiles de durée du diabète.

La durée du diabète était associée à l'atteinte microvasculaire estimée par la présence d'une microalbuminurie (Tableau 7), indépendamment de variables

confondantes comme le sexe, la pression moyenne, la fonction rénale et l'âge, tandis que la rigidité artérielle, mais pas la durée, était indépendamment corrélée avec la prévalence des événements cardiovasculaires.

Tableau 7. Variables associées avec la prévalence de microalbuminurie.

	OR	95% IC		p
Sexe, m/f	1.667	1.107	2.51	**0.0144**
PAM brachiale, mmHg	1.350	1.113	1.638	**0.0024**
Durée du diabetes (tertiles)	1.315	1.064	1.625	**0.0114**
Creatinine*, µmol/L	1.243	1.027	1.506	**0.0256**
Age, ans	1.116	0.899	1.386	0.3196

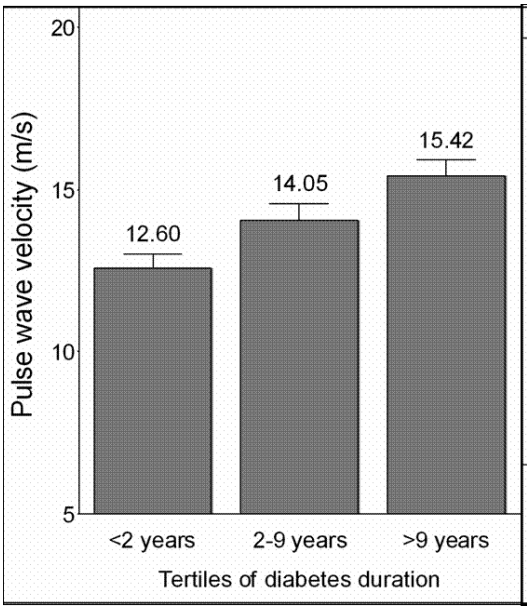
OR: rapport de odd; IC interval de confience; PAM: pression artérielle moyenne. Pour les variables continues les Ors ont été calculé pour le changement d'un écart type. * Transformée en logarithme.

Tableau 8. Variable associées aux modifications de la vitesse de l'onde de pouls.

	beta	ES	R^2	p
Age, ans	0.12	0.011	0.157	<.0001
PAM brachiale, mmHg	0.059	0.01	0.054	<.0001
Durée du diabetes (tertiles)	0.771	0.155	0.039	<.0001
Fréquence cardiaque, bpm	0.042	0.009	0.035	<.0001
Syndrome metabolique	0.649	0.286	0.008	0.023
R^2 ajusté			0.329	

PAM: pression artérielle moyenne; ES: erreur standard de la moyenne.

Nous avons montré une forte corrélation entre l'ancienneté du diabète et la rigidité artérielle, qui était indépendante des facteurs confondants (Figure 39).



Multicomparison difference between tertiles (Tukey adjustment):

	1 vs 2	1 vs 3	2 vs 3	p for trend
unadjusted	**<.0001**	**<.0001**	**<0.001**	**<.0001**
Model 1: age	**0.020**	**<.0001**	**0.018**	**<.0001**
Model 2: age, MAP	0.085	**<.0001**	**0.015**	**<.0001**
Model 3: age, MAP, gender	0.209	**<.0001**	**0.009**	**<.0001**
Model 4: age, MAP, gender, HR	0.094	**<.0001**	**0.016**	**<.0001**
Model 5: MAP, HR, eGFR(MDRD)	**0.003**	**<.0001**	**0.001**	**<.0001**
Model 6: age, insulin therapy	0.262	**<.0001**	**0.005**	**<.0001**
Model 7: age, microalbuminuria	0.193	**<0.001**	**0.040**	**<.0001**

MAP indicates mean arterial pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; MDRD, Modification of diet in renal disease formula. Significant p values are presented in bold.

Figure 39. Relation entre l'ancienneté du diabète et la vitesse de l'onde de pouls, avec multiples modèles d'ajustement.

Cette relation avait certaines caractéristiques :

- elle présentait un comportement différent selon l'âge ; en effet, ce n'était que chez les patients plus jeunes (dans les deux premiers quartiles d'âge) qu'elle était significative, alors que chez les patients plus âgés elle perdait son degré de signification (Figure 40).

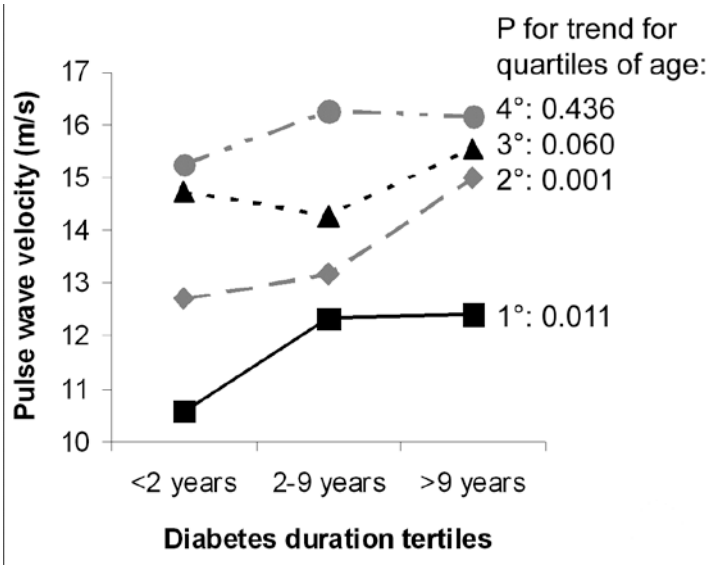


Figure 40. Relation entre l'ancienneté du diabète et la vitesse de l'onde de pouls selon les quartiles d'âge.

- Elle ne se comportait pas de la même façon selon que le diabète était précoce ou ancien. En effet, les patients avec une durée moyenne de 5 ans (deuxième tertile) avaient une vitesse de l'onde de pouls comparable à celle des patients avec une durée moyenne inférieure à un an, si l'on prenait en considération des facteurs confondants comme l'âge, la pression moyenne, la microalbuminurie ; tandis que les patients avec plus longue durée (moyenne 15 ans, troisième tertile) avait une rigidité accrue, indépendamment de toutes variables confondantes (Figure 39).

THE INFLUENCE OF DIABETES DURATION IN AORTIC STIFFNESS IN TYPE 2 DIABETES MELLITUS

From

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Abstract

Background and aim: Complications of diabetes increase with progression and duration of the disease. Aortic stiffness is considered an integrated marker of the combined effect of cardiovascular risk factors, age being considered a surrogate for the duration of the exposition to them. To our knowledge, no study was carried out specifically about the relationship between aortic stiffness and diabetes duration.

Methods: 618 type 2 diabetic patients (259-men) attending the Department of Internal Medicine of Tizi-Ouzou Hospital (Algeria) were studied. Anthropometric, clinical and biological data were sampled; brachial blood pressure was measured, and aortic stiffness was estimated by carotid-femoral pulse wave velocity (cf-PWV).

Results: From lower to higher tertile of diabetes duration, age, brachial blood pressure and cf-PWV (12.6±3.4 to 15.4±3.5 m/s) increased, while diabetes control and renal function worsened (all $p<0.01$). Diabetes duration was independently associated with aortic stiffness ($R^2=0.39$, $p<0.0001$), after adjustment for age, heart rate, blood pressure, and metabolic syndrome. Diabetes duration was also correlated to the prevalence of microalbuminuria (OR[95%CL] 1.3[1.06-1.63], p=0.01), independently of age, gender, BP and renal function. Aortic stiffness but not diabetes duration was independently associated to prevalence of cardiovascular events (OR[95%CL] 1.46[1.19-1.80], $p<0.001$).

Conclusion: Diabetes duration is an independent determinant of aortic stiffness in type 2 diabetics, causing about 4% of cf-PWV variability, from low to high tertiles. Diabetes duration is independently associated to microvascular complications, while aortic stiffness was associated to diabetic macrovascular complications. Aortic stiffness could be considered an integrated risk marker between diabetes and cardiovascular disease.

Keywords: diabetes mellitus; aortic stiffness; diabetes duration; cardiovascular risk; microvascular complications.

Introduction

Type 2 diabetes mellitus (T2DM) is an established cardiovascular risk (CVR) factor, affecting several million of people in the world. Metabolic factors, glycation products, endothelial dysfunction, and inflammation are possible contributors in the pathogenesis of T2DM-induced cardiovascular disease [1]. Such alterations involve functional/structural properties of the arterial tree,

which are strictly correlated to CVR. Since almost 10 years, alterations of central hemodynamics have been found in diabetic patients, who present increased central blood pressure (BP) and aortic stiffness with regard to control populations [2,3].

Diabetes related complications increase with progressing of the disease and therefore diabetes duration may be considered as a reflex of both aging and diabetic cardiovascular complications. Indeed, diabetes duration has been found to independently increase the risk of death for coronary heart disease [4–6], of death from natural causes [7], and of alterations of myocardial function [8].

Aortic stiffness, measured by the carotid-femoral pulse wave velocity (cf-PWV) is considered an integrated marker of the combined effect of cardiovascular risk factors [9], and could represent the link between diabetes and cardiovascular disease.

In literature, some studies investigated the relationship between T2DM duration and arterial stiffness. Van Dijk et al.[10] and Wadwa et al.[11] found that in patients (81 and 60, respectively) with relatively short history of diabetes (3 years) arterial stiffness was not related with diabetes duration. Another trial on 165 T2DM patients without macro- microvascular complications confirmed no association between aortic stiffness and duration [12]. Conversely, Cardoso et al.[13] investigated T2DM patients and found that diabetes duration (13 years) was independently associated to increased cf-PWV (>12 m/s). Other two trials found similar results in diabetic patients with mean diabetes duration of 10-11 years [14,15].

Unfortunately, these studies present small sample sizes and/or patients with very different characteristics. Furthermore, to our knowledge, no study was carried out specifically focusing on the relationship between aortic stiffness and T2DM duration.

Our aim was thus to investigate this relationship in a relatively large number of T2DM patients, providing insight on plausible patho-physiologic mechanism leading from diabetes to cardiovascular disease and death.

Methods

Study cohort

From 2005 to 2009, a cross-sectional study was carried out in patients with T2DM referred to the Department of Internal Medicine of Tizi Ouzou Hospital (Algeria), either from general practitioner or from in-hospital medical consulting. Our data analysis was conducted in Paris in 2012. T2DM was defined classically as blood fasting glucose greater than 6.93 mmol/L or 11 mmol/L at any time tested twice or those with antidiabetic dietary or treated with either oral hypoglycemic agents or insulin or both. Patients with malignancies, type 1 diabetes mellitus, or severe renal insufficiency (serum creatinine > 300 µmol/L) were not included in the study. The first 693 consecutive patients were examined, and patients presenting both central hemodynamic and laboratory measurements were selected for the analysis. After exclusion of 32 patients due to cardiac rhythm troubles or poor quality waveform analysis, and 43 patients without valid laboratory measurements, the study cohort was finally composed of 618 patients (259 males, 359 females), with mean age ± standard deviation (SD) of 59.4 ± 11.5 years. Each subject provided informed consent for the study, which was approved by the local institutional review board.

Anthropometric measurements and clinical information

Information obtained from a questionnaire included gender, age, weight and height, body mass index (weight in kilograms divided by the square of the height in meters), family (first-degree relatives) history of premature CV events, personal history of dyslipidaemia, hypertension, smoking habits, previous diseases and use of medications including antidiabetics, lipid-lowering agents and antihypertensive drugs. Cardiovascular events (peripheral vascular disease, cerebro-vascular and cardiovascular events) were retrospectively assessed. In patients without previously diagnosed hypertension, hypertension was defined as brachial systolic BP (SBP) $\geqslant$140 mm Hg and/or diastolic BP (DBP) $\geqslant$90 mm Hg, measured by sphygmomanometry, in the supine position with a minimum of 3 casual measurements during the last month, or the presence of anti-hypertensive drugs. Metabolic syndrome was defined according to ATPIII criteria [16]. The ankle brachial index (ABI) was determined according to the consensus statement of the American Diabetes Association [17]. Glomerular filtration rate (eGFR) was estimated by the Modification of Diet in Renal Disease (MDRD) formula [18].

Hemodynamic measurements

Analyses were performed in the morning after an overnight fast, each patient being in supine position. Brachial BP was measured at the right arm using an automatic BP monitor (OMRON 705 CP II IT, Omron Healthcare, Kyoto Japan) after 5 minutes of rest. Three measurements 2 minutes apart were performed and the average of the last two measures was considered. Mean arterial pressure (MAP) was calculated from systolic (SBP) and diastolic BP (DBP) as MAP = DBP + [(SBP-DBP)/3].

After BP determination, the cf-PWV was measured by a validated device (Complior - Colson, France), which allowed an on-line pulse wave recording and automatic calculation of cf-PWV [19]. The direct distance between carotid and femoral arteries was measured and divided by the time delay between pulse waves of the two arteries. Details, validation and reproducibility of this procedure have been previously published [19].

Heart period, ECG left ventricular hypertrophy and waist circumference determinations were also measured. Venous blood samples were obtained in subjects after an overnight fast.

Statistical analysis

Statistics were performed with SAS software version 9.0 (SAS Institute, Cary, NC). A $p \leqslant 0.05$ was considered as statistically significant. We represented quantitative variables as mean $\pm$ SD and qualitative variables as frequency (percentage). Non-normal variables were log transformed for analysis and presented as median (interquartile range[IQ]).

Diabetes duration presented a very skewed distribution, and in order to have enough statistical power, study population was divided into tertiles of diabetes duration (1st: <2years; 2nd: $\geqslant$2 and <9years; 3rd: $\geqslant$9 years), and differences in clinical, biological and hemodynamic parameters were tested with the ANOVA. Univariate and multivariate linear regression models were built to find factors associated with cf-PWV. Logistic regressions were used to calculate odds ratios for the discrete dependent variables. General linear model (GLM) analysis was performed to test the difference in cf-PWV between diabetes duration tertiles adjusting for consecutive models, and obtain multiple comparison tests between tertiles with the Tukey-Kramer adjustment. Interaction between age quartiles and diabetes duration tertiles was also tested by the GLM analysis.

Results

Population characteristics

Tertiles of diabetes duration regrouped 223 patients in the first (median[IQ] 0 [0-1] years), 194 in the second (5[4-7] years), and 201 in the third (15[12-20]) tertile (table 1). Mean age increased from 55.4±11.7 to 64.1±10.1 years (p<0.0001). Brachial BP parameters also increased: SBP from 141.3±20.8 to 154.0±24.4 mmHg; pulse pressure (PP) from 61.0±17.3 to 74.0±21.0 mmHg; and MAP from 100.7±11.8 to 104.7±13.4 mmHg (all p < 0.01); while DBP was unchanged. Cf-PWV increased by almost 2.8 m/s (p<0.0001). Diabetes related parameters showed a progressive worsening of T2DM (increased fasting glucose from 9.02±3.52 to 10.67±4.46 mmol/L, and glycated hemoglobin from 7.79±2.42 to 8.77±2.24%). Renal function also presented significant worsening, with serum creatinine shifting from 0.82[0.7-1.0] to 0.9[07-1.2] mg/dL (p=0.001), and eGFR from 85.7±24.2 to 74.3±29.1 ml/min/1.73m2 (p<0.0001).

The proportion of patients who smoked, or with sedentary living or metabolic syndrome did not significantly change (all p>0.06). At the contrary, the prevalence of hypertension, cardiovascular events, and microalbuminuria was higher in the third tertile of diabetes duration than in the first (all p<0.01). Use of both antihypertensive and hypocholesterolemic drugs were more prevalent in higher tertiles. In the first tertile, there were more patients treated with oral antidiabetic drugs than in the last one (from 87% to 50%, p<0.0001), while less patients were treated with insulin therapy (9% to 44%, p<0.0001).

Analysis on cf-PWV

In table 2, independent variables associated with cf-PWV are shown. We found that the model explained the 33% of the variance of cf-PWV. Age, MAP, tertiles of diabetes duration, and heart rate independently contributed to variation of cf-PWV respectively for the 16%, 5.4%, 3.9%, and 3.5% (all p<0.0001). The presence of metabolic syndrome was also significant in the model (p=0.023) but its contribution was negligible (R2=0.008). At the contrary gender was not significantly associated to cf-PWV. Insulin therapy, when added either instead of or together with diabetes duration tertiles, in the regression model, was not a significant determinant of cf-PWV (data not shown).

Analyzing the relationship between cf-PWV and diabetes duration tertiles (figure 1), we found that a significant trend persisted after adjustment for every models (all p<0.0001), containing age, MAP, HR, gender, eGFR, insulin therapy, and microalbuminuria. Considering the comparison between tertiles, we found that the difference in cf-PWV between the first and the second tertile of diabetes duration was significant only for the unadjusted analysis, for model 1 (with only age) and for model 5 (with MAP, HR, and eGFR). In particular, models containing both age and MAP did not present a significant difference between 1st and 2nd tertile. At the contrary, the differences between the first and the third tertile and between the second and the third tertile were significant for all the adjustment models (all p$\leqslant$0.04).

We also found a significant interaction between age and diabetes duration and analyzed it by stratifying by classes of age (quartiles of age), in figure 2 left-panel. While in the first and second quartiles of age cf-PWV significantly increased from the first to the third tertile of diabetes duration (p for trend all $\leqslant$0.011), in the latter two quartiles the significance was lost (p for trend all $\geqslant$0.06).

Microalbuminuria

In table 3, factors associated with the presence of microalbuminuria were examined. Male gender (OR[95%CL] 1.67[1.11-2.51] vs. female, p=0.014), higher MAP (OR[95%CL] 1.35[1.11-1.64], p=0.002), longer diabetes duration (OR[95%CL] 1.32[1.06-1.63], p=0.011), and higher serum creatinine (OR[95%CL] 1.24[1.03-1.51], p=0.026) were found to be independently related to microalbuminuria, adjusting also for age, which was not significantly associated.

Cardiovascular events

In a separate analysis, we investigated the determinants of cardiovascular events (table 4). Smoking habits (OR[95%CL] 2.21[1.42-3.46], p=0.0004), the metabolic syndrome (OR[95%CL] 1.81[1.09-3.02], p=0.023), higher age (OR[95%CL] 1.71[1.35-2.16], p<0.0001), higher serum creatinine (OR[95%CL] 1.66[1.36-2.03], p<0.0001), and higher cf-PWV (OR[95%CL] 1.46[1.19-1.80], p=0.0003) were significantly associated to the presence of cardiovascular events. At the contrary, gender was not a significant determinant.

The relationship between tertiles of diabetes duration and the prevalence of cardiovascular events by quartiles of age is presented in figure 2 right-panel. The interaction between age and tertiles

of diabetes duration was significant (p=0.002), and only in the first quartile of age we found a significant increase of prevalence of cardiovascular events along the tertiles of diabetes duration (p<0.0001, adjusted for gender, mean arterial pressure, microalbuminuria, metabolic syndrome, and serum creatinine). In the remaining quartiles of age, the trend was non-significant.

Discussion

Our investigation revealed that in diabetic subjects aortic stiffness, an integrated marker of cardiovascular impairment, is strictly correlated to diabetes duration, independently of blood pressure level and other confounders. Furthermore, diabetes duration was related with microvascular impairment, while aortic stiffness reflected macrovascular events.

Microcirculation

In literature, diabetes duration is known to be associated to cardiovascular disease and prognosis [4–8]. Both hypertension and diabetes cause alterations of the glomerular basement membrane that lead to the appearance of microalbuminuria, which is associated with an increased risk of cardiovascular mortality [20]. In our study, we showed that higher diabetes duration was associated to the presence of microvascular impairment, as depicted by higher prevalence of microalbuminuria, independently of renal function, BP, gender and age (table 3).

Macrocirculation

Recently we have shown that aortic stiffness can be considered a strong independent marker of CV disease in T2DM patients, improving the risk prediction of cardiovascular disease [21]. Furthermore, aortic stiffness has been found to be related to survival in T2DM [22]. In the present analysis, aortic stiffness, but not diabetes duration, was an independent determinant of the presence of cardiovascular event. Thus, our present results seem indicate that stiffening of large arteries, a pathologic modification shared by both diabetes and cardiovascular disease, could represent an integrated marker between these two conditions.

Relationship between arterial stiffness and diabetes duration

Even though in the literature some studies reported information on the relationship between diabetes duration and aortic stiffness [10–15,23], to our knowledge, this is the first study addressing specifically this relationship, in a quite large population sample. Notably, one recent publication presented the relation between metabolic parameters and arterial stiffness in T2DM [23]: diabetes duration was independently associated with aortic stiffness, with an R2 of 0.9%. In our analysis, we found that diabetes duration, contributed up to 4% to the variability of cf-PWV, independently of age, BP, and metabolic parameters. These findings suggest that even if diabetes duration is a marker of the severity of the disease, and is associated to cardiovascular risk, in late stages of diabetes the long-lasting establishing of vascular damage, caused by a series of irreversible phenomena, consistently leads to increased arterial stiffening, depending on diabetes duration, and independently of age, BP, and other risk factors.

Inter-tertiles analysis

Subgroup analysis between tertiles (figure 1) suggested a different role of BP and microvascular impairment during the first years of the natural history of diabetes (as expressed by the differences in tertiles 1 vs 2) than in the later development of the disease (tertiles 2 vs 3). In particular, this relation seems to be weak at the early years of diabetes, where taking into account mainly age, BP and microvascular renal disease makes the relation to lose significance. At the contrary, considering longer duration, this relationship is stronger and becomes independent. Far from being conclusive, this finding suggests that controlling metabolic and cardiovascular risk factors is more effective on hemodynamic status at early stages than late stages of diabetes.

Interaction analysis

As shown in figure 2 left-panel, we found a significant interaction between age and diabetes duration. This led to the finding that cf-PWV significantly increases along diabetes duration tertiles only for relatively low age classes (1st and 2nd quartiles), becoming stable thereafter. On one hand, this may be due to the fact that aortic stiffness reflects at the same time hypertension and diabetes related complications [2,24], which are growing and superposing with aging. Therefore, at higher age, it is likely that diabetes duration alone might no more justify large modification in aortic stiffness. On the other hand, in very elderly people, classical risk factors, like BP, plasma cholesterol, albumin, and BMI,

lose their prognostic significance and may even have an opposite effect on mortality prediction [25]; furthermore, recent data seem to suggest that, in an old population, neither BP nor cf-PWV are still related to total and cardiovascular mortality [26]. The latter might also suggest that data on the elderly are biased due to the natural survival selection.

Limitations

Our study presents some limitations. Firstly, our data refers to an Algerian diabetic population and therefore results may not be extrapolated to other populations. Secondly, the cross-sectional setting of the study does not allow an extrapolation about causal relationship between variables. Regression model and adjusted analysis are strongly dependent on variables' distribution and on multiple interactions. In our study, we checked for normality and used log-transformation or discrete variables to increase the statistical power; furthermore, even after multiple adjustments, principal results presented a very high statistical significance. Another limitation is that, as diabetes duration was calculated from the year of diagnosis, patients having a diagnosis of T2DM in the same year, but with several month of distance, were considered belonging to the same year of diabetes diagnosis. Moreover, in a clinical setting, the diagnosis of T2DM can be delayed by several months or even years with respect to the real disease onset. A further limitation consists in the fact that CV events were not systematically investigated.

Perspectives

We have shown that diabetes duration is a principal and independent determinant of aortic stiffness in type 2 diabetics, contributing to up to 4% of the variability of cf-PWV, independently of confounders. Furthermore, while diabetes duration is also related to the prevalence of microvascular impairment, only aortic stiffness is mainly associated to diabetic macrovascular complications, and therefore could be considered an integrated marker of T2DM and cardiovascular disease.

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Novelty and Significance:

1) What Is New

- A strong relation between diabetes duration and aortic stiffness exists, independently of age, blood pressure, and metabolic factors.
- A strong association between diabetes duration and the prevalence of microvascular disease exists independently of age, blood pressure, and metabolic factors.
- Only aortic stiffness, but not the presence of microvascular disease, was associated to the prevalence of macrovascular complications.
- The relationship between diabetes duration seems to be weaker in early than in late stages of diabetes.
- Aortic stiffness is associated with diabetes duration mainly in young patients.

2) What Is Relevant?

Aortic stiffness could be considered an integrated marker of type 2 diabetes and cardiovascular disease.

Summary

Diabetes duration is a principal and independent determinant of aortic stiffness in type 2 diabetics, contributing to up to 4% of the variability of aortic pulse wave velocity. Diabetes duration is also related to the prevalence of microvascular impairment; aortic stiffness, but not microvascular impairment, is associated to diabetic macrovascular complications; aortic stiffness could be considered an integrated marker of type 2 diabetes and cardiovascular disease.

Figure legend

Figure 1. Pulse wave velocity by tertiles of diabetes duration.

Figure 2. *Left-panel:* Relation between pulse wave velocity and diabetes duration tertiles by age category. P values are assessed by ANCOVA, adjusted for mean arterial pressure and gender. P for interaction=0.02. *Right-panel:* Prevalence of cardiovascular events (CVE) among tertiles of diabetes duration by quartiles of age. P for interaction=0.001. * P values are assessed by ANCOVA, adjusted for gender, mean arterial pressure, microalbuminuria, metabolic syndrome, and serum creatinine.

Table 1. Population characteristics.

	Tertiles of diabetes duration			
	1° <2 years (n=223)	2° 2-9 years (n=194)	3° >9 years (n=201)	p value
Male gender, n(%)	107(48)	67(35)	85(42)	**0.021**
Age, years	55.4±11.7	59.1±10.9	64.1±10.1	**<.0001**
Diabetes duration, years	0(0-1)	5(4-7)	15(12-20)	**<.0001**
Waist circumference, mm	96.7±12.6	98.4±12.8	97.8±12.5	0.372
Body mass index, kg/m2	27.7±5.8	28.5±5.9	27.3±5.5	0.100
Hemodynamic parameters				
SBP, mmHg	141.3±20.8	148.5±22.6	154.0±24.4	**<.0001**
DBP, mmHg	80.3±9.7	82.0±10.6	80.1±10.8	0.139
PP, mmHg	61.0±17.3	66.4±17.9	74.0±21.0	**<.0001**
MAP, mmHg	100.7±11.8	104.1±13.2	104.7±13.4	**0.002**
Heart rate, bpm	77.0±14.9	75.6±13.7	76.0±12.9	0.565
PWV, m/s	12.6±3.4	14.1±3.7	15.4±3.5	**<.0001**
Biological parameters				
Fasting plasma glucose, mmol/L	9.02±3.52	10.01±4.18	10.67±4.46	**<0.001**
HbA1C, %	7.79±2.42	8.07±2.34	8.77±2.24	**<.0001**
Total cholesterol, mmol/L	1.88±0.42	1.87±0.37	1.78±0.43	**0.030**
HDL cholesterol, mmol/L	0.48±0.15	0.49±0.15	0.47±0.15	0.315
Serum creatinine, µmol/L	73(62-88)	80(62-88)	80(64-106)	**0.001**
eGFR (MDRD), ml/min/1.73m^2	85.7±24.2	80.4±24.0	74.3±29.1	**<.0001**
Anamnestic information				
Smoking (past or current), n(%)	71(32)	46(24)	46(23)	0.067
Sedentary living, n(%)	109(49)	99(51)	117(58)	0.138
Metabolic syndrome, n(%)	153(69)	145(75)	152(76)	0.206
Hypertension, n(%)	166(74)	172(89)	188(94)	**<.0001**
CV events, n(%)	33(15)	35(18)	59(29)	**0.001**
Microalbuminuria, n(%)	30(13)	41(21)	55(27)	**0.002**

	Tertiles of diabetes duration			
	1° <2 years (n=223)	2° 2-9 years (n=194)	3° >9 years (n=201)	p value
Antihypertensive drugs, n(%)	86(39)	120(62)	131(65)	**<.0001**
Hypocholesterolemic drugs, n(%);	27(12)	45(23)	64(32)	**<.0001**
Oral antidiabetic drugs, n(%)	193(87)	148(76)	101(50)	**<.0001**
Insulin therapy, n(%)	19(9)	32(16)	88(44)	**<.0001**

Values are presented as mean ± standard deviation, or median (interquartile range) for non-normal distributed variables.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP pulse pressure; MAP, mean arterial pressure; cf-PWV, carotid-femoral pulse wave velocity; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula.

Table 2. Factors associated with pulse wave velocity.

	beta	SE	R2	P value
Age, years	0.12	0.011	0.157	<.0001
MAP - brachial, mmHg	0.059	0.01	0.054	<.0001
Tertiles of diabetes duration	0.771	0.155	0.039	<.0001
Heart rate, bpm	0.042	0.009	0.035	<.0001
Metabolic syndrome	0.649	0.286	0.008	0.023
Adjusted R2			0.329	

MAP indicates mean arterial pressure; SE, standard error.

Insulin therapy was not significant if added in the model either instead of or together with tertiles of diabetes duration tertiles.

Table 3. Factors associated to the presence of microalbuminuria (logistic regression).

	OR	95% CI		p value
Gender, m/f	1.667	1.107	2.51	**0.0144**
MAP - brachial, mmHg	1.350	1.113	1.638	**0.0024**
Tertiles of diabetes duration,	1.315	1.064	1.625	**0.0114**
Serum creatinine*, µmol/L	1.243	1.027	1.506	**0.0256**
Age, years	1.116	0.899	1.386	0.3196

OR indicates odds ratio; CI, confidence intervals limits; MAP, mean arterial pressure. For continuous variables, ORs are calculated for change in one standard deviation.

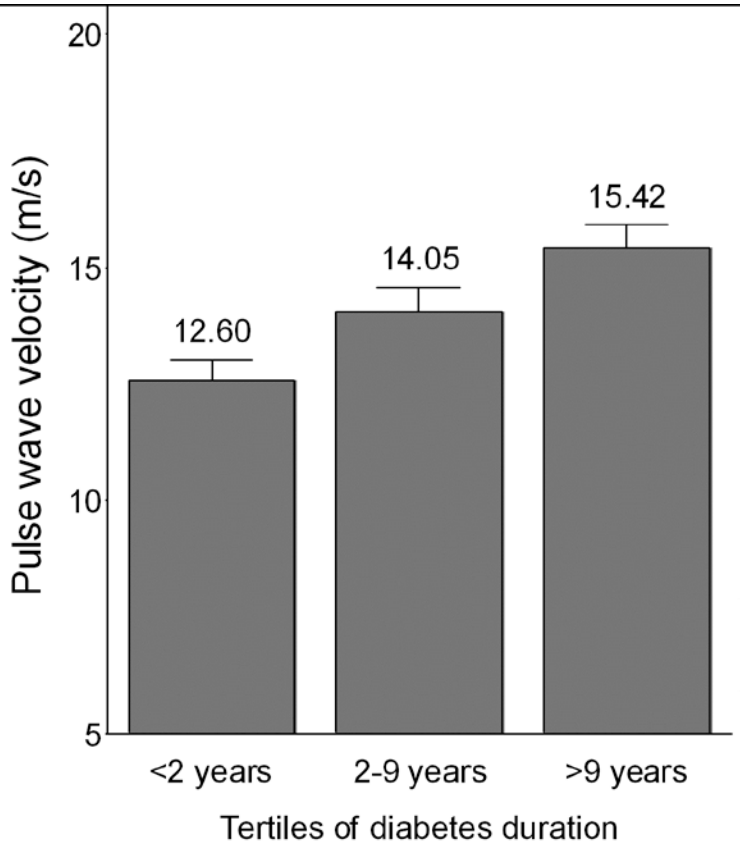
* log transformed for non-normal distribution.

Table 4. Factors associated to the presence of cardiovascular events (logistic regression).

	OR	95% CI		P value
Smoking, y/n	2.218	1.424	3.455	0.0004
Metabolic syndrome, y/n	1.811	1.087	3.017	0.0225
Age, years	1.711	1.352	2.164	<.0001
Serum creatinine*, µmol/L	1.658	1.356	2.029	<.0001
Pulse wave velocity, m/s	1.460	1.187	1.796	0.0003

OR indicates odds ratio; CI, confidence intervals limits. For continuous variables, ORs are calculated for change in one standard deviation.

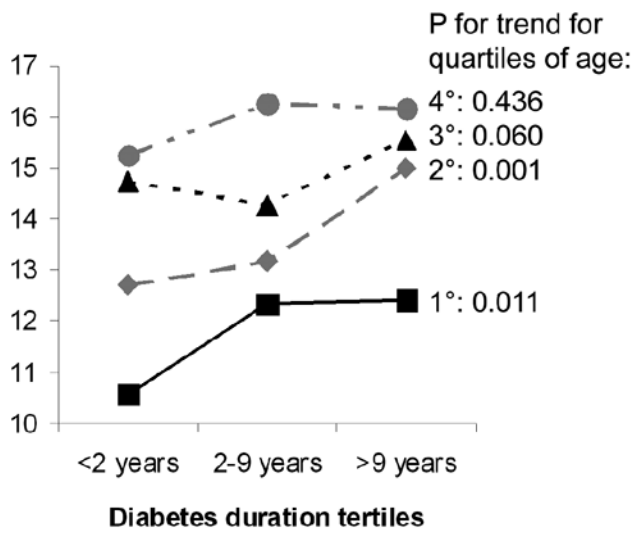
* log transformed for non-normal distribution.

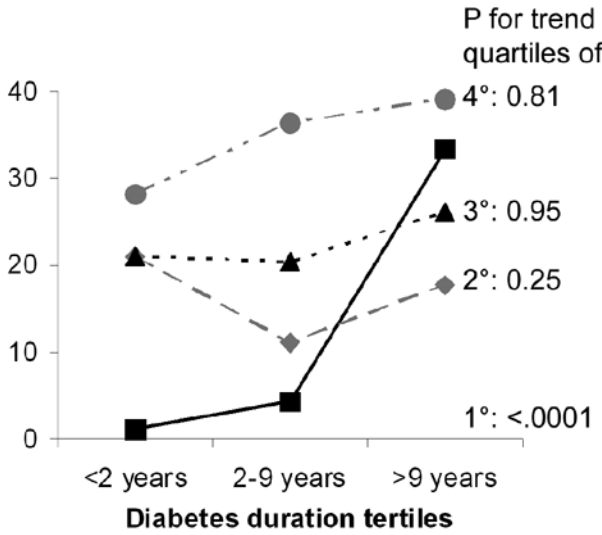


Multicomparison difference between tertiles (Tukey adjustment):

	1 vs 2	1 vs 3	2 vs 3	p for trend
unadjusted	**<.0001**	**<.0001**	**<0.001**	**<.0001**
Model 1: age	**0.020**	**<.0001**	**0.018**	**<.0001**
Model 2: age, MAP	0.085	**<.0001**	**0.015**	**<.0001**
Model 3: age, MAP, gender	0.209	**<.0001**	**0.009**	**<.0001**
Model 4: age, MAP, gender, HR	0.094	**<.0001**	**0.016**	**<.0001**
Model 5: MAP, HR, eGFR(MDRD)	**0.003**	**<.0001**	**0.001**	**<.0001**
Model 6: age, insulin therapy	0.262	**<.0001**	**0.005**	**<.0001**
Model 7: age, microalbuminuria	0.193	**<0.001**	**0.040**	**<.0001**

MAP indicates mean arterial pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; MDRD, Modification of diet in renal disease formula. Significant p values are presented in bold.





Definition of quartiles of age

	Mean (SD)	Range
1°	44.5 (5.8)	26-51
2°	55.1 (1.9)	52-58
3°	63.1 (2.6)	59-67
4°	74.2 (4.9)	68-92

II.3.2. Conclusion de l'ARTICLE 11

Ces résultats mettent donc en avant l'ancienneté du diabète comme facteur principal dans la prise en charge de la maladie. En particulier nous avons montré quatre aspects fondamentaux.

1. En plus d'être liée à la mortalité,[145] l'ancienneté du diabète est aussi potentiellement corrélée à la survenue de complications microvasculaires.

2. Il semblerait que chez les patients les plus âgés l'ancienneté du diabète seule ne soit pas capable d'expliquer de grandes variations de rigidité artérielle. En effet, chez ces patients âgés, l'accumulation des complications métaboliques, rénales et cardiovasculaires serait responsable de l'augmentation de la rigidité artérielle, par des effets chroniques à la fois sur la paroi artérielle (comme la formation de produits de glycation avancée), sur l'état inflammatoire, sur le stress oxydatif et sur la fonction endothéliale. D'autre part, il faut rappeler que, chez les sujets très âgés, les facteurs de risque cardiovasculaire classiques comme la pression artérielle, le cholestérol, l'albumine et l'index de masse corporelle, perdent leur capacité pronostique, pouvant aussi présenter un effet contraire sur la prédiction de mortalité.[155] En outre, des données récentes suggèrent que ni la rigidité artérielle ni la pression artérielle ne soient corrélées à la mortalité cardiovasculaire et globale chez les sujets très âgés, ce qui pourrait confirmer nos résultats.

3. Un résultat intéressant concerne la relation entre l'ancienneté du diabète et la rigidité artérielle. Nos résultats montrent une association qui serait responsable de 4

% de variabilité de la vitesse de l'onde de pouls, toutes variables confondues, et qui semblerait être plus forte une fois dépassée la durée de 5 ans. Cela confirme que la durée du diabète n'est pas qu'un marqueur de la sévérité de la maladie, et suggère qu'elle pourrait être considérée comme un marqueur de la durée de l'exposition du système cardiovasculaire aux altérations métaboliques typiques du diabète, capables de provoquer une atteinte vasculaire. Il semble donc raisonnable de penser que des petites variations de durée ne sont pas corrélées aux modifications de la rigidité artérielle, alors que le contraire se produit en présence d'un diabète plus ancien ou de grandes variations de durée.

4. Enfin, comme nous l'avons déjà mentionné, le fait que la vitesse de l'onde de pouls soit positivement associée à la prévalence de la maladie cardiovasculaire n'est pas nouveau, même chez le diabétique. Toutefois, le fait que l'ancienneté du diabète ne rende pas compte de la maladie cardiovasculaire, contrairement à la rigidité artérielle, nous fait penser que la vitesse de l'onde de pouls pourrait lier, d'un point de vue à la fois physiopathologique et pronostique, le diabète et la maladie cardiovasculaire, et pourrait être considérée comme un marqueur intégré des deux maladies.

Cependant, il faut préciser que les résultats dérivant des analyses en sous groupes dans le cadre d'une étude transversale sont à considérer avec précaution, du fait de la faible puissance statistique de ces analyses.

Conclusion

Nous avons montré dans cette deuxième partie la relation complexe qui existe entre la maladie cardiovasculaire et son expression clinique (atteinte d'organe et modifications hémodynamiques), et la maladie métabolique.

Il semble de plus en plus évident que le diabète est responsable d'altérations à plusieurs niveaux : au niveau purement métabolique, comprenant l'hyperglycémie, l'élévation des acides gras libres, les altérations des lipoprotéines ; au niveau du stress oxydatif ; au niveau de la fonction endothéliale, de l'inflammation, et de l'équilibre entre thrombose et fibrinolyse.

Ces altérations qui accompagnent le diabète sont associées elles-mêmes à une atteinte vasculaire qui s'exprime par une rigidification de l'arbre artériel.

C'est pour cela que les paramètres hémodynamiques, à partir de la pression centrale, des ondes de réflexion et de la rigidité artérielle, pourraient être considérés comme marqueurs de l'effet global des altérations métaboliques cumulées dans le temps. En particulier, la vitesse de l'onde de pouls, comme mesure de la rigidité aortique, semble être un paramètre capable de quantifier le degré de l'atteinte artérielle et donc le sur-risque cardiovasculaire chez les patients diabétiques.

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I Le vieillissement

Grâce aux progrès de la médecine en termes de diagnostic, de thérapeutique et de prévention, l'espérance de vie est en train d'augmenter et, dans la pratique clinique, le médecin est appelé à être confronté à une patientèle toujours plus âgée.

L'augmentation du nombre de personnes âgées, et notamment de plus de 80 ans, s'accompagne de l'augmentation d'une population particulièrement fragile avec de multiples comorbidités et une autonomie altérée. Cette population nécessite une approche diagnostique et thérapeutique propre à la Gériatrie. Cette approche ne peut découler d'une simple extrapolation d'études réalisées chez les sujets plus jeunes, ni même chez les patients du même âge mais bien portants. L'évaluation du risque cardiovasculaire dans cette population est un enjeu majeur.[156] L'hypertension artérielle, en particulier la pression artérielle systolique élevée, est un marqueur important de morbimortalité cardiovasculaire chez les patients âgés. De plus, la baisse de la pression artérielle par médicament a démontré un bénéfice net, même après 80 ans. Ce résultat a été obtenu sur une population certes âgée mais avec peu de comorbidités. A vrai dire l'association hypertension artérielle et risque cardiovasculaire chez les patients très âgés est sujette à controverse, notamment quand la pression artérielle périphérique est prise en compte. D'où l'intérêt d'utiliser d'autres marqueurs dans cette population. L'évaluation des propriétés mécaniques des parois artérielles telle que vitesse de l'onde de pouls et amplification de la pression pulsée, peut se révéler intéressante dans ce cas. Le développement récent de méthodes de mesures non invasives a permis une analyse de ces paramètres, dont plusieurs études ont montré qu'ils pouvaient améliorer l'évaluation du risque cardiovasculaire en plus de la pression artérielle périphérique, chez des patients d'âge moyen et chez quelques patients âgés.

La rigidité aortique augmente de façon exponentielle avec l'âge [157,158] et ce processus est accéléré en présence d'hypertension.[92,159,160] Des études récentes indiquent aussi que l'incrément de la vitesse de l'onde de pouls avec le vieillissement n'est pas uniforme le long de l'aorte.[161–163] En particulier, les différences majeures de rigidité artérielle se retrouvent au niveau abdominal, alors que le diamètre augmente prioritairement dans l'aorte ascendante.[161] Ce comportement de l'aorte face au vieillissement doit être pris en compte dans l'analyse de la rigidité aortique chez les patients âgés, notamment vis-à-vis des valeurs de référence.

Récemment, le groupe de collaboration pour la rigidité artérielle a publié des recommandations sur les valeurs de référence de la vitesse de l'onde de pouls carotidofémorale, en étudiant 16 867 sujets.[158] Pour les patients non hypertendus les valeurs de référence à l'âge de 60-69 ans seraient > 13,6 m/s, tandis que pour les patients de plus de 70 ans elles seraient > 17,5 m/s. D'autre part, chez 445 sujets âgés de 60 à 75 ans, Alecu et al. ont montré que les valeurs de référence étaient > 13 m/s.[164]

Des études ont aussi rapporté que l'aorte des sujets âgés est plus longue et large, surtout dans sa portion ascendante.[161,165,166] Cependant, cette contrainte n'affecterait pas la mesure de la vitesse de l'onde de pouls si l'on mesure la distance indirecte (méthode de soustraction, voir page 69).[166]

Même si la vitesse de l'onde de pouls est un marqueur de mortalité bien établi dans plusieurs populations,[8,14,23,167,168] sa valeur prédictive chez les sujets âgés est encore controversée. L'étude de Sutton-Tyrrell et al. a montré que chez 2488 sujets sains, d'âge moyen 74 ans, le quartile le plus élevé de vitesse de l'onde de pouls carotidofémorale était associé à un risque de mortalité toute cause 1,7 fois supérieur à celui du quartile inférieur.[16] De même, Meaume et al. ont indiqué que

l'incrément de vitesse de l'onde de pouls d'un m/s était associé avec un odds ratio de 1,19 sur la mortalité cardiovasculaire.[169] Au contraire, la valeur prédictive de la rigidité aortique devenait non significative dans l'étude PROTEGER, chez 331 patients hospitalisés, âgés de 87 ans en moyenne.[170]

Nous avons aussi montré dans l'étude PROTEGER que le cholestérol plasmatique, l'albuminémie et le poids corporel étaient négativement associés à la mortalité (ANNEXE 2, page 455).[171] Dans la même population, chez les patients diabétiques l'index de masse corporelle était un prédicteur négatif de mortalité, alors que des index d'inflammation, tels l'orosomucoïde et les leucocytes, étaient positivement associés à la mortalité (ANNEXE 3, page 465) ;[172] par contre, la pression diastolique a montré clairement une relation inverse avec la mortalité.[155]

Les paramètres classiquement liés au risque cardiovasculaire, comme la pression artérielle, le poids et l'index de masse corporelle, ou le cholestérol, semblent donc perdre leur signification chez les sujets âgés, chez qui ils peuvent avoir même un effet inverse sur la mortalité.

Dans l'étude PARTAGE (ANNEXE 4, page 475), nous présentons des résultats concernant une population de 1 126 sujets très âgés (âge moyen 88 ans), vivant dans des maisons de retraite. Chez ces sujets, les pressions artérielles systolique, diastolique et pulsée, ainsi que la vitesse de l'onde de pouls n'étaient pas des prédicteurs de mortalité toute cause ni des événements cardiovasculaires majeurs. Au contraire, une augmentation de 10 % d'amplification était associée à une diminution de mortalité totale de 24 % ($p < 0,0003$) et des événements cardiovasculaires majeurs de 17 % ($p < 0,01$).[91] Ces résultats peuvent être expliqués par le fait que la vitesse de l'onde de pouls estime la structure et la fonction des artères, mais est aussi très dépendante du niveau de pression artérielle. Ainsi, toute

comorbidité amenant une diminution de la pression artérielle, par perte de poids ou par déshydratation par exemple, peut aussi causer une diminution de la vitesse de l'onde de pouls, même en présence d'altérations des propriétés mécaniques des artères.

Dans ce contexte, l'amplification de la pression pulsée, en tant que rapport entre deux pressions, estime la rigidité artérielle et les ondes de réflexion indépendamment du niveau tensionnel et pourrait représenter un paramètre de grand intérêt dans cette population.

II La variabilité tensionnelle (annexe 5)

Les premières études faisant état d'une éventuelle relation entre la variabilité de la pression artérielle et le risque cardiovasculaire datent des années 1970.[173] En 1980, a été publiée une étude faisant état de l'absence de relation entre la variabilité de la pression artérielle mesurée sur la population de Framingham et le niveau de risque cardiovasculaire. Cette étude négative a probablement suffisamment marqué les esprits pour que ce concept de variabilité de pression artérielle ne soit que peu étudié pendant 10 ou 20 ans.[174] Puis, dans les années 1990 et les années 2000, quelques nouveaux rapports faisaient état d'un risque de complications de l'hypertension artérielle (HTA) qui serait plus élevé, bien entendu chez les patients porteurs d'une pression artérielle plus élevée mais aussi, à même niveau de pression artérielle, chez les patients porteurs d'une variabilité tensionnelle accrue. Ces données concordaient avec d'autres études portant sur l'hypotension orthostatique ; chez les patients âgés et même chez les patients d'âge moyen, l'hypotension orthostatique était associée à une augmentation du risque cardiovasculaire. En revanche, l'avènement des mesures ambulatoires de pression artérielle dans les années 1990 a donné des informations qui semblaient contradictoires, plus la variabilité de la pression artérielle entre le jour et la nuit était prononcée, meilleur était le pronostic. Mancia et al.[175] ont été les premiers à montrer une relation étroite entre la variabilité tensionnelle, obtenue par mesure ambulatoire de la pression artérielle (MAPA), et l'atteinte d'organes cibles chez les patients hypertendus. Cependant, la valeur prédictive de la variabilité tensionnelle sur la mortalité cardiovasculaire et toute cause a été longtemps l'objet de débats.[176–182]

Dans l'étude ASCOT-BPLA publiée en 2005, les patients étaient randomisés pour deux stratégies thérapeutiques : amlodipine / périndopril et aténolol / thiazidique. Le groupe amlodipine avait moins d'évènements cardiovasculaires que le groupe

aténolol, pour une différence de niveau de pression artérielle non significative.[60] Quelques mois plus tard, une sous-étude, ASCOT-CAFE, a montré qu'à même niveau de pression artérielle périphérique, l'amlodipine faisait diminuer de manière plus importante la pression artérielle centrale. L'effet supérieur de l'amlodipine serait donc expliqué par son action plus importante sur la pression centrale.[183] Mais cette explication n'a pas contenté l'ensemble de la communauté scientifique. En effet, depuis 2010, l'équipe de Peter M Rothwell (Centre de Recherche sur la Prévention des AVC, Neurologie, hôpital de Radcliffe, Oxford) a publié plusieurs articles dans le Lancet et le Lancet Neurology suggérant l'existence d'un nouveau marqueur de risque vasculaire, à savoir la variabilité tensionnelle intervisites. Cette variabilité serait non seulement un puissant marqueur de risque cardiovasculaire, mais expliquerait également la différence d'efficacité entre l'amlodipine et l'aténolol. L'amlodipine était plus efficace car « stabilisait » mieux la pression artérielle dans le temps que l'aténolol.

Les travaux de Rothwell ont la particularité d'être innovants car ils prennent en compte la variabilité tensionnelle dans le temps, sur une longue période. Jusque-là, lorsqu'on parle de variabilité, c'est essentiellement la variabilité intravisite ou sur 24 heures qui est prise en compte. Ces deux paramètres sont de moins bons marqueurs de risque.[57]

Pour Rothwell et al., il existe plusieurs arguments pour s'intéresser à d'autres paramètres que la PA systolique moyenne. Le premier paramètre est l'importance des valeurs maximales de la PA systolique, et notamment les valeurs élevées isolées. L'étude de deux cohortes de patients ayant fait un accident ischémique transitoire, UK-TAI et Oxford Vascular Study révèle l'existence d'un pic hypertensif non traité dans les dix années précédant l'évènement. Dans UK-TAI, 12

% des sujets seulement avaient une HTA stable et 69 % avaient une mesure élevée dans les dix ans. Dans Oxford Vascular study, 87 % des patients avaient une mesure supérieure à 160 mmHg dans les dix ans. Le deuxième paramètre est la variabilité tensionnelle intervisites. Son importance s'appuie sur des arguments épidémiologiques : l'effet blouse blanche et l'HTA masquée sont liés à long terme à des dommages des organes et seraient une forme clinique de la variabilité intervisites, tout comme les facteurs modifiant la pression artérielle à court terme (stress, hyperactivité sympathique, hypertension orthostatique, hypotension orthostatique).

L'HTA est un facteur de risque de démence et, dans l'étude Syst Eur trial, le traitement de l'HTA s'accompagne d'une diminution de la démence par les bloqueurs des canaux calciques. Cette même classe thérapeutique diminuerait également la variabilité de la PA intervisites. Le dernier paramètre est la variabilité intervisites résiduelle sous traitement ou stabilité de l'HTA traitée. Ce paramètre pourrait expliquer l'efficacité supérieure de l'amlodipine dans la prévention des AVC.[57]

L'ensemble des travaux de Rothwell et al. révèle plusieurs points importants :

- la variabilité intervisites de la PA systolique semble être un bon marqueur de risque d'AVC et d'évènements coronaires et ce indépendamment de la PA systolique moyenne ;
- une variabilité intervisites résiduelle élevée des patients traités et les valeurs élevées isolées de PA systolique ont un moins bon pronostic que l'HTA stabilisée ;
- ces données pourraient modifier la pratique quotidienne pour le diagnostic, le traitement et le suivi des patients hypertendus.

Néanmoins, ces travaux présentent des limites importantes. Une partie de la variabilité observée dans ces études peut être liée à une erreur de mesure. En effet,

dans UK-TIA et Deutch-TIA, les mesures ne sont pas standardisées comme dans ASCOT et peu de mesures sont retenues. L'observance thérapeutique n'a pas été évaluée et le défaut d'observance peut participer à la variabilité intervisites. Dans ASCOT-BPLA, il ne s'agit pas d'une comparaison aténolol versus amlodipine, puisque dans chaque groupe, les médecins pouvaient ajouter soit un inhibiteur de l'enzyme de conversion, soit un thiazidique pour optimiser la baisse de la PA. Il s'agit d'analyses *post-hoc* qui ont des biais liés à cette méthode, en particulier le lien de causalité entre variabilité et risque d'AVC n'est pas démontré. La variabilité intervisites ne serait qu'un reflet de la rigidité artérielle, puisque ces deux paramètres partagent des déterminants communs. Elle a par ailleurs déjà été étudiée dans d'autres études prospectives.[184] Cette variabilité tensionnelle a été identifié dès 1966 par Armitage et al.[184] qui avaient suivi 10 sujets normotendus et avaient constaté des écarts de 42 mmHg pour la PAS et 12 pour la PAD entre la première et la 20^{e} consultation. D'autres observations ont confirmé ce constat, si bien que l'introduction d'un traitement antihypertenseur ne se fait que si plusieurs chiffres de PA sont élevés. D'autres études sont nécessaires pour mieux comprendre la nature et les conséquences de la variabilité intervisites et voir comment évaluer cette variabilité dans la pratique quotidienne. D'autres facteurs de variabilité n'ont pas été évalués dans ces travaux comme la réponse à un stimulus, l'instabilité posturale, l'émotion …

Dans le cadre d'une étude randomisée et contrôlée (X-CELLENT) déjà présentée à page 239, nous avons analysé l'effet de trois médicaments antihypertenseurs sur la variabilité tensionnelle (cf ANNEXE 6, page 487).[109] Le candesartan n'a pas montré d'effets sur la variabilité, alors que l'amlodipine a réduit la variabilité diurne, nocturne et de 24 heures de la pression systolique, et

l'indapamide a diminué la variabilité diurne et de 24 heures de la pression systolique après trois mois de traitement. L'âge, le niveau tensionnel et la variabilité de la fréquence cardiaque (FC) étaient les déterminants majeurs de la variabilité tensionnelle.

La relation entre la fréquence cardiaque et la pression systolique (PAS), expression de l'effet régulateur du système autonome, pourrait être évaluée grâce à la MAPA, par un index mettant en rapport les variations de FC (dFC) avec les variations de PAS (dPAS). Chez les mêmes patients de l'étude X-CELLENT, nous avons aussi évalué l'effet du système autonome sur la variabilité tensionnelle (cf ANNEXE 7, page 505).[185] L'index dFC / dPAS était significativement corrélé à une augmentation de la PAS diurne et une baisse de la PAS nocturne, et donc à une augmentation du gradient jour-nuit de la PAS. De plus, la dysrégulation du système autonome était associée à la variabilité tensionnelle diurne et nocturne. Nous avons donc proposé un nouvel index de dysfonction du système autonome qui semble être en relation avec les variations circadiennes de pression artérielle systolique.

Au final, la variabilité tensionnelle représente une nouvelle approche du risque cardiovasculaire, qui semble prometteuse et mérite des études ultérieures pour en définir le rôle potentiel dans la pratique clinique.

III Le rôle des produits de glycation avancée

III.1. Aspects biologiques

Les produits de glycation avancée, *advanced glycation end products* (AGEs), se forment à la suite d'une modification irréversible post-translationnelle des protéines, des lipides ou des acides nucléiques. Ils passent à travers une chaîne de réactions chimiques, la réaction de Maillard. La première réaction entre les sucres réducteurs (ou des produits dérivés du sucre) et les groupes aminiques des protéines, des lipides, ou des acides nucléiques est appelée glycation précoce et représente une réaction non enzymatique réversible qui mène à la formation des produits de Amadori (dont l'hémoglobine glyquée est l'un des plus connus). Ces produits de Amadori sont ultérieurement déshydratés et oxydés, et finalement réarrangés et fragmentés, entrainant la formation irréversible des AGEs. Ces produits sont donc des dérivatifs très stables et hétérogènes de l'interaction entre sucre et macromolécules. Cet ensemble de réactions non enzymatiques est normalement lent et survient sur des mois, voire des années, mais il est accéléré par le stress oxydatif, les ions de métal et d'autres facteurs. Il faut rappeler que les AGEs sont un groupe hétérogène de molécules dont seulement environ 25 ont été complètement caractérisés. Les hydroïmidazolones (methylglyoxal et 3-deoxylglucosone), dérivés du glyoxale, semblent être les AGEs le plus souvent détectables ; la N-e-(carboxymethyl)lysine est l'AGE le plus simple et le mieux caractérisé et est utilisé pour le dosage plasmatique des AGEs. Certains AGEs ont aussi des propriétés d'autofluorescence, ce qui permet la mesure des AGEs cutanés, comme indiqué ci-dessous.

Les AGEs sont corrélés au vieillissement, à la présence du diabète, à l'insuffisance rénale, à l'amyloïdose et à l'inflammation chronique.[186–195] Les effets

négatifs des AGEs s'expriment à deux niveaux. En premier lieu, la formation de ces macromolécules, à travers des liens croisés (*cross-link*), dans les tissus provoque des modifications structurelles des protéines et une altération de leur fonctionnement. Par exemple, les modifications induites par les AGEs au niveau de la structure du collagène de la paroi vasculaire entraînent un changement de densité du collagène, de sa disposition spatiale, ainsi qu'une réduction de sa stabilité thermique et une résistance excessive à la digestion protéolytique. Cela amène irrévocablement à la réduction de la compliance vasculaire.[196,197] D'autre part, le lien entre les AGEs et leurs récepteurs (RAGE) entraîne la production de radicaux de l'oxygène et stimule la voie du facteur NF-kB, qui contribue à l'activation des différents gènes associés à l'inflammation, l'apoptose et l'athérosclérose.[198]

III.2. Aspects cliniques

III.2.1. 1. AGEs plasmatiques

Sur le plan clinique, le taux des AGEs plasmatiques (pAGEs), mesuré par différentes méthodes, a montré une association avec l'hypertension,[196] le diabète,[199,200] ainsi que la morbimortalité cardiovasculaire.[200–202] De plus, des études ont montré une association entre les pAGEs et la rigidité artérielle.[196,200,203,204] Chez les patients atteints par de maladies inflammatoires (comme la polyarthrite rhumatoïde et le lupus) une association de pAGEs et de l'inflammation a aussi été montrée.[205–207]

III.2.2. 2. AGEs cutanés et autofluorescence

Récemment, de nouveaux appareils pour mesurer les AGEs cutanés ont été mis sur le marché. Il s'agit d'une mesure par autofluorescence (AF) qui permet de mesurer la quantité d'énergie lumineuse émise par les AGEs quand ils sont stimulés par une lumière laser. Même si l'on sait que tous les AGEs n'émettent pas de radiations lumineuses et que la mesure d'autofluorescence ne peut mesurer que les AGEs qui ont cette propriété, les études de validation montrent une corrélation entre les AGEs cutanés mesurés par autofluorescence et par biopsie cutanée, ainsi qu'entre les AGEs cutanés et plasmatiques.[199]

De plus en plus, l'AF est étudiée comme un paramètre lié au diabète et ses complications cardiovasculaires,[187,208,209] à la dysfonction vasculaire[189] et à l'insuffisance rénale.[210] En outre, l'AF a montré un pouvoir de prédiction du pronostic cardiovasculaire [187,199,211] et une association avec les maladies inflammatoires chroniques.[188,190]

III.3. Les AGEs et la rigidité artérielle

Les altérations des protéines de la matrice à l'intérieur de la paroi artérielle jouent un rôle important sur les propriétés structurelles des artères, du fait des *cross-links* qui se forment de façon non-enzymatique entre le glucose (ou d'autres sucres) et les groupes aminiques qui génèrent les AGEs.[212,213] Les AGEs s'accumulent lentement sur les protéines de la matrice comme le collagène et l'élastine produisant une rigidification des artères et du cœur. Des études ont montré que des médicaments capables de réduire la formation des AGEs ou de couper ces *cross-links* pourraient améliorer la compliance artérielle.[214–217] En particulier, une étude

récente a montré que l'exercice physique associé à un médicament qui coupe les *cross-links* (alagebrium) peut améliorer la dysfonction systolique et diastolique, la contractilité du ventricule gauche et la compliance artérielle dans un modèle de vieillissement de rats.[218]

L'interaction entre AGEs et RAGE contribue en grande partie aux effets délétères vasculaires ; cependant, actuellement très peu d'études ont évalué la corrélation entre AGEs et vitesse de l'onde de pouls. Semba et al ont notamment montré qu'il existe une corrélation entre les pAGEs et la vitesse de l'onde de pouls chez les patients sains ;[203] par contre, une autre étude n'a pas trouvé de relation indépendante de la pression artérielle et de l'âge entre l'AF et la vitesse de l'onde de pouls, suggérant un comportement différent entre pAGEs et AGEs cutanés. Chez les hypertendus, une étude a montré une relation positive entre pAGEs et vitesse de l'onde de pouls.[196] Dans le diabète, trois études ont évalué le rôle de l'AF sur le système cardiovasculaire, montrant une relation de l'AF avec le risque cardiovasculaire à 10 ans,[187] avec les complications micro- et macrovasculaires,[208,209,211,219] et l'élasticité des petites artères.[189]

La pathologie coronarienne représente un problème de santé publique, avec l'essor des anomalies métaboliques et le vieillissement de la population. L'ischémie myocardique, symptomatique ou silencieuse, est un facteur prédictif du risque d'événements coronariens et de mort subite, et représente donc une cible primordiale du dépistage cardiovasculaire chez nos patients. Les outils diagnostiques de premier niveau sont (en plus de l'examen physique, de l'anamnèse personnelle et familiale, des paramètres biologiques) l'électrocardiogramme, l'échographie cardiaque et l'épreuve d'effort couplée à la scintigraphie myocardique, examen de référence améliorant la performance de l'épreuve d'effort par l'étude de la perfusion

myocardique et la fonction ventriculaire gauche (sensibilité 89 %, spécificité 75 %[220]). De cette évaluation dépend la réalisation de la coronarographie, examen invasif à visée diagnostique et thérapeutique. En cas d'épreuve d'effort litigieuse (discordance ou doute interprétatif des résultats), la réalisation de la coronarographie dépend de nombreux facteurs qui sont notamment le terrain, la symptomatologie, l'importance et l'étendue des anomalies électriques et scintigraphiques. Ceux-ci constituent autant de critères à prendre en compte dans la balance bénéfice-risque pour la décision d'une coronarographie diagnostique. En cas d'épreuve d'effort positive, la présence d'une sténose hémodynamiquement significative à la coronarographie n'est pas systématique. La valeur prédictive positive de l'épreuve d'effort étant limitée par plusieurs facteurs confondants, l'apport de mesures complémentaires non invasives de l'état artériel et métabolique pourrait en améliorer la puissance diagnostique.

En raison de ces médiocres valeurs prédictives positive et négative, nous avons décidé dans le service de "professionnaliser" toute décision de réalisation de coronarographie suite à la réalisation des examens de dépistage cardiovasculaire. Les décisions sont prises par les médecins du staff (cardiologues, médecins vasculaires, médecins généralistes, endocrinologues-diabétologues et cardiologues interventionnels). Malgré cette décision collégiale tendant à réduire l'hétérogénéité des arguments de décisions il existe une forte proportion de coronarographies sans lésion hémodynamiquement significative si ce n'est normales ; il existe aussi probablement beaucoup de patients chez lesquels il est décidé de ne pas réaliser de coronarographie mais qui ont probablement une ou plusieurs lésions des artères coronaires (cette proportion n'est bien entendu pas connue en l'absence de réalisation d'examens systématiques). Il est important de noter qu'une des raisons principales de notre faible performance dans le dépistage de la maladie coronaire est

représentée par certaines spécificités de notre patientèle ; on sait notamment que les diabétiques ont plus fréquemment une maladie coronaire asymptomatique, les obèses plus fréquemment une fausse positivité à l'épreuve d'effort et à la scintigraphie myocardique ; enfin, les hypertendus qui représentent la part la plus importante de nos patients en raison du retentissement cardiaque de l'hypertension artérielle (hypertrophie ventriculaire gauche), ont plus fréquemment une fausse positivité scintigraphique (et électrocardiographique).

La rigidité aortique et la mesure cutanée des produits de glycation sont deux biomarqueurs intégrateurs à la fois de l'intensité et de la durée d'exposition aux facteurs de risque cardiovasculaire, et des prédicteurs indépendants de morbimortalité cardiovasculaire. Ils représentent donc des candidats potentiels pour l'amélioration de la prise en charge diagnostique de patients à risque de coronaropathie.

Nous avons mis en place un protocole d'étude qui s'inscrit donc dans l'amélioration de la prédiction individuelle de la maladie coronaire par la réalisation d'explorations non invasives métaboliques et hémodynamiques. L'objectif ultime est de pouvoir créer un nouvel algorithme de décision dans différentes sous-populations incluant ces paramètres intégrateurs. Dans un premier temps, il va falloir montrer que le niveau d'altération de ces paramètres intégrateurs est quantitativement associé à la maladie coronaire ; puis, dans un second temps, que la réalisation de ces paramètres rajoute à la prédiction utilisant les facteurs de risque conventionnels, avant que d'envisager une modification des algorithmes décisionnels.

La reclassification du risque coronarien des patients à l'aide de ces mesures, en plus de la prise en charge diagnostique conventionnelle, pourrait apporter un

bénéfice pour le patient en termes à la fois de réduction d'examens invasifs inappropriés, de risque procédural, et d'amélioration de la pratique clinique courante.

Chez ces patients, il sera possible aussi d'analyser les relations existant entre la rigidité artérielle et les AGEs dans des sous-groupes de patients, comme les hypertendus traités et non traités, et selon le type de traitement. Des résultats préliminaires sont attendus vers la fin de 2013.

IV La rigidité artérielle et l'inflammation

La rigidité artérielle est associée à l'augmentation de l'activité de l'angiotensine II, résultant en une augmentation de l'activité de l'enzyme NADPH oxydase, une réduction de la biodisponibilité de l'oxyde nitrique et une production exagérée des dérivés réactifs de l'oxygène.[221–223] L'inflammation semble jouer un rôle dans la pathogenèse de la rigidité artérielle :[221] les cytokines inflammatoires stimulent la production locale de la protéine C réactive (CRP) par les cellules musculaires lisses vasculaires. La CRP a aussi un rôle actif dans la promotion de l'inflammation vasculaire et la réduction de la fonction endothéliale,[224–226] et des études récentes ont montré une association entre la CRP et la rigidité artérielle.[227–229] D'autres ont montré que la rigidité artérielle est augmentée dans des pathologies inflammatoires chroniques, comme la polyarthrite rhumatoïde, dont le traitement par anti TNF alpha serait responsable d'une amélioration de la rigidité elle-même.[230]

Cependant, il n'existe pas d'informations sur la nature de cette relation, notamment de savoir si l'inflammation cause une détérioration des propriétés élastiques des artères ou si la rigidité artérielle n'est qu'un épiphénomène. A ce sujet, Vlachopoulos et al. ont déjà montré chez des sujets normaux que l'inflammation aiguë a un impact différent selon le territoire artériel considéré, augmentant la rigidité des grosses artères élastiques et réduisant les ondes de réflexion par une vasodilatation périphérique. De plus, le pré traitement par aspirine était capable d'annuler l'effet de l'inflammation sur la rigidité artérielle et sur l'index d'augmentation.[231]

D'une part, le diabète est associé à une élévation des produits de glycation avancée qui activent la voie de l'inflammation par le lien avec leur récepteur, et seraient associés à la rigidité artérielle ; d'autre part, l'inflammation est, elle aussi, corrélée à la rigidité artérielle. Le panorama qui semble se dessiner amènerait donc

à étudier les effets des différentes pathologies sur l'inflammation et l'effet de l'inflammation sur la rigidité artérielle, dans le but de montrer une possible voie commune aux maladies cardiovasculaires et non cardiovasculaires dans l'atteinte artérielle.

V Un regard personnel sur l'hémodynamique

Dans notre exposé, nous avons montré l'intérêt intellectuel et pratique des paramètres hémodynamiques centraux. Un vrai chercheur souhaiterait maintenant une destinée glorieuse pour ces mesures : la possibilité d'une utilisation simple et économique, pour la majorité des patients, dans la pratique clinique. Les dernières recommandations de la Société Européenne d'Hypertension seraient donc décevantes dans cet aspect, laissant un rôle très limité à l'étude de l'hémodynamique dans la prise en charge du patient hypertendu.[78]

Le diagnostic des patients hypertendus se base en réalité sur des mesures « classiques », comme la pression brachiale au cabinet, ambulatoire sur 24 heures, ou par automesure. Les complications sont dépistées par l'échographie cardiaque, les épreuves d'effort, voire la coronarographie. De même, l'échodoppler des artères périphériques, la creatininemie et la protéinurie sont des examens complemantaire dans le dépistage des complications.

L'utilisation des paramètres hémodynamiques centraux semble utile pour approcher au mieux le risque cardiovasculaire, mais que peut-on attendre réellement de ces paramètres dans notre pratique ? Un patient hypertendu avec altération de la pression centrale, de l'amplification et de la rigidité aortique, qui présente probablement un sur risque cardiovasculaire, doit-il être traité différemment et par quel traitement spécifique ? Quelle approche particulière mérite un patient diabétique présentant une rigidité artérielle très élevée ?

Même si certains médicaments semblent avoir un effet positif sur l'équilibre hémodynamique ou sur le vieillissement accéléré dû à la glycation avancée, à ce jour les preuves scientifiques disponibles ne nous permettent pas de répondre à ces interrogations. Une étude française (SPARTE) qui a pour but d'analyser l'efficacité

d'une stratégie de prévention basée sur la rigidité artérielle pourra peut-être donner des informations supplémentaires.

En attendant de répondre à ces questions, il est intéressant de considérer quelques problématiques émergentes dans le champ de la recherche.

V.1. Le problème des validations

Nous avons déjà remarqué que le nombre d'appareils non invasifs mesurant la pression centrale est toujours grandissant, mais ce qui est déconcertant est l'absence totale d'un protocole unifié qui en permette la validation. Par conséquent, un appareil sera validé par voie invasive, un autre par voie non invasive, et chacun selon des critères différents, mais la valeur fournie par tout appareil sera la même : la pression systolique centrale. Or, il faut se poser la question de savoir si on s'attend à ce que les appareils soient interchangeables.

Avec les preuves disponibles, il semblerait évident que les appareils ne donnent pas de valeurs interchangeables de pression : des études de validation invasive ont montré clairement des différences significatives de pression centrale entre les différents appareils observés, même si les résultats étaient très corrélés.[232,233] En outre, dans notre étude de comparaison, nous avons montré que deux appareils validés invasivement, présentant la même technique de mesure (la tonométrie d'applanation) et le même calibrage, ne sont pas superposables (cf ARTICLE 6, page 209). Qu'en serait-il alors de confronter deux appareils avec des systèmes différents pour calculer la pression centrale, avec des calibrages différents…

Le premier point que nous voulons souligner est que, même en présence de validations invasives, les résultats fournis par les différents appareils ne sont pas égaux, mais souvent très fortement corrélés.

Admettons que la méthode idéale de validation, c'est-à-dire la voie invasive, ne puisse pas être appliquée à large échelle, qu'elle pose des problèmes éthiques, et qu'elle ne concerne que des sujets soumis à coronarographie, ce qui réduit sa généralisation. Ces contraintes semblent autoriser l'emploi d'une autre méthode de validation qui consiste à comparer le nouvel appareil avec un appareil déjà validé invasivement et reconnu fiable par la « société scientifique ». Nous en avons montré un exemple dans l'ARTICLE 3, page 145. Dans ce cas, les erreurs dans la mesure non invasive de la pression brachiale et dans les différentes méthodes de calibrage disponibles, les approximations propres aux appareils déjà validés, ne permettent pas d'assurer une homogénéité des résultats. Pour donner un exemple : pendant une validation récente d'un appareil très connu comme le SphygmoCor, on s'est rendu compte que, si les courbes de pression étaient calibrées avec des pressions invasives, les valeurs de pression centrale obtenues par tonométrie étaient très proches de celles obtenues par cathéter ; par contre, quand les courbes de pression étaient calibrées avec des pressions obtenues par tensiomètre brachial, les valeurs de pression centrale du tonomètre s'éloignaient des pressions invasives, avec des différences de 2,8 à 11,9 mmHg.[233]

Il est donc évident que la comparaison d'une comparaison ne pourra jamais résulter en une mesure précise de la pression centrale.

Par conséquent, le risque qui surgit dans la mesure de la pression centrale est que les valeurs obtenues avec chaque appareil, étant « propres » à cet appareil,

ne peuvent être interprétées qu'avec une échelle de références propre à cet appareil. Cela pourrait toutefois amener à une confusion d'interprétation de la part des médecins utilisant des appareils différents.

A ce point, la deuxième question qu'il faut se poser est donc : a-t-on intérêt à s'approcher d'une mesure véritable de la pression centrale, ou peut-on se contenter de bonne corrélation ?

Malheureusement nous n'avons pas de réponse à cette question, mais il faut se rappeler que les grandes études cliniques capables de prouver le rôle diagnostique, thérapeutique et prognostique de la mesure de la pression centrale se sont basées, se basent et se baseront sur l'emploi d'appareils différents, validés de façon différente. De plus, jusqu'à présent il n'existe pas de valeurs de normalité pour la pression centrale, mais après ce qu'on vient d'énoncer, comment pourra-t-on établir des plages de normalité « universelles », comme pour la pression brachiale ?

Dans l'attente de nouvelles technologies ou d'idées originales, nous nous permettons de proposer une « solution », qui s'étaye sur les principes suivants :

- depuis qu'elle existe, la médecine clinique se base sur la possibilité de mesurer ;

- le contrôle de qualité, ainsi que sa certification, sont couramment requis pour chaque nouveau produit, dans tout domaine du commerce et de la santé ;

- la validation invasive, comportant des contraintes de faisabilité, d'expertise et d'éthique, semble ne pas pouvoir être applicable à la totalité des validations de nouveaux appareils ;

- la tonométrie artérielle d'applanation est l'outil qui s'approche le plus d'une mesure fiable de la pression artérielle centrale, si elle est correctement utilisée ;

- la courbe de pression carotidienne pourrait être considérée superposable à la courbe de pression aortique, et les pressions carotidiennes équivalentes aux pressions aortiques ;

- le calibrage idéal consisterait dans la mesure de la pression moyenne par la méthode de l'aire sous la courbe tonométrique brachiale, quand elle est calibrée par les pressions systolique et diastolique obtenues par un tensiomètre brachial.

Nous envisageons d'abord une étude invasive validant :

- la tonométrie brachiale comme étant réalisable et fiable ;

- les pressions carotidiennes, obtenues par calibration des courbes carotidiennes avec la pression moyenne calculée par tonométrie brachiale, comme succédané des pressions aortiques ;

- un protocole non invasif de validation, basé sur la comparaison des nouveaux appareils avec la technique décrite ;

- des nouveaux critères qui définissent les marges d'erreurs par rapport à la pression centrale.

Puis, dans un deuxième temps, la création de groupes certifiés pour la validation non invasive des appareils, selon les standards du nouveau protocole.

V.2. Les succédanés du succédané

Tout comme les comparaisons des pressions centrales, les mesures de rigidité artérielle peuvent aujourd'hui être réalisées par plusieurs méthodes et appareils.

Voici quelques exemples :

vitesse de l'onde de pouls	appareil	signification
carotidofémorale	tonomètre	rigidité aortique
carotidofémorale	tonomètre + brassard oscillométrique	rigidité aortique
carotidofémorale	brassard oscillométrique	rigidité aortique
aortique	brassard oscillométrique	rigidité aortique
bras cheville	brassard oscillométrique	rigidité vasculaire
doigt orteil	photopletysmographie	rigidité vasculaire
cœur cheville	brassard oscillométrique+microphone	rigidité vasculaire

Selon la Société Européenne d'Hypertension, le gold standard pour la mesure de la rigidité aortique est la vitesse de l'onde de pouls carotidofémorale.[78]

Outre la tonométrie d'applanation, des mesures d'utilisation facile sont de plus en plus employées (par exemple à l'aide de brassards oscillométriques) car elles sont automatiques et ne dépendent pas de l'opérateur.

Avec ces procédures, peuvent se poser principalement deux ordres de problèmes.

1. Rigidité aortique *versus* rigidité vasculaire : si la tonométrie carotidofémorale mesure la vitesse de l'onde de pouls aortique et donc la rigidité aortique, la mesure par oscillométrie de la vitesse de l'onde de pouls entre le bras et la cheville serait un index de rigidité vasculaire. Les études de validation de cette méthode retrouvent de bonnes corrélations entre les deux vitesses[234] et montrent aussi le pouvoir prognostique de la rigidité vasculaire,[235] mais comment interpréter cette rigidité vasculaire ? En réalité, la vitesse de l'onde de pouls bras-cheville contient en soi des informations sur la rigidité des artères à la fois élastiques, comme l'aorte, et musculaires, comme les artères humérale, fémorale et tibiale. Nous avons montré le comportement différent en termes de rigidité des deux typologies des artères (cf ARTICLE

2, page 87). La mesure de la vitesse de l'onde de pouls bras-cheville nous semble donc un succédané de la vitesse de l'onde de pouls aortique, qui est, elle, un succédané de la rigidité aortique.

2. Un site *versus* deux sites : si la mesure classique de la vitesse de l'onde de pouls prévoit l'enregistrement des ondes de pression (tonométrique ou oscillométrique) au niveau de deux sites artériels, d'autres appareils en proposent une mesure à partir d'un seul site et, notamment, l'artère brachiale, par oscillométrie. Comment justifier cela ? Cette méthode se base sur la notion que, dans les artères du membre supérieur, on observe l'arrivée des ondes de réflexion provenant du bas du corps (cf page 127) qui définit, semble-t-il, un deuxième pic sur la courbe de pression. Comme nous l'avons montré, cela implique la présence d'un seul site de réflexion majeur (la bifurcation iliaque) et la présence d'une seule onde de réflexion. La mesure du décalage entre les deux pics systoliques permettrait de calculer la vitesse de l'onde de pouls aortique. Or, la présence d'un site unique de réflexion ainsi que d'une seule onde centripète n'est pas prouvée et constitue encore aujourd'hui un sujet de débat.[84]

Dans notre exposé nous avons essayé de donner l'idée de la complexité du système cardiovasculaire. Ces méthodes de mesure ont été mises au point par des experts, avec originalité, pour tenter une approche hémodynamique simple et non invasive, fondamentale dans notre domaine.

Cependant, par les quelques exemples que nous avons donnés, nous sommes amenés à considérer le risque des concessions : se contenter des bonnes corrélations au lieu de chercher des mesures véritables ; se contenter de modèles

approximatifs et non pas prouvés ; se contenter de succédanés des succédanés, sans savoir ce que l'on mesure en réalité.

Cela conduirait aussi à des effets négatifs dans la gestion des résultats des études, comme le fait de devoir gérer des entités mesurables qui en contiennent d'autres, dont il ne serait plus possible d'identifier la contribution spécifique ; par conséquent, tous les modèles d'ajustement (que chaque chercheur connait bien) risqueraient de contenir deux ou trois fois le même paramètre, sans le savoir, ce qui porterait à des sur-ajustements, limitant fortement la validité scientifique des relations indépendantes retrouvées.

Il nous semble donc que, d'un point de vue à la fois « théorétique » et pratique, cette approche de la recherche ne convient ni à la société scientifique ni à la médecine clinique.

Revenons alors à l'aorte.

V.3. Le couplage cœur/vaisseaux

Les avances des technologies, des modèles mathématiques et de l'industrie ont permis de comprendre certains aspects du système cardiovasculaire, d'en visualiser le comportement, d'avancer dans la mesure de la pression artérielle périphérique et centrale. Les logiciels associés aux appareils de mesure sont de plus en plus complets, offrant souvent la possibilité d'envoyer les données automatiquement par Internet. Les données attestant l'intérêt des mesures hémodynamiques prolifèrent parallèlement à la disponibilité des nouveaux appareils sur le marché.

Toutefois, la résistance des sociétés scientifiques, comme les Sociétés Française et Européenne d'Hypertension, à recommander l'utilisation de ces paramètres dans la pratique clinique, pose des questions au monde de la recherche. En effet, depuis les années '60, quand furent créés les grands modèles hémodynamiques, l'étude et la compréhension des mécanismes propres au système cardiovasculaire, sa modélisation et l'application pratique des modèles, n'ont pas vraiment avancé. Si après la lecture de cet exposé on relisait l'introduction à la première partie, avec la citation de O'Rourke, on pourrait penser que tout (ou presque) avait déjà été dit, ou au moins théorisé.

Après ces trois années de thèse, pour différentes raisons que nous avons essayé de présenter, il nous semble avoir compris qu'il faudrait revenir à l'étude de l'aorte et du couplage cœur/vaisseaux, au lieu que d'en s'éloigner toujours plus.

D'un point de vue théorique, le dialogue permanent entre le cœur et l'aorte représente encore le point le plus fascinant et pourtant obscur du système cardiovasculaire. L'impédance, la relation entre la pression et le flux, la capacité des artères à recevoir la pulsatilité envoyée par le cœur et à la transformer, et, de retour, l'influence des réponses artérielles sur la fonctionnalité cardiaque sont en permanente adaptation les uns avec les autres, et sont des éléments de grand intérêt scientifique, dont la compréhension pourrait apporter une aide concrète dans la gestion clinique des patients.

Il nous semble donc que la possibilité de mesurer à la fois la courbe de pression carotidienne, la distensibilité de la paroi carotidienne, la fonction ventriculaire gauche systolique et diastolique, et les flux aortique et carotidien, pourrait amener à l'idéation de nouveaux modèles pour la compréhension de

l’impédance et du rôle des artères dans le système cardiovasculaire, comme l'ont déjà proposé récemment quelques auteurs.[236–238]

Conclusion générale

Notre travail de recherche de ces dernières années a été caractérisé par deux thématiques principales : l'étude de la mécanique vasculaire et des problématiques associées à la mesure des paramètres centraux ; l'intérêt de l'hémodynamique sur les maladies métaboliques.

Les modifications physiopathologiques artérielles qui participent au développement de la maladie cardiovasculaire peuvent être étudiées par les modèles et les paramètres hémodynamiques centraux.

Le système cardiovasculaire, conçu dans le but de fournir l'énergie aux tissus pour leur fonctionnement avec une moindre dépense d'énergie, est caractérisé par la pulsatilité cardiaque et la compliance artérielle. Si la pulsatilité engendrée par le cœur est principalement énergie qui se traduit en système ondulatoire, avec la présence des phénomènes de résonance et de réflexion, la compliance est la manière dont la matière physique (les artères) accueille et modifie la pulsatilité ; si les ondes de pression et de flux représentent la propagation de l'énergie pulsatile du cœur aux tissus, la relation complexe entre les deux (pression et flux) est le dialogue entre le ventricule gauche et les vaisseaux. Les artères répondent aux sollicitations cardiaques et modifient la propagation de l'énergie de la façon la plus adaptée possible.

Les ondes de pression peuvent facilement être mesurées par différentes techniques, la plus fiable étant la tonométrie artérielle d'applanation. La procédure de calibrage des ondes permet d'obtenir les valeurs finales de pression artérielle, mais comporte des approximations et des contraintes qui ne sont pas encore résolues et que nous avons essayé d'analyser. Des calibrages différents peuvent notamment amener à des valeurs de pression très différentes.

Les deux propriétés fondamentales de la propagation de la pulsatilité dans les artères sont l'augmentation des oscillations de pression observée du centre à la périphérie du système, et la vitesse de propagation des ondes. Si la vitesse de l'onde de pouls donne des informations sur la qualité de la composition de la paroi artérielle, l'étude de la pression centrale et de son rapport avec la pression périphérique permet d'évaluer la relation dynamique entre la rigidité/compliance artérielle, les résistances périphériques et les ondes de réflexion. L'amplification de la pression pulsée est un paramètre qui réfléchit les propriétés mécaniques des artères indépendamment du niveau tensionnel ; elle a montré un impact sur le pronostic cardiovasculaire dans différentes populations, notamment les sujets très âgés, et elle pourrait jouer un rôle dans l'évaluation de l'efficacité du traitement antihypertenseur.

Nous avons montré la relation complexe qui existe entre la maladie cardiovasculaire et son expression clinique (atteinte d'organes cibles et modifications hémodynamiques), et la maladie métabolique. Il semble de plus en plus évident que le diabète est responsable d'altérations à plusieurs niveaux : au niveau purement métabolique, comprenant l'hyperglycémie, l'élévation des acides gras libres, les altérations des lipoprotéines ; au niveau du stress oxydatif ; au niveau de la fonction endothéliale, de l'inflammation, et de l'équilibre entre thrombose et fibrinolyse. Ces altérations qui accompagnent le diabète sont associées elles-mêmes à une atteinte vasculaire qui s'exprime par une rigidification de l'arbre artériel. C'est pour cela que les paramètres hémodynamiques, à partir de la pression centrale, des ondes de réflexion et de la rigidité artérielle, pourraient être considérés comme marqueurs de l'effet global des altérations métaboliques cumulées dans le temps. En particulier, la vitesse de l'onde de pouls, comme mesure de la rigidité aortique, semble être un paramètre capable de quantifier le degré de l'atteinte artérielle et donc le sur-risque

cardiovasculaire chez les patients diabétiques, indépendamment et au-delà de l'hypertension artérielle.

Les paramètres classiquement liés au risque cardiovasculaire, comme la pression artérielle, le poids et l'index de masse corporelle, ou le cholestérol, semblent perdre leur signification chez les sujets âgés, chez qui ils peuvent avoir même un effet inverse sur la mortalité. Le vieillissement de l'arbre artériel s'accompagne de changements structurels des parois des artères, dont l'intérêt prognostique persiste dans les phases avancées de la vie, là où le défi de la prise en charge médicamenteuse est le plus grand. L'étude des paramètres hémodynamiques centraux pourrait donc améliorer la prévention et la prise en charge chez le sujet âgé.

La variabilité tensionnelle semble être un paramètre complémentaire capable d'investiguer dans la temporalité les modifications de la pression artérielle, et donc la capacité adaptative du système cardiovasculaire.

L'accumulation des produits de glycation avancée et l'inflammation pourraient présenter une voie commune dans les modifications de la rigidité artérielle auxquelles ils s'associent. L'évaluation de la relation entre la glycation non enzymatique et la rigidité artérielle pourrait avoir un rôle à la fois pronostique et diagnostique sur la maladie coronaire.

Le dialogue entre le cœur et l'aorte représente encore le point le plus fascinant et pourtant obscur du système cardiovasculaire. L'impédance, la relation entre la pression et le flux, la capacité des artères de recevoir la pulsatilité envoyée par le cœur et de la transformer, et, de retour, l'influence des réponses artérielles sur la fonctionnalité cardiaque sont des éléments de grand intérêt scientifique, dont la

compréhension pourrait apporter une aide concrète dans la gestion clinique des patients.

La communauté scientifique tirerait un bénéfice de mesures de pression centrale et de rigidité artérielle toujours plus proches de la réalité. Pour cela, des protocoles de validation standardisés semblent être indispensables. On n'a pas encore atteint l'exhaustivité dans la compréhension et la modélisation du comportement des artères, et l'investigation du couplage cœur/vaisseaux en est une voie prometteuse.

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ANNEXES

ANNEXE 1

Vascular Health and Risk Management

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REVIEW

Validation of four automatic devices for self-measurement of blood pressure according to the international protocol of the European Society of Hypertension

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Background: Four oscillometric devices for self-measurement of blood pressure (SBPM) were evaluated according to the European Society of Hypertension (ESH) international protocol and its 2010 revision in four separate studies. The Omron® M2, Omron M3, and Omron M6 measure blood pressure (BP) at the brachial level, while the Omron R2 measures BP at the wrist level.
Methods: The international protocol requires a total number of 33 subjects in which the validation is performed. The Omron M2 and Omron R2 were validated in 2009 according to the ESH international protocol, while the Omron M3 and Omron M6 were validated in 2010–2011 according to the 2010 ESH international protocol revision. The protocol procedures were followed precisely.
Results: All four tested devices passed the validation process. The mean differences between the device and mercury readings were 2.7 ± 5.0 and −1.4 ± 3.2 mmHg for systolic and diastolic BP, respectively, using the Omron M2 device, and 1.7 ± 3.2 and −0.9 ± 2.6 mmHg using the Omron M3, 1.6 ± 2.9 and −0.9 ± 2.5 mmHg using the Omron M6, and −1.1 ± 4.8 and −0.9 ± 4.3 mmHg using the Omron R2.
Conclusion: Readings from the Omron M2, Omron M3, Omron M6, and Omron R2, differing by less than 5, 10, and 15 mmHg, fulfill the ESH international protocol and its 2010 revision requirements. Therefore, each of these four devices can be used by patients for SBPM.
Keywords: Omron R2, M2, M3, M6, blood pressure measurement, validation, international protocol, European Society of Hypertension

Introduction

The advantages of blood pressure (BP) self-measurement have been well documented.[1,2] Indeed, self-BP measurement (SBPM) not only provides valuable information for diagnosis of hypertension but also for BP control in the treated patient, and improves patient compliance with antihypertensive therapy.[1–3] Therefore, it is appropriate to encourage widespread use of SBPM as an important adjunct to the clinical care of patients with hypertension.[2] Clinical indications for SBPM have recently been highlighted in several guidelines and consensus conferences.[1–6] Obviously, SBPM is only practicably useful if the devices are user-friendly and accurate. Recommended devices for SBPM should be submitted to independent validation procedures. Currently, only a few of the devices available on the market have been validated and are recommended for patient use.[7] Validation has to be performed according to recognized protocols specifically designed for this purpose, such as the British Hypertension Society protocol,[8] the Association for the Advancement of Medical Instrumentation protocol,[9] and the

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international protocol published by the European Society of Hypertension (ESH).[10,11] In this study, four devices for SBPM were validated according to the international protocol in four separate studies.

Methods and materials

Devices

Omron M2

The Omron® M2 (HEM-7117-E) device records brachial BP using the oscillometric method with a pressure range of 0–299 mmHg and pulse rate range of 40–180 beats/minute. Systolic BP, diastolic BP, and pulse rate are displayed on a liquid crystal digital (LCD) screen. The device can detect and display a symbol on the LCD screen if an irregular heart beat defined by a heart beat rhythm that varies by more than 25% from the average heart beat rhythm is detected while the unit is measuring the systolic and diastolic BP. It includes memory for 21 measurements. The unit weighs approximately 260 g without batteries. Four AAA batteries are needed with an approximate capacity of 300 measurements. The standard cuff included is applicable to arm circumferences ranging from 22 to 32 cm; a large cuff is also available for arm circumferences of 32–42 cm.

Omron M3

The Omron M3 (HEM-7200-E) device records brachial BP using the oscillometric method with a pressure range of 0–299 mmHg and pulse rate range of 40–180 beats/minute. Inflation is performed using a fuzzy-logic electric pumping system and deflation by an automatic pressure release valve. At the end of each measurement, systolic BP, diastolic BP, and pulse rate are displayed on a LCD screen. The device can detect and display a symbol on the LCD screen if an irregular heart beat defined by a heart beat rhythm that varies by more than 25% from the average heart beat rhythm is detected while the unit is measuring the systolic and diastolic BP. The monitor automatically stores results for up to 60 sets. It can also calculate an average reading based on measurements from the last three readings taken within 10 minutes. The unit weighs approximately 340 g without batteries. Four AA alkaline batteries are needed with an approximate capacity for 1500 measurements. Two sizes of cuffs, ie, standard and large, are available. The standard cuff is adapted to an arm circumference of 22–32 cm and the large cuff to an arm circumference of 32–42 cm.

Omron M6

The Omron M6 (HEM-7211-E) device records brachial BP using the oscillometric method with a pressure range of 0–299 mmHg and pulse rate range of 40–180 beats/minute. Inflation is performed using a fuzzy-logic electric pumping system and deflation by an automatic pressure release valve. At the end of each measurement, systolic BP, diastolic BP, and pulse rate are displayed on a LCD screen. The device can detect and display a symbol on the LCD screen if an irregular heart beat defined by a heart beat rhythm that varies by more than 25% from the average heart beat rhythm detected while the unit is measuring the systolic and diastolic BP. The monitor automatically stores results for up to 90 sets. It can also calculate an average reading based on measurements from the last three readings taken within 10 minutes. The unit weighs approximately 380 g without batteries. Four AA alkaline batteries are needed with an approximate capacity for 1500 measurements. Three sizes of cuffs, ie, small, standard, and large, are available. The standard cuff is adapted to an arm circumference of 22–32 cm, the small cuff to an arm circumference of 17–22 cm, and the large cuff to an arm circumference of 32–42 cm.

Omron R2

The Omron R2 (HEM-6113-E) device is an automatic oscillometric device for SBPM, measuring radial BP at the wrist level. This device uses automatic inflation by pump and automatic rapid deflation. It measures a BP range of 1–299 mmHg and a pulse rate range of 40–180 beats/minute, and values are displayed on a LCD screen. The unit includes memory for 30 measurements. It weighs approximately 117 g without batteries. Two AAA alkaline batteries are needed with an approximate capacity for 300 measurements. The device can be used for wrist circumferences of 13.5–21.5 cm.

BP measurements

For each study, the manufacturer was asked to provide three complete devices, declared by the manufacturer as standard production models. Before the validation study per se, a familiarization period of about one week took place in an outpatient clinic. During this period, the investigators familiarized themselves with use of the tested device. Each validation study was performed using one device chosen randomly by the investigator from the three provided by the manufacturer.

The validation team for each study consisted of three persons experienced in BP measurement. Investigators underwent training on the basis of a CD-ROM specifically developed by the French Society of Hypertension for the certification of observers involved in clinical studies. Two of the three observers measured BP using a teaching stethoscope for simultaneous

measurements (Y tube, Littmann, Schaumburg, IL) and two standard mercury sphygmomanometers, the components of which had been carefully checked before the study. The third observer was the supervisor who checked the agreement of BP values obtained by the two observers who were blinded to each other's readings. In one study (of the Omron M6), the second observer was also the supervisor (JT).

Patient population

The four validation studies were performed in the general population. According to the international protocol, a total of 33 participants who fulfilled the age, gender, and entry BP requirements (age ≥25 years, at least 10 men and 10 women, 11 participants with entry BP within each of the ranges 90–129 mmHg, 130–160 mmHg, and 161–180 for systolic BP and 40–79 mmHg, 80–100 mmHg, and 101–130 mmHg for diastolic BP). Arm circumference is distributed by chance. In order to optimize recruitment, it was recommended that subjects for the high diastolic BP and low systolic BP groups should be recruited first, then those with high systolic BP and low diastolic BP, and finally the remaining gaps should be filled. In these four studies, subjects were preselected in order to avoid a high number of subjects being excluded because of their BP range.

Procedure

Subjects were seated in a quiet room and BP measurements started after a 10-minute rest period. Arm circumference was measured and the cuff size was adapted. All measurements were performed in the left arm at the heart level. BP was measured simultaneously by the two observers alternately with the automatic device as mentioned earlier. Nine consecutive measurements were carried out according to the procedure described in detail elsewhere.[10] The validation studies of the Omron R2 and the Omron M2 were performed during the last quarter of 2009 according to the first version of the international protocol;[10] those for the Omron M3 and the Omron M6 were performed at the end of 2010 and 2011 according to the 2010 international protocol revision. In each of the four studies, the ESH International protocol and its revision 2010 were followed precisely.

Data analysis

Differences between the tested device and control measurements were classified according to whether they were within 5, 10, or 15 mmHg. Differences were calculated by subtracting the observer measurement from the device measurement; they were classified separately in this way for both systolic BP and diastolic BP. The number of differences in each zone was calculated and compared with the number required by the international protocol and its 2010 revision. Details of the analysis procedure have already been published elsewhere.[10,11]

Results

Omron M2

This study included 33 subjects (20 men and 13 women) with a mean age of 58 ± 11 (range 37–80) years, and a mean arm circumference of 28 ± 4 (range 20–34) cm. A standard size cuff was used in 30 subjects and a large cuff in three subjects. At entry, the mean BP values were, respectively, 142 ± 23 (range 101–180) mmHg for systolic BP and 86 ± 18 (range 53–110) mmHg for diastolic BP. The difference between the two observers was 0.1 ± 2.1 mmHg and 0.3 ± 2.1 mmHg for systolic BP and diastolic BP, respectively. The mean differences between the observers and the tested device were 2.7 ± 5.0 and –1.4 ± 3.2 mmHg for systolic BP and diastolic BP, respectively.

The numbers of measurements differing from the mercury standard by 5, 10, and 15 mmHg or less are shown in Table 1. The difference between the device readings and the mean BP of the device and the two observers for all 99 points of systolic BP and diastolic BP are displayed in Figure 1. These results are in agreement with the international protocol requirements for the primary and secondary phases. Thus, the Omron M2 device fulfills the validation criteria of the international protocol.

Omron M3

This study included 33 subjects (16 men and 17 women) with a mean age of 60 ± 11 (range 31–78) years and a mean arm circumference of 29 ± 3 (range 25–36) cm. A standard size cuff was used in 29 subjects and a large cuff in four subjects. At entry, the mean BP values were, respectively, 142 ± 25 (range 90–179) mmHg for systolic BP and 85 ± 18 (range 50–119) mmHg for diastolic BP. The difference between the two observers was 0.1 ± 0.8 and –0.2 ± 1.0 mmHg for systolic BP and diastolic BP, respectively. The mean differences between the observers and the tested device were 1.7 ± 3.2 and –0.9 ± 2.6 mmHg for systolic BP and diastolic BP, respectively.

The numbers of measurements differing from the mercury standard by 5, 10, and 15 mmHg or less are shown in Table 2. The difference between the device readings and the mean BP of the device and the two observers for all 99 points of systolic BP and diastolic BP are displayed in Figure 2.

Table 1 Results for the Omron M2 device according to the ESH international protocol

Phase 1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Recommendation**		
Required	One of	25	35	40			
Achieved	SBP	23	38	42	Continue		
	DBP	40	45	45	Continue		
Phase 2.1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Recommendation**	**Mean difference (mmHg)**	**SD**
Required	Two of	65	80	95			
	All of	60	75	90			
Achieved	SBP	73	92	96	Pass	2.7	5.0
	DBP	88	99	99	Pass	−1.4	3.2
Phase 2.2		**2/3 ≤ 5 mmHg**	**0/3 ≤ 5 mmHg**		**Recommendation**		
Required		≥22	≤3				
Achieved	SBP	25	3		Pass		
	DBP	31	0		Pass		

Abbreviations: ESH, European Society for Hypertension; SD, standard deviation (mmHg); SDP, systolic blood pressure; DBP, diastolic blood pressure.

These results are in concordance with the 2010 international protocol revision requirements. Thus, the Omron M3 device fulfills the validation criteria of the 2010 ESH international protocol revision.

Omron M6

This study included 33 subjects (15 men and 18 women) with a mean age of 60 ± 13 (range 25–79) years and a mean arm circumference of 29 ± 3 (range 25–36) cm. A standard size cuff was used in 32 subjects and a large cuff in one subject. At entry, the mean BP values were, respectively, 144 ± 25 (range 96–180) mmHg for systolic BP and 86 ± 18 (range 50–119) mmHg for diastolic BP. The difference between the two observers was 0.2 ± 1.1 and –0.1 ± 1.1 mmHg for systolic BP and diastolic BP, respectively. The mean differences between the observers and the tested device were 1.6 ± 2.9 and –0.9 ± 2.5 mmHg for systolic BP and diastolic BP, respectively.

The numbers of measurements differing from the mercury standard by 5, 10, and 15 mmHg or less are shown in Table 3. The difference between the device readings and the mean BP of the device and the two observers for all 99 points of systolic BP and diastolic BP are displayed in Figure 3. These results are in concordance with the 2010 international protocol revision requirements. Thus, the Omron M6 device fulfills the validation criteria of the 2010 ESH international protocol revision.

Omron R2

This study included 33 subjects (19 men and 14 women) with a mean age of 58 ± 11 (range 37–80) years and a mean wrist circumference of 18 ± 2 (range 14–22) cm. A standard brachial size cuff was used in 31 subjects and a large cuff in two subjects. At entry, the mean BP values were, respectively, 142 ± 24 (range 101–179) mmHg for systolic BP and 86 ± 18 (range 53–111) mmHg for diastolic BP. The difference between the two observers was 0.3 ± 2.2 and 0.3 ± 1.8 mmHg for systolic BP and diastolic BP, respectively. The mean differences between the observers and the tested device were –1.1 ± 4.8 and –0.9 ± 4.3 mmHg for systolic BP and diastolic BP, respectively.

The numbers of measurements differing from the mercury standard by 5, 10, and 15 mmHg or less are shown in Table 4. The difference between the device readings and the mean BP of the device and the two observers for all 99 points of systolic BP and diastolic BP are displayed in Figure 4. These results are in concordance with the requested criteria of the international protocol for the primary and secondary phases. Thus, the Omron R2 device fulfills the validation criteria of the international protocol.

Discussion

This study provides information on the accuracy of four devices for SBPM measurement. The Omron M2, Omron M3, and Omron M6 measure BP at the brachial level, whereas the Omron R2 measures radial BP at the wrist level. The results show that all four devices met the validation requirements of the ESH international protocol and its 2010 revision, provided that they are used by well trained observers and considering the factors affecting measurement accuracy as described by the manufacturers. The Omron M2 and R2 were validated according to the international protocol version 2002 because these studies were performed during the last quarter of 2009, whereas the Omron M3 and Omron M6 were validated according to the 2010 international protocol revision because these two studies were performed after its publication during 2010 and 2011.

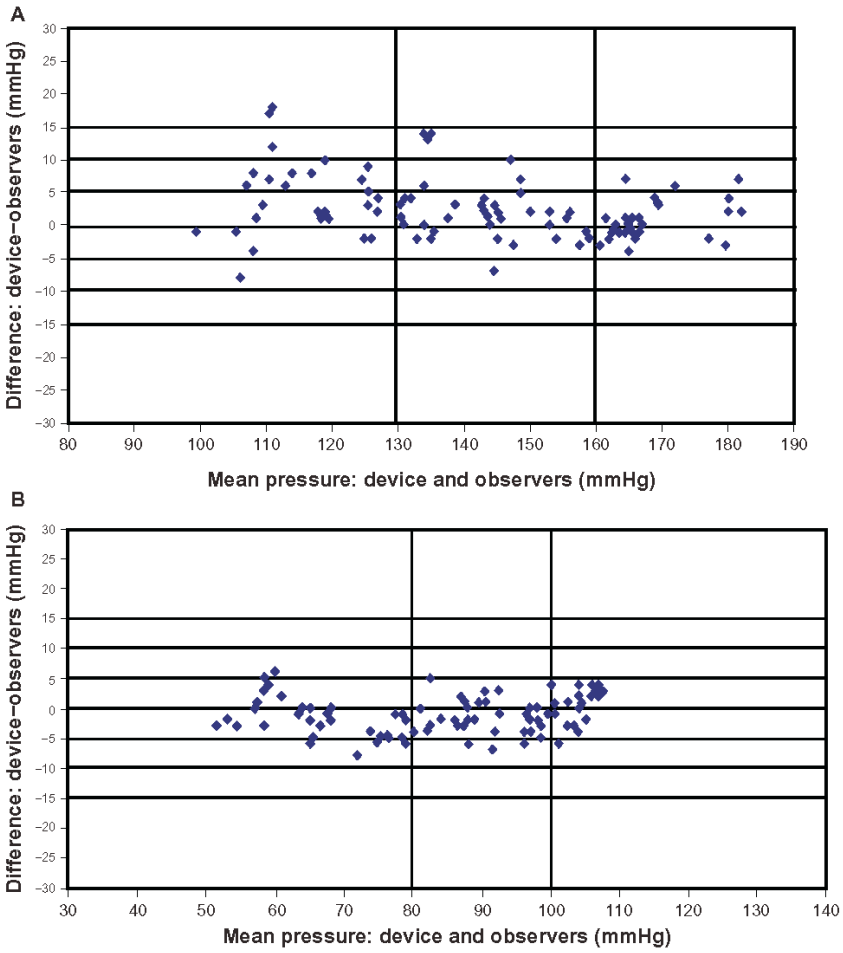

Figure 1 Plots of systolic (A) and diastolic (B) blood pressure differences between the Omron M2 readings and the mean of two observer readings in 33 participants (n = 99).

The four present validation studies were performed by well trained observers, who used the tested devices as recommended by the manufacturers and considered the factors affecting measurement accuracy. The latter is particularly important for the wrist BP device. BP measurements at the wrist level are prone to a number of errors, most of them related to how the patient uses the device. The wrist cuff has to be wrapped in a correct way and measurements performed in the correct posture, ie, the arm held across the chest, the wrist at the heart level, the arm relaxed without

Table 2 Results for the Omron M3 device according to the ESH international protocol revision 2010

Part 1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Grade 1**	**Mean difference**	**SD**
Required	Two of	73	87	96			
	All of	65	81	93			
Achieved	SBP	86	99	99	Pass	1.7	3.2
	DBP	94	99	99	Pass	−0.9	2.6
Part 2		**2/3 ≤ 5 mmHg**	**0/3 ≤ 5 mmHg**		**Grade 2**		**Grade 3**
Required		≥24	≤3				
Achieved	SBP	31	0		Pass		Pass
	DBP	33	0		Pass		Pass
Part 3							**PASS**

Abbreviations: ESH, European Society for Hypertension; SD, standard deviation (mmHg); SDP, systolic blood pressure; DBP, diastolic blood pressure.

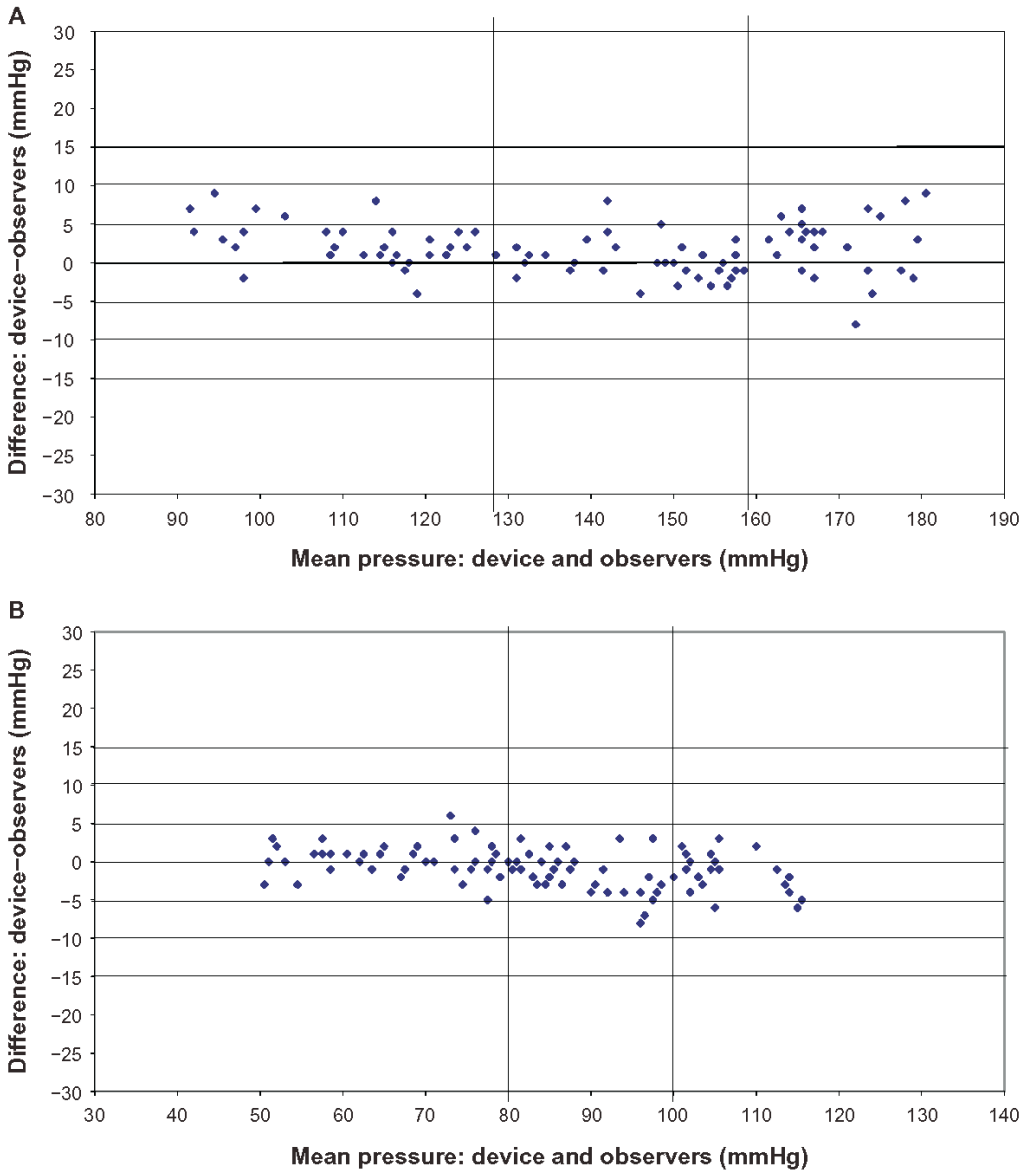

Figure 2 Plots of systolic (A) and diastolic (B) blood pressure differences between the Omron M3 readings and mean of the two observer readings in 33 participants (n = 99).

Table 3 Results for the Omron M6 device according to the ESH international protocol revision 2010

Part 1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Grade 1**	**Mean difference**	**SD**
Required	Two of	73	87	96			
	All of	65	81	93			
Achieved	SBP	89	99	99	Pass	1.6	2.9
	DBP	96	99	99	Pass	−0.9	2.5
Part 2		**2/3 ≤ 5 mmHg**	**0/3 ≤ 5 mmHg**		**Grade 2**		**Grade 3**
Required		≥24	≤3				
Achieved	SBP	32	0		Pass		Pass
	DBP	33	0		Pass		Pass
Part 3							**PASS**

Abbreviations: ESH, European Society for Hypertension; SD, standard deviation (mmHg); SDP, systolic blood pressure; DBP, diastolic blood pressure.

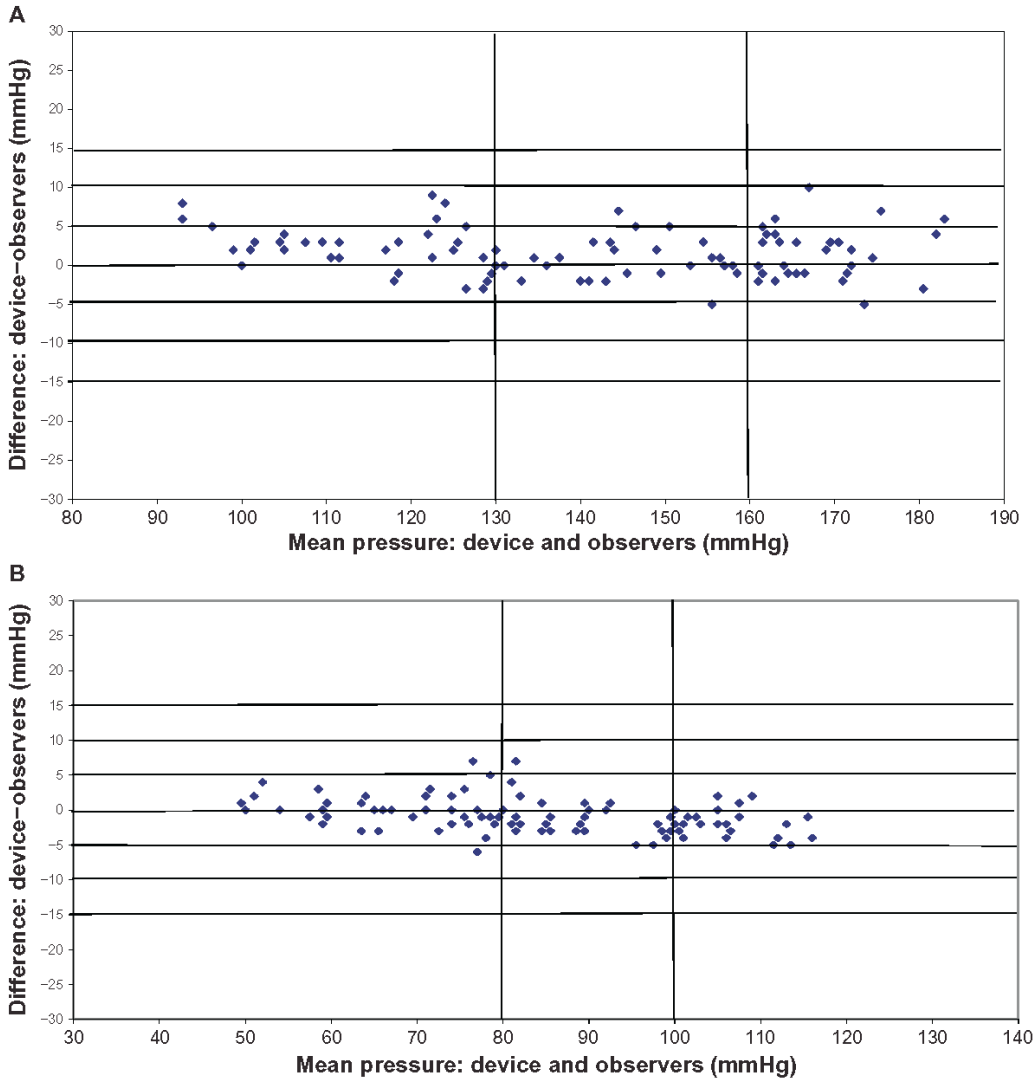

Figure 3 Plots of systolic (**A**) and diastolic (**B**) blood pressure differences between the Omron M6 readings and the mean of two observer readings in 33 participants (n = 99).

Table 4 Results of the Omron R2 device according to the ESH international protocol

Phase 1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Recommendation**		
Required	One of	25	35	40			
Achieved	SBP	38	41	45	Continue		
	DBP	37	44	45	Continue		
Phase 2.1		**≤5 mmHg**	**≤10 mmHg**	**≤15 mmHg**	**Recommendation**	**Mean difference**	**SD**
Required	Two of	65	80	95			
	All of	60	75	90			
Achieved	SBP	81	92	99	Pass	−1.1	4.8
	DBP	82	94	99	Pass	−0.9	4.3
Phase 2.2		**2/3 ≤ 5 mmHg**	**0/3 ≤ 5 mmHg**		**Recommendation**		
Required		≥22	≤3				
Achieved	SBP	29	2		Pass		
	DBP	29	3		Pass		

Abbreviations: ESH, European Society for Hypertension; SD, standard deviation (mmHg); SDP, systolic blood pressure; DBP, diastolic blood pressure.

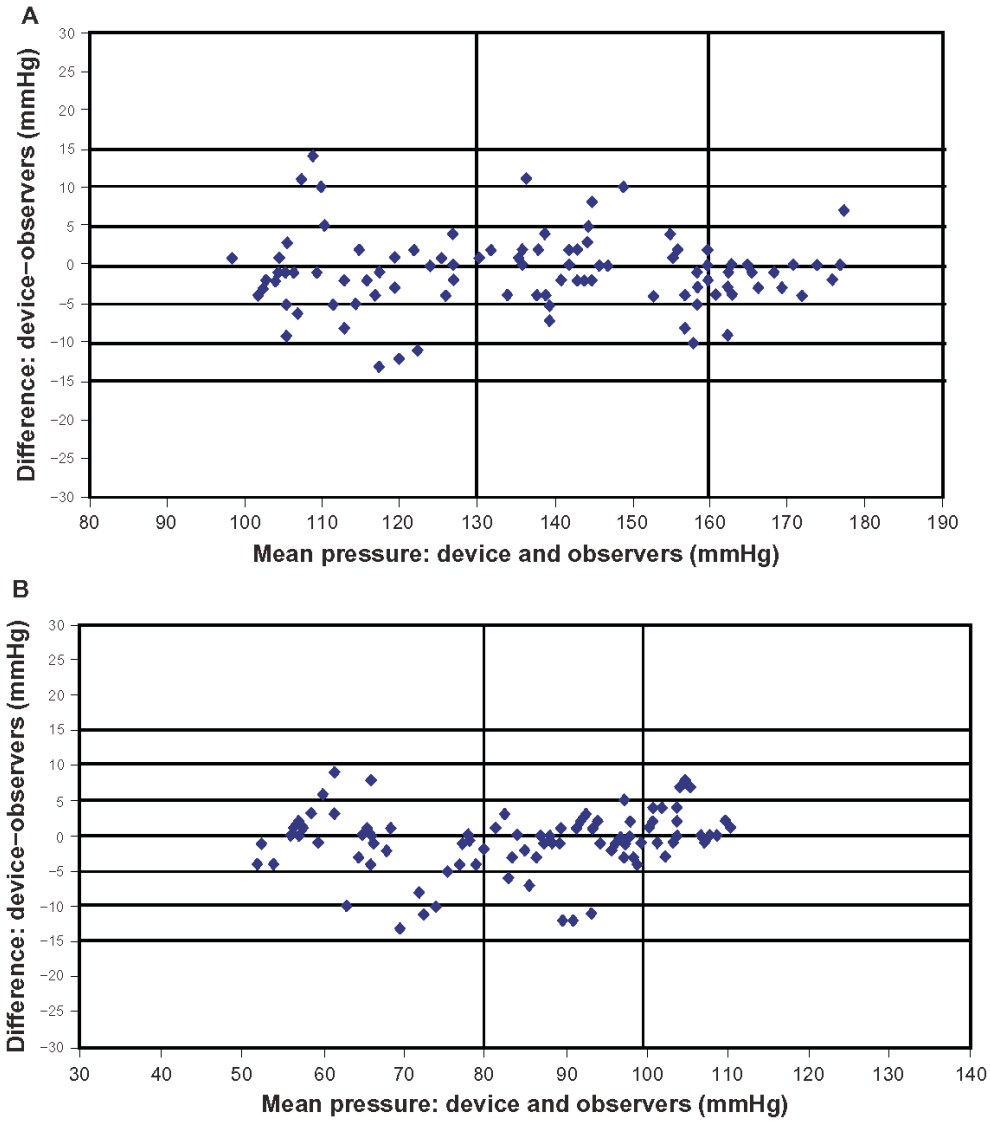

Figure 4 Plots of systolic (A) and diastolic (B) blood pressure differences between the OmronR2 readings and the mean of two observer readings in 33 participants (n = 99).

excessive extension or flexion and without a clenched fist. In practice, these recommendations are usually not fully followed, so experts prefer to use a device measuring BP at the brachial level.

In this study, validation was performed according to the international protocol. This protocol was published in 2002 by the ESH[10] aiming to simplify the other two available protocols, ie, the British Hypertension Society[8] and Association for the Advancement of Medical Instrumentation[9] protocols, without compromising their integrity. The main advantage of this protocol is that it requires a smaller number of subjects (n = 33) than the 85 required for the two other protocols. However, this protocol had some limitations. First, the population required in the international protocol is confined to adults >30 years (>25 years in the 2010 revision) with specifications in terms of age, gender, BP level, and arm circumference. Because this selected population is only a part of the large heterogeneous population affected by hypertension, extrapolation of results to other specific populations may be hazardous and risky. Specific validation studies are needed if the devices are to be used by specific populations, eg, pregnant women, the elderly, the obese, children,

or patients with specific conditions, such as arrhythmia. Second, the number of validation studies needed to confirm device accuracy is an important issue. The international protocol does not specify the number of devices or study sites recommended to optimize accuracy of measurements. Experts agree that it would be important to have at least two validation studies conducted in different centers and various populations. In this regard, the Association for the Advancement of Medical Instrumentation protocol recommends more than one study but does not specify the number of studies or devices. Therefore, because none of the four tested devices in the present study went through prior validation, it would be important to undertake at least one further study in a specific population before recommending their widespread use in the clinic.

Conclusion

The results of the present study show that the four tested devices, ie, the Omron M2, Omron M3, and Omron M6 which measure BP at the brachial level (arm) and the Omron R2 which measures the BP at the radial level (wrist) meet the requirements of the ESH international protocol and its 2010 revision in a general population. Therefore, any of these four devices can be used by patients for SBPM if used correctly according to the manufacturer recommendations. Because of certain limitations of the international protocol, it would be desirable to corroborate the present results by other studies performed in both the general population and in selected patient populations.

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Disclosure

The authors report no conflicts of interest in this work. The study was sponsored by Omron Healthcare Europe.

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ANNEXE 2

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ORIGINAL ARTICLE

Aortic stiffness, inflammation, denutrition and prognosis in the oldest people

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Observational studies have shown that some of the classic CV risk factors, namely hypertension or hypercholesterolemia, become nebulous, or even act in the reverse direction, in the oldest people. We investigated whether in the elderly, increased aortic stiffness was associated with higher mortality risk, before and after adjustments on common geriatric confounders. In a cohort of 331 (86 men) subjects aged >70 years (mean age (±s.d.): 85±7 years), aortic stiffness was assessed by carotid–femoral pulse wave velocity (PWV). Classical CV risk factors were determined simultaneously, in association with inflammation and denutrition parameters. One hundred and ten subjects died during a 2-year follow-up period. In crude analysis, a positive non-significant trend was observed between PWV and mortality risk. Multivariate Cox regression analysis showed that five parameters entered the prediction model: two were positively related to mortality risk, PWV ($P=0.008$) and orosomucoide ($P=0.045$), and three were related negatively, total cholesterol ($P=0.006$), albumin ($P=0.026$) and body weight ($P=0.035$). Interaction analysis revealed that the effect of PWV on mortality was increased in the presence of renal dysfunction and increased inflammation. In conclusion, although marginally significant in crude analysis, PWV is a powerful determinant of prognosis in the oldest people taking into account inflammation and denutrition.
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Keywords: arterial stiffness; mortality; elderly; denutrition; inflammation

Introduction

Aging of the arterial system is accompanied by structural changes, including fragmentation and degeneration of elastin, increases in collagen, thickening of the arterial wall and progressive dilation of the arteries. These changes result in a gradual stiffening of the vasculature and an increase in the velocity of the pressure wave as it travels down the aorta. In a normal elastic aorta, the pressure wave reflects from the periphery and returns to the heart during diastole. Thus, it increases coronary perfusion during diastole. As the aorta stiffens, the velocity of the pressure wave increases, and the reflected pressure wave eventually reaches the heart at systole instead of diastole, causing augmentation of the systolic blood pressure (SBP) and increased cardiac afterload. The diminished elastic recoil of the stiff aorta, combined with the absence of diastolic augmentation from the reflected pressure wave, has the potential to reduce coronary filling.[1,2]

With increasing age, there is a gradual shift from diastolic BP (DBP) to SBP and then to pulse pressure (PP) as predictors of cardiovascular (CV) risk, mainly from coronary heart disease. In patients <50 years of age, DBP is the strongest CV predictor. The age range of 50–59 years is a transition period when all three BP indices are comparable predictors, and, from 60 years of age, PP becomes superior to both SBP and DBP to predict myocardial infarction.[3] In addition, because for a given ventricular ejection aortic stiffness is the major determinant of PP, increased aortic pulse wave velocity (PWV), a classic marker of arterial rigidity, has also been identified as an independent predictor of CV risk in numerous populations.[4–16] Only three studies took place in the elderly;[7,13,16] none was specifically designed to test the multi-adjusted added value of aortic PWV in term of all-cause mortality prediction. Finally, very few studies addressed the potential validity of these - pathophysiological considerations in the frail oldest old with a high burden of CV disease.

In the present study, a cohort of very old frail subjects (mean age (±s.d.): 85±7 years) was investigated prospectively. We tried to delineate

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the role of aortic PWV on total mortality, after taking into consideration specific geriatric confounders, namely inflammation and denutrition.

Methods

Study cohort

From May 2000 to November 2001, 331 consecutive patients entering the Geriatric Departments of Charles Foix and Emile Roux Hospitals, Ile de France region (France), were included in the Pronostic cardiovasculaire et Optimisation Thérapeutique En GÉRiatrie (PROTEGER) Study in respect to the following inclusion criteria: age >70 years old; past history of CV disease involving either coronary heart disease, cerebrovascular disease, hypertension or any other CV events of the upper or lower limbs, thoracic or abdominal aorta, or renal arteries; Mini Mental Status Examination $>15/30$; absence of fatal disease with life expectancy <1 month and willingness to give a written informed consent to participate in this study. Patients with cachexia (body mass index (BMI) $<17\,kg\,m^{-2}$) and/or evolutive cancer and/or advanced renal failure (plasma creatinine $>250\,\mu mol\,l^{-1}$) were not included in the study.

The PROTEGER Study has been described in detail elsewhere;[17–19] briefly, the study cohort was then composed of 331 subjects (86 men and 245 women) with mean age ($\pm$s.d.) of 85 ± 7 years. The PROTEGER study was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Germain Hospital (Ile de France), and by the CNIL. Written informed consent was obtained from all participants, after information of themselves and of their relatives. Only the parameters, which were relevant to the present analysis, are presented here.

Collection of baseline data

Information compiled from the questionnaire filled out at inclusion included gender, age, anthropometric markers, personal history of CV event, the presence of diabetes mellitus, dyslipidemia, hypertension, smoking habits and previous diseases. The reason for hospitalization and the level of education were also registered.

In all cases, such information agreed with that given by relatives and/or recorded from the most recent previous hospitalization.

Because some patients were not able to stand up, height was estimated for all patients from the knee height as described previously by Chumlea *et al.*:[20] Height $=78.31+(1.94$ knee height (cm)$)-(0.14\times$ age (years)) for men; and Height $=82.21+(1.85$ knee height (cm)$)-(0.21\times$ age (years)) for women. BMI ($kg\,m^{-2}$) was calculated as body weight/(estimated height)^2. Body composition (fat mass) was measured, for patients able to stand up, by using the Tanita DC-320 (Tanita Corp., 232 Tokyo, Japan) BIA device based on four separate foot-pad electrodes mounted on the system's base,[21] with subjects in indoor clothing and no shoes.

Medications

Antihypertensive drugs included the following: diuretics (38.0%), calcium channel antagonists (27.9%), angiotensin-converting enzyme inhibitors (26.1%), β-blockers (12.3%), α-blockers (4.0%), central-acting agents (3.1%), either alone or in combination. Three percent of the patients were medically treated for dyslipidemia (drugs including statins or fibrates), and 14 percent of the patients were medically treated for diabetes mellitus (drugs including sulfonamides and/or biguanids, and/or insulin).

Assessment of BP and arterial stiffness

The measurements were performed in the morning, after an overnight fast, each patient being in supine position. Brachial BP was measured after 15 min of rest, by using the semi-automatic oscillometric device, Dynamap (KONTRON, Paris, France). Five measurements 2 min apart were averaged. Data on the validity of the oscillometric devices in the elderly, and especially in the presence of increased levels of arterial stiffness, are lacking, therefore our results should be viewed under this limitation.

Aortic PWV was determined by using the foot-to-foot method as described previously[22] (Complior, Colson, Paris); it was available in $n=283$ subjects. The superficial distance covered by the pulse wave was measured directly from the carotid to the femoral artery. This method for distance assessment may overestimate PWV by approximately $2\,m\,s^{-1}$ on average.[23]

Measurement of biological parameters

Venous blood samples were obtained in subjects after an overnight fast. Plasma was separated without delay at 4 °C in a refrigerated centrifuge and stored at 4 °C (for the determination of routine chemistry profile by standard methods) until analysis. Total cholesterol and triglycerides were determined by using a Technicon Chem assay (Technicon Instruments, Elkhart, IN, USA), and high-density lipoprotein cholesterol was measured in the supernatant after precipitation of apolipoprotein-B-containing lipoproteins with heparin-manganese chloride. Plasma creatinine concentration (Hitachi 911 analyzer with Roche reagents) was measured. Plasma albumin and orosomucoid were determined by immunonephelometric methods by using the Immage system (Beckman Coulter, Villepinte, France). Creatinine clearance was assessed according to both the Cockcroft and Gault[24]

and the Modification of Diet in Renal Disease (MDRD) formula.[25]

Follow-up procedures

Follow-up started from the baseline examination and lasted until April 2004. Of all 331 participants in the present study, three (1%) were lost to follow-up. Information was obtained from the patient himself/herself, from relatives or from general practitioners. Interim telephone and clinic contacts were used to assess all hospitalizations and outpatient CV diagnoses, and overall mortality. In case of hospitalization, discharge reports from medical specialists were obtained. Fatal and non-fatal CV events, and all-cause mortality, were reported. Follow-up time was defined by the time from the baseline visit until the first event date (for those who had an event), or was censored at the last contact date (for those who did not have any event or for the three patients that were lost to follow-up).

Statistical analysis

In this exploratory analysis, subjects' characteristics were compared according to mortality event by Student's *t*-test for normal continuous data and χ^2-test for qualitative data.

Martingale residuals analysis has been used to assess the proportional hazards assumption over time of a Cox model. A Cox regression model was used to determine the independent predictors of total mortality. The best model verified by the last stepwise method (entering level = 0.10, removing level = 0.05) contains five characteristics weight, PWV, albumin, orosomucoïd and cholesterol. Tests for interaction were performed by likelihood ratio test of models with and without interaction terms.

Table 1 Baseline clinical and hemodynamic parameters in surviving and deceased subjects at the end of follow-up

	Alive (n = 221)	*Dead (n = 110)*	P
Age (years)	84 ± 7	87 ± 7	<0.001
Gender (% men)	25	28	0.51
Weight (kg)	63 ± 15	58 ± 12	0.005
Body mass index (kg m $^{-2}$)	27.8 ± 6.0	26.0 ± 4.8	0.008
Fat mass percentage (%)	39.5 ± 7.4	36.6 ± 6.0	0.09
Calf circumference (cm)	31.6 ± 4.2	30.7 ± 4.2	0.02
Arm circumference (cm)	26.5 ± 3.8	25.4 ± 3.5	0.01
Sub scapular skinfold (mm)	10.4 ± 4.0	9.7 ± 3.8	0.24
Bicipital skinfold (mm)	9.4 ± 3.2	7.3 ± 3.4	0.08
Tricipital skinfold (mm)	10.3 ± 4.1	9.4 ± 3.5	0.07
Current smokers (%)	6	5	0.75
Hypertensives (%)	76	74	0.83
Dyslipidemia (%)	19	14	0.34
Diabetes mellitus (%)	18	27	0.04
Previous stroke (%)	26	34	0.09
Heart failure (%)	19	28	0.06
Heart rate (b.p.m.)	71 ± 10	69 ± 10	0.28
Systolic blood pressure (mm Hg)	136 ± 20	136 ± 21	0.92
Diastolic blood pressure (mm Hg)	66 ± 11	63 ± 12	0.04
Pulse wave velocity (m s $^{-1}$)	14.2 ± 3.3	14.8 ± 3.5	0.11

For testing the different interactions (2 by 2 only because of power), the population was divided into two groups (low-value/high-value) for each variable entering the multivariate Cox regression model, and each interaction was tested by introducing in the model the interaction terms 1 by 1 (that is, PWV × creatinine).

Statistical analyses were performed by using the SAS software (version 9.1; SAS Institute, Cary, NC, USA). A two-tailed $P < 0.05$ was considered significant.

Results

Baseline characteristics of study participants

The population was composed of 331 patients (86 men and 245 women), with a mean age ± s.d. of 85 ± 7 years. At inclusion, 75% of the patients were hypertensive, 32% had a history of clinical heart failure and 79% were at the stage of CV secondary prevention (coronary heart disease or cerebrovascular disease, or peripheral arterial disease).

After a mean follow-up of 14 months, 110 subjects (33%) were deceased.

Table 1 compares the general clinical and hemodynamic parameters of the deceased versus the surviving subjects at the end of follow-up. Older age, lower weight and low DBP were significantly associated with death. Personal CV history did not affect the incidence of mortality at the end of follow-up: There was no statistical difference in mortality whether the patients had a history of coronary heart disease, stroke or heart failure, or another CV past event (data not shown). Traditional CV risk factors were not significantly different in the deceased than in the surviving group, except for diabetes mellitus. In Table 2, we show that total and low-density lipoprotein cholesterol, hemoglobin, creatinine clearance and plasma albumin levels were significantly lower ($P < 0.001$), and plasma creatinine and orosomucoid levels were higher ($P < 0.01$), in the deceased group by comparison with survivors.

Table 2 Baseline biological parameters in surviving and deceased subjects at the end of follow-up

	Alive (n = 221)	*Dead (n = 110)*	P
Total cholesterol (mmol l $^{-1}$)	5.44 ± 1.16	4.92 ± 1.14	<0.001
HDL cholesterol (mmol l $^{-1}$)	1.14 ± 0.32	1.06 ± 0.30	0.04
LDL cholesterol (mmol l $^{-1}$)	3.63 ± 0.92	3.12 ± 0.89	<0.001
Hemoglobin (g dl $^{-1}$)	12.4 ± 2.7	11.9 ± 1.9	0.05
Glucose (mmol l $^{-1}$)	5.8 ± 2.0	6.2 ± 2.8	0.28
Creatinine (μmol l $^{-1}$)	76 ± 28	91 ± 38	<0.001
Cockroft Creat. clearance (ml min $^{-1}$)	56 ± 28	42 ± 19	<0.001
MDRD Creat. clearance (ml min $^{-1}$)	48 ± 31	40 ± 18	<0.001
Albumine (g l $^{-1}$)	35 ± 4	33 ± 5	0.001
Serum prealbumin (g l $^{-1}$)	0.41 ± 0.53	0.32 ± 0.34	0.09
hs C-Reactive Protein (mg l $^{-1}$)	20 ± 41	28 ± 37	0.08
Leucocytes (g l $^{-1}$)	7.0 ± 2.0	7.5 ± 2.8	0.07
Sedimentation rate first hour (mm)	31 ± 24	32 ± 24	0.79
Orosomucoid (g l $^{-1}$)	1.17 ± 0.39	1.34 ± 0.47	<0.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease.

Table 3 Associations between selected parameters and total mortality analyzed by multi-parametric survival Cox model in the entire cohort

Independent predictors	*HR*	*95% CI*	P
Total cholesterol (per 1.2 mmol l $^{-1}$)	0.72	0.56–0.91	0.006
PWV (per 3.3 m s $^{-1}$)	1.33	1.08–1.65	0.008
Albumin (per 4 g l $^{-1}$)	0.72	0.53–0.96	0.026
Body weight (per 14 kg)	0.74	0.57–0.98	0.035
Orosomucoid (per 0.4 g l $^{-1}$)	1.31	1.01–1.71	0.045
Creatinine (per 31 μmol l $^{-1}$)	1.21	0.98–1.48	0.07

Abbreviations: CI, confident interval; HR, hazard rate; PWV, pulse wave velocity.
HRs were calculated for an augmentation of 1 s.d. of each parameter.

Models predicting survival by Cox regression analysis
In crude analysis, a positive non-significant trend was observed between PWV and mortality risk. Multivariate Cox regression analysis showed that five parameters entered the prediction model (with creatinine being marginally significant ($P=0.07$)): Two were positively related to mortality risk, PWV ($P=0.008$) and orosomucoide ($P=0.045$), and three were related negatively, total cholesterol ($P=0.006$), albumin ($P=0.026$) and body weight ($P=0.035$) (Table 3). It is important to note that age was initially the strongest parameter in the model, but after entering other variables by a stepwise forward procedure, the level of significance of this parameter progressively decreased and was finally no more statistically significant in the last models building procedures. This was partially due to an inter-correlation between age and other parameters, namely weight.

A significant interaction ($P<0.05$), between the presence of renal dysfunction and aortic stiffness on the one hand, and between the presence of increased inflammation and aortic stiffness on the other hand, regarding their effect on mortality, was observed when their product was introduced in the Cox regression model, indicating that the effect of PWV on mortality was increased in the presence of renal dysfunction and in the presence of increased inflammation (data not shown).

Finally, the ability of this five-variable model for predicting death was relatively high, with an area under the receiver operating characteristic curve of 0.71 ± 0.04 (data not shown).

Discussion

This study was the first prospective investigation in a very old population, in which arterial stiffness was measured and related to prognosis in conjunction with specific geriatric confounders. We showed that, in this very aged population, although marginally significant in crude analysis, PWV is a powerful determinant of prognosis after considering inflammation and denutrition.

Denutrition and prognosis
The association between low BMI and mortality has been reported previously in the elderly.[26,27] Aging is variably associated with a progressive decrease in muscle mass and a relative increase in fat mass,[28] both of which are independently associated with mortality.[29] Recent weight loss, which could not be ascertained in our study, may reflect chronic disease or malnutrition, and confound the expected association between mortality and BMI.

A recent report suggested that the increase in the risk of death associated with a low BMI is driven primarily by respiratory and other causes, whereas the increased risk associated with a high BMI is driven by CV causes and cancer.[30] In our population, it was not possible to determine precisely the cause of death as invasive explorations were rarely performed for ethical reasons.

Inflammation and prognosis
Inflammation has an important role in both aging and chronic disease. Aging is characterized by chronic low-grade inflammation,[31] and a growing body of evidence suggests that inflammatory derangements are associated with unfavorable prognosis in the elderly. Several markers of inflammations, such as C-reactive protein, orosomucoide, α-1 acid glycoprotein and interleukin-6,[32–35] have emerged as strong predictors of all-cause mortality in the aging population. In our population, orosomucoid was more closely related to all-cause mortality than C-reactive protein, leukocyte count or sedimentation rate.

Arterial stiffness and prognosis
For the present study, we used PWV as a marker of aortic stiffness because it is related to the square root of the aortic elasticity modulus and to the thickness-radius ratio.[36] The PWV, determined from the foot-to-foot transit time in the aorta, offers a simple, reproducible and non-invasive evaluation of regional arterial stiffness. This non-invasive, superficial measurement merely estimates the distance traveled by the pulse, and accurate measurements of this distance can only be obtained with invasive procedures. Regarding subjects >70 years of age, because arteries become longer and more convoluted, the path lengths determined from superficial linear measurements are obviously underestimated. Furthermore, aortic PWV may be considered a more reliable index than SBP itself, owing to the frequency of 'pseudo-hypertension' in this elderly population.[37]

The major finding of the present study was that PWV was a predictor of overall mortality, after taking into account inflammation and denutrition. Interestingly, in the present elderly population, BP and particularly SBP and PP did not influence CV mortality. This finding raises the question as to

whether BP (mainly SBP or PP), aortic stiffness or even a combination of both might be the best therapeutic target to reduce CV mortality in the elderly.[38] In patients with end-stage renal disease undergoing hemodialysis, Guerin *et al.*[39] have shown that for the same MBP reduction under drug treatment, PWV was reduced in survivors but remained unmodified in deceased patients. It is noteworthy that in such patients, hypertension has the same clinical features as in the elderly, involving increased aortic stiffness and a disproportionate elevation of SBP over DBP.[1,2]

Furthermore, the predictive value of several CV risk factors decreases with age because of selective survival and the influence of comorbidity on risk factors levels.[40,41] By contrast, vascular stiffness increases steadily with age and could be considered a cumulative measure of previous exposures.

Considerations on the population

This population carries many particularities, which need to be detailed. First, and because of the inclusion criteria, there was a high prevalence of patent CV disease: Coronary, cerebral and peripheral vascular diseases affect approximately 62% of all patients. Second, this population was also extremely old: Only 80 subjects were <80 years of age, and 131 were >90 years old (mean age: 85.1 years; range: 70–103 years). This major trait might be responsible for a number of CV particularities, not particularly related to atherosclerosis, but more to 'physiological' CV aging. Third, carotid femoral PWV was consistently augmented, over-passing the $20\,m\,s^{-1}$ in almost 10% of the population (mean PWV $14.4\,m\,s^{-1}$ (7.2–28.9). We have shown in the past that, over 70 years of age, PWV no longer correlated with age.[42] Taken together, these findings suggest that the overall population was composed mainly of 'survivors'.[43] Our population is composed of very old institutionalized subject, with a characteristic risk profile. This makes our results hardly referable to different setting populations, like younger individuals, extremely old aged people and non-hospitalized populations. As mortality risks are different in institutionalized and non-institutionalized elderly population, the determinants of mortality could be different in those two groups.

Our negative results concerning the prediction of mortality by systolic and PP are important to consider. Previous study in the oldest old reported this absence of relation between SBP and overall mortality.[7] One could consider that patients with more severe hypertension had probably died before having the 'age opportunity' of entering this study. The remaining poorly controlled hypertensives in this survey could benefit of a survival effect. Similar explanation could be given for PP.

Perspectives

In our elderly cohort, a trend was observed between carotid–femoral PWV and mortality risk in crude analysis. Multivariate Cox regression analysis showed that five parameters entered the prediction model: two were positively related to mortality risk, arterial stiffness and orosomucoide, and three were related negatively, total cholesterol, albumin and weight. Although a relation between arterial stiffness measured as PWV was not positively, strongly and linearly associated with mortality risk, mainly because of survival effect, vascular stiffness increases steadily with age and could be considered a cumulative measure of previous exposures.

In conclusion, we showed that in the frail oldest old with a high burden of CV disease, although marginally significant in crude analysis, PWV was a powerful determinant of prognosis in the oldest people after considering inflammation and denutrition.

What is known about this topic

- Increased aortic PWV, a classic marker of arterial rigidity, has been identified as an independent predictor of CV risk in numerous populations. But only three studies took place in the elderly and none was specifically designed to test the multi-adjusted added value of aortic PWV in terms of all-cause mortality prediction.
- Few studies addressed the potential validity of mechanical factors in the frail old subjects with a high burden of CV disease.

What this study adds

- We showed that, in this very aged population, although marginally significant in crude analysis, arterial stiffness, as assessed by carotid–femoral PWV, is a powerful determinant of prognosis after considering inflammation and denutrition.
- In this population, multivariate Cox regression analysis showed that five parameters entered the prediction model: two were positively related to mortality risk, arterial stiffness and orosomucoide, and three were related negatively, total cholesterol, albumin and weight.
- Although the relation between arterial stiffness measured as carotid–femoral PWV was not positively, strongly and linearly associated with mortality risk, mainly because of survival effect, vascular stiffness increases steadily with age and could be considered a cumulative measure of previous exposures.

Conflict of interest

The authors declare no conflict of interest.

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ANNEXE 3

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Original article

Aortic stiffness, inflammation, denutrition and type 2 diabetes in the elderly

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Abstract

Aim. – Observational studies in the elderly have shown that some of the classical cardiovascular (CV) risk factors are difficult to interpret. Thus, our study investigated whether increased aortic stiffness is associated with higher mortality risk in both the diabetic and non-diabetic elderly before and after adjusting for geriatric confounders such as inflammation (sedimentation rate, C-reactive protein, orosomucoid levels, leukocyte count) and denutrition parameters (body weight, body mass index [BMI], plasma albumin and prealbumin).

Methods. – In a cohort of 324 (84 men) hospitalized elderly subjects, including 255 non-diabetic and 69 diabetic subjects, aortic stiffness was assessed by carotid–femoral pulse wave velocity (PWV) together with CV risk factors. Subjects were studied over a 2-year mean follow-up period, thus enabling evaluation of long-term all-cause mortality.

Results. – A total of 105 subjects died during the follow-up. Kaplan–Meier curves showed a significantly higher mortality in the diabetics ($P = 0.024$). Multivariate Cox analyses differed for non-diabetic subjects and diabetics. In the former, the hazard ratio (HR) for an increase of 1 SD (with confidence intervals) was 1.36 (1.07–1.72) for PWV, 0.73 (0.52–1.01) for plasma albumin and 0.63 (0.45–0.89) for BMI. In diabetic patients, the HR was 1.60 (1.02–2.50) for leukocyte count, 1.75 (1.03–2.96) for orosomucoid levels and 0.32 (0.15–0.68) for BMI.

Conclusion. – In this very elderly population, although marginally significant on crude analysis, PWV, but not systolic or pulse pressure, was a powerful determinant of total mortality after taking into account the important role of type 2 diabetes. In diabetics, inflammation and denutrition predominated over mechanical factors.

Keywords: Arterial stiffness; Cardiovascular risk factor; Pulse wave velocity; Mortality; Elderly; Denutrition; Inflammation; Type 2 diabetes

Résumé

Rigidité artérielle, inflammation, dénutrition et diabète chez les sujets âgés.

But. – Les études observationnelles réalisées chez des patients très âgés ont montré que certains facteurs de risque cardiovasculaire étaient d'interprétation difficile et agissaient même en sens contraire. Nous avons tenté d'analyser les relations existant entre la rigidité artérielle et le risque de mortalité, à la fois chez des diabétiques et des non-diabétiques, avant et après ajustement sur des facteurs confondants spécifiquement gériatriques incluant l'inflammation (vitesse de sédimentation, protéine C réactive, orosomucoïde, nombre de globules blancs) et les paramètres de dénutrition (poids, indice de masse corporelle [IMC], albumine et pré-albumine plasmatiques).

Méthode. – Dans une cohorte de 324 sujets âgés hospitalisés (84 hommes) incluant 69 patients diabétiques et 255 non-diabétiques, la rigidité aortique a été mesurée par la vitesse de l'onde de pouls (VOP) carotido-fémorale en même temps que l'évaluation des facteurs de risque cardiovasculaire. Les sujets ont été suivis pendant une période de deux ans en moyenne, permettant l'évaluation de la mortalité toutes causes confondues.

Résultats. – Cent cinq sujets sont morts pendant le suivi. Les courbes de Kaplan-Meier ont montré une mortalité accrue chez les diabétiques ($P = 0{,}024$). Des analyses de Cox multiparamétriques ont été réalisées chez les sujets diabétiques et les sujets non diabétiques. Chez les sujets non diabétiques, le risque relatif pour une augmentation d'une déviation standard était 1,36 (1,07-1,72) pour la VOP, 0,73 (0,52-1,01) pour l'albumine plasmatique et 0,63 (0,45-0,89) pour l'IMC. Chez les diabétiques, les risques relatifs étaient respectivement de 1,60 (1,02-2,50) pour le nombre de globules blancs, 1,75 (1,03-2,96) pour les concentrations plasmatiques d'orosomucoïde et 0,32 (0,15-0,68) pour l'IMC.

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Conclusion. – Dans cette population très âgée, bien qu'à la limite de la significativité en analyse brute, la vitesse de l'onde de pouls, mais non la pression artérielle systolique ou pulsée, était fortement associée au pronostic de mortalité, après prise en considération du rôle important du diabète de type 2. Chez les diabétiques, l'inflammation et la dénutrition prédominaient sur les facteurs mécaniques.

Mots clés : Rigidité artérielle ; Vitesse de l'onde de pouls ; Mortalité ; Sujets âgés ; Dénutrition ; Inflammation ; Facteurs de risque cardiovasculaire ; Diabète de type 2

1. Introduction

The incidence of cardiovascular (CV) and overall mortality increases with advancing age [1]. The role of CV risk factors such as hypertension, aortic pulse wave velocity (PWV), smoking, dyslipidaemia, obesity, diabetes and insulin resistance have been extensively investigated in young adults. However, the significance of such risk factors in the very elderly population is still a subject of debate.

Arterial hypertension remains a predictor of stroke and heart failure even in patients aged over 80 years [2,3]. However, population studies have reported poor inverse associations between blood pressure (BP) and mortality [2–4]. The presence of low diastolic blood pressure (DBP) has also been reported as a CV risk factor in the elderly [5]. Elevated total and low-density lipoprotein (LDL) cholesterol are potent risk factors for coronary heart disease (CHD) in young adults [6], but predict lower survival in the elderly [7–9]. Nevertheless, high-density lipoprotein (HDL) cholesterol remains a strong risk factor even in older subjects [10,11], probably due to a combination of CV disease and malnutrition [12,13]. Whereas obesity is a risk factor for diabetes and CV disease in young adults, a low body mass index (BMI) has significantly predicted mortality in several elderly populations [14,15]. Furthermore, insulin resistance is considered a common denominator of the metabolic syndrome and type 2 diabetes, and has also been proposed to be an independent CV risk factor [16,17]. Indeed, as insulin resistance may be modified by age, malnutrition and chronic disease, the association between malnutrition, inflammation and type 2 diabetes becomes more frequent in older subjects. However, few investigations have been made on the relationship of such comorbidities with overall and CV risk factors.

The PROTEGER prospective cohort study was carried out to determine the relevance of haemodynamic and metabolic risk factors in a high-risk population of very old subjects [5]. Multiple parameters were recorded to determine which individual components of the various previously identified mechanical and/or biochemical factors remained significant predictors of mortality in such a population. Their relative strengths and associations with malnutrition and inflammation were also pointed out. It was recently shown that, in geriatric patients, a cluster comprising low BMI, low DBP, low total and high-density lipoprotein (HDL) cholesterol, and high insulin sensitivity, was a significant predictor of mortality [18]. However, the role of mechanical factors, such as BP and/or aortic PWV, has not been evaluated yet.

In the present study, a cohort of very old frail subjects (mean ± SD age: 85 ± 7 years) was prospectively investigated. The study also aimed to delineate, for the first time, the role of aortic PWV in total mortality in both diabetic and non-diabetic subjects, while taking into consideration specific geriatric situations, including inflammation and denutrition.

2. Methods

2.1. Study cohort

From May 2000 to November 2001, 331 consecutive patients entering the geriatric departments of Charles Foix and Emile Roux Hospitals, Ile de France region (France), were included in the *Pronostic Cardiovasculaire et Optimisation Thérapeutique en Gériatrie* (Cardiovascular Prognosis and Therapeutic Optimization in Geriatrics; PROTEGER) Study according to the following inclusion criteria:

- age over 70 years;
- past history of CV disease involving either coronary heart disease, cerebrovascular disease, hypertension or any other CV event of the upper or lower limbs, thoracic or abdominal aorta, or renal arteries;
- Mini-Mental State Examination (MMSE) score greater 15/30;
- absence of fatal disease with a life expectancy less than 1 month;
- and willingness to give written informed consent to participate in the study.

Patients with cachexia (BMI < 17 kg/m^2) and/or progressive cancer and/or advanced renal failure (plasma creatinine > 250 μmol/L) were not included in the study.

The PROTEGER Study has been described in detail elsewhere [5,18]. Briefly, the study cohort was composed of 324 subjects (84 men and 240 women) with a mean ± SD age of 87 ± 7 years. The study was approved by both the Committee for the Protection of Human Subjects in Biomedical Research of Saint Germain Hospital (Ile de France) and the Commission Nationale de l'Informatique et des Libertés [CNIL]; French Data Protection Authority). Written informed consent was obtained from all participants, as well as the relevant information from the subjects themselves and their relatives.

2.2. Social, anthropometric and clinical parameters

Information compiled from a questionnaire filled out at inclusion included gender, age, anthropometric markers [19], personal history of CV event, presence of type 2 diabetes, dyslipidaemia, hypertension, smoking habits and previous diseases.

The reasons for hospitalization and level of education were also registered.

In all cases, the information agreed with that provided by relatives and/or recorded during their most recent hospitalization.

2.3. Medications

The participants' antihypertensive drugs included diuretics (38%), calcium-channel antagonists (28%), angiotensin-converting enzyme (ACE) inhibitors (26%), beta-blockers (12%), alpha-blockers (4%) and centrally acting agents (3%), either alone or in combination. In addition, 3% were being medically treated for dyslipidaemia (including statins and fibrates), and 14% were being medically treated for type 2 diabetes (including sulphonamides and/or biguanides and/or insulin).

2.4. Assessment of BP and arterial stiffness

Arterial measurements have been described in detail elsewhere [5,18]. Aortic PWV, determined by the foot-to-foot method (Complior®, Colson, Paris) as previously described [20], was available for 276 subjects. Determinations of central (carotid) BP and wave reflections (carotid augmentation index [CAI] in %, with and without heart rate adjustment) were made using pulse wave analysis as previously described [5,21]. Also, systemic haemodynamics were performed in parallel [21].

2.5. Measurement of biological parameters

Biological parameters were assessed using standard methods as described in detail elsewhere [5,18].

2.6. Follow-up procedures

Follow-up began with the baseline examination and continued until April 2004. Of the 331 participants in the original cohort, seven did not participate in the statistical analysis because their survival was less than 1 month. Thus, the analysis involved 324 subjects. Information was obtained from the patients themselves, their relatives and/or their general practitioners. Interim telephone and clinic-based contact was used to assess all hospitalizations and outpatients CV diagnoses, and overall mortality. In cases of hospitalization, discharge reports from medical specialists were obtained. Fatal and non-fatal CV events, and all-cause mortality, were also reported. Follow-up duration was defined as the time from the baseline visit until the first event date (for those who had an event) or the last contact date (for those who were event-free and for the three patients who were lost to follow-up).

2.7. Statistical analysis

In this exploratory analysis, the participants' characteristics were compared according to the mortality event using Student's t test for normal continuous data and Chi^2 tests for qualitative data. Subjects were divided into those without ($n=255$) and with ($n=69$) type 2 diabetes from a total of 324 subjects with plasma glucose levels greater or equal to 7 mmol/L and/or taking antidiabetic treatment.

Martingale residuals analysis was used to assess the proportional hazards assumption over time in the Cox model. Cox's regression model was used to determine the independent predictors of total mortality. The best model verified by the last stepwise method (entering level = 0.10, removal level = 0.05) contained five characteristics (BMI, albumin, presence of diabetes, orosomucoid and PWV). Tests for interactions were performed with the likelihood-ratio test of models with and without interaction terms. For testing the different interactions (only two by two because of power), the population was divided into two groups (low value/high value) for each variable entered into the multivariate Cox regression model, and each interaction was tested by introducing into the model the interaction terms one by one (for example, PWV × orosomucoid). Also, no interaction term was entered into the model because of lack of statistical significance.

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute). A two-tailed $P<0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of study participants

The population included 84 men and 240 women with a mean age ± SD of 87 ± 7 years. Data on their personal history of clinical heart failure showed that 75% of patients were hypertensive and 22% had a history of clinical heart failure. After a mean follow-up of 13 months, 105 subjects (32%) were deceased.

Table 1 compares the general clinical and haemodynamic parameters of the deceased *vs* the survivors at the end of follow-up. Older age, lower weight and low DBP were significantly associated with death. Personal CV history had no effect on the incidence of mortality at the end of follow-up: there was no statistical difference in mortality whether or not the patients had a history of coronary heart disease, stroke or heart failure, or any other CV past event (data not shown). Traditional CV risk factors were not significantly different in the deceased and survivor groups, except for type 2 diabetes ($P=0.027$). Total cholesterol ($P<0.001$), haemoglobin ($P=0.045$), plasma creatinine ($P=0.023$) and albumin levels ($P=0.024$) were significantly lower, while plasma creatinine ($P=0.023$) and orosomucoid levels ($P=0.017$) were all significantly higher in the deceased compared with the survivors. In addition, there was no significant difference in PWV between the two populations ($P=0.125$).

3.2. Comparisons between non-diabetic and diabetic subjects

Table S1 (see supplementary material associated with this article online) compares the general clinical and haemodynamic parameters in the non-diabetic *vs* diabetic groups. Compared with non-diabetic subjects, diabetic patients were significantly younger ($P=0.009$), but of greater weight ($P<0.001$), height ($P=0.014$) and BMI ($P<0.001$). Brachial SBP ($P=0.032$) and

Table 1
Overall study population: living and deceased subjects.

	Living ($n=219$)	Deceased ($n=105$)	P value
Gender (% men)	25	30	0.400
Age (years)	86 ± 7	88 ± 7	0.050
Weight (kg)	63 ± 15	59 ± 12	0.045
Height (m)	1.50 ± 0.10	1.50 ± 0.09	0.642
Body mass index (kg/m^2)	27.8 ± 6.1	25.9 ± 4.6	0.018
Calf circumference (cm)	31.5 ± 4.1	30.7 ± 4.2	*0.054*
Arm circumference (cm)	26.5 ± 3.9	25.4 ± 3.6	0.024
Subscapular cutaneous skinfold (mm)	10.4 ± 4.1	9.7 ± 3.8	0.672
Bicipital cutaneous skinfold (mm)	9.4 ± 3.2	7.3 ± 3.4	0.627
Tricipital cutaneous skinfold (mm)	10.2 ± 4.1	9.2 ± 3.4	0.413
Fat mass (%)	39 ± 7	36 ± 6	0.116
Brachial SBP (mmHg)	136 ± 20	136 ± 20	1.000
Brachial DBP (mmHg)	70 ± 10	69 ± 11	0.366
Brachial mean BP	92 ± 14	89 ± 15	0.104
Brachial PP	66 ± 18	67 ± 17	0.655
Heart rate (beats/min)	71 ± 10	69 ± 10	0.461
Carotid SBP (mmHg)	124 ± 20	125 ± 21	0.817
Carotid DBP (mmHg)	72 ± 10	70 ± 12	0.323
Carotid mean BP	94 ± 13	93 ± 14	0.529
Carotid PP (mmHg)	56 ± 18	59 ± 17	0.051
PWV (m/s)	14.2 ± 3.6	14.9 ± 3.6	0.125
Carotid augmentation index (%)	118 ± 23	117 ± 22	0.516
Adj carotid augmentation index to heart rate (%)	119 ± 23	116 ± 24	0.406
Total peripheral vascular resistance	0.17 ± 0.07	0.17 ± 0.06	0.703
Left diastolic carotid diameter (mm)	7.75 ± 1.03	7.70 ± 0.89	0.942
Left intima–media carotid thickness (mm)	0.84 ± 0.14	0.85 ± 0.16	0.826
Right intima–media carotid thickness (mm)	0.84 ± 0.14	0.79 ± 0.12	0.119
Diabetes (%)	18	29	0.027
Haemoglobin (g/dL)	12.4 ± 2.7	11.9 ± 1.9	0.045
Leukocytes (× 10^3/mm^3)	7.01 ± 2.07	7.52 ± 2.83	0.217
Neutrophils (%)	64 ± 10	66 ± 11	0.324
Lymphocytes (%)	25 ± 10	23 ± 9	0.182
Sedimentation rate, first hour (mm)	32 ± 24	34 ± 24	0.994
C-reactive protein (mg/L)	20 ± 41	28 ± 37	0.121
Orosomucoid (g/L)	1.17 ± 0.40	1.33 ± 0.46	0.017
Serum albumin (g/L)	35 ± 5	33 ± 5	0.024
Serum prealbumin (g/L)	0.40 ± 0.56	0.31 ± 0.38	0.164
Serum creatinine (μmol/L)	76 ± 28	92 ± 39	0.023
Total cholesterol (mmol/L)	5.44 ± 1.17	4.91 ± 1.15	< 0.001
HDL cholesterol (mmol/L)	1.14 ± 0.32	1.07 ± 0.30	0.150

Data are expressed as means ± SD; SBP/DBP: systolic/diastolic blood pressure; PP: pulse pressure; PWV: pulse wave velocity; adj: adjusted; HDL: high-density lipoprotein.

pulse pressure (PP; $P=0.025$) as well as carotid SBP ($P=0.015$) were significantly lower in the diabetics, whereas PWV, carotid PP and total peripheral resistance do not differ significantly. Furthermore, low haemoglobin ($P=0.030$), high leukocyte counts ($P=0.017$) and low HDL cholesterol ($P=0.006$) were observed in the diabetic patients.

The Kaplan–Meier curves showed that cumulative survival was significantly lower ($P=0.024$; Fig. 1) in diabetic than in non-diabetic subjects.

3.3. Cox regression analysis

Cox regression analysis of the whole population is presented in Table 2. As the presence of diabetes was a significant and independent determinant of mortality, separate prediction analyses were performed in both diabetic and non-diabetic populations. The analysis indicated that predictors of overall mortality risk differed in diabetic and non-diabetic subjects (Table 3). In non-diabetic subjects, the HR for an increase of 1 SD (with confidence intervals) was 1.36 (1.07–1.72) for PWV, 0.73 (0.52–1.01) for plasma albumin and 0.63 (0.45–0.89) for BMI. In diabetic patients, the HR was 1.60 (1.02–2.50) for leukocyte counts, 1.75 (1.03–2.96) for orosomucoid levels and 0.32 (0.15–0.68) for BMI.

Values for receiver operating characteristic (ROC) curves were 70.0% and 85.4% for non-diabetic and diabetic subjects, respectively (Fig. S1; see supplementary material associated with this article online), thus confirming the ability of the respective models to predict overall death.

4. Discussion

The present study was the first prospective investigation of a very elderly population in which arterial stiffness was measured

Table 2
Factors predicting overall mortality in the whole study population.

Whole study population ($n = 324$) Variable	Parameter estimate	Standard error	Chi^2	$Pr > Chi^2$	Hazard ratio[a]	95% CI	
BMI (kg/m^2)	−0.55766	0.16204	11.8445	< 0.001	0.57	0.42	0.79
Albumin (g/L)	−0.38016	0.14826	6.5753	0.010	0.68	0.51	0.91
Diabetes (0/1)	0.71370	0.29067	6.0288	0.014	2.04	1.16	3.61
Orosomucoid (g/L)	0.28016	0.13811	4.1150	0.043	1.32	1.01	1.73
PWV (m/s)	0.21495	0.10793	3.9662	0.046	1.24	1.00	1.53
Leucocytes ($10^3/mm^3$)	0.11694	0.14468	0.6532	0.419	1.12	0.85	1.49

BMI: body mass index; PWV: pulse wave velocity.
[a] Built for an increase of 1 SD for each parameter for all variables.

Table 3
Factors predicting overall mortality in diabetic and non-diabetic subjects.

Variable	Parameter estimate	Standard error	Chi^2	$Pr > Chi^2$	Hazard ratio[a]	95% CI	95% CI
Non-diabetics ($n = 255$)							
BMI (k/m^2)	−0.4607	0.17385	7.0221	0.008	0.63	0.45	0.89
PWV (m/s)	0.30758	0.12106	6.4559	0.011	1.36	1.07	1.72
Albumin (g/L)	−0.32217	0.16944	3.6154	0.057	0.73	0.52	1.01
Diabetics ($n = 69$)							
BMI (k/m^2)	−1.14343	0.38814	8.6787	0.003	0.32	0.15	0.68
Orosomucoid (g/L)	0.55855	0.26866	4.3221	0.038	1.75	1.03	2.96
Leucocytes ($10^3/mm^3$)	0.46597	0.22876	4.1492	0.042	1.59	1.02	2.50

BMI: body mass index; PWV: pulse wave velocity.
[a] Built for an increase of 1 SD for each parameter for all variables.

and related to prognosis as well as with specific geriatric confounders. The study showed that, in this very aged population, taking into account the important role of type 2 diabetes, PWV is a powerful determinant of total mortality, even with only marginal significance on crude analysis.

Our study population had many peculiarities that need to be detailed. First, and because of our inclusion criteria, there was a high prevalence of patent CV disease, with coronary, cerebral and peripheral vascular diseases affecting approximately 41% of our participants, which might potentially limit the extrapolation of our results to other elderly populations. Second, the population was extremely old: only 76 subjects were less than 80 years of age, while 124 were over 90 years old (mean age: 87 years; range: 71–104 years). This major trait could be responsible for a number of CV peculiarities that were not particularly related to atherosclerosis, but more to "physiological" CV ageing. Third, carotid–femoral PWV was consistently augmented, surpassing 20 m/s in almost 7% of the population (mean PWV: 14.4 m/s; range: 7.2–28.9 m/s). In the past, it has been shown that, at over 70 years of age, PWV is no longer correlated with age [22]. Taken altogether, these findings suggest that the overall study population was composed mostly of "survivors" [5,18].

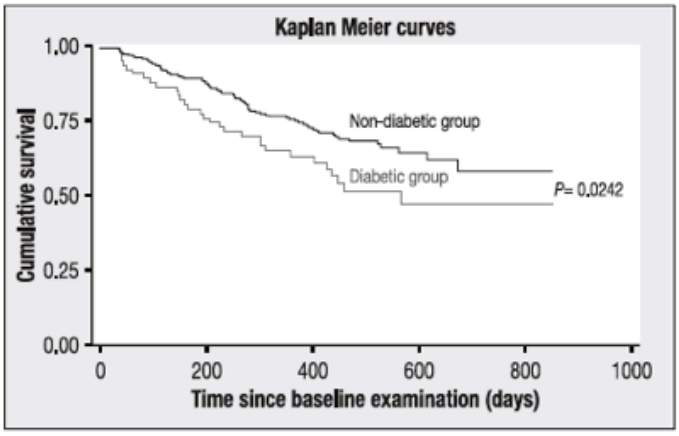

Fig. 1. Kaplan–Meier curves for diabetic and non-diabetic subjects.

Our negative results on mortality prediction by SBP and PP are also worth noting. Previous studies in the oldest old have reported the absence of a relationship between SBP and overall mortality [1,4,5,18]. It may be that the patients with the more severe hypertension had probably died before having the age-related opportunity to enter our present study. The remaining poorly controlled hypertensives in the present survey could benefit from a survival effect. A similar explanation might also be given for PP.

On the other hand, it may be worthwhile considering the hypothesis that the lack of BP mortality prediction was due to a lack of precision in BP assessment. Our BP measurement protocol probably does not reflect the usual BP of such hospitalized patients. It is well known that repeated measurements and/or ambulatory BP monitoring are widely recommended in the elderly because of both the "white-coat" effect and wide variability [23]. Also, the Dinamap device used in our study achieved only a grade D in accuracy for the measurement of DBP, which makes the analysis of PP even more debatable [24]. These limitations need to be taken into account on assessing the

statistical results indicating an apparent lack of impact of SBP and PP on mortality.

The present study used PWV as a marker of aortic stiffness, as this is related to both the square root of the aortic elasticity modulus and the thickness-to-radius ratio [21]. The PWV, determined from the foot-to-foot transit time in the aorta, offers a simple, reproducible and non-invasive evaluation of regional arterial stiffness. However, this superficial measurement merely estimates the distance travelled by the pulse, and accurate measurements of this distance can only be obtained with invasive procedures. Regarding subjects over 70 years of age, because their arteries have become longer and more convoluted, the distances determined by superficial linear measurements are clearly underestimated. Furthermore, aortic PWV may be considered a more reliable index than SBP itself due to the frequency of pseudohypertension observed in such an elderly population [1,21,25].

The main finding of the present study was that, in non-diabetic subjects, PWV is a strong predictor of CV risk, independently of inflammation and denutrition. Interestingly, in the present elderly population, SBP and PP in particular, had no influence on CV mortality. Thus, this finding raises the question of whether BP (mainly SBP or PP), aortic stiffness or even a combination of the two might be the best therapeutic target for reducing CV mortality in the elderly [26]. In patients with end-stage renal disease undergoing haemodialysis, Guerin et al. [27] showed that, for the same mean BP reduction with drug treatment, PWV was reduced in survivors, but remained unmodified in the deceased. It is also noteworthy that, in such end-stage renal disease patients, hypertension has the same clinical features as in the elderly, with increased aortic stiffness and a disproportionate rise in SBP over DBP [1]. Moreover, C-reactive protein was increased in these subjects.

In our very aged population, the present study showed that, in diabetics, PWV was not a powerful prognostic determinant and that, in addition to denutrition, inflammation was a major factor to consider in relation to mortality.

The association between low BMI and mortality has previously been reported in the elderly [14,15,28–30]. Ageing is variably associated with a progressive decrease in muscle mass and a relative increase in fat mass, both of which are independently associated with mortality [30]. Recent weight loss, which could not be ascertained in our present study, might reflect chronic disease and malnutrition and, thus, confound the expected association between mortality and BMI. A recent report suggested that the increased risk of death associated with low BMI is driven primarily by respiratory and other causes, whereas the increased risk associated with high BMI is driven by CV causes and cancer [30]. In our study population, it was difficult to determine the cause of death, as invasive explorations and autopsy were not performed for ethical reasons. Denutrition was a predictor of mortality whether or not subjects were diabetic.

Inflammation plays an important role in both ageing and chronic disease. Ageing is characterized by chronic low-grade inflammation [31], and a growing body of evidence suggests that inflammatory derangements are associated with unfavourable prognoses in the elderly. Several markers of inflammation, such as C-reactive protein, orosomucoid, alpha-1-acid glycoprotein and interleukin (IL)-6 [32–34] have emerged as strong predictors of all-cause mortality in the ageing population, particularly in diabetic and atherosclerotic subjects [35,36]. In our present study population, leukocyte counts and orosomucoid levels were more closely related to all-cause mortality than was C-reactive protein.

5. Conclusion

The present study has shown that aortic PWV was elevated to the same extent in diabetic and non-diabetic subjects, but that the predictive value of this parameter was observed only in non-diabetic subjects. Also, the diabetics who had the age criteria to enter the PROTEGER Study should probably be considered "survivors" and, thus, are not representative of the general diabetic population. Physiologically, increased PWV is associated with normal or increased aortic insufficiency (AI), thus causing low DBP and coronary ischaemia, as seen in non-diabetic subjects [1,21]. However, the process of AI attenuation is reduced with age and/or the presence of type 2 diabetes. In fact, the association of high PWV and attenuated AI reflects an increase in the distance between the heart and reflection sites, which are much closer to target organs such as the kidney [37,38]. In the presence of defective organ autoregulation (as in diabetic kidney), this process leads to increased PP transmission, inflammation of glomerular microvessels and, ultimately, fibrosis and major target-organ damage [39–41]. Furthermore, it is important to stress the fact that there were only 69 diabetic patients in our study and that, in this specific population, the model's power was lower than for the 255 non-diabetics.

Our study was the first prospective investigation of a very elderly population in which arterial stiffness was measured and related to prognosis as well as to specific geriatric confounders. In non-diabetic elderly subjects, arterial stiffness, but not SBP, was a strong determinant of total mortality whereas, in diabetics, inflammation and denutrition predominated over mechanical factors.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary materials

Supplementary materials (Table S1 and Fig. S1) associated with this article can be found at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2011.07.006.

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ANNEXE 4

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Mortality and Cardiovascular Events Are Best Predicted by Low Central/Peripheral Pulse Pressure Amplification But Not by High Blood Pressure Levels in Elderly Nursing Home Subjects

The PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) Study

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Objectives The aim of the longitudinal PARTAGE study was to determine the predictive value of blood pressure (BP) and pulse pressure amplification, a marker of arterial function, for overall mortality (primary endpoint) and major cardiovascular (CV) events, in subjects older than 80 years of age living in a nursing home.

Background Assessment of pulse indexes may be important in the evaluation of the CV risk in very elderly frail subjects.

Methods A total of 1,126 subjects (874 women) who were living in French and Italian nursing homes were enrolled (mean age, 88 ± 5 years). Central (carotid) to peripheral (brachial) pulse pressure amplification (PPA) was calculated with the help of an arterial tonometer. Clinical and 3-day self-measurements of BP were conducted.

Results During the 2-year follow-up, 247 subjects died, and 228 experienced major CV events. The PPA was a predictor of total mortality and major CV events in this population. A 10% increase in PPA was associated with a 24% ($p < 0.0003$) decrease in total mortality and a 17% ($p < 0.01$) decrease in major CV events. Systolic BP, diastolic BP, or pulse pressure were either not associated or inversely correlated with total mortality and major CV events.

Conclusions In very elderly individuals living in nursing homes, low PPA from central to peripheral arteries strongly predicts mortality and adverse effects. Assessment of this parameter could help in risk estimation and improve diagnostic and therapeutic strategies in very old, polymedicated persons. In contrast, high BP is not associated with higher risk of mortality or major CV events in this population. (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population [PARTAGE]; NCT00901355) (J Am Coll Cardiol 2012;60:1503–11) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ADL = activity of daily living
AI = augmentation index
CV = cardiovascular
DBP = diastolic blood pressure
MAP = mean arterial pressure
PP = pulse pressure
PPA = pulse pressure amplification
PWV = pulsed wave velocity
SBP = systolic blood pressure

The dramatic increase in the number of elderly people, especially those 80 years of age and older, has translated into a growing population that is increasingly prone to frailty, multiple comorbidities, and partial loss of autonomy. This is now one of the target populations for geriatric medicine, necessitating the development of specific diagnostic and therapeutic approaches (1). These approaches cannot be derived, however, from a simple extrapolation of the strategies applied in younger populations or even in very elderly robust populations. Thus, assessment of cardiovascular (CV) risk in these individuals represents a major issue.

High blood pressure (BP), especially systolic hypertension, is a major determinant of morbidity and mortality in the elderly (2) In addition, a decrease in BP with antihypertensive treatment in individuals 80 years of age or older has been shown to be beneficial (3). However, these results were obtained in community-dwelling individuals without major comorbidities. Actually, the association between BP levels and morbidity and mortality in very elderly persons with several comorbidities remains a controversial issue, with several studies showing a lack of such a relationship (4–6) or even an inverse relationship (7,8). It is therefore logical to seek alternative approaches to estimate CV risk in these individuals. Assessment of arterial mechanical properties by measuring pulse indexes such as pulsed wave velocity (PWV), pulse contour analysis, and pulse pressure (PP) amplification (PPA) may be of interest in this respect. The recent development of several noninvasive validated devices has allowed the possibility of such measurements in several populations (9,10). Clinical studies have shown in middle-age and older populations that such measurements can provide additional BP information for the prediction of CV risk (11,12). To date, no large study has evaluated the predictive value of PP and of pulse indexes for morbidity and mortality in very elderly individuals living in nursing homes.

The aim of the present study was to evaluate the prognostic value of arterial mechanical parameters (PPA and PWV) and BP on total mortality and major CV events in very elderly individuals living in nursing homes.

Methods

The PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study is a multicenter, longitudinal study aimed at determining the 2-year predictive value of BP and arterial functional parameters on total mortality (primary endpoint) as well as major CV outcomes and cognitive decline (secondary endpoints) in a large population of individuals 80 years of age and older living in nursing homes. The rationale and baseline parameters of this study were previously described (13).

Participants were enrolled in 4 French (Nancy, Dijon, Paris, Toulouse) and 2 Italian (Cesena and Verona) university hospital centers between January 2006 and June 2008. A total of 72 nursing homes participated in this study in France and Italy (13).

Participants were included if they were 80 years of age and over, living in nursing homes, and signed the informed consent. Subjects were excluded if they had severe dementia (Mini-Mental Status Examination score <12 out of 30), a low level of autonomy (Activity of Daily Living [ADL] scale score ≤2 out of 6) or were under guardianship or some measure of legal protection. No other exclusion criteria were applied. The family and/or the physician of the patient were informed of the study and gave their approval.

According to the inclusion criteria, 1,259 individuals living in the nursing homes participating in this study were eligible. Among them, 1,130 (89%) agreed to participate and were enrolled in this study. Four subjects were excluded from the present analysis because they did not have self-measured BP. Therefore, 1,126 subjects (874 women and 252 men) were analyzed.

This study was approved by the respective regional ethics committees in France (Comité de Protection des Personnes) and in Italy (Comitato Etico Area Vasta Romagna and Comitato Etico della Provincia di Verona), and all participants gave written informed consent before the study.

2-year follow-up. Patients were included from January 2007 to June 2008 and were followed for 2 years. Adverse outcomes were recorded every 3 months from inclusion to the end of the study, using a questionnaire addressed to the physicians at each nursing home. In addition, 2 visits were conducted by the study investigators at the end of the first and second year of follow-up.

Clinical data collection. All geriatric assessment instruments and arterial measurements were performed in the nursing homes by a trained medical research investigator present at each university hospital center participating in the study. Clinical data collection was performed during face-to-face interviews and acquired from the patients' medical records.

Arterial functional parameters. Central BP values and aortic pressure waveforms were obtained directly from the common carotid artery using an applanation tonometer (9,14). Arterial tonometry was performed on right common carotid artery and femoral artery using a PulsePen device (DiaTecne srl, Milan, Italy) (10). As previously demonstrated, the pressure waves recorded noninvasively by the PulsePen tonometer at the site of the common carotid artery are similar to pressure waveforms obtained invasively by means of an intra-arterial catheter (10). Moreover, several studies demonstrated that central BP values and pulsed wave analysis recorded in the common carotid artery are a reliable surrogate of analysis recorded in the aorta by invasive methods (9,12,15). Central BP values were obtained by the carotid BP curve integral after calibration with brachial mean and diastolic BP (DBP) mea-

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sured noninvasively by a validated oscillometric sphygmomanometer (16) at the brachial artery (Omron 705IT, Omron Co., Kyoto, Japan). The PPA was the percentage of increase of PP in the brachial artery (PP_B) relative to central PP (PP_C), according to the formula: $PPA = 100 \cdot (PP_B - PP_C)/PP_C$. The augmentation index (AI) was measured from the analysis of carotid pulsed waves according to the previously reported method (10).

The PulsePen device was also used for measuring carotid-femoral PWV, which is considered the gold standard for measuring arterial stiffness (10,11,13). The procedure was described in detail previously (13). For technical reasons, arterial measurements were not obtained in 66 (for PPA and AI) and 56 (for PWV) subjects.

BP measurement. BP and heart rate measurements were performed at the brachial artery level using the validated automated oscillometric device Colson DM-H20 (Dupont Médical, Frouard, France). The midarm circumference was measured and the cuff width adapted accordingly.

Self-measurements of BP were performed following the "rule of 3" (3 measurements with intervals of 1 min in the morning and evening for 3 consecutive days) according to the protocol proposed by the French Society of Hypertension (17). The procedure was described previously (13). In the present study, the average of the BP values of the 3 days (morning and evening) was used for the different analyses.

Mean arterial pressure (MAP) was calculated as: DBP + 1/3 PP.

Endpoints. The primary endpoint was overall mortality during the 2-year follow-up period.

The secondary pre-specified endpoints were major CV events. Major CV events (CV morbidity and mortality) included both nonfatal CV events that led to hospitalization or a specific long-term new treatment as well as death from cardiac, cerebrovascular, and other vascular causes.

Information on the cause of death and adverse cardiac events were reported by the physicians at the nursing homes every 3 months according to the procedure detailed previously.

According to the reported information, 2 investigators in our group (S.G., P.S.) classified subjects with or without CV events. At the end of the study, all events were re-evaluated in a blinded manner by a third investigator (A.B.). In few cases, in which the 2 classifications differed, a third consensus review was conducted with the 2 investigators. Less than 5% of such differences were observed, and in all cases, consensus was reached during the consensus meetings.

Statistical analysis. Descriptive values are expressed as mean ± SD or number and percentage. For the comparisons of men and women (Table 1), the Wilcoxon rank sum test was used for continuous variables, the chi-square test for discrete variables, and the log-rank test for 2-year mortality

Table 1 Main Clinical Characteristics in Men and Women

Parameters	All	Men	Women	p Value*
n (%)	1,126	252 (22)	874 (78)	
Age, yrs	88 ± 5	87 ± 5	88 ± 5	0.25
BMI, kg/m^2	26 ± 5	25 ± 4	26 ± 5	0.17
MMSE score, 0–30	23 ± 5	24 ± 5	23 ± 5	0.25
Katz ADL scale score, 0–36	5.0 ± 1.1	5.0 ± 1.1	5.0 ± 1.0	0.59
Charlson comorbidity index	6.0 ± 1.9	6.5 ± 2.0	5.9 ± 1.8	<0.00001
Smoking (past + current), %	22	61	10	<0.00001
Total no. of drugs	7.1 ± 3.4	6.5 ± 3.1	7.2 ± 3.4	0.007
History of CV disease, %	52	58	50	0.034
Diabetes, %	16	17	16	0.89
Dyslipidemia, %	25	21	26	0.12
History of hypertension, %	72	60	76	<0.00001
Current hypertension treatment, %	95	91	96	0.0057
No. of antihypertensive drugs	2.2 ± 1.0	2.1 ± 0.9	2.2 ± 1.1	0.18
SBP, mm Hg	138 ± 17	135 ± 17	138 ± 17	0.002
DBP, mm Hg	73 ± 9	73 ± 9	73 ± 9	0.71
PP, mm Hg	65 ± 13	62 ± 13	66 ± 13	<0.00001
Heart rate, beats/min	74 ± 11	73 ± 12	74 ± 10	0.042
AI	28 ± 14	23 ± 15	29 ± 13	<0.00001
CF PWV, m/s	14.3 ± 5.1	15.0 ± 5.4	14.1 ± 5.0	0.045
Central PP, mm Hg	55 ± 15	53 ± 16	55 ± 15	0.03
PPA, %	24 ± 10	23 ± 11	24 ± 10	0.57
2-yr total mortality, %	22	33	19	<0.00001
2-yr major CV events, %	22	25	21	0.16

Values are mean ± SD or %. *p values determined with Wilcoxon rank sum test for continuous variables, χ^2 test for discrete variables, and log-rank test for mortality and major CV events.

ADL = activities day living; AI = augmentation index; BMI = body mass index; CF PWV = carotid-femoral pulse wave velocity; CV = cardiovascular; DBP = diastolic blood pressure; MMSE = Mini-Mental Status Examination; PP = pulse pressure; PPA = pulse pressure amplification (peripheral-central/central); SBP = systolic blood pressure.

and major CV events. Univariate correlations were made with Pearson's parametric test. The occurrence of total mortality and major CV events according to tertiles of each hemodynamic parameter was estimated using Kaplan-Meier curves for graphic representation and compared by the log-rank test. Cox regression multivariate models were used to assess the relative risk (hazard ratio and 95% confidence interval) of total mortality and of major CV events, according to each hemodynamic parameter as a continuous variable. According to the univariate analyses, the following variables were associated at the 0.10 level with total mortality and subsequently included in the multivariate Cox models: sex, age, ADL, body mass index, Charlson comorbidity index, and history of CV disease. For major CV events, by using the same procedure, age, ADL, a history of CV disease, and the presence of antihypertensive treatment were included. For PPA and PWV, additional adjustments for MAP and heart rate were made. This was necessary to ascertain whether the possible effect of PPA on endpoints was independent of BP and heart rate. The interaction between arterial parameters and current antihypertensive treatment on mortality and major CV events was tested with the Cox model by including the interaction term in the model. The term relative risk is used for hazard ratio throughout this paper. The proportional hazards assumption was assessed on the basis of a test of Schoenfeld residuals with the Cox regression using NCSS 2000 software (NCSS, LLC, Kaysville, Utah). A p value <0.05 was considered statistically significant. Statistical analyses were performed using NCSS 2000 statistical software package.

Table 2 Correlation Coefficients (Pearson) of Univariate Correlations Between Blood Pressure and Arterial Parameters

	PP	Central PP	PPA	PWV	AI
MAP	0.38‡	0.33‡	0.07*	0.19‡	0.11‡
PP		0.95‡	−0.10†	0.22‡	0.17‡
Central PP			−0.39‡	0.19‡	0.20‡
PPA				0.02	−0.16‡
PWV					−0.19‡

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$.
MAP = mean arterial pressure; other abbreviations as in Table 1.

Results

Among the 1,126 subjects of a mean age of 88 ± 5 years, 78% were women. Table 1 shows the main demographic and clinical characteristics of the men and women as well as the rates of total mortality and major CV events.

Table 2 shows that among arterial functional parameters, PWV showed the strongest relationship with MAP, whereas PPA showed the weakest relationship with MAP. Interestingly, PWV was not correlated with PPA. Multivariate analysis showed that PPA was positively associated with heart rate ($p < 0.001$) and negatively associated with age ($p < 0.002$) and AI ($p < 0.02$). Sex, MAP, and PWV were not associated with PPA on multivariate analysis.

Relationships of PPA and PWV with total mortality and major CV events. Among the 1,126 patients enrolled in the study, 839 completed the 2-year follow-up (Fig. 1). Among the remaining 287 subjects, 247 died and 40 were lost to follow-up. During the 2-year follow-up, 228 subjects

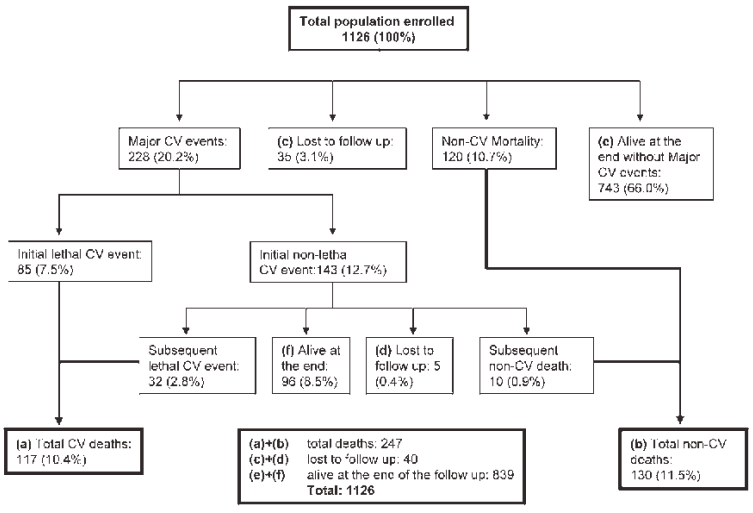

Figure 1 Flow Chart With Data Concerning Deaths and Major CV Events During the Follow-Up Period

Among the 1,126 subjects enrolled in the study, 839 completed the 2-year follow-up, 247 died, and 40 were lost to follow-up. During the 2-year follow-up, 228 subjects experienced major cardiovascular (CV) events.

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experienced major CV events. At the 6 centers, no significant differences were observed for total mortality (20% to 28%; p = 0.34) and major CV events (19% to 33%; p = 0.10).

Figure 2 shows the survival curves for total mortality and major CV events according to the tertiles of PPA and PWV. A lower PPA was significantly associated with both higher total mortality (p = 0.003) and more major CV events (p = 0.004). By contrast, PWV was not associated with total mortality or with major CV events.

The role of PPA and PWV in total mortality or major CV events was also assessed by considering these parameters as continuous variables. Figure 3 depicts the relationships between PPA and total mortality (Fig. 3A) or major CV events (Fig 3B). On both univariate and multivariate analyses, the higher the PPA was, the lower the total mortality and major CV events. In this multivariate model, a 10% increase in PPA was associated with a significant 24% decrease in total mortality and 17% decrease in major CV events. Older age, low ADL scale score, and low body mass index were determinants of total mortality (Fig. 3A). In addition, male sex (p = 0.0003), high Charlson morbidity index score (p = 0.045), low MAP (p = 0.026), and high heart rate (p = 0.0007) were independent determinants of total mortality. A low ADL scale score was associated with major CV events (Fig. 3B).

With regard to PWV, the multivariate analyses confirmed the results of the univariate analyses (i.e., the absence of any relationship between PWV and total mortality or major CV events) (Table 3). A strong interaction was found between antihypertensive treatment and PWV in major CV events (p = 0.001) and was still significant after adjustment for covariates (p = 0.002). After these results, we conducted separate analyses to assess the influence of PWV on major CV events in subjects with and without antihypertensive therapy. In subjects not receiving antihypertensive treatment (n = 231), an increase in PWV of 1 m/s was associated with a 9% higher risk of major CV events (p = 0.003) (Fig. 4). By contrast, in subjects receiving antihypertensive treatment (n = 895), no such an association was found. No association was found between the AI and total mortality or major CV events in the entire population and in the subgroups with or without treatment (data not shown).

Relationships between BP and total mortality and major CV events. Figure 5 shows the survival curves for total mortality and major CV events according to the tertiles of self-measured BP. Higher mortality was significantly associated with lower DBP (log-rank, p = 0.021). The association between SBP or PP tertiles and total mortality did not reach significance (p = 0.057 and p = 0.15, respectively). No association was found between any of the BP measure-

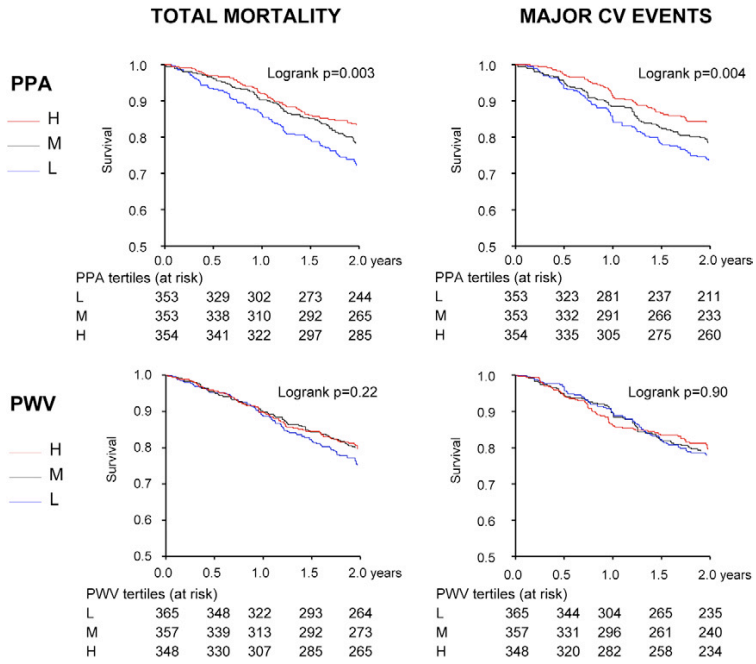

Figure 2 Survival Curves (Log-Rank Analyses) for Total Mortality and Major CV Events in 1,126 Subjects According to the Tertiles of PPA and PWV

Tertiles were defined, respectively, as low (L), mid (M), and high (H). PPA: 0 to 18.8%, 18.9 to 28.0; 28.1% to 58.7%; PWV: 6.0 to 11.5 m/s, 11.6 to 15.5 m/s, 15.6 to 35.0 m/s; PPA = pulse pressure amplification; PWV = pulsed wave velocity.

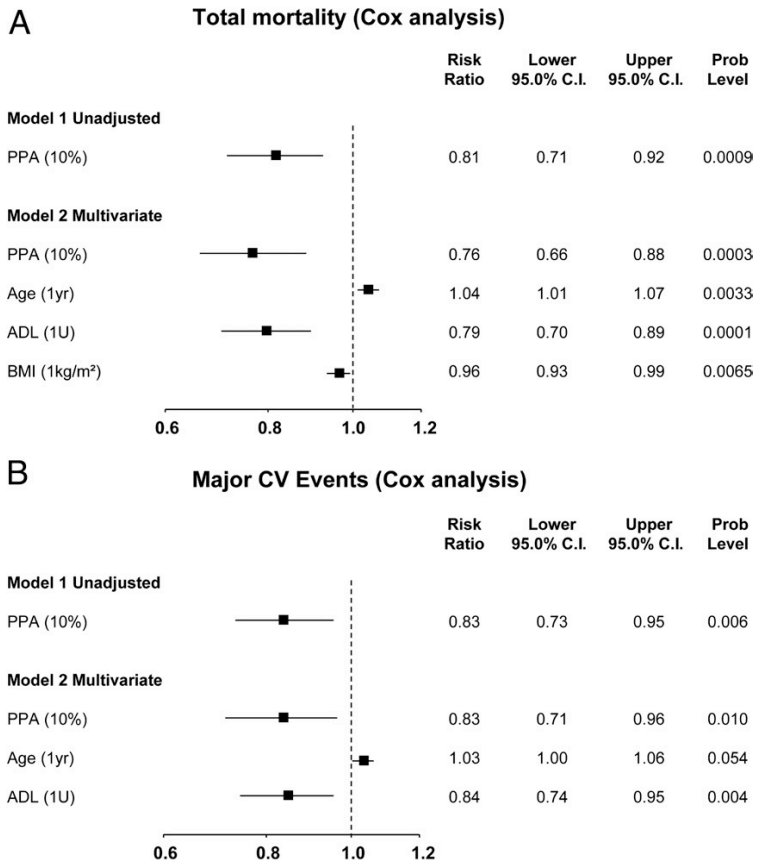

Figure 3 Relationships Between PPA and Total Mortality or Major CV Events Assessed on Both Univariate and Multivariate Analyses

Relative risk (hazard ratio [95% confidence interval (CI)]) for total mortality **(A)** and major CV events **(B)** corresponding to the 10% increment in the PPA assessed in univariate or multivariate Cox models. The multivariate analyses also present the risk related to the increase in age (1 year), activities of daily living (ADL) (1 point), and body mass index (BMI) (1 kg/m^2) (only for total mortality). This multivariate Cox model for total mortality **(A)** was also adjusted for sex, Charlson comorbidity index, history of CV disease, MAP, and heart rate. For major CV events **(B)**, the multivariate Cox analysis was also adjusted for Charlson comorbidity index, history of CV disease, presence of antihypertensive treatment, mean arterial pressure, and heart rate. Prob = probability; other abbreviations as in Figure 2.

ments and major CV events. Central PP (not shown) was not associated with total mortality or major CV events. The results of the multivariate analyses are shown in Table 3. A 10-mm Hg increase in SBP, DBP, or MAP was associated with a significant decrease in the risk of total mortality by 9%, 16%, and 15%, respectively. BP levels were not associated with major CV events (Table 3).

With regard to BP levels, similar results were observed when BP measured by a clinician, instead of self-measured BP, was considered (data not shown).

Discussion

This longitudinal study performed in subjects 80 years of age and older and living in nursing homes provides 2 major original findings. 1) The increase in PP from central (carotid) to peripheral (brachial) arteries is a good predictor of total mortality and major CV events in this population. The lower the PPA is, the higher the total mortality and major CV events. 2) Self-measured BP is either not associated or inversely associated with total mortality and major CV events, confirming previously reported data obtained with standard BP measurements in very elderly subjects.

Influence of PPA on total mortality and major CV events. Several reports have indicated interest in assessing PPA to predict CV complications and benefits of antihypertensive treatment (12,18,19). We recently reported in a large middle-age population study (20,21) that calculated PPA was strongly associated with both CV and total mortality and that this association was stronger than the association between mortality and central or peripheral PP, each taken separately.

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Table 3 Risk Ratio (Cox Regression Analysis) for Total Mortality and Major CV Events According to Blood Pressure and Pulse Wave Velocity

	Risk Ratio	95% CI	p Value
Total mortality			
PWV, +1 m/s	1.00	0.97–1.03	0.792
SBP, +10 mm Hg	0.91	0.84–0.98	0.017
DBP, +10 mm Hg	0.84	0.72–0.99	0.037
MAP, +10 mm Hg	0.85	0.75–0.97	0.016
PP, +10 mm Hg	0.90	0.81–1.00	0.057
Major CV events			
PWV, +1 m/s	1.00	0.98–1.03	0.797
SBP, +10 mm Hg	0.98	0.91–1.06	0.674
DBP, +10 mm Hg	0.97	0.84–1.13	0.716
MAP, +10 mm Hg	0.96	0.84–1.09	0.524
PP, +10 mm Hg	0.98	0.89–1.09	0.741

Each variable presented in this table was included in a multivariate Cox model with the following covariates: age, sex, body mass index, activities of daily living, Charlson comorbidity index, and history of CV disease for total mortality; age, activities of daily living, Charlson comorbidity index, history of CV disease, and antihypertensive treatment for major CV events. For PWV, mean arterial pressure and heart rate were added in the multivariate models.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

The present longitudinal analysis shows that an increase of 10% in PPA (corresponding to ~1 SD) was associated with a decrease of 24% and 17% in total mortality and major CV events, respectively. Of note, the association between PPA and the endpoints was markedly significant after adjusting for several confounders, including history of CV disease. This adjustment was necessary because in a cross-sectional analysis of the baseline data of the present study (22), we demonstrated a link between a history of heart disease and PPA levels. We also tested this association after adjusting for heart rate because the latter is a significant determinant of PPA and may also influence CV events. Again, the association between PPA and mortality or CV events remained highly significant.

Influence of SBP, DBP, and PP on total mortality and major CV events. This study provides significant new information showing that PPA has a prognostic value in an elderly population, whereas BP measurements do not. In fact, in this population, the association between BP and endpoints was either absent (for major CV events) or even negative (for total mortality). Previous studies showed that the respective roles of SBP, DBP, and PP are modified with advanced age with a weakening in the impact of DBP and an increasing role of SBP and PP (23,24).

However, in the present study, similar results were also observed for the other 2 components of BP (i.e., SBP and PP). Previous relatively small studies in very elderly subjects have reported the absence of any prognostic value of BP (4–6) or even negative associations between BP levels and morbidity and mortality (7,8). These paradoxical results can be explained by the fact that in these very elderly frail individuals, a low SBP may not simply be a sign of so-called good arterial health but often of malnutrition and comorbidities such as heart failure, neurological disorders, and other comorbidities associated with poor prognosis. Irrespective of the underlying explanation, the present results indicate that the BP levels in very elderly frail individuals are evidently not reliable, whereas PPA provides more pertinent information about the patient's prognosis. Interestingly, PPA is a ratio of 2 pressures, and therefore this parameter is weakly or even not related to absolute BP levels.

PWV, total mortality, and major CV events. In the present study, we found no relationship between PWV and total mortality or major CV events in the entire population. In middle-age and elderly populations, high PWV, a strong indicator of high aortic stiffness, is a determinant of CV events (11,24–27). We previously showed in a smaller population of subjects younger than 70 years of age living in a long-stay geriatric rehabilitation department that high PWV was associated with increased CV mortality but not with total mortality (6). In the present study, high PWV was associated with major CV events only in individuals without antihypertensive treatment, probably because those who were treated had more comorbidities. This result may be related to the fact that although PWV is determined by arterial structure and function, it is also influenced by BP levels. Therefore, any comorbidity that tends to decrease BP can also decrease PWV and therefore one can have a relatively low PWV despite alterations in arterial mechanical properties. However, contrary to what was observed with BP levels, high PWV was never associated with lower total mortality.

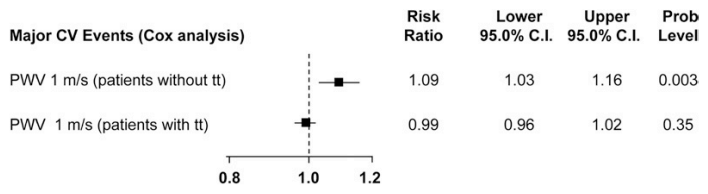

Figure 4 Relative Risk (Hazard Ratio [95% CI]) for Major CV Events Corresponding to the 1-m/s Increment in PWV in Subjects Receiving (n = 895) or Not Receiving (n = 231) Antihypertensive Treatment

The multivariate Cox analysis model included ADL, age, Charlson comorbidity index, history of CV disease, mean arterial pressure, and heart rate. tt = treatment; other abbreviations as in Figure 3.

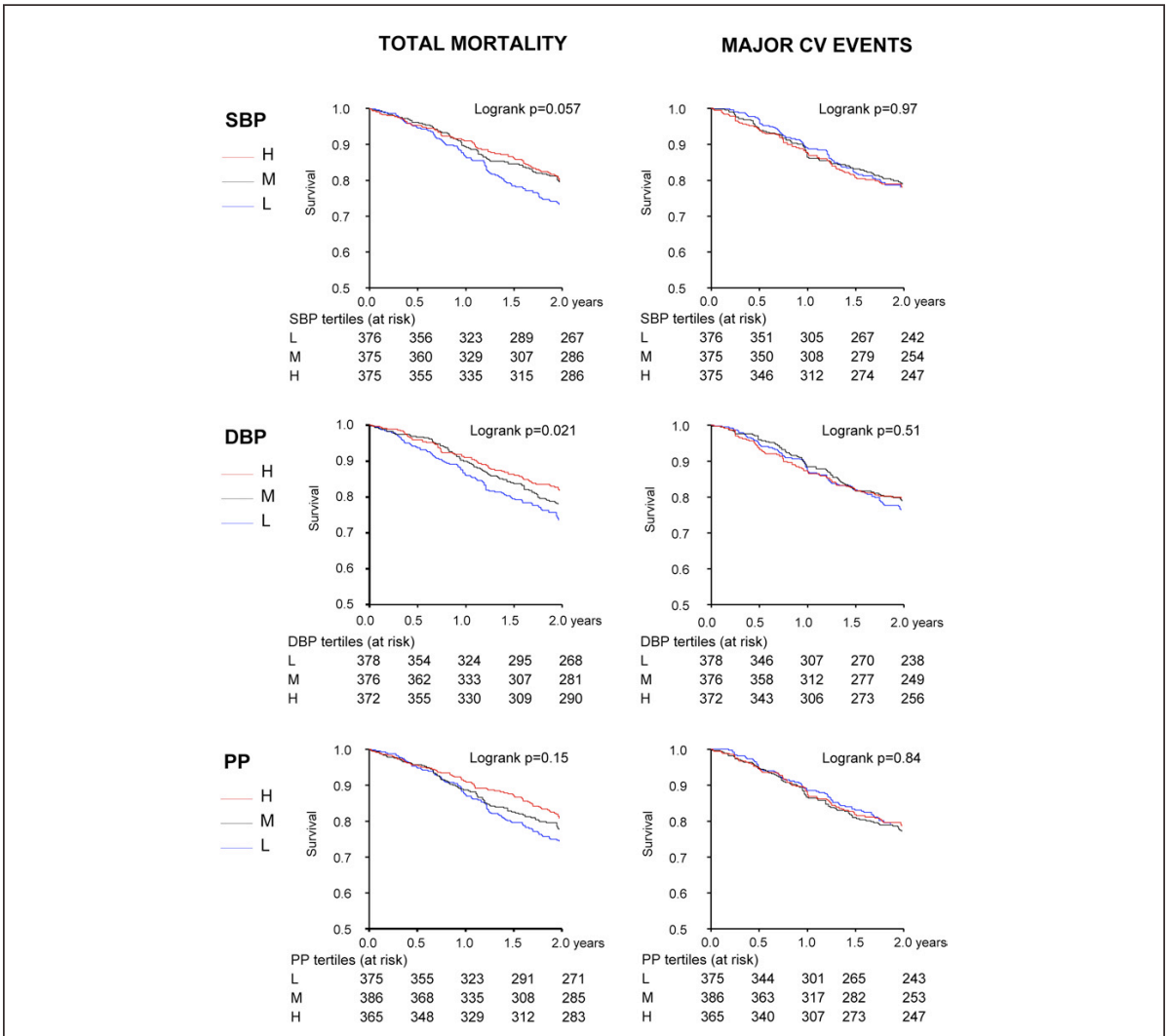

Figure 5 Survival Curves (Log-Rank Analyses) for Total Mortality and Major CV Events in 1,126 Subjects According to the Tertiles of Self-Measured SBP, DBP, and PP

Tertiles were defined, respectively, as L, M, and H (mm Hg). SBP: 85.0 to 129.5, 129.7 to 143.7, and 143.8 to 201.3; DBP: 49.3 to 68.5, 68.6 to 76.3, and 76 to 106.5; PP: 25.5 to 58.3, 58.5 to 69.3, and 69.5 to 124.7. DBP = diastolic blood pressure; PP = pulse pressure; SBP = systolic blood pressure; other abbreviations as in Figure 2.

Study limitations. The main limitation of the present study is the absence of biological markers of frailty to better understand the underlying conditions explaining these findings. However, under the present conditions, the drawing of blood in nursing homes could have potentially resulted in the nonadherence of a large number of subjects with the subsequent risk of selection bias.

Conclusions

Our results provide new information concerning the assessment of risks in a dramatically growing elderly population living in nursing homes and representing a major challenge for geriatric care. The important finding is that in this frail population in which blood pressure measurements may be misleading, PPA constitutes a noninvasive appropriate method for assessing prognosis.

Of particular interest, these are polypathological, polymedicated individuals and are, in the large majority, treated for hypertension. Although the design of the present study does not allow the possibility to conclude on the previously reported interest in controlling high BP with drugs (3), the present findings do raise the issue of the utility of BP levels as an indicator of protection in these individuals. This is of major interest because iatrogenic-induced problems are also a major issue in the elderly.

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In summary, low PPA from central to peripheral arteries strongly predicts mortality and CV adverse events. Assessment of this parameter could help in risk assessment and improve diagnostic and therapeutic strategies in very elderly, frail, and polymedicated persons. In contrast, high BP is not associated with a higher risk of mortality and major CV events in very elderly individuals living in nursing homes.

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Key Words: blood pressure ■ elderly ■ mortality ■ nursing home ■ pulse pressure amplification.

ANNEXE 5

Journées européennes de la Société française de cardiologie
Dossier thématique
en ligne sur / on line on
www.em-consulte.com/revue/lpm
www.sciencedirect.com
Presse Med. 2012; 41: 650-654

Mise au point

Variabilité tensionnelle intervisite : quelle signification pronostique ?

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Key points

Visit-to-visit variability: Prognostic significance?

Hypertension is the most prevalent treatable risk factor for stroke. *Treatment of hypertension is based on usual blood pressure, which is evaluated by repeated measurement.*
When only few measurements show high blood pressure, this is considered as a background noise generally due to white coat effect.
Rothwell et al. challenged this notion and presented data from post-hoc analyses *of three randomized trials and one meta-analysis, where 3 parameters are strongly associated with the risk of stroke: visit-to-visit variability of systolic blood pressure, increased residual variability in treated patients, and episodic hypertension.*
These findings are not proof of a causal link *between variability and vascular risk.*
However, ***a new window has been opened in clinical practice, giving new implications in the choice of treatment****, and, for next trials, highlighting the importance of including variability and patients with episodic hypertension.*

Points essentiels

L'hypertension artérielle est le plus important facteur de risque d'accident vasculaire cérébral modifiable. La cible thérapeutique est le niveau de pression artérielle systolique moyen.
La multiplication des mesures permet d'évaluer au mieux ce niveau de pression artérielle. Les chiffres élevés inhabituels sont considérés comme un bruit de fond en général attribués à l'effet blouse blanche. **Rothwell et al. ont publié une série de travaux qui remet en cause le manque d'intérêt pour ce bruit de fond.**
Rothwell et al. reprennent plusieurs cohortes de patients hypertendus et analysent de manière rétrospective le lien entre risque d'accident vasculaire cérébral et ce que nous considérons comme un bruit de fond : variabilité intervisite, variabilité résiduelle sous traitement, valeur maximale de la pression artérielle systolique, et notamment les valeurs élevées.
Cette analyse post-hoc trouve un lien fort entre ces paramètres et le risque d'accident vasculaire cérébral et bien que le lien de causalité ne soit pas prouvé, cette analyse est innovante.
En effet, cette analyse a des **implications cliniques immédiates dans le choix thérapeutique** et pour les études à venir, elle suggère de prendre en compte **la variabilité tensionnelle**, ainsi que les patients avec **hypertension épisodique**.

Les premières études faisant état d'une éventuelle relation entre la variabilité de la pression artérielle et le risque cardiovasculaire datent des années 1970 [1]. En 1980, a été publiée une étude faisant état de l'absence de relation entre la variabilité de la pression artérielle mesurée sur la population de Framingham et le niveau de risque cardiovasculaire. Cette étude négative a probablement suffisamment marqué les esprits pour que ce concept de variabilité de pression artérielle ne soit que peu étudié pendant 10 ou 20 ans [2]. Puis, dans les années 1990 et les années 2000, quelques nouveaux rapports faisaient état d'un risque de complications de l'hypertension artérielle (HTA) qui serait plus élevée, bien entendu chez les patients porteurs d'une pression artérielle plus élevée mais aussi, à même niveau de pression artérielle, chez les patients porteurs d'une variabilité tensionnelle accrue. Ces données concordaient avec d'autres études portant sur l'hypotension orthostatique ; chez les patients âgés et même chez les patients d'âge moyen, l'hypotension orthostatique était associée à une augmentation du risque cardiovasculaire. En revanche, l'avènement des mesures ambulatoires de pression artérielle dans les années 1990 a donné des informations qui semblaient contradictoires, plus la variabilité de la pression artérielle entre le jour et la nuit était prononcée, meilleur était le pronostic.

L'HTA est le facteur de risque d'accident vasculaire cérébrale (AVC) modifiable le plus important [3]. L'indication du traitement et l'évaluation de son efficacité sont basées sur la mesure répétée de la pression artérielle (PA) afin d'évaluer le niveau de PA systolique moyen d'un individu. Les essais thérapeutiques ont utilisé ce paramètre pour juger de l'efficacité d'un traitement. La multiplication des mesures au cabinet et/ou à domicile (mesure ambulatoire de 24 h ou auto-mesures) permet de limiter le bruit de fond et de cibler au mieux ce niveau de PA systolique moyen tant pour l'indication d'un traitement que pour son suivi. Selon les recommandations françaises, le choix entre les cinq classes thérapeutiques est laissé à la discrétion du praticien et le bénéfice du traitement semble lié principalement à la baisse de la PA [4].

Les choses ont évolué depuis la publication de plusieurs études suggérant une efficacité classe dépendante de la prévention des AVC. Dans l'étude ASCOT-BPLA publiée en 2005, les patients étaient randomisés à 2 stratégies thérapeutiques : amlodipine ± périndopril et aténolol ± thiazidiques. Le groupe amlodipine avait moins d'évènements cardiovasculaires que le groupe aténolol, pour une différence de niveau de pression artérielle non significative [5]. Quelques mois plus tard, une sous-étude, ASCOT-CAFE, a montré qu'à même niveau de pression artérielle périphérique, l'amlodipine faisait diminuer de manière plus importante la pression artérielle centrale. L'effet supérieur de l'amlodipine serait donc expliquer par son effet plus important sur la pression centrale [6].

Mais cette explication n'a pas contenté l'ensemble de la communauté scientifique. En effet, depuis 2010, l'équipe de Peter M Rothwell (centre de recherche sur la prévention des AVC, neurologie, hôpital de Radcliffe, Oxford) a publié plusieurs articles dans le *Lancet* et le *Lancet Neurology* suggérant l'existence d'un nouveau marqueur de risque vasculaire, à savoir la variabilité tensionnelle intervisites. Cette variabilité serait non seulement un puissant marqueur de risque cardiovasculaire, mais expliquerait également la différence d'efficacité entre l'amlodipine et l'aténolol. L'amlodipine était plus efficace car « stabilisait » mieux la pression artérielle dans le temps que l'aténolol.

Un concept nouveau

Les travaux de Rothwell ont la particularité d'être innovants car ils prennent en compte la variabilité tensionnelle dans le temps, sur une longue période. Jusque là, lorsqu'on parle de variabilité, c'est essentiellement la variabilité intravisite ou sur 24 heures qui est pris en compte. Ces 2 paramètres sont de moins bons marqueurs de risque. On sait que la pression artérielle systolique moyenne [7].

Postulat initial

Pour Rothwell et al., il existe plusieurs arguments pour s'intéresser à d'autres paramètres que la PA systolique moyenne. Le premier paramètre est l'importance des valeurs maximales de la PA systolique, et notamment les valeurs élevées isolées. L'étude de 2 cohortes de patients ayant fait un accident ischémique transitoire, UK-TAI et Oxford Vascular Study révèle l'existence d'un pic hypertensif non traité dans les dix années précédant l'évènement. Dans UK-TAI, 12 % seulement avaient une HTA stable et 69 % avaient une mesure élevée dans les dix ans. Dans Oxford Vascular study, 87 % des patients avaient une mesure supérieure à 160 mmHg dans les dix ans.

Le deuxième paramètre est la variabilité tensionnelle intervisites. Son importance s'appuie sur des arguments épidémiologiques : l'effet blouse blanche et l'HTA masquée sont liés à long terme à des dommages des organes et seraient une forme clinique de la variabilité intervisite, tout comme les facteurs modifiant la pression artérielle à court terme (stress, hyperactivité sympathique, hypertension orthostatique, hypotension orthostatique). Le risque d'AVC est plus important chez les femmes et chez les sujets issus d'ethnies noires à niveau de pression artérielle et d'autres facteurs de risque égaux. Et coïncidence, ces personnes ont une variabilité intervisite plus importante. L'HTA est un facteur de risque de démence et dans l'étude Syst Eur trial, le traitement de l'HTA s'accompagne d'une diminution de la démence par les bloqueurs des canaux calciques. Cette même classe thérapeutique diminuerait également la variabilité de la PA intervisite.

Le dernier paramètre est la variabilité intervisites résiduelle sous traitement ou stabilité de l'HTA traitée. Ce paramètre pourrait expliquer l'efficacité supérieure de l'amlodipine dans la prévention des AVC [7].

Travaux de Rothwell et son équipe

Rothwell et al. se proposent d'analyser la variabilité tensionnelle intervisites, la valeur maximale de la pression systolique et la variabilité résiduelle intervisites sous traitement dans quatre études : l'UK-TIA, l'étude européenne Stroke prevention study, la Deutsche TIA et l'étude ASCOT-BPLA [8].

L'étude UK-TIA est une étude randomisée en double aveugle comparant l'aspirine (1200 mg versus 300 mg) au placebo chez 2435 patients ayant fait un accident ischémique transitoire ou constitué récent. Rothwell n'a inclut que les patients ayant fait un AIT soit 2006 patients. La pression artérielle a été mesurée tous les quatre mois, en position assise avec un manomètre à mercure, après cinq minutes de repos.

L'étude européenne Stroke prevention study a randomisé en double aveugle 2500 patients atteints d'un AIT (aspirine + dipyridamole versus placebo). La pression artérielle a été mesurée de la même manière tous les 3 mois. Seul le groupe placebo a été pris en compte pour ne pas prendre en compte les effets vasculaires du dipyridamole.

Dans la Deutsche TIA, 3150 patients ont été randomisés (aspirine 30 mg versus 283 mg) et un sous-groupe de 1473 patients a reçu aténolol versus placebo. La mesure de la pression artérielle a été faite de la même manière tous les 4 mois.

Dans ASCOT-BPLA, 19 257 patients hypertendus de 40 à 79 ans ont été randomisé à un bras amlodipine ± périndopril et à un bras aténolol ± bendrofluméthiazide. Ces patients avaient au moins trois autres facteurs de risque mais aucun antécédent coronarien. Le traitement était titré pour un objectif inférieur à 140/90 mmHg (130/80 chez le diabétique). La pression artérielle a été mesurée trois fois en position assise après 5 minutes de repos à l'aide d'un appareil semi-automatique validé. Cette mesure a été faite à 6 semaines, 3 mois, 6 mois et tous les 6 mois. Certains centres investigateurs avaient également effectué une mesure ambulatoire de 24 heures (1905 patients), 18 530 patients (96 %) ont été retenus dans l'étude car ils avaient aux moins 2 visites programmées après 6 mois de suivi.

Dans l'analyse statistique, la variabilité intervisite est définie comme la déviation standard (SD) ou le coefficient de variation (rapport entre SD et la moyenne de toutes les pressions systoliques mesurées). Cette analyse a été réalisée avec les valeurs de PA des 7 premières visites correspondant aux 2 premières années et avec les valeurs des 10 premières visites (36 premiers mois). Le niveau de PA systolique moyenne a été divisé en décile. Le rapport de risque (HR) d'AVC a été calculé dans le groupe du décile le plus élevé par rapport au groupe du décile le plus bas pour UK-TIA, l'étude européenne Stroke prevention et la Deutsche TIA. Pour ASCOT-BPLA, le HR a été calculé par rapport au premier décile du groupe amlodipine.

Dans l'étude UK-TIA, les patients avaient en moyenne 10 consultations avant l'apparition d'un évènement (AVC ou décès). On note une diminution de la PAS moyenne de 4 mmHg (150 à 146 mmHg) au bout de la première année et par la suite, le niveau de PA systolique reste stable.

Lors des 7 premières visites, 270 évènements cardiovasculaires ont été diagnostiqués (104 AVC et 166 évènements coronariens). La PA systolique moyenne est un bon marqueur prédictif d'AVC (HR 1,43 pour une baisse de 20 mmHg). Après ajustement avec l'âge, le sexe et les autres facteurs de risque cardiovasculaire, elle est plus performante (HR 2,44 par rapport au premier décile).

La variabilité intervisites de la PA systolique semble plus performante pour prédire le risque d'AVC (HR 6,22 [4,16–9,29] par rapport au premier décile ; HR 12,08 lorsqu'on prend les 10 premières visites). Elle est indépendante de la PAS moyenne, du sexe, du traitement antihypertenseur, de la fréquence cardiaque et de sa variabilité. Elle est également indépendante de l'effet blouse blanche. Sa puissance diminue avec l'âge. Elle prédit également le risque d'infarctus et d'insuffisance cardiaque.

La pression artérielle systolique maximale prédit également le risque d'AVC (HR 3,63 [2,41–5,48] par rapport au premier décile) indépendamment de la PA systolique moyenne. Et ce d'autant plus que le patient est jeune.

La variabilité de la PA diastolique est moins prédictive que ne l'est la variabilité de la PA systolique. Quant à la variabilité intravisite, elle n'est pas prédictive d'AVC, ni de variabilité intervisite. Les patients avec une PA systolique élevée de manière isolée avaient un risque d'AVC plus élevé que les patients avec une HTA stable (13,7 % vs 4,5 %, $p = 0{,}003$) en dépit d'une PA systolique moyenne plus basse (158 mmHg vs 167 mmHg, $p = 0{,}001$).

Ces résultats ont été confirmés dans les 3 autres cohortes *(tableau I)*.

Dans ASCOT-BPLA, la différence de pression systolique moyenne entre les 2 groupes est de 2,7 mmHg en faveur de l'amlodipine ($p < 0{,}0001$). Il y avait plus d'AVC dans le groupe aténolol (350 AVC et 704 évènements coronariens dans le groupe aténolol versus 279 AVC et 611 évènements coronariens dans le groupe amlodipine). La variabilité intervisite reste un puissant marqueur de risque d'AVC*(tableau I)*. Elle prédit également le risque d'infarctus du myocarde et d'insuffisance cardiaque (1,23, [1,08–1,41], par rapport au premier décile du groupe amlodipine). Cette valeur pronostic est indépendante de la fréquence cardiaque [9].

Par ailleurs, la variabilité de la pression artérielle intervisite est supérieure dans le groupe aténolol (SD 12,15 mmHg pour amlodipine vs 9,47 mmHg pour aténolol, $p < 0{,}0001$). Plus

TABLEAU I

Valeur prédictive d'accident vasculaire cérébrale (AVC) des différents paramètres étudiés

Études	UK-TIA	ASCOT-BPLA Aténolol	ASCOT-BPLA Amlodipine	ESPS	Dutch TIA
Patients[1]	1324	1012	999	1247	3150
Fréquences visites (mois)	4	6	6	3	4
PA systolique à l'entrée	150,2 (25,3)	163,7 (18,7)	164,4 (17,9)	156,3 (22,7)	157,9 (26,3)
PA systolique à 1 an	146,6 (23,4)	148,3 (19,7)	143,3 (17,4)	154,8 (22,3)	151,7 (22,5)
Variabilité SD	14,2 (6,6)	14,4 (6,1)	11,4 (4,9)	14,6 (6,8)	14,9 (6,4)
HR AVC					
PA systolique	3,63 (2,41–5,48)	1,81 (0,89–3,67)	0,94 (0,36–2,42)	1,89 (0,96–3,71)	2, 34 (1,41–3,89)
SD	6,22 (4,16–9,29)	4,37 (1,85–10,33)	4,46 (1,73–1,5)	1,90 (1,34–2,7)	4,35 (2,17–8,69)
HR AVC[2]					
SD	4,84 (3,03–7,74)	4,29 (1,78–10,36)	4,39 (1,68–11,5)	1,78 (1,21–2,62)	3,35 (1,63–6,87)

SD : déviation standard.

[1] Patients ayant eu au moins 7 visites.

[2] Ajusté à la PA systolique.

de patients dans le groupe aténolol avaient des chiffres de PA supérieure à 180 mmHg (OR 2,44 [2,05–2,86]), voire 200 mmHg (OR 3,45 [2,35–5]). Cette différence n'est pas due à un manque d'observance au traitement puisqu'elle s'accentue lorsque l'analyse est faite en intention de traiter. Les bêtabloquants ne sont pas protecteurs dans les 2–3 premières années malgré une baisse de PA de 10 mmHg.

Un sous-groupe de 1905 patients a eu une mesure ambulatoire de la PA (MAPA). En moyenne, 3,5 MAPA ont été réalisées pendant 6 mois. Huit cent quarante-trois patients avaient eu au moins 4 MAPA et dans ce groupe, la variabilité de la pression artérielle systolique diurne par rapport à la première MAPA est fortement corrélée à la variabilité intervisite durant la même période de mesure. La variabilité de la PA systolique à la MAPA est un plus faible prédicateur des évènements vasculaires que ne l'est la variabilité intervisite de la PA systolique [9].

L'efficacité supérieure de l'amlodipine serait en lien avec son pouvoir de « stabilisation » de la PA dans le temps. Du point de vu physiopathologique, l'amlodipine diminuerait la rigidité artérielle, ce qui diminuerait également les variations du flux sanguin dans les vaisseaux intracérébraux [9].

Un des point intéressant de l'analyse de ASCOT-BPLA repose sur le constat que la variabilité résiduelle est aussi importante dans cette cohorte que dans UK-TIA en dépit d'une mesure standardisée de la PA et d'une stratégie thérapeutique plus agressive. Ce qui suggère l'importance de cette variabilité résiduelle malgré un meilleur contrôle du niveau de PA.

Cette efficacité classe dépendante sur la variabilité tensionnelle a été étudiée dans une méta-analyse réalisée par la même équipe. Les auteurs ont repris les PA à l'entrée et au cours du suivi recueillies dans 389 essais. Il ne s'agit pas de données individuelles mais de la variabilité de la PA de chaque groupe de traitement, substitut de variabilité individuelle. Les effets des traitements antihypertenseurs sur la variation interindividuelle de la PA ont été exprimés en tant que ratio de la variance et sont corrélés aux évènements cliniques. La variabilité interindividuelle est très différente selon les essais et 68 % de cette différence serait attribuable au traitement. Elle est moins importante sous anticalciques (0,81 ; $p > 0,001$) et thiazidiques (0,87 ; p à 0,007) que sous IEC (1,08 ; p à 0,008), ARA2 (1,16 ; p à 0,002) et bêtabloquants (1,17 ; p à 0,0007), où elle augmente. Les groupes avec une faible variabilité tensionnelle faisaient également moins d'AVC. L'association entre AVC et variabilité tensionnelle est plus forte après ajustement sur la PA systolique moyenne [10]. Ces résultats suggèrent un effet classe sur la variabilité tensionnelle. Mais dans cette méta-analyse, il s'agit de la variabilité interindividuelle à savoir celle du groupe et non de la variabilité individuelle intervisite à proprement parler.

Une idée innovante

L'ensemble des travaux de Rothwell et al. révèle plusieurs points importants :

- la variabilité intervisites de la PA systolique semble être un bon marqueur de risque d'AVC et d'évènements coronaires et ce indépendamment de la PA systolique moyenne ;
- une variabilité intervisites résiduelle élevée des patients traités et les valeurs élevées isolées de PA systolique ont un moins bon pronostic que l'HTA stabilisée.
- ces données pourraient modifier la pratique quotidienne pour le diagnostic, le traitement et le suivi des patients hypertendus.

Limites des travaux de Rothwell

Une partie de la variabilité observée dans ces études peut être liée à une erreur de mesure. En effet, dans UK-TIA et Deutch-TIA, les mesures ne sont pas standardisées comme dans ASCOT et peu de mesures sont retenues. L'observance thérapeutique n'a pas été évaluée et le défaut d'observance peut participer à la variabilité intervisites.

Dans ASCOT-BPLA, il ne s'agit d'une comparaison aténolol versus amlodipine, puisque dans chaque groupe, les médecins pouvaient ajouter soit un inhibiteur de l'enzyme de conversion, soit un thiazidique pour optimiser la baisse de la PA. Il s'agit d'analyses post-hoc qui ont des biais liés à cette méthode, en particulier, le lien de causalité entre variabilité et risque d'AVC n'est pas démontré.

La variabilité intervisites ne serait qu'un reflet de la rigidité artérielle, puisque ces 2 paramètres partagent des déterminants communs. Elle a par ailleurs déjà été étudiée dans d'autres études prospectives [11]. Cette variabilité tensionnelle a été identifié dès 1966 par Armitage et Rose [11] qui avaient suivi 10 personnes normotendues et avaient constaté des écarts de 42 mmHg pour la PAS et 12 pour la PAD entre la première et la 20eme consultation. D'autres observations ont confirmé ce constat. Si bien que l'introduction d'un traitement antihypertenseur ne se fait que si plusieurs chiffres de PA sont élevés. D'autres études sont nécessaires pour mieux comprendre la nature et les conséquences de la variabilité intervisites et pour voir comment évaluer cette variabilité dans la pratique quotidienne. D'autres facteurs de variabilité n'ont pas été évalués dans ces travaux comme la réponse à un stimulus, l'instabilité posturale, l'émotion...

Perspectives

Ces données pourraient avoir des implications cliniques immédiates :

- dans le choix de la classe thérapeutique en pratique courante ;
- inclure la variabilité inter visite et la variabilité résiduelle dans les essais thérapeutiques de classes connues ou de nouvelles classes thérapeutiques ;
- inclure des patients avec HTA épisodique dans les essais thérapeutiques.

Conclusion

Les travaux de Rothwell et al. ont mis en évidence de nouveaux marqueurs de risque cardiovasculaire originaux et innovants : la variabilité intervisite, la variabilité résiduelle sous traitement, l'importance de l'HTA épisodique, l'importance des valeurs maximales de la PA systolique. Même s'il s'agit d'analyses post-hoc ne prouvant pas de liens de causalité entre le risque d'AVC et ces paramètres, ces données ouvrent de nouvelles perspectives : choix de la classe thérapeutique, prise en compte de ces paramètres dans les prochains essais thérapeutiques, inclusion des patients ayant une HTA épisodique dans les essais d'intervention.

Déclaration d'intérêts : les auteurs déclarent ne pas avoir de conflits d'intérêts en relation avec cet article.

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ANNEXE 6

Hypertension
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Effect of Antihypertensive Agents on Blood Pressure Variability : The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study

Yi Zhang, Davide Agnoletti, Michel E. Safar and Jacques Blacher

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Effect of Antihypertensive Agents on Blood Pressure Variability

The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study

Yi Zhang, Davide Agnoletti, Michel E. Safar, Jacques Blacher

See Editorial Commentary, pp 133–135

Abstract—To investigate the effect of different antihypertensive agents on blood pressure (BP) variability (BPV) and the underlying mechanism, we analyzed the ambulatory BP monitoring data of 577 patients before and after 3-month antihypertensive treatment, in the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (placebo, candesartan, indapamide sustained release, and amlodipine). Within-subject mean and SD of 24-hour BP, weighted by time interval between consecutive readings, were calculated in 3 time frames (daytime, nighttime, and 24 hours) to evaluate BP and BPV. The mean 24-hour heart rate (HR) and HR variability were calculated with the same algorithms. We found that the 3 antihypertensive drugs had a similar BP-lowering effect ($P<0.001$ for all), but amlodipine ($P<0.007$) and indapamide sustained release ($P<0.04$) were the only agents associated with a significantly decreased BPV after 3-month treatment. On the other hand, the major determinants of BPV at baseline were age, mean BP, and the corresponding HR variability. However, the reduction in BPV by amlodipine was significantly associated with the reduction in BP ($P<0.006$) and the reduction in HR variability ($P<0.02$), whereas the corresponding reduction by indapamide sustained release was only associated with the reduction in HR variability at night ($P=0.004$). In summary, 3-month amlodipine or indapamide sustained release treatment was associated with a significant reduction in BPV, and the mechanism of those reductions was possibly attributable to lowering BP or ameliorating the autonomic nervous system regulation or both. The combination of the 2 agents might help to optimize such properties. **(*Hypertension*. 2011;58:155-160.)**

Key Words: ambulatory blood pressure monitoring ■ calcium channel blocker ■ diuretics ■ blood pressure variability ■ heart rate variability

For many decades, the main goal of antihypertensive treatment was to lower blood pressure (BP) to a defined level. Recently, several investigators have shown that BP variability (BPV) is another critical cardiovascular risk factor, which should also be emphasized in the treatment of hypertension. Mancia et al[1] were the first to report a close association of BPV, assessed by 24-hour ambulatory BP monitoring (ABPM), with target-organ damage in hypertensive patients. Carotid artery damage[1] and increased left ventricular mass index[2] were, therefore, investigated in the first instance. However, the predictive value of BPV concerning cardiovascular and all-cause mortality has long been a matter of debate.[3–9] More recently, nighttime BPV was considered to be a more pronounced risk factor than daytime BPV.[10,11] Finally, Rothwell[12] showed that visit-to-visit BPV was an independent and strong predictor of cardiovascular events, such as stroke and coronary heart disease, and calcium channel blockers and nonloop diuretics were the most effective antihypertensive agents in reducing BPV and in preventing stroke.[13]

However, the unique effect of these agents in terms of BPV reduction is still unproved in the setting of randomized, double-blind, placebo-controlled study. Similar observations can be made regarding other antihypertensive agents as diuretics, β-blocking agents, and blockers of the renin-angiotensin-aldosterone system. Finally, the determinants of BPV remain unclear, and the underlying mechanism of BPV

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Table 1. Characteristics of Subjects at Baseline

Characteristics	Placebo (n=141)	Candesartan (n=141)	Indapamide SR (n=146)	Amlodipine (n=149)	P
Age, y	58.9±10.1	59.0±10.2	58.6±10.2	59.4±10.1	0.93
Male, n (%)	69 (48.9)	57 (40.4)	75 (51.4)	84 (56.4)	0.06
Body mass index, g/m^2	26.8±3.0	27.1±3.1	27.1±3.1	26.8±3.2	0.67
Current smoking, n (%)	18 (12.8)	20 (14.2)	24 (16.4)	25 (16.8)	0.37
Systolic blood pressure, mm Hg	141.5±12.5	140.9±13.3	140.8±12.1	141.8±13.2	0.90
Diastolic blood pressure, mm Hg	85.4±9.1	85.1±9.6	85.1±8.6	86.0±9.3	0.81
Heart rate, bpm	75.8±10.2	75.2±9.2	75.0±9.5	74.7±10.4	0.83
Previous antihypertensive therapy, n (%)	82 (58.2)	82 (58.2)	77 (52.7)	86 (57.7)	0.74
Daytime systolic blood pressure SD, mm Hg	13.0±3.7	12.8±3.2	12.9±3.2	12.7±3.1	0.86
Nighttime systolic blood pressure SD, mm Hg	11.0±3.3	10.9±2.8	10.9±3.3	10.9±3.3	0.99
Daily systolic blood pressure SD, mm Hg	12.3±3.2	12.0±2.5	12.2±2.7	12.1±2.6	0.84
ARV, mm Hg	9.3±1.8	9.4±1.7	9.5±1.9	9.5±1.8	0.61
Plasma glucose, mmol/L	5.26±0.68	5.12±0.73	5.27±1.06	5.25±0.67	0.34
Total cholesterol, mmol/L	5.76±1.03	5.72±0.98	5.74±0.94	5.80±0.99	0.92
High-density lipoprotein cholesterol, mmol/L	1.56±0.41	1.52±0.35	1.56±0.40	1.53±0.33	0.78
Low-density lipoprotein cholesterol, mmol/L	3.51±0.93	3.54±0.85	3.49±0.88	3.60±0.86	0.74
Triglycerides, mmol/L	1.52±1.01	1.46±0.83	1.48±0.83	1.49±0.92	0.94

Values are mean±SD or No. with percentage in parenthesis. ARV indicates the read-to-read average real variability, which is calculated by the formula mentioned in Methods; SR, sustained release.

reduction has never been elucidated precisely in subjects with hypertension.

We analyzed the ABPM data of 577 patients before and after 3-month antihypertensive treatment, in a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients [X-CELLENT] Study), to investigate the effect of different antihypertensive agents on BPV and the underlying mechanism.

Methods

Study Design

The X-CELLENT Study was conducted in 2370 outpatients (aged between 40 and 80 years) with essential hypertension. The inclusion criteria included 150 mm Hg ≤ systolic BP <180 mm Hg and 95 mm Hg ≤ diastolic BP <110 mm Hg or 160 mm Hg ≤ systolic BP <180 mm Hg and diastolic BP <90 mm Hg. The exclusion criteria were a history of coronary artery disease, heart failure, stroke or transient ischemic attack, left ventricular hypertrophy, diabetes mellitus (type 1 or type 2), and renal failure. A total of 608 subjects were excluded from the study because of BP criteria not met (n=341), medical reasons (n=197), and nonmedical reasons (n=70). After a 4-week selection and run-in placebo period, 1762 subjects were randomized to receive placebo, indapamide (1.5 mg) sustained release (SR), candesartan (8.0 mg), or amlodipine (5.0 mg), all given once daily in the morning for a treatment period of 12 weeks. Further information concerning the study design can be found in a previous publication.[14] The study protocol was approved by the ethics committees of each country involved, and written informed consent was obtained from each study participant.

Ambulatory BP Monitoring

A total of 577 patients participated in an ABPM ancillary study, and 496 of them underwent repeat ABPM after 3-month antihypertensive treatment. The ABPM was performed with SpaceLabs 90202 or 90207 (SpaceLabs, Redmond, WA), 4±3 days before the week 0 and week 12 visits and according to the European Society of Hypertension recommendations.[15] Reproducibility of the ABPM measurements had been reported before.[16] The frequency of the ABPM was every 15 minutes throughout the whole day, and the sleep and wake-up times were reported by participants and recorded for further calculations. Daytime and nighttime were defined as from wake-up to sleep time and from sleep to wake-up time, respectively, for each participant.

Calculation of BP and Heart Rate Variability

To minimize the effects of recording errors during the 24-hour ABPM, we used the within-subject mean and SD, weighted for the time interval between consecutive validated readings, to evaluate BP and BPV. Considering nighttime dipping, mean and SD were calculated for the times awake and asleep, as daytime mean, daytime SD, nighttime mean, and nighttime SD. The overall mean and SD, as daily mean and daily SD, were assessed using the following 2 formulas: (1) daily mean=(daytime mean×AT+nighttime mean×ST)/(AT+ST) and (2) daily SD=(daytime SD×AT+nighttime SD×ST)/(AT+ST), where AT and ST stand for awake time and sleeping time in hours.

Another parameter, read-to-read average real variability (ARV), recently proposed by other investigators,[9] was also used to evaluate BPV, as calculated by the following formula:

$$ARV=\frac{1}{\sum w}\sum_{k=1}^{n} w\times|BP_k-BP_{k-1}|$$

where k ranges from 1 to N, w is the time interval between BP_{k-1} and BP_k, and n is the number of BP readings in 24 hours.

The mean value of 24-hour heart rate (HR) and HR variability (HRV) were assessed with the same algorithms as the BP.

Statistical Analysis

Quantitative and qualitative parameters were presented as mean±SD and absolute number with percentage in parentheses, respectively. We used the ANOVA to compare the mean and variability of BP, as well as biochemical variables, between subjects with different antihypertensive treatments at baseline, and applied the Student t test

Table 2. Changes in Systolic Blood Pressure and Its Variability by Treatment Group vs Placebo After 3-mo Treatment

Variables	Placebo (n=120)	Candesartan (n=120)	Indapamide SR (n=133)	Amlodipine (n=123)
Systolic blood pressure, mm Hg				
Daytime mean	146.6±13.8	135.7±14.0	137.4±12.8	137.3±10.3
Change vs placebo		−10.9 (−14.5, −7.4)	−9.2 (−12.5, −5.9)	−9.3 (−12.4, −6.2)
P		<0.001	<0.001	<0.001
Nighttime mean	131.2±14.8	120.2±16.7	120.9±12.8	120.8±10.5
Change vs placebo		−11.0 (−15.2, −6.8)	−10.3 (−13.8, −6.8)	−10.5 (−13.8, −7.2)
P		<0.001	<0.001	<0.001
Daily mean	141.9±13.5	130.6±13.7	132.0±11.7	131.9±9.3
Change vs placebo		−11.2 (−14.8, −7.6)	−9.8 (−13.1, −6.6)	−9.9 (−12.9, −6.9)
P		<0.001	<0.001	<0.001
Systolic blood pressure variability, mm Hg				
Daytime SD	13.2±3.4	12.6±3.2	12.3±3.0	12.0±3.1
Change vs placebo		−0.6 (−1.4, 0.3)	−0.9 (−1.7, −0.1)	−1.1 (−1.9, −0.3)
P		0.20	0.03	0.008
P after adjustment		0.23	0.04	0.009
Nighttime SD	11.4±3.2	11.4±3.3	10.7±3.3	10.2±3.1
Change vs placebo		−0.3 (−0.8, 0.9)	−0.7 (−1.5, 0.2)	−1.2 (−2.0, −0.4)
P		0.95	0.12	0.005
P after adjustment		0.92	0.17	0.006
Daily SD	12.4±2.7	12.2±2.7	11.7±2.5	11.5±2.6
Change vs placebo		−0.3 (−1.0, 0.4)	−0.7 (−1.4, −0.1)	−1.0 (−1.6, −0.3)
P		0.47	0.03	0.007
P after adjustment		0.58	0.06	0.008
ARV	9.5±1.7	9.3±1.9	9.3±1.9	8.9±1.7
Change vs placebo		−0.2 (−0.7, 0.3)	−0.3 (−0.7, 0.2)	−0.6 (−1.0, −0.2)
P		0.42	0.25	0.007
P after adjustment		0.42	0.40	0.007

Values are mean±SD. Daytime mean and SD=time-weighted mean and SD of 24-h systolic blood pressure readings during awake time; nighttime mean and SD=time-weighted mean and SD of 24-h systolic blood pressure readings during sleeping time; daily mean and SD=(daytime mean [SD]×awake time+nighttime mean [SD]×sleeping time)/(awake time+sleeping time). ARV indicates the read-to-read average real variability, which is calculated by the formula mentioned in the Methods. Change vs placebo indicates value from treatment groups minus that from placebo, and mean and 95% CI are presented. *P* after adjustment indicates *P* after adjustment for the corresponding mean blood pressure reduction.

and the generalized linear regression to compared BPV between treatment and placebo groups, before and after adjustment for corresponding BP reduction. Multivariate linear regression analysis was used to investigate determinants of BPV and the reduction in BPV by indapamide SR and amlodipine, separately. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). $P<0.05$ was considered as statistically significant.

Results

Table 1 shows the characteristics of subjects at baseline according to randomized antihypertensive therapy. There was no significant difference between groups. After 3-month antihypertensive treatment, 496 subjects underwent a second ABPM, and there was no significant difference in characteristics between subjects with (n=497) or without the repeat ABPM (n=82).

In Table 2, compared with placebo, all 3 of the antihypertensive agents significantly decreased systolic BP in the 3 time frames, daytime, nighttime, and 24 hours ($P<0.001$ for all), whereas amlodipine and indapamide SR were the only antihypertensive agents to significantly decrease systolic BPV. Specifically, amlodipine significantly decreased systolic BPV in the 3 time frames ($P<0.008$ for all), and indapamide SR significantly decreased systolic BPV in the daytime ($P=0.03$) and 24 hours ($P=0.03$). However, candesartan did not reduce systolic BPV in any time frame. The similar findings are presented in the Figure. In addition, although no significant difference in systolic BPV was observed in the 24-hour read-to-read ARV mode after 3-month different antihypertensive treatments ($P=0.08$), the reduction in ARV by amlodipine also reached statistical significance ($P=0.007$). Furthermore, even after adjustment for the corresponding mean BP reduction, the present findings remained unaltered, except that the reduction in daily BPV by indapamide lost its previous significance ($P=0.06$).

When subjects at baseline were investigated, the determinants of systolic BPV were studied in different modes, such

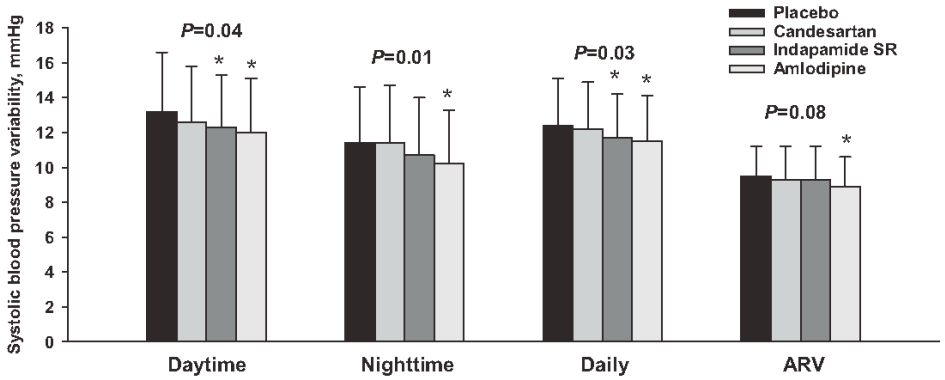

Figure. Comparisons of systolic blood pressure variability after 3-month antihypertensive treatment. ARV indicates the read-to-read average real variability. After 3-month antihypertensive treatment, systolic blood pressure variability in subjects with placebo (black bar), candesartan (gray bar), indapamide SR (light black bar), and amlodipine (light gray bar) were compared in the daytime, nighttime, daily, and ARV setting. Systolic blood pressure variability was assessed by the SD of 24-hour systolic blood pressure readings or read-to-read ARV mode. *$P<0.05$ for the subgroup comparison between subjects with treatment and those with placebo.

as in the daytime, nighttime, 24-hour, and 24-hour read-to-read ARV modes (Table 3). Age, mean systolic BP, and HRV evaluated by the corresponding mode were major determinants of systolic BPV.

As shown in Table 4, the reduction in systolic BPV by amlodipine in different time frames and modes was largely attributable to the reduction in mean systolic BP ($P<0.006$) and the reduction in the corresponding HRV ($P<0.02$), whereas the corresponding reduction by indapamide SR was only attributed to the reduction in HRV at night ($P=0.004$) and mean BP ($P=0.003$).

Discussion

In the present study, the 3 main findings were as follows: (1) although no effect on BPV was noted for candesartan, 3-month amlodipine treatment decreased systolic BPV in the daytime, nighttime, and 24 hours, and 3-month indapamide SR therapy reduced systolic BPV in the daytime and 24 hours; (2) the major determinants of baseline systolic BPV were age, mean systolic BP, and HRV; and (3) the reduction in systolic BPV by amlodipine was attributable to the reduction in mean systolic BP and in HRV, whereas the cause of the corresponding reduction by indapamide SR was largely unknown.

In the literature, several investigators have shown that calcium channel blockers significantly reduce BPV, as assessed by the SD of 24-hour BP,[17–19] and which is in line with the present study. However, some of these investigators also reported that, when BPV is assessed by coefficient of variability, calculated as SD divided by mean BP, the previous significant reduction is absent.[17,19] In this respect, we preferred to assess BPV by using SD, for 2 main reasons. First, from a statistical point of view, it is not valid to evaluate the reduction in BPV independent of BP level with a robust division as using coefficient of variability, because some statistical efficacy would be lost. For instance, in the present study, we did not find a significant decrease of BPV in terms of coefficient of variability, but the statistical significance was preserved when we compared the after-treatment BPV between different treatment groups, after adjustment for the mean value of BP (data not shown). Second, from a prognostic viewpoint, a close association of target-organ damage, cardiovascular events, and mortality with SD of 24-hour BP has frequently been reported in various population-based studies,[1–4,8,10,11] but the prognostic value concerning the coefficient of variability of BP is very limited in literature. Accordingly, we assessed the BPV by SD of 24-hour BP and found that amlodipine and indapamide SR were effective antihypertensive agents in reducing BPV, independent of mean BP, in different time frames and modes.

BPV is a multifaceted phenomenon influenced by human activity, psychology, compliance to antihypertensive treat-

Table 3. Determinants of Systolic Blood Pressure Variability in Subjects at Baseline

	Daytime SD			Nighttime SD			Daily SD			ARV		
Variables	β	Partial R^2	P	β	Partial R^2	P	β	Partial R^2	P	β	Partial R^2	P
Age, y	0.06	0.03	<0.001	0.07	0.03	<0.001	0.07	0.06	<0.001	0.05	0.07	<0.001
Mean SBP, mm Hg	0.06	0.05	<0.001	0.01	0.01	0.14	0.05	0.06	<0.001	0.04	0.07	<0.001
HR SD, bpm	0.21	0.02	<0.001	0.29	0.04	<0.001	0.17	0.01	0.003	0.25	0.04	<0.001

Age, sex, and body mass index, as well as mean systolic blood pressure, mean heart rate, and its variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD=time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD=time-weighted SD of 24-h systolic blood pressure readings during sleeping time; Daily SD=(daytime SD×awake time+nighttime SD×sleeping time)/(awake time+sleeping time).

Table 4. Determinants of the Reduction of Systolic Blood Pressure Variability by Amlodipine and Indapamide Sustained Release

	Daytime SD Reduction			Nighttime SD Reduction			Daily SD Reduction			ARV Reduction		
Variables	β	Partial R^2	*P*	β	Partial R^2	*P*	β	Partial R^2	*P*	β	Partial R^2	*P*
Subjects taking amlodipine (n=123)												
Mean SBP reduction, mm Hg	0.08	0.06	0.005	0.02	0.01	0.42	0.07	0.07	0.006	0.04	0.03	0.01
HR SD reduction, bpm	0.19	0.04	0.02	0.46	0.12	<0.001	0.27	0.07	0.003	0.25	0.17	<0.001
Subjects taking indapamide SR (n=133)												
Mean SBP reduction, mm Hg	0.04	0.02	0.14	0.01	0.01	0.84	0.05	0.03	0.058	0.05	0.08	0.003
HR SD reduction, bpm	0.01	0.01	0.89	0.37	0.07	0.004	0.03	0.01	0.79	0.05	0.01	0.45

Age, sex, body mass index, as well as systolic blood pressure reduction and the reduction of heart rate variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. Reduction indicates the after-treatment value minus the corresponding value at baseline. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD=time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD=time-weighted SD of 24-h systolic blood pressure readings during sleeping time; daily SD=(daytime SD×awake time+nighttime SD×sleeping time)/(awake time+sleeping time).

ment, and the nervous and humoral systems, and reflects the magnitude of BP fluctuation. The determinants of BPV were investigated in several population studies,[17,20] in which age, BP, HR, and sex were frequently reported. In the present study, we also indicated that age and BP were major determinants of BPV. We also took HRV into account and found that it was another important factor of BPV. From a physiological point of view, autonomic nervous system (ANS) regulates BP and HR synchronously and, therefore, contributes to stabilizing their fluctuation. The close association of BPV with HRV in different time frames is probably a universal phenomenon, which could be a consequence of the ANS regulation. Furthermore, the significant relationship between the reduction in BPV and in HRV, consistently observed in the present study, indicates a proportional decrease in the fluctuation of both BP and HR, which is probably attributable to amelioration of the ANS regulation. However, the pharmaceutical mechanism is still unknown.

In literature, there is limited information concerning the underlying mechanism of reduction in BPV. In the amlodipine group of the present study, we found that the reduction in BPV was mainly attributed to the reduction in BP and the reduction in HRV. On the other hand, in the indapamide SR group, we only found limited information with regard to determinants of the reduction in BPV. This difference indicates the distinct mechanism of those 2 antihypertensive agents. In the present study, we found that the effect of amlodipine on BPV was probably attributable to lowering BP and ameliorating the ANS regulation, whereas mechanism of indapamide SR in reducing BPV is largely unknown. Dabire et al[21] reported that, in spontaneous hypertensive rats, increased BPV was significantly associated with arterial stiffening. The similar finding was also achieved in sinoaortic-denervated rats by Lacolley et al.[22] However, whether indapamide SR could possibly reduce BPV through arterial destiffening is still unclear, and further studies are warranted.

The strengths of the present study include the randomized, double-blind, placebo-controlled design, enabling comparison among the 4 treatment groups, and in 4 different time frames and modes. The study's limitations were the relatively small number of subjects and the relatively short therapeutic duration. However, with the significant reduction in BPV after 3-month treatment, we had sufficient statistical power to confirm our findings.

Perspectives

In this study, we have shown that age, BP, and HRV were the major determinants of BPV. Amlodipine and indapamide SR were the only effective antihypertensive agents in decreasing BPV by lowering BP or ameliorating the ANS regulation or both. Their combination might help to optimize such properties. However, the mechanism underlying the reduction in BPV has yet to be clarified, especially its potential interaction with arterial stiffness and/or reflection waves. Given the increasing importance of BPV in the prevention of stroke, as well as other target-organ damage, further studies are undoubtedly warranted.

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ANNEXE 7

Hypertension Research (2012) 35, 399–403

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ORIGINAL ARTICLE

Blood pressure variability in relation to autonomic nervous system dysregulation: the X-CELLENT study

Yi Zhang[1,2], Davide Agnoletti[1], Jacques Blacher[1] and Michel E Safar[1]

The purpose of this study was to investigate the association of autonomic nervous system dysregulation with blood pressure variability. Among the 2370 participants in the X-CELLENT study, 577 patients (59.0 ± 10.2 years) were randomly selected to participate in an ancillary ambulatory blood-pressure monitoring study. We proposed a novel autonomic nervous system regulation index termed dSBP/dHR, which was defined as the steepness of the slope of the relationship between the 24-h systolic blood pressure (SBP) and the heart rate (HR) for each participant. Within-subjects s.d. of SBP, weighted for the time interval between consecutive validated readings from 24-h ambulatory blood pressure monitoring, was used to evaluate blood pressure variability. When dSBP/dHR was divided into tertiles, we observed a progressive increase from tertile 1 to tertile 3 in the daytime SBP, a progressive decrease in nighttime SBP, and consequently a progressive increase in the day–night SBP gradient ($P<0.001$). The s.d. of both daytime and nighttime SBPs were consistently and significantly increased from tertile 1 to tertile 3 ($P<0.01$). Both before and after adjustment for age, gender and 24-h mean blood pressure, all of these increasing and decreasing trends reached statistical significance ($P<0.01$). Furthermore, in our sensitivity analysis, when men and women were considered separately, the findings remained unaltered. In summary, autonomic nervous system dysfunction was associated with a heightened day–night SBP gradient and more variable SBP over 24 h in patients with essential hypertension.
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Keywords: autonomic nervous system; blood pressure variability; systolic blood pressure

INTRODUCTION

There are several lines of evidence that indicate blood pressure variability (BPV) is a major determinant of cardiovascular (CV) events and mortality in various populations.[1–4] Furthermore, some investigators have demonstrated that the nighttime BPV, assessed by s.d. of nighttime systolic blood pressure (SBP) using a 24-h ambulatory blood pressure monitor (ABPM), is more strongly associated with target organ damage than is daytime BPV.[5–7] From a physiological point of view, without the various daytime influences that affect the blood pressure (BP), such as food digestion and physical exercise, the BP is mainly regulated by the autonomic nervous system (ANS) during sleep. Moreover, it has recently been reported that impaired ANS regulation was significantly associated with an increased carotid intima-media thickness.[8] Because both nighttime BPV and ANS dysregulation are significantly associated with target organ damage, it would be interesting to know whether ANS dysregulation could be the cause of the increased BP variation and consequently has an impact on target organ damage. However, data are limited with regard to the association of ANS regulation with BPV. Accordingly, we proposed a novel ANS regulation index that is calculated by conventional 24-h ABPM, and investigated its potential relationship with daytime and nighttime BPV in the X-CELLENT study.

METHODS

Study design

The X-CELLENT study (NatriliX SR *vs.* CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs) is a multicenter, multinational, randomized, double-blinded, and placebo-controlled study with four parallel treatment arms (placebo, indapamide, candesartan and amlodipine). In total, 2370 outpatients (aged 40–80 years) with essential hypertension were recruited. The inclusion criteria included 150 mm Hg ⩽SBP< 180 mm Hg and 95 mm Hg ⩽ diastolic blood pressure (DBP) <110 mm Hg or 160 mm Hg ⩽ SBP<180 mm Hg and DBP<90 mm Hg. The exclusion criteria included a history of coronary artery disease, heart failure, stroke or transient ischemic attack, left ventricular hypertrophy, diabetes mellitus (type 1 or type 2), and renal failure. More details concerning the X-CELLENT study can be found in our previous publications.[9] From the X-CELLENT study population, 577 patients (aged 59.0 ± 10.2 years) were randomly selected to participate in an ancillary ABPM study. Furthermore, because the effects of treatment were withheld from the present analysis, only the baseline data were present. The local Ethics Committee approved the study protocol and written informed consent was obtained from each study participant.

Anthropometric and BP measurements

Body weight and body height were measured for each subject at the inclusion, and the body mass index was calculated as the body weight in kg divided by the

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square of the body height in meters. After at least 5 min of rest in the sitting position, BP was measured three times with a validated oscillometric BP monitor (Omron 705CP, Kyoto, Japan), and those readings were averaged for further analysis.

ABPM

The ABPM was performed on 577 participants according to the recommendations of the European Society of Hypertension.[10] The frequency of ABPM capture was every 15 min over the entire 24 h. Patients' wakeful and sleeping time were self-reported and recorded for further calculation. The daytime and nighttime were defined as the time from waking until sleep and from sleep until waking, respectively, for each participant.

To minimize the effects of recording errors during the 24-h ABPM, we used the within-subject mean and s.d., weighted for the time interval between consecutive validated readings, to evaluate the mean BP level and variability. Considering the nighttime dipping effect, the mean and s.d. were calculated for the awake and sleeping periods, as daytime mean and s.d. and nighttime mean and s.d., respectively.

We also examined the relationship between SBP (*y*-axis) and heart rate (HR) (*x*-axis) on the basis of the 24-h SBP–HR correlation plots for each participant. Then, the steepness of the slope of the relationship between SBP and HR was calculated as dSBP/dHR, an ambulatory index representing the change in SBP per 1-unit change in HR (mm Hg per beat min $^{-1}$). For example, as shown in Figure 1, with a 10 beat min $^{-1}$ increase in HR, patient B is expected to have an increase in SBP of 7.5 mm Hg, whereas patient A would have an increase of 13.1 mm Hg.

The day–night SBP gradient was defined as the difference in SBP between day and night.

Statistical analysis

Quantitative and qualitative parameters are presented as the mean ± s.d. and numbers with percentages in parentheses, respectively. Individual correlation plots were performed by a simple linear regression between 24-h SBP and HR. Next, the dSBP/dHR term was defined as the steepness of the slope of the relationship between SBP and HR in each participant. We applied the ANOVA and chi-square tests to compare quantitative and qualitative variables, respectively, between subjects in different groups classified by tertiles of dSBP/dHR. Similar analyses were performed to compare the mean SBP, SBP s.d. and day–night SBP gradient, and their trends were tested in a linear model after adjustment for age, gender and 24-h mean BP, which were all significantly associated with the dSBP/dHR in the univariate analysis. Sensitivity analyses were conducted in men and women separately. The statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

RESULTS

Characteristics of participants

Table 1 shows the characteristics of the participants classified into tertiles by dSBP/dHR. There was no significant association of the dSBP/dHR with the participants' baseline characteristics, with the exception of male gender and 24-h BP. Specifically, the proportion of men increased significantly ($P=0.02$), with 46.6, 44.0 and 57.4% in tertiles 1, 2 and 3 of dSBP/dHR, respectively, and the increasing trend of 24-h mean SBP was marginally significant from tertile 1 to tertile 3 of dSBP/dHR ($P=0.05$), with 141.4 ± 13.3, 139.6 ± 11.8 and 142.7 ± 13.1 mm Hg in tertiles 1, 2 and 3 of dSBP/dHR, respectively.

Association of autonomic dysregulation with the nocturnal BP dipping pattern

The nocturnal BP dipping pattern and its association with dSBP/dHR were also investigated. The proportions of Risers (the nighttime SBP is greater than daytime SBP), Non-dippers (the nighttime SBP decreases between 0 and 10% compared with daytime SBP), Dippers (the nighttime SBP decreases between 10 and 20%) and Extreme-dippers (the nighttime SBP decreases more than 20%) were 10.4, 34.0, 47.0 and 8.6%, respectively. The incidence of Riser and Non-dipper decreased, whereas the incidence of Dipper and Extreme-dipper increased progressively and significantly from tertile 1 to tertile 3 ($P<0.001$, Table 2).

Association of autonomic dysregulation with BP and BP variability

As shown in Table 2, when the dSBP/dHR was used to divide the subjects into tertiles, we observed a progressive increase in the daytime SBP, a progressive decrease in the nighttime SBP, and consequently, a progressive increase in the day–night SBP gradient, from tertile 1 to tertile 3 ($P<0.001$). Moreover, the daytime and nighttime SBP s.d. were consistently and significantly increased from tertile 1 to tertile 3 ($P<0.01$). Both before and after adjustment for age, gender and 24-h mean SBP, all of these increasing or decreasing trends reached statistical significance ($P<0.01$). These findings were confirmed in our sensitivity analyses of men and women, separately (Figures 2 and 3).

Furthermore, the steepness of the slope between 24-h DBP and HR, termed dDBP/dHR, was calculated with the same algorithm as the dSBP/dHR. When the dDBP/dHR was divided into tertiles, with values of 0.015–0.428 mm Hg per beat min^{-1} for tertile 1, 0.429–0.650 mm Hg per beat min^{-1} for tertile 2 and 0.651–1.914 mm Hg per beat min^{-1} for tertile 3, the results were similar to those observed with

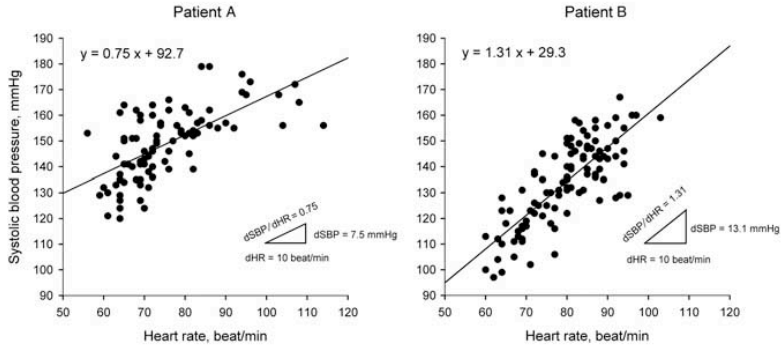

Figure 1 The definition of dSBP/dHR. Correlation plots between SBP and HR from the 24-h ambulatory blood pressure monitor are presented for patients A and B. The dSBP/dHR indicates the steepness of the slope of the relationship between the 24-h SBP (*y*-axis) and the HR (*x*-axis) for each subject. For example, for a 10 beat min $^{-1}$ change in HR, the SBP increased by 7.5 mm Hg in patient A and by 13.1 mm Hg in patient B.

Table 1 Characteristics of participants in subjects with different tertiles of dSBP/dHR

	dSBP/dHR			
	Tertile 1 0.003–0.465	*Tertile 2 0.465–0.803*	*Tertile 3 0.803–2.386*	P
Age, years	59.5 ± 10.0	57.8 ± 10.4	59.6 ± 10.0	0.15
Male gender, *n* (%)	89 (46.6)	84 (44.0)	112 (57.4)	**0.02**
Caucasian, *n* (%)	183 (95.8)	188 (98.4)	191 (98.0)	0.50
Body height, cm	166.2 ± 9.1	164.6 ± 8.6	166.6 ± 8.4	0.06
Body weight, kg	74.8 ± 12.0	72.8 ± 12.7	75.5 ± 12.3	0.09
Body mass index, g m^{-2}	27.0 ± 3.1	26.8 ± 3.1	27.1 ± 3.2	0.68
Smoke, *n* (%)	22 (11.5)	27 (14.1)	38 (19.5)	0.06
SBP, mm Hg	163.9 ± 8.2	163.3 ± 9.2	164.3 ± 8.4	0.87
DBP, mm Hg	95.8 ± 6.8	95.5 ± 7.2	95.6 ± 7.1	0.92
24-hour mean SBP, mm Hg	141.4 ± 13.3	139.6 ± 11.8	142.7 ± 13.1	**0.05**
24-hour mean DBP, mm Hg	86.5 ± 9.6	84.8 ± 9.3	84.9 ± 8.5	0.11
24-hour mean HR, b.p.m.	75.6 ± 10.2	75.5 ± 9.6	74.4 ± 9.6	0.43
Prior antihypertensive treatment, *n* (%)	110 (57.6)	112 (58.6)	105 (53.9)	0.67

Abbreviations: b.p.m., beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
Values are presented as mean ± s.d. or number with percentage in parenthesis. Smoke indicates the current smoking; dSBP/dHR indicates the steepness of the slope of the relationship between 24-hour SBP (y-axis) and HR (x-axis) for each subject.

Table 2 Comparisons of daytime and nighttime SBP and blood pressure variability between tertiles of dSBP/dHR

	dSBP/dHR				
	Tertile 1 0.003–0.465	*Tertile 2 0.465–0.803*	*Tertile 3 0.803–2.386*	P	P*
Daytime SBP, mm Hg	144.3 ± 13.1	144.8 ± 11.7	150.0 ± 12.8	<0.001	<0.001
Nighttime SBP, mm Hg	134.7 ± 16.2	127.7 ± 13.0	127.8 ± 15.6	<0.001	<0.001
Day–night SBP gradient, mm Hg	9.7 ± 11.4	16.8 ± 7.7	22.2 ± 10.5	<0.001	<0.001
Riser pattern, *n* (%)	32 (53.3)	20 (33.3)	8 (13.3)	<0.001	<0.001
Non-dipper pattern, *n* (%)	107 (54.6)	60 (30.6)	29 (14.8)	<0.001	<0.001
Dipper pattern, *n* (%)	47 (17.3)	102 (37.6)	122 (45.0)	<0.001	<0.001
Extreme-dipper pattern, *n* (%)	5 (10.0)	9 (18.0)	36 (72.0)	<0.001	<0.001
Daytime s.d., mm Hg	12.6 ± 3.3	12.5 ± 3.3	13.6 ± 3.4	0.002	0.007
Nighttime s.d., mm Hg	10.5 ± 3.2	10.4 ± 2.8	11.8 ± 3.5	<0.001	<0.001

Abbreviations: HR, heart rate; SBP, systolic blood pressure
Values are mean ± s.d. *P** indicated the *P* for trend after adjustment for age, sex and mean blood pressure. Daytime s.d. indicates time-weighted s.d. of SBP during awake time; Nighttime s.d. indicates time-weighted s.d. of SBP during sleeping time; Daytime and nighttime SBP are calculated with same algorithm; Day–night SBP gradient indicates the difference between daytime and nighttime SBP. Riser, non-dipper, dipper and extreme-dipper pattern was defined as nighttime SBP decreases greater than daytime SBP, and nighttime SBP decreases between 0% and 10%, between 10% and 20%, and over 20%, respectively, as compared with daytime BP. dSBP/dHR indicates the steepness of the slope of the relationship between 24-hour SBP (y-axis) and HR (x-axis) for each subject.

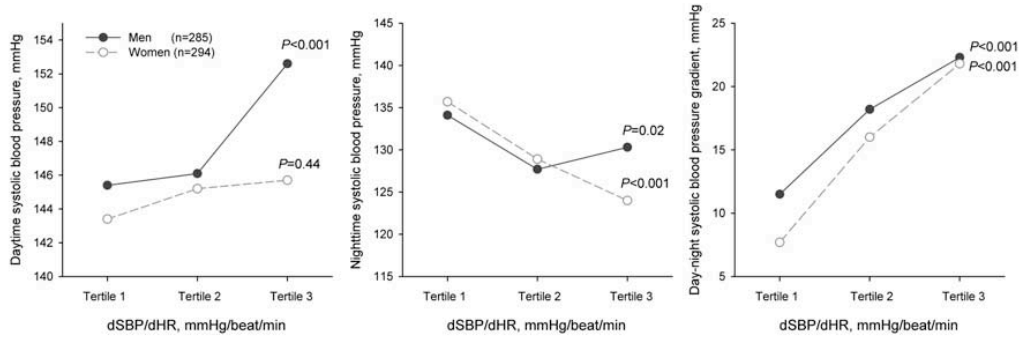

Figure 2 The association of the daytime and nighttime SBP and the day night SBP gradient with tertiles of dSBP/dHR by gender. Men are represented by filled circles with solid lines, and women are represented by unfilled circles with dashed lines. The dSBP/dHR indicates the steepness of the slope of the relationship between the 24-h SBP (*y*-axis) and the HR (*x*-axis) for each subject and is studied in tertiles. The day night SBP gradient indicates the difference between the daytime and nighttime SBP. A full color version of this figure is available at the *Hypertension Research* journal online.

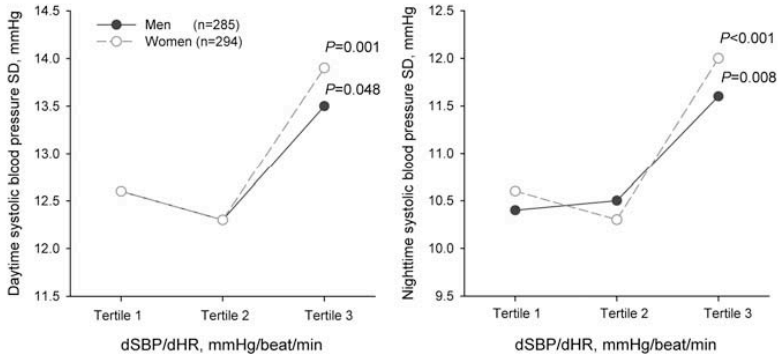

Figure 3 The association of the daytime and nighttime SBP s.d. with the tertiles of dSBP/dHR by gender. Men are represented by filled circles with solid lines, and women are represented by unfilled circles with dashed lines. The dSBP/dHR indicates the steepness of the slope of the relationship between the 24-h SBP (y-axis) and the HR (x-axis) for each subject and is studied in tertiles. The daytime s.d. indicates the time-weighted s.d. of the SBP during wakefulness; the nighttime s.d. indicates the time-weighted s.d. of the SBP during sleep. A full color version of this figure is available at the *Hypertension Research* journal online.

the SBP. The daytime DBP increased; however, the nighttime DBP decreased progressively and significantly from tertile 1 to 3 of the dDBP/dHR ($P<0.001$), with values of 88.9 ± 9.9, 89.9 ± 9.4, 90.6 ± 8.8 mm Hg for daytime DBP and 79.7 ± 10.3, 76.6 ± 9.7, 72.4 ± 9.2 mm Hg for nighttime DBP in tertiles 1, 2 and 3, respectively. Furthermore, both before and after adjustment for age, gender and 24-h mean DBP, the daytime and nighttime DBP s.d. increased consistently and significantly from tertile 1 to tertile 3 ($P<0.001$), with values of 9.4 ± 2.4, 9.4 ± 2.3, 10.1 ± 2.5 mm Hg for the daytime DBP s.d. and 8.2 ± 2.3, 8.4 ± 2.4, 9.5 ± 2.6 mm Hg for the nighttime DBP s.d. in tertiles 1, 2 and 3, respectively.

DISCUSSION

The main findings of the present study are twofold. First, ANS dysregulation, as evaluated with a novel index termed the dSBP/dHR derived from 24-h ABPM, was significantly associated with an increase in the daytime SBP, a decrease in the nighttime SBP, and therefore an increase in the day–night SBP gradient. Second, ANS regulation was also significantly associated with increased daytime and nighttime BPVs when evaluated by the s.d. of daytime and nighttime SBP. The sensitivity analysis confirmed these two findings in men and women, separately.

Based on readings of 24-h ABPM, we proposed a novel ambulatory index that represents the amplitude of change in SBP per 1-unit change in HR. This means that for a given change in HR, subjects with a higher dSBP/dHR are expected to have a greater modification in SBP than subjects with a lower dSBP/dHR. Similarly, Coats *et al.*[11] proposed another index calculated as the slope of the relationship between the R-R interval (*y*-axis) and the SBP (*x*-axis), and reported that it was inversely correlated with the baroreflex sensitivity as evaluated with the phenylephrine method ($r=-0.55$, $P<0.001$). A more complicated methodology involving spectral analysis of the R-R interval and the SBP variability was employed by Lucini *et al.* to investigate the impaired ANS regulation in hypertensive patients.[12,13] Compared with those parameters, our dSBP/dHR is the simplest index and is conveniently derived from 24-h ABPM, thereby rendering it more pragmatic for clinical practice.

In the literature, the relationship between HR and BP has been studied on conscious rats before and after spinal cord transaction[14] as a model in which the SBP–HR relationship indicates the autonomic nervous function. From a physiological point of view, the existing SBP–HR relationship could reflect not only the baroreflex sensitivity, but also sympathetic and parasympathetic cardiac control and vasomotor modulation. Therefore, the dSBP/dHR from the 24-h ABPM could be considered to be a robust yet practical index that represents the magnitude of CV ANS regulation. Moreover, we also found that the dDBP/dHR, another ANS regulation index derived with a similar algorithm, was also positively and significantly associated with BP and variability in the present study. This finding confirmed that ANS dysregulation, whether assessed by changes in the SBP or the DBP per unit change in HR, had a significant influence on BP and its variability. Furthermore, Eguchi *et al.*[15] reported that some ANS regulation indices, such as the nighttime HR variability and the HR–SBP relationship from 24-h ABPM, could significantly predict CV events in diabetic patients.

In this study, when the dSBP/dHR was divided into 3 tertiles, the subjects with the highest dSBP/dHR (tertile 3) also had the highest daytime SBP, the lowest nighttime SBP, and the largest day–night SBP gradient. From a pathophysiological viewpoint, this finding may be attributable to overactive sympathetic control (in the daytime) and overactive vagal control (in the nighttime) of the cardiac and vascular regulation system. Furthermore, subjects with higher dSBP/dHR values are prone to have a more variable SBP in both the daytime and the nighttime, indicating that the ANS dysregulation also contributes to the increased daytime and nighttime BPV. Ichihara *et al.*[16] reported a positive relationship between the BPV and arterial stiffness as assessed by pulse wave velocity in patients with hypertension, whereas in this study, we indicated that the BPV was also significantly associated with ANS dysregulation in both men and women. Further studies are warranted to elucidate whether arterial stiffening and ANS dysregulation synergistically or separately influence the arterial BPV. Moreover, in a meta-analysis, Webb *et al.*[17] summarized that calcium channel blockers and non-loop diuretics could effectively reduce the BPV in hypertensive patients. However, whether the effectiveness of these two agents on the BPV

control is due to arterial de-stiffening or to a re-balancing of the sympathetic and vagal CV regulation remains unknown. The underlying mechanisms need to be revealed by further fundamental studies.

It is counterintuitive that the dipper pattern (an increase in the day–night SBP gradient) is normally considered to a healthy regulation of BP, whereas increased beat-to-beat BPV always indicates an unhealthy BP regulation. This is a paradox, because the lowering of BP is often associated with an increase in BPV. For example, in this study, we found that the dSBP/dHR index of ANS regulation was associated with an increased BP and variability ($P<0.001$), but also with an increased incidence of the dipper pattern ($P<0.001$). Theoretically, the dipper pattern is defined by a presumption that the nighttime SBP should decrease 10–20% due to dominant vagal CV control at night, which suggests that this index is more sensitive to nighttime ANS regulation. In contrast, the dSBP/dHR is defined as the slope of regression plots of the 24-h BP recordings, which reflect 24-h BP regulation that includes not only the dominant nighttime vagal control but also the dominant daytime sympathetic control. This also helps to explain the observation that when both daytime and nighttime SBP are taken into account, the incidence of the extreme-dipper pattern is positively and significantly associated with the dSBP/dHR ($P<0.001$).

Our findings should be interpreted within the context of their limitations. First, the major limitation of this study is the lack of a validation test of the dSBP/dHR in assessing ANS regulation to compare it with other classical indices, such as the HR variability, the ratio between the R-R interval and SBP (baroreflex sensitivity), or serum catecholamine levels. However, the aim of this study is not to validate another index reflecting ANS regulation in a hemodynamic laboratory, but to propose a novel index that can be conveniently derived from a 24-h ABPM recording and is associated with daytime and nighttime BP variabilities, as well as with the BP itself. Our sensitivity analysis, conducted in men and women separately, also confirmed these finding. Further study is still warranted to test the accuracy of this index in reflecting ANS regulation. Second, because this is a cross-sectional study, we are not able to distinguish the cause and consequence of any two related factors; however, as an ongoing prospective clinical trial, future data would provide valuable information in this respect.

In summary, we found that ANS dysregulation as evaluated by a simple ambulatory index derived from a 24-h ABPM was significantly associated with an increased daytime SBP, a decreased nighttime SBP, and a consequently increased day–night SBP gradient, as well as with a more variable SBP in both the daytime and the nighttime in hypertensive patients.

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Résumés

Italien

NUOVI APPROCCI AL RISCHIO CARDIOVASCOLARE E METABOLICO

Riassunto

Il nostro lavoro di ricerca durante questi anni è stato caratterizzato da due tematiche principali : lo studio della meccanica vascolare et delle problematiche associate alla misurazione dei parametri emodinamici centrali ; la rilevanza dell'emodinamica per le malattie metaboliche. Il sistema cardiovascolare è caratterizzato, da un lato, dalle onde di pressione e di flusso, che rappresentano la propagazione dell'energia pulsatile del cuore ai tessuti; dall'altro lato, dalla complessa relazione esistente fra i due (la pression e il flusso), che consiste nel dialogo permanente fra il ventricolo sinistro e i vasi sanguigni. Le onde di pressione possono essere misurate con diverse tecniche, ma la calibrazione delle onde, che permette di ottenere i valori precisi di pressione arteriosa, comporta delle approssimazioni e delle limitazioni non ancora risolte. In particolare, differenti calibrazioni possono portare a valori molto diversi di pressione. Il nostro lavoro mostra che lo studio dell'amplificazione della pressione differenziale permette di superare i problemi legati alla calibrazione, et avrebbe un'importanza non trascurabile sulle strategie di valutazione et di riduzione del rischio cardiovascolare. I nostri risultati suggeriscono che l'emodinamica centrale sia uno strumento utile per studiare le modificazioni fisiopatologiche arteriose generate da malattie cardiovascolari e metaboliche. Nei pazienti affetti da tali malattie, la misura della rigidità arteriosa sembra poter quantificare il grado di danno arterioso et quindi il rischio cardiovascolare in eccesso, indipendentemente e aldilà dell'ipertensione arteriosa.

Parole chiave

Grossi tronchi arteriosi – Rigidità arteriosa – Velocità dell'onda di polso – Amplificazione – Pressione pulsata – Calibrazione – Rischio cardiovascolare – Malattie metaboliche – Diabete.

Anglais

NEW APPROCHES TO THE CARDIOVASCULAR AND METABOLIC RISK

Abstract

During these last years, our work has been focussed on two main topics: the investigation of vascular mechanics and of the issues associated with the measurement of central hemodynamic parameters on one hand; and the interest of hemodynamics concerning metabolic diseases on the other hand. The cardiovascular system is characterized by the pressure and flow waves, representing the propagation of the pulsatile power of the heart towards tissues; but also by the complex relation between them (the pressure and the flow), which is the permanent dialogue between the left ventricle and the arterial tree. Pressure waves can be measured by several techniques, but the wave calibration, which leads to precise values of blood pressure, is subject to approximations and limitations that are not yet solved. In particular, different calibrations may result in very different values of blood pressure. Our work shows that the investigation of the pulse pressure amplification can overcome those issues related to calibration, and it could deserve a non negligible importance in the cardiovascular risk assessment and reduction strategies. Our results suggest that central hemodynamics may allow the investigation of physiopathological arterial modifications in the course of cardiovascular and metabolic diseases. In patients presenting such diseases, the measurement of arterial stiffness seems to have the ability to quantify the degree of arterial impairment and, thus, the cardiovascular risk excess, independently of and above arterial hypertension.

Keywords

Large arteries – Arterial stiffness – Pulse wave velocity – Amplification – Pulse pressure – Calibration – Cardiovascular risk – Metabolic disease – Diabetes.

Francais

NOUVELLES APPROCHES DU RISQUE CARDIOVASCULAIRE ET METABOLIQUE

Davide AGNOLETTI

Résumé

Notre travail de recherche de ces dernières années a été caractérisé par deux thématiques principales : l'étude de la mécanique vasculaire et des problématiques associées à la mesure des paramètres hémodynamiques centraux ; l'intérêt de l'hémodynamique pour les maladies métaboliques. Le système cardiovasculaire est caractérisé, d'une part, par les ondes de pression et de flux qui représentent la propagation de l'énergie pulsatile du cœur aux tissus ; et d'autre part par la relation complexe entre les deux (pression et flux), qui est le dialogue permanent entre le ventricule gauche et les vaisseaux. Les ondes de pression peuvent être mesurées par différentes techniques, mais la calibration des ondes, permettant d'obtenir les valeurs précises de pression artérielle, comporte des approximations et des contraintes qui ne sont pas encore résolues. Notamment, des calibrations différentes peuvent aboutir à des valeurs de pression très différentes. Notre travail montre que l'étude de l'amplification de la pression pulsée permet de dépasser les problèmes liés à la calibration, et aurait une importance non négligeable en matière de stratégies d'évaluation et de réduction du risque cardiovasculaire. Nos résultats suggèrent que l'hémodynamique centrale est un outil permettant d'étudier les modifications physiopathologiques artérielles occasionnées par les maladies cardiovasculaires et métaboliques. Chez les patients porteurs de ces maladies, la mesure de la rigidité aortique semble être capable de quantifier le degré de l'atteinte artérielle et donc le sur-risque cardiovasculaire, indépendamment et au-delà de l'hypertension artérielle.

Mots clés

Gros troncs artériels – Rigidité artérielle – Vitesse de l'onde de pouls – Amplification – Pression pulsée – Calibration – Risque cardiovasculaire – Maladies métaboliques – Diabète.

NOUVELLES APPROCHES DU RISQUE CARDIOVASCULAIRE ET METABOLIQUE

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Résumé

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Mots clés

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