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Titre :

Paramètres hémodynamiques artériels : Approche du risque cardiovasculaire individuel et apport diagnostique dans la maladie coronaire

(Arterial hemodynamic parameters in risk assessment strategies and coronary artery disease screening)

Sous la Direction des Professeurs Jacques BLACHER et Michel E. SAFAR

JURY

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à Michel E. Safar

Ithaque

Costas Cavafis

Quand tu partiras pour Ithaque,
souhaite que le chemin soit long,
riche en aventures, en connaissances.

. . .

Garde sans cesse Ithaque présente à ton esprit.
Ton but final est d'y parvenir,

. . .

Et si tu la trouves pauvre, Ithaque ne t'a pas trompé.
Sage comme tu l'es devenu, avec tant d'expérience,
tu as surement compris ce que symbolisent les Ithaques.

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Présentation des publications et manuscrits

Article 1 : Yannoutsos A, Safar M.E., Blacher J. Le retentissement vasculaire de l'hypertension artérielle. Traité d'Angiologie, Encyclopédie Médico-Chirurgicale 2012. [19-0500]-Doi: 10.1016/S1290-0176(12)56550-6.

Article 2 : Yannoutsos A, Levy BI, Safar M.E., Slama G, Blacher J. Pathophysiology of hypertension: interactions between macro and microvascular alterations through endothelial dysfunction. J Hypertens 2014; 32(2):216-224.

Article 3 : Yannoutsos A, Rinaldi ER, Zhang Y, Protogerou AD, Safar M.E., Blacher J. Central hemodynamics in risk assessment strategies: additive value over and above brachial blood pressure. Curr Pharm Des 2015; 21(6):719-729.

Article 4 : Rinaldi ER, Yannoutsos A, Borghi C, Safar M.E., Blacher J. Central hemodynamics for risk reduction strategies: additive value over and above brachial blood pressure. Curr Pharm Des 2015; 21(6):730-736.

Article 5 : Kheder-Elfekih R, Yannoutsos A, Blacher J, London GM, Safar ME. Hypertension and chronic kidney disease: respective contribution of mean and pulse pressure and arterial stiffness. J Hypertens. 2015; 33(10):2010-2015.

Article 6 : Yannoutsos A, Ahouah M, Dreyfuss Tubiana C, Topouchian J, Touboul C, Safar M.E., Blacher J. Hemodynamic parameters in hypertensive diabetic patients. Submitted.

Article 7 : Yannoutsos A, Agnoletti D, Peroz-Froz J, Ly C, Lelong H, Topouchian J, Gilquin J, Boucly S, Rostane H, Safar M.E., Viard JP, Blacher J. Structural and functional arterial parameters, immunovirological control and vitamin D in HIV-infected patients. J AIDS Clin Res 2014; 5:375. doi: 10.4172/2155-6113.1000375.

Article 8 : Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar M.E, Ouerdane S, Blacher J. Aortic stiffness and cardiovascular risk in type 2 diabetes. J Hypertens 2013; 31(8):1584-1592.

Article 9 : Yannoutsos A, Ahouah M, Dreyfuss Tubiana C, Topouchian J, Safar M.E, Blacher J. Aortic stiffness improves the prediction of both diagnosis and severity of coronary artery disease. Submitted.

Paramètres hémodynamiques artériels : approche du risque cardiovasculaire individuel et apport diagnostique dans la maladie coronaire

Résumé

Le traitement combiné des facteurs de risque, notamment d'une hypertension artérielle et d'un diabète, reste insuffisant pour obtenir une réduction substantielle de la morbidité et de la mortalité cardiovasculaire. Ce risque résiduel peut être considéré comme le reflet d'une maladie artérielle infra clinique. La rigidité aortique et l'amplification de la pression pulsée sont des marqueurs hémodynamiques de l'atteinte artérielle et peuvent être étudiés de manière non invasive. L'objectif de ce travail a été dans un premier temps de décrire la maladie artérielle infra clinique et ses déterminants au sein de deux cohortes de patients à risque cardiovasculaire, hypertendus et/ou diabétiques et patients suivis pour une infection au virus de l'immunodéficience humaine (VIH). L'apport de la mesure non invasive de la rigidité aortique dans l'estimation du risque chez des patients diabétiques de type 2 a été évalué au sein d'une troisième cohorte. La deuxième partie de ce travail a été orientée vers le dépistage de la maladie coronaire. L'apport de la rigidité aortique dans l'amélioration de la valeur prédictive positive des examens de dépistage a été étudié dans le cadre d'un bilan cardiovasculaire réalisé en hôpital de jour. La conclusion principale de ce travail est que la maladie artérielle infra clinique permet d'une part de cibler le patient à haut risque et, d'autre part, d'améliorer le dépistage de la maladie coronaire à l'échelle individuelle. Le suivi de l'évolution, sous traitement, du degré de rigidité aortique et du niveau de pression pulsée centrale, en parallèle avec l'incidence des événements cardiovasculaires, doit permettre désormais de préciser l'importance de ces paramètres dans la prise en charge thérapeutique au-delà du contrôle des facteurs de risque « traditionnels ».

DISCIPLINE Santé et Santé Publique

MOTS-CLÉS Rigidité aortique, vitesse de l'onde de pouls, amplification, pression pulsée, pression centrale, maladie coronaire, hypertension artérielle, maladie diabétique.

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Arterial hemodynamic parameters in risk assessment strategies and coronary artery disease screening

Abstract

The combined treatment of risk factors, in particular hypertension and diabetes, appears insufficient to achieve a substantial reduction in cardiovascular morbidity and mortality. This residual risk may be indicative of adverse responses of subclinical, structural and functional arterial damage, illustrated by aortic stiffness and pressure wave reflection. These hemodynamic parameters are considered to be associated with central pulse pressure level. Central blood pressure appears closely related to the development and complications of atherosclerosis as well as microvascular organ damage. Firstly, the objective of this work was to study subclinical arterial damage by non-invasive measurement of aortic stiffness and pressure wave reflection, and their determinants, in two cohorts of patients with increased cardiovascular risk, hypertensive and / or diabetic patients and patients with HIV infection. In a third cohort, composed of patients with type 2 diabetes, we studied aortic stiffness as an independent marker of cardiovascular disease. Secondly, we investigated whether non invasive aortic stiffness assessment improves diagnostic accuracy of coronary artery disease screening. The contribution of aortic stiffness in improving the detection of coronary artery disease was studied as part of a complete cardiovascular evaluation. The main conclusion of this work is that assessment of subclinical arterial damage provide a clinically useful tool to individualize high-risk patients and to improve coronary artery disease screening. Prospective evaluation of aortic stiffness and central pulse pressure level in parallel with the incidence of cardiovascular events would clarify the importance of these hemodynamic parameters in the management of the residual risk, over and above the control of "traditional" risk factors.

Key words

Aortic stiffness, pulse wave velocity, pulse pressure amplification, central blood pressure, coronary heart disease, hypertension, diabetes.

Introduction générale

Malgré les avancées dans la prise en charge diagnostique et thérapeutique, la maladie cardiovasculaire représente toujours un enjeu principal de santé publique. L'amélioration de la prise en charge préventive d'un patient requiert une estimation fiable du risque cardiovasculaire individuel. Cette estimation est le reflet du statut vasculaire et métabolique du patient. Les outils dont dispose le clinicien en matière d'estimation du risque ne suffisent pas à intégrer tous les facteurs de risque cardiovasculaire, leur durée d'évolution et la qualité de leur contrôle à l'échelle individuelle. Ces outils ne permettent donc pas d'apprécier l'hétérogénéité du risque de survenue d'événements en présence de facteurs de risque. De plus, l'existence d'un risque résiduel persistant malgré le contrôle de la pression artérielle et de la glycémie chez les patients hypertendus et diabétiques, pourrait indiquer la présence d'une atteinte artérielle infra clinique insuffisamment prise en charge. En particulier, la rigidité aortique est considérée comme le marqueur de l'altération des propriétés structurales et fonctionnelles de la paroi des gros troncs artériels. Ce marqueur présente une valeur prédictive indépendante pour la mortalité totale et cardiovasculaire, mise en évidence pour la première fois dans une population de patients avec insuffisance rénale terminale (1). Parallèlement, l'existence d'une relation en courbe en J entre des objectifs trop stricts de pression artérielle ou de glycémie et la survenue d'événements souligne l'importance d'une prise en charge individualisée complétant la simple mesure de paramètres hémodynamiques ou biologiques de consultation.

Etroitement associé à l'enjeu reposant sur l'amélioration de la prise en charge préventive individuelle, le dépistage de la maladie coronaire reste limité par la valeur prédictive insuffisante des examens non invasifs de première intention. L'atteinte artérielle infra-

clinique, illustrée par la rigidité aortique et le phénomène des ondes de réflexion, permettrait d'intégrer l'intensité et la durée d'exposition aux facteurs de risque cardiovasculaire. Ces paramètres hémodynamiques artériels pourraient aider à améliorer l'estimation du risque individuel et le dépistage de la maladie coronaire.

Notre travail s'est articulé autour de quatre études observationnelles transversales chez des patients à risque cardiovasculaire.

Trois objectifs ont été fixés :

1) Déterminer les facteurs associés aux paramètres hémodynamiques artériels pour mieux comprendre et traiter la maladie artérielle infra clinique. Ces paramètres hémodynamiques ont été étudiés au sein de deux cohortes de patients, hypertendus et/ou diabétiques et patients avec infection au virus de l'immunodéficience humaine (VIH) lors d'un hôpital de jour programmé au cours du suivi pour bilan cardiovasculaire.
2) Evaluer l'apport de la mesure non invasive de la rigidité aortique dans l'estimation du risque cardiovasculaire au sein d'une troisième cohorte de patients, diabétiques de type 2.
3) Evaluer l'apport de la mesure non invasive de la rigidité aortique dans l'amélioration du dépistage de la maladie coronaire. Cette étude a été réalisée dans le cadre d'un hôpital de jour programmé pour bilan cardiovasculaire au sein de la cohorte de patients hypertendus et/ou diabétiques.

Les résultats de ces études seront présentés après avoir exposé les données de la littérature soulignant l'importance de ces paramètres artériels dans l'amélioration de la prise en charge du patient à risque cardiovasculaire.

Chapitre 1
Maladie artérielle chez le patient hypertendu

L'hypertension artérielle constitue un facteur de risque majeur de complications cardiovasculaires, cérébrovasculaires et rénales par l'intermédiaire d'atteintes macro- et micro vasculaires. La rigidité aortique et la raréfaction artériolo-capillaire sont considérées comme des dénominateurs communs de l'atteinte des organes cibles et des facteurs prédictifs indépendants d'événements cardiovasculaires chez les patients hypertendus (2-5). Les altérations des propriétés de la paroi des gros troncs artériels et les altérations artériolo-capillaires paraissent corrélées entre elles. Elles sont la traduction de l'atteinte artérielle au cours de la maladie hypertensive mais peuvent également être considérées comme les causes d'une majoration de la pression artérielle. L'atteinte artérielle associée à la présence de facteurs de risque autres que l'hypertension, en particulier la maladie diabétique et la maladie rénale chronique, pourrait présenter un rôle précurseur dans la pathogenèse de l'hypertension artérielle (6,7). La relation temporelle entre la présence d'une hypertension artérielle et les altérations macro et micro vasculaires semble par conséquent être bidirectionnelle (8). L'hypothèse d'un rôle précurseur de la rigidité aortique et des anomalies de la microcirculation dans l'apparition d'une hypertension artérielle a suscité l'intérêt pour de nouvelles perspectives dans la prise en charge préventive et thérapeutique des patients.

1.1 Définitions en hémodynamique

Les gros troncs artériels sont caractérisés par leur fonction de « conduit », assurant la connexion entre le cœur et les organes, et « d'amortissement » du débit sanguin pulsé

provenant du cœur en un débit continu en périphérie (9). La compliance et la distensibilité sont les deux propriétés mécaniques physiologiques principales de la paroi aortique. Elles sont le reflet de la capacité d'amortissement de la pulsatilité artérielle entre le ventricule gauche et l'aorte proximale. L'élasticité de la paroi aortique lui permet de se déformer de manière progressive, consécutivement à la contrainte mécanique liée à la pression. Le rapport entre contrainte appliquée (pression) sur déformation (étirement pariétal) est défini par le module de Young, indice caractéristique de l'élasticité de la paroi aortique. Plus cet indice est élevé, plus la paroi de l'aorte est rigide. La relation entre contrainte et déformation pariétale n'est pas linéaire mais est représentée par une courbe concave : pour des contraintes mécaniques faibles, l'étirement pariétal (augmentation du diamètre interne de l'aorte) augmente presque linéairement. A des niveaux de pression artérielle plus élevés, cette déformation circonférentielle de la paroi aortique est, de manière adaptée, moindre. La distensibilité de la paroi aortique est définie par sa capacité de déformation sous l'effet d'une contrainte et dépend essentiellement des propriétés élastiques de la paroi ; la compliance aortique est définie par la capacité d'augmentation du volume artériel pour une contrainte de pression intraluminale imposée. A la fin de la systole cardiaque, un tiers du volume sanguin éjecté est emmagasiné en périphérie au niveau des parois de l'aorte ascendante. Ce volume sanguin est ensuite restitué par la rétraction élastique de la paroi de l'aorte pendant la diastole cardiaque. Ainsi, les propriétés viscoélastiques de la paroi vasculaire permettent à l'aorte de résister à l'expansion systolique suite à l'éjection ventriculaire gauche et de réduire la pulsatilité artérielle, transformant le flux sanguin pulsatile en un écoulement plus régulier et continu en aval. Une perfusion d'organe optimale est ainsi maintenue au cours de la diastole cardiaque et la contrainte pulsatile imposée à la microcirculation est limitée (10). Le modèle de Windkessel a été proposé dès la fin du 19ème siècle pour décrire l'interaction entre le ventricule gauche et l'aorte en faisant intervenir deux paramètres physiologiques que sont la compliance

artérielle et la résistance périphérique. Ce modèle a permis d'illustrer la relation entre variation de pression et élasticité de la paroi artérielle. Le physiologiste Otto Frank proposa le modèle d'un circuit hydraulique fermé, constitué d'une pompe et d'une chambre à air se remplissant d'eau. L'eau ainsi pompée comprime la poche d'air qui en retour expulse le volume d'eau à l'extérieur de la chambre avec une constante de temps qui est fonction de la compliance de la chambre (plus la chambre est compliante, plus le volume d'eau stoké sera important) et de la résistance périphérique d'aval. Ce modèle, dit « Windkessel », a permis de modéliser la mécanique du cycle cardiaque et la transformation du flux sanguin pulsatile à la sortie de la pompe en un écoulement continu d'aval pendant la diastole par analogie à la compliance de la paroi de l'aorte ascendante. Ainsi, dès la fermeture de la valve aortique, la pression diminue de façon exponentielle selon une constante de temps (τ) qui est fonction des résistances périphériques (R) et de la compliance de la paroi artérielle (C) selon la relation $\tau = R * C$. Comme $R = P / Q$, la relation entre la pression artérielle moyenne (P), le débit sanguin moyen (Q) et la compliance artérielle (C) en est ainsi déduite.

Le versant artériel de la microcirculation est représenté par les petites artères (diamètre inférieur à 150 microns) et les artérioles pré-capillaires (10). Le tonus myogénique est une propriété physiologique inhérente et essentielle du muscle lisse vasculaire des petites artères de résistance. Il rend compte de leur capacité à se contracter en réponse à une augmentation des contraintes mécaniques pariétales liées à la pression. Cette propriété physiologique du muscle lisse vasculaire rend compte de la capacité d'autorégulation de la perfusion de l'organe. La vasoconstriction adaptative liée au tonus myogénique est imperceptible au niveau des gros troncs artériels et augmente au fur et à mesure que le calibre artériel diminue, devenant maximale dans les artérioles pré-capillaires. C'est un mécanisme essentiel de contrôle de la tension pariétale qui a pour objectif principal de protéger les capillaires fragiles

d'une augmentation de la pression sanguine transmurale.

Un second mécanisme de protection de la microcirculation vis-à-vis de la pulsatilité du flux artériel est représenté par le mismatch d'impédance entre l'aorte et ses principales branches (11). Ce mécanisme de protection est en particulier essentiel pour le cerveau et les reins, organes à haut débit de perfusion avec résistances d'aval basses. L'impédance dépend des propriétés visco-élastiques pariétales et du diamètre d'une artère donnée et représente la capacité d'un territoire vasculaire à se protéger contre un influx pulsatile. Ainsi, l'impédance est inversement corrélée à l'élasticité de la paroi artérielle. D'importantes disparités d'impédance existent de manière physiologique entre l'aorte, très compliante, et ses différentes branches artérielles. La transmission de l'énergie pulsatile à la microcirculation et aux capillaires est donc limitée.

La courbe de pression artérielle peut être définie par une composante continue, la pression artérielle moyenne, et une composante pulsatile, qui est la différence entre la pression artérielle systolique et la pression artérielle diastolique. La fonction cardiaque, les propriétés visco-élastiques de la paroi aortique et les résistances vasculaires systémiques modulent de manière différente le niveau de pression artérielle moyenne et pulsée. Le débit cardiaque et les résistances vasculaires périphériques déterminent la composante continue de la pression artérielle. La pression pulsée dépend du volume d'éjection systolique et des propriétés structurales et fonctionnelles de la paroi aortique. Les pressions artérielles diastolique et moyenne diminuent progressivement, bien que très modérément, de l'aorte vers les artères périphériques alors que les pressions artérielles systolique et pulsée montrent une nette augmentation du centre vers la périphérie. L'amplification physiologique de la pression artérielle pulsée illustre le phénomène de propagation et de réflexion des ondes de pression. A

chaque point de l'arbre artériel, la forme de l'onde de pression est déterminée par la somme de l'onde de pression incidente (secondaire à l'éjection ventriculaire) et des ondes de pression réfléchies provenant des bifurcations artérielles périphériques et des petites artères de résistance. L'onde de pression présente donc un pic systolique précoce et un pic systolique tardif secondaire au retour des ondes réfléchies. Les plus petites artères et artérioles de résistance répondent de manière adaptée à l'augmentation des contraintes mécaniques par une réduction de leur lumière artérielle secondaire au tonus myogénique. Cette caractéristique physiologique des artérioles distales rend compte en grande partie des résistances périphériques totales (9).

L'amplification de la pression pulsée est définie par le rapport entre la pression pulsée périphérique (brachiale) et centrale (aortique ou carotidienne). Le phénomène d'amplification diminue physiologiquement avec l'âge et dépend du temps de transit et de l'amplitude des ondes réfléchies (12).

Le temps de transit est associé à la vitesse de propagation des ondes de pression et au rythme cardiaque. La vitesse (c) à laquelle les ondes de pression se propagent est physiologiquement liée à l'élasticité et à la géométrie de la paroi artérielle, et dépend donc du niveau de pression artérielle, ainsi qu'à la densité du sang. Ce concept est illustré par les modèles mathématiques de Moens-Korteweg et de Bramwell-Hill :

- Equation de Moens-Korteweg : $c^2 = (h * E) / (2 * r * \rho)$, où E est le module de Young, h est l'épaisseur de la paroi, r le rayon de l'artère et ρ la densité du sang.
- Equation de Bramwell-Hill, $c^2 = V/\rho * 1/C$, où V est le volume, C la compliance et ρ la densité du sang.

La compliance artérielle diminue progressivement le long de l'arbre artériel vers la périphérie avec pour conséquence une augmentation de la vitesse de propagation de l'onde incidente et

une diminution du temps de transit des ondes réfléchies (13). L'augmentation du rythme cardiaque est également associée à une réduction du temps de transit des ondes de réflexion. Ceci a pour conséquence une amplification accrue de la pression artérielle systolique et pulsée du centre vers la périphérie, indépendamment du niveau de rigidité artérielle (14). Et inversement, l'amplification de la pression pulsée tend à diminuer avec une fréquence cardiaque réduite.

L'amplitude des ondes réfléchies dépend en partie du tonus vasomoteur des artérioles de résistance et de la densité artériolo-capillaire. Au niveau des sites périphériques, les ondes de pression réfléchies amplifient physiologiquement la pression artérielle systolique. Au niveau central, les ondes réfléchies arrivent à la fin de la systole cardiaque, renforçant ainsi la perfusion coronarienne pendant la diastole et limitant la post-charge du ventricule gauche (9) **(figure 1)**. Il existe un recoupement manifeste entre les pressions systoliques centrales des adultes hypertendus et des adultes ayant des valeurs dites normales de pression artérielle brachiale (12). Plus de 70 % des adultes (hommes et femmes) ayant une pression artérielle systolique brachiale considérée comme normale haute seraient ainsi exposés à une pression systolique centrale similaire à celle des adultes avec hypertension artérielle légère. Le sexe influence également l'amplification, qui est physiologiquement plus élevée chez les hommes que chez les femmes, indépendamment des différences de taille (12). Une différence de pression pulsée centrale et périphérique reste encore mesurable chez les femmes à des âges extrêmes (> 80 ans) (12).

L'âge et le sexe représentent deux facteurs déterminants des propriétés vasculaires. L'intérêt clinique du vieillissement artériel est classiquement illustré par la valeur pronostique des pressions artérielles systolique et diastolique pour le risque coronarien en fonction de l'âge. Chez l'adulte jeune (<50 ans), la pression artérielle diastolique est associée à la plus

forte valeur prédictive pour le risque coronarien (15). Chez le patient de plus de 60 ans, les composantes systolique et pulsée de la pression artérielle sont plus représentatives du risque d'événements cardiovasculaires. Il existe en parallèle une relation inverse entre la pression artérielle diastolique et le risque coronarien chez le sujet âgé (15,16).

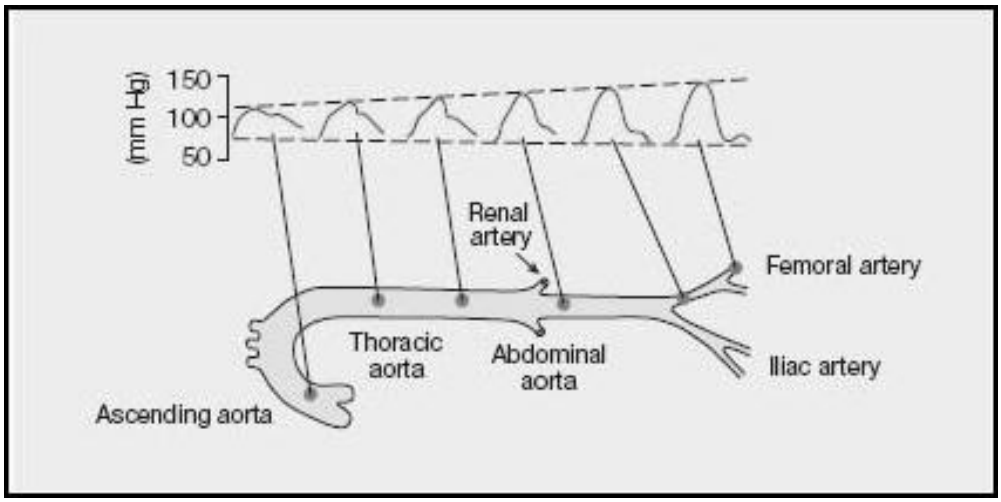

Figure 1: Amplification de la pression artérielle systolique et pulsée le long de l'arbre artériel chez un jeune individu. Référence 9: Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

La rigidité aortique et le phénomène d'amplification de la pression artérielle peut rendre compte de la relation entre composantes de la pression artérielle et risque cardiovasculaire au cours du vieillissement (17). Chez l'adulte jeune, l'amplification tend à diminuer quand la pression diastolique augmente. Une augmentation de l'intensité des ondes de réflexion pourrait expliquer cette relation inverse entre amplification et pression diastolique, non retrouvée chez le sujet âgé. La pression diastolique chez un sujet jeune apparaît donc comme « le reflet » de la pression pulsée centrale (17). Chez l'adulte d'âge moyen, la perte progressive de la compliance aortique est associée à une augmentation de la vitesse de propagation des ondes de pression. Il a été initialement supposé que le retour prématuré au niveau central, lors de la systole cardiaque, des ondes de réflexion contribuait majoritairement à l'augmentation

de la pression artérielle centrale systolique et pulsée associée à une atténuation du phénomène d'amplification. Cependant, le profil d'éjection du ventricule gauche ainsi que la forme de l'onde de pression incidente doivent également être considérés. Au cours du vieillissement physiologique, l'amplitude des ondes de pression réfléchies n'est que peu modifiée alors que l'amplitude de l'onde pression incidente augmente de manière continue. Cette observation suggère que l'augmentation de la pression pulsée centrale et périphérique avec l'avancée en âge est principalement en rapport à une augmentation de la rigidité de l'aorte ascendante. Chez l'adulte plus âgé, après 60 ans, la composante pulsatile de la pression artérielle, et non la pression artérielle moyenne, est corrélée au risque de premier événement cardiovasculaire (18). Plus particulièrement, l'amplitude de l'onde de pression incidente (une mesure de la rigidité de l'aorte proximale) apparaît comme un facteur prédictif indépendant du risque cardiovasculaire. L'amplitude des ondes de pression réfléchies et le coefficient de réflexion global (rapport entre l'amplitude des ondes réfléchies et l'amplitude de l'onde incidente) n'apparaissent pas corrélés au risque de premier événement (18). La majoration de la rigidité aortique entraînerait la disparition progressive du mismatch d'impédance physiologique entre l'aorte et ses collatérales. La perte de ce gradient physiologique de rigidité artérielle pourrait être associée à une atténuation du phénomène d'amplification. La réflexion des ondes de pression étant réduite, celles-ci seraient plus facilement transmises à la microcirculation périphérique.

Les paramètres hémodynamiques artériels pourraient également rendre compte des particularités cliniques décrites entre hommes et femmes en termes de morbidité cardiovasculaire (19). La morbidité et la mortalité sont plus importantes chez les femmes après un infarctus du myocarde (20), avec une fréquence plus élevée d'insuffisance cardiaque à fraction d'éjection préservée (21). Au cours du vieillissement, l'augmentation de la pression

pulsée est plus prononcée chez les femmes que chez les hommes (22). De plus, l'augmentation avec l'âge de la pression systolique centrale semble plus importante chez les femmes que chez les hommes, secondaire à une atténuation plus marquée du phénomène d'amplification chez les femmes de plus de 50 ans. Des différences significatives pour les propriétés artérielles ont également été décrites. L'augmentation de la pression systolique centrale, plus importante chez les femmes, pourrait être expliquée par une plus grande amplitude de l'onde de pression incidente et des ondes réfléchies (23). L'augmentation de la post-charge ventriculaire gauche, plus prononcée chez les femmes, est associée à l'hypertrophie ventriculaire gauche et à l'altération de la relaxation ventriculaire gauche diastolique. Cette observation peut rendre compte chez les femmes âgées d'une prédisposition à l'insuffisance cardiaque à fraction d'éjection ventriculaire gauche préservée.

1.2 Le retentissement vasculaire de l'hypertension artérielle (Article 1).

1.2.1 Introduction de l'article 1

L'hypertension artérielle occupe le premier rang à l'échelle mondiale en termes de mortalité attribuable de par sa fréquence élevée et de la morbidité générée. L'hypertension artérielle est définie par une pression artérielle brachiale systolique (PAS) ≥140 mm Hg et/ou une pression artérielle brachiale diastolique (PAD) ≥90 mm Hg chez les adultes jeunes, d'âge moyen et les sujets âgés. L'hypertension artérielle est un facteur de risque majeur de maladie coronaire et d'accident vasculaire cérébral (24), d'insuffisance cardiaque (25), d'insuffisance rénale terminale (26) et de démence (27). Le bénéfice du traitement antihypertenseur a clairement été démontré en termes de morbi-mortalité cardiovasculaire (24), cérébrovasculaire (28) et de néphroprotection (29). Une baisse de 7 % de la mortalité par coronaropathie et de 10 % de la mortalité par accident vasculaire cérébral est attendue pour

une réduction de 2 mm Hg de la pression systolique (24). Chez les patients hypertendus âgés, l'efficacité du traitement antihypertenseur est également mise en évidence par plusieurs études (30). L'étude SHEP (31) retrouvait une réduction significative de l'incidence d'accident vasculaire cérébral et d'infarctus du myocarde chez les patients ayant des chiffres tensionnels en moyenne à 142/68 mm Hg comparativement à ceux avec une tension artérielle à 171/77 mm Hg. L'étude HYVET (32) conforte l'existence d'un bénéfice cardiovasculaire du traitement antihypertenseur dans le grand âge. Le traitement antihypertenseur chez les patients hypertendus de 80 ans et plus réduit significativement la mortalité globale, la mortalité par accident vasculaire cérébral et la morbidité cardiovasculaire. De plus, le traitement de l'hypertension artérielle présente un effet préventif dans la survenue de troubles cognitifs.

Les notions de risque attribuable, de réversibilité du risque et l'existence d'outils thérapeutiques efficaces encouragent à l'exigence en matière de contrôle tensionnel. Celui-ci reste encore insuffisant, effectif seulement chez la moitié des 12 millions de patients hypertendus traités en France. Les résultats de l'étude nationale nutrition santé (ENNS) mettent l'accent sur l'importance du problème de santé publique que représente l'hypertension artérielle, par sa prévalence et son contrôle insuffisant dans une population d'adultes âgés de 18 à 74 ans en France de 2006 et 2007 : 23 % des adultes sont hypertendus, seuls 15,6 % sont traités. Le contrôle tensionnel n'est effectif que chez la moitié des patients traités. L'hypertension artérielle représente le critère le plus fréquent du syndrome métabolique d'après les résultats de l'étude française DESIR (33). L'association entre hypertension artérielle et insulino-résistance rend plus difficile le contrôle tensionnel et représente un effet multiplicateur sur le risque global (34).

Une stratégie thérapeutique personnalisée est recommandée (35). A l'exception de l'effet protecteur des bêtabloquants dans l'insuffisance cardiaque ou initiés précocement après un infarctus de myocarde et de celui plus discret des inhibiteurs calciques dans la protection cérébrale, l'accent est mis sur l'importance de la réduction tensionnelle dans la prévention cardiovasculaire chez le patient hypertendu. Le choix du traitement est fonction de l'existence de comorbidités contre indiquant certaines classes médicamenteuses et de la notion de persistance au traitement associant tolérance, efficacité et observance.

L'article présenté ici décrit les complications macro vasculaires et micro vasculaires dans l'atteinte des organes cibles chez le patient hypertendu ainsi que les implications thérapeutiques. L'importance du dépistage de l'atteinte artérielle infra clinique dans l'estimation du risque cardiovasculaire est introduite.

1.2.2 Article 1

A. Yannoutsos, M.E. Safar, J. Blacher.

Le retentissement vasculaire de l'hypertension artérielle.

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19-0500

Retentissement vasculaire de l'hypertension artérielle

A. Yannoutsos, M. Safar, J. Blacher

Maladie systémique silencieuse, l'hypertension artérielle est impliquée dans l'atteinte de tous les organes par l'intermédiaire de complications macro- et microvasculaires. Les anomalies structurales et fonctionnelles artérielles, conséquences entre autres du stress oxydatif et d'une dysfonction endothéliale induits par l'augmentation chronique des contraintes mécaniques, sont à l'origine de l'athérosclérose et de l'artériolosclérose touchant la vascularisation des organes cibles. Principale cause de morbimortalité cardio- et cérébrovasculaire, l'athérosclérose est caractérisée par l'organisation de plaques à part lipidique dont la rupture entraîne des complications thromboemboliques à l'origine d'accidents ischémiques coronariens et cérébraux en particulier. L'artériolosclérose se définit par une rigidité et un épaississement diffus de l'intima évoluant vers un mode occlusif des petites artères périphériques, en particulier épicardiques et intrarénales. L'optimisation de la stratégie thérapeutique implique l'identification des patients les plus à risque. Le dépistage des facteurs de risque classiques est la première étape dans l'évaluation du risque cardiovasculaire global. Les altérations artérielles subcliniques, observées à un stade précoce de la maladie cardiovasculaire et de l'exposition aux facteurs de risque, représentent un outil complémentaire d'évaluation du risque cardiovasculaire. Cible et dénominateur commun des complications cardiovasculaires, les anomalies structurales et fonctionnelles des artères peuvent être étudiées par des méthodes non invasives : mesure de la vitesse de l'onde de pouls, de l'épaisseur intima-média, de l'indice de pression systolique. Ces marqueurs représentent un outil essentiel dans la stratégie de dépistage du risque artériel chez le patient hypertendu.

Mots clés : Dysfonction endothéliale ; Athérosclérose ; Risque cardiovasculaire ; Marqueur de risque ; Dépistage

Plan

Introduction

L'hypertension artérielle (HTA), facteur de risque cardiovasculaire majeur, est un important problème de santé dont la prise en charge reste insuffisante, malgré son impact majeur dans la morbimortalité cardio- et cérébrovasculaire, ainsi que dans l'altération de la fonction rénale. L'augmentation du risque cardiovasculaire est proportionnelle à l'augmentation des chiffres tensionnels, et ce même pour une tension « normale haute ». Plus de 26 % de la population mondiale est hypertendue et ce chiffre pourrait augmenter d'ici 2025 [1]. En France, selon les données de l'Étude nationale nutrition santé (ENNS) de 2006, 31 % des adultes sont hypertendus, près de 20 % des hypertendus connus ne sont pas traités et lorsqu'ils le sont, seul un patient sur deux est équilibré. De plus, l'existence d'un risque résiduel sous traitement [2], après ajustement aux autres facteurs de risque et pour un même niveau de pression artérielle, doit encourager le praticien à être plus exigeant en matière d'objectifs tensionnels et à individualiser la stratégie thérapeutique, débutant le traitement antihypertenseur plus précocement chez les patients les plus à risque et renforçant la prise en charge des facteurs de risque associés. L'évaluation du risque cardiovasculaire est par conséquent une étape essentielle dans l'optimisation de la prise en charge thérapeutique du patient

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hypertendu. Le calcul du score de Framingham, représentant le risque absolu de survenue du premier événement coronarien à 10 ans, est largement validé et utilisé. Cependant, la prédiction du risque est imparfaite chez certains patients, en particulier les plus jeunes. Selon les recommandations françaises, le haut risque cardiovasculaire est défini par la présence d'une HTA permanente sévère, d'une atteinte des organes cibles (hypertrophie ventriculaire gauche, altération du débit de filtration glomérulaire ou présence de microalbuminurie), de l'association à un diabète de type 2 ou à trois facteurs de risque, et/ou en prévention secondaire d'une maladie cardiovasculaire avérée. Le risque artériel d'un patient hypertendu en prévention primaire avec des chiffres tensionnels modérément élevés et ayant moins de trois facteurs de risque peut être sous-évalué en l'absence de prise en compte d'une éventuelle atteinte artérielle infraclinique. La présence de celle-ci permettrait de reclasser le patient dans la catégorie à haut risque et d'encourager le renforcement de sa prise en charge sur la réduction du risque cardiovasculaire global. Le développement des techniques d'exploration vasculaire non invasives, en particulier par échographie-Doppler et échotracking, a permis le dépistage avec une grande reproductibilité des anomalies artérielles morphologiques et fonctionnelles.

■ Des anomalies structurales aux anomalies fonctionnelles artérielles

La courbe de pression artérielle peut être divisée en deux composantes. La première, continue, est à rapporter à la pression moyenne, produit du débit cardiaque par les résistances périphériques, et influencée par le calibre des petites artères. La deuxième, pulsatile, est à rapporter à la pression pulsée, différence entre pression systolique et diastolique, tenant compte du mouvement alternatif de la pompe cardiaque. Elle dépend de la vitesse d'éjection ventriculaire, de la rigidité aortique, et du transit des ondes de réflexion. D'après les caractéristiques de la courbe de pression artérielle, la grande hétérogénéité morphologique, histologique, hémodynamique et pathologique du système artériel peut facilement se comprendre. Les grandes artères élastiques ont principalement une fonction de conduit et d'amortissement, transformant le débit sanguin pulsé naissant du cœur en débit continu au niveau des organes. Elles sont caractérisées par leur compliance et leur distensibilité : une partie du volume d'éjection systolique s'accumulant autour de la paroi artérielle à la fin de la systole, est restituée en périphérie par la rétraction élastique pariétale durant la diastole. C'est l'effet Windkessel, permettant un débit sanguin tissulaire continu. Les petites artères musculaires sont caractérisées par leur fonction de distribution et de résistance périphérique. Le remodelage artériel dans l'HTA est expliqué par des phénomènes mécaniques adaptatifs mais aussi inflammatoires. L'augmentation chronique des contraintes mécaniques exercées sur l'endothélium vasculaire stimule des mécanismes inflammatoires et oxydants à l'origine de l'altération de la vasoréactivité artérielle. L'implication du stress oxydatif dans la genèse des maladies cardiovasculaires devient mieux appréciée.

Dysfonction endothéliale et stress oxydatif

L'endothélium vasculaire, volumineuse glande paracrine de l'organisme constituée d'une couche monocellulaire tapissant la face interne des vaisseaux et des cavités cardiaques, possède une activité sécrétoire, de transferts cellulaires et de régulation de la vasomotricité. De nombreuses substances vasoactives ayant des effets vasodilatateurs (en particulier le monoxyde d'azote) ou vasoconstricteurs (l'endothéline), myorelaxants et antiagrégants sont sécrétées par l'endothélium et permettent l'autorégulation du calibre artériel et des résistances vasculaires. Quelle que soit la nature de l'agression cellulaire (inflammatoire, infectieuse, hypoxique, mécanique ou traumatique), les conséquences sur l'endothélium vasculaire sont marquées par l'altération de sa perméabilité, l'adhésion leucocytaire, la sécrétion de substances vasoactives et l'acquisition d'une activité procoagulante. La dysfonction endothéliale, à la fois cause et conséquence de l'augmentation chronique des chiffres tensionnels, est donc étroitement associée à l'inflammation vasculaire et au stress oxydatif, et représente l'étape précoce de l'athérogenèse. Dans l'exemple de l'HTA, l'augmentation des contraintes mécaniques sur la paroi artérielle entraîne une agression cellulaire à l'origine de la production de cytokines stimulant différentes enzymes intracellulaires, dont les nicotinamide-adénosine-dinucléotide phosphate (NADPH)-oxydases, source importante de dérivés actifs de l'oxygène. Ces radicaux libres stimulent à leur tour les facteurs de transcription des gènes des cytokines, à l'origine de boucles d'amplification entre stress oxydatif et inflammation. Ce stimulus de production anormale de radicaux libres entraîne un déséquilibre pro-oxydant, en défaveur de la synthèse de monoxyde d'azote principal facteur vasodilatateur, et favorise l'oxydation des lipoprotéines de basse densité (*low density lipoproteins* [LDL]) du cholestérol, la libération de facteurs pro-inflammatoires ou favorisant la prolifération cellulaire. De multiples dysfonctionnements phénotypiques cellulaires sont ainsi la conséquence du stress oxydatif et de l'inflammation :

- les propriétés antiagrégantes et de vasodilatation de l'endothélium sont altérées au profit de propriétés prothrombotiques et vasoconstrictrices ;
- les LDL oxydés, cytotoxiques pour les cellules endothéliales, stimulent l'agrégation plaquettaire, la synthèse de substances procoagulantes et de facteurs de croissance entraînant ainsi la multiplication des cellules musculaires lisses ;
- les cellules musculaires lisses contractiles acquièrent un phénotype sécrétoire, augmentant la matrice extracellulaire par synthèse de collagène et ainsi l'épaisseur intima-média ;
- les macrophages, monocytes et cellules musculaires lisses, opsonisant les LDL oxydés, deviennent des cellules spumeuses initiant la formation de la plaque d'athérome.

L'inflammation occupe donc un rôle primordial dans la pathogenèse de la maladie athéroscléreuse. La protéine C réactive (CRP), marqueur systémique de l'inflammation synthétisée dans le foie sous l'action des cytokines, est le témoin d'une réaction inflammatoire aiguë mais aussi chronique à bas bruit. Plusieurs travaux se sont intéressés à la CRP comme marqueur précoce et acteur de l'athérogenèse, en particulier dans la maladie coronarienne [3, 4]. Molécule effectrice, opsonine favorisant la phagocytose des LDL oxydés par les macrophages, elle recrute les cellules inflammatoires, active les cellules musculaires lisses, altère la vasoréactivité et initie la coagulation favorisant le phénomène de thrombose vasculaire. Ainsi, la CRP favorise la genèse et la progression de la plaque d'athérosclérose : le processus inflammatoire est à l'origine d'une déstabilisation de la chape fibreuse entraînant la rupture de plaque et le risque de complications thromboemboliques. La CRP semble par conséquent être un marqueur de risque cardiovasculaire et module la valeur prédictive d'autres facteurs de risque tels que la dyslipidémie. Cependant, de nombreuses limites et facteurs confondants augmentent le taux de CRP. Il n'existe pas de recommandations précises sur l'utilité de son dosage, et à l'heure actuelle, le dépistage des facteurs de risque classiques prime sur celui des marqueurs biologiques dans l'évaluation du risque cardiovasculaire individuel.

Anomalies structurales de la paroi artérielle

Les anomalies pariétales des artères s'associent à une altération des mécanismes de régulation de la pression artérielle mais aussi de la fonction cardiaque. Quatre processus cellulaires, croissance, hypertrophie, apoptose et production ou dégradation de matrice extracellulaire, interviennent dans le remodelage vasculaire, et dépendent de facteurs de croissance, de substances vasoactives et de stimuli hémodynamiques [5].

Remodelage vasculaire

Concept clé de la physiopathologie de l'HTA et de son retentissement, le remodelage vasculaire est représenté sur le plan structural par un épaississement pariétal, processus adaptatif en présence d'une augmentation des contraintes mécaniques [6], mais

avec des conséquences pathologiques sur le long terme, responsable de l'accélération des lésions d'athérosclérose. Il diffère selon le site artériel concerné [7] : l'hypertrophie excentrique est caractéristique du remodelage pariétal des grosses artères élastiques alors que les artères musculaires présentent un remodelage concentrique (« eutrophique interne») sans augmentation de la surface de section, entraînant une diminution de la lumière du vaisseau.

La couche moyenne de la paroi artérielle, la média, est la plus impliquée dans les phénomènes de remodelage vasculaire. Rendant compte de l'épaisseur de la paroi artérielle, elle est constituée de cellules musculaires lisses organisées en unités lamellaires et entourées de tissu de soutien, dont les principaux composants sont le collagène, l'élastine et les mucopolysaccharides. La majoration des tensions pariétales induites par l'HTA entraîne une stimulation des cellules musculaires lisses par l'intermédiaire de facteurs de croissance (dont les catécholamines et l'angiotensine II) ayant pour conséquences une hypertrophie et une hyperplasie cellulaires [8]. D'un phénotype contractile, les cellules musculaires lisses deviennent sécrétoires entraînant le développement de la matrice extracellulaire par synthèse de collagène. Les altérations observées au niveau de l'intima artérielle sont proches de celles observées pendant le vieillissement et l'hyperlipidémie : synthèse de substances vasoactives, augmentation de la perméabilité de l'intima aux lipoprotéines et autres composants plasmatiques, adhésion et pénétration leucocytaire entraînant une accumulation de macrophages dans l'intima, prolifération des cellules endothéliales et musculaires lisses, migration des cellules musculaires lisses sécrétoires de la média vers l'intima.

L'augmentation de l'épaisseur intima-média (EIM), conséquence des altérations cellulaires et extracellulaires de la média et de l'intima, représente un marqueur précoce du risque artériel induit par l'HTA et favorise la formation de plaque d'athérosclérose en présence d'une hyperlipidémie. Intégrateur des principaux facteurs de risque cardiovasculaire, l'augmentation de l'EIM est associée à une majoration de l'incidence d'événements coronaires et cérébrovasculaires [9].

Formation des lésions athéromateuses

L'hypertrophie de l'intima-média, conséquence du remodelage artériel, et la dysfonction endothéliale sont deux facteurs potentialisant les lésions d'athérosclérose [10], en particulier au niveau des bifurcations artérielles. L'Organisation mondiale de la Santé (OMS) définit l'athérosclérose comme « une association variable de remaniements de l'intima des artères de gros et moyen calibre consistant en une accumulation locale de lipides, de glucides complexes, de sang et de produits sanguins, de tissu fibreux et de dépôts calcaires ; le tout s'accompagnant de modifications de la média». La première étape de l'athérosclérose consiste en l'accumulation de lipoprotéines de basse densité (LDL-cholestérol), dans l'intima, phénomène directement lié à la quantité de LDL-cholestérol plasmatique et suivi de leur oxydation. Le recrutement de cellules inflammatoires à la surface de l'endothélium, monocytes et macrophages, entraîne une réaction inflammatoire locale et la production de cytokine pro-inflammatoires favorisant la formation, la croissance et la fragilisation de la plaque d'athérosclérose. Les différents mécanismes de formation de la plaque d'athérome permettent de distinguer les lésions précoces et tardives dans l'histoire naturelle de l'athérosclérose. Les lésions précoces sont illustrées par l'accumulation de macrophages spumeux isolés dans l'intima des artères puis, à partir de 20 ans, les stries lipidiques, petits dépôts de lipides extracellulaires sans cœur lipidique. Ces lésions peuvent régresser et n'entraînent pas de manifestations cliniques. Les lésions constituées, plus tardives, peuvent être symptomatiques (Fig. 1, 2). Elles sont représentées par le cœur lipidique dans la paroi artérielle évoluant vers le fibroathérome (plaque d'athérosclérose constituée par un cœur lipidique entouré de fibrose) et enfin la plaque compliquée (ulcération, hémorragie intraplaque, thrombose). La chape fibreuse, constituée de cellules musculaires lisses, de collagène et de matrice extracellulaire, est un facteur de stabilité de la plaque. L'évolution peut également être

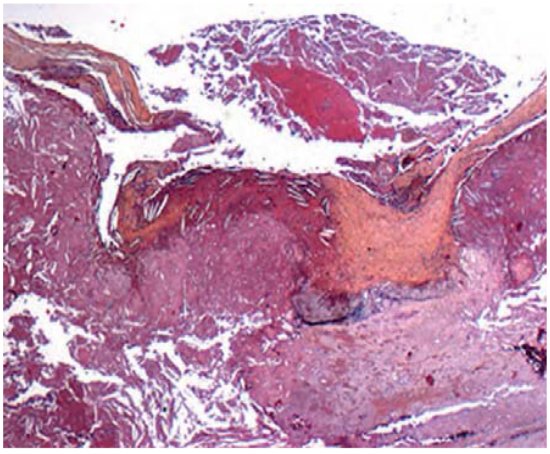

Figure 1. Plaque athéromateuse ulcérée : rupture de la chape fibreuse, hémorragie intraplaque, thrombus dans la lumière du vaisseau (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

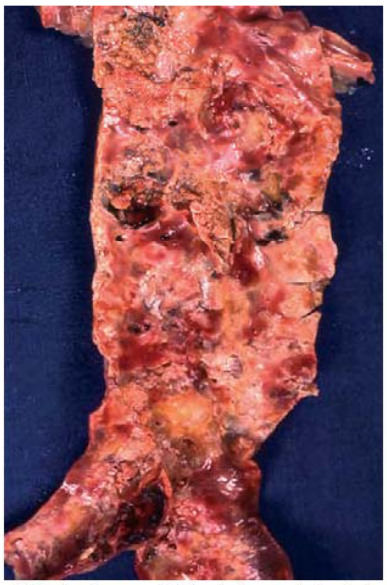

Figure 2. Multiples plaques ulcérées de l'aorte abdominale sous-rénale (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

représentée par un aspect très calcifié ou fibreux de la plaque, la symptomatologie dépendant essentiellement du degré de sténose.

Anomalies fonctionnelles de la paroi artérielle

Le remodelage vasculaire, phénomène adaptatif, permet dans un premier temps la préservation des propriétés élastiques de la paroi artérielle, mais à plus long terme favorise l'organisation des plaques d'athérome, augmentant ainsi la morbimortalité cardiovasculaire. Les anomalies fonctionnelles pariétales sont étudiées en fonction du calibre artériel. La paroi des gros troncs artériels est caractérisée par la diminution de sa compliance et de sa distensibilité. La rigidité des gros troncs artériels, caractéristique du vieillissement mais aussi d'un stade avancé de l'HTA, contribue à l'augmentation de la pression pulsée, facteur déterminant de l'atteinte des organes cibles et d'augmentation de l'EIM. Le remodelage des petites artères musculaires entraîne l'augmentation de

la réactivité vasculaire, des résistances vasculaires périphériques et ainsi de la pression moyenne. La diminution de la réserve de perfusion des organes cible, témoin de l'altération des capacités de vasodilatation et de la raréfaction artériolaire, entraîne une ischémie tissulaire dans des conditions de demande métabolique augmentée. De plus, les mécanismes d'autorégulation, permettant le maintien d'un débit de perfusion constant lors des niveaux de pression élevés, sont mis à l'épreuve en contexte de baisse tensionnelle (même à des chiffres considérés comme normaux), entraînant une hypoperfusion cérébrale, coronaire ou rénale.

“ *Point fort*

HTA et remodelage vasculaire

Stress oxydatif et dysfonction endothéliale

- altération de la perméabilité endothéliale et adhésion leucocytaire ;
- sécrétion de substances vasoactives et acquisition d'une activité procoagulante.

Anomalies structurales pariétales

- épaississement pariétal avec hypertrophie excentrique pour les grosses artères et concentrique pour les petites artères ;
- augmentation de l'épaisseur intima-média ;
- formation de la plaque d'athérome : accumulation de macrophages spumeux dans l'intima, stries lipidiques, cœur lipidique, fibroathérome, plaque compliquée (ulcération, hémorragie intraplaque, thrombose).

Anomalies fonctionnelles pariétales

- rigidité des gros troncs artériels : diminution de compliance et de distensibilité, augmentation de la pression pulsée ;
- augmentation de la réactivité vasculaire des artères résistives : altération des capacités de vasodilatation, augmentation des résistances vasculaires périphériques et de la pression moyenne ;
- raréfaction artériolaire ;
- altération des mécanismes d'autorégulation avec risque d'hypoperfusion d'organe ;
- accélération des lésions d'athérosclérose.

■ Conséquences cliniques sur les organes cibles

L'HTA est un facteur de risque majeur de complications cardiovasculaires par l'intermédiaire d'atteintes macro- et microvasculaires. Les lésions macrovasculaires sont rapportées à l'athérosclérose, maladie inflammatoire de la paroi artérielle et évolutive à travers les facteurs de risque et l'âge. La plaque d'athérome siège sur les artères de gros et moyen calibre : l'aorte, les branches à destinée viscérale (par exemple, les premiers centimètres des artères rénales), les artères coronaires épicardiques, les artères cervicales et intracrâniennes extraencéphaliques, les sous-clavières, les iliaques et les artères des membres (artère humérale et artères des membres inférieurs jusqu'au tiers supérieur des axes de jambes). Les complications microvasculaires sont liées à l'artériolosclérose entraînant une rigidification de la paroi et un rétrécissement de la lumière des petites artères.

Complications macrovasculaires

Toute atteinte artérielle périphérique ou d'un organe cible impose un bilan d'extension de la maladie athéroscléreuse avec recherche d'antécédents et de symptômes cérébrovasculaires ou coronariens, mesure de l'indice de pression systolique à la cheville, échographie-Doppler artérielle de l'aorte abdominale et des membres inférieurs, échographie-Doppler des troncs supra-aortiques, échographie cardiaque, électrocardiogramme (ECG) de repos et souvent test d'effort.

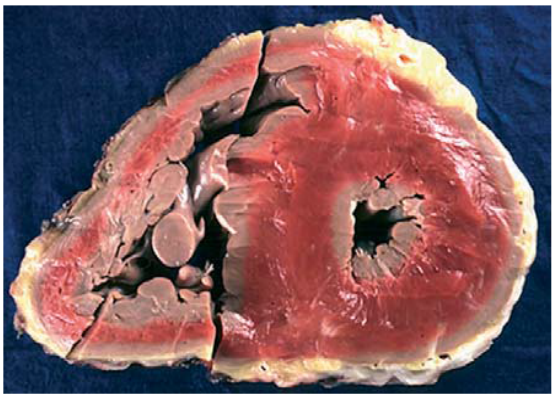

Figure 3. Cardiopathie hypertrophique hypertensive, avec hypertrophie concentrique du ventricule gauche (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

Cardiaques

Les conséquences des lésions artérielles sur la structure et la fonction cardiaque sont dominées par l'hypertrophie ventriculaire gauche, la cardiomyopathie hypertensive évoluant vers l'insuffisance cardiaque diastolique puis systolique et la maladie coronarienne.

Modifications structurales et fonctionnelles myocardiques

La réduction de distensibilité des grosses artères entraîne une élévation de la pression pulsée et par conséquent une augmentation du travail du ventricule gauche (VG). L'HTA favorise, par augmentation de la post-charge, l'hypertrophie ventriculaire gauche (HVG) s'accompagnant d'une dysfonction diastolique et associant trouble de la relaxation et de la compliance ventriculaire. Le remodelage de la paroi ventriculaire par majoration de la masse du VG correspond initialement à un phénomène adaptatif (selon la loi de Laplace) permettant la réduction de la tension pariétale et le maintien de la fonction systolique, mais ayant des conséquences néfastes à plus long terme. Ce phénomène aboutit à une HVG concentrique (augmentation du rapport épaisseur pariétale sur rayon > à 0,45) intéressant de façon homogène l'ensemble des parois ventriculaires (Fig. 3). Les altérations cellulaires (hypertrophie, apoptose et nécrose des cardiomyocytes), la fibrose interstitielle, vasculaire et périvasculaire, et la raréfaction capillaire sont les caractéristiques de ce remodelage pathologique.

Les conséquences cliniques sont représentées par le risque d'arythmie ventriculaire et de mort subite, de cardiomyopathie hypertensive évoluant vers l'insuffisance cardiaque par dysfonction diastolique puis systolique, et d'ischémie sous-endocardique par raréfaction capillaire. L'autorégulation de perfusion coronarienne est altérée même en l'absence de lésion sténosante. L'HVG représente un marqueur de risque et un excellent critère intermédiaire : en présence d'une HVG, la morbimortalité cardio- et cérébrovasculaire ainsi que les décès de toutes causes augmentent, après ajustement aux facteurs de risque classiques, et ceci à valeur HVG dépendante. Cible thérapeutique, la régression de l'HVG sous traitement antihypertenseur par antagonistes du système rénine-angiotensine améliore le pronostic cardiovasculaire au-delà de la baisse tensionnelle[11, 12]. La détection d'HVG se fait sur l'ECG et sur l'échographie-Doppler cardiaque. Les indices de Sokolow Lyon (SV1 + RV5 ou RV6 ≥ 38 mm) et de Cornell (SV3 + RVL > 24 mm chez l'homme et 20 mm chez la femme) ont une bonne spécificité mais des sensibilités médiocres. L'indice de Cornell associé à la largeur du QRS (Cornell (mm) × durée QRS (ms) > 2440) présente une sensibilité plus élevée pour la détection de l'HVG. L'échographie cardiaque permet la mesure de la paroi

postérieure, du septum interventriculaire (évoquant une HVG si > 15 mm chez l'homme et > 13 mm chez la femme) et de la masse VG (≥ 125 g/m^2 chez l'homme et ≥ 110 g/m^2 chez la femme). L'utilisation de l'imagerie par résonance magnétique (IRM) appartient au domaine de la recherche, examen de référence et de reproductibilité excellente pour la détection d'une HVG.

Modifications structurales et fonctionnelles coronaires

Le remodelage artériel a été décrit par Glagov en 1987 [13] sur des coupes histologiques du tronc commun coronaire. L'élargissement compensateur de la paroi artérielle préserve la surface luminale pour des sténoses allant jusqu'à 40 %. Au-delà, la capacité du vaisseau à se dilater est dépassée. L'altération des propriétés vasodilatatrices de l'endothélium de la paroi des coronaires épicardiques, conséquence de la dysfonction endothéliale, entraîne une vasoconstriction pathologique des artères en réponse à des stimuli devant physiologiquement entraîner une vasodilatation (par exemple : la présence d'acétylcholine, le test au froid ou l'effort physique). Il existe une inadaptation du débit cardiaque aux besoins lors de demande métabolique augmentée, comme par exemple en contexte d'effort physique. Ce déséquilibre entre la demande et l'apport en oxygène au niveau des cardiomyocytes est à l'origine d'épisodes d'ischémie silencieuse ou d'angor spastique entraînant dysfonction et détérioration des cardiomyocytes évoluant vers l'insuffisance ventriculaire gauche. L'infarctus du myocarde, manifestation d'insuffisance coronarienne aiguë, est lié le plus souvent à une occlusion artérielle thrombotique au contact d'une plaque d'athérosclérose sténosante ou compliquée de rupture, d'ulcération. La vulnérabilité de la plaque est principalement fonction de l'importance du cœur lipidique, liée à la concentration de LDL-cholestérol plasmatique, de la chape fibreuse et des processus inflammatoires locaux, auxquels s'associent des facteurs systémiques (« événements gâchette ») comme une poussée hypertensive [14, 15]. La mort cellulaire des myocytes de la zone infarcie est suivie de processus inflammatoires locaux puis cicatriciels par prolifération de fibroblastes produisant de la matrice extracellulaire et évoluant vers une cicatrice fibreuse avec atrophie. L'akinésie de la paroi infarcie entraîne des phénomènes partiellement compensateurs afin de maintenir le volume d'éjection systolique : hyperkinésie des autres parois et dilatation ventriculaire gauche en diastole. Très rapidement, la compliance du ventricule gauche s'altère entraînant les phénomènes de remodelage du VG à moyen et long terme : atrophie et dilatation de la zone infarcie, hypertrophie et dilatation des zones non intéressées par l'infarctus. L'augmentation des contraintes pariétales qui s'ensuit, aggravée par l'existence d'une HTA, favorise le remodelage ventriculaire évoluant vers la dilatation cavitaire, la perte de la fonction diastolique puis systolique ventriculaire gauche et l'insuffisance cardiaque.

Cérébrales

Les complications cérébrales sont dominées par l'accident vasculaire cérébral (AVC), pathologie grave et fréquente constituant une urgence thérapeutique, et devant idéalement être pris en charge en unité neurovasculaire. Les AVC sont la première cause de handicap neurologique, la deuxième cause de démence et la troisième cause de mortalité. L'incidence générale est de 2/1 000 habitants par an en France soit 150 000 nouveaux cas par an, et de 15/1 000 chez les plus de 75 ans. L'AVC est défini par le développement rapide de signes de dysfonction du système nerveux central, secondaire à une thrombose (AVC ischémique dans 80 % des cas) ou une rupture (AVC hémorragique dans 20 % des cas) vasculaire. L'HTA est le principal facteur de risque quel que soit le sous-type d'AVC, et sans valeur tensionnelle-seuil. Une imagerie cérébrale en urgence est indispensable à des fins diagnostiques. Le scanner sans injection est l'examen d'urgence et de débrouillage permettant le diagnostic d'AVC hémorragique. Les signes d'ischémie peuvent ne pas être visibles dans les premières heures suivant l'accident. L'IRM cérébrale, examen plus spécialisé, est supérieure au scanner, permettant le diagnostic positif précoce, étiologique, différentiel, et pronostique (étendue des lésions, retentissement hémodynamique et perméabilité des vaisseaux intracrâniens). Il doit être réalisé en première intention en fonction de la disponibilité et de l'absence de contre-indications. Le protocole en cas d'AVC comporte plusieurs séquences : séquences pondérées en T2 écho de gradient (T2*) permettant le diagnostic d'hémorragie cérébrale dès la première heure (lésion en hyposignal), séquences FLAIR pour la recherche de lésions vasculaires anciennes, séquences de diffusion faisant le diagnostic d'ischémie cérébrale dès la première heure (œdème cytotoxique en hypersignal) et de perfusion individualisant la zone de pénombre ischémique (tissu hypoperfusé non nécrosé susceptible de régresser sous traitement fibrinolytique), et enfin l'angiographie par résonance magnétique (ARM) en temps de vol recherchant le niveau d'occlusion artérielle (en hypersignal).

Tableau 1.
Score ABCD(2).

Risque à 7 jours d'AVC après AIT	
Âge ≥ à 60 ans	1 point
Pression artérielle (première mesure après l'AIT) PAS ≥ 140 mmHg ou PAD ≥ 90 mmHg	1 point
Clinique :	
- déficit moteur unilatéral	2 points
- troubles phasiques isolés	1 point
Durée de l'AIT :	
- ≥ à 60 minutes	2 points
- entre 10 et 59 minutes	1 point
Diabète	1 point
Score entre 0 et 3 : bilan étiologique à effectuer rapidement. Risque d'AVC estimé à 1 % dans les 48 heures Score entre 4 et 5 : hospitaliser le patient pour bilan. Risque d'AVC estimé à 4 % dans les 48 heures Score entre 6 et 7 : hospitaliser le patient en unité de soins intensifs neurovasculaires, réaliser une IRM cérébrale en urgence. Risque d'AVC estimé à 8 % dans les 48 heures	

AVC : accident vasculaire cérébral ; AIT : accident ischémique transitoire ; PAD : pression artérielle diastolique ; PAS : pression artérielle systolique ; IRM : imagerie par résonance magnétique.

Accidents transitoires et AVC ischémiques

L'accident ischémique transitoire (AIT) correspond à une perte brutale d'une fonction cérébrale ou oculaire durant moins de 1 heure supposée due à une embolie ou à une thrombose vasculaire, avec une imagerie (IRM de diffusion) normale. Il représente un syndrome de menace, à haut risque de récidive à court terme, et constitue une urgence diagnostique et thérapeutique. Le score ABCD(2) [16] permet de préciser le risque de récidive et d'adapter au mieux la prise en charge médicale (Tableau 1). Cependant, d'autres situations cliniques augmentant le risque d'infarctus cérébral à court terme doivent également être prises en compte : AIT crescendo ou récidive sous antiagrégant plaquettaire, suspicion de cardiopathie emboligène, cécité monoculaire transitoire très évocatrice de sténose serrée carotidienne, hypersignal à l'IRM de diffusion après un AIT de longue durée. Le risque de récidive de l'AVC ischémique ou de l'AIT est maximal immédiatement après le premier épisode et évalué à 5 % par an. Le risque de mortalité d'origine cardiaque est également majoré : un tiers des décès survenant après le premier mois est d'origine vasculaire, deux tiers d'entre eux étant d'origine cardiaque. En plus du bilan étiologique de l'AVC, il est donc nécessaire d'identifier les patients à haut risque cardiaque.

La prise en charge en phase aiguë de l'AVC a pour principal objectif de poser ou de réfuter l'indication d'une thrombolyse intraveineuse, permettant une réduction de 40 % de mortalité et de handicap mais au prix d'un risque hémorragique majoré.

Selon les recommandations de l'HAS en 2009, la thrombolyse intraveineuse est indiquée dans l'infarctus cérébral, après avoir éliminé une hémorragie intracrânienne à l'imagerie, si le délai écoulé entre le début des symptômes et la prise en charge est inférieur à 4 h 30 (pour les patients de plus de 80 ans le délai doit être inférieur à 3 h), en l'absence de chirurgie récente ou autre contre-indication

de la thrombolyse, avec un score du National Institut of Health Stroke Score (NIHSS) entre 5 et 25 (sévérité moyenne à modérée), et si la pression artérielle ne dépasse pas 185 mmHg/110 mmHg. Elle doit être effectuée le plus précocement possible.

Le bilan étiologique à réaliser devant un AVC ischémique doit rechercher une athérosclérose carotidienne, une dissection artérielle, une cardiopathie emboligène. Les infarctus lacunaires, complications microvasculaires de l'HTA, sont détaillés plus loin.

L'athérome carotidien, siégeant préférentiellement sur la bifurcation carotidienne, est bien étudié en échographie-Doppler, par l'intermédiaire de critères vélocimétriques et morphologiques, et l'association à un angioscanner ou à une angio-IRM permet de porter l'indication opératoire. Les critères vélocimétriques de sténose carotidienne serrée, correspondant morphologiquement à une réduction de diamètre de plus de 70 %, sont représentés par un pic de vitesse systolique supérieur à 210 cm/s, une vitesse télédiastolique supérieure à 70 cm/s et un rapport carotidien (pic de vitesse systolique de la carotide interne/carotide primitive) supérieur à 3. Les turbulences au site de sténose sont associées à des signes d'aval tels que l'amortissement et la démodulation du flux. Attention cependant aux pièges et diagnostics différentiels d'accélération du flux artériel : dysplasie fibromusculaire, boucle artérielle, hyperthermie, hyperthyroïdie, anémie ou fistule artérioveineuse. Parallèlement, un flux amorti peut se voir en pathologie valvulaire cardiaque (rétrécissement aortique). L'évaluation morphologique du degré de sténose permet une estimation de la réduction en diamètre sur une coupe longitudinale de l'artère au site de sténose le plus serré : la méthode European Carotid Surgery Trial (ECST) utilise le diamètre du bulbe carotidien pour dénominateur, alors que la méthode North American Symptomatic Carotid Endarterectomy Trial (NASCET) s'intéresse au diamètre de l'artère carotide saine en aval de la sténose. D'autre part, la caractérisation de la plaque d'athérosclérose permet d'évaluer son potentiel emboligène (plaque hétérogène à prédominance hypoéchogène, de surface irrégulière, anfractueuse, ulcérée, évocatrice d'hémorragie intraplaque). Bien que ces derniers critères n'interviennent pas encore dans la décision d'intervention chirurgicale selon les recommandations, ils représentent un argument supplémentaire pour l'endartériectomie carotidienne.

Le risque de récidive ou de survenue d'un AVC est significativement réduit après endartériectomie carotidienne pour des sténoses serrées symptomatiques (études NASCET et ECST) ou asymptomatiques (études Asymptomatic Carotid Atherosclerosis Study [ACAS] et Asymptomatic Carotid Surgery Trial [ACST]). Le taux de morbimortalité chirurgicale ne doit pas dépasser 6 % et 3 % à j30 respectivement pour des sténoses symptomatiques ou asymptomatiques. Actuellement, l'endartériectomie carotidienne est recommandée pour des sténoses de la carotide interne symptomatiques évaluées entre 70 % et 99 % (selon NASCET) chez des patients avec AVC ischémique non invalidant ou AIT, datant de moins de 6 mois. L'intervention apporte un bénéfice d'autant plus important qu'elle est réalisée tôt, dans les 2 semaines suivant l'accident. Pour des sténoses carotidiennes comprises entre 50 % et 69 %, la décision chirurgicale doit être prise après évaluation des caractéristiques du patient et de l'AVC : le bénéfice de la chirurgie est plus important chez les hommes, âgés de 75 ans et plus et en cas de symptômes hémisphériques. Il n'existe pas actuellement de recommandation pour l'endartériectomie des sténoses inférieures à 50 % [17]. Chez les patients asymptomatiques, un geste de revascularisation chirurgicale peut être discuté pour des sténoses carotidiennes supérieures ou égales à 60 % en fonction de l'espérance de vie du patient et des comorbidités.

La prise en charge des sténoses athéromateuses symptomatiques de l'artère vertébrale extracrânienne est moins bien codifiée. Elles peuvent faire l'objet d'une prise en charge chirurgicale après concertation multidisciplinaire en cas d'infarctus ou d'accidents transitoires récidivants malgré le traitement médicamenteux maximal.

La dissection carotidienne ou vertébrale extracrânienne peut survenir en contexte d'HTA mal équilibrée et n'est pas liée à l'athérosclérose. Elle est révélée par un tableau d'AVC ischémique douloureux carotidien ou vertébrobasilaire, le plus souvent du sujet jeune, associant céphalées, cervicalgies inaugurales, signe de Claude-Bernard-Horner (myosis, ptôsis et énophtalmie homolatérale) pour la dissection carotidienne, et déficit neurologique cérébral ou rétinien.

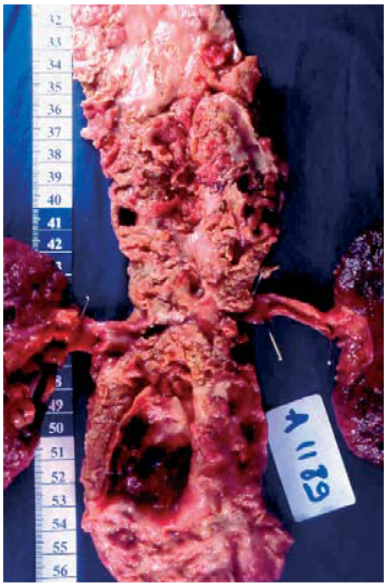

Figure 4. Anévrisme de l'aorte abdominale sous-rénale. Reins d'aspect « bosselé » en faveur d'une néphropathie parenchymateuse secondaire à l'hypertension artérielle (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

AVC hémorragiques

L'AVC hémorragique parenchymateux et l'hémorragie méningée, urgences vitales, peuvent nécessiter une prise en charge neurochirurgicale immédiate. L'HTA est responsable de 80 % des hémorragies cérébrales parenchymateuses par rupture de microanévrismes des petites artères siégeant dans le tronc cérébral ou les noyaux gris centraux. La lésion causale peut également être un cavernome, une malformation ou une fistule artérioveineuse. L'hémorragie méningée se caractérise par un syndrome méningé aigu, par irruption de sang dans les espaces sous-arachnoïdiens, dont la principale complication immédiate est le spasme artériel qui doit être systématiquement recherché au doppler transcrânien et prévenu. Le scanner cérébral sans injection est l'examen de première intention dès qu'un AVC hémorragique est suspecté : une hyperdensité parenchymateuse, des citernes de la base et des vallées sylviennes est recherchée. Cependant, l'hyperdensité s'atténue à partir du 3e jour et peut être absente pour de discrètes hémorragies. Un scanner normal n'élimine pas le diagnostic et il est nécessaire alors de réaliser une IRM avec séquences T2* et FLAIR permettant la détection d'hémorragie récente ou ancienne. L'artériographie cérébrale présente un intérêt diagnostique et thérapeutique. Le traitement des ruptures d'anévrismes cérébraux est une urgence et se fait par voie endovasculaire par embolisation de coils à détachement contrôlé.

Vasculaires

Les principales complications artérielles périphériques sont dominées par les sténoses athéroscléreuses, les complications à type d'ulcération, de thrombose ou d'embolie périphérique, les anévrismes et dissections artérielles.

Atteinte aortique

L'anévrisme athéroscléreux de l'aorte abdominale (AAA), en particulier sous-rénal (dans plus de 90 % des cas), est une pathologie fréquente découverte le plus souvent de façon fortuite (Fig. 4). Elle est définie par la perte du parallélisme des bords entraînant une dilatation artérielle localisée et permanente. Le support lésionnel est l'atteinte de la média : son épaisseur diminue, les

cellules musculaires lisses et les fibres élastiques disparaissent, remplacées par de la fibrose. La prévalence en population générale est estimée à 3 %. La présence d'un AAA est plus fréquente chez les hommes de plus de 65 ans hypertendus sur terrain athéroscléreux (maladie coronarienne ou artériopathie oblitérante des membres inférieurs). Dans près de la moitié des cas, il existe une association à un anévrisme fémoropoplité [18]. Les complications sont marquées par la rupture, entraînant le décès dans 80 % des cas, les embolies périphériques pouvant être responsables d'ischémie artérielle aiguë, la thrombose anévrismale, l'infection (artérite septique), et le risque de compression en particulier veineuse évoluant vers la thrombose iliocave. L'évolutivité et le risque de rupture sont corrélés au plus grand diamètre anévrismal. L'échographie abdominale est l'examen de référence pour le dépistage et la surveillance des AAA. L'angioscanner est essentiel au choix de la technique opératoire, précisant les rapports avec les artères rénales et iliaques, et pour la surveillance des endoprothèses. La recherche systématique d'autres localisations anévrismales (iliaques primitives et externes, fémoropoplitées) ainsi qu'un bilan d'extension de la maladie athéromateuse sont essentiels, chez des patients souvent polyvasculaires. Les AAA symptomatiques quel qu'en soit le diamètre, les AAA d'un diamètre supérieur ou égal à 55 mm ou dont la croissance est supérieure ou égale à 10 mm par an, bénéficient d'un traitement chirurgical en première intention (par mise à plat et greffe prothétique). Le traitement endovasculaire (exclusion de l'AAA par endoprothèse) est privilégié si la chirurgie est à haut risque, en particulier pour les patients âgés fragiles (âge supérieur à 80 ans, cardiopathie évoluée, insuffisance respiratoire sévère, obésité, cirrhose hépatique). La mortalité opératoire est faible, moins de 5 %, comparé au risque vital en cas de rupture anévrismale (mortalité de 60 % à 80 %).

La dissection aortique correspond au clivage de la paroi artérielle au niveau de la média. La porte d'entrée est une déchirure intimomédiale et la zone de clivage est soit occluse (par coagulation du sang), soit perméable correspondant au faux chenal. Les principales étiologies des dissections sont l'HTA, le vieillissement, les dysplasies, les artérites inflammatoires, les traumatismes iatrogènes ou non, mais pas l'athérosclérose. La clinique est marquée par une douleur thoracique brutale, plus ou moins migratrice, l'asymétrie ou l'abolition d'un pouls, une anisotension, et le risque de mauvaise tolérance hémodynamique. Plusieurs autres symptômes peuvent se rencontrer en rapport avec l'occlusion ou le bas débit d'une artère à destinée cérébrale ou viscérale. La classification de Stanford présente un intérêt thérapeutique :

- la dissection de type A intéresse l'aorte thoracique ascendante intrapéricardique, avec plus ou moins une extension distale. C'est une urgence chirurgicale. Les complications sont dominées par le risque d'ischémie cérébrale par extension de la dissection aux carotides, d'ischémie coronaire, d'insuffisance aortique aiguë et de tamponnade ;
- la dissection de type B n'intéresse pas l'aorte ascendante. Sa prise en charge repose sur le traitement médical et le contrôle strict de la tension artérielle. Les complications sont dominées par le risque d'ischémie dans le territoire irrigué (rénal, hépatodigestif, artériel périphérique, spinal).

Atteinte artérielle périphérique

L'artériopathie oblitérante des membres inférieurs (AOMI) est une pathologie sous-diagnostiquée et sous-traitée, représentant un marqueur indépendant de risque cardiovasculaire que le patient soit symptomatique ou non. Ces patients à haut risque présentent une mortalité spontanée de 25 % à 30 % à 5 ans, en particulier coronaire et cérébrovasculaire [19], et doivent être considérés comme polyvasculaires jusqu'à preuve du contraire. Le risque de morbimortalité cardiovasculaire est inversement proportionnel à la valeur de l'indice de pression systolique à la cheville (IPS) [20].

À la classique classification de Leriche et Fontaine présentant les différents stades de gravité croissante de l'AOMI, trois tableaux cliniques sont actuellement distingués :

- l'AOMI asymptomatique, dont le dépistage permet d'identifier une population à haut risque cardiovasculaire ;
- l'ischémie d'effort marquée par la claudication douloureuse intermittente des membres inférieurs ;
- l'ischémie permanente chronique marquée par la douleur de décubitus ou le trouble trophique d'orteil, confirmée au plan hémodynamique par une pression d'orteil inférieure à 50 mmHg, une $TcPO_2$ en dessous de 30 mmHg ou une pression de cheville inférieure à 70 mmHg. L'ischémie critique met en jeu le pronostic fonctionnel et vital du membre, et est définie par une pression d'orteil inférieure à 30 mmHg, une $TcPO_2$ en dessous de 10 mmHg ou une pression de cheville inférieure à 50 mmHg.

L'examen clinique recherche l'abolition des pouls périphériques et des signes d'ischémie chronique tels que la pâleur de surélévation, l'érythrose de déclivité, l'œdème distal et l'augmentation du temps de recoloration cutanée. Des ulcérations hyperalgiques creusantes doivent être recherchées au niveau des orteils, des espaces interdigitaux, du dos et du bord externe du pied ou du talon et sur la face antérieure de jambe. La présence d'une masse pulsatile expansive aortique fémorale commune ou poplitée est systématiquement recherchée. En particulier, l'anévrisme poplité rétroarticulaire comme l'AAA, est à l'origine de complications aiguës telles que l'ischémie périphérique aiguë par thrombose sur embolies. Il peut également se compliquer de surinfection ou être paucisymptomatique, par thrombose chronique de la poche anévrismale, ou destruction à bas bruit progressive du lit artériel d'aval par microembolies périphériques. La rupture est exceptionnelle. Un anévrisme poplité symptomatique ou de plus de 2 cm de diamètre ou avec thrombus mural, bénéficie d'une prise en charge chirurgicale. Le traitement de l'AOMI, associé à la prise en charge du risque cardiovasculaire global et des facteurs de risque associés, dépend du stade de la maladie et de l'existence de lésions menaçantes par leur topographie (trépied fémoral, axe vasculaire principal en l'absence de collatéralité, etc.), leur nature (anévrisme aortique ou fémoropoplité) et leur répercussion hémodynamique.

L'ischémie artérielle aiguë est une urgence médicochirurgicale, de diagnostic clinique, mettant en jeu le pronostic fonctionnel et vital du patient (10 % de décès, 25 % d'amputation, 15 % de séquelles). La sévérité de l'atteinte ischémique dépend de l'existence de collatérales. Le mécanisme est embolique ou thrombotique. Les lésions tissulaires nerveuses et musculaires sont irréversibles si le délai de prise en charge dépasse 6 heures. Le tableau clinique associe l'abolition des pouls à des signes sensitifs (douleur, pâleur, froideur, paresthésies). Le risque évolutif est marqué par l'apparition de signes moteurs à type de paralysie, une urgence thérapeutique majeure : aucune exploration complémentaire ne doit retarder l'intervention. Le traitement comporte deux volets simultanés, auxquels s'associe la prise en charge étiologique :

- médical par héparinothérapie intraveineuse, antalgiques de niveau 3, nursing, optimisation de l'état hémodynamique, prévention des conséquences métaboliques de l'ischémie et de la revascularisation (rhabdomyolyse avec risque d'acidose, hyperkaliémie, insuffisance rénale) ;
- chirurgical par embolectomie, thromboaspiration, ou pontage selon le mécanisme de l'atteinte artérielle, associé à une aponévrotomie de décharge.

La maladie des emboles de cristaux de cholestérol survient en contexte d'athérome évolué, sur des plaques ulcérées de l'aorte et des gros troncs, avec un facteur déclenchant fréquemment retrouvé (chirurgie aortique, cathétérisme artériel, anticoagulation, traumatisme thoracique). La maladie est souvent asymptomatique cliniquement mais à haut risque de récidive, faisant toute la gravité de celle-ci. Son pronostic est sévère par les lésions ischémiques induites mais aussi par le terrain athéroscléreux à un stade avancé qu'elle reflète [21]. Le diagnostic est clinique, la peau étant le principal point d'appel préférentiellement au niveau des membres inférieurs : orteils pourpres et livedo, avec parfois des ulcérations ou gangrènes distales. La biopsie cutanée ou le fond d'œil en cas d'atteinte cérébrale peuvent aider parfois au diagnostic, mettant en évidence les cristaux de cholestérol. À l'expression cutanée, peuvent s'associer une atteinte rénale aiguë ou lente et retardée imposant dans certains cas le recours à la dialyse et à l'origine de poussées

tensionnelles difficilement contrôlables, une atteinte digestive ischémique avec perforations ou nécroses segmentaires du tube digestif, une atteinte neurologique centrale ou périphérique. Le tableau clinique peut être extrêmement riche et trompeur faisant toute la difficulté diagnostique avec les vascularites systémiques. Le traitement est principalement symptomatique et préventif en évitant les facteurs déclenchants des récidives et en évaluant la balance bénéfice/risque lors de tout acte invasif.

L'artère sous-clavière peut également présenter une atteinte athéroscléreuse à type de sténose ou d'anévrisme pouvant avoir des répercussions hémodynamiques sur la vascularisation du membre supérieur et de l'axe vertébrobasilaire en cas de sténose sous-clavière prévertébrale. L'atteinte occlusive est dominante ayant pour conséquences une ischémie à l'effort du membre supérieur, mais pouvant être aussi le point de départ d'une pathologie thromboembolique. En cas de sténose prévertébrale, un vol vertébral intermittent ou permanent peut exister : le flux de l'artère vertébrale homolatérale est inversé pour assurer la vascularisation du membre supérieur. Les signes d'ischémie vertébrobasilaire sont habituellement associés à des lésions des troncs supra-aortiques concomitantes, en particulier l'occlusion de l'artère vertébrale controlatérale pouvant entraîner une inversion du flux dans le tronc basilaire. La symptomatologie guide l'indication du traitement chirurgical.

Rénales

La sténose de l'artère rénale (SAR) est, dans sa forme athéroscléreuse, la principale cause d'hypertension rénovasculaire. Elle est le témoin d'une maladie athéromateuse diffuse associée à une morbimortalité cardiovasculaire accrue. Les principaux signes cliniques évoquant une HTA rénovasculaire sur terrain athéroscléreux sont une HTA accélérée, maligne ou résistante, des œdèmes aigus pulmonaires récidivants non expliqués par une dysfonction cardiaque systolique, une aggravation brutale de l'HTA et de la fonction rénale, une élévation de plus de 20 % de la créatininémie ou « trop belle » réponse tensionnelle sous inhibiteurs du système rénine-angiotensine, la présence d'un souffle abdominal, une hypokaliémie avec kaliurèse inadaptée. Le dépistage de la sténose athéroscléreuse de l'artère rénale est justifié par la nécessité d'une prise en charge renforcée chez ces patients à haut risque cardiovasculaire. L'objectif est de proposer un traitement susceptible d'améliorer non seulement l'HTA mais également de sauvegarder un bon fonctionnement du rein et de réduire le risque de survenue d'événements cardiovasculaires et de décès. L'échographie-Doppler, l'angiotomodensitométrie (TDM) et l'angio-IRM sont les examens non invasifs de première intention pour le dépistage d'une SAR. Les éléments en faveur d'une revascularisation, associée au traitement médical, sont une HTA résistante au traitement médical optimal, une dégradation progressive ou rapide de la fonction rénale sous traitement antihypertenseur, en particulier par inhibiteurs du système rénine-angiotensine, une insuffisance cardiaque congestive récurrente chez un patient avec fonction systolique ventriculaire gauche conservée. La décision de revascularisation doit être prise après avoir évalué la balance bénéfice/risque de l'intervention.

Complications microvasculaires

Cérébrales

La chronicité de l'HTA est associée à un risque majoré de déclin cognitif et de démences toutes causes confondues. La démence vasculaire est la deuxième cause de démence, après la maladie d'Alzheimer, et survient chez près d'un tiers des patients ayant eu un AVC. Cependant, chez les personnes âgées indemnes de troubles cognitifs ou d'antécédent d'AVC, le risque de déclin cognitif est associé à l'existence de facteurs de risque d'AVC tels que l'âge, l'HTA, le diabète, l'existence d'une maladie cardiovasculaire ou rénale, d'une HVG ou d'une arythmie par fibrillation auriculaire[22]. La démence vasculaire peut être la conséquence d'une pathologie macro- et microvasculaire : la macroangiopathie se révèle par des accidents vasculaires cérébraux, infarctus multiples cortico-sous-corticaux ou stratégiques (par exemple AVC

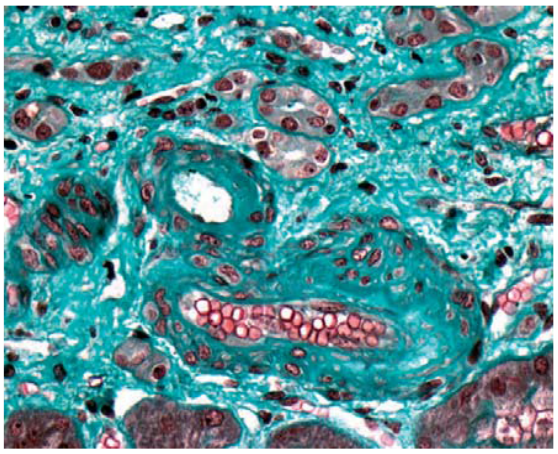

Figure 5. Hyalinose artériolaire et artériolosclérose (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

bithalamique) ; la microangiopathie cérébrale se révèle par des lacunes stratégiques (thalamiques), des lacunes multiples ou une ischémie de la substance blanche (leucoaraïose). Les mécanismes impliqués dans la microangiopathie cérébrale mettent en jeu les phénomènes d'artériolosclérose par lipohyalinose, entraînant une occlusion artériolaire par une substance hyaline lipidique pariétale. La démence vasculaire est distinguée de la démence dégénérative type maladie d'Alzheimer ou éthylique. Cependant, le diagnostic de démence s'inscrit souvent dans le cadre d'une multipathologie, dégénérative et vasculaire[23], appelée démence mixte. Les critères diagnostiques de la National Institute for Neurological Disorders and Stroke-Association internationale pour la recherche et l'enseignement des neurosciences (NINDS-AIREN) proposent de retenir le terme de « maladie d'Alzheimer avec maladie cérébrovasculaire », à distinguer d'une démence vasculaire pure. La première est caractérisée par une évolution progressive et une atteinte sévère de la mémoire épisodique. La seconde est caractérisée par une détérioration brutale des fonctions cognitives, d'apparition dans les 3 mois suivant un AVC, ou une aggravation typiquement en marche d'escalier. Les troubles dysexécutifs sont au premier plan associés à des troubles de la marche, des chutes, des troubles sphinctériens. La démence mixte et la démence vasculaire pure sont toutes deux associées aux facteurs de risque cardiovasculaires et présentent des signes neuroradiologiques compatibles avec ceux d'un AVC ou des lésions de la substance blanche. La forte prévalence en histopathologie de lésions vasculaires chez des patients souffrant de maladie d'Alzheimer et inversement, suggère l'implication des facteurs de risque cardiovasculaire dans la genèse de la maladie d'Alzheimer, une ischémie pouvant être la cause du développement des lésions bêta amyloïdes et des dégénérescences neurofibrillaires.

Rénales

L'atteinte rénale est un marqueur et un facteur de risque cardiovasculaire. Une HTA ancienne, souvent insuffisamment contrôlée et associée au vieillissement physiologique des artères, entraîne une insuffisance rénale lentement progressive par néphroangiosclérose, évoluant vers le stade terminal, et associée à une morbimortalité cardio- et cérébrovasculaire accrue. Une augmentation même modeste des chiffres tensionnels (tension normale haute) représente un facteur de risque indépendant d'insuffisance rénale chronique terminale. Le diagnostic de néphroangiosclérose est histologique et se caractérise par une atteinte des artères de moyen calibre et des artérioles, associée à une atteinte glomérulaire et interstitielle (Fig. 5, 6) : rétrécissement artériel, épaississement fibroélastique de l'intima, hypertrophie de la média en réponse à l'augmentation chronique des contraintes mécaniques, hyalinose artérielle, lésions d'ischémie et de sclérose

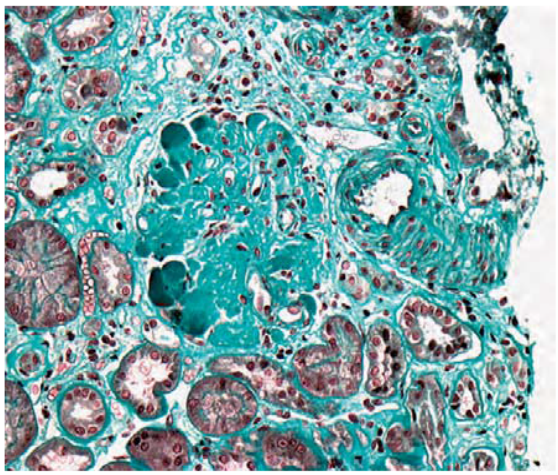

Figure 6. Hyalinose glomérulaire (cliché du Pr Bruneval, service d'anatomie et cytologie pathologiques, Hôpital européen Georges Pompidou, Paris).

glomérulaire, atrophie tubulaire et fibrose interstitielle. Cependant, ce tableau de néphropathie microvasculaire doit être intégré dans celui plus large de maladie rénale athéromateuse associant de manière variable des lésions non spécifiques liées au vieillissement, des lésions de néphroangiosclérose, une atteinte athéromateuse des artères rénales proximales, de l'aorte, et des lésions secondaires à la maladie des emboles de cholestérol.

Arythmie par fibrillation auriculaire

La physiopathologie de la fibrillation atriale (FA), comme celle de la démence en particulier, présente des altérations microvasculaires liées à des décennies d'HTA. La prévalence de la FA augmente avec l'âge, atteignant 10 % après 80 ans, et en présence d'une cardiopathie. Selon l'étude de Framingham, il existe une relation indépendante entre fibrillation auriculaire et mortalité toutes causes avec un risque relatif égal à 2. Les mécanismes impliqués dans la survenue d'une arythmie supraventriculaire associent altérations de la matrice extracellulaire (fibrose interstitielle et inflammation), anomalies des cardiomyocytes (dédifférenciation, hypertrophie, apoptose, nécrose) et altérations microvasculaires à l'origine de modifications électriques précoces, de dilatation de l'oreillette gauche par fibrose atriale et d'HVG. L'évolution est marquée par le risque thromboembolique, estimé par le score CHA2DS2-VASc[24] (Tableau 2), le risque d'insuffisance cardiaque, la survenue de vertiges et de syncopes. Pour la prévention des événements thromboemboliques, l'anticoagulation orale est

Tableau 2.
Score de CHA2DS2-VASc.

Facteurs de risque dans la survenue d'un AVC ou autre épisode thrombo-embolique en contexte de FA	Score
Insuffisance cardiaque ou dysfonction systolique du VG (FE<40 %)	1
HTA	1
Âge ≥ 75 ans	2
Diabète	1
Antécédent d'AVC, AIT ou autre épisode thromboembolique	2
Pathologie vasculaire (infarctus du myocarde, maladie vasculaire périphérique ou plaque de l'aorte)	1
Âge entre 65 et 74 ans	1
Sexe féminin	1

AVC : accident vasculaire cérébral ; FA : fibrillation auriculaire ; VG : ventricule gauche ; HTA : hypertension artérielle ; AIT : accident ischémique transitoire.

Tableau 3.
Classification de Kirkendall.

Rétinopathie hypertensive	
Stade I	Rétrécissement artériel sévère et disséminé
Stade II	Stade I + hémorragies rétiniennes et nodules cotonneux
Stade III	Stade II + œdème papillaire
Artériosclérose rétinienne	
Stade I	Signe du croisement artérioveineux
Stade II	Stade I + rétrécissement artériolaire localisé en regard
Stade III	Stade II + occlusions veineuses et engainements vasculaires

recommandée en cas de score supérieur ou égal à 2 et préférée à l'aspirine en cas de score égal à 1. En l'absence de facteurs de risque, il est recommandé en première intention de ne pas débuter de traitement antithrombotique. Le risque hémorragique doit également être évalué dans la stratégie thérapeutique, selon le score HAS-BLED[24] (hypertension, anomalie fonction rénale et/ou hépatique, AVC, hémorragie, *international normalized ratio* [INR] labiles, âge > 65 ans, et prise de drogues et/ou d'alcool).

Rétiniennes

Les modifications de la vascularisation rétinienne, reflet de la circulation cérébrale, renseignent sur l'évolutivité de l'HTA illustrée par des lésions chroniques irréversibles ou aiguës et réversibles. Le fond d'œil permet la détection d'accidents vasculaires rétiniens graves, parfois définitifs. La vascularisation rétinienne présente deux caractéristiques : la capacité d'autorégulation du calibre artériolaire permettant un débit rétinien stable face aux modifications tensionnelles (vasoconstriction artérielle active en présence d'une HTA) et l'existence d'une barrière hémato-rétinienne dont la rupture participe à la genèse des lésions de rétinopathie hypertensive. La classification de Kirkendall (Tableau 3) permet la distinction entre lésions rétiniennes hypertensives et artérioscléreuses. Les lésions de rétinopathie hypertensive liées directement à l'élévation des chiffres tensionnels sont le plus souvent réversibles par le traitement de l'HTA. Celles liées à l'artériolosclérose rétinienne représentent des modifications chroniques irréversibles asymptomatiques. Le stade ultime de la rétinopathie hypertensive est caractérisé par la présence d'un œdème papillaire dans un contexte d'HTA sévère ou d'installation rapide ayant pour traduction clinique un agrandissement de la tâche aveugle puis une baisse d'acuité visuelle par atrophie papillaire. C'est une urgence hypertensive devant le risque d'encéphalopathie hypertensive avec atteinte neurologique non focale (céphalées, nausées, vomissements, troubles de la conscience, troubles visuels, épilepsie). La mortalité est estimée à 50 % dans les 6 mois en l'absence de traitement. Les lésions d'artériolosclérose sont responsables de complications vasculaires à type d'occlusion de la veine ou de l'artère centrale de la rétine, d'ischémie choroïdienne, de macroanévrisme et de neuropathie optique ischémique antérieure aiguë. Il existe une étroite relation entre importance de l'atteinte vasculaire rétinienne et morbimortalité cardio- et cérébrovasculaire. L'existence d'une rétinopathie, illustrant l'atteinte d'un organe cible de l'HTA, confère au patient un haut risque cardiovasculaire.

■ Stratégie de dépistage de l'atteinte artérielle infraclinique

La décision de mise en route du traitement médicamenteux chez le patient hypertendu repose sur l'évaluation du risque cardiovasculaire global. La recherche des autres facteurs de risque cardiovasculaire, d'une maladie cardiovasculaire ou rénale avérée et de l'atteinte des organes cibles permet de cibler les

patients les plus à risque. Une attention toute particulière doit être portée au dépistage précoce d'une atteinte vasculaire infraclinique mettant en évidence une progression de la maladie cardiovasculaire et majorant le risque au-delà de la présence de facteurs de risque [25, 26]. Le concept d'un continuum de la maladie cardiovasculaire implique le rôle du stress oxydatif, de la dysfonction endothéliale, des processus inflammatoires et du remodelage vasculaire, dans l'initiation et la progression de l'athérosclérose [27]. L'European Society of Hypertension (ESH) en 2007 attire l'attention sur la majoration du risque cardiovasculaire, définie selon le score de Framingham comme un risque de plus de 20 % à 10 ans d'événement cardiovasculaire fatal ou non, lors d'une atteinte infraclinique d'un organe cible. Ainsi, les recommandations européennes présentent les paramètres cardiaques, rénaux et vasculaires dans l'évaluation de l'atteinte des organes cibles : HVG électrique ou échographique, créatininémie, débit de filtration glomérulaire, microalbuminurie, EIM carotidienne ou plaque d'athérome, vitesse de l'onde de pouls carotidofémorale, IPS cheville/bras. Le dépistage des marqueurs précoces du remodelage artériel est à privilégier par le caractère prédictif de complications cardiovasculaires et par la simplicité de mesure, validée et précise.

Épaisseur intima-média et plaques carotidiennes

L'EIM est définie par l'échostructure des parois superficielle et profonde de l'artère carotide commune en coupe longitudinale limitée par l'interface sang circulant-intima, et par l'interface média-adventice. Ce marqueur est un prédicteur indépendant d'apparition de plaque d'athérosclérose carotidienne. Il est à distinguer de la plaque, définie, selon le consensus de Mannheim, par le décrochage dans la lumière artérielle d'une échostructure d'épaisseur au moins égale à 0,5 mm ou à 50 % de l'EIM ou supérieure à 1,5 mm lorsqu'elle est mesurée de l'interface endoluminale à l'interface média-adventice [28]. L'échographie haute résolution (échotracking) permet une mesure de l'EIM avec une précision suffisante (de l'ordre de 2,5 µm), 5 à 10 mm sous la bifurcation carotidienne, sur la paroi distale et à distance d'une plaque. La valeur prédictive de l'EIM sur le risque de survenue d'un accident cardio- ou cérébrovasculaire a été largement démontrée [29]. Cependant l'apport de celui-ci dans l'évaluation du risque cardiovasculaire, après mesure des facteurs de risque conventionnels, semble modeste [30]. Même si ce marqueur ne présente pas toutes les qualités d'un critère de substitution, en particulier il serait insuffisamment prédictif de l'action des antihypertenseurs, son association aux autres marqueurs d'athérosclérose infraclinique pourrait améliorer l'évaluation du risque cardiovasculaire chez le patient classé à risque faible ou intermédiaire en le reclassant dans la catégorie à haut risque, et permettant ainsi une prise en charge plus précoce et renforcée du risque global. L'ESH recommande la mesure de ce paramètre artériel en proposant la valeur seuil de 1,16 mm en 2009 (paramètre rehaussé par rapport à la valeur de 0,9 mm en 2007), à interpréter en fonction de l'âge, chez l'homme et la femme.

Pression centrale, index d'augmentation et vitesse de l'onde de pouls

La rigidité des gros troncs artériels, en particulier aortique, est un marqueur prédictif indépendant de mortalité toutes causes et de morbidité cardiovasculaire chez les patients hypertendus. L'estimation non invasive de la pression centrale, de l'index d'augmentation et de la vitesse de l'onde de pouls (VOP) permet une étude simple de la compliance artérielle. Ces trois marqueurs sont significativement corrélés à l'incidence des événements cardiovasculaires. La mesure de la VOP est possible par l'enregistrement simultané de deux ondes de pouls artériels : les principales zones de perception du flux pulsé sont l'artère temporale, carotide, humérale, radiale, fémorale et pédieuse. La technique de référence pour la mesure de la rigidité régionale aortique est la tonométrie d'aplanation évaluant la VOP carotido-fémorale : plus la VOP est grande, plus la compliance aortique est diminuée. Des altérations significatives de l'aorte chez les sujets hypertendus sont illustrées par une valeur-seuil de VOP à 12 m/s. Ce paramètre a été rehaussé à 16,3 m/s en 2009 suite à la relecture des recommandations européennes, en gardant à l'esprit que la relation entre rigidité aortique et événements cardiovasculaires est continue. La rigidité artérielle peut également être évaluée par l'analyse de l'onde de pouls. Une estimation informatisée de la pression aortique centrale est assurée par l'analyse de la forme de l'onde de pouls au niveau périphérique. L'amplitude de l'onde de pression au niveau de l'aorte provient de la sommation de l'onde incidente (après éjection ventriculaire) et de l'onde réfléchie (naissant au niveau des bifurcations artérielles). Chez les sujets sains, l'onde réfléchie revient vers le cœur en diastole, favorisant ainsi la perfusion coronaire. La rigidité artérielle, liée au vieillissement et à des décennies d'HTA, favorise le retour plus rapide, durant la systole de l'onde de réflexion (index d'augmentation de l'onde de pouls due à l'onde réfléchie), à l'origine d'une HTA systolique et du risque d'hypertrophie cardiaque. La pression diastolique diminue, parallèlement à l'augmentation de la pression pulsée, et implique l'existence d'un risque accru d'ischémie coronaire. L'échodoppler de la carotide par échotracking de la paroi permet également l'évaluation de la compliance artérielle mais n'est pas proposé actuellement dans le dépistage systématique du risque artériel du fait de la durée de l'examen et du haut niveau de compétence requis de l'opérateur.

Index de pression systolique à la cheville

Examen facile, reproductible et non invasif, la mesure de l'IPS doit être réalisée en première intention pour le diagnostic positif et de sévérité d'une AOMI ainsi que pour sa surveillance ultérieure (que le traitement soit ou non chirurgical). Prédicteur indépendant de morbimortalité cardio- et cérébrovasculaire, l'IPS constitue un paramètre de premier plan dans l'évaluation du risque artériel. Les guides de bonne pratique ne proposent pas de définition claire pour le calcul de l'IPS. L'American Heart Association recommande d'utiliser la valeur la plus haute des pressions de cheville. Cependant, il existe un intérêt à retenir la valeur la plus basse des pressions systoliques de cheville et la valeur la plus élevée de la pression systolique humérale dans le calcul de l'IPS, pour le diagnostic positif de l'AOMI et le pronostic en termes d'incidence et de survie sans événements cardiovasculaires [31]. L'association de signaux Doppler normaux et d'un IPS normal exclut une AOMI avec une fiabilité supérieure à 90 %. Les seuils de normalité de l'IPS sont 0,90 et 1,30. Un IPS cheville/bras inférieur à 0,9 au Doppler continu affirme l'existence d'une AOMI avancée. Au-dessus de 1,30, l'IPS définit une médiacalcose jambière. Les limites et causes d'erreur (surestimation de l'IPS) sont représentées par la médiacalcose (fréquente en cas de diabète, insuffisance rénale chronique terminale, grand âge), par un artefact ou obstacle à l'occlusion artérielle (lipodystrophie, œdème, ulcère), par l'existence de sténoses proximales courtes avec bon lit d'aval et les lésions des artères du pied ou autres sténoses artérielles en dehors de l'axe aorte-cheville.

■ Implications thérapeutiques

Parallèlement aux règles hygiénodiététiques, la prise en charge pharmacologique des facteurs de risque a démontré son efficacité dans la réduction de la morbimortalité cardiovasculaire, stabilisant la progression dans le continuum de la maladie athéroscléreuse. La stratégie thérapeutique globale du patient hypertendu avec atteinte athérosclérose diffuse doit faire intervenir le plus souvent une polythérapie antihypertensive, une statine et un antiagrégant plaquettaire.

Traitement antihypertenseur

Il existe une relation linéaire, sans seuil, entre la tension artérielle à partir de 115/75 mmHg et la mortalité cardiovasculaire et globale [32]. Le bénéfice du traitement antihypertenseur

> **Point fort**
>
> **Dépistage de l'atteinte artérielle infra-clinique**
>
> Marqueurs prédicteurs indépendants du risque de survenue d'un accident cardio- ou cérébrovasculaire :
> • EIM ≥ valeur-seuil de 1,16 mm ou présence de plaques d'athérome ;
> • VOP ≥ valeur-seuil de 16,3 m/s ;
> • IPS à la cheville < 0,9 ou >1,3.
>
> Association au dépistage des facteurs de risque classique et à l'atteinte des organes cibles (HVG électrique ou échographique, augmentation de la créatininémie ou baisse du débit de filtration glomérulaire, microalbuminurie ou protéinurie).
>
> Objectif : identifier les patients à plus haut risque cardiovasculaire que ne le révèlent les facteurs de risque classiques seuls.

a clairement été démontré en prévention primaire et secondaire en termes de morbimortalité cardio- et cérébrovasculaires et de néphroprotection. Chez les patients hypertendus âgés, l'efficacité du traitement antihypertenseur est également mise en évidence par plusieurs études [33, 34]. Les cinq principales classes d'antihypertenseurs se sont avérées efficaces dans la réduction des chiffres tensionnels et du risque cardiovasculaire. Cependant, certaines classes présentent un bénéfice supplémentaire au-delà de la baisse des chiffres tensionnels. Ainsi, les inhibiteurs de l'enzyme de conversion de l'angiotensine (IEC), les antagonistes des récepteurs de l'angiotensine II (ARAII) et les antagonistes calciques semblent plus efficaces pour réduire l'HVG, améliorant ainsi le pronostic cardiovasculaire [35]. Les ARAII apportent un bénéfice dans la réduction du risque d'arythmie complète par fibrillation auriculaire de novo ou récidivante, corrélée à la régression de l'HVG. Quant aux IEC, ils occupent une place incontournable dans le postinfarctus mais également dans la prise en charge pharmacologique du patient athéroscléreux par leurs effets vasculoprotecteurs propres [12, 36], inhibant la conversion de l'angiotensine I en angiotensine II, acteur puissant du stress oxydatif.

Statine

Régulant la synthèse de cholestérol endogène par inhibition de l'hydroxy-3-méthyl glutaryl coenzyme A (HMG-CoA) réductase, les statines semblent également avoir une action sur la diminution de la dysfonction endothéliale, des marqueurs de l'inflammation et sur la stabilisation de la plaque d'athérome. En prévention secondaire comme en prévention primaire, le bénéfice des statines sur la morbimortalité cardio- et cérébrovasculaire a bien été démontré [37, 38]. Les patients hypertendus ayant une maladie cardiovasculaire avérée doivent recevoir un traitement par statine avec une cible de LDL cholestérol inférieure à 1 g/l. En prévention primaire, chez le patient à haut risque, cette attitude thérapeutique est recommandée par L'ESH même en l'absence de dyslipidémie. Il faut être cependant prudent quant à une baisse excessive du taux de LDL avec de fortes doses de statine : il existe un risque de mauvaise observance ou d'arrêt du traitement pour majoration des effets indésirables. Les patients âgés, insuffisants rénaux, un contexte d'hypothyroïdie, d'éthylisme ou de maladie neuromusculaire sont autant de circonstances devant encourager le dépistage d'effets indésirables par un suivi clinique et biologique rapproché.

Antiagrégant plaquettaire

La réduction du risque d'infarctus du myocarde et d'AVC est observée lors du traitement par antiagrégant plaquettaire, en particulier aspirine à faible dose, chez les patients en prévention secondaire ou primaire à haut risque cardiovasculaire [39] et dans un contexte d'équilibre tensionnel. Le risque d'accident hémorragique doit être pris en compte lors de la décision de traiter : en prévention primaire, chez les patients à moindre risque l'aspirine semble être plus délétère que bénéfique [40].

Conclusion

L'athérosclérose est la principale cause de morbimortalité cardio- et cérébrovasculaire dans le monde. L'HTA, facteur de risque majeur de développement et de progression de la maladie athéroscléreuse, est à l'origine d'une atteinte des organes cibles par l'intermédiaire d'altérations micro- et macrovasculaires. L'optimisation de la prise en charge du patient hypertendu nécessite l'évaluation du risque cardiovasculaire global la plus fiable possible. L'importance de la cible artérielle réside en la possibilité de détecter le retentissement vasculaire de l'HTA à un stade précoce de la maladie athéroscléreuse avant sa traduction clinique. La recherche des facteurs de risque classiques représente la première étape dans l'évaluation du risque artériel. Le dépistage non invasif d'une atteinte artérielle infraclinique permet de rehausser le risque du patient hypertendu, imposant une prise en charge thérapeutique plus agressive pour lutter efficacement contre le risque de maladie coronaire et d'AVC.

Références

[1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global Burden of hypertension: analysis of worldwide data. *Lancet* 2005;**365**:217–23.

[2] Blacher J, Evans A, Arveiler D, Amouyel P, Ferrières J, Bingham A, et al. Residual cardiovascular risk in treated hypertension and hyperlipidaemia: The PRIME study. *J Hum Hypertens* 2010;**24**: 19–26.

[3] Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen. C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998;**279**:1477–82.

[4] Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;**340**:115–21.

[5] Gibbons GH, Dzau VJ. The Emerging Concept of Vascular Remodeling. *N Engl J Med* 1994;**330**:1431–8.

[6] Safar ME, London GM, Asmar R, Frohlich ED. Recent advances on large arteries in hypertension. *Hypertension* 1998;**32**:156–61.

[7] Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty AM, Korsgaard N, Schiffrin EL, et al. Vascular remodeling. *Hypertension* 1996;**28**: 505–6.

[8] Chobanian AV. 1989 Corcoran lecture: adaptive and maladaptive responses of the arterial wall to hypertension. *Hypertension* 1990;**15**:666–74.

[9] O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK, Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;**340**:14–22.

[10] Zureik M, Ducimetière P, Touboul PJ, Courbon D, Bonithon-Kopp C, Berr C, et al. Common carotid intima-media thickness predicts occurrence of carotid atherosclerotic plaques: longitudinal results from the aging vascular study (EVA) Study. *Arterioscler Thromb Vasc Biol* 2000;**20**:1622–9.

[11] Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995–1003.

[12] Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.

[13] Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis G. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;**316**:1371–5.

[14] Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: The lexicon of a new frontier. *J Am Coll Cardiol* 1994;**23**:809–13.
[15] Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: Role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993;**69**:377–81.
[16] Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;**369**: 283.
[17] Haute Autorité de Santé (HAS). Recommandation professionnelle. Prévention vasculaire après un infarctus cérébral ou un accident ischémique transitoire, argumentaire, mars 2008.
[18] Taylor Jr LM, Porter JM. Basic data related to clinical decision-making in abdominal aortic aneurysms. *Ann Vasc Surg* 1987;**1**: 502–4.
[19] Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease. *J Am Coll Cardiol* 2006;**47**: 1–192.
[20] Diehm C, Lange S, Darius H, Pittrow D, von Stritzky B, Tepohl G, et al. Association of low ankle brachial index with high mortality in primary care. *Eur Heart J* 2006;**27**:1743–9.
[21] Fine MJ, Kapoor W, Falanga V. Cholesterol crystal embolization: a review of 221 cases in the English litterature. *Angiology* 1987;**38**:769–84.
[22] Elkins JS, O'Meara ES, Longstreth WT, Carlson MC, Manolio TA, Johnston SC. Stroke risk factors and loss of high cognitive function. *Neurology* 2004;**63**:793–9.
[23] Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. *J Am Geriatr Soc* 2002;**50**:1431–8.
[24] Camm J, Kirchhof P, Lip G, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010;doi:10.1093/eurheartj/ehq278.
[25] Recommandations Européennes 2007. Guidelines for management of hypertension. *J Hypertens* 2007;**25**:1105–87.
[26] Réévaluation 2009 des recommandations européennes pour la prise en charge de l'HTA. Reappraisal of European guidelines on hypertension: a European society of hypertension task force document. *J Hypertens* 2009;**27**:2121–58.
[27] Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes: Part I: Pathophysiology and Clinical Trial Evidence (Risk Factors Through Stable Coronary Artery Disease). *Circulation* 2006;**114**: 2850–70.
[28] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006): An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007;**23**:75–80.
[29] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardio-vascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* 2007;**115**:459–67.
[30] Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. *Circulation* 2007;**116**:32–8.
[31] Espinola-Klein C, Rupprecht HJ, Bickel C, Lackner K, Savvidis S, Messow CM, et al. Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. *Circulation* 2008;**118**:961–7.
[32] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–13.
[33] Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999;**353**:793–6.
[34] Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;**358**:1887–98.
[35] Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003;**115**:41–6.
[36] The European trial on reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–8.
[37] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
[38] Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial: Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149–58.
[39] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;**324**:71–86.
[40] Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755–62.

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1.2.3 Conclusion de l'article 1

Parallèlement au contrôle des autres facteurs de risque, l'optimisation de la prise en charge thérapeutique du patient hypertendu ne devrait pas se restreindre au seul contrôle du niveau de pression artérielle brachiale en consultation. Deux constats, le risque cardiovasculaire résiduel sous traitement et le phénomène de la courbe en J, encouragent à affiner l'estimation du risque cardiovasculaire individuel et à personnaliser les stratégies thérapeutiques.

L'existence d'un risque résiduel, après ajustement aux autres facteurs de risque et pour un même niveau tensionnel, a été initialement mise en évidence par l'étude PRIME (36). La prise d'un traitement antihypertenseur est associée à un niveau plus élevé d'événements coronariens, cérébro-vasculaires et à la mortalité cardiovasculaire. La question de l'objectif tensionnel optimal s'est donc posée. Les recommandations européennes proposaient il y a quelques années une cible inférieure à 140/90 mm Hg pour l'hypertension essentielle non compliquée et inférieure à 130/80 mm Hg en prévention secondaire, chez les patients diabétiques ou les patients avec maladie rénale (37). Cependant cet objectif plus strict chez le patient à haut risque cardiovasculaire n'est pas conforté par les grands essais cliniques, pouvant même être délétère dans certaines situations. Le concept "the lower the better" est aujourd'hui abandonné. Depuis plus de trois décennies, l'attention est attirée sur le risque d'une augmentation paradoxale de la morbi-mortalité cardiovasculaire associée à une baisse trop importante des chiffres tensionnels (concept de la "courbe en J") (38). L'existence d'une relation inverse entre la mortalité et les événements cardiovasculaires et la pression artérielle systolique et diastolique au cours du traitement antihypertenseur semble exister pour les patients fragiles en particulier le sujet âgé, en présence de comorbidités ou d'une coronaropathie (39). De plus, indépendamment de la présence ou non d'un traitement antihypertenseur, une pression diastolique inférieure à 70 mm Hg, en comparaison à une

pression diastolique entre 70 et 89 mm Hg, est un facteur prédictif de survenue d'événements cardiovasculaires chez les patients avec hypertension artérielle systolique isolée (40, 41). Ce risque majoré d'événements cardiovasculaires a été mis en évidence dans une population d'âge moyen et plus, en prévention primaire ou secondaire. La pression pulsée était positivement associée au risque de survenue d'événements chez les patients avec pression diastolique inférieure à 70 mm Hg.

Cette relation inverse entre les chiffres de pression artérielle les plus bas et la mortalité cardiovasculaire impose une attitude thérapeutique prudente et adaptée à chaque patient. Depuis 2009, la révision des recommandations européennes met en garde contre une diminution tensionnelle trop ambitieuse et propose un seuil tensionnel à ne pas dépasser de 130/80 mm Hg chez le patient à haut risque (42). En accord avec les recommandations de la Société Européenne d'Hypertension, les recommandations françaises préconisent de ne fixer qu'un seul objectif tensionnel, entre 130/80 mm Hg et 140/90 mm Hg, quel que soit le niveau de risque. Chez le sujet très âgé, il est rappelé que l'objectif tensionnel systolique est moins strict, entre 140 et 150 mm Hg (35).

1.3 Physiopathologie de l'hypertension artérielle : interactions entre atteintes artérielles macro et micro vasculaires (Article 2)

Le risque résiduel sous traitement antihypertenseur et la relation de courbe en J entre pression artérielle et mortalité pourraient être des indicateurs d'une maladie artérielle insuffisamment évaluée par la mesure de pression artérielle brachiale en consultation. L'article présenté ci-après décrit les anomalies artérielles macro et micro vasculaires au cours de la maladie hypertensive et leurs interactions respectives dans l'atteinte des organes cibles. De récentes études expérimentales et épidémiologiques suggèrent que les altérations vasculaires

pourraient également avoir un rôle précurseur dans l'augmentation de la pression artérielle. La maladie artérielle apparaît être une cible thérapeutique mais aussi préventive avant l'apparition d'une hypertension artérielle chez les patients à risque.

1.3.1 Introduction de l'article 2

Chez le patient hypertendu, la rigidité aortique et les altérations de la microcirculation sont considérées comme les dénominateurs communs de l'atteinte des organes cibles, en particulier le cœur, le cerveau et les reins (11). La rigidité aortique est considérée comme le marqueur de l'altération structurale et fonctionnelle de la paroi des gros troncs artériels. Les modifications de la structure pariétale représentent une réponse adaptative de la paroi artérielle aux contraintes liées à l'augmentation de la pression transmurale (43). Parallèlement, la répétition des cycles cardiaques au cours du vieillissement physiologique entraîne une altération de la structure pariétale aortique (44). Les modifications structurales associent une augmentation de la densité des fibres de collagène, une diminution et une altération des fibres musculaires lisses ainsi qu'une hypertrophie et une modulation phénotypique des cellules musculaires lisses. Il en résulte une augmentation de l'épaisseur et de la rigidité pariétales (45). Selon l'équation de Laplace (T=PR/h, où T est la contrainte liée à l'étirement pariétal; P, la pression transmurale; R, le rayon interne de l'artère ; h, l'épaisseur de la paroi artérielle), il existe une relation directe entre la contrainte mécanique pariétale liée à la pression (« wall tensile stress ») et la structure de la paroi artérielle exposée. L'augmentation chronique de la pression artérielle moyenne est associée à une augmentation du calibre artériel au niveau de la macrocirculation : une corrélation positive entre pression artérielle moyenne et diamètre de l'artère brachiale avant et après traitement par dihydralazine a été mise en évidence chez des patients hypertendus (46). Une modulation adaptative du phénotype des cellules musculaires lisses vasculaires se fait en réponse à l'augmentation de R secondaire à

l'étirement pariétal : les cellules musculaires lisses s'hypertrophient, leur phénotype physiologique contractile est modifié pour un phénotype sécrétoire et prolifératif. L'augmentation des fibres de collagène et des fibres d'élastine de la matrice extracellulaire, secondaire à ces modifications phénotypiques, entraîne un remodelage de la paroi artérielle résultant en une augmentation de l'épaisseur de la média. L'objectif principal de cette réponse adaptative structurale des gros troncs artériels est de maintenir la contrainte mécanique pariétale à ses valeurs de base.

Ces modifications structurales de la paroi aortique sont parallèlement associées à une altération fonctionnelle pariétale avec une réduction de la compliance artérielle. L'amplitude de l'onde de pression incidente et l'amplitude et le temps de transit des ondes réfléchies en sont par conséquent modifiés et contribuent à l'augmentation de pression systolique centrale (23, 47). L'augmentation de la pression systolique et pulsée centrale paraît étroitement associée à l'atteinte des organes cibles. Au niveau du cœur, la réduction de la compliance aortique est corrélée à une augmentation de la post-charge et au degré d'hypertrophie ventriculaire gauche chez les patients hypertendus (48). Parallèlement à l'augmentation de la post-charge, la baisse de perfusion coronaire durant la diastole est une conséquence attendue de l'augmentation de la pression pulsée centrale. Le cerveau et les reins sont des organes présentant un débit de perfusion élevé systolo-diastolique et apparaissent également particulièrement sensibles à la pression pulsée centrale (49, 50). Une explication physiopathologique a été proposée, basée sur la perte progressive du mismatch d'impédance entre l'aorte et ses branches avec l'âge et en présence de divers facteurs de risque vasculaire (49, 51). La transmission excessive de la pulsatilité de la pression et du flux à la microcirculation est évitée par le mismatch d'impédance existant de manière physiologique entre l'aorte (compliante, à basse impédance) et ses branches artérielles, en particulier les

carotides communes et les artères rénales (à impédance plus élevée). Ce mismatch d'impédance apparaît être un mécanisme de protection rendant compte du phénomène de réflexion des ondes de pression à l'interface aorte- branche artérielle. Une rigidité aortique excessive peut rendre compte d'une impédance comparable à l'interface aorte-branche artérielle avec pour conséquence une diminution du phénomène de réflexion des ondes de pression. La transmission de l'énergie pulsatile excessive à la microcirculation est ainsi facilitée (49, 52).

Au cours de la maladie hypertensive, l'augmentation chronique des contraintes pariétales au niveau microcirculatoire est associée à une réduction de la lumière des artérioles (53, 54). Cette vasoconstriction artériolaire peut aller jusqu'à l'occlusion complète de la lumière vasculaire secondaire à une réponse myogénique excessive. La réponse adaptative structurale de la paroi des petites artères est quant à elle inversement corrélée à l'amplitude du tonus myogénique. L'amplitude de la réponse myogénique augmente au fur et à mesure que le diamètre du vaisseau diminue, le tonus myogénique étant maximal au niveau des artérioles de résistance pré-capillaires. La lumière de ces plus petites artères diminue mais leur paroi ne présente pas d'hypertrophie médiale du fait de la normalisation des contraintes mécaniques pariétales secondaire à la réponse myogénique (54). Les artérioles de plus grand diamètre (100-300 microns) présentent une réduction de leur lumière associée à un remodelage hypertrophique de leur paroi du fait de la moindre amplitude de leur réponse myogénique (53). La sollicitation chronique et excessive du tonus myogénique au cours de la maladie hypertensive entraîne par conséquent une raréfaction fonctionnelle microcirculatoire. La disparition des contraintes mécaniques physiologiques exercées par l'écoulement du sang sur l'endothélium vasculaire (« shear stress ») entraîne une involution de ces micro-vaisseaux et donc une raréfaction structurale micro vasculaire. Il en résulte un déséquilibre entre l'apport

et les besoins métaboliques locaux avec le risque d'ischémie tissulaire en cas de demande en oxygène augmentée.

La rigidité aortique et l'atteinte de la microcirculation sont ainsi considérées comme les conséquences de la maladie hypertensive. La revue de la littérature présentée ici souligne l'interaction entre les anomalies macro vasculaires et micro vasculaires dans l'atteinte des organes cibles au cours de la maladie hypertensive. Des données épidémiologiques et expérimentales suggèrent que l'atteinte artérielle macro et micro vasculaire précède la survenue de l'hypertension artérielle et contribue à sa pathogénèse. En particulier, la dysfonction endothéliale présente un rôle clé dans l'atteinte artérielle. Constitué à l'état basal d'une monocouche de cellules fines adjacentes situées à l'interface sang-paroi vasculaire et parallèles au flux sanguin, l'endothélium présente des propriétés essentielles au maintien de l'intégrité vasculaire : barrière de perméabilité vasculaire, surface anti-thrombotique et anti-inflammatoire, régulant les processus de coagulation et d'hémostase, et principal donneur physiologique de monoxyde d'azote (NO). La dysfonction endothéliale, caractérisée par la perte de la vasodilatation NO-dépendante apparaît être un précurseur de la pathogenèse de l'hypertension artérielle par l'intermédiaire d'une raréfaction artériolo-capillaire.

1.3.2 Article 2

Yannoutsos A, Levy BI, Safar M.E., Slama G, Blacher J.

Pathophysiology of hypertension: interactions between macro and microvascular alterations through endothelial dysfunction.

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Review

Pathophysiology of hypertension: interactions between macro and microvascular alterations through endothelial dysfunction

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Hypertension is a multifactorial systemic chronic disorder through functional and structural macrovascular and microvascular alterations. Macrovascular alterations are featured by arterial stiffening, disturbed wave reflection and altered central to peripheral pulse pressure amplification. Microvascular alterations, including altered wall-to-lumen ratio of larger arterioles, vasomotor tone abnormalities and network rarefaction, lead to disturbed tissue perfusion and susceptibility to ischemia. Central arterial stiffness and microvascular alterations are common denominators of organ damages. Vascular alterations are intercorrelated, amplifying the haemodynamic load and causing further damage in the arterial network. A plausible precursor role of vascular alterations in incident hypertension provides new insights for preventive and therapeutic strategies targeting macro and microvasculature. Cumulative metabolic burden and oxidative stress lead to chronic endothelial injury, promoting structural and functional vascular alterations, especially in the microvascular network. Pathophysiology of hypertension may then be revisited, based on both macrovascular and microvascular alterations, with a precursor role of endothelial dysfunction for the latter.

Keywords: aortic stiffness, arterial wall remodelling, endothelial dysfunction, microcirculation, microvascular dysfunction

Abbreviations: AGE, advanced glycation end-products; TGF-β, transforming growth factor-beta

INTRODUCTION

Hypertension is a major cardiovascular risk factor through functional and structural, macro and microvascular alterations. Large artery stiffness and microvascular alterations (abnormalities in vasomotor tone, functional and structural network rarefaction, decreased vasodilation reserve and altered wall-to-lumen ratio of larger arterioles) are considered as common denominators of most target organ damages, especially those having high blood flow perfusion such as kidneys, heart and brain. Both aortic stiffness and microcirculatory structural alterations are independent predictors of cardiovascular events in hypertensive patients [1–3]. Alterations in properties of large arteries and arteriolo-capillaries are consequences of hypertension and even amplify the haemodynamic load.

The adaptive response of vasculature to wall tensile stress during hypertensive disease depends on the level of myogenic constriction ability, which is inversely related to the diameter of the vessel [4]. Myogenic response to increased wall tensile stress is almost imperceptible in large conduit arteries, whereas resistance precapillary arteries (<100 μm) show the largest myogenic constriction response. Wall tensile stress is an important determinant of vascular adaptive remodelling during hypertensive disease. Structural changes including medial hypertrophy (and increased wall-to-lumen ratio) are inversely related to the myogenic response of the vessel. Increase in wall thickness is a necessary adaptive response in large arteries, including the aorta and others conduit arteries, during high blood pressure exposition, to maintain wall tensile stress constant [5]. Small resistance arterioles (<100 μm) do not undergo hypertrophic remodelling (but eutrophic inward remodelling without growth process) because of the inherent myogenic response leading to normalized wall tensile stress by lumen reduction [6]. Larger arterioles (100–300 μm) with lower myogenic tone undergo a combination of growth process leading to wall hypertrophy and lumen reduction [4]. Microvascular control mechanisms aim to protect fragile capillaries from excessive pressure exposure but are necessarily associated with a reduced mean blood flow and a resulting mismatch with local tissue metabolic demands in chronic hypertensive disease.

Macro and microvascular alterations are intercorrelated. Stiffening of the aortic wall leads to increased pulse wave velocity and premature reflected waves with elevated systolic and pulsatile central haemodynamic load resulting in

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peripheral tissues microcirculatory damages. Aortic stiffening is associated with increased vascular resistance, which depends on microvascular density, tone and structure [7]. Vascular remodelling in larger arterioles (associated with increased media-to-lumen ratio), directly and noninvasively measurable by scanning laser Doppler flowmetry in retinal circulation, is independently associated with central pulse pressure [8]. Inversely, increased peripheral resistance, secondary to altered microcirculatory vasomotor tone and/or to progressive loss of microvessels, leads to chronic elevated blood pressure [9], a major determinant of aortic stiffness. In hypertensive patients, increased media-to-lumen ration of subcutaneous arterioles (100–300 μm) are positively correlated with carotid-femoral pulse wave velocity (the gold standard noninvasive measurement for aortic stiffness) independently of age and mean blood pressure [10]. Microcirculatory structural damages possibly contribute to an increase in central systolic and pulse pressure by enhancing the phenomenon of reflected pressure waves [10].

The presence of adventitial microvascular network alterations and the concomitant inability to match blood flow supply with the wall of conduit artery metabolic demand may further accentuate large artery disease [11].

Microvascular alterations are commonly associated with other cardiovascular risk factors, especially chronic renal insufficiency [12], diabetes (or prediabetic conditions) [13], obesity [14] and dyslipidemia [15], and occur early in the pathogenesis and progression of related macrovascular alterations and cardiovascular complications. In addition to the frequent association between traditional risk factors, leading to enhanced vascular abnormalities, it has been suggested that vascular changes resulting from one risk factor independently of blood pressure present a key role in the pathogenesis of hypertension [16,17].

Temporal relationships between hypertension with macro and microvascular alterations seem therefore to be bidirectional [18]. Rather than a consequence of chronic elevated blood pressure, the potential precursor role of aortic stiffness and microvascular alterations in incident hypertension has raised interest with new insights in preventive and therapeutic strategies.

It has been suggested that microcirculatory alterations may precede larger artery dysfunction and atherosclerosis [19]. Endothelial dysfunction has a key role in microvascular alterations and is closely but not specifically related to hypertension. Endothelial dysfunction appears to be associated with other risk factors with a predictive value for atherosclerotic damages and cardiovascular events over and above Framingham risk score [20,21]. Endothelial dysfunction, a multifactorial disorder, may have a precursor and pivotal role in the pathogenesis of macro and microvascular alterations and therefore in incident hypertension. Endothelial dysfunction is characterized by impairment in nitric oxide dependent vasodilation secondary to decreased bioavailability of nitric oxide in particular owing to enhanced reactive oxygen species production. Oxidative stress associated with cumulative metabolic burden and chronic inflammation may therefore play an important role in the pathogenesis of incident hypertension through structural and functional vascular alterations secondary to endothelial dysfunction.

The present article describes arterial damages in macrovascular and microvascular networks as a consequence of hypertension and focuses on their interactions leading to the development and progression of target organ damages. Beyond the important precursor role of endothelial dysfunction, the present review also considers recent epidemiologic and experimental evidences suggesting that arterial damages may precede the onset of high blood pressure and may therefore represent not only therapeutic but also preventive targets for incident hypertension.

MACROVASCULAR ALTERATIONS IN HYPERTENSIVE PATIENTS

Aortic stiffness as target organ damage

Physiologic mechanical properties of the aortic wall account for the ability of the aorta to reduce the pulsatility of the ventricular ejection (damping) and to transform pulsatile to more steady (continuous) downstream blood flow, for lowering energetic cost of organ perfusion and to limit the pulsatile strain imposed to the peripheral microcirculation. Increased aortic stiffness due to ageing and cardiovascular risk factors is associated with structural and functional changes of the aortic wall. Structural changes include increased content of stiff wall materials such as collagen, associated with alterations of elastin fibres, inflammation, medial smooth muscle cell alterations (hypertrophy, phenotype modulation) and increased endothelial permeability with diffusion of macromolecules within the arterial wall [22]. The latter participates in the initial phase of atherogenesis [23].

There is a direct relationship between wall tensile stress and the structure of the exposed arterial wall. According to Laplace's equation ($T=PR/h$, T, wall tensile stress; P, pressure in the vessel; R, internal artery radius; h, arterial wall thickness), there is an adaptive phenotype modulation of vascular smooth cells in response to increased R secondary to elevated wall tensile stress: smooth muscle cells undergo hypertrophy and change from the physiological contractile phenotype to a secretory and proliferating phenotype. The increase in collagen and elastin contents of the extracellular matrix, which follows these functional changes, consists in arterial wall remodelling resulting in increased arterial wall thickness. The main objective of this structural adaptive response of large arteries is to maintain the wall tensile stress roughly at its baseline values; in parallel, increased arterial wall thickness leads to increased vascular stiffness [24].

Disturbed wave reflection and altered central to peripheral pulse pressure amplification give further information about structural and functional altered properties of the central and peripheral arteries [25]. Increased aortic stiffness leads to increased pulse wave velocity. The central pressure waveform is composed by an inflection point that divides the pressure wave into an early systolic peak and a subsequent peak due to the return of the reflected wave coming from the periphery (arterial bifurcations, small resistance arteries). An earlier reflected wave to the central circulation, due to increased pulse wave velocity related to aortic stiffness, amplifies the primary wave in systole rather

than diastole leading to an increase of central systolic and pulse pressures, both closely related to target organ damage.

Aortic stiffness is strongly associated with high blood pressure, as well as ageing, and presents an independent predictive value for cardiovascular events in patients with risk factors or in general population, first shown in high cardiovascular risk patients with end-stage renal disease [26]. The European guidelines recommend to determine noninvasively aortic stiffness by aplanation tonometry measurement of carotid-femoral pulse wave velocity for subclinical target organ damage and risk assessment in hypertensive patients [27].

Aortic stiffness as a predictor of incident hypertension

It is well recognized that aortic stiffness depends on the imposed wall tensile stress to the arterial wall and, hence, on cumulative exposure to elevated haemodynamic load [28]. Epidemiologic evidence suggests a strong interrelationship between aortic stiffness, systolic and pulse arterial pressure. Stiffening of the aortic wall is usually associated with increased pressure pulsatility and appears as the most important determinant of elevated SBP. In the Atherosclerosis Risk in Communities (ARIC) Study [29], carotid arterial elasticity was an independent predictor of incident hypertension in normotensive participants over a 6-year mean follow-up. In the Baltimore Longitudinal Study of Aging [30], carotid-femoral pulse wave velocity, the most widely used index of central arterial stiffness, was an independent predictor of the longitudinal increase in SBP and of incident hypertension in normotensive patients followed up for longer than 4 years. Recently, longitudinal assessment of the temporal relationship between aortic stiffness, wave reflection and incident hypertension suggests a precursor role of aortic stiffening in future altered systolic haemodynamic load [31].

Hypothetical pathogenesis of aortic wall alterations, independently of hypertension, includes physiological age-related modifications, epigenetic factors and pathological conditions associated with diabetes and metabolic syndrome [32], chronic renal insufficiency as well as nutritional habits. Ageing is a major predictor of aortic stiffening and a significant determinant of pulse wave velocity progression independently of blood pressure, in hypertensive patients and in normotensive individuals [33]. Physiological changes in arterial structure, composition and mechanical function with ageing have been reported [34,35]: luminal enlargement, stiffening of the arterial wall related to decreased elastin content and fragmented fibres associated with increased collagen content secondary to repeated cycles of high stress/strain and elastic recoils of the arterial wall, diffuse intimal thickening and vascular smooth muscle cells hyperplasia with increased extracellular matrix. The activated renin-angiotensin system exhibits pleiotropic effects on arterial wall remodelling via inflammatory and profibrotic actions of angiotensin II and aldosterone on the vascular cells. The physiological aortic wall age-related modifications likely account for the high prevalence of systolic hypertension among older adults. In addition to hypertension and age-related modifications, stiffening of the large artery wall may partly be determined and accelerated by other physio-pathological conditions:

1. Cumulative metabolic burden related to type 2 diabetes, fasting plasma glucose and fasting insulin levels, dyslipidemia and metabolic syndrome [16,36–38] lead to structural and functional arterial wall damages via oxidative stress, inflammation and advanced glycation end-products (AGE) accumulation. The latter is related to nonenzymatic protein glycation and forms irreversible and stiff cross-links in tissue proteins of the arterial wall, altering their structure and mechanical function.
2. Patients in end-stage renal disease present a burden of metabolic disorders related to frequent association to other cardiovascular risk factors. It has been suggested that increased aortic pulse wave velocity is influenced by the presence of aortic calcifications and diabetes mellitus, independently of age and blood pressure in patients with end-stage renal disease [39]. Diabetic patients with end-stage renal disease present accelerated atherosclerosis partly due to increased AGEs refractory to removal by current dialysis treatments [40].
3. Excess dietary salt intake promotes arterial stiffness via enhanced transforming growth factor-beta (TGF-β) production by endothelial cells [41]. The multifunctional growth factor TGF-β is associated with several cellular mechanisms, including cell growth control, cell differentiation and expression of extracellular matrix proteins with possible deleterious pro-fibrotic effects [42]. TGF-β may influence arterial stiffness [22].
4. Genetic and environmental determinants may also be related to aortic stiffening. Genome-wide linkage approach in the Framingham Heart Study has suggested potential loci in different credible candidate genes for aortic stiffness [43]. The Strong Heart Study has suggested carotid stiffness heritability in adult men and women, estimating by the residual phenotypic variance independently of confounding factors [44]. Arterial stiffness appears to be partly determined independently of the influence of blood pressure, age, heart rate, height and other cardiovascular risk factors [45].
5. In addition, epidemiologic and experimental evidences highlight the importance of environmental factors acting during in-utero and perinatal development in disease causation, in particular for pathogenesis of cardiovascular diseases, diabetes, metabolic syndrome and hypertension [46]. The structural and functional target organs 'reprogramming' (kidneys, heart, renin-angiotensin system, vascular smooth cells, endothelial cells) in response to abnormal stimuli during perinatal development include epigenetic modifications such as methylation, acetylation of gene or promoter sequences and posttranscriptional regulation of gene expression by micro-RNA. Low birth-weight has been associated with increased susceptibility for adult cardiovascular diseases,

possibly via premature alterations in structure and function of large and small arteries [47]. Nutritional restrictions [48] or diabetic intrauterine environment exposition [49] lead to salt-sensitive adult hypertension susceptibility in offspring through endothelial dysfunction and impairment of renal development with nephronic restriction [50].

The complex temporal relationship between aortic stiffening and hypertension in terms of cause and effect is theoretically bidirectional but remains unclear because of the strong correlation between large artery stiffening and blood pressure and the multiplicity of causal factors potentially implicated in both pathophysiological mechanisms.

MICROVASCULAR ALTERATIONS IN HYPERTENSIVE PATIENTS

Microcirculation includes the smallest arteries, arterioles, capillaries and venules. Resistance arterioles present a physiologic inherent characteristic to respond to increasing pressure mainly by a myogenic reduction in lumen diameter [51]. The microcirculatory network is essential for tissue perfusion and organ function via three main mechanisms: tissue nutritive role in response to variations in demand, capillaries protection against the potential damaging blood pressure increase, and local and systemic peripheral resistance determination [16]. Microvascular alterations, and in particular rarefaction, may have consequences not only for tissue perfusion, metabolism and susceptibility to ischemia but also for peripheral vascular resistance and blood pressure increase. Microcirculatory damages appear to represent a systemic condition [16,52] and skin capillaries may reflect microvascular network in different vascular beds, being a surrogate marker of systemic microvascular function and resistance [52–54]. Recently introduced and deserving further evaluation, retinal circulation offers an easily accessible and noninvasive method to study structural alterations in larger arterioles using scanning laser Doppler flowmetry [55].

Microvascular alterations as target organ damage

Chronic high blood pressure is usually associated with altered structure and function of microvessels. Increased myogenic tone and arteriolar vasoconstriction help protect downstream capillaries but promote functional rarefaction (increased number of nonperfused microvessels) that can progress to structural rarefaction (anatomical absence of microvessels). Well described in large arteries in response to increased wall tensile stress, remodelling of the arterial wall in resistance arteries is modest or absent compared with that of the large arterial wall because of the smaller R/h ratio (1/1 in arterioles versus 1/12 at the aortic level) and the inherent myogenic tone [56,57]. Increased blood pressure in resistance arterioles induces local vasoconstriction via the myogenic tone effect. The arteriolar wall tensile stress is thus maintained at normal or even lower values. In the absence of an increase in resistance arteriole wall tensile stress, there is no remodelling of these arterioles [4,57]. However, in larger arterioles with lower myogenic tone, remodelling contributes to the progressive reduction in vascular lumen and progressive limitation of capillary perfusion.

Rarefaction appears to be at first functional (with increased vasoconstriction secondary to excessive myogenic tone in response to high blood pressure) leading to structural (anatomical disappearance of nonperfused vessels) in hypertensive patients [58]. Structural rarefaction possibly occurs by destructive process or insufficient angiogenesis secondary to decreased bioavailability of nitric oxide, a major endothelial vasodilating, proangiogenic and antiapoptotic factor:

1. The loss of shear stress in nonperfused microvessels leads to decreased nitric oxide production, promoting endothelial cell apoptosis and microvascular rarefaction [59–61].
2. Destructive nitric oxide process by reactive oxygen species occurs secondary to activation of renin-angiotensin system in hypertensive patients: angiotensin II activates endothelial NADPH oxidase leading to oxidative stress with peroxynitrite formation [62].

Microvascular damage is a predictor of adverse long-term cardiovascular prognosis. Among individuals with normal or minimally diseased coronary arteries, reduced coronary flow reserve, an indicator of microvascular dysfunction in the myocardium, is an independent predictor of cardiovascular events within the next decade [63]. In hypertensive patients, whether treated or not, the Framingham score for cardiovascular risk appears to be negatively correlated to skin capillary density [64]. Further prospective study is needed to determine whether capillary rarefaction presents a clinically relevant predictive value. Structural changes, characterized by a decreased lumen and an increased media-to-lumen ratio in larger arterioles, present an independent predictive value for cardiovascular events in hypertensive patients [65,66]. Structural changes of media-to-lumen ratio in larger subcutaneous arterioles during antihypertensive drug treatment have a prognostic significance in terms of cardiovascular events in patients with essential hypertension independently of blood pressure and despite blood pressure normalization. Reduction of media-to-lumen ratio in larger subcutaneous arterioles may then be considered as an intermediate endpoint to evaluate effect of antihypertensive treatment over and above blood pressure reduction [67].

Cross-talk between macro and microvascular alterations

Aortic wall stiffening leads to enhanced central pulse and systolic pressures. Increased pressure pulsatility promotes deleterious effects on target organs largely related to specific microcirculatory damages, as assessed with the relationship between macrovascular alterations and vascular remodelling in the retinal circulation, which is closely related to the cerebral microcirculation [8]. Noninvasive measurement of media-to-lumen ratio of retinal arterioles using scanning laser Doppler flowmetry may provide similar prognostic information compared with micromyographic measurement of subcutaneous larger arterioles [55].

In the case of the myocardium, the cross-talk between macrovascular and microvascular alterations contributes to the pathophysiology of cardiovascular diseases. Decreased large epicardial, and thus intramyocardial precapillary, coronary vascular tree perfusion during diastole is a consequence of enhanced central pulsatility and leads to decreased coronary flow reserve, a surrogate marker of hypertensive heart damage [68]. Intramyocardial coronary artery rarefaction and remodelling [69], left ventricular hypertrophy (resulting from long-term enhanced cardiac load) and impairment in left ventricular diastolic function in hypertensive patients further contribute to microcirculatory flow reserve reduction, impaired tissue perfusion and susceptibility in ischemia during high metabolic and oxygen demand [16,68]. Coronary microcirculation and epicardial artery diseases contribute each other to the pathogenesis of ischemic heart disease and amplify their respective deleterious role [70]. Microcirculatory abnormalities may further represent an indirect marker of large vessel dysfunction and atherosclerosis with a predictive ability, providing additional information to angiographic and risk factors assessment [71].

Structural rarefaction and remodelling of the microvessels in turn account for long-term elevation of systemic vascular resistance and enhanced wave reflection, contributing to aortic wall stiffening [7,9,10,72,73]. This vicious circle accounts for the intercorrelation between large and small resistance arteries alterations leading to difficult blood pressure control and antihypertensive treatment resistance.

Microvascular alterations as a predictor of incident hypertension

Mounting evidence highlights bidirectional relationship between microvascular network and hypertension. An increase in vascular resistances secondary to microvascular rarefaction results in an increase in mean arterial pressure. Rarefaction may therefore represent one of causal components rather than only a consequence of hypertension [16,27]. It has been demonstrated that skin capillary density appears to be inversely correlated to blood pressure levels in hypertensive and normotensive individuals [74,75]. In hypertensive patients, capillary rarefaction in skeletal muscle has been correlated with an increase in mean arterial pressure [76]. Structural rarefaction in skin capillaries can be a primary process, detected in normotensive individuals with familial history of hypertension [77]. Moreover, a causal and effect relation between microvascular network and blood pressure is supported by two observations:

1. increased skin capillary density detected in treated hypertensive patients [64];
2. blood pressure reduction correlated with decreased systemic resistance secondary to enhanced angiogenesis in spontaneously hypertensive rats exposed to chronic hypoxia. Chronic hypoxia also prevents (via endothelial nitric oxide and induction of vascular endothelial growth factor) the occurrence of hypertension in young prehypertensive rats by the same physiological and molecular mechanisms [78].

Thus, microvascular alterations may both result from and cause hypertension. Abnormality in the microvascular system appears to be common to conventional cardiovascular risk factors, including diabetes mellitus, dyslipidemia and obesity and is strongly associated with ageing. Altered microcirculatory network appears as a hallmark of long-term complications in diabetic, whether normotensive or hypertensive patients, including severe hypertrophic remodelling in larger arterioles [79], skeletal muscle capillary rarefaction [80] and impaired coronary flow reserve in the absence of coronary artery stenosis [14]. Experimental studies in obese Zucker rats (with defective leptin receptor gene leading to obesity, type 2 diabetes and hypertension) highlighted microvascular rarefaction in skeletal muscle before any elevation of blood pressure has occurred. Rarefaction is not a consequence of hypertension, in this experimental rat model as prevention of hypertension by hydralazine treatment (a direct-acting smooth muscle relaxant) does not prevent reduction in skeletal muscle microvessel density in the obese Zucker rats [81]. Structural changes of arterioles and capillary rarefaction are also hallmarks of metabolic syndrome, an important component of insulin resistance, defined by three or more characteristics, including abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia and hypo–high-density lipoprotein cholesterolemia [82]. In addition to structural rarefaction in microvascular network, obesity-associated insulin resistance is also featured by microvascular functional abnormalities [83]. Insulin promotes capillary recruitment [84] and presents vasodilatory as well as vasoconstrictive properties in resistance arteries via endothelium nitric oxide and endothelin release, respectively [83]. In healthy individuals, the net effect of insulin-mediated vasoreactivity tends to endothelium-dependent vasodilation, whereas in obese individuals, the balance is shifted towards vasoconstriction. In obese individuals, endothelium dysfunction and thus decreased sensitivity of resistance arteries to insulin-mediated endothelium-dependent vasodilation has been ascertained [83,85], several pathways being potentially implicated. First, abnormal endothelial intracellular signalling leads to decreased insulin-mediated endothelial nitric oxide production, intact insulin mediated vasoconstriction secondary to endothelin release and shift from dilation towards constriction vasoreactivity. Second, obesity is associated with increased reactive oxygen species production leading to reduction in nitric oxide bioavailability. Third, endocrine mechanisms inherent to adipose tissue include multiple adipokines and all the components of the renin–angiotensin system generating vasoconstrictor angiotensin II. Obesity-associated microvascular dysfunction may therefore represent a mechanism via insulin resistance leading to obesity-associated hypertension.

Apart from increased systemic resistance, the precursor role of microvascular network alterations in incident hypertension may theoretically be determined directly by adventitial microcirculation abnormalities in large vessels. Adventitia is considered as the vital wall of conduit arteries, which protects and nourishes large vessels. Vasa vasorum microcirculation network alterations appear to have a potential deleterious role on aortic stiffness [86,87] and therefore may have causal effect in incident hypertension.

Endothelial dysfunction and microvascular alterations

Microvascular network may represent a promising therapeutic and preventive target, considering the important role of microcirculation on target organ damage, on macrovascular dysfunction and potentially on incident hypertension. This distal part of the vascular tree is highly sensitive to vasoactive substances of endothelial origin [19], and thus, endothelial dysfunction appears to have a precursor role in microvascular alterations.

Vascular endothelium is a dynamic organ constituted of a single layer of endothelial cells tapered at the interface blood/vessel wall and parallel to the blood flow. The endothelium presents an essential role in vascular integrity maintenance, exposed to shear forces generated from blood flow. Laminar shear elicits anticoagulant, antiatherosclerotic and antithrombotic pathways, in particular via endothelial-derived nitric oxide [88,89]. This major vasodilating and pro-angiogenic factor contributes to local vascular tone and blood pressure regulation and stimulates the release of vascular endothelial growth factor for controlling vasculogenesis and vascular remodelling in response to shear stress. The anti-inflammatory, antiatherogenic and antithrombotic properties of nitric oxide are demonstrated through its ability to inhibit platelet agregation, endothelial leukocyte adhesion and smooth muscle cell proliferation and migration. Endothelial function is usually evaluated by measuring the nitric oxide-dependent vasodilation stimulated by mechanical (flow-mediated vasodilation) or pharmacological (after acetylcholine perfusion) mechanisms [90].

Endothelial dysfunction, characterized by loss of nitric oxide dependent vasodilation, may be the earliest vascular manifestation of macro and microvascular dysfunction. It has been suggested that endothelial cells may modulate large arterial stiffness, but endothelial function in central arteries has not been directly assessed in humans. The role of endothelium-mediated factors appears to predominate in distal resistance arteries [19] and endothelial dysfunction (or endothelial activation) promotes arterial structural and functional abnormalities:

1. Endothelial cell apoptosis or insufficient angiogenesis secondary to loss of endothelial nitric oxide mediated properties may both lead to microvascular rarefaction [59–62].
2. Impaired endothelial-dependent coronary vasoreactivity characterized by vasoconstrictor response to acetylcholine infusion (an endothelium-dependent dilator in physiological conditions) appears as an independent predictor of atherosclerotic disease progression and cardiovascular events [91].

Oxidative environment, a multifactorial disorder generated by cumulative exposition to cardiovascular risk factors, leads to endothelium activation. Quiescent endothelial phenotype exposed to reactive oxygen species switches into a pro-inflammatory phenotype, with hydrogen peroxyde accumulation, redox signalling [20] and decreased nitric oxide bioavailability. Plausible hypothesis in the pathogenesis of incident hypertension may involve endothelial dysfunction with a precursor role: cumulative metabolic burden and chronic oxydative stress may lead to chronic endothelial injury and activation, promoting structural and functional vascular alterations, in particular in the microvascular network.

CONCLUSION

Functional and structural macro and microvascular alterations appear as common denominators to target organ damage in hypertensive patients. Bidirectional relationship between aortic stiffness and systolic hypertension is supported by epidemiologic evidence, suggesting a precursor role of aortic stiffening in incident hypertension. The complex relationship between aortic stiffening and hypertension in terms of cause and effect remains unclear because of the multiplicity of causal factors potentially implicated in their pathophysiology, including genetic, epigenetic, environmental, nutritional and metabolic factors as well as physiological vascular ageing. There is observational and experimental support for the suggestion that microvascular network alterations precede and even predict incident hypertension. Pathophysiology of hypertension may then be revisited, based on both macrovascular and microvascular alterations, with a precursor role of endothelial dysfunction for the latter. Both large and small arteries should be targeted by antihypertensive strategies. Microvascular network may represent not only a promising therapeutic but also preventive target for incident hypertension via pharmacological and nonpharmacological strategies to reduce insulin resistance and renin–angiotensin system activation.

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Conflicts of interest

There is no conflict of interest for any of the authors.

REFERENCES

1. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002; 39:10–15.
2. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241.
3. De Ciuceis C, Porteri E, Rizzoni D, Rizzardi N, Paiardi S, Boari GE, *et al.* Structural alterations of subcutaneous small-resistance arteries may predict major cardiovascular events in patients with hypertension. *Am J Hypertens* 2007; 20:846–852.
4. Allen SP, Wade SS, Prewitt RL. Myogenic tone attenuates pressure-induced gene expression in isolated small arteries. *Hypertension* 1997; 30:203–208.
5. Stacy DL, Prewitt RL. Effects of chronic hypertension and its reversal on arteries and arterioles. *Circ Res* 1989; 65:869–879.
6. Ono Z, Prewitt RL, Stacy DL. Arteriolar changes in developing and chronic stages of two-kidney, one clip hypertension. *Hypertension* 1989; 14:36–43.
7. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, *et al.* Cross-sectional relations of peripheral microvascular function,

cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 2005; 112:3722–3728.
8. Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE. Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. *Hypertension* 2013; 61:1340–1345.
9. Kubis N, Richer C, Domergue V, Giudicelli JF, Lévy BI. Role of microvascular rarefaction in the increased arterial pressure in mice lacking for the endothelial nitric oxide synthase gene (eNOS3pt-/-). *J Hypertens* 2002; 20:1581–1587.
10. Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, *et al.* Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. *Hypertension* 2013; 61:130–136.
11. Stefanadis C, Vlachopoulos C, Karayannacos P, Boudoulas H, Stratos C, Filippides T, *et al.* Effect of vasa vasorum flow on structure and function of the aorta in experimental animals. *Circulation* 1995; 91:2669–2678.
12. Kruger A, Stewart J, Sahityani R, O'Riordan E, Thompson C, Adler S, *et al.* Laser Doppler flowmetry detection of endothelial dysfunction in end-stage renal disease patients: correlation with cardiovascular risk. *Kidney Int* 2006; 70:157–164.
13. Prior JO, Quiñones MJ, Hernandez-Pampaloni M, Facta AD, Schindler TH, Sayre JW, *et al.* Coronary circulatory dysfunction in insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus. *Circulation* 2005; 111:2291–2298.
14. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, *et al.* Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. *J Am Coll Cardiol* 2006; 47:1188–1195.
15. Kaufmann PA, Gnecchi-Ruscone T, Schafers KP, Luscher TF, Camici PG. Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. *J Am Coll Cardiol* 2000; 36:103–109.
16. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, Struijker-Boudier HA. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 2008; 118:968–976.
17. Serné EH, de Jongh RT, Eringa EC, IJzerman RG, Stehouwer CDA. Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. *Hypertension* 2007; 50:204–211.
18. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; 107:2864–2869.
19. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, *et al.*, Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. *J Hypertens* 2005; 23:233–246.
20. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005; 111:363–368.
21. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, *et al.* Assessment of endothelial function by noninvasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010; 31:1142–1148.
22. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; 25:932–943.
23. Hirase T, Node K. Endothelial dysfunction as a cellular mechanism for vascular failure. *Am J Physiol Heart Circ Physiol* 2012; 302:H499–H505.
24. Humphrey JD. Mechanisms of arterial remodeling in hypertension: coupled roles of wall shear and intramural stress. *Hypertension* 2008; 52:195–200.
25. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, *et al.* Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009; 54:375–383.
26. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; 99:2434–2439.
27. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; 27:2121–2158.
28. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension* 2009; 54:1328–1336.
29. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G. Arterial stiffness and the development of hypertension: the ARIC Study. *Hypertension* 1999; 34:201–206.
30. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, *et al.* Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2008; 51:1377–1383.
31. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, *et al.* Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; 308:875–881.
32. Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, *et al.* Hypertension and vascular dynamics in men and women with metabolic syndrome. *J Am Coll Cardiol* 2013; 61:12–19.
33. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, *et al.* Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002; 105:1202–1207.
34. Najjar SS, Scuteri A, Lakatta EG. Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension* 2005; 46:454–462.
35. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. *Hypertension* 2005; 45:652–658.
36. Czernichow S, Greenfield JR, Galan P, Jellouli F, Safar ME, Blacher J, *et al.* Macrovascular and microvascular dysfunction in the metabolic syndrome. *Hypertens Res* 2010; 33:293–297.
37. Liang J, Zhou N, Teng F, Zou C, Xue Y, Yang M, *et al.* Hemoglobin A1c levels and aortic arterial stiffness: the Cardiometabolic Risk in Chinese (CRC) Study. *PLoS One* 2012; 7:e38485.
38. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008; 51:527–539.
39. Blacher J, Demuth K, Guerin AP, Safar ME, Moatti N, London GM. Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 1998; 18:535–541.
40. Makita Z, Bucala R, Rayfield EJ, Friedman EA, Kaufman AM, Korbet SM, *et al.* Reactive glycosylation endproducts in diabetic uraemia and treatment of renal failure. *Lancet* 1994; 343:1519–1522.
41. Sanders PW. Vascular consequences of dietary salt intake. *Am J Physiol Renal Physiol* 2009; 297:F237–F243.
42. Ruiz-Ortega M, Rodríguez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. TGF-β signaling in vascular fibrosis. *Cardiovasc Res* 2007; 74:196–206.
43. Mitchell GF, DeStefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, *et al.* Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. *Circulation* 2005; 112:194–199.
44. North KE, MacCluer JW, Devereux RB, Howard BV, Welty TK, Best LG, *et al.*, Strong Heart Family Study. Heritability of carotid artery structure and function: the Strong Heart Family Study. *Arterioscler Thromb Vasc Biol* 2002; 22:1698–1703.
45. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension* 2005; 45:1050–1055.
46. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 2005; 85:571–633.
47. Martin H, Hu J, Gennser G, Norman M. Impaired endothelial function and increased carotid stiffness in 9-year-old children with low birthweight. *Circulation* 2000; 102:2739–2744.
48. Woods LL, Weeks DA, Rasch R. Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. *Kidney Int* 2004; 65:1339–1348.
49. Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of fetal exposure to maternal diabetes in offspring. *J Clin Endocrinol Metab* 2006; 91:3718–3724.
50. Brawley L, Itoh S, Torrens C, Barker A, Bertram C, Poston L, Hanson M. Dietary protein restriction in pregnancy induces hypertension and vascular defects in rat male offspring. *Pediatr Res* 2003; 54:83–90.
51. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation* 2001; 104:735–740.

52. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozakova M, La Canna G, *et al.* Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens* 2003; 21:625–631.
53. Holowatz LA, Thompson-Torgerson CS, Kenney WL. The human cutaneous circulation as a model of generalized microvascular function. *J Appl Physiol* 2008; 105:370–372.
54. Rossi M, Carpi A, Galetta F, Franzoni F, Santoro G. The investigation of skin blood flowmotion: a new approach to study the microcirculatory impairment in vascular diseases? *Biomed Pharmacother* 2006; 60:437–442.
55. Rizzoni D, Porteri E, Duse S, De Ciuceis C, Rosei CA, La Boria E, *et al.* Relationship between media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles evaluated non-invasively by scanning laser Doppler flowmetry. *J Hypertens* 2012; 30:1169–1175.
56. Glagov S, Vito R, Giddens DP, Zarins CK. Micro-architecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress. *J Hypertens* 1992; 10 (Suppl): S101–S104.
57. Prewitt RL, Rice DC, Dobrian AD. Adaptation of resistance arteries to increases in pressure. *Microcirculation* 2002; 9:295–304.
58. Prewitt RL, Hashimoto H, Stacy DL. Structural and functional rarefaction of microvessels in hypertension. In: Lee R, editor. *Blood vessel changes in hypertension: structure and function*. Boca Raton, FL: CRC Press; 1990. pp. 71–90.
59. Vion AC, Ramkhelawon B, Loyer X, Chironi G, Devue C, Loirand G, *et al.* Shear stress regulates endothelial microparticle release. *Circ Res* 2013; 112:1323–1333.
60. Tian S, Bai Y, Yang L, Wang X, Wu Y, Jia J, *et al.* Shear stress inhibits apoptosis of ischemic brain microvascular endothelial cells. *Int J Mol Sci* 2013; 14:1412–1427.
61. dela Paz NG, Walshe TE, Leach LL, Saint-Geniez M, D'Amore PA. Role of shear-stress-induced VEGF expression in endothelial cell survival. *J Cell Sci* 2012; 125 (Pt 4):831–843.
62. Gongora MC, Qin Z, Laude K, Kim HW, McCann L, Folz JR, *et al.* Role of extracellular superoxide dismutase in hypertension. *Hypertension* 2006; 48:473–481.
63. Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular outcome. *Coron Artery Dis* 2004; 15:259–264.
64. Debbabi H, Uzan L, Mourad JJ, Safar M, Levy BI, Tibiriçà E. Increased skin capillary density in treated essential hypertensive patients. *Am J Hypertens* 2006; 19:477–483.
65. Mathiassen ON, Buus NH, Sihm I, Thybo NK, Morn B, Schroeder AP, *et al.* Small artery structure is an independent predictor of cardiovascular events in essential hypertension. *J Hypertens* 2007; 25:1021–1026.
66. Rizzoni D, Porteri E, Boari GE, De Ciuceis C, Sleiman I, Muiesan ML, *et al.* Prognostic significance of small-artery structure in hypertension. *Circulation* 2003; 108:2230–2235.
67. Buus NH, Mathiassen ON, Fenger-Grøn M, Præstholm MN, Sihm I, Thybo NK, *et al.* Small artery structure during antihypertensive therapy is an independent predictor of cardiovascular events in essential hypertension. *J Hypertens* 2013; 31:791–797.
68. Erdogan D, Yildirim I, Ciftci O, Ozer I, Caliskan M, Gullu H, Muderrisoglu H. Effects of normal blood pressure, prehypertension, and hypertension on coronary microvascular function. *Circulation* 2007; 115:593–599.
69. Feihl F, Liaudet L, Levy BI, Waeber B. Hypertension and microvascular remodeling. *Cardiovasc Res* 2008; 78:274–285.
70. Beyer AM, Gutterman DD. Regulation of the human coronary microcirculation. *J Mol Cell Cardiol* 2012; 52:814–821.
71. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al.* Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; 106:653–658.
72. Laurent S, Briet M, Boutouyrie P. Large and small artery cross-talk and recent morbidity-mortality trials in hypertension. *Hypertension* 2009; 54:388–392.
73. Mourad JJ, des Guetz G, Debbabi H, Levy BI. Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann Oncol* 2008; 19:927–934.
74. Noon JP, Walker BR, Webb DJ, Shore AC, Holton DW, Edwards HV, Watt GC. Impaired microvascular dilatation and capillary rarefaction in young adults with a predisposition to high blood pressure. *J Clin Invest* 1997; 99:1873–1879.
75. Semé EH, Gans RO, ter Maaten JC, ter Wee PM, Donker AJ, Stehouwer CD. Capillary recruitment is impaired in essential hypertension and relates to insulin's metabolic and vascular actions. *Cardiovasc Res* 2001; 49:161–168.
76. Hedman A, Reneland R, Lithell HO. Alterations in skeletal muscle morphology in glucose-tolerant elderly hypertensive men: relationship to development of hypertension and heart rate. *J Hypertens* 2000; 18:559–565.
77. Antonios TF, Rattray FM, Singer DR, Markandu ND, Mortimer PS, MacGregor GA. Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension. *Heart* 2003; 89: 175–178.
78. Vilar J, Waeckel L, Bonnin P, Cochain C, Loinard C, Duriez M, *et al.* Chronic hypoxia-induced angiogenesis normalizes blood pressure in spontaneously hypertensive rats. *Circ Res* 2008; 103:761–769.
79. Rizzoni D, Porteri E, Guelfi D, Muiesan ML, Valentini U, Cimino A, *et al.* Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with noninsulin-dependent diabetes mellitus. *Circulation* 2001; 103:1238–1244.
80. Marin P, Andersson B, Krotkiewski M, Bjorntorp P. Muscle fiber composition and capillary density in women and men with NIDDM. *Diabetes Care* 1994; 17:382–386.
81. Frisbee JC. Hypertension-independent microvascular rarefaction in the obese Zucker rat model of the metabolic syndrome. *Microcirculation* 2005; 12:383–392.
82. Czernichow S, Greenfield JR, Galan P, Bastard JP, Charnaux N, Samaras K, *et al.* Microvascular dysfunction in healthy insulin-sensitive overweight individuals. *J Hypertens* 2010; 28:325–332.
83. Jonk AM, Houben AJ, de Jongh RT, Semé EH, Schaper NC, Stehouwer CD. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. *Physiology* 2007; 22:252–260.
84. Muris DM, Houben AJ, Schram MT, Stehouwer CD. Microvascular dysfunction: an emerging pathway in the pathogenesis of obesity-related insulin resistance. *Rev Endocr Metab Disord* 2013; 14:29–38.
85. Polderman KH, Stehouwer CD, van Kamp GJ, Gooren LJ. Effects of insulin infusion on endothelium-derived vasoactive substances. *Diabetologia* 1996; 39:1284–1292.
86. Et-Taouil K, Safar M, Plante GE. Mechanisms and consequences of large artery rigidity. *Can J Physiol Pharmacol* 2003; 81:205–211.
87. Gingras M, Farand P, Safar ME, Plante GE. Adventitia: the vital wall of conduit arteries. *J Am Soc Hypertens* 2009; 3:166–183.
88. Chen BP, Li YS, Zhao Y, Chen KD, Li S, Lao J, *et al.* DNA microarray analysis of gene expression in endothelial cells in response to 24-h shear stress. *Physiol Genomics* 2001; 7:55–63.
89. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999; 282:2035–2042.
90. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007; 115:1285–1295.
91. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; 101:1899–1906.

Reviewers' Summary Evaluations

Reviewer 1

This is an interesting and comprehensive review focused on interactions between macrovasculature and microcirculation, also considering a possible important role of endothelial dysfunction. The paper is well written and balanced.

Reviewer 2

Important structural and functional changes in the macrovasculature and the microvasculature are present

in hypertension. These changes appear correlated and the aim of this review is to provide an overview on the nature of this association between macro- and microvascular changes. Important conclusions are that both the macro and the microvasculature should be targeted for treatment and potentially the microvasculature in addition targeted for prevention. No strong conclusion on the interrelationship between the changes in the macro- and microvasculature is provided.

1.3.3 Conclusion de l'article 2

La pathogénèse de l'hypertension artérielle a traditionnellement été associée à une augmentation du débit cardiaque secondaire notamment à une hyperactivité du système rénine-angiotensine et du système nerveux sympathique. Puis, les modifications de la structure et de la fonction des artérioles étaient associées à une augmentation progressive des résistances périphériques et de la pression artérielle moyenne. Il apparaît cependant que les propriétés de la paroi aortique pourraient contribuer substantiellement à la pathogénèse de l'hypertension artérielle. Dans ce paradigme, la pression pulsée périphérique au cours du vieillissement de 19 à 90 ans, augmente en parallèle avec l'amplitude de l'onde de pression incidente, marqueur direct de la rigidité de l'aorte ascendante (55). L'intensité des ondes de réflexion et le niveau de pression pulsée apparaissent divergents : chez les plus jeunes participants, la pression pulsée diminue jusqu'à l'âge de 50 ans alors que l'intensité des ondes de réflexion augmente progressivement ; après 50 ans, la pression pulsée augmente progressivement, parallèlement au degré de rigidité aortique, alors que le marqueur de l'intensité des ondes de réflexion suit une pente décroissante. La Baltimore Longitudinal Study of Aging (56), sur un suivi de plus 4 ans, mettait en évidence la valeur prédictive indépendante de la rigidité aortique dans l'augmentation longitudinale de la pression artérielle systolique et dans l'apparition d'une hypertension. Plus récemment, l'étude de la relation temporelle entre rigidité aortique, phénomène des ondes de réflexion et hypertension suggère un rôle précurseur de la rigidité aortique dans l'augmentation progressive de la pression artérielle systolique (57). La rigidité aortique peut être déterminée et accélérée par des facteurs autres que la présence d'une hypertension artérielle. En particulier le vieillissement physiologique (44), les facteurs épigénétiques (58) ou certaines comorbidités telles que la présence d'un syndrome métabolique (59), d'une maladie diabétique (60) ou d'une insuffisance rénale chronique (61) sont corrélés au niveau de rigidité aortique. La relation temporelle de cause à effet entre

rigidité aortique et hypertension artérielle est théoriquement bidirectionnelle. La temporalité reste cependant difficile à affirmer en raison de la forte corrélation entre anomalies structurales/fonctionnelles des gros troncs artériels et hypertension artérielle et de la multiplicité des facteurs pouvant être impliqués dans les deux mécanismes physiopathologiques. En particulier sur le plan thérapeutique, la majorité des patients avec hypertension artérielle non contrôlée présentent une élévation persistante, souvent isolée, de la pression artérielle systolique et donc de la pression pulsée. L'échec du contrôle de la pression pulsée illustre l'échec de la prise en charge thérapeutique de la rigidité aortique. Les molécules antihypertensives ont été proposées pour leur aptitude à diminuer les résistances vasculaires périphériques par leurs propriétés vasodilatatrices et/ou à diminuer le débit cardiaque. A ce jour, la pression pulsée périphérique ne représente pas une cible thérapeutique spécifique chez le patient hypertendu malgré les données épidémiologiques suggérant le rôle de la rigidité aortique dans le non contrôle de l'hypertension artérielle (62).

Le deuxième paradigme dans la pathogénèse de l'hypertension artérielle souligne le rôle précurseur de l'atteinte microcirculatoire. Parallèlement, plusieurs données expérimentales et épidémiologiques soulignent la relation temporelle bidirectionnelle entre altérations microcirculatoires et hypertension artérielle. Une diminution de la densité capillaire au niveau du muscle squelettique chez des patients hypertendus non traités a été associée à une augmentation de la pression artérielle moyenne sur une période de 20 ans (63). La raréfaction artériolo-capillaire peut donc représenter un mécanisme précurseur plutôt que seulement une conséquence de l'hypertension artérielle (64).

La relation de cause à effet entre microcirculation et pression artérielle est supportée par deux observations :

- Une étude observationnelle en population : l'augmentation de la densité capillaire

cutanée chez des patients hypertendus traités contrôlés en comparaison à des patients hypertendus nouvellement diagnostiqués non traités (65);

- Une étude expérimentale : la normalisation de la pression artérielle secondaire au processus d'angiogenèse chez des rats spontanément hypertendus exposés à l'hypoxie chronique. De plus, l'hypoxie chronique prévient l'apparition d'une hypertension artérielle chez des jeunes rats pré-hypertendus par l'intermédiaire de la production de NO endothélial et du Vascular Endothelial Growth Factor (VEGF) (66).

Les altérations micro vasculaires associées en particulier au syndrome métabolique (67) et à l'obésité (68) peuvent précéder l'apparition d'une hypertension artérielle. Le rôle précurseur de la dysfonction endothéliale peut être proposé dans la pathogenèse et la progression des altérations micro et macro vasculaires et dans la survenue des complications cardiovasculaires. La physiopathologie de l'hypertension peut alors être revisitée, par l'intermédiaire d'altérations artérielles micro et macro vasculaires, avec un rôle de précurseur de la dysfonction endothéliale. La rigidité aortique et la raréfaction artériolo-capillaire pourraient être les cibles thérapeutiques à privilégier au cours de la maladie hypertensive. Plus particulièrement, le réseau microcirculatoire pourrait représenter une cible thérapeutique mais aussi préventive dans l'apparition d'une hypertension artérielle associée au syndrome métabolique. Les stratégies pharmacologiques et non pharmacologiques candidates paraissent être celles visant à réduire la résistance à l'insuline (69) et l'activation du système rénine-angiotensine (70).

Chapitre 2
Paramètres hémodynamiques artériels et estimation du risque cardiovasculaire

2.1 Description de la méthode d'évaluation non invasive des paramètres hémodynamiques artériels

L'appareil SphygmoCor (AtCor Medical, Australia) est un système de référence pour la mesure non-invasive de la pression artérielle centrale et de la vitesse de l'onde de pouls (VOP) carotido-fémorale. La méthode de mesure utilisée est la tonométrie d'aplanation à l'aide d'une sonde de haute-fidélité sensible aux variations de pression artérielle (71,72). Le principe de la tonométrie consiste à aplanir légèrement l'artère de telle sorte que la pression exercée par le capteur ne modifie pas la pression intra-artérielle, mais égale la pression exercée par le sang sur la paroi. Le tonomètre détecte des variations de pression artérielle qu'il transforme en variations de courant électrique. Le signal électrique est transmis au logiciel intégré dans l'appareil Sphygmocor qui permet de le visualiser sous la forme d'une courbe de pression.

Le profil de l'onde de pression centrale peut être estimé par tonométrie d'aplanation radiale ou carotidienne. L'onde de pression au niveau radial, obtenue par le logiciel, est calibrée à partir des pressions artérielles systolique et diastolique brachiales précédemment mesurées. La forme de l'onde de pression aortique et les paramètres qui la caractérisent sont ensuite calculés automatiquement à partir de la forme de l'onde de pression radiale, en utilisant une fonction de transfert selon une méthode validée et intégrée au logiciel de mesure (71). La forme de l'onde de pression aortique peut être estimée directement par tonométrie carotidienne en calibrant la courbe de pression obtenue avec les valeurs de pression moyenne

et diastolique, considérées comme constantes sur l'arbre artériel. L'index d'augmentation (AIx) est le rapport entre l'amplitude des ondes de réflexion arrivant au niveau central pendant la systole cardiaque et la pression pulsée aortique. L'amplitude des ondes de réflexion, appelée augmentation de pression (AP), est définie par le point d'inflexion systolique, premier épaulement de la courbe de pression, et le pic de pression systolique **(figure 2)**. Par convention, l'AIx est négatif si le point d'inflexion (rencontre de l'onde de pression incidente et des ondes de pression réfléchies) se situe après le pic systolique. L'AIx est positif si le point d'inflexion se situe avant ou pendant le pic systolique. L'augmentation de pression (AP) et l'AIx sont corrélés à l'âge, au sexe, à la VOP carotido-fémorale, à la pression artérielle moyenne et à la fréquence cardiaque (73). L'amplification de la pression pulsée est définie par le rapport entre la pression pulsée brachiale et la pression pulsée centrale. D'après les modèles multivariés, seulement 36 % à 70 % de l'amplification de la pression peut être expliqué, principalement par l'AIx, la compliance artérielle et la fréquence cardiaque, avec l'âge comme déterminant majeur (74). Les facteurs de risque cardio-vasculaire tels que l'hypertension, le tabagisme, la dyslipidémie et la maladie diabétique, rendent compte chacun de seulement 1 % de l'amplification (12). Ce paramètre hémodynamique est un phénomène multifactoriel complexe qui ne peut pas être estimé avec précision avec des modèles d'équations. La pression centrale nécessite donc une mesure non invasive directe (tonométrie radiale ou carotidienne).

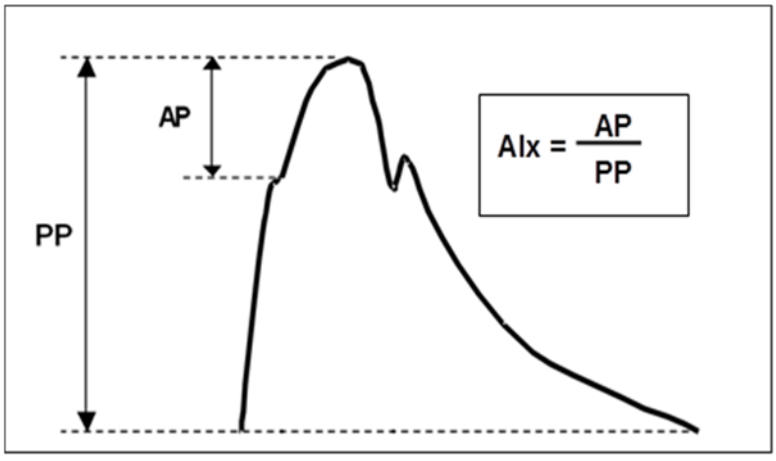

Figure 2 : Profil de l'onde de pression : AIx: Index d'augmentation;
AP: Augmentation de pression, différence entre les deux pics de pression (pic systolique précoce et pic systolique retardé);
PP : Pression pulsée.

La VOP carotido-fémorale (en m/sec) est la méthode de référence pour la mesure directe et non invasive de la rigidité aortique. Elle est calculée automatiquement par le logiciel à partir de la distance entre l'artère carotide et l'artère fémorale, divisée par le temps écoulé entre le pied des deux ondes de pression au niveau carotide et fémoral, mesurées par tonométrie. La distance entre l'artère carotide et fémorale est la distance directe corrigée par un facteur 0.8 afin de standardiser la méthode de mesure selon le consensus d'experts (75). Les ondes de pression sont enregistrées séquentiellement sur les deux sites (carotidien et fémoral), parallèlement à l'enregistrement du rythme cardiaque. Le temps de transit de l'onde de pouls d'un site anatomique à l'autre correspond au décalage temporel en prenant l'onde R du signal électrocardiogramme comme base de temps **(figure 3)**. L'évaluation de la rigidité artérielle sur d'autres sites est possible par la même méthode de mesure. Seule la VOP carotido-fémorale présente à ce jour une valeur prédictive positive en termes de morbi-mortalité cardiovasculaire et de mortalité toutes causes (76).

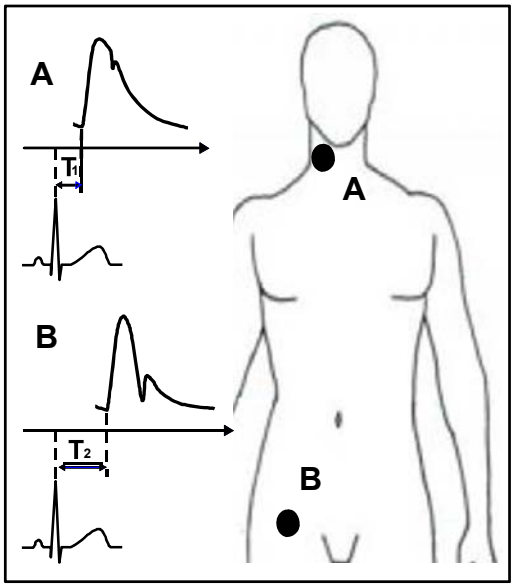

Figure 3: Méthode de mesure de la vitesse de l'onde de pouls carotido-fémorale.
Ondes de pression mesurées séquentiellement aux sites carotidien A et fémoral B; le temps de transit carotido-fémoral est le temps mesuré entre l'onde R à l'ECG et le pied de l'onde de pression au site B (T2), que diminue le temps mesuré entre l'onde R à l'ECG et le pied de l'onde de pression au site A (T1). La vitesse de l'onde de pouls carotido-fémorale est calculée par la distance directe AB que divise le temps de transit.

2.2 Paramètres hémodynamiques artériels et approche du risque cardiovasculaire individuel : revue de la littérature (Article 3)

2.2.1 Introduction de l'article 3

L'intérêt de l'évaluation du niveau de pression artérielle la plus fiable possible à l'origine de l'atteinte des organes cibles a suscité un changement de paradigme. Premièrement, le diagnostic de l'hypertension était posé, jusqu'à une période récente, par la mesure de la pression artérielle effectuée au cabinet médical. L'étude SHEAF (77) a clairement montré que les chiffres de pression artérielle mesurés en automesure étaient plus étroitement associés à la survenue d'événements cardiovasculaires que les chiffres mesurés au cabinet médical. Les patients hypertendus en automesure, même s'ils étaient normotendus au cabinet médical (hypertension artérielle masquée) avaient un niveau de risque équivalent aux patients hypertendus à même niveau de pression artérielle. En automesure, une augmentation de la pression artérielle systolique de 10 mm Hg était corrélée à une augmentation du risque d'événement cardio-vasculaire de 17,2 % et une élévation de la pression artérielle diastolique de 5 mm Hg augmentait ce même risque de 11,7 %. Pour la même augmentation de la pression artérielle mesurée au cabinet médical, le risque d'événements cardio-vasculaires n'était pas significativement augmenté. Cette étude suggère donc la supériorité prédictive de l'automesure tensionnelle par rapport à la mesure conventionnelle au cabinet médical en termes de pronostic cardio-vasculaire. Deuxièmement, la multiplication des mesures tensionnelles en ambulatoire traduit la volonté de la communauté médicale de s'affranchir autant que possible de la variabilité des chiffres tensionnels afin d'adapter la stratégie thérapeutique. Cependant, la notion de variabilité tensionnelle, à court terme (78), sur les 24 heures (79) ou inter-visites (80), chez les patients hypertendus traités apparaît depuis peu comme un facteur prédictif indépendant pour

la survenue d'événements cardiovasculaires. Des données récentes suggèrent que la variabilité de la pression artérielle systolique sur 24 heures est corrélée à l'atteinte des gros troncs artériels chez les patients hypertendus traités (81). Enfin, par opposition aux chiffres de pression artérielle systolique et diastolique pris en compte isolément, la composante pulsatile de la pression artérielle apparaît être le plus important facteur de risque hémodynamique chez le patient hypertendu âgé (16) et le patient coronarien (82). La pression centrale est considérée comme étant plus représentative du niveau tensionnel imposé aux coronaires et aux artères à destinée cérébrale. Le niveau de pression pulsée centrale est ainsi considéré comme un meilleur marqueur de l'atteinte artérielle et facteur prédictif du risque d'événements cardiovasculaires par rapport à la pression artérielle périphérique brachiale **(Tableau 1).** En particulier chez le patient coronarien (82), la pression pulsée aortique mesurée au cours de la coronarographie, est corrélée au risque de survenue d'événement cardiovasculaire indépendamment du sexe, de la présence d'antécédent coronarien, du degré de sténose coronaire, de la fraction d'éjection, du débit de filtration glomérulaire et de la présence d'un diabète. Inversement, la pression pulsée mesurée au niveau périphérique n'était pas corrélée au risque de survenue d'événement dans ce modèle multivarié (82). Chez des patients avec maladie rénale terminale, la pression pulsée mesurée au niveau carotidien, mais non la pression pulsée brachiale, présente une valeur prédictive pour la mortalité totale indépendamment de l'âge, de la présence d'antécédent cardiovasculaire et de la durée depuis la mise en dialyse (84). En population générale, l'étude de l'association entre paramètres hémodynamiques centraux et périphériques et la mortalité cardiovasculaire et totale a été évaluée sur un suivi longitudinal de 10 ans (50). Dans cette étude prospective, le pouvoir prédictif de chaque paramètre hémodynamique a été évalué au sein d'un modèle multivarié, isolément puis deux par deux. Ainsi, seule la pression systolique centrale évaluée par tonométrie carotidienne a démontré sa capacité prédictive pour la mortalité cardiovasculaire dans un modèle multivarié

comprenant la pression brachiale (systolique ou pulsée mais qui n'atteignaient pas la significativité statistique), l'âge, le sexe, les facteurs de risque traditionnels, la VOP carotido-fémorale et la présence d'atteinte d'organe cible (hypertrophie ventriculaire gauche, débit de filtration glomérulaire et épaisseur intima-média) (50).

Tableau 1 (Article 3) : Pression centrale : facteur prédictif indépendant du risque cardiovasculaire.

Référence	Année	Population	Durée du Suivi	Paramètre étudié	Critère étudié
Safar *et al.* (84)	2002, France	Maladie rénale terminale	52 mois	PP centrale (C)	Mortalité totale et CV
Jankowski *et al.* (82)	2008, Pologne	Maladie coronaire	4.5 ans	PP centrale (D)	Morbi-mortalité CV
Pini *et al.* (85)	2008, Italie	Population âgée	8 ans	PAS centrale (C)	Mortalité CV
Roman *et al.* (83,86)	2007 et 2009, USA	Population à haut risque CV	4.8 ans	PP centrale (R)	Morbi-mortalité CV
Wang *et al.* (50)	2009, Taiwan	Population générale	10.8 ans	PAS Centrale (C)	Mortalité CV

Ces études ont démontré la supériorité prédictive de la pression centrale par rapport à la mesure périphérique de la pression artérielle pour la survenue d'événements cardiovasculaires. (C), pression centrale estimée de manière non-invasive à partir de la forme de l'onde de pression carotidienne; (D), mesure directe invasive; (R), pression centrale estimée de manière non-invasive à partir de la forme de l'onde de pression au niveau radiale; PAS, pression artérielle systolique; PP, pression pulsée; CV, cardiovasculaire.

2.2.2 Article 3

Yannoutsos A, Rinaldi ER, Zhang Y, Protogerou AD, Safar ME, Blacher J.

Central hemodynamics in risk assessment strategies: additive value over and above brachial blood pressure.

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Central Hemodynamics in Risk Assessment Strategies: Additive Value Over and Above Brachial Blood Pressure

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Abstract: Although the clinical relevance of brachial blood pressure (BP) measurement for cardiovascular (CV) risk stratification is nowadays widely accepted, this approach can nevertheless present several limitations. Pulse pressure (PP) amplification accounts for the notable increase in PP from central to peripheral arterial sites. Target organs are more greatly exposed to central hemodynamic changes than peripheral organs. The pathophysiological significance of local BP pulsatility, which has a role in the pathogenesis of target organ damage in both the macro- and the microcirculation, may therefore not be accurately captured by brachial BP as traditionally evaluated with cuff measurements. The predictive value of central systolic BP and PP over brachial BP for major clinical outcomes has been demonstrated in the general population, in elderly adults and in patients at high CV risk, irrespective of the invasive or non-invasive methods used to assess central BP. Aortic stiffness, timing and intensity of wave reflections, and cardiac performance appear as major factors influencing central PP. Great emphasis has been placed on the role of aortic stiffness, disturbed arterial wave reflections and their intercorrelation in the pathophysiological mechanisms of CV diseases as well as on their capacity to predict target organ damage and clinical events. Comorbidities and age-related changes, together with gender-related specificities of arterial and cardiac parameters, are known to affect the predictive ability of central hemodynamics on individual CV risk.

Keywords: Cardiovascular risk prediction, central pulse pressure, aortic stiffness, wave reflections, atherosclerosis, microcirculatory damage.

1. INTRODUCTION

Hypertension is a widely established, major cardiovascular (CV) risk factor that is strongly correlated with coronary heart disease, stroke, heart failure, nephropathy and dementia [1, 2, 3]. From a clinical standpoint, measuring blood pressure (BP) with the cuff technique at the brachial artery site has been shown to be an extremely reliable technique for the diagnosis of hypertension, and for treatment decisions, and also to have a strong predictive value. Based on evidence from randomized controlled trials, hypertension is defined as brachial systolic BP values ≥140 mmHg and/or brachial diastolic BP ≥90 mmHg, in young, middle-aged and elderly subjects. There is a continuous relationship between brachial BP levels from 115/75 mm Hg and cardio- and cerebrovascular events [1]. The benefit of antihypertensive treatment is proportional to the reduction in BP and has been clearly demonstrated in terms of cardio- and cerebrovascular morbidity and mortality, and nephroprotection [4, 5, 6]. Despite steady improvements in the diagnosis and therapeutic management of CV diseases and hypertension, they still remain the most prevalent cause of death, and the most frequently encountered CV risk factor in the aging population, respectively. The considerable residual risk for vascular events that is observed despite brachial BP control, in treated hypertensive patients [7], has highlighted the need for improved CV risk prediction and prevention. The notion of residual risk has been specifically demonstrated in hypertensive patients, and may be indicative of adverse responses of subclinical, structural and functional arterial damage. Subclinical arterial damage is characterized by aortic stiffness, disturbed wave reflection and impaired central to peripheral pulse pressure (PP) amplification. Central hemodynamic parameters may improve risk prediction by providing a more accurate representation of subclinical arterial damage as well as the load and pulsatile conditions to which target organs are subjected.

The aim of this review is to present the growing body of evidence on the capacity of central hemodynamic parameters to predict CV events. Central hemodynamic parameters, including PP amplification, aortic stiffness and arterial wave reflections, will be described in detail. First, we will discuss the limited predictive capacity of standard brachial BP measurements and then the pathophysiological relevance of central BP in the pathogenesis of target organ damage. Recent prospective studies have illustrated the incremental value of central BP over peripheral BP for CV risk prediction. Finally, the clinical relevance of vascular phenotypes and cardiac performance will be discussed in the context of risk prediction as well as the clinical implications of BP-associated risk stratification at the individual level.

2. HEMODYNAMICS: BASIC CONCEPTS

Compliance and distensibility are two main physiologic, mechanical properties of the aortic wall, reflecting the buffering and damping capacities, respectively, of the proximal aorta (the so-called Windkessel effect). The viscoelastic properties of large conduit arteries account for the ability of the aorta to withstand systolic expansion, absorbing the energy of left ventricular ejection, and to reduce the pulsatility of ventricular ejection, transforming the pulsatile blood flow into a more steady flow downstream. Optimal organ perfusion is thus maintained during diastole and the pulsatile strain imposed on the peripheral microcirculation is limited. The conduit function of the aorta and large arteries is related to mean (steady) BP and to blood flow to ensure adequate blood supply to organs.

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The arterial BP curve can be defined by a steady component, mean arterial pressure, and a pulsatile component, which is the difference between the peak systolic and minimum diastolic values of BP. Interactions between systolic volume, heart rate, arterial stiffness and systemic vascular resistance have varying effects on mean arterial pressure and PP. Cardiac output, which is regulated by heart rate and stroke volume, and peripheral vascular resistance, which is regulated by density, tone and structure of the arterioles and capillaries, determine the steady component of BP. Pulse pressure depends on stroke volume, and on functional and structural properties of the arteries, as illustrated by aortic stiffness, and amplitude and timing of wave reflections. Mean and diastolic BP values decrease progressively, albeit marginally, from the aorta towards peripheral arteries whereas systolic and pulse pressures show a marked increase from central to peripheral arterial sites. At each point on the arterial tree, the pressure waveform is determined by the summation of the primary wave (secondary to ventricular ejection) and the reflected waves coming from the peripheral arterial bifurcations and small resistance arteries, with an early systolic peak and then a subsequent peak due to the return of reflected waves. The smallest arteries and arterioles respond to wall tensile stress by a myogenic reduction in lumen diameter. This physiolcgically inherent characteristic of small distal arteries largely accounts for total peripheral resistance [8]. The incident pressure wave, which is driven away from the heart, encounters impedance mismatch at the junction with highly conductive arteries and high resistance arterioles, and is reflected backwards towards the heart. Wave reflections are originate from any structural and/or functional discontinuity of the arterial tree (where there is a mismatch in impedance), mainly from high resistance arterioles and their bifurcations [8, 9].

Amplification of systolic and pulse pressures from central to peripheral sites depends on the timing and amplitude of the reflected waves, both of which are related to the distance from the heart of the "effective" reflecting site. The timing of reflected waves is physiologically related to the length of the aortic path travelled and to changes in arterial compliance, with the proximal arteries being more elastic, and arterial stiffness progressively increasing along the arterial tree. Changes in arterial compliance result in changes in the transit time of both the primary and the reflected waves (the greater the arterial stiffness, the greater the velocity of incident and reflected waves) [10]. Increased heart rate is associated with a reduction in the time required for the backward pressure wave to return to the heart. Increased heart rate is further associated with enhanced PP amplification without any change in arterial stiffness [11]. In contrast, PP amplification from central to peripheral sites tends to be reduced with reduced heart rate. The intensity of reflected waves depends on the "effective" reflecting site, namely arterial bifurcations, impedance mismatch and arteriolar vasomotor tone. In peripheral sites, reflected waves physiologically amplify the primary wave in systole rather than in diastole leading to an increase in systolic and pulse pressures, whereas in the aorta, the reflected waves arrive at the end of systole, thus boosting coronary vascular tree perfusion during diastole and limiting cardiac afterload [8] **(Fig. 1)**.

Arterial applanation tonometry is widely used to record the pressure wave at different arterial sites, thus enabling non-invasive assessment of structural and functional arterial parameters [12, 13]. Applanation tonometry has been extensively validated against invasive central BP measurements. The central pressure waveform can be derived from radial applanation tonometry, with a validated mathematical transfer function, or from the common carotid pressure waveform. Using either radial or carotid sites, central pressures (PP, augmentation pressure, and systolic BP) can be calibrated from brachial artery pressures. Mean and diastolic pressures are considered almost unchanged along the arterial tree, although slightly decreased as the circulating blood moves away from the heart. Carotid-femoral pulse wave velocity (PWV) is the gold standard for direct non-invasive assessment of aortic stiffness. The shape of the central pulse waveform and the amplification of PP from central to peripheral sites give a non-invasive determination of the phenomenon of wave reflection (Fig. **2**).

Augmentation index (AIx) is defined as the pressure augmentation (which is the difference between the second and first systolic peaks) expressed as a percentage of PP. AIx is frequently used to assess wave reflection, and is affected by both timing and amplitude of the reflected waves. This index is therefore expressed as either a negative or a positive value depending on whether the reflected waves arrive at the central site after or before the systolic peak of the forward pressure wave, respectively. PP amplification is quantified as the ratio of PP amplitude between the brachial artery and the aorta. PP amplification increases with heart rate and height, and decreases with aging [14]. Gender also influences PP amplification, which is higher in men than in women. Differences between aortic and brachial PP are still measurable in women in the oldest age category (>80 years) [14]. According to multivariable models, only 36% to 70% of the variability in PP amplification can be explained, mainly by carotid AIx, arterial compliance and heart rate [15], with age as a major determinant [14]. Cardiovascular risk factors such as hypertension, smoking, hypercholesterolemia, and diabetes mellitus, may each explain only 1% of the variance in the amplification ratio [14], highlighting the fact that pressure amplification is a complex, multifactorial phenomenon that cannot be estimated accurately with equation models. Central BP might therefore not be

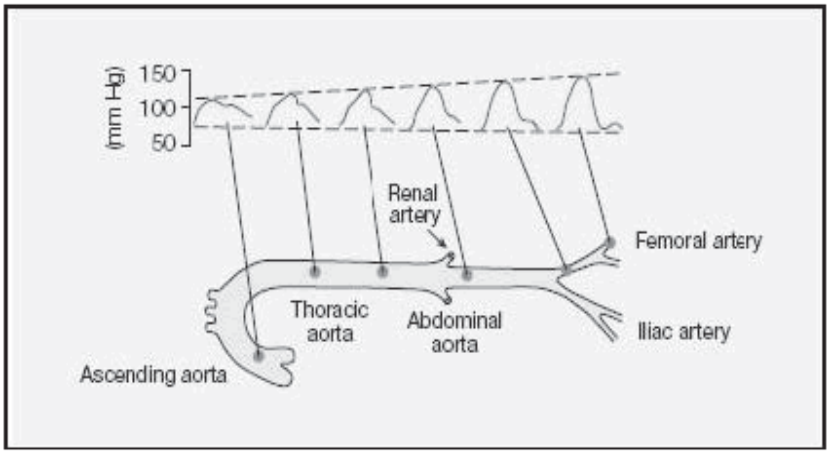

Fig. (1). Wave amplification of systolic blood pressure and pulse pressure along the aorta in a young individual. From reference 8: Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

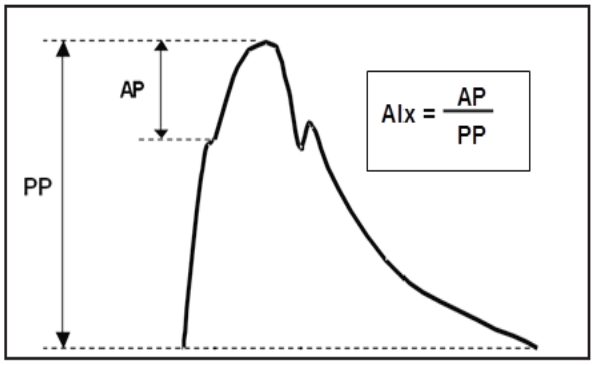

Fig. (2). Arterial pressure waveform. Augmentation index (AIx): ratio of augmented pressure (AP) to pulse pressure (PP). Augmented pressure (AP): height of the late systolic peak above the inflection point, which indicates the arrival of the reflected wave.

predicted with sufficient accuracy from brachial BP measurements using statistical models and requires direct non-invasive measurement. The structural and functional, pathophysiological parameters of the macro- and microcirculation of a given individual, as well as the characteristics of cardiac performance and the dynamic interactions, account for the considerable variability in PP amplification from central to peripheral sites with predictable clinical implications.

3. LIMITATIONS OF BRACHIAL BLOOD PRESSURE MEASUREMENTS

The conventional method of measuring brachial BP has been the auscultatory method using a sphygmomanometer. The limited accuracy of the Korotkoff sound method (with typically, underestimation of brachial systolic pressure and overestimation of diastolic pressure) [16], has led to the widespread use of automated devices with oscillometric measurement, estimating systolic and diastolic pressures indirectly according to an empirically-derived algorithm [17]. Additionally, the risk of misclassification of patients with white-coat hypertension (isolated office hypertension) or masked hypertension (isolated ambulatory hypertension) has led to the increasing use of ambulatory brachial BP monitoring.

The crude estimation of pressure levels in clinical practice can be accounted for by a certain number of conditions and most importantly, the short-term 24-hour variability of BP that is related to behavioral and non-behavioral factors including beat-to-beat BP variability and influences operated via the baroreflex system. Age, mean systolic BP, and heart rate variability appear to be major determinants of 24-hour systolic BP variability [18]. Indeed, increased systolic BP variability with steeper pressure changes has been reported in hypertensive patients as compared with normotensive individuals [19].

Body position and arm level also affect hemodynamic parameters. Guidelines recommend that peripheral BP should be measured in the brachial artery at the level of the heart, the patient in the sitting position [20]. Higher systolic and diastolic BP levels are obtained if the upper arm is below the level of the heart. These discrepancies between BP measurements can be attributed to the effects of hydrostatic pressure. Even when the arm position is adjusted so that the cuff is at the level of the heart, body position has been shown to affect BP measurements [20]. Whereas mean BP does not vary whether the patient is in the sitting or supine position, it has been shown that brachial diastolic BP measured in the sitting position is higher than when measured supine (by around 5 mmHg). In contrast, brachial systolic BP has been reported to be higher in the supine than the sitting position (by around 8 mmHg). Recently, significant differences were found between sitting and supine measurements of brachial PP as well as of central PP and PP amplification. Higher values of brachial and central PP, and lower PP amplification were observed in patients in the supine compared to the sitting position [21]. Uniform BP measurement techniques are essential for the results of clinical trials to be applied as recommendations for daily practice.

3.1. Brachial Systolic and Diastolic Cut-Off Values and Prognostic Information for Cardiovascular Risk

Brachial BP, as traditionally evaluated with cuff measurement, presents several limitations for risk prediction. Firstly, hypertension has generally been attributed to arteriolar vasoconstriction resulting in an increase in total peripheral vascular resistances with chronically elevated mean arterial pressure. Hypertension is conventionally defined as elevated brachial systolic and/or diastolic BP, considered alone and regardless of age. The importance of the pulsatile component of BP can thus be ignored [22]. Although consensus exists with regard to cut-off systolic and diastolic BP levels, there is no definition of abnormal values for mean and pulse pressures; PP ≥60 mmHg is described as asymptomatic arterial damage only in elderly hypertensive patients. From a pathophysiological standpoint, while mean BP is maintained throughout the vascular bed, increased pressure pulsatility with aging and CV risk factors, applied to distributing arteries of target organs, is the major determinant of CV risk in hypertensive patients [23, 24]. The pulsatile component of BP plays a role in the development of atherosclerosis [25, 26] and microvascular target organ damage [27]; it is also affected, for a given cardiac performance, by large artery stiffening and wave reflections, and appears more closely related to CV events than does mean BP, with an independent predictive value [28]. For any given level of systolic BP, the wider PP appears to be associated with a risk of overall and CV mortality, and CV morbidity (coronary events and stroke) [24] whereas low diastolic BP may be associated with reduced survival in very elderly patients [29].

Secondly, there is a physiological increase in systolic and pulse pressures from central (thoracic aorta, carotid artery) to peripheral (brachial artery) sites because of the amplification phenomenon [30]. Central arterial sites may be the most reliable for BP measurements to estimate CV risk, because target organs, the heart, and coronary and carotid arteries in particular, are more exposed to central than peripheral hemodynamic changes. A considerable overlap between central and brachial systolic pressures has been reported in adults throughout normal ranges of brachial BP as well as in different stages of hypertension, according to conventional definitions of BP [14]. More than 70% of adults (men as well as women) with a high-normal brachial systolic BP range exhibited similar aortic systolic BP to that of adults with stage 1 hypertension. There is considerable evidence indicating that PP measured non-invasively at the central level may predict CV outcomes more strongly than brachial BP measurements [31].

Thirdly, traditional BP measurement techniques appear to be inadequate for estimating the CV risk attributable to hemodynamic factors because of the clinically relevant different patterns in 24-

hour and visit-to-visit BP fluctuations. Although the conditions and techniques of measurement still need to be validated further, the independent predictive value for CV events has been demonstrated for short-term [32], 24-hour [33] and visit-to-visit brachial BP variability [34]. Recent observational data have suggested that average real variability of 24-hour systolic BP is independently related to large artery stiffness in hypertensive patients [35].

Fourthly, current guidelines recommend the therapeutic approach to hypertensive patients should include global CV risk, and call for more intensive risk-reducing measures in high- or very high-risk patients [5]. Because of their inability to integrate individual levels of intensity and exposure to all CV risk factors, current models of risk stratification may underestimate the CV risk associated with hemodynamic factors in asymptomatic hypertensive patients, particularly in women, younger patients, and middle-aged individuals or those with metabolic syndrome [5, 36]. Circulating biomarkers present inconsistent results for risk prediction [37], in contrast to central hemodynamic parameters and subclinical arterial damage [5, 36].

3.2. Differential Impact of Age and Gender on Vascular Properties

Apart from the epidemiological evidence of the heritability of the arterial stiffness phenotype [38], the impact of aging and gender, which are two major, non-modifiable determinants of vascular properties, cannot be fully understood from brachial BP measurements.

The significance of vascular aging is classically illustrated by the different prognostic values for peripheral systolic and diastolic BP, with a gradual shift away from diastolic, towards systolic BP, and PP, as predictors of coronary heart disease risk in patients under 50, between 50 and 59, and above 60 years of age, respectively, all three BP components being comparable predictors between 50 and 59 years of age [39]. The age-related disparities in terms of prognosis according to peripheral BP measurements may be related to central hemodynamic differences and especially to PP amplification [40]. One clinical illustration of these disparities may be the common isolated systolic hypertension phenotype, which highlights the contrasting central hemodynamic patterns between elderly and young hypertensive patients and the possible consequences on therapeutic strategies and as such, is a challenge for physicians. Over the age of 50, hypertensive vascular damage includes increased aortic stiffness, increased peripheral vascular resistance and decreased PP amplification, leading to a disproportionate increase in systolic over diastolic BP, together with an increase in central PP. Isolated systolic hypertension in young adults is associated with higher stroke volume and/or aortic stiffness than in age-matched normotensive adults or those with essential hypertension. In contrast, essential hypertension, which involves elevated systolic and diastolic pressures, is associated with higher peripheral vascular resistance and lower PP amplification compared to age-matched normotensive adults and those with isolated systolic hypertension [41]. Importantly, young adults with isolated systolic hypertension have higher central and peripheral PP than age-matched normotensive adults and those with essential hypertension, while there are no significant differences in PP amplification between normotensive adults and those with systolic hypertension. Systolic hypertension in younger subjects may therefore not be benign or limited to wider PP amplification.

Cardiovascular diseases affect men and women differently. Higher morbidity and mortality after myocardial infarction [42, 43], and a higher frequency of heart failure with preserved ejection fraction [44] have been described in women and may be related to gender differences in terms of central hemodynamic parameters, leading to a pronounced increase in cardiac afterload in women [45]. Gender appears to differentially influence BP components with aging, the increase in PP being more pronounced in women than in men [46]. The increase in central systolic pressure appears more prominent in women than in men with a more marked decrease in PP amplification in women over 50 years. Significant differences in arterial properties have been described between men and women, with a decrease in PP amplification being associated with increased arterial stiffness and earlier wave reflection in women, though this is only partly related to shorter body length in women [47, 48]. Sympathetic activity of the autonomic nervous system and postmenopausal hormone disorders have been associated with increased systemic arterial resistances, earlier and enhanced reflected waves, and increased aortic stiffness [49, 50]. The deleterious effects of earlier wave reflection and higher pulse wave augmentation on left diastolic ventricular function might also be more pronounced in women than in men, suggesting a possible pathophysiological mechanism accounting for the greater susceptibility to heart failure with preserved left ventricular ejection fraction in women [51].

4. CENTRAL BLOOD PRESSURE

Together with the substantial variability in PP amplification from central to peripheral sites, the clinical relevance of central BP over and above brachial BP measurements for the prediction of CV risk is supported by the pathophysiological significance of central systolic and pulse pressures in target organ damage and CV outcomes, potentially through damage to the microcirculation and atherosclerosis. Central BP may have incremental value over peripheral BP measurement for CV risk prediction.

4.1. Pathophysiological Relevance of Central Blood Pressure in Target Organ Damage

4.1.1. Central Blood Pressure and Microcirculatory Target Organ Damage

Increased central pressure pulsatility promotes deleterious effects on target organs, particularly those with high blood flow perfusion such as the heart [52], the brain [53] and the kidneys [54], which share predominantly structural and functional microvascular alterations, with blunted microvascular reactivity to ischemic stress [55]. The heart, brain and kidneys appear to be differentially affected by increased systolic and pulsatile hemodynamic load.

Coronary vascular tree perfusion pressure is exclusively related to diastolic BP. Decreased diastolic coronary vascular tree perfusion, and thus decreased coronary flow reserve, is a consequence of earlier reflected waves added to the late systolic pressure. Microcirculatory flow reserve reduction is aggravated by left ventricular hypertrophy, which occurs as a response to increased cardiac afterload related to the systolic component of central BP. Myocardial oxygen demand is further augmented while diastolic aortic pressure is reduced [56]. Epidemiological evidence from large population-based studies has highlighted the closer relationship between left ventricular mass index and central rather than brachial systolic BP [57, 58]. In animal models, left ventricular hypertrophy has been associated with a decrease in anastomotic and branching capillaries and a decline in capillary density [59]. The resulting myocardial hypoperfusion during high metabolic and oxygen demand is further associated with susceptibility to ischemia, independently from the atherosclerotic process [60, 61].

The brain and kidneys, which are high flow organs during both systole and diastole, also appear to be particularly susceptible to central pressure pulsatility. Epidemiological evidence suggests that central systolic and pulse pressures are more strongly related to glomerular filtration rate than brachial systolic and pulse pressures [57]. An independent relationship between kidney function (assessed with plasma creatinine and proteinuria) and invasively measured PP in the ascending aorta and in renal arteries has been shown in high-risk patients. In contrast, plasma creatinine and proteinuria did not correlate with iliac PP or with mean BP [62]. Central PP and flow pulsatility in the carotid artery have been associated with diffuse microvascular brain lesions; indeed, excessive

flow pulsatility into the cerebral circulation is known to be strongly and independently associated with reduced cognitive scores [53]. A pathophysiological explanation has been proposed, based on progressive loss of the normal impedance mismatch at the junction between the aorta and branch vessels with advancing age and in the presence of various vascular risk factors [53, 63, 64]. Transmission of excessive pressure and flow pulsatility to the microvasculature is generally prevented by the mismatch in impedance existing between the aorta (physiologically compliant with low impedance) and branch vessels, the carotid and renal arteries exhibiting higher impedance. It has been hypothesized that an impedance mismatch may be a protective mechanism accounting for wave reflection and limiting exposure of the distal microcirculation to excessive pulsatility [65]. Increased aortic stiffness leads to progressive impedance matching at the site of branch vessels with reduced wave reflections. Transmission of excessive pulsatility into the microcirculation may be thus facilitated [53, 65]. In hypertensive patients, the adaptive myogenic response of small resistance arterioles to increased wall tensile stress results in chronic lumen reduction, protecting fragile capillaries from exposure to excessive pressure [66]. Chronic increased myogenic tone is ultimately associated with functional and structural arteriolar rarefaction. In contrast, with aging, there may be a defective pressure-induced myogenic tone with pathological transmission of pulsatility in high blood-flow perfusion organs.

4.1.2. Central Blood Pressure and Atherosclerosis

A causal relationship between central PP and atherosclerosis, due to focal accumulation of cholesterol associated with severe tissue inflammation, has been postulated based on observations from cross-sectional studies focusing on the presence, extent and severity of coronary and carotid artery plaque. In patients with preserved left ventricular ejection fraction, carotid systolic and pulse pressures (but not brachial BP) are independently correlated with the severity of coronary artery stenosis; carotid PP is the best discriminator with highly significant differences between controls, and patients with moderate or severe coronary artery stenosis [67]. During coronarography in middle-aged patients with confirmed coronary artery disease and preserved left ventricular function, ascending aorta pulsatility is correlated with the risk of three-vessel disease whereas brachial BP measurement is not [68]. The pulsatile component of BP appears to be more strongly related to vascular hypertrophy and to the extent of atherosclerosis than the systolic component, with central PP exhibiting a higher correlation coefficient for intima-media thickness, vascular mass and extent of atherosclerosis than brachial PP in a large cross-sectional analysis of middle-aged patients [31]. From a pathophysiological standpoint, pressure pulsatility is related to cyclic strain (Laplace's law), a mechanical factor that affects all structures of the arterial wall, including vascular smooth muscle cells and the endothelium. Inflammatory cell migration [69], expression of adhesion molecules in the endothelium [70] and lipid arterial wall infiltration [71, 72] appear to be driven by pressure pulsatility and lead to the pathogenesis and progression of atherosclerotic damage [73]. Furthermore, the degree of pulsatile stress in the vascular tree, which is associated with the development of atherosclerotic plaque, appears to be closely correlated with the risk of plaque disruption leading to acute vascular ischemic syndrome [74].

4.2. Central Blood Pressure: Predictive Ability for Cardiovascular Events Over and Above Brachial Blood Pressure

Longitudinal studies have highlighted the strong, independent predictive value of central PP over brachial PP for CV risk. Office central PP may have better predictive ability for all-cause mortality even than the reference, out-of-office ambulatory peripheral BP measurement [75]. The predictive value of central systolic and/or pulse pressure over brachial BP for major clinical outcomes has been consistently demonstrated in the general population, in elderly adults and in patients at high CV risk, including patients with end-stage renal disease (ESRD) or coronary heart disease. Across different ethnic groups, the predictive ability of central pressure indices has been demonstrated regardless of whether central pressure has been derived from pulse wave analysis or measured invasively during coronarography (Table **1**).

The strong independent predictive value of non-invasive measurement of central pressure indices for CV events was first shown in high risk patients with ESRD undergoing hemodialysis. Increased Aix, measured noninvasively in the common carotid artery, was shown to be highly predictive of all-cause and CV mortality, independently of age, aortic PWV, low diastolic BP and preexisting CV disease [76]. In ESRD patients, carotid PP, PP amplification from carotid to brachial artery, and aortic PWV were the three mechanical factors that emerged as significant independent predictors for overall mortality [77]. Central PP measured at the site of the carotid artery was a more powerful predictor of overall mortality than brachial PP. Importantly, and independently of heart rate, attenuated amplification of PP from central to peripheral sites was associated with significantly increased mortality in ESRD patients; PP amplification was therefore the strongest predictor of outcomes as calculated by the area under receiver operating characteristic curves [77].

In patients with suspected coronary artery disease and undergoing coronary angiography with invasive measurement of central pressure indices, central PP was strongly related to CV risk, in contrast to peripheral BP components, independently of all predictors, including ejection fraction, mean coronary stenosis, previous myocardial infarction, gender, glomerular filtration rate and diabetes [28]. Importantly, the predictive value of central PP for CV events appeared to be independent of the extent of coronary atherosclerosis in patients with coronary artery disease.

In a low-risk, community-based population, central systolic BP, but not PP or brachial BP variables, predicted CV mortality independently of age, gender, heart rate, CV risk factors, target organ damage (left ventricular mass, carotid intima-media thickness and estimated glomerular filtration rate) and independently of aortic stiffness [57]. A threshold of increased adverse CV outcomes has been suggested for central PP $\geq$50mmHg in men and women, in diabetic and non-diabetic patients and in patients over 60 years of age [78].

In an unselected cohort of elderly adults, despite the decrease in PP amplification from central to peripheral sites with aging, central systolic BP confirmed its predictive superiority for CV events over brachial BP and independently of the other predictive factors including age, male gender, presence of carotid plaque and coronary heart disease [79].

5. CLINICAL RELEVANCE OF VASCULAR PHENOTYPE AND CARDIAC PERFORMANCE IN CARDIOVASCULAR RISK ESTIMATION

The clinical relevance of central pressure is calculated on the basis of PP amplification from central to peripheral sites; PP amplification is related in part to the amplitude and timing of wave reflections. Pulse pressure is also dependent upon cardiac performance, which is influenced by stroke volume, heart rate and ventricular-vascular coupling. Comorbidities and age-related changes, together with gender-related specificities of arterial and cardiac parameters, can be expected to affect the predictive ability of central hemodynamic parameters for individual CV risk.

Great emphasis has been placed on the role of aortic stiffness, disturbed arterial wave reflections and their inter-correlation in the pathophysiological mechanisms of CV diseases as well as on their predictive ability for target organ damage and clinical events [80]. Moreover, a combined effect on mortality of aortic PWV and wave reflections has been described in a population of elderly hospital-

Table 1. Incremental value of central blood pressure over peripheral blood pressure for the prediction of cardiovascular risk.

Reference	Year, Country	Population	Follow-up	Parameter	End-Point
Safar *et al.* [77]	2002, France	ESRD	52-mo FU	Central PP (C)	All-cause and CV mortality
Jankowski *et al.* [28]	2008, Poland	CAD	4.5-y FU	Central PP (D)	CV mortality and events
Pini *et al.* [79]	2008, Italy	Unselected elderly population	8-y FU	Central SBP (C)	CV mortality
Roman *et al.* [31, 78]	2007 and 2009, USA	High-risk	4.8-y FU	Central PP (R)	CV mortality and events
Wang *et al.* [57]	2009, Taiwan	Community-based	10.8-y FU	Central SBP (C)	CV mortality

These studies all demonstrated the incremental value of central blood pressure over peripheral blood pressure.
FU, follow-up; (C), central pressure derived from carotid pulse wave analysis; (D), direct invasive measurement; (R), central pressure derived from radial pulse wave analysis; ESRD, end-stage renal disease; SBP, systolic blood pressure; PP, pulse pressure; CV, cardiovascular; CAD, coronary artery disease;

ized patients with CV disease. Interestingly, only subjects presenting combined high PWV and AIx had lower survival compared with subjects who showed dissociation between PWV and AIx [81].

Although it is accepted that wave reflections and aortic stiffness are important determinants of central PP, the predictive information for CV risk, driven by enhanced wave reflections and increased aortic PWV, might not be limited to the deleterious effects of the resulting enhanced central PP. Results from prospective studies have suggested that the predictive value for CV events of a vascular phenotype may be distinguishable from that of central BP (Table **2**). As will be discussed later, the relationship between aortic PWV and first-onset CV events was shown to be distinguishable from excessive central pressure pulsatility in Framingham Heart Study participants [82]. Aortic augmentation pressure and aortic AIx both predict major CV events independently of PP in men with established coronary artery disease [83]. Finally, PP amplification may provide a higher predictive value than carotid PP for overall and CV mortality in a large population study [84].

5.1. Aortic Stiffness

Advancing age and distending pressure appear to be the most important determinants of altered buffering function resulting from aortic wall stiffening [85]. Aortic wall stiffening represents an adaptive structural response of large arteries to increased tensile stress in hypertensive patients and to long-term cyclic pulsatile distension with aging [9, 86]. Carotid to femoral PWV, as a direct measure of aortic stiffness, has the largest amount of evidence regarding added predictive value for risk, over and above traditional risk factors, in terms of all-cause and CV mortalities, fatal and non-fatal coronary events, and fatal strokes in patients with essential hypertension [87, 88], type 2 diabetes [89], ESRD [90], elderly adults [91] and in the general population [82, 92]. A recent, large-scale meta-analysis of prospective observational data confirmed the strong predictive ability, with incremental value for risk, of aortic stiffness that may be considered as subclinical arterial damage conferring a high risk for CV events, and all-cause and CV mortality above the traditional risk factors including brachial BP [93, 94].

In middle-aged and older participants, with 58% of women, in the community-based Framingham Heart Study, aortic stiffness improved risk prediction for CV events independently of risk factors whereas AIx, central PP, and PP amplification were not associated with CV outcomes in models that included standard risk factors [82]. The lack of predictive ability of central PP may be due to the absence of systolic amplification detection between carotid and brachial arteries or to methodological difficulties that lead to inaccurate estimation of the actual brachial PP, central PP and PP amplification. In middle-aged and older patients, and women especially, PP amplification decreases substantially and the predictive ability may be difficult to assess with non-invasive methods [95]. Importantly, because of the existence of systolic pressure amplification between brachial and radial arteries, central PP may be underestimated by current radial applanation tonometry with brachial BP values for calibration and, to a lesser extent, by the generalized radial-to-aorta pressure transfer function [96]. In the Framingham Heart Study, direct measurement of carotid and brachial pressure waveforms, with calibration of the brachial waveform to brachial cuff pressure, may have avoided over-estimation of aortic-brachial amplification. It has also been clearly demonstrated that more than one third of analyzed events were episodes of heart failure [97]. Pulse pressure may lack predictive value for CV outcomes related to heart failure because of the strong dependency of pressure pulsatility on stroke volume. Aortic stiffness may also provide a stronger predictive value for risk than central PP in middle-aged and older patients because PP and aortic PWV increase exponentially beyond the age of 60, whereas changes in AIx are more marked in younger individuals [95]. Additionally, the age-related contribution of cardiac and arterial parameters to PP appears to be different in young, middle-aged and elderly patients. Middle-age may be a transition point where stroke volume contributes to a lesser extent to the rise in PP with age whereas reduced aortic distensibility with aging may have a greater impact on high pressure pulsatility [98].

5.2. Wave Reflections

The predictive value of carotid AIx for all-cause and CV mortality was first shown in a population of high risk patients with ESRD on hemodialysis, independently of age, aortic PWV or prior CV events [76]. Importantly, in this population, the predictive value of aortic PWV and carotid AIx for adverse outcomes was shown to be superior to that of PP alone. Carotid AIx, often considered as an indirect marker of aortic stiffness, was strongly associated with CV mortality in the group of patients with a less stiff aorta and may thus add to the predictive value of aortic PWV for mortality in ESRD patients. In patients with coronary heart disease, augmentation pressure and AIx, derived from the aortic pressure waveform during coronarography, were both independent predictors of major adverse CV events after adjustment for risk factors, including age and PP, and independently of angiographic severity of coronary heart disease [83]. The added, short- and long-term prognostic values of increased arterial wave reflections, assessed by aortic AIx using applanation tonometry of the radial artery and a validated transfer function, following percutaneous coronary interventions, has been demonstrated for death, myocardial infarction and restenosis over and above clinical risk factors, angiographic variables, and medications [99]. In a meta-analysis of pooled data from studies focusing on the predictive ability of central hemodynamic indices, central systolic and PP as well as central AIx conferred a significant predictive value for CV events with marginally but not significantly better predictive ability when compared to peripheral PP [100]. Central AIx but not central pulse or systolic pressures was signifi-

Table 2. Independent predictive value of aortic stiffness, wave reflections and pulse pressure amplification for cardiovascular events.

Reference	Year, Country	Population	Design	Parameter	End-Point
Safar *et al.* [77]	2002, France	ESRD	52-mo FU	PP amplification [α]	All-cause and CV mortality
Chirinos *et al.* [83]	2005, USA	CAD	3.2-y FU	Aortic Pressure Augmentation [β]	CV mortality and events
Mitchell *et al.* [82]	2010, USA	Community-based	7.8-y FU	Aortic PWV [γ]	First-onset major CV event
Benetos *et al.* [84]	2010, France	Community-based	12-y FU	PP amplification [δ]	All-cause and CV mortality

FU, follow-up; ESRD, end-stage renal disease; PP, pulse pressure; CV, cardiovascular; PWV, pulse wave velocity; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty.

[α] Carotid pulse pressure, brachial/carotid pulse pressure and aortic PWV were predictors of all-cause mortality. The predictive value of pulse pressure amplification was superior to that of carotid pulse pressure, as calculated by the area under receiver operating characteristic curve.

[β] Aortic pressure augmentation was an independent predictor of major adverse cardiovascular events after adjusting for risk factors, including age and pulse pressure.

[γ] Augmentation index, central pulse pressure and pulse pressure amplification were not related to *cardiovascular* disease outcomes in multivariable models.

[δ] Pulse pressure amplification had predictive value for all-cause and cardiovascular mortality, with the highest hazard ratio as compared to brachial and carotid pulse pressures.

cantly predictive of overall mortality after adjustment for age and heart rate.

These results have yet to be confirmed with individual data and according to methodological limits in central BP and AIx assessment. It has been shown that the transfer function may have limited use in central AIx assessment from the pressure waveform recorded at the radial artery. The accuracy of the transfer function for estimating central systolic BP from the radial pulse has been established in patients undergoing cardiac catheterization. Importantly, higher discrepancies were observed between values of central AIx obtained from a transfer function and measured values [101]. Moreover, epidemiological evidence in community-based populations has highlighted the lack of predictive value of AIx and augmented pressure in women. Augmentation index and augmented pressure are both dependent upon reflected wave transit time and thus do not necessarily indicate an increase in wave reflection intensity. In contrast, the absolute magnitude of the reflected wave, independently of timing, may represent a relevant marker of increased wave reflections with predictive ability for cardiovascular mortality in both men and women, independently of carotid-femoral PWV [102].

5.3. Aortic Stiffness and Wave Reflections

From a pathophysiological point of view, it is important to highlight the fact that impedance matching between the carotid artery and a stiff aorta is associated with reduced wave reflections (and reduced central AIx) leading to excessive transmission of pulsatility to the downstream arterial network. In an older (69-93 years), community-based population, central arterial parameters, including carotid-femoral PWV, central PP, AIx and carotid pulsatility index, were evaluated in relation to microvascular cerebral damage and cognitive performance [53]. A positive association was observed between pressure and flow pulsatility, and carotid-femoral PWV with diffuse microvascular brain lesions on MRI, and reduced cognitive scores. In memory models, only the carotid pulsatility index, related to flow pulse amplitude and negatively correlated with the carotid reflection coefficient, was significantly associated with cognitive impairment. Augmentation index, derived from the carotid pressure waveform, was not related to prevalent cortical or subcortical infarcts or to cognitive scores. These results suggest that the adverse effects of aortic stiffness and wave reflections may be largely mediated by excessive flow pulsatility in the cerebral microcirculation. In addition, in older individuals or patients with greater aortic stiffness, there may be a dissociation between target organ damage and AIx that fails to capture the deleterious effects of aortic stiffness and wave reflections [53]. These observational data suggest that wave reflections, as assessed with augmented aortic pressure in late systole or AIx, might be more predictive for CV events with cardiac rather than cerebral outcomes, as earlier reflected waves in the central aorta are associated with increased left ventricular after-load and myocardial oxygen consumption and decreased coronary perfusion pressure.

5.4. Pulse Pressure Amplification as a Surrogate of Vascular Phenotype in Hypertension

Target organs are exposed to central rather than peripheral PP, which may differ because of the PP amplification phenomenon. Central PP and PP amplification measurements may therefore have incremental value for CV risk stratification. Despite similar brachial BP values, amplification of PP is highly variable between individuals but also on an intra-individual level, especially during antihypertensive treatment, with consequences on the central hemodynamic load. Advancing age is known to have a major impact on PP amplification, which has been shown to be negatively associated with hypertension, diabetes, hypercholesterolemia, smoking and established CV disease, independently of heart rate, height and gender [14]. The strong predictive value of PP amplification on hard end-points was first demonstrated in a middle-aged population of ESRD patients on hemodialysis. Carotid PP, brachial/carotid PP, and aortic PWV were independent predictors of all-cause and CV mortality, after adjustment for age, time on dialysis and previous CV events, whereas brachial PP had no predictive value for adverse outcomes after adjustment. The disappearance of the amplification phenomenon has been shown to be predictive of an increased risk of mortality; indeed, the area under receiver operating characteristic curves showed this to be the most significant parameter [77]. In a large community-based study, PP amplification confirmed its predictive value for all-cause and CV mortality, with the highest hazard ratio as compared to brachial and carotid PP [84]. These results suggest that the predictive information provided by PP amplification cannot be limited to the deleterious effects of increased central hemodynamic load. Timing and intensity of arterial wave reflections, which determine the PP amplification phenomenon, are modulated by vascular properties, including aortic stiffness and arteriolar vasomotor tone, and by heart rate. Pulse pressure amplification may therefore represent a marker that combines vascular damage in both macro- and microvascular networks of a given individual, as well as the effect of the autonomic nervous system aiming to protect the heart from an elevated afterload.

Clinical implication may be thus considered in young patients, in patients with numerous comorbidities and in the frail, elderly individuals with different information for risk. High PP amplification in young patients with isolated brachial systolic hypertension may be an important factor to consider for diagnostic purposes and

treatment decisions [5]. Increased heart rate in healthy individuals leads to higher PP amplification and cardiac index with no changes in ejection fraction, which is a major determinant of systolic and pulse pressures. Aging and co-morbidities differentially influence the impact of cardiac factors on the clinical relevance of PP amplification. In patients with coronary heart disease or those with hypertensive heart disease, elevated heart rate is associated with increased left ventricular end-diastolic pressure and myocardial oxygen consumption, and with decreased stroke volume [103]. As a consequence, PP is likely to decrease and may lack predictive ability for adverse outcomes [104]. Importantly, PP was shown to be inversely correlated with overall mortality in the frail, very elderly individuals [105], with coronary artery occlusion in patients with severe ischemic heart disease [106], and with mortality in patients with decompensated heart failure [107]. Interestingly, because distending pressure is a major determinant of aortic PWV, this biomarker may also lack predictive power in frail patients [105]. Since PP amplification is commonly defined as the ratio between brachial and central PP, it is not related to the absolute BP levels and remains a strong predictor of overall mortality and CV events in frail individuals [105].

There is now epidemiological evidence for additive and independent information of PP amplification for CV risk at the individual level. However, to be clinical useful for risk prediction, assessment of PP must be non-invasive, reproducible and feasible in both peripheral and central sites, the latter being dependent upon the calibration of the radial pressure waveform.

6. CENTRAL HEMODYNAMICS IN FUTURE CLINICAL PRACTICE

In patients with low or intermediate estimated CV risk, central hemodynamics in clinical practice can be expected to provide reclassification improvement leading to a more accurate representation of the subclinical arterial damage as well as the loading and pulsatile conditions imposed on the heart and brain. At an individual level, and according to age and gender, central hemodynamic parameters may present different predictive abilities for CV events thus providing potentially useful information about specific organ damage to enable targeted therapeutic interventions to correct residual risk. In high risk patients, those with severe coronary artery disease or heart failure, patients with comorbidities, and in frail, elderly individuals, central hemodynamic parameters may provide information about the risk of iatrogenic side effects of antihypertensive treatment, thus avoiding a possible J-shaped relation between intensified treatment and the incidence of CV events.

The pulse pressure waveform depends on left ventricular contractility and heart rate as well as on functional and structural properties of large and small arteries [9]. Central hemodynamic parameters are multi-parametric measurements derived from pulse wave analysis and strongly influenced by age and brachial BP levels. The predictive information they provide for CV risk is thus interrelated. Age, gender and comorbidities may influence the choice of central hemodynamic parameter to improve risk prediction. Only large-scale, observational epidemiological studies, in different age subgroups, in healthy individuals as well as in patients with CV risk factors, would provide evidence of the additive information for risk prediction of each central hemodynamic parameter over and above brachial BP measurement.

The superior predictive ability of central systolic and pulse pressures, PP amplification and carotid-to-femoral PWV over peripheral BP measurements does not imply direct causation, even though the pathophysiological importance of each parameter has been demonstrated. Whether central BP should be considered as a specific hemodynamic risk factor, and PP amplification and/or aortic PWV as surrogate end-points for clinical events has yet to be established in clinical trials with targeted treatment intervention. In this respect, central PP would be easier to use in clinical practice with validated automatic oscillometric devices for estimating aortic BP rather than radial or carotid applanation tonometry.

7. CONCLUSION

Central hemodynamic parameters appear to be relevant for improving risk prediction at the individual level and may well prove to be clinically relevant targets for risk-reduction strategies. It has however yet to be determined which central hemodynamic parameter, alone or in combination with others, is relevant for improving risk classification, is reproducible, and easy to assess in clinical practice. In addition, age, gender and comorbidities impact on vascular damage, on the adaptive interactions between cardiac and arterial systems and thus, on the predictive ability of each central hemodynamic parameter. Sound epidemiological evidence is required to compare their respective predictive values for cardiac, cerebral and renal events in different populations. Improved CV risk estimation at the individual level can be expected to have consequences on risk-reduction strategies with more accurate treatment targets and fewer iatrogenic side effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Lewington S, Clarke R, Qizilbash N, *et al.* Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.

[2] Lloyd-Jones DM, Larson MG, Leip EP, *et al.* Lifetime risk for developing congestive heart failure. The Framingham Heart Study. Circulation 2002; 106: 3068-72.

[3] Staessen JA, Richart T, Birkenhäger WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension 2007; 49: 389-400.

[4] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009; 338: b1665.

[5] Mancia G, Fagard R, Narkiewicz K, *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159-219.

[6] Beckett NS, Peters R, Fletcher AE, *et al.* HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358: 1887-98.

[7] Blacher J, Evans A, Arveiler D, *et al.* PRIME Study Group. Residual coronary risk in men aged 50-59 years treated for hypertension and hyperlipidaemia in the population: the PRIME study. J Hypertens 2004; 22: 415-23.

[8] Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

[9] Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003; 107: 2864-9.

[10] Avolio A, Van Bortel L, Boutouyrie P, *et al.* The role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension 2009; 54: 375-83.

[11] Albaladejo P, Copie X, Boutouyrie P, *et al.* Heart Rate, Arterial Stiffness, and Wave Reflections in Paced Patients. Hypertension 2001; 38: 949-52.

[12] Wilkinson IB, Fuchs SA, Jansen IM, *et al.* Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998; 16: 2079-84.

[13] Laurent S, Cockcroft J, Van Bortel L, *et al.* on behalf of the European Network for Non-invasive Investigation of Large Arteries.

Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588-605.

[14] McEniery CM, Yasmin, McDonnell B, *et al.* on Behalf of the Anglo-Cardiff Collaborative Trial Investigators. Central Pressure: Variability and Impact of Cardiovascular Risk Factors. The Anglo-Cardiff Collaborative Trial II. Hypertension 2008; 51: 1476-82.

[15] Segers P, Mahieu D, Kips J, *et al.* for the Asklepios investigators. Amplification of the Pressure Pulse in the Upper Limb in Healthy, Middle-Aged Men and Women. Hypertension 2009; 54: 414-20.

[16] Thomas G. Pickering, John E. Hall, *et al.* Recommendations for Blood Pressure Measurement in Humans and Experimental Animals: Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005; 111: 697-716.

[17] Van Montfrans GA. Oscillometric blood pressure measurement: progress and problems. Blood Press Monit 2001; 6: 287-90.

[18] Zhang Y, Agnoletti D, Safar ME, *et al.* 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. Hypertension 2011; 58: 155-60.

[19] Mancia G, Parati G, Castiglioni P, *et al.* Daily Life Blood Pressure Changes Are Steeper in Hypertensive Than in Normotensive Subjects. Hypertension 2003; 42: 277-82.

[20] Pickering TG, Hall JE, Appel LJ, *et al.* Recommendations for Blood Pressure Measurement in Humans and Experimental Animals: Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals. From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005; 111: 697-716.

[21] Vrachatis D, Papaioannou TG, Konstantopoulou A, *et al.* Effect of supine versus sitting position on noninvasive assessment of aortic pressure waveform: a randomized cross-over study. J Hum Hypertens 2014; 28: 236-41.

[22] Franklin SS, Gustin W IV, Wong ND, *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997; 96: 308-15.

[23] Safar ME. Pulse pressure, arterial stiffness, and cardiovascular risk. Curr Opin Cardiol 2000; 15: 258-63.

[24] Blacher J, Staessen JA, Girerd X, *et al.* Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000; 160: 1085-9.

[25] Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure – its role in the pathogenesis of atherosclerosis. Blood Press 2007; 16: 238-45.

[26] Kiefer CR, McKenney JB, Trainor JF, *et al.* Pulse pressure-driven neutral lipid accumulation and correlative proinflammatory markers of accelerated atherogenesis. Atherosclerosis 2005; 183: 17-24.

[27] Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol 2008; 105: 1652-60.

[28] Jankowski P, Kawecka-Jaszcz K, Czarnecka D, *et al.* on behalf of the Aortic Blood Pressure and Survival Study Group. Pulsatile but Not Steady Component of Blood Pressure Predicts Cardiovascular Events in Coronary Patients. Hypertension 2008; 51: 848-55.

[29] Protogerou AD, Safar ME, Iaria P, *et al.* Diastolic Blood Pressure and Mortality in the Elderly With Cardiovascular Disease. Hypertension 2007; 50: 172-80.

[30] Safar ME, London GM, Asmar R, *et al.* Third Workshop on Structure and Function of Large Arteries: Part I. Recent Advances on Large Arteries in Hypertension. Hypertension 1998; 32: 156-61.

[31] Roman MJ, Devereux RB, Kizer JR, *et al.* Central Pressure More Strongly Relates to Vascular Disease and Outcome Than Does Brachial Pressure: The Strong Heart Study. Hypertension 2007; 50: 197-203.

[32] Kario K, Shimada K, Pickering TG. Clinical implication of morning blood pressure surge in hypertension. J Cardiovasc Pharmacol 2003; 42 Suppl 1: S87-91.

[33] Mena LJ, Maestre GE, Hansen TW, *et al.* International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. How many measurements are needed to estimate blood pressure variability without loss of prognostic information? Am J Hypertens 2014; 27: 46-55.

[34] Rothwell PM, Howard SC, Dolan E *et al.* Prognostic significance of visit-to-visit variability, maximal systolic blood pressure, and episodic hypertension. Lancet 2010; 375: 895-905.

[35] Schillaci G, Bilo G, Pucci G, *et al.* Relationship Between Short-Term Blood Pressure Variability and Large-Artery Stiffness in Human Hypertension. Findings From 2 Large Databases. Hypertension 2012; 60: 369-77.

[36] Perk J, De Backer G, Gohlke H, *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33: 1635-701.

[37] Wang TJ, Gona P, Larson MG, *et al.* Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006; 355: 2631-39.

[38] Mitchell GF, DeStefano AL, Larson MG, *et al.* Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. Circulation 2005; 112: 194-9.

[39] Franklin SS, Larson MG, Khan SA, *et al.* Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001; 103: 1245-9.

[40] Wilkinson IB, Franklin SS, Hall IR, *et al.* Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. Hypertension 2001; 38: 1461-6.

[41] McEniery CM, Yasmin, Wallace S, *et al.* on behalf of the ENIGMA Study Investigators. Increased Stroke Volume and Aortic Stiffness Contribute to Isolated Systolic Hypertension in Young Adults. Hypertension 2005; 46: 221-6.

[42] Vaccarino V, Parsons L, Peterson ED, *et al.* Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med 2009; 169: 1767-74.

[43] O'Connor CM, Hathaway WR, Bates ER, *et al.* Clinical characteristics and long-term outcome of patients in whom congestive heart failure develops after thrombolytic therapy for acute myocardial infarction: development of a predictive model. Am Heart J 1997; 133: 663-73.

[44] Devereux RB, Roman MJ, Liu JE, *et al.* Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000; 86: 1090-6.

[45] Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. J Am Coll Cardiol 1997; 30: 1863-71.

[46] Smulyan H, Asmar RG, Rudnicki A, *et al.* Comparative effects of aging in men and women on the properties of the arterial tree. J Am Coll Cardiol 2001; 37: 1374-80.

[47] Gatzka CD, Kingwell BA, Cameron JD, *et al.* Gender differences in the timing of arterial wave reflection beyond differences in body height. J Hypertens 2001; 19: 2197-203.

[48] Russo C, Jin Z, Palmieri V, *et al.* Arterial Stiffness and Wave Reflection: Sex Differences and Relationship with Left Ventricular Diastolic Function. Hypertension 2012; 60: 362-8.

[49] Barnes JN, Hart EC, Curry TB, *et al.* Aging Enhances Autonomic Support of Blood Pressure in Women. Hypertension 2014; 63: 303-8.

[50] Rajkumar C, Kingwell BA, Cameron JD, *et al.* Hormonal Therapy Increases Arterial Compliance in Postmenopausal Women. J Am Coll Cardiol 1997; 30: 350-6.

[51] Shim CY, Park S, Choi D, *et al.* Sex Differences in Central Hemodynamics and Their Relationship to Left Ventricular Diastolic Function. J Am Coll Cardiol 2011; 57: 1226-33.

[52] Fukuda D, Yoshiyama M, Shimada K, *et al.* Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. Heart 2006; 92: 759-62.

[53] Mitchell GF, van Buchem MA, Sigurdsson S, *et al.* Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/ Environment Susceptibility – Reykjavik Study. Brain 2011: 134; 3398-407.

[54] Safar ME, London GM, Plante GE. Arterial Stiffness and Kidney Function. Hypertension 2004; 43: 163-8.

[55] Mitchell GF, Vita JA, Larson MG, *et al.* Cross-Sectional Relations of Peripheral Microvascular Function, Cardiovascular Disease Risk Factors, and Aortic Stiffness: The Framingham Heart Study. Circulation 2005; 112: 3722-8.

[56] O'Rourke MF. Arterial aging: pathophysiological principles. Vasc Med 2007; 12: 329-41.
[57] Wang KL, Cheng HM, Chuang SY, *et al.* Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertens 2009; 27: 461-7.
[58] Roman MJ, Okin P M, Kizer JR *et al.* Relations of central and brachial blood pressure to left ventricular hypertrophy and geometry: the strong heart study. J Hypertens 2010; 28: 384-8.
[59] Tomanek RJ, Searls JC, Lachenbruch PA. Quantitative Changes in the Capillary Bed during Developing, Peak, and Stabilized Cardiac Hypertrophy in the Spontaneously Hypertensive Rat. Circ Res 1982; 51: 295-304.
[60] Erdogan D, Yildirim I, Ciftci O, *et al.* Effects of Normal Blood Pressure, Prehypertension, and Hypertension on Coronary Microvascular Function. Circulation 2007; 115: 593-9.
[61] Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular outcome. Coron Artery Dis 2004; 15: 259-64.
[62] Temmar M, Jankowski P, Peltier M, *et al.* Intraaortic Pulse Pressure Amplification in Subjects at High Coronary Risk. Hypertension 2010; 55: 327-32.
[63] Verhave JC, Fesler P, du Cailar G, *et al.* Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. Hypertension 2005; 45: 586-91.
[64] O'Rourke MF, Safar ME. Relationship Between Aortic Stiffening and Micro vascular Disease in Brain and Kidney. Cause and Logic of Therapy. Hypertension 2005; 46: 200-4.
[65] Mitchell GF, Parise H, Benjamin EJ, *et al.* Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women. The Framingham Heart Study. Hypertension 2004; 43: 1239-45.
[66] Prewitt RL, Rice DC, Dobrian AD. Adaptation of resistance arteries to increases in pressure. Microcirculation 2002; 9: 295-304.
[67] Waddell TK, Dart AM, Medley TL, *et al.* Carotid pressure is a better predictor of coronary artery disease severity than brachial pressure. Hypertension 2001; 38: 927-31.
[68] Jankowski P, Kawecka-Jaszcz K, Czarnecka D, *et al.* Ascending aortic, but not brachial blood pressure-derived indices are related to coronary atherosclerosis. Atherosclerosis 2004; 176: 151-5.
[69] Yamamoto K, Ikeda U, Shimada K. Role of mechanical stress in monocytes/macrophages: implications for atherosclerosis. Curr Vasc Pharmacol 2003; 1: 315-9.
[70] Cheng JJ, Wung BS, Chao YJ, *et al.* Cyclic strain enhances adhesion of monocytes to endothelial cells by increasing intercellular adhesion molecule-1 expression. Hypertension 1996; 28: 386-91.
[71] Kiefer CR, McKenney JB, Trainor JF, *et al.* Pulse pressure-driven neutral lipid accumulation and correlative proinflammatory markers of accelerated atherogenesis. Atherosclerosis 2005; 183: 17-24.
[72] Sakamoto H, Aikawa M, Hill CC, *et al.* Biomechanical strain induces class a scavenger receptor expression in human monocyte/macrophages and THP-1 cells: a potential mechanism of increased atherosclerosis in hypertension. Circulation 2001; 104: 109-14.
[73] Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure – Its role in the pathogenesis of atherosclerosis. Blood Press 2007; 16: 238-45.
[74] Lovett JK, Howard SC, Rothwell PM. Pulse pressure is independently associated with carotid plaque ulceration. J Hypertens 2003; 21: 1669-76.
[75] Huang CM, Wang KL, Cheng HM, *et al.* Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. J Hypertens 2011; 29: 454-9.
[76] London GM, Blacher J, Pannier B, *et al.* Arterial Wave Reflections and Survival in End-Stage Renal Failure. Hypertension 2001; 38: 434-8.
[77] Safar ME, Blacher J, Pannier B, *et al.* Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002; 39: 735-8.
[78] Roman MJ, Devereux RB, Kizer JR, *et al.* High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. J Am Coll Cardiol 2009; 54: 1730-4.
[79] Pini R, Cavallini MC, Palmieri V, *et al.* Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population. The ICARe Dicomano study. J Am Coll Cardiol 2008; 51: 2432-9.
[80] Agabiti-Rosei E, Mancia G, O'Rourke MF, *et al.* Central Blood Pressure Measurements and Antihypertensive Therapy: A Consensus Document. Hypertension 2007; 50: 154-60.
[81] Protogerou AD, Safar ME, Papaioannou TG, *et al.* The combined effect of aortic stiffness and pressure wave reflections on mortality in the very old with cardiovascular disease: the PROTEGER Study. Hypertens Res 2011; 34: 803-8.
[82] Mitchell GF, Hwang SJ, Vasan RS, *et al.* Arterial Stiffness and Cardiovascular Events: The Framingham Heart Study. Circulation 2010; 121: 505-11.
[83] Chirinos JA, Zambrano JP, Chakko S, *et al.* Aortic Pressure Augmentation Predicts Adverse Cardiovascular Events in Patients With Established Coronary Artery Disease. Hypertension 2005; 45: 980-5.
[84] Benetos A, Thomas F, Joly L. Pulse pressure amplification: a mechanical biomarker of cardiovascular risk. J Am Coll Cardiol 2010; 55: 1032-7.
[85] Cecelja M, Chowienczyk P. Dissociation of Aortic Pulse Wave Velocity with Risk Factors for Cardiovascular Disease Other Than Hypertension: A Systematic Review. Hypertension 2009; 54: 1328-36.
[86] Safar ME and Lacolley P. Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage. Am J Physiol Heart Circ Physiol 2007; 293: H1–H7.
[87] Laurent S, Boutouyrie P, Asmar R, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236-41.
[88] Boutouyrie P, Tropeano AI, Asmar R, *et al.* Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002; 39: 10-15.
[89] Cardoso CR, Ferreira MT, Leite NC, *et al.* Prognostic impact of aortic stiffness in high-risk type 2 diabetic patients: The Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetes Care 2013; 36: 3772-8.
[90] Blacher J, Guerin AP, Pannier B, *et al.* Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999; 99: 2434-9.
[91] Meaume S, Benetos A, Henry OF, *et al.* Aortic pulse wave velocity predicts cardiovascular mortality in subjects > 70 years of age. Arterioscler Thromb Vasc Biol 2001; 21: 2046-50.
[92] Mattace-Raso FU, van der Cammen TJ, Hofman A, *et al.* Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006; 113: 657-3.
[93] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55: 1318-27.
[94] Ben-Shlomo Y, Spears M, Boustred C, *et al.* Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17, 635 subjects. J Am Coll Cardiol 2014; 63: 636-46.
[95] McEniery CM, Yasmin, Hall IR, *et al.* Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 2005; 46: 1753-60.
[96] Verbeke F, Segers P, Heireman S, *et al.* Noninvasive assessment of local pulse pressure: importance of brachial-to-radial pressure amplification. Hypertension 2005; 46: 244-8.
[97] Mitchell GF, Hwang SJ, Vasan RS, *et al.* Response to Letters Regarding Article, "Arterial Stiffness and Cardiovascular Events: The Framingham Heart Study". Circulation 2010; 122: e515.
[98] Alfie J, Waisman GD, Galarza CR, *et al.* Contribution of stroke volume to the change in pulse pressure pattern with age. Hypertension 1999; 34: 808-12.
[99] Weber T, Auer J, O'Rourke MF, *et al.* Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. Eur Heart J 2005; 26: 2657-63.
[100] Vlachopoulos C, Aznaouridis K, O'Rourke MF, *et al.* Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010; 31: 1865-71.
[101] Millasseau SC, Patel SJ, Redwood SR, *et al.* Pressure Wave Reflection Assessed From the Peripheral Pulse Is a Transfer Function Necessary? Hypertension 2003; 41: 1016-20.
[102] Wang KL, Cheng HM, Sung SH, *et al.* Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular

mortalities: a community-based study. Hypertension 2010; 55: 799-805.

[103] Göhl K, Perl S, Wortmann A and K. Bachmann. Ventricular performance in relation to heart rate and AV delay at rest. Eur Heart J 1992; 13 Suppl E: 91-8.

[104] Jankowski P, Kawecka-Jaszcz K, Czarnecka D, *et al.* Ascending aortic blood pressure-derived indices are not correlated with the extent of coronary artery disease in patients with impaired left ventricular function. Atherosclerosis 2006; 184: 370-6.

[105] Benetos A, Gautier S, Labat C, *et al.* 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. J Am Coll Cardiol 2012; 60: 1503-11.

[106] Mourad J-J, Danchin N, Rudnichi A, *et al.* on behalf of the ESCAPP investigators. Aortic pulse pressure and atherosclerotic structural alterations of coronary arteries. J Hum Hypertens 2010; 24: 51-7.

[107] Aronson D, Burger AJ. Relation between pulse pressure and survival in patients with decompensated heart failure. Am J Cardiol 2004; 93: 785-8.

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2.2.3 Conclusion de l'article 3

L'intérêt clinique de l'estimation de la pression artérielle centrale est basé sur le phénomène physiologique des ondes de réflexion et de l'amplification de la pression artérielle systolique et pulsée du centre vers la périphérie. La pression pulsée est également influencée par le volume d'éjection systolique, la fréquence cardiaque et le couplage entre le ventricule gauche et l'aorte ascendante (87). L'avancée en âge et les comorbidités associées, en particulier l'insuffisance cardiaque, auront donc une influence sur la valeur prédictive de la pression pulsée. Parallèlement, l'atteinte des gros troncs artériels et le phénomène des ondes de réflexion ont également été impliqués dans les mécanismes physiopathologiques de l'atteinte des organes cibles et de la survenue d'événements cardiovasculaires (88,89) **(Tableau 2)**. La valeur prédictive indépendante de la rigidité aortique en termes de mortalité cardiovasculaire et toutes causes a été mise en évidence pour la première fois chez des patients en insuffisance rénale terminale (1). L'augmentation de la VOP carotido-fémorale a été identifiée par la suite dans plusieurs études comme un marqueur prédictif indépendant de mortalité cardiovasculaire et toutes causes, d'événements coronariens et vasculaires cérébraux chez les patients hypertendus (2,3), les patients âgés (90) et dans la population générale (91,92).

La valeur prédictive de l'AIx pour la mortalité cardiovasculaire et toutes causes a été également mise en évidence pour la première fois dans une population de patients avec maladie rénale terminale (93). La valeur prédictive de l'AIx a été confirmée indépendamment de l'âge, de la rigidité aortique et de la présence d'antécédents cardiovasculaires. Chez les patients coronariens, l'AP et l'AIx, dérivés de la forme de l'onde de pression aortique lors de la coronarographie, étaient des facteurs prédictifs indépendants d'événements cardiovasculaires après ajustement à l'âge et la pression pulsée et indépendamment de la sévérité angiographique de maladie coronarienne (94). Cependant, l'estimation de ces deux paramètres

hémodynamiques centraux reste limitée par la méthode de mesure utilisant la tonométrie radiale et la fonction de transfert intégrée au logiciel (95). De plus, l'AIx et l'AP restent très dépendants du temps de transit des ondes de pression et ne peuvent donc pas être considérés comme des marqueurs directs de l'amplitude des ondes réfléchies (96). De manière théorique, il est décrit qu'une augmentation de rigidité aortique est associée à un retour plus rapide au niveau central, en systole, des ondes de pression réfléchies avec augmentation de l'AIx. Cependant, il est souligné que l'AIx et la VOP carotido-fémorale peuvent ne pas être corrélés ou même dissociés particulièrement au cours du vieillissement, du syndrome métabolique, d'une augmentation de l'activité du système nerveux autonome ou lors d'un traitement antihypertenseur (97,98). L'index d'augmentation ne peut donc pas être considéré comme un marqueur de rigidité aortique et manque de puissance prédictive au cours du vieillissement (97,99).

L'amplification de la pression pulsée est un marqueur hémodynamique très variable à l'échelle inter mais aussi intra-individuelle, particulièrement au cours du traitement antihypertenseur (100). Dans une population de patients avec insuffisance rénale chronique terminale, la pression pulsée centrale et l'amplification de la pression pulsée étaient des facteurs indépendants de mortalité cardiovasculaire et toutes causes. L'amplification de la pression pulsée présentait la plus forte valeur prédictive (84). Ces résultats ont été confirmés dans une large étude en population générale (101). Ce paramètre hémodynamique est défini par le rapport de la pression pulsée brachiale sur la pression pulsée centrale et n'est donc pas corrélé aux valeurs absolues de pression artérielle. L'amplification de la pression pulsée représente donc un facteur prédictif du risque cardiovasculaire aussi bien en population générale que chez les patients fragiles. En effet, chez les patients âgés institutionnalisés ou avec comorbidités, en particulier en présence d'une fonction ventriculaire gauche altérée,

le niveau de pression artérielle manque de puissance prédictive (102) et peut même présenter une relation inverse avec la mortalité (103).

La prise en considération de la pression pulsée centrale, de l'amplification de la pression pulsée et de la VOP carotido-fémorale devrait permettre d'optimiser la stratégie d'évaluation du risque individuel. En conséquence, des thérapeutiques plus ciblées pourraient être étudiées pour une meilleure prévention cardiovasculaire.

Tableau 2 (Article 3) : Rigidité aortique, ondes de réflexion et amplification de la pression pulsée : Facteurs prédictifs indépendants du risque cardiovasculaire.

Référence	Année	Population	Durée du Suivi	Paramètre hémodynamique étudié	Critère étudié
Safar *et al.* (84)	2002, France	Maladie rénale terminale	52 mois	Amplification PP**α**	Mortalité toutes causes et CV
Chirinos *et al.* (94)	2005, USA	Maladie coronaire	3.2 ans	Augmentation pression aortique**β**	Morbi-mortalité CV
Mitchell *et al.* (99)	2010, USA	Population générale	7.8 ans	VOP aortique **γ**	Evénement CV majeur
Benetos *et al.* (101)	2010, France	Population générale	12 ans	Amplification PP**δ**	Mortalité toutes causes et CV

PP, pression pulsée; CV, cardiovasculaire; VOP aortique, vitesse de l'onde de pouls carotido- fémorale.

α La PP carotidienne, l'amplification de la PP et la VOP carotido-fémorale étaient des facteurs prédictifs de la mortalité toutes causes. La valeur prédictive de l'amplification de la PP était supérieure à celle de la PP carotidienne.

β L'augmentation de la pression aortique était un facteur prédictif indépendant de la survenue d'événement CV majeur après ajustement aux facteurs de risque (dont l'âge et la PP).

γ L'index d'augmentation, la PP central et l'amplification de la PP n'étaient pas corrélés à la survenue d'événements CV dans les modèles multivariés.

δ L'amplification de la PP présentait la valeur prédictive la plus importante pour la mortalité toutes causes et CV en comparaison à la PP brachiale et carotidienne.

2.3 Paramètres hémodynamiques artériels et stratégies de réduction du risque cardiovasculaire : revue de la littérature (Article 4)

2.3.1 Introduction de l'article 4

D'après les nouvelles recommandations de la Société Française d'Hypertension Artérielle (35), le choix du traitement dépend de l'existence de comorbidités contre-indiquant certains antihypertenseurs et de la notion de persistance au traitement qui associe tolérance, efficacité et observance. Cinq classes d'antihypertenseurs ont démontré leur efficacité en prévention primaire et secondaire en termes d'événements coronariens et d'accidents vasculaires cérébraux chez les patients hypertendus. Il s'agit des diurétiques thiazidiques, des bétabloquants, des antagonistes calciques, des inhibiteurs de l'enzyme de conversion (IEC) et des antagonistes des récepteurs à l'angiotensine 2 (ARA2). L'accent est mis sur l'importance de la réduction tensionnelle dans la prévention cardiovasculaire: une réduction de 22 % des événements coronariens et de 41 % des accidents cérébraux est obtenue avec une réduction de pression artérielle systolique de 10 mm Hg et de pression artérielle diastolique de 5 mm Hg sous traitement, et ce indépendamment du niveau de pression artérielle initiale (104).

Cependant, pour un même niveau de pression artérielle brachiale, certaines classes d'antihypertenseurs apparaissent associées à une meilleure prévention des accidents cardiovasculaires. Ce bénéfice supplémentaire, indépendant de la baisse de pression artérielle périphérique, est associé à un effet pléiotropique des IEC, des ARA2 et des inhibiteurs calciques sur les paramètres hémodynamiques artériels et le remodelage vasculaire (100, 105). Les IEC et les ARA2 inhibent le système rénine-angiotensine : les IEC diminuent la concentration d'angiotensine II circulante et inhibent la dégradation de la bradykinine ; les ARA2 bloquent de manière spécifique et sélective les récepteurs AT1, présents en

quantité élevée dans les cellules musculaires lisses vasculaires. Les effets physiopathologiques de l'angiotensine II via le récepteur AT1 incluent notamment un remodelage vasculaire avec hypertrophie des cellules musculaires lisses, une vasoconstriction et une altération des propriétés de vasodilatation NO-dépendante, ainsi que la stimulation de la sécrétion d'aldostérone par la corticosurrénale. Les inhibiteurs calciques agissent en empêchant l'entrée du calcium extracellulaire dans la cellule musculaire lisse vasculaire et permettent donc de limiter le tonus myogénique excessif existant en contexte d'hypertension artérielle. Ils entraînent une vasodilatation artériolaire, et ainsi une baisse des résistances périphériques, secondaire au blocage des canaux calciques. Les inhibiteurs calciques dihydropyridiniques sont à distinguer des non-dihydropyridiniques par leurs effets hémodynamiques à court et long terme. Les inhibiteurs calciques dihydropyridiniques agissent sur les cellules musculaires lisses vasculaires, entraînant une baisse rapide de la pression artérielle moyenne ainsi qu'une augmentation réflexe à court terme du rythme cardiaque et du débit cardiaque. Le vérapamil, inhibiteur calcique non dihydropyridinique dérivé de la papavérine, présente en plus des effets chronotrope, dromotrope et inotrope négatifs cardiaques, en association à la vasodilatation artériolaire périphérique. L'effet hémodynamique du diltiazem, inhibiteur calcique non dihydropyridinique dérivé des benzothiazépines, est illustré par une vasodilatation artériolaire ainsi qu'une vasodilatation au niveau gros troncs artériels (mise en évidence sur l'artère brachiale) associée à une augmentation du flux sanguin (106). Les inhibiteurs calciques présenteraient également des effets vasculo-protecteurs notamment par l'inhibition de la prolifération des cellules musculaires lisses vasculaires et par la stimulation de production de NO. Les résultats des études HOPE (IEC versus placebo) (107), LIFE (ARA2 versus aténolol) (108) et ASCOT (inhibiteur calcique versus aténolol) (109),

chez des patients hypertendus à haut risque, soulignent la supériorité d'un traitement comprenant un inhibiteur du système rénine-angiotensine ou un inhibiteur calcique en termes de réduction des événements cardiovasculaires. Ces résultats positifs ont été soulignés au-delà du contrôle de la pression artérielle périphérique. L'étude CAFE (110), au sein de l'essai ASCOT, a examiné l'impact des traitements par aténolol ± diurétique thiazidique et amlodipine ± périndopril sur les paramètres hémodynamiques centraux. La réduction plus marquée de la pression artérielle centrale sous un traitement à base d'amlodipine ± périndopril, à même niveau de pression artérielle périphérique, pourrait expliquer le bénéfice supplémentaire de ce traitement en termes d'événements cardiovasculaires. Les pressions pulsées périphérique et centrale présentaient un risque relatif très similaire de survenue d'événement cardiovasculaire. Cependant, alors que la différence de pression pulsée périphérique entre les deux groupes de traitement n'atteignait pas la significativité statistique (de plus, le niveau de pression pulsée périphérique apparaissait plus élevé dans le groupe amlodipine), le niveau de pression pulsée centrale dans le groupe amlodipine ± périndopril était significativement plus bas. Une diminution de l'amplitude ou du temps de transit des ondes de réflexion pourraient être impliqués dans la réduction plus marquée de la pression pulsée centrale dans le groupe amlodipine ± périndopril. La vasodilatation artériolaire et la fréquence cardiaque plus élevée expliqueraient une amplification plus importante de la pression pulsée dans le groupe traitement à base d'amlodipine ± périndopril comparativement au groupe aténolol (111, 112). C'est l'étude REASON, randomisée en double aveugle menée chez des patients hypertendus, qui avait initialement souligné les effets pléiotropiques artériels des molécules antihypertensives (113). Une baisse plus marquée de la pression systolique centrale sous traitement associant périndopril/indapamide en comparaison à l'aténolol avait été mise en évidence après un an de traitement. L'amplification de la pression systolique du centre vers la périphérie ne différait pas entre les deux groupes de traitement en

début d'étude. A un an de traitement, la valeur de l'amplification était maintenue dans le groupe périndopril/indapamide alors qu'elle était réduite ou presque inexistante dans le groupe aténolol, avec une différence significative entre les deux groupes de traitement. La baisse de la pression artérielle moyenne était un facteur déterminant de la baisse de la pression artérielle systolique brachiale dans le groupe aténolol mais n'influençait pas les paramètres hémodynamiques centraux sous périndopril/indapamide. La rigidité aortique et les ondes de réflexion représentaient les facteurs hémodynamiques associés à la baisse marquée de la pression systolique centrale sous périndopril/indapamide.

2.3.2 Article 4

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Central hemodynamics for risk reduction strategies: additive value over and above brachial blood pressure.

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Central Hemodynamics for Risk Reduction Strategies: Additive Value Over and Above Brachial Blood Pressure

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Abstract: Reduction strategies of blood pressure, as a modifiable cardiovascular risk, are currently based on office assessment of brachial artery blood pressure. However, antihypertensive treatment based on brachial BP values reduces cardiovascular risk but cannot completely reverse the hypertension-induced risk of morbidity events. As is well known, BP varies in different arterial systems and invasive and non-invasive studies have demonstrated that brachial BP does not necessarily reflect central aortic BP. Emerging evidences now suggest that central pressure may predict cardiovascular diseases better than brachial BP; moreover, it may differently respond to certain antihypertensive drugs. The potential effects beyond peripheral BP control may be due to specific protective properties of different antihypertensive drugs in affecting central aortic pressure and arterial stiffness. Although data on direct cardiovascular benefit impact of central blood pressure treatment in randomized clinical trials are still lacking, it is likely that the improvement of quality of care and the individualized assessment of the hypertension-associated cardiovascular risk are achievable with the use of central hemodynamics. Therefore, basing antihypertensive treatment guidance on central pressures rather than on peripheral blood pressure may be the key for future antihypertensive strategies.

Keywords: Cardiovascular risk reduction, central pulse pressure, aortic stiffness, anti-hypertensive treatment.

INTRODUCTION

In most industrialized countries, cardiovascular diseases are the leading cause of morbidity and mortality, and elevated artery blood pressure (BP) is a classic major risk factor and a powerful predictor of cardiovascular (CV) damage, morbidity and mortality [1]. Several clinical data have shown that lowering brachial blood pressure in hypertensive individuals is substantially associated with reduced CV events [2, 3]. Therefore, reduction strategies of BP as a modifiable CV risk are currently based on office assessment of brachial artery BP. Antihypertensive treatment based on brachial BP values reduces CV risk but cannot completely reverse the hypertension-induced risk of morbidity events. Previous data suggested a residual CV risk in treated hypertensive patients even with controlled blood pressure levels [4, 5, 6], and more recent studies support that treatment by antihypertensive agents is associated with an increased residual CV risk in middle-aged man in primary cardiovascular prevention, after adjusting for classical risk factors [7]. This finding can be attributed to a significant underestimation of CV risk in the population and, from a physiopathological point of view, it can be explained by the presence in hypertensive patients, even when correctly treated, of structural and functional macro and micro alterations (such as left ventricular hypertrophy, diastolic dysfunction, aortic stiffness, endothelial dysfunction, vascular inflammation, glomerular sclerosis, renal impairment) [2].

On the other side, there is an emerging risk of over-treatment based on a strong post-hoc evidence from several randomized trials with antihypertensive treatment of a J-shape relationship (the so called J-curve phenomenon) between both diastolic and systolic BP and main outcomes in hypertensive patients as well as in high-risk populations (including patients with coronary artery diseases, diabetes, left ventricular hypertrophy and elderly subjects) [8]. As is well known, BP varies in different arterial systems and invasive and non-invasive studies during the past decades have demonstrated that brachial BP does not necessarily reflect central aortic BP [9]. In fact, central aortic pressure parameters and left ventricular load are determined not only by cardiac output and peripheral resistance but also by arterial stiffness and timing and magnitude of wave reflections. Central pressures (aortic and carotid) are physiopathologically more relevant than peripheral pressures in the pathogenesis of CV diseases, and recent evidences have shown that central BP may predict CV diseases [10, 11] better than brachial BP does and responds differently to certain treatments [12]. In this scenario, it's emerging the need to clinically target relevant biomarkers, which can improve the ability to predict and treat CV risk when added to existing CV risk scores, and might improve the individualized assessment of the hypertension-associated CV risk.

CLINICAL RELEVANCE OF CENTRAL HEMODYNAMICS

-Physiopathological Concepts

The shape of the pressure waveform changes continuously throughout the arterial tree. It is the sum of the forward traveling waveform generated by the left ventricular ejection and the backward traveling wave due to the incident wave reflected at peripheral sites of impedance mismatch, arterial bifurcation and arteriolar vasomotor tone (vasodilation and vasoconstriction). When large arteries are compliant, the reflected wave merges with the forward wave in the proximal aorta during diastole, aiding coronary perfusion with increased diastolic BP. Differently, when large arteries become stiff, we assist to an increased pulse wave velocity that accelerates the incident and reflected waves. Thus, the reflected wave merges with the incident wave during systole and *augments* systolic BP more than diastolic BP, generating left ventricular overload and reducing coronary perfusion. The augmented pressure related to the central pulse pressure, called *augmentation index,* provides information about the amplitude and timing of backward-traveling waves within the central arteries [13].

Pulse pressure (PP) is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Central PP is physiologically lower than brachial PP for the same mean blood pressure (MBP) and diastolic blood pressure (DBP). The difference

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between brachial and central PP is called PP *amplification* and arises because of an increase in arterial stiffness moving away from the heart. PP amplification is principally generated by arterial stiffness and wave reflections; in fact, as the pulse wave passes through arterial conduits that are characterized by progressive reduction in diameter and increased stiffness, peripheral PP becomes higher than central PP. While MBP and DBP parameters remain relatively stable, SBP may be much higher in brachial artery than in aorta [14], exerting the main influence on PP amplification. Consequently, the pulsatile component of central and peripheral pressures may vary significantly. Under physiological conditions, the pulsatile burden is lower in central than in peripheral arteries, in order to protect heart from overload and, consequently, coronary hypo-perfusion. PP amplification not only is due to the propagation and reflection of the waves along the arterial tree, but it also depends on a number of variables as well, including gender, age, vascular systemic disease, height, heart rate and ethnicity [15, 16, 17]. Previous studies have shown that PP amplification might be a higher risk factor than brachial and aortic pressure alone, in particular in patients with advance renal failure and elderly [11, 18]. In a recent study, it has been demonstrated that both carotid and brachial PP have a significant predictive value on overall and CV mortality risk, independently of CV risk factors, whereas PP amplification is strongly associated with CV and overall mortality risk with the highest HRs [19].

-Aortic Stiffness

Decreased arterial distensibility is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall. The aorta is a major vessel of interest because it makes the largest contribution to the buffering function and it is the major location of atherosclerosis. Stiffening of the aortic wall is associated with alterations in pulsatile hemodynamic, including an increase in forward arterial pressure wave amplitude and consequently in increased PP. Stiffening of the aortic wall is also associated with elevated pulse wave velocity (PWV) and premature wave reflection. Available data indicate that uncontrolled BP and aging are the two major factors leading to a synergistic increase in arterial stiffness. Arterial stiffness contributes to CV risk through influences on left ventricular after-load and hypertrophy reducing diastolic coronary flow and determining magnitude and timing of any reflected pressure wave, with microcirculation damages in high-flow organs such as the kidneys and brain. Recently, several data have recently shown that arterial stiffness may even antedate and contribute to the development of BP [20]. Therefore, arterial stiffness is increasingly recognized as an important marker of CV risk in various populations and reflects the cumulative effect of CV risk factors on large arteries. Cross-sectional studies have shown that arterial stiffness is associated not only with age but also with the presence of many CV risk factors such has hypertension, obesity, dyslipidemia and impaired glucose tolerance. Carotid-femoral PWV, a global measure of aortic stiffness, has been recognized as the most direct index, valuable biomarker for CV prediction [21]. Importantly, it has been shown to be an independent predictor of coronary heart diseases and stroke in healthy subjects [22] and an independent predictor of total mortality in specific populations [23, 24]. Moreover, a meta-analysis including more than 16.000 subjects confirmed that aortic PWV is an independent predictor of adverse CV events and all-cause mortality: an increase in aortic PWV of 1 m/s raises CV risk more than 10% [25].

A recent meta-analysis by Ben-Shlomo *et al.* has taken a step further. It has been demonstrated that aortic PWV improves prediction of CV events beyond conventional risk factors, showing that 19% and 22% of intermediate risk individuals were reclassified into higher or lower quartiles of risk for coronary heart disease and stroke outcomes, respectively [26]. The same results have been observed in diabetic patients and in the Framingham study, in which patients can be reclassified into different CV risk class when arterial stiffness measurement was added [27, 9].

-Relevance of Central Pressure

As previously exposed, central BP may predict cardiovascular outcomes better than brachial BP. This evidence is supported by many recently published studies concerning the relationship between central pressure and both surrogate markers of CV risk and hard endpoints [28]. The mechanism leading to this observation can be detected in the more relevant relation between central BP and pre-clinical organ damages (cardiac and vascular) due to the major exposure of heart, kidneys, and brain to aortic pressure rather than brachial pressure. The most relevant studied vascular and heart phenotypes are left ventricular mass (LVM) and common carotid artery (particularly intima-media thickness, IMT), that can be easily and carefully measured by non-invasive techniques. In the REASON Study, the regression of LVM was more strongly related to changes in central pressure compared with brachial pressure and, after adjustment, only central pressure remained predictive (either systolic or pulse pressure) [29]. Furthermore, parameters of diastolic dysfunction (such as E/e' and left atrial volume) are more strongly related to central than brachial PP [30]. Regarding vascular phenotypes, many studies have documented a higher correlation of central pressure (mainly pulse pressure) to atherosclerosis, IMT, and vascular mass [31, 32], compared to brachial pressure. During the past 2 decades, the importance of central pressure and its predictive value on CV events has been evaluated in different patient cohorts. Most of these studies reported that central pressure was independently related to future CV events. The Strong Heart Study, evaluating disease-free individuals, showed that central PP predicts incident CV diseases better than the corresponding brachial PP does [10]. This predictive value is confirmed even when subclinical atherosclerosis is taken into account. Previously, Safar *et al.* have shown that in patients with renal failure, after adjustment for confounders, only central pressure remained predictive [11]. In addition, a recent meta-analysis suggested that central PP may be a better predictor of CV events than peripheral pressures, confirming the independent predictive value of central pressure [33]. All these findings suggest the importance of central pressure but, in this context, it is important to understand whether central BP provides incremental value over and above peripheral BP.

POTENTIAL MECHANISMS OF REDUCTION OF CV EVENTS OVER AND ABOVE BRACHIAL BP REDUCTION

Blood pressure reduction *per se* is considered the major determinant of the efficacy of antihypertensive drugs. The available antihypertensive drugs reduce BP mainly by decreasing peripheral resistance and cardiac output. However, during the last decade, accumulating data suggest that, despite similar brachial arterial BP-lowering effects, the impact of antihypertensive drug classes on cardiovascular outcomes is different and may be associated to pleiotropic effects of some molecules on arterial network with reduced aortic stiffness and/or wave reflections. Several intervention studies observed that clinical benefit was greater than the one expected from the decrease in peripheral BP and demonstrated significant differences in cause-specific outcomes beyond peripheral BP control. Aortic PWV, a marker of aortic stiffness, and increased central augmentation index (AIx), a marker of intensity of arterial wave reflection, appear as major factors influencing central PP and leading to increased central hemodynamic load with expected clinical implications.

-Anti-Hypertensive Treatment and Aortic Pulse Wave Velocity

As previously assessed, arterial stiffness is an independent CV risk factor. The simple, non-invasive measurement of PWV as aortic stiffness marker was recently confirmed in official guidelines and is increasingly used in clinical assessment of hypertensive patients. Several studies have shown that some antihypertensive treatment can improve arterial stiffness [34] and non-antihypertensive drugs, such as anti-inflammatory and anti-diabetic (breakers

of advanced glycation end products), may have a lowering effect on arterial stiffness [35]. As aging and distending pressure are the two major determinants of aortic stiffness, BP control under antihypertensive treatment is expected to be the determinant of aortic PWV reduction. However, recent evidences highlighted the hypothesis that the effect of some antihypertensive treatment on arterial stiffness is due not only to BP lowering, but also to additional BP-independent effects.

A recent meta-analysis comparing different antihypertensive drugs and/or placebo in short and long-term, showed that active treatment was associated with a reduction in arterial stiffness compared to placebo. PWV reduction was greater in long-term antihypertensive therapy and changes in PWV were dependent on changes in mean BP and PP. Particularly, in long-terms trials Angiotensin-converting enzyme inhibitors (ACEi) were more effective than calcium channel blockers (CCB), beta blockers (BB) and diuretics, independently of changes in BP [36].

Similarly, another meta-analysis evidenced that ACEi reduce PWV and AIx in patients with different pathological conditions, compared to placebo. However, ACEi didn't show the same effect on PWV compared to other anti-hypertensive agents. The effect on arterial stiffness seemed to be independent of the ability of ACEi to reduce BP, but the superior effect compared to other drug classes wasn't confirmed [37].

In patients with isolated systolic hypertension PWV wasn't improved by any of the traditional anti-hypertensive therapy. In this little study, 4 major drug classes (ACEi, BB, CCB and ARBs) similarly reduced peripheral SBP and peripheral PP, but had no effect on PWV. Moreover, atenolol was significantly less effective than other drugs in reducing central PP. Being aware that the study considered a small population and was maybe underpowered, the authors concluded that patients with isolated systolic hypertension might be less responsive to traditional anti-hypertensive therapy due to their condition of stiffer arteries [38].

Other studies confirmed that these effects on arterial stiffness beyond BP control were mainly obtained with renin-angiotensin system inhibitors (RASi), and were amplified with high dose and long-term treatment [39]. Previously, Guerin *et al*. showed that, in high risk patients with end-stage renal failure, age, absence of PWV decrease and increased LVM index were independent predictors of all-cause mortality, and the use of ACEi had a favorable effect on survival. The predictive value of all these parameters was independent of changes in BP (Fig. **1**) [23].

A recent review has evaluated the effect of various antihypertensive drugs on arterial stiffness [35] and confirmed these findings. Generally, drugs antagonizing the RAS system have been demonstrated to be far superior to other classes in reducing arterial stiffness. A potential mechanism suggested by the authors was related to the potent pro-fibrotic effect of the RAS system. Moreover, most of CCB reduced PWV and wave reflection, but their effect on arterial stiffness was less pronounced than the one of RASi. With the only exception of antialdosterone agents, diuretics have shown to have a rather neutral effect on arterial stiffness and wave reflection. Regarding BB, they have shown to be inferior to angiotensin receptor blockers (ARBs), ACEi and CCB. However, the studies were mostly obtained with atenolol, which is a non-vasodilating BB. Newer vasodilating BB may act differently, but further evidences are required.

-Anti-Hypertensive Treatment and Pulse Pressure Amplification

Central PP appears to reflect PP amplification, which is related to the timing and intensity of arterial wave reflections. Beyond brachial BP reduction, the benefit effects of some drug classes on CV outcomes may be related to a more beneficial effect on PP amplification and thus on central BP. Results from clinical trials support the hypothesis that blockers of the RAS system may reduce CV outcomes beyond peripheral BP control and that an additional effect of CCB exists in preventing stroke. A potential explanation of the observed inequality in risk prevention among anti-hypertensive drugs may be based on their differential impact on arterial properties and central BP. Head to head comparison of the effect on central BP of antihypertensive drug as monotherapy highlighted the inferiority of BB agent (atenolol was the most commonly used) versus ACEi, ARBs or diuretics in reducing central BP. ACEi, ARBs and CCB are powerful vasodilators with beneficial effect on wave reflections and central BP [39, 40, 41]. While blockers of the RAS system and CCB lead to increased BP amplification from central to peripheral arterial site, BBs exhibit reduced BP amplification impact, and diuretics have little or no effect on the amplification phenomenon. Results from HOPE [42] (angiotensin-converting enzyme inhibitor versus placebo), LIFE (angiotensin receptor blocker versus atenolol), and ASCOT (calcium channel blocker-based versus atenolol-based) trials in high risk patients highlighted that ACEi, ARBs and CCB based regimen reduced CV outcomes beyond peripheral BP control. Particularly, in the LIFE study in hypertensive patients with left ventricular hypertrophy, cardiovas-

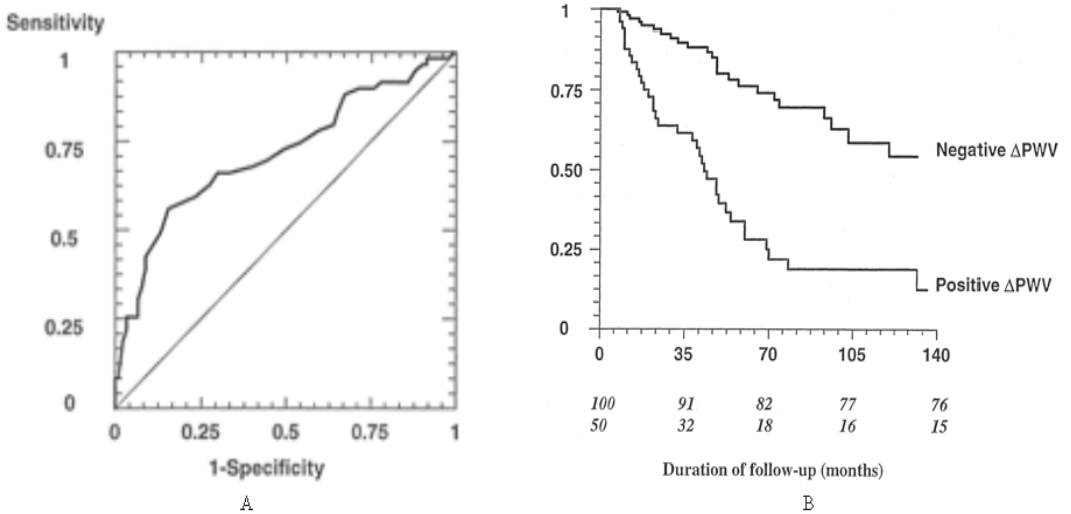

Fig. (1). **A**; ROC curve: ability of adjusted aortic PWV change between inclusion and target BP to predict death. Area under curve is 0.72±0.11. **B**; Probability of all-cause survival according to ΔPWV under antihypertensive therapy. Comparison between BP responders (negative ΔPWV) and non-responders (positive ΔPWV) was highly significant (χ^2=28.03, P<0.00001). Numbers of patients at each time point are in italics (top row, responders; bottom row, non-responders).

cular death, stroke, and myocardial infarction were reduced by losartan vs atenolol; in the highest vs lowest quartile of PP there was a significantly increased risk for stroke and total mortality with atenolol-based treatment [43]. Similarly, the ASCOT study demonstrated superiority in CV outcomes over primary treatment of hypertension with CCB (amlodipine) compared to BB (atenolol) [44]. CV beneficial impact of these anti-hypertensive classes may be based on their pleiotropic effects on arterial properties with central PP reduction, beyond peripheral BP control and independently of MAP. Physiopathological hypothesis may include chronic remodeling of the small arteries, with the result of a reduced reflection coefficients independently of aortic PWV [45].

The CAFÉ study, a major sub-study within the ASCOT trial, examined the impact of different BP lowering-regimens (atenolol ± thiazide-based versus amlodipine ± perindopril-based therapy) on derived central aortic pressures and hemodynamics. The authors highlighted the importance of central BP as a treatment target based on the relationship between central PP and a post hoc-defined composite outcome of CV events and development of renal impairment. Central PP may be considered as the potential mechanism accounting for the different clinical outcomes between the anti-hypertensive treatment arms in ASCOT trial. The authors discussed the possible mechanisms accounting for the marked reduction in central PP in the amlodipine ± perindopril based therapy: while no significant difference existed according to aortic PWV, there was a significant reduction in AIx in the amlodipine ± perindopril treatment group, suggesting a distal shift of the effective reflecting sites and/or higher heart rate (with lower systolic ejection time) (Fig. **2**). Importantly, central aortic PP was a determinant of clinical outcomes [46].

Supported by earlier experimental evidences [47, 48], the relative arteriolar vasoconstriction and the expected slower heart rate with BB based treatment may have resulted in earlier wave reflections with pressure wave augmentation during systole. Importantly, the advantages of ARBs over atenolol remained significant even after CCB combined treatment and adjustment to changes in heart rate with decrease in central systolic BP and PP as well as Aix, with similar reduction in brachial BP and aortic PWV [45]. The peripheral vasoconstriction associated with atenolol may be the additional mechanism which can explain the increased negative effect on wave reflection. Newer BB, such as nebivolol and celiprolol, present vasodilation properties and may act differently. In particular, two small studies comparing atenolol versus nebivolol achieved similar results: despite similar effects on brachial BP and aortic stiffness, there was less increase in AIx and less reduction in heart rate in the nebivolol group vs atenolol. Aortic pulse pressure was significantly lower in the nebivolol group [49, 50]. Moreover, a randomized, double blind study comparing the effect of nebivolol

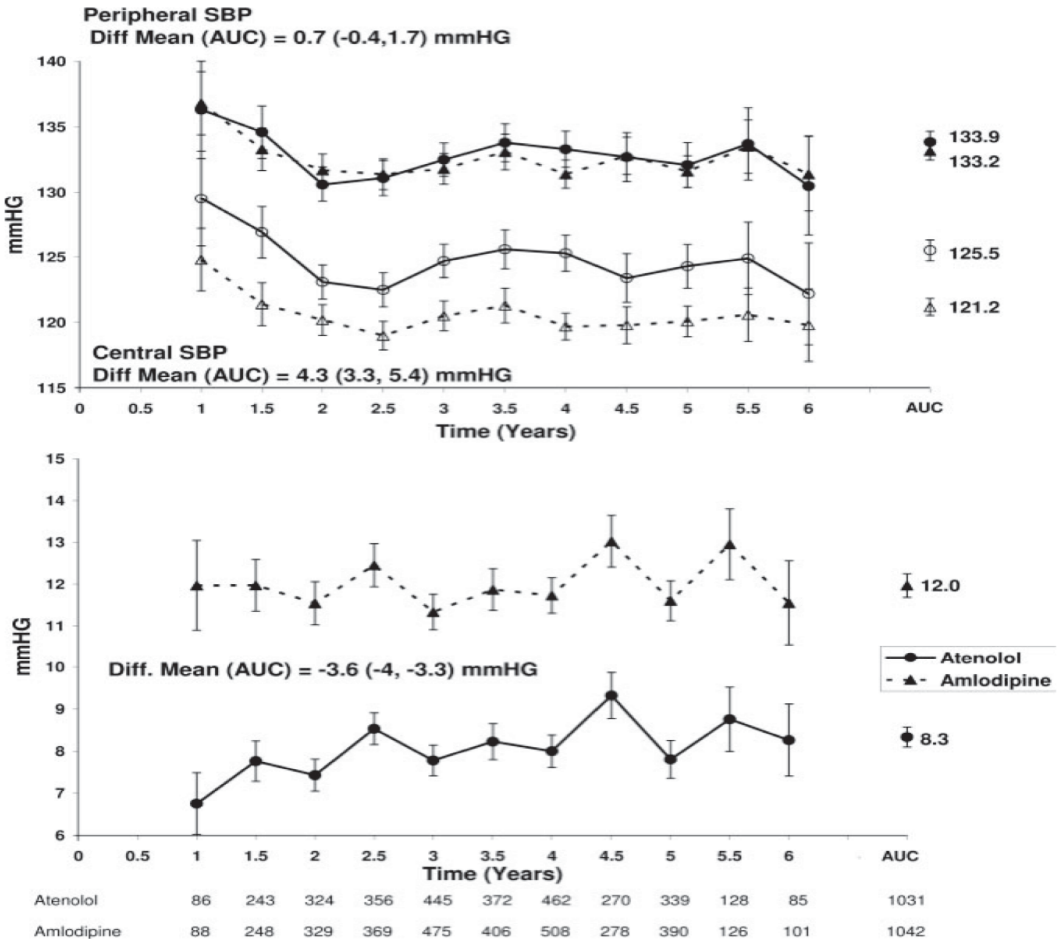

Fig. (2). Top, Brachial (solid symbols) and derived central aortic (open symbols) systolic blood pressure with time (mean, 95% CI) for patients randomized to receive atenolol-thiazide- or amlodipine-perindopril based therapy. Bottom, Systolic blood pressure difference (brachial minus central aortic; mean, 95% CI) with time. For calculation of AUC, see the Data Supplement. Numbers below abscissa represent the number of patients seen at each time point. Time represents the duration from randomization into ASCOT to patient follow-up visit at which tonometry measurement was made in the CAFE study.

PP indicates pulse pressure.

and metoprolol (betal selective BB) on central pressure and left ventricular wall thickness, showed a similar reduction in heart rate and brachial BP with both drugs. After 1 year of treatment, central aortic BP, PP and left ventricular septal wall were significantly reduced in the nebivolol group only [51]. These possible beneficial effects of nebivolol may be attributable to its capability to release endothelium-derived nitric oxide, improving consequently endothelial function and reducing arterial stiffness. With the expectation to be further established, the less effective impact on central aortic pressure of BB antihypertensive treatment might be partly counterbalanced by the reduction of myocardium oxygen demand and the use of vasodilating BB treatment regimen. Currently, it would be interesting to compare selective BB to agents that reduce heart rate without acting on BP, to better understand the real negative cause-effect of heart rate on central pressure.

More recently, the importance of central systolic BP as treatment target (intervention group) compared with current best practice care in guiding hypertension management was underlined for the first time in a 12-month prospective randomized trial. In this study, the use of central BP in hypertension management determined a high reduction in the quantity of antihypertensive medication (all classes) without differences in LVM, aortic stiffness and quality of life between groups, and with similar brachial BP control achieved (Fig. **3**). Notably, even if the difference in LVM was not statistically significant, the central aortic BP group showed a trend for a reduction [52]. Therefore, Sharman *et al.* demonstrated that central BP could give advantages in treatment of lower to medium-risk patients with hypertension and they provided the basis for further investigations.

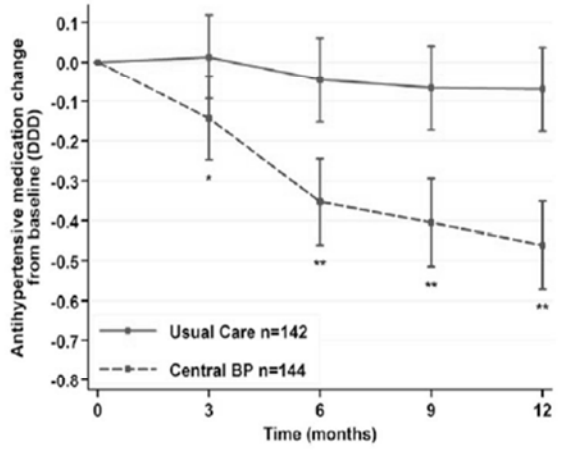

Fig. (3). Between-group change in daily defined dose (DDD) of antihypertensive medications. Change is from baseline to each follow-up, adjusting for age, sex and body mass index. Error bars indicate 95% confidence interval and *P=0.008, **P<0.001. BP indicates blood pressure.

PERSPECTIVE

Current guidelines for diagnosis and treatment of hypertension are based merely on brachial BP. However, when we stratified patients on the basis of brachial BP, we observed a considerable overlap between aortic systolic BP and brachial systolic BP in separate categories of brachial BP (classified according to the international guidelines). In particular, >30% of men and >10% of women with normal brachial BP have aortic systolic BP similar to the aortic systolic BP of individuals at stage 1 hypertension, and >70% subjects classified as high-normal brachial BP have the same aortic pressure as those with stage 1 hypertension [53]. This evidence, taking into account central pressure as a better predictor of CV risk, can clearly have important clinical and therapeutical implications. Currently, with the simply assessment of brachial BP and without considering the effects that central pressure has on CV events and end-organ damages, we are maybe treating or over-treating subjects who may not require to, and not treating subjects who should be treated. Moreover, these findings highlight the need for the identification of specific populations that might benefit more from central BP assessment and provide the basis for further investigations. Clinical trials with hard end-points and designed on the basis of central and peripheral BP assessment are now required to confirm current data and to provide evidence that treatment guidance based on measurements of central BP results in better outcomes. As a consequence, this might pave the way for the consideration to enter central BP assessment in the clinical management of hypertension.

CONCLUSION

Several evidences suggest that central hemodynamics correlate with intermediate measures of CV risk more than peripheral BP, and (that) they independently predict future CV events [18]. Moreover, additional observations highlight that the effects of antihypertensive therapy on brachial BP components do not closely reflect those seen at central level, while CV outcome protection above the reduction of brachial blood pressure has been ascertained for some classes of anti-hypertensive drugs. Although data on direct CV beneficial impact of central BP treatment in randomized clinical trials are still lacking, the above mentioned indirect indices support the clinical importance of central BP assessment. Recently, the importance of central systolic BP as treatment target in guiding hypertension management was for the first time underlined. Therefore, it is likely that the improvement of quality of care and individualized assessment of the hypertension-associated CV risk may be achievable with the use of central BP. Basing antihypertensive treatment guidance on central pressure rather than on peripheral BP may be the key for future antihypertensive strategies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.

[2] Mancia G, De Backer G, Dominiczak A, *et al.* Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105-87.

[3] Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003; 362: 1527-35.

[4] Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L. Survival in treated hypertension: follow up study after two decades. BMJ 1998; 317: 167-71.

[5] Glynn RJ, L'Italien GJ, Sesso HD, Jackson EA, Buring JE. Development of predictive models for long-term cardiovascular risk associated with systolic and diastolic blood pressure. Hypertension 2002; 39: 105-10.

[6] Blacher J, Evans A, Arveiler D, *et al.* on behalf of the PRIME Study Group. Residual coronary risk in men aged 50-59 treated for hypertension and hyperlipidemia in the population. The PRIME study. J Hypertens 2004; 22: 415-23.

[7] Blacher J, Evans A, Arveiler D, *et al.* Residual cardiovascular risk in treated hypertension and hyperlipidaemia: the PRIME Study. Journal of Human Hypertension 2010; 24: 19-26

[8] Maciej Banach, Wilbert S. Aronow Blood Pressure J-Curve: Current Concepts. Curr Hypertens Rep (2012) 14: 556-66

[9] Mitchell GF, Hwang SJ, Vasan RS, *et al.* Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010; 121: 505-11.

[10] Roman MJ, Devereux RB, Kizer JR, *et al.* Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 2007; 50: 197-203.

[11] Safar ME, Blacher J, Pannier B, *et al.* Central pulse pressure and mortality in end-stage renal disease. Hypertension2002; 39: 735-8.

[12] Asmar RG, London GM, O'Rourke ME, Safar ME. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension 2001; 38: 922-6.

[13] Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's Blood Flow in Arteries: Theoretic, Experimental and Clinical Principles. 6th Edition. Edward Arnold, London, 2011

[14] Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001; 38: 932-7

[15] McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity the anglo-cardiff collaborative trial (ACCT). J Am Coll Cardiol 2005; 46: 1753-60

[16] Wilkinson IB, Mohammad NH, Tyrrell S, *et al.* Heart rate dependency of pulse pressure amplification and arterial stiffness. Am J Hypertens 2002; 15: 24-30.

[17] London GM, Guerin AP, Pannier BM, Marchais SJ, Metivier F. Body height as a determinant of carotid pulse contour in humans. J Hypertens Suppl 1992; 10: S93-5

[18] Agabiti-Rosei E, Mancia G, O'Rourke MF, *et al.* Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension 2007; 50: 154-60.

[19] Benetos A, Thomas F, Joly L, *et al.* Pulse pressure amplification a mechanical biomarker of cardiovascular risk J Am Coll Cardiol 2010; 55: 1032-7. doi: 10.1016/j.jacc.2009.09.061

[20] Najjar SS, Scuteri A, Shetty V, *et al.* Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol 2008; 51: 1377-83.

[21] Laurent S, Cockcroft J, Van Bortel L, *et al.* European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588-605

[22] Mattace-Raso FU, van der Cammen TJ, Hofman A, *et al.* Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006; 113: 657-63

[23] Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; 20: 103: 987-92.

[24] Laurent Stéphane, Boutouyrie Pierre, Asmar Roland, Gautier Isabelle, Laloux Brigitte, Guize Louis, Ducimetiere Pierre and Benetos Athanase Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients. *Hypertension 20*01; 37: 1236-41

[25] Vlachopoulos Charalambos, Aznaouridis Konstantinos, Stefanadis Christodoulos, Prediction of Cardiovascular Events and All-Cause Mortality With Arterial StiffnessA Systematic Review and Meta-Analysis. J Am College Cardiol 2010; 55(13):

[26] Ben Schlomo Y, Spears M, Boustred C, *et al.* Predictive value of pulse wave velocity for cardiovascular events in 15, 220 subjects: an individual participant meta-analysis on behalf of the PWV collaborative group. *J Hypertens* 2010; 28(suppl A)E446

[27] Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar ME, Ouerdane S, Blaher J Aortic stiffness and cardiovascuolar risk in type 2 diabetes. Hypertens 2013; 31: 1584-92. doi: 10.1097/HJH.0b013e3283613074.

[28] Laurent S, Cockcroft JR, van Bortel LM, *et al.* Abridged version of the expert consensus document. Artery Res 2007; 1: 2-12.

[29] De Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/ indapamide in hypertensive subjects. J Hypertens 2004; 22: 1623-30

[30] Shim CY, Park S, Choi D, *et al.* Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. J AmCollCardiol 2011; 57(10): 1226-33. 10.1016/j.jacc.2010.09.067.

[31] Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation 1999; 100: 1387-93.

[32] Wang KL, Cheng HM, Chuang SY, *et al.* Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality?. J Hypertens 2009; 27: 461-7.

[33] Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010; 31: 1865-71

[34] Mahmud A, Feely J. Antihypertensive drugs and arterial stiffness. Expert Rev Cardiovasc Ther 2003; 1: 65-78

[35] Boutouyrie P, Lacolley P, Briet M, *et al.* Pharmacological modulation of arterial stiffness. Drugs 2011; 71: 1689-701.

[36] Ong KT, Delerme S, Pannier B, *et al.* Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. J Hypertens 2011; 29(6): 1034-42

[37] Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2012; 221(1): 18-33.

[38] Mackenzie IS, McEniery CM, Dhakam Z, Brown MJ, Cockcroft JR, Wilkinson IB. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. Hypertension 2009; 54(2): 409-13.

[39] Tropeano AI, Boutouyrie P, Pannier B, *et al.* Brachial pressure independent reduction in carotid stiffness after long-term angiotensin converting enzyme inhibition in diabetic hypertensives. Hypertension 2006; 48: 80-6.

[40] Mahmud A, Feely J. Favourable effects on arterial wave reflection and pulse pressure amplification of adding angiotensin II receptor blockade in resistant hypertension. J Hum Hypertens 2000; 14: 541-6.

[41] Mahmud A. Reducing arterial stiffness and wave reflection: quest for the Holy Grail. Artery Research 2007; 1: 13-9.

[42] Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145-53

[43] Dahlöf Björn, Devereux Richard B, Kjeldsen Sverre E, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995-1003

[44] Dahlöf B, Sever PS, Poulter NR, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366(9489): 895-906

[45] Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension 2010; 55: 1314-22

[46] Williams B, Lacy PS, Thom SM, *et al.* Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113(9): 1213-25.

[47] London GM, Asmar RG, O'Rourke MF, Safar ME. REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J Am Coll Cardiol 2004; 43(1): 92-9.

[48] Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000; 525: 263-70.

[49] Dhakam Z, Yasmin, McEniery CM, Burton T, Brown MJ, Wilkinson IB. A comparison of atenolol and nebivolol in isolated systolic hypertension. J Hypertens 2008; 26: 351-6

[50] Morgan T, Lauri J, Bertram D, Anderson A. Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004; 17: 118-23.

[51] Kampus P, Serg M, Kals J, *et al.* Differential effects of nebivolol and metoprolol on central aortic pressure and left ventricular wall thickness. Hypertension 2011; 57: 1122-8.

[52] Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M; BP GUIDE (value of central Blood Pressure for GUIDing managEment of hypertension) study investigators. Randomized Trial of Guiding Hypertension Management Using Central Aortic Blood Pressure Compared With Best-Practice Care: Principal Findings of the BP GUIDE Study. Hypertension 2013; 62(6): 1138-45

[53] McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe CV, Cockcroft JR, Wilkinson IB. Central pressure: variability and impact of cardiovascu- lar risk factors: the Anglo-Cardiff Collaborative Trial II. Hypertension 2008; 51: 1476-82.

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2.3.3 Conclusion de l'article 4

Les essais cliniques randomisés apportant la preuve du bénéfice cardiovasculaire d'un traitement ciblé de la rigidité aortique ou de la pression artérielle centrale font encore défaut. Cependant les preuves expérimentales et épidémiologiques indirectes mentionnées confirment l'intérêt clinique de l'évaluation de ces paramètres hémodynamiques à l'échelle individuelle. Pour retenir la valeur de critère de substitution d'un paramètre hémodynamique, il est nécessaire de :

- Montrer une différence significative de niveau du paramètre entre les patients ayant un événement cardiovasculaire et ceux indemnes d'événements ;
- Montrer la valeur prédictive du paramètre pour les événements cardiovasculaires ;
- Montrer la valeur prédictive additive du paramètre au-delà de la prise en compte des facteurs de risque classiques ;
- Démontrer l'utilité clinique de la mesure de ce paramètre en termes de prédiction du risque pour recommander une modification de traitement.

Ces quatre premières étapes ont été validées pour la rigidité aortique. L'utilité clinique de la mesure de la pression centrale dans l'estimation du risque cardiovasculaire, au-delà des paramètres hémodynamiques périphériques, continue à faire débat (114). Un accord professionnel concernant la méthode d'estimation de la pression centrale, facilitée actuellement par la mesure automatique oscillométrique, serait la prochaine étape utile à la validation de ce paramètre en pratique clinique. Il sera nécessaire de montrer qu'une stratégie de prise en charge thérapeutique ciblée sur la rigidité aortique ou sur la pression centrale entraîne un bénéfice en termes d'incidence d'événements cardiovasculaires au-delà du contrôle des facteurs de risque « traditionnels ». Des preuves indirectes soutiennent ce dernier point. L'essai évaluant l'impact de la rigidité aortique sur la survie chez des patients avec insuffisance rénale terminale (115) souligne un niveau plus faible

d'évènements chez ceux dont la VOP carotido-fémorale baisse sous traitement antihypertenseur en comparaison aux patients présentant le même niveau de rigidité aortique sous traitement, à même réduction de pression artérielle brachiale. L'intérêt clinique de la mesure de la pression systolique centrale en tant que cible thérapeutique a été récemment présenté dans un essai randomisé prospectif sur 12 mois en comparaison à la prise en charge de l'hypertension artérielle selon les recommandations de bonnes pratiques actuelles (116). Le contrôle de l'hypertension artérielle au regard de la mesure ambulatoire de la pression centrale a été obtenu avec moins de molécules antihypertensives en comparaison aux patients dont le traitement était adapté en fonction des chiffres de pression artérielle brachiale. Il n'y a pas eu d'effets adverses sur l'atteinte des organes cibles (hypertrophie ventriculaire gauche ou rigidité aortique). De plus, aucune différence significative n'a été notée pour la pression artérielle brachiale ou pour la fréquence cardiaque entre les deux groupes de patients au début ou à la fin de l'étude.

Chapitre 3
Paramètres hémodynamiques artériels et leurs déterminants chez le patient à risque cardiovasculaire

3.1 Paramètres hémodynamiques artériels et maladie rénale chronique (Article 5)

3.1.1 Introduction de l'article 5

L'évolution des néphropathies chroniques est marquée par le développement progressif de lésions de glomérulosclérose et de fibrose interstitielle, jusqu'à l'insuffisance rénale terminale et la nécessité des techniques de suppléance. La pathologie cardiovasculaire représente la principale cause de mortalité dans cette population de patients (117, 118).

L'insuffisance rénale chronique est un facteur de risque cardiovasculaire et un marqueur d'atteinte d'organe cible. Un débit de filtration glomérulaire inférieur ou égal à 30 ml/mn est équivalent à une prévention cardiovasculaire secondaire. Indépendamment de l'étiologie de la maladie rénale, le risque de mortalité et d'événements cardiovasculaires augmente avec le degré de l'insuffisance rénale selon une relation exponentielle inverse avec le débit de filtration glomérulaire (119). Cet excès de mortalité reste significatif pour les âges extrêmes, de 80 ans et plus (120). L'estimation du risque cardiovasculaire individuel reste sous-évaluée par les scores prédictifs traditionnels, le débit de filtration glomérulaire ou la quantification d'une protéinurie n'étant pas pris en compte dans ces modèles de calcul du risque (121).

La pathologie coronarienne, la survenue d'une arythmie, d'une insuffisance cardiaque congestive et la mort subite représentent les principales causes de mortalité cardiovasculaire chez le patient insuffisant rénal (122). Les liens physiopathologiques entre

maladie rénale et survenue d'événements cardiovasculaires paraissent partiellement élucidés. La majorité des facteurs de risque « traditionnels », tels que l'âge, le diabète, l'hypertension artérielle ou un taux bas de HDL cholestérol présentent une prévalence élevée chez ces patients (122). Les facteurs de risque cardiovasculaire plus spécifiques de la maladie rénale chronique associent l'anémie, le syndrome inflammatoire chronique et les perturbations du métabolisme phosphocalcique avec l'apparition progressive d'une hypocalcémie, d'une hyperphosphorémie, d'une hyperparathyroïdie secondaire et d'une carence en vitamine D (123, 124).

La rigidité aortique apparaît être un marqueur d'atteinte artérielle faisant le lien sur le plan physiopathologique entre la maladie rénale chronique et la survenue d'événements cardiovasculaires (125). Le profil hémodynamique des patients avec maladie rénale chronique est marqué par une hypertension artérielle systolique isolée avec baisse de la pression diastolique, majoration de la pression systolique et pulsée, associée à la rigidité aortique. Le vieillissement accéléré des gros troncs artériels, indépendamment de l'âge et de la pression artérielle moyenne, est caractéristique de la maladie rénale chronique (126). Ce vieillissement artériel accéléré peut être associé d'une part à la présence d'une maladie hypertensive non contrôlée évoluant depuis plusieurs années ou à la présence de désordres métaboliques, en particulier la maladie diabétique (61, 125). Des facteurs plus spécifiques de la maladie rénale apparaissent également impliqués dans l'atteinte des gros troncs artériels tels que la surcharge volémique, la présence de calcifications pariétales vasculaires (61, 125), l'environnement inflammatoire (125), l'activité du système rénine angiotensine avec production accrue d'angiotensine II (125) et l'accumulation de produits de glycation avancée (127).

Le rôle prédictif indépendant de la rigidité aortique pour la mortalité toute cause et

principalement cardiovasculaire a été pour la première fois démontré en 1999 (1) chez des patients avec maladie rénale terminale. Son intérêt clinique en tant que marqueur de substitution a été suggéré dans cette même population de patients à très haut risque cardiovasculaire (115). L'atténuation de la rigidité aortique en réponse à la baisse tensionnelle sous traitement a été associée à un meilleur pronostic cardiovasculaire. La rigidité aortique a été par la suite étudiée dans une population de patients avec insuffisance rénale modérée (128). Cette étude a confirmé le pouvoir prédictif indépendant de la VOP carotido-fémorale pour la mortalité toute cause et la morbi-mortalité cardiovasculaire dans cette population.

La revue de la littérature présentée ici souligne le bénéfice des stratégies thérapeutiques antihypertensives basées sur la baisse de la pression artérielle moyenne, en termes de mortalité et de survenue d'événements cardiovasculaires chez le patient avec maladie rénale chronique. Elle revient également sur la nécessité d'affiner les cibles thérapeutiques, plus particulièrement au regard de la rigidité aortique et de la pression pulsée dans cette population de patients à haut risque.

3.1.2 Article 5

Kheder-Elfekih R, Yannoutsos A, Blacher J, London GM, Safar ME.

Hypertension and chronic kidney disease: respective contribution of mean and pulse pressure and arterial stiffness.

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Review

Hypertension and chronic kidney disease: respective contribution of mean and pulse pressure and arterial stiffness

Rania Kheder-Elfekih, Alexandra Yannoutsos, Jacques Blacher, Gérard M. London, and Michel E. Safar

Hypertension (HTN) in chronic kidney disease (CKD) is influenced by blood pressure (BP) and the progression of CKD, including hemodialysis and renal transplantation. To date, the efficacy of antihypertensive drug strategies has chiefly been assessed by measuring steady-state systolic, diastolic and mean arterial pressures (MAP). However, recently elucidated features of the BP curve have highlighted other important goals, that is, the specific roles of pulse pressure (PP), arterial stiffness, pulse wave velocity (PWV) and wave reflections as potentially deleterious factors affecting the progression of HTN and CKD. Pharmacological strategies to date have included progressive withdrawal of alpha-blocking agents; efficacy of beta-blockers for coronary prevention; use of angiotensin blockade in HTN with glomerular injury, using angiotensin-converting enzyme inhibition or receptor blockade, as mono but never double-blockade, to avoid major complications; development of combination therapies with diuretics and/or calcium channel blockers. Nowadays, most clinical trials show that SBP, DBP and MAP-lowering is an effective strategy, although results no longer show preference for any specific drug class. Studies of arterial stiffness in CKD have become crucial. In older individuals, PWV is considerably elevated. The 'stiffness gradient' disappears or is inverted (normally, aortic PWV is lower than brachial PWV). Despite BP-lowering, PP is insufficiently dampened, thus promoting microcirculatory damage, progression of arterial calcifications and disturbed wave reflections, which all increase the risk of mortality. In the absence of effective hemodialysis or graft, increased arterial stiffness is therefore a major cardiovascular risk factor in CKD.

Keywords: arterial stiffness, hypertension, kidney disease

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARBs, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; EEGN, endo and extra-capillary glomerulonephritis; eGFR, estimated glomerular filtration rate; ERBP, European Renal Best Practice; ESRD, end-stage renal disease; FSS, focal segmental sclerosis; HCTZ, hydrochlorothiazide; HTN, hypertension; KDIGO, Kidney Disease Improving Global Outcomes; MAP, mean arterial pressure; MGN, membranous glomerulonephritis; MPGN, membranous proliferative glomerulonephritis; PP, pulse pressure; PWV, pulse wave velocity; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trials

INTRODUCTION

Cardiovascular diseases are among the leading causes of death worldwide. Regardless of the socio-economic status, increased blood pressure (BP) is the most readily treatable cause of premature death [1,2]. Chronic kidney disease (CKD) is recognized as the strongest independent risk factor affecting hypertensive patients. The prevalence of hypertension (HTN) is high among patients with CKD, and is closely dependent on the type of nephropathy and the degree of renal failure [3]. HTN can be the cause or the consequence of CKD; uncontrolled HTN is known to strongly influence the progression of renal failure, in many cases leading to end-stage renal disease (ESRD) and the need to initiate renal replacement therapies such as hemodialysis, peritoneal dialysis or kidney transplantation. Given these observations, understanding the basic status of hypertension itself can be seen to be critical and is the main purpose of this study.

The conventional approach to vascular hemodynamics presents the arterial system as a steady-flow vessel system; this is based on mean values of cardiac output, SBP, DBP, and above all, mean arterial pressure (MAP) and total peripheral resistance. This classic view is in line with flow conditions in the microcirculation, and maintaining optimal oxygen and nutrient delivery to tissues, while minimizing

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BP fluctuations [4]. In this setting, CKD is studied in typical, steady-state pressure and flow conditions.

By definition, however, this model ignores the fact that blood flow is pulsatile and not constant, and that arterial homeostasis is modulated by these flow conditions [4–7]. In recent years, epidemiological studies have shown that increased pulsatility, as assessed from pulse pressure (PP), is a powerful predictor of cardiovascular risk, independently of MAP. Thus, it is nowadays widely accepted that the level of arterial stiffness, as well as the presence of branching points and potential vascular calcifications, generates a multitude of pressure wave reflections along the arterial bed. Current investigations even suggest that the final pattern of the recorded arterial pressure wave, at any given location along the arterial tree, results from the summation of forward and backward-propagating pressure waves [7]. And lastly, arterial stiffness and pulse wave velocity (PWV), as well as pressure wave reflections, are nowadays considered as the main parameters modulating the arterial pressure waveform. The specific profile of patients with CKD shows that SBP and PP both increase with age and are strongly correlated with cardiovascular risk and events [4–7]. Patients with impaired renal function seem to have higher SBP and PP and lower DBP levels with higher aortic PWV values than control individuals with normal renal function [4–7]. The basic concepts of aortic stiffness and wave reflections are therefore important considerations in this review, which focus on the links between hypertension and CKD.

Most hypertension management strategies developed in recent years have raised specific issues relating to patients with CKD. The present study addresses two major questions: first, what are the main characteristics of antihypertensive drugs and their combinations for the pharmacological treatment of patients with CKD? These issues refer predominantly to middle-aged CKD patients and have mainly been investigated in the context of steady BP and blood flow. Second, what is the role of antihypertensive agents in individuals with disturbed pulsatile BP? These questions refer mainly to older individuals with long-standing increased arterial stiffness and disturbed wave reflections. Both questions are clearly largely inter-related and the first is often a prerequisite for improving our understanding of older CKD patients with increased aortic stiffness and wave reflections.

ANTIHYPERTENSIVE AGENTS, ALONE AND IN COMBINATION THERAPIES, FOR CHRONIC KIDNEY DISEASE PATIENTS: SBP, DBP AND MEAN ARTERIAL PRESSURE

In March 2014, the 'European Renal Best Practice (ERBP) Work Group' published a position statement on the Kidney Disease: Improving Global Outcomes ('KDIGO') Clinical Practice Guideline for the Management of BP in CKD [8]. The KDIGO guidelines suggested the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for both diabetic and nondiabetic patients with proteinuria and CKD, in whom treatment with BP-lowering drugs is indicated. The rationale was that microalbuminuria and albuminuria are both risk factors for cardiovascular disease and CKD progression. However, the ERBP group did recommend caution with regard to the rennin–angiotensin–aldosterone system (RAAS) blockade in patients with severe CKD, particularly those without proteinuria, because of the risk of hyperkalemia.

Experimental and clinical research has clearly established that regardless of the initial injury, there is a common mechanism to the progression of renal disease, which leads to compensatory glomerular hemodynamic changes [9,10]. In the model of nephron reduction based on radical nephrectomy, the remnant glomeruli undergo hypertrophy and hyperfiltration. Increases in glomerular pressure rather than in blood flow appear to be the major determinant of this hyperfiltration, with angiotensin II playing a key role via elevated BP and vasoconstriction in the efferent arteriole [10,11]. Steady increases in glomerular pressure result in excessive protein ultrafiltration. Indeed, angiotensin II is believed to trigger progressive renal damage directly through different mechanisms such as increased expression and activity of pro-fibrotic mediators, extracellular matrix deposits and immune activation [12–14]. These mechanisms all suggest that drugs that interfere with the RAAS can be considered as nephroprotective.

Since most patients with CKD also have hypertension, it is legitimate to speculate whether the renoprotective specificity of RAAS blockade in these patients is independent from BP-lowering or not? Although the importance of high BP as an independent risk factor for renal disease progression has been highlighted by recent meta-analyses, the results of several clinical trials have shown greater reductions in proteinuria, as well as better outcomes for renal end points with RAAS blockade than with other antihypertensive regimens in diabetic and nondiabetic nephropathies, despite similar BP control [15–17]. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, ARB therapy was associated with reductions of 16% for the primary end point, that is, a composite of a doubling of serum creatinine concentrations, end-stage renal disease, or death from any cause [18]. However, a meta-analysis that searched three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) for randomized controlled trials investigating any antihypertensive drug and progression of human renal disease, actually found very few studies reporting benefits of ACEI or ARB therapy in this population. Analyses of the results by study size showed a smaller benefit in large studies. The results did, however, confirm the importance of BP control *per se* in preventing the progression of renal disease [9].

In CKD patients with hypertension, two or more antihypertensive agents are required to achieve an adequate BP goal. The most widely used associations combine RAAS blockade (ACEIs or ARBs) with a thiazide diuretic and/or a calcium channel blocker (CCB). In one study of 60 adults with stage 3 CKD, the recommended dose of losartan was compared with a combination of losartan and hydrochlorothiazide (HCTZ). Results showed a greater reduction in proteinuria and more effective BP control in the group on the combination therapy [19]. A subset of 834 patients with

CKD from the Combination Therapy of Hypertension to Prevent Cardiovascular Events study [20] were randomized to three groups of combination antihypertensive therapies with an ARB, a thiazide diuretic, or a beta-blocker, in addition to a CCB as baseline medication. The combination therapies tested showed comparable efficacy in terms of cardiovascular outcomes, with no worsening of the estimated glomerular filtration rate (eGFR). The TRINITY study showed the safety of a triple combination of olmesartan, amlodipine, and HCTZ in patients with diabetes and CKD, with optimal BP control [21]. Although dual blockade of the RAAS is not recommended in patients with CKD, one randomized trial of 67 CKD patients showed additive PWV reductions with dual blockade of the RAAS compared with single blockade [22].

Finally, on the basis of 26 trials (152 290 participants) including 30 295 individuals with reduced eGFR, Ninomiya *et al.* [23] showed that compared with placebo, BP-lowering regimens reduced the risk of major cardiovascular events by about one-sixth for every incremental 5 mmHg reduction in SBP, in individuals with or without reduced eGFR. The results were similar, irrespective of whether BP was reduced by regimens based on ACEI, calcium antagonists, or diuretics/beta-blockers. There was no evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR. These overviews do not support the preferential choice of any particular drug class for the prevention of cardiovascular events in CKD. However, all the observations refer exclusively to steady pressure hemodynamic measurements of SBP, DBP, or MAP; data on PP and aortic stiffness are lacking.

PULSE PRESSURE AND ARTERIAL STIFFNESS IN CHRONIC KIDNEY DISEASE

Basic concepts

In young, healthy individuals, central (aortic) SBP is lower than peripheral (brachial) SBP, whereas MAP and DBP remain more or less steady throughout the arterial tree [24]. This difference is usually called SBP or PP amplification and can be expressed, in terms of PWV, by the concept of 'stiffness gradient', in which case central (aortic) PWV is significantly lower than peripheral (brachial) PWV. Amplification is considered to be the consequence of increased stiffness gradient and the presence of pressure wave reflections along the arterial tree [24]. Various age-related patterns of central pressure waveforms have been described in the literature, according to the early (during systole) or late (during diastole) summation of forward and backward-propagating waves along the arterial tree.

In older individuals (>60 years), PP amplification is reduced as a consequence of increased aortic stiffness and also the early return of reflected waves in the central arteries [25]. The relative 'timing' of pressure waves that merge as a result of forward and backward travelling may therefore be considered as one of the main parameters defining BP. The augmentation index, which is the currently used index to describe the relative increase in central BP due to pressure wave reflections, includes both the magnitude and the timing of reflected pressure waves, and is therefore dependent upon both arterial stiffness and heart rate. This description of arterial mechanics provides a model to explain how heart rate and primarily left ventricular ejection time, stroke volume, the distance of the reflected site (thus body height), and PWV [25] all interplay to define the timing of the forward and backward-travelling pressure waves within the central arteries – a foremost subject of the current research.

TABLE 1. Interactions between arterial stiffness, vascular resistance, and organ damage in the heart and kidney

Arterial stiffness (AS)	VSMC dysfunction Reduction of NO and eNOS activity VSMC proliferation, migration, and osteoblast transdifferentiation Increased oxidative stress, inflammation, PAI-1/TPA, and $ONOO^-$ Increased collagen Increased TG2 activity
Heart dysfunction	Left ventricular hypertrophy Impaired coronary blood flow Impaired diastolic relaxation Impaired ischemic reconditioning Heart failure with preserved ejection
Chronic kidney disease	Proteinuria NADPH oxidase ROS production Na^+ retention Hyperuricemia Glomerular sclerosis Tubulointerstitial fibrosis

AS increases pulse wave velocity (PWV) resulting in cardiac remodeling and kidney dysfunction, thereby causing ventricular changes and the development of coronary disease. Conversely, kidney dysfunction further aggravates arterial injury. NO, nitric oxide; $ONOO^-$, peroxynitrite; PAI, plasminogen activator inhibitor; TG, triglyceride; TPA, tissue plasminogen activator; VSMC, vascular smooth muscle cell. See reference [40].

These parameters are all closely inter-related and may be modulated by several factors (Table 1) such as the autonomic nervous system, neurohormonal factors (e.g. the RAAS, sex hormones), systemic inflammation, and also the presence of ethnic and geographical parameters [26,27]. Current data suggest that a dissociation of PWV and augmentation index may appear in various conditions such as insulin resistance [28], inflammation, and also the presence of CKD. In this context, and in the presence of a significant arterial stiffness gradient (aortic PWV < peripheral PWV), it is important to note that partial reflection sites occur at a distance from the microcirculation and play a part in its protection. If the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), PP is inadequately dampened thus damaging the microcirculation.

This study looks at the specific role of hypertension and CKD in different circumstances that affect PP and arterial stiffness in particular, as shown in the table of supplementary data. Because of the possible role of ethnic and geographical factors, the studies analyzed were mainly conducted in European, Mediterranean, and African countries.

Clinical applications

In a first study, Kheder *et al.* [29] evaluated the incidence of HTN in 359 patients with glomerulonephritis, and who underwent renal biopsy. There were 68 patients with minimal lesions, 54 patients with membranous glomerulonephritis (MGN), 125 with membranous proliferative

glomerulonephritis (MPGN), 52 with endo and extracapillary glomerulonephritis (EEGN), and 60 with focal segmental sclerosis (FSS). The total prevalence of hypertension was 42%. Multiple regression analysis showed that BP levels were influenced by the following four factors: age, BMI, degree of renal insufficiency, and presence of proliferative glomerular alterations (MPGN and EEGN); the latter, together with renal insufficiency, were shown to be responsible for the development of hypertension.

In a more recent study, Temmar *et al.* [30] determined aortic PP amplification in hypertensive patients with elevated coronary risk; particular emphasis was given to the role of associated CKD factors. BP was measured invasively in the ascending aorta, the abdominal aorta (at the kidney level), and the iliac artery in 101 patients (mean age 63 ± 11 years; 61 men) undergoing coronary angiography. Independently of age, sex, and the presence of coronary stenosis, the increase in PP between the ascending and the terminal aorta was greater than 10 mmHg ($P < 0.001$), whereas MAP remained unchanged. Calculated PP amplification did not differ significantly between patients with or without coronary artery stenosis. Irrespective of confounding variables, high PP measured in the ascending aorta and in the renal arteries (but not in the iliac artery) was independently correlated with the presence of significant proteinuria. The increase in PP from the ascending aorta to the renal level was negatively associated with leukocyte count, even after multivariate adjustments. And most notably, increased plasma creatinine and aortic PWV were independently and positively correlated [beta coefficient 0.36; confidence intervals (CIs) 0.18–0.54, $P < 0.001$], independently of age and MAP. Thus, in individuals with a high risk of coronary disease, aortic stiffness and PP are an integral part of the predictive value of kidney factors in patients with chronic renal failure. Similar findings are observed in cross-sectional studies of individuals with mild to moderate CKD and in longitudinal investigations of patients with chronic hemodialysis and kidney grafts [31–33].

Taken together, these results clearly show that in CKD, BP, and histological findings are not the only important considerations in the prognosis, but that PP, arterial stiffness, and PP amplification also play a role.

The meaning of arterial calcifications in chronic kidney disease

The findings of this review show that not only is increased SBP the most challenging form of hypertension today, but also that increased PP is an independent cardiovascular risk factor, thus focusing attention on the fact that arterial stiffness and wave reflections are the most important factors determining these pressures. In addition, increased arterial stiffness is linked to reduced eGFR and is predictive of kidney disease progression and the patients' cardiovascular outcome. Thus, premature vascular aging and increased arterial stiffening are observed as CKD progresses and ESRD develops [34]. This process of accelerated aging is characterized by outward remodeling of large vessels, which leads to an increased arterial radius that is not totally compensated for by subsequent arterial wall hypertrophy, but is significantly associated with the presence of extensive arterial calcifications [35,36]. It is therefore important to note that, with aging, increased arterial stiffness is more pronounced in the aorta and its main branches than in brachial conduit arteries; increased aortic stiffness is associated with arterial calcifications that are responsible for wave reflections and increased aortic PP; such changes lead to the disappearance or inversion of the arterial stiffness gradient and to increased rates of premature cardiovascular and non-cardiovascular death. Finally, the presence and extent of arterial calcifications are significant predictors of all-cause and cardiovascular mortality. In this context, measurement of the carotid incremental modulus may have an additive predictive value [36].

Arterial stiffness and specific causes of chronic kidney disease

Increased arterial stiffness in CKD is explained by traditional and nontraditional cardiovascular risk factors. Variables that are unique to CKD include vascular calcifications, chronic inflammation, accumulation of advanced glycation end products, and fluid overload. Although a link between eGFR and arterial stiffness has been suggested and described in various studies, the true predictive value of eGFR levels on increasing PWV has not yet been clearly established [37,38]. In one study comparing arterial stiffness in patients with IgA nephropathy and early kidney disease with that of sex and blood pressure-matched healthy controls, IgA nephropathy was found to be associated with increased arterial stiffness, increased RAAS activity, and with decreased arterial sensitivity to Ang II challenge, suggesting a loss of adaptive response to the increased intraglomerular RAAS activity due to prolonged exposure to polymeric IgA 1, thus confirming the beneficial action of RAAS blockade in this population [39]. However, the correlation of these findings to the degree of proteinuria and to the importance of histological lesions still requires further investigation. Proteinuria is often the first sign of renal disease in patients with glomerulonephritis. However, since the onset does not follow a regular pattern within these diseases, the relationship between aortic stiffness and proteinuria is difficult to establish. In a cross-sectional study of 144 patients with stage 2–5 CKD of different causes and analyzed for aortic stiffness, Pan *et al.* [40] found that proteinuria and aortic stiffness are interdependent, with a time-related aggravation pattern (as already shown in general, hypertensive, and diabetic populations). However, although apparent proteinuria was shown to be predictive of aortic stiffness, stiffness did not predict proteinuria in this study.

Finally, patients with autosomal dominant polycystic kidney disease (ADPKD) and with manifest polycystic kidney disease are an interesting model of early increased aortic stiffness, which appears even before hypertension or reduced eGFR. This is clearly highlighted by increased inflammatory biomarkers, such as interleukin (IL)-6, INF alpha, highly sensitive C-reactive protein (hsCRP), and a state of oxidative stress, which together lead to the progression of ADPKD on one hand, and to vascular remodeling on the other. These observations suggest potential therapeutic pathways to be explored for slowing down cardiovascular complications in these patients [41,42].

PROSPECTIVE VIEWS

In conclusion, this review has shown that effective BP-lowering through SBP, DBP, and also MAP reduction can be obtained in hypertensive patients with CKD. This reduction occurs regardless of the drug classes used and even of eGFR levels. However, independently of BP reduction, there are other important factors to be considered with regard to the drug strategy and which primarily affect PP, the level of aortic stiffness, and the extent of wave reflections. These aspects are now to be considered prospectively [37–39,43] (see Table 1).

In patients with hypertension, the main objective of drug treatment is to reduce both SBP and DBP since they are practically the sole mechanical factors affecting cardiovascular risk. Innovative studies have shown that arterial stiffness should now be considered as an independent parameter in the reduction of cardiovascular risk and that it relates mainly to PP, and not to MAP and exclusive SBP and DBP reduction. The presence of increased aortic stiffness, as assessed indirectly from PP measurements, not only requires SBP to be reduced but also DBP levels to be maintained and/or even increased to ensure PP reduction [25]. Although counter-intuitive, low DBP is known to be a significant risk factor for cardiac complications, particularly in the elderly [25]. Research by Mitchell *et al.* [44] and Mansour *et al.* [45] has shown that PP and aortic stiffness measurements can improve the Framingham score status, which usually involves a large number of metabolic parameters, but remains limited to SBP and DBP measurements in the context of important mechanical factors in hypertension. Finally, a small number of novel antihypertensive agents have been suggested in recent years, including nitrates and spironolactone-like compounds [46–48], and more recently, cross-link breakers [49], metalloproteinase inhibitors [50], omapatrilate [51], and neprilysin inhibitors [52,53].

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Conflicts of interest

The authors have no conflicts of interest pertaining to the content of this study.

REFERENCES

1. Kowal P, Arokiasamy P, Lopez Ridaura R, Yong J, Minicuci N, Chatterji S. Hypertension in developing countries. *Lancet* 2012; 380:1471.
2. Ben Romdhane H, Ben Ali S, Skhiri H, Traissac P, Bougatef S, Maire B, *et al.* Hypertension among Tunisian adults: results of the TAHINA project. *Hypertens Res* 2012; 35:341–347.
3. Ridao N, Luno J, Garcia de Vinuesa S, Gomez F, Tejedor A, Valderrabano F. Prevalence of hypertension in renal disease. *Nephrol Dial Transplant* 2001; 16 (Suppl 1):70–73.
4. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; 107:2864–2869.
5. Dame B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension* 1989; 13:392–400.
6. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation* 1999; 100:354–360.
7. Nichols WW, O'Rourke MF. McDonald's blood flow in arteries. Theoretical, experimental and clinical principles. 4th ed. London: Edward Arnold; 2006. pp. 49–94, 193–233, 339–402, 435–502.
8. Verbeke F, Lindley E, Van Bortel L, Vanholder R, London G, Cochat P, *et al.* A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in nondialysis-dependent chronic kidney disease: an endorsement with some caveats for real-life application. *Nephrol Dial Transplant* 2014; 29:490–496.
9. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; 366:2026–2033.
10. van der Meer IM, Cravedi P, Remuzzi G. The role of renin angiotensin system inhibition in kidney repair. *Fibrogenesis Tissue Repair* 2010; 3:7.
11. Neuringer JR, Brenner BM. Hemodynamic theory of progressive renal disease: a 10-year update in brief review. *Am J Kidney Dis* 1993; 22:98–104.
12. Ma LJ, Fogo AB. Modulation of glomerulosclerosis. *Semin Immunopathol* 2007; 29:385–395.
13. Mahmud A, Feely J. Arterial stiffness and the renin-angiotensin-aldosterone system. *J Renin Angiotensin Aldosterone Syst* 2004; 5:102–108.
14. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. *Hypertension* 2004; 44:595–601.
15. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139:244–252.
16. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, *et al.*, African American Study of Kidney, and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002; 288:2421–2431.
17. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; 354:131–140.
18. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al.*, RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345:861–869.
19. Abe M, Okada K, Maruyama T, Matsumoto K. Antiproteinuric and blood pressure-lowering effects of a fixed-dose combination of losartan and hydrochlorothiazide in hypertensive patients with stage 3 chronic kidney disease. *Pharmacotherapy* 2009; 29:1061–1072.
20. Rakugi H, Ogihara T, Umemoto S, Matsuzaki M, Matsuoka H, Shimada K, *et al.* Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial, Combination therapy for hypertension in patients with CKD: a subanalysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial. *Hypertens Res* 2013; 36:947–958.
21. Kereiakes DJ, Chrysant SG, Izzo JL Jr, Littlejohn T 3rd, Melino M, Lee J, *et al.* Olmesartan/amlodipine/hydrochlorothiazide in participants with hypertension and diabetes, chronic kidney disease, or chronic cardiovascular disease: a subanalysis of the multicenter, randomized, double-blind, parallel-group TRINITY study. *Cardiovasc Diabetol* 2012; 11:134.
22. Frimodt-Moller M, Kamper AL, Strandgaard S, Kreiner S, Nielsen AH. Beneficial effects on arterial stiffness and pulse-wave reflection of combined enalapril and candesartan in chronic kidney disease: a randomized trial. *PLoS One* 2012; 7:e41757.
23. Blood Pressure Lowering Treatment Trialists' CollaborationNinomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, Cass A, *et al.* . Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ* 2013; 347:f5680.
24. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, *et al.* Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009; 54:375–383.
25. Protogerou AD, Papaioannou TG, Blacher J, Papamichael CM, Lekakis JP, Safar ME. Central blood pressures: do we need them in the management of cardiovascular disease? Is it a feasible therapeutic target? *J Hypertens* 2007; 25:265–272.

26. Reusz GS, Cseprekal O, Temmar M, Kis E, Cherif AB, Thaleb A, *et al.* Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension* 2010; 56:217–224.
27. Salvi P, Meriem C, Temmar M, Marino F, Sari-Ahmed M, Labat C, *et al.* Association of current weight and birth weight with blood pressure levels in Saharan and European teenager populations. *Am J Hypertens* 2010; 23:379–386.
28. Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, *et al.* Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. *Circulation* 2005; 112:2193–2200.
29. Kheder MA, Ben Maiz H, Abderrahim E, el Younsi F, Ben Moussa F, Safar ME, Ben Ayed H. Hypertension in primary chronic glomerulonephritis analysis of 359 cases. *Nephron* 1993; 63:140–144.
30. Temmar M, Jankowski P, Peltier M, Mouquet V, Debicka-Dabrowska D, Hamida F, *et al.* Intraaortic pulse pressure amplification in subjects at high coronary risk. *Hypertension* 2010; 55:327–332.
31. Bahous SA, Stephan A, Blacher J, Safar ME. Aortic stiffness, living donors, and renal transplantation. *Hypertension* 2006; 47:216–221.
32. Mourad JJ, Pannier B, Blacher J, Rudnichi A, Benetos A, London GM, Safar ME. Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. *Kidney Int* 2001; 59:1834–1841.
33. Safar ME, London GM, Plante GE. Arterial stiffness and kidney function. *Hypertension* 2004; 43:163–168.
34. Briet M, Boutouyrie P, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012; 82:388–400.
35. London GM, Pannier B, Marchais SJ. Vascular calcifications, arterial aging and arterial remodeling in ESRD. *Blood Purif* 2013; 35:16–21.
36. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001; 38:938–942.
37. Safar ME, Plante GE, Mimran A. Arterial stiffness, pulse pressure, and the kidney. *Am J Hypertens* 2014; 28:561–569.
38. Laffin LJ, Bakris GL. Renal denervation for resistant hypertension and beyond. *Adv Chronic Kidney Dis* 2015; 22:133–139.
39. Parati G, Ochoa JE, Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. *Curr Hypertens Rep* 2012; 14:421–431.
40. Pan CR, Roos M, Schmaderer C, Lutz J, Wang JG, Heemann U, Baumann M. Interrelationship between aortic stiffness and proteinuria in chronic kidney disease. *J Hum Hypertens* 2010; 24:593–599.
41. Kocyigit I, Kaya MG, Orscelik O, Kaya C, Akpek M, Zengin H, *et al.* Early arterial stiffness and inflammatory bio-markers in normotensive polycystic kidney disease patients. *Am J Nephrol* 2012; 36:11–18.
42. Menon V, Rudym D, Chandra P, Miskulin D, Perrone R, Sarnak M. Inflammation, oxidative stress, and insulin resistance in polycystic kidney disease. *Clin J Am Soc Nephrol* 2011; 6:7–13.
43. Jia G, Aroor AR, Sowers JR. Arterial stiffness: a nexus between cardiac and renal disease. *Cardiorenal Med* 2014; 4:60–71.
44. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, *et al.* Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010; 121:505–511.
45. Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar ME, Ouerdane S, Blacher J. Aortic stiffness and cardiovascular risk in type 2 diabetes. *J Hypertens* 2013; 31:1584–1592.
46. Stewart AD, Jiang B, Millasseau SC, Ritter JM, Chowienczyk PJ. Acute reduction of blood pressure by nitroglycerin does not normalize large artery stiffness in essential hypertension. *Hypertension* 2006; 48:404–410.
47. Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol* 2009; 54:505–512.
48. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats. *Arterioscler Thromb Vasc Biol* 1997; 17:1152–1156.
49. Kass DA, Shapiro EP, Kawaguchi M, Capriotti AR, Scuteri A, deGroof RC, Lakatta EG. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation* 2001; 104:1464–1470.
50. Mitchell GF, Izzo JL Jr, Lacourciere Y, Ouellet JP, Neutel J, Qian C, *et al.* Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. *Circulation* 2002; 105:2955–2961.
51. Wang M, Zhang J, Telljohann R, Jiang L, Wu J, Monticone RE, *et al.* Chronic matrix metalloproteinase inhibition retards age-associated arterial proinflammation and increase in blood pressure. *Hypertension* 2012; 60:459–466.
52. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet* 2010; 375:1255–1266.
53. Williams B, Cockcroft JR, Kario K, Zappe DH, Cardenas P, Hester A, *et al.* Rationale and study design of the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study. *Br Med J Open* 2014; 4:e004254.

3.1.3 Conclusion de l'article 5

Les stratégies thérapeutiques antihypertensives chez le patient insuffisant rénal rejoignent celles de la prise en charge du patient avec hypertension artérielle essentielle. Le bénéfice de la baisse de la pression artérielle est au premier plan en termes d'incidence d'événements cardiovasculaires (129). La question de la cible tensionnelle reste toujours débattue, en particulier chez les patients âgés (130, 131). Elle reste dépendante du niveau de protéinurie, selon les recommandations de bonnes pratiques du KDIGO (Kidney Disease: Improving Global Outcomes) (130), indépendamment du stade d'insuffisance rénale ou de la présence d'une maladie diabétique. En l'absence de microalbuminurie avant traitement, la cible tensionnelle doit être entre 130-139/80-89 mm Hg chez les patients insuffisants rénaux, diabétiques ou non diabétiques, quel que soit le stade de la maladie rénale. Une cible tensionnelle plus basse, inférieure ou égale à 130/80 mm Hg, est discutée chez les patients insuffisants rénaux avec microalbuminurie (130).

Des spécificités existent pour la stratégie thérapeutique antihypertensive en contexte de maladie rénale. Le blocage du système rénine angiotensine aldostérone est privilégié en première ligne de traitement (à l'exclusion du double blocage) (130). Les modèles expérimentaux d'hypertension mettent en évidence une activation du système rénine-angiotensine avec formation accrue non contrôlée d'angiotensine II intra-rénale. L'angiotensine II stimule la production d'aldostérone, provoque une vasoconstriction prédominant sur l'artériole efférente du glomérule, favorise la réabsorption du sodium tubulaire et la libération de cytokines et facteurs de croissance tels que le TGF-β1. Ce dernier facteur est impliqué dans la progression des lésions de fibrose rénale (132,133). Les IEC et les ARA2 ralentissent le déclin de la fonction rénale indépendamment de la baisse tensionnelle (134,135). La microalbuminurie et la protéinurie sont des marqueurs d'évolution vers

l'insuffisance rénale terminale et de morbi-mortalité cardiovasculaire. Leur réduction sous traitement inhibant le système rénine angiotensine indépendamment de la baisse tensionnelle constitue une cible thérapeutique en termes de néphroprotection (136, 137).

Le contrôle de la pression artérielle chez les patients insuffisants rénaux requérant l'association de deux ou plusieurs classes antihypertensives, les inhibiteurs calciques et les diurétiques de type thiazidique restent les plus utilisées. Cependant, les recommandations soulignent quelques spécificités concernant les stratégies thérapeutiques à privilégier et notamment pour les inhibiteurs calciques. Il existe une efficacité antihypertensive similaire pour les deux sous-classes, dihydropyridines et non-dihydropyridines. Une réduction plus marquée de la protéinurie a cependant été observée avec les inhibiteurs calciques non-dihydropyridiniques, en présence ou non de diabète (138). Basé sur ces résultats, les inhibiteurs calciques non-dihydropyridinique, seuls ou en combinaison avec un IEC ou un ARA2, sont préférés pour le traitement de l'hypertension artérielle chez les patients présentant une néphropathie associée à une protéinurie. L'utilisation des dihydropyridines reste possible dans le cadre d'une association à un IEC ou ARA2 (139).

Une autre spécificité de la maladie rénale concerne le vieillissement artériel accéléré. Cependant la pression pulsée et la rigidité aortique, caractéristiques du profil hémodynamique de ces patients, ne sont pas prises en compte dans les stratégies thérapeutiques antihypertensives. La rigidité aortique et la pression pulsée centrale ont démontré leur pouvoir prédictif pour la mortalité chez les patients avec insuffisance rénale chronique terminale (84). Ces paramètres hémodynamiques devraient donc être étudiés pour évaluer l'efficacité et la tolérance des traitements antihypertenseurs. La réduction de la rigidité aortique ou de la pression pulsée centrale sous traitement pourrait être associée un meilleur pronostic,

indépendamment du bénéfice de la baisse tensionnelle périphérique (115).

3.2 Paramètres hémodynamiques artériels, hypertension et diabète (Article 6)

3.2.1 Introduction de l'article 6

La gestion du haut risque cardiovasculaire chez les patients hypertendus diabétiques requiert une prise en charge multifactorielle des facteurs de risque. Cependant, le traitement combiné de l'hypertension artérielle et du diabète reste insuffisant pour obtenir une réduction substantielle de la morbidité et de la mortalité cardiovasculaire (140). De plus, le traitement intensif de l'hypertension artérielle (141, 142) et du diabète (143, 144, 145) n'apporte pas de bénéfice supplémentaire par rapport à la prise en charge conventionnelle, pouvant même être délétère chez ces certains patients (141, 144).

Ce risque résiduel pourrait être le reflet de la maladie artérielle infra clinique. La rigidité aortique et l'atteinte micro vasculaire apparaissent comme des dénominateurs communs de l'atteinte des organes cibles chez les patients hypertendus (2, 146) et les patients diabétiques (147, 148). Le rôle de la fréquence cardiaque paraît majeur dans la modulation du phénomène des ondes de réflexion chez les patients hypertendus avec syndrome métabolique (149, 150). L'étude des paramètres hémodynamiques artériels et de leurs déterminants chez les patients hypertendus diabétiques, en comparaison aux hypertendus non diabétiques, peut aider à proposer de nouvelles stratégies thérapeutiques chez ces patients à très haut risque.

L'objectif de ce travail a été d'étudier les facteurs associés à la rigidité aortique et à l'amplification de la pression pulsée chez les patients hypertendus en présence ou non

d'un diabète, et plus particulièrement : (1) d'étudier l'impact de l'association hypertension artérielle et diabète sur les paramètres hémodynamiques artériels; (2) de rechercher une éventuelle corrélation entre rigidité aortique et amplification de la pression pulsée ; (3) d'étudier le rôle de la fréquence cardiaque dans la modulation des paramètres hémodynamiques artériels et de préciser les traitements médicamenteux corrélés à ces paramètres.

De décembre 2012 à septembre 2014, 399 patients ont été inclus consécutivement après leur consentement dans cette étude observationnelle transversale lors de leur suivi cardiovasculaire en hôpital de jour à l'Hôtel-Dieu. Les mesures hémodynamiques ont pu être réalisées de manière adéquate chez 351 patients (205 hommes et 146 femmes) : 134 patients hypertendus sans diabète, 128 patients hypertendus diabétiques, 30 patients diabétiques non hypertendus et 59 patients non hypertendus non diabétiques. Un antécédent de maladie cardiovasculaire était présent chez 76 patients, intéressant au moins un site vasculaire : 52 (15 %) patients présentaient une maladie coronaire, 21 (6 %) patients présentaient une maladie artérielle périphérique et 12 (3 %) patients, une maladie cérébro-vasculaire.

3.2.2 Article 6

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Hemodynamic parameters in hypertensive diabetic patients.

Submitted.

Hemodynamic parameters in hypertensive diabetic patients

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ABSTRACT

Objective(s). Despite adequate glycemic and blood pressure (BP) control, diabetic hypertensives remain at increased cardiovascular (CV) risk. Aortic stiffness and pulse pressure (PP) amplification may provide complementary information to correct CV risk. We aim to determine whether these hemodynamic parameters are interrelated or not and to explore the factors related to pressure pulsatility. ***Methods.*** A cross-sectional study was conducted in 351 patients, involving controls, hypertensives without diabetes and diabetic patients with or without hypertension. Hemodynamic parameters were determined by applanation tonometry. Multivariate regression analyses evaluated the interest of therapeutic strategies. ***Results.*** Aortic stiffness and PP amplification were not interrelated ($p=0.32$) in multivariate-adjusted analysis and were both independently associated with previous CV events. Although disproportionately increased aortic stiffness in diabetic hypertensives ($p<0.001$), no difference was found for PP amplification. The present dissociation between these two hemodynamic parameters may be related to the effect of increased heart rate ($p<0.001$) in the presence of diabetes, in men and women. In diabetic hypertensives, aortic stiffness was correlated with glycated hemoglobin level ($p=0.04$), but not with blood pressure or heart rate. Antihypertensive and statin treatments were correlated with PP amplification but not with aortic stiffness. ***Conclusions.*** Aortic stiffness and PP amplification were not interrelated, suggesting that these markers may provide complementary information for CV risk. New therapeutic strategies targeting pressure pulsatility should take into account the impact of hyperglycemia and increased heart rate in diabetic hypertensives. Gender influence on the role of autonomic nervous system in attenuating pressure wave reflections remains to be further established. **KEYWORDS:** aortic stiffness, pulse wave velocity, pulse pressure amplification, hypertension, diabetes.

INTRODUCTION

Hypertension and diabetes are worldwide health problems and two of the most leading risk factors for cardiovascular (CV) morbidity and mortality. Epidemiological evidence highlights the frequent association between hypertension and diabetes mellitus, reflecting substantial overlap in the pathophysiology of the two diseases and leading to additive increase in the risk of CV events [1-3].

Multifactorial risk factor management is required for effective CV disease prevention in this high-risk population. However, along with this multifactorial approach, combined treatment of hypertension and diabetes per se may appear insufficient to obtain a substantial reduction in CV morbidity and mortality despite adequate glycemic and blood pressure (BP) control [4-6]. This approach may be indicative of adverse responses of subclinical, structural and functional arterial damage. Nowadays, large artery stiffness and micro vascular arterial alterations appear as common denominators to target organ damage in hypertensive [7, 8] and diabetic patients [9, 10]. Most of these arterial parameters may be investigated in large populations from non-invasive determination of aortic stiffness [11, 12] and central to peripheral pulse pressure (PP) amplification [13] with different but complementary information for CV risk.

Because of the presence of both steady and pulsatile stress in subjects with hypertension and diabetes [14], there is a significant increase in systolic and pulse pressures from central (thoracic aorta, carotid artery) to peripheral (brachial artery) sites. This phenomenon depends on the timing and amplitude of the forward and reflected BP waves [15] and is classically modulated by several factors involving age, gender, arterial stiffness, arteriolar vasomotor tone and mostly heart rate and wave reflections [16,17]. Advancing age and high BP appear to be the most important determinants of aortic stiffness [18]. Compared to hypertensive non diabetic patients, coexistence of hypertension and diabetes is further

associated with increased aortic stiffness [19, 20] which may be indicative of a supplementary increase of CV risk [21]. Insulin resistance syndrome has also been linked to increased heart rate [22], a parameter commonly associated to PP amplification and aortic stiffening.

In this investigation, hemodynamic parameters in hypertensive subjects appear to be highly modulated by the presence of diabetes mellitus. Furthermore, despite similar brachial BP values, aortic stiffness [23] and PP amplification [24] can be pharmacologically modulated. Factors associated with aortic stiffness and PP amplification in treated hypertensive diabetic patients have been poorly studied in comparison to hypertensive non diabetic patients and to normotensives with or without diabetes [25]. Study of such factors could provide consistent data enabling to correct CV risk. The purpose of the present cross-sectional study was: (1) to determine the impact of the association of hypertensive and diabetic status on hemodynamic parameters; (2) to determine whether aortic stiffness and PP amplification are interrelated or not; (3) to explore the role of heart rate and the association between drug classes and hemodynamic parameters.

METHODS

Overall population

From December 2012 to September 2014, 399 consecutive patients, men and women, with or without previously identified CV events, were eligible in this cross-sectional study during their follow-up at the Paris Hôtel-Dieu University Hospital. All patients were recruited after visit in the Diagnosis and Therapeutics Centre of Hôtel-Dieu University Hospital. The majority of patients were in-hospital source of patients, with routine CV follow-up, and the others were referred by their general practitioner for a CV check-up because of the presence of one or more CV risk factors. Patients provided informed consent for additional noninvasive hemodynamic measurements and data collection during the day hospital for the CV screening.

Exclusion criteria were age under 18, acute medical conditions and atrial fibrillation. The study complies with the Declaration of Helsinki. The study was registered in the French National Agency for Medicines and Health Products Safety (No. 2013-A00227-38) and was approved by the locally appointed ethics committee, the Advisory Committee for Protection of Persons in Biomedical Research.

Study cohort

From the totality of patients entered in day hospitalization for a CV check-up, 48 patients were excluded due to missing data (central hemodynamic measurements have not been performed successfully because of frequent extrasystoles or poor quality waveform). The study cohort was then composed of 351 consecutive patients, 134 hypertensive patients without diabetes, 128 hypertensive diabetic patients, 30 normotensive diabetic patients and 59 normotensive patients without diabetes. All patients with diabetes mellitus were eligible in this cross-sectional study. Hemodynamic parameters were available in 158 diabetic patients and the study cohort included 17 type 1 diabetic patients and 141 type 2 diabetic patients. Hypertensive patients with or without diabetes were all receiving antihypertensive drug treatment.

Clinical and laboratory parameters

Information compiled from the questionnaire filled out at inclusion during the day hospital for CV screening included gender, age, weight and height, body mass index (BMI, 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 (coronary heart disease, cerebro-vascular disease and peripheral vascular disease) were retrospectively assessed: scan

imaging-documented stroke for cerebrovascular disease; past medical history of documented myocardial infarction, coronary revascularization or epicardial coronary artery disease diagnosed during coronography for patients with symptoms or typical electrocardiographic modifications for coronary heart disease; ankle-brachial pressure index value less than 0.90, imaging-documented atherosclerotic vascular disease including asymptomatic severe carotid artery stenosis, peripheral vascular disease and abdominal aortic aneurysm, arterial revascularization or lower limb amputation.

Definition of diabetes mellitus was classical: patients with fasting blood glucose greater than 1.26g/l or 2g/l at any time tested twice or those treated with oral hypoglycemic agents or with insulin therapy. Dyslipidaemia was defined as a total/HDL cholesterol ratio > 5 or the presence of a hypocholesterolemic drug.

Laboratory parameters, including plasma glucose and glycated hemoglobin, cholesterol (total, LDL and HDL) and triglycerides, plasma creatinine and creatinine clearance rate, and presence of microalbuminuria (on 24-hour urine collection) were determined on the day of hemodynamic measurements.

Central and peripheral arterial parameters

Hemodynamic measurements were performed in the morning after an overnight fast, in supine position. Brachial systolic BP and diastolic BP were measured at both arms using an automatic BP monitor (OMRON 705 CP II IT) after 5 minutes of rest. Five measurements 2 minutes apart were averaged. Heart rate was recorded.

After BP determination, structural and functional parameters of the arterial wall were measured noninvasively by applanation tonometry: this measure provides an accurate profile of intra-arterial BP curves, with a continuous beat-to-beat monitoring, by applying a piezoelectric sensor, the tonometer, over an artery. The reproducibility of these measurements,

in our group and in others, has been previously published in detail [26, 27].

- Carotid-femoral pulse wave velocity (PWV) was performed using an automatic device (SphygmoCor AtCor, Sydney, Australia), with simultaneous three-lead orthogonal electrocardiogram [28]. Pulse waveforms were obtained transcutaneously using applanation tonometry over the common carotid and femoral arteries. Aortic PWV was calculated as the direct distance between carotid and femoral arteries, divided by the time interval between the feet of the pressure waves at the recording sites. Direct distance was multiplied by a scaling factor of 0.8 to obtained "real PWV" as previously described [29].
- Central BP components were estimated using applanation tonometry over the radial artery and application of a validated generalized transfer function [30]. Mean arterial pressure was defined as the integral of the radial pressure waveform. Brachial systolic and diastolic BP were used for radial pressure waveform calibration. Pulse pressure amplification was defined as the brachial PP-to-aortic PP ratio.

Carotid arteries, abdominal aorta and limb arteries were scanned ultrasonographically for the detection of atherosclerotic plaques.

Statistical analysis

Statistics were performed using R 3.1.2. A p-value <0.05 was considered statistically significant. Continuous variables were represented as mean ± standard deviation (±SD). Qualitative variables were expressed as frequency with percentage. Relationships between hypertension or diabetes and participants' characteristics were analyzed by Student test for continuous variables. These analyses included age, BMI, brachial and central systolic and diastolic BP, MAP and biological parameters. Pearson's Chi-square test was performed for categorical variables including gender and drug treatments. Two-way ANOVA or logistic

regressions were used for assessing interaction between hypertension and diabetes in the association with the different patient's characteristics. Pearson's correlations were performed to assess relationships between aortic PWV, PP amplification and patient's characteristics. On the basis of "diabetic-hypertensive status", considered as a discrete variable, we categorized patients into 4 groups: "diabetes only", "hypertension only", "both diabetes and hypertension", and "neither diabetes nor hypertension" which was considered as the control group. In order to analyze factors independently associated with aortic PWV and PP amplification, ANCOVA or multiple linear regressions were performed. Finally, a logistic regression was used to evaluate association of previous CV events with patient's characteristics including CV risk factors and hemodynamic parameters. Regressions models were obtained by stepwise selection, containing all variables that were significantly correlated in univariate analysis and based on their physiopathological plausibility.

RESULTS

Study cohort

The study cohort was composed of 351 patients, 205 men (43 % with diabetes) and 146 women (47 % with diabetes). Previous CV events were present in 76 patients, involving at least one vascular site: coronary heart disease in 52 (15 %) patients, peripheral vascular disease in 21 (6 %) patients and cerebro-vascular disease in 12 (3 %) patients. Clinical and biological parameters of the study participants are given in table 1. The only parameter associated with a significant interaction between hypertensive and diabetic status was glycated haemoglobin level (p for interaction = 0.006). Hypertensive status was associated with the presence of carotid plaque and with higher frequency of patients in secondary CV prevention, with no interaction between hypertension and diabetes for previous CV events (p for

interaction = 0.22).

Hemodynamic parameters of the study participants are given in table 2 according to hypertensive and diabetic status. Mean arterial pressure, brachial and central systolic blood pressures were higher in hypertensive patients with or without diabetes compared to normotensive subjects. Heart rate was increased in diabetic patients. Heart rate remained significantly increased in hypertensive diabetic patients ($p<0.001$), compared to normotensive non diabetic patients after adjusting for age, gender, MAP and beta-blocker treatment. Hypertensive and diabetic status were both associated with increased aortic PWV with no interaction between hypertension and diabetes (p for interaction = 0.24). Diabetic status with or without hypertension was associated with increased PP amplification with no interaction between hypertension and diabetes (p for interaction = 0.89).

Statin therapy was more frequently observed in hypertensive diabetic patients compared to the other patients ($p<0.05$). Treatment with angiotensin II receptor blockers (ARBs) or angiotensin-converting-enzyme (ACE) inhibitor or with thiazide diuretic was more frequently observed in hypertensive diabetic patients compared to hypertensive non diabetic patients ($p<0.05$). There was no statistically significant difference according to treatment with beta blockers, calcium blockers or aldosterone receptor antagonists among hypertensive patients with or without diabetes. Among diabetic patients with or without hypertension, 90 (57 %) patients were on oral antidiabetic drugs, 25 (16 %) patients on insulin therapy alone and 28 (18 %) patients on both oral treatment and insulin therapy.

Factors associated with arterial hemodynamic parameters

Factors associated with aortic PWV in univariate analysis were age, heart rate, MAP, creatinine clearance, glycated haemoglobin, diabetic status, hypertensive status, treatment with ARBs, ACE inhibitor or thiazide diuretic.

Age ($p<0.001$), MAP ($p<0.001$) and heart rate ($p=0.001$) were independently modulating aortic PWV in multivariate analysis, with a positive correlation (Table 3). Hypertensive status with diabetes ($p<0.001$) or without diabetes ($p=0.02$) and diabetic status without hypertension ($p=0.047$) were associated with significantly increased aortic PWV compared to controls independently of age, MAP and heart rate. Hypertensive diabetic patients presented with higher aortic PWV values compared to the other patients (Figure 1). Gender was not correlated with aortic PWV.

Factors associated with PP amplification in univariate analysis were age, gender, height, heart rate, MAP, glycated haemoglobin, diabetic status with or without hypertension, treatment with ARBs, ACE inhibitor, beta-blocker or statin.

Age ($p<0.001$) and MAP ($p<0.001$) were modulating negatively PP amplification whereas heart rate ($p<0.001$), male gender ($p<0.001$) and height ($p=0.02$) were the independent factors modulating PP amplification with a positive correlation in multivariate analysis (Table 3). Compared to controls, diabetic hypertensives presented with higher PP amplification ($p=0.005$) after adjusting for age, gender, height and MAP but this result became non-significant after heart rate adjustment. Pulse pressure amplification was highly related to gender in the entire population: women showed marked decrease in PP amplification compared to men independently of diabetic-hypertensive status ($p<0.001$) (Figure 1).

No correlation was found between aortic PWV and PP amplification, even after adjustment for age, gender, MAP, heart rate and diabetic-hypertensive status (p-value = 0.32).

Specific results affecting hypertensive diabetic patients:

Age ($p<0.001$) and glycated hemoglobin level ($p=0.04$) were the only parameters associated with increased aortic stiffness after adjusting for gender, heart rate and MAP which were not statistically significant (Table 4). Drug treatment was not independently associated

with aortic PWV in the multivariate analysis.

Age (p=0.02) and MAP (p=0.006) were the independent factors modulating negatively PP amplification whereas heart rate (p<0.001) was the independent factor modulating PP amplification with a positive correlation in multivariate analysis (Table 4). After adjusting for height, gender was not correlated with PP amplification phenomenon in hypertensive diabetic patients. When drug treatment was included in multivariate analysis, beta-blocker treatment (p=0.04) and statin treatment (p=0.02) were correlated negatively with PP amplification. A positive trend toward significance was noted for ARBs or ACE inhibitor treatment with PP amplification (p=0.07) (Supplementary Table S1).

No correlation was found between aortic PWV and PP amplification, even after adjusting for age, gender, MAP and heart rate (p-value=0.65).

Factors modulating the presence of previous CV events

The independent factors associated positively with the presence of previous CV events in multivariate analysis were male gender (p<0.001), dyslipidaemia (p=0.04), presence of carotid plaque (p=0.016) and aortic PWV (p=0.04) whereas MAP (p=0.012), heart rate (p=0.013) and PP amplification (p=0.03) were associated negatively with the presence of previous CV events after adjusting for age, smoking status and diabetic-hypertensive status (Table 5).

DISCUSSION

In the entire study population as well as in the subgroup of hypertensive diabetic patients, aortic stiffness and PP amplification were not interrelated in multivariate-adjusted analysis, suggesting that these markers may provide different and complementary information for CV risk. In particular, association of hypertension and diabetes did not impact PP

amplification level although presence of disproportionately increased aortic stiffness compared to the other patients. The present dissociation between these two hemodynamic parameters may be related to the effect of increased heart rate observed in the presence of diabetes. In hypertensive diabetic patients, aortic stiffness was correlated positively with glycated hemoglobin level, but not with MAP or heart rate, independently of age. Finally, gender influence on PP amplification phenomenon was not significant in hypertensive diabetic patients. In the presence of diabetes, the impact of hyperglycemia, increased heart rate and gender influence on hemodynamic parameters have to be considered for new therapeutic strategies targeting pressure pulsatility.

Aortic PWV

In the present study, hypertensive diabetic patients presented with disproportionately increased aortic stiffness compared to hypertensive non diabetic patients and to normotensives with or without diabetes. The other major factors correlated with aortic stiffness in the study population were age, MAP and heart rate. Treated hypertensive patients are known to have significantly increased aortic stiffness, compared with normotensive subjects, even after correction for age and MAP [29]. Indeed, aortic wall stiffening is considered as an adaptive structural response of large artery to increased tensile stress, related to distending BP and hence to MAP, and to long-term repeated cycles of high stress/strain and elastic recoils of the arterial wall, related to heart rate and aging [31]. Structural changes include increased content of stiff wall materials associated with alterations of elastin fibers, resulting in increased arterial wall thickness [32] and increased vascular stiffness [33]. Stiffening of the aortic wall may also partly be determined and accelerated by other physio-pathological conditions related to diabetes mellitus [19, 34]. In hypertensive diabetic patients, age and glycated hemoglobin were the only variables independently associated with increased aortic stiffness whereas MAP

and heart rate did not reach statistical significance. These results suggest that pathophysiological mechanisms leading to increased vascular stiffness may differ in hypertensive patients with and without diabetes [34]. Diabetic status considered individually has already been related to increased aortic stiffness via medial calcification, oxidative stress, inflammation and advanced glycation end products accumulation [34, 35]. In line with previously published data [19], hyperglycemia may be one of the major independent determinant of aortic stiffening independently of BP level, heart rate and age-related modifications.

Increased aortic PWV, that follows these structural changes, is considered as an important parameter related to increased pressure pulsatility [36]. Pressure pulsatility is known to impact in turn on large-artery wall remodeling independently of MAP [37] but also promotes microcirculatory damages [38]. An advanced degree of arterial stiffness, driven by a delayed onset date of diabetic treatment and delayed glycemic control, may partly account for the lack of optimal treatment benefit on CV morbi-mortality in hypertensive diabetic patients [4, 5, 6]. Plasma glucose may remain an important determinant of arterial stiffening over years and should be taken into account for new and earlier therapeutic strategies targeting increased pressure pulsatility in high risk patients.

Pulse pressure amplification

In the entire study population, the independent factors related to PP amplification were age, gender, height, MAP and heart rate, consistently with findings in the literature [17]. Significant differences in arterial properties have been described between men and women with lower PP amplification in women beyond differences in body height [17, 39, 40]. Furthermore, hemodynamic parameters in hypertensive subjects appear to be highly modulated by the presence of metabolic syndrome [19, 41]. In the present study, a particular attention was given to gender influence on PP amplification in hypertension with diabetes, a

condition associated to a marked increase in arterial stiffness. Results have shown two principal findings. First, in the entire study population as well as in the subgroup of hypertensive diabetic patients, aortic stiffness and PP amplification were not interrelated in multivariate-adjusted analysis. Association of hypertension and diabetes did not impact PP amplification level although presence of disproportionately increased aortic stiffness compared to the other patients. The present dissociation between aortic stiffness and PP amplification may be related to the effect of increased heart rate observed in the presence of diabetes [42]. These results are also consistent with previously published data highlighting that, in the presence of metabolic syndrome, PP amplification is increased due to the effect of increased heart rate and attenuated pressure wave reflections [20, 41]. Second, PP amplification was highly related to gender in the entire population but not in the subgroup of hypertensive diabetic patients. After adjusting for height, hypertensive diabetic women did not presented marked decreased in PP amplification compared to men. Pulse pressure amplification appears as a complex, multifactorial hemodynamic phenomenon which highly accounts for the differences in CV risk between men and women [13, 43]. An important unresolved issue is the extent to which increased heart rate in hypertensive diabetic patients, and particularly in women, is related to an adaptive cardiac and vascular coupling in response to increased aortic stiffness.

In our study population, PP amplification and aortic stiffness were both independently associated with the presence of previous CV events in multivariate-adjusted analysis including age, gender, MAP, heart rate and CV risk factors. Pulse pressure amplification appears as a strong independent marker of the presence of established CV disease in our study population. Aortic stiffness and PP amplification were not interrelated which reinforce the concept that these markers of arterial damage might not be interchangeable for CV risk prediction.

Class-Effects of drugs on hemodynamic parameters

Mounting evidence suggest that hemodynamic parameters can be pharmacologically modulated [23]. More recently, interest has grown for pharmacological modulation of central PP and PP amplification [24]. Both heart rate [44, 45] and wave reflections [44, 46, 47] appear to account for the class-effect of antihypertensive drugs on PP amplification. In line with these previously published data, beta blocker and, to a lesser extent, ARBs or ACE inhibitor treatments were independently associated respectively with a negative and with a positive correlation with PP amplification in hypertensive diabetic patients. Above the effect on heart rate, beta blocker treatment was associated with lower PP amplification. With the exception of coronary heart disease, this result has to be considered for the choice of therapeutic strategy, in particular in women, given the clinical significance of PP amplification. None of antihypertensive drug classes were associated with aortic stiffness beyond MAP level in the present investigation.

Lipid-lowering drugs and drugs targeting glycaemic control have also been shown to modulate hemodynamic parameters [23]. However, we could not address an association between antidiabetic treatment or insulin therapy with hemodynamic parameters, possibly due to the relative small size of the diabetic population. Statin therapy, apart of the action on plasma cholesterol, may have pleiotropic effect on the arterial wall [48, 49]. However, an inverse relation was found between statin therapy and PP amplification in hypertensive diabetic patients. It has been shown that, at the beginning of treatment, statins may be associated with an increase in aortic PWV along with an increase in collagen content within the arterial wall [50]. Aortic stiffness and statin therapy were not yet correlated in the subgroup of hypertensive diabetic patients. We hypothesized that this drug prescription may reflect an increased arterial damage in the subgroup of hypertensive diabetic patients and does not necessarily imply any direct effect on amplification phenomenon in the current study.

However, the efficacy of statin therapy on hemodynamic parameters should remain an important issue, especially when treatment is started or the dose increased too late [51].

Limitations

Pharmacological remodeling of small and large arteries is considered as a long-lasting process. Duration of treatment under antihypertensive drug classes or under statin therapy has not been taken into account, because of a lack of informative data. This might explain why we could not address an association between drug classes and aortic stiffness in the present study, although evidence suggest that antihypertensive treatments improve arterial stiffness beyond their effect on BP [23]. Amplification phenomenon is considered as a multifactorial hemodynamic phenomenon, strongly related to heart rate and wave reflections. Thus, PP amplification may be easier to modulate under drug treatment combinations than aortic stiffness which implies established structural damage of the arterial wall. Finally, the heterogeneity among beta-blocker molecules has not been taken into account. Newer beta-blockers with a peripheral vasodilatory effect may act differently on PP amplification, reducing pressure wave reflection and thus partially counterbalance the effect of heart rate deceleration [52].

CONCLUSION

The principal finding of the present study is that aortic stiffness and PP amplification are not interrelated and are both independently correlated with the presence of previous CV events. These arterial markers may thus provide different and complementary information for CV risk. In particular, association of hypertension and diabetes did not impact PP amplification level although presence of disproportionately increased aortic stiffness. The present dissociation between these two hemodynamic parameters may be related to the effect

of increased heart rate observed in the presence of diabetes. Beyond BP control and independently of age-related modifications, hyperglycemia, but not heart rate, appears as an important determinant of increased aortic stiffness and should be taken into account for new and earlier therapeutic strategies targeting pressure pulsatility in high-risk patients. Gender influence on the role of autonomic nervous system in attenuating pressure wave reflections remains to be further established. A long-term follow-up is needed to evaluate the potential clinical significance of increased heart rate in the presence of diabetes, in men and women.

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CONFLICT OF INTEREST/DISCLOSURE

None.

REFERENCES

[1] Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321:412-419.

[2] Jonk AM, Houben AJ, de Jongh RT, Serné EH, Schaper NC, Stehouwer CD. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology (Bethesda) 2007; 22:252-260.

[3] Assmann G, Schulte H. The Prospective Cardiovascular Münster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. Am Heart J 1988; 116:1713-1724.

[4] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood

glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560-2572.

[5] Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545-2559.

[6] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360:129-139.

[7] Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic Pulse Wave Velocity as a Marker of Cardiovascular Risk in Hypertensive Patients. Hypertension 1999; 33:1111-1117.

[8] De Ciuceis C, Porteri E, Rizzoni D, Rizzardi N, Paiardi S, Boari GE, et al. Structural Alterations of Subcutaneous Small-Resistance Arteries May Predict Major Cardiovascular Events in Patients With Hypertension. Am J Hypertens 2007; 20:846-852.

[9] Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002; 106:2085-2090.

[10] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321:405-412.

[11] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55:1318-1327.

[12] Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014; 63:636-646.

[13] Benetos A, Thomas F, Joly L. Pulse pressure amplification: a mechanical biomarker of cardiovascular risk. J Am Coll Cardiol 2010; 55:1032-1307.

[14] Safar ME, London GM, Asmar R, Frohlich ED. Third Workshop on Structure and Function of Large Arteries: Part I. Recent Advances on Large Arteries in Hypertension. Hypertension 1998; 32:156-161.

[15] Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

[16] Segers P, Mahieu D, Kips J, Rietzschel E, De Buyzere M, De Bacquer D, et al. Amplification of the Pressure Pulse in the Upper Limb in Healthy, Middle-Aged Men and Women. Hypertension 2009; 54:414-420.

[17] McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe CV, et al. Central Pressure: Variability and Impact of Cardiovascular Risk Factors. The Anglo-Cardiff Collaborative Trial II. Hypertension 2008; 51:1476-1482.

[18] Cecelja M, Chowienczyk P. Dissociation of Aortic Pulse Wave Velocity with Risk Factors for Cardiovascular Disease Other Than Hypertension: A Systematic Review. Hypertension 2009; 54:1328-1336.

[19] Tedesco MA, Natale F, Di Salvo G, Caputo S, Capasso M, Calabró R. Effects of coexisting hypertension and type 2 diabetes mellitus on arterial stiffness. J Human Hypertens 2004; 18:469-473.

[20] Protogerou AD, Blacher J, Mavrikakis M, Lekakis J, Safar ME. Increased pulse pressure amplification in treated hypertensive subjects with metabolic syndrome. Am J Hypertens 2007; 20:127-133.

[21] Cardoso CR, Ferreira MT, Leite NC, Salles GF. Prognostic impact of aortic stiffness in high-risk type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetes Care 2013; 36:3772-3778.

[22] Palatini P, Casiglia E, Pauletto P, Staessen J, Kaciroti N, Julius S. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension 1997; 30:1267-1273.

[23] Boutouyrie P, Lacolley P, Briet M, Regnault V, Stanton A, Laurent S, Mahmud A. Pharmacological modulation of arterial stiffness. Drugs 2011; 71:1689-1701.

[24] Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: Evidence for specific class-effects of antihypertensive drugs on pressure amplification. Curr Pharm Des 2009; 15:272-289.

[25] Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, et al. Hypertension and vascular dynamics in men and women with metabolic syndrome. J Am Coll Cardiol 2013; 61:12-19.

[26] Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998; 16:2079-2084.

[27] Lieber A, Millasseau S, Bourhis L, Blacher J, Protogerou A, Levy BI, Safar ME. Aortic wave reflection in women and men. Am J Physiol Heart Circ Physiol 2010; 299:H236-242.

[28] Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. Hypertension 1995; 26:485-490.

[29] Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 2010; 31:2338-2350.

[30] Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry

pressure: validation of generalized transfer function. Circulation 1997; 95:1827-1836.

[31] Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, et al. Determinants of Accelerated Progression of Arterial Stiffness in Normotensive Subjects and in Treated Hypertensive Subjects Over a 6-Year Period. Circulation 2002; 105:1202-1207.

[32] Zieman SJ, Melenovsky V, Kass DA. Mechanisms, Pathophysiology, and Therapy of Arterial Stiffness. Arterioscler Thromb Vasc Biol 2005; 25:932-943.

[33] Humphrey JD. Mechanisms of Arterial Remodeling in Hypertension: Coupled Roles of Wall Shear and Intramural Stress. Hypertension 2008;52:195-200.

[34] Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008; 51:527-539.

[35] Rogers MA, Aikawa E. Modifying vascular calcification in diabetes mellitus: contribution of O-GlcNAcylation. Circ Res 2014; 114:1074-1076.

[36] Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol 2008; 51:1377-1383.

[37] Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation 1999; 100:1387-1393.

[38] Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, et al. Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. Hypertension 2013; 61:130-136.

[39] Gatzka CD, Kingwell BA, Cameron JD, Berry KL, Liang YL, Dewar EM, et al. Gender differences in the timing of arterial wave reflection beyond differences in body height. J Hypertens 2001; 19:2197-2203.

[40] Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, et al. Arterial Stiffness and Wave Reflection: Sex Differences and Relationship with Left Ventricular Diastolic Function. Hypertension 2012; 60:362-368.

[41] Vergnaud AC, Protogerou AD, Li Y, Czernichow S, Vesin C, Blacher J, Safar ME. Pulse pressure amplification, adiposity and metabolic syndrome in subjects under chronic antihypertensive therapy: The role of heart rate. Atherosclerosis 2008; 199:222-229.

[42] Albaladejo P, Copie X, Boutouyrie P, Laloux B, Déclère AD, Smulyan H, Bénétos A. Heart Rate, Arterial Stiffness, and Wave Reflections in Paced Patients. Hypertension 2001; 38:949-952.

[43] Regnault V, Thomas F, Safar ME, Osborne-Pellegrin M, Khalil RA, Pannier B, Lacolley P. Sex difference in cardiovascular risk: role of pulse pressure amplification. J Am Coll Cardiol 2012; 59:1771-1777.

[44] Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension 2010; 55:1314-1322.

[45] Pucci G, Battista F, Schillaci G. Effects of antihypertensive drugs on central blood pressure: new evidence, more challenges. Hypertens Res 2014; 37:10-12.

[46] Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113:1213-1225.

[47] London GM, Asmar RG, O'Rourke MF, Safar ME. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J Am Coll Cardiol 2004; 43:92-99.

[48] Orr JS, Dengo AL, Rivero JM, Davy KP. Arterial destiffening with atorvastatin in

overweight and obese middle-aged and older adults. Hypertension 2009; 54:763-768.

[49] Takagi H, Umemoto T. A low-density lipoprotein-dependent effect of atorvastatin upon the systolic blood pressure reduction: meta-regression analyses of randomized trials. Int J Cardiol 2013; 170:e14-16.

[50] Raison J, Rudnichi A, Safar ME. Effects of atorvastatin on aortic pulse wave velocity in patients with hypertension and hypercholesterolaemia: a preliminary study. J Hum Hypertens 2002; 16:705-710.

[51] Safar ME, Protogerou AD, Blacher J. Statins, central blood pressure, and blood pressure amplification. Circulation 2009; 119:9-12.

[52] Wehland M, Grosse J, Simonsen U, Infanger M, Bauer J, Grimm D. The effects of newer beta-adrenoceptor antagonists on vascular function in cardiovascular disease. Curr Vasc Pharmacol 2012; 10:378-390.

Table 1: Clinical and biological parameters of the study participants according to hypertensive and diabetic status.

	NT without diabetes (N= 59)	NT with diabetes (N= 30)	HTN without diabetes (N= 134)	HTN with diabetes (N=128)	HTN Effect p	Diabetes Effect p	Interaction p
Gender/ female (%)	25 (42)	16 (53)	52 (39)	53 (41)	0.38	0.54	0.52
Age (years)	59.3 ± 10.3	62.7 ± 8.1	62.7 ± 11.0	62.9 ± 10.3	**< 0.001**	0.89	0.37
BMI (Kg/m^2)	26.5 ± 5.0	27.43 ± 4.0	28.3 ± 4.6	29.9 ± 4.5	**< 0.001**	**0.001**	0.61
Smoking* (%)	35 (59)	13 (43)	49 (37)	55 (43)	**0.03**	0.98	0.08
Dyslipidemia (%)**	19 (32)	16 (53)	59 (44)	96 (75)	**0.04**	**< 0.001**	0.15
HTN duration (years)	-	-	11.7 ± 10.7	12.2 ± 9.2	-	-	-
Diabetes duration (years)	-	13.3 ± 8.1	-	15.6 ± 11.7	-	-	-
Carotid Plaque (%)	30 (51)	11 (37)	75 (56)	85 (66)	**0.03**	0.71	0.09
Previous CV event (%)	6 (10)	1 (3)	33 (25)	36 (28)	**0.001**	0.36	0.17
Glycated hemoglobin (%)	5.5 ± 0.3	8.0 ± 2.2	5.7 ± 0.4	7.4 ± 1.3	0.27	**< 0.001**	**0.006**
Creatinine clearance§	84.9 ± 19.8	85.2 ± 21.5	77.2 ± 20.8	75.4 ± 21.6	**0.001**	0.50	0.71
Microalbuminuria §§ (%)	2 (3)	5 (17)	16 (12)	34 (27)	**0.04**	**0.001**	0.68

NT, normotensives; HTN, hypertension; BMI, Body Mass Index; * Past and current smokers;

** Patients receiving lipid lowering medication or classified as dyslipidemic; CV, cardiovascular;

§ Creatinine clearance using MDRD formula; §§ Microalbuminuria defined as urinary albumin excretion of 30-300 mg/day.

Table 2: Hemodynamic parameters of the study participants according to hypertensive and diabetic status.

	NT without Diabetes (N= 59)	NT with Diabetes (N= 30)	HTN Without Diabetes (N= 134)	HTN with Diabetes (N=128)	HTN Effect p	Diabetes Effect p	Interaction p
Heart rate (bpm)	69 ± 10	71 ± 11	68 ± 11	74 ± 11	0.27	**< 0.001**	0.13
Brachial SBP (mm Hg)	127 ± 12	128 ± 13	137 ± 14	139 ± 15	**< 0.001**	0.6	0.53
Brachial DBP (mm Hg)	78 ± 10	76 ± 9	80 ± 10	78 ± 9	0.10	0.19	0.96
Central SBP (mm Hg)	118 ± 14	115 ± 11	126 ± 14	125 ± 14	**< 0.001**	0.91	0.40
Central DBP (mm Hg)	79 ± 11	77 ± 9	80 ± 10	79 ± 8	0.10	0.21	0.87
Mean arterial BP (mm Hg)	95 ± 10	93 ± 9	99 ± 10	99 ± 9	**< 0.001**	0.78	0.73
PP amplification	1.31 ± 0.17	1.38 ± 0.18	1.29 ± 0.15	1.36 ± 0.16	0.88	**< 0.001**	0.89
Pulse wave velocity (m/s)	8.9 ± 1.4	9.5 ± 2.1	10.3 ± 2.5	11.6 ± 2.6	**< 0.001**	**< 0.001**	0.24

NT, normotensives; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; PP, pulse pressure.

Table 3: Multivariate linear regression: determinants of aortic PWV and PP amplification in the study population (N=351).

	Aortic PWV			PP amplification		
	Coefficient	**SE**	**p**	**Coefficient**	**SE**	**p**
Age	0.12	0.01	**< 0.001**	-0.002	0.001	**< 0.001**
MAP	0.06	0.01	**< 0.001**	-0.003	0.001	**< 0.001**
Heart rate	0.03	0.01	**0.001**	0.01	0.001	**< 0.001**
Gender (Male)	0.07	0.21	0.75	0.06	0.02	**< 0.001**
Height	-	-	-	0.002	0.001	**0.02**
Diabetes-HTN Status*						
• **Diabetes only**	0.87	0.44	**0.047**	0.04	0.03	0.11
• **HTN only**	0.71	0.31	**0.020**	0.01	0.02	0.65
• **Both HTN & Diabetes**	1.73	0.32	**< 0.001**	0.03	0.02	0.18
	R^2= 41%			**R^2= 46%**		

HTN, hypertension; PWV, pulse wave velocity; PP, pulse pressure; MAP, mean arterial pressure.
* "neither diabetes nor hypertension" is considered as the reference group.

Table 4: Multivariate linear regression: determinants of aortic PWV and PP amplification in hypertensive diabetic patients (N=128).

	Aortic PWV			PP amplification		
	Coefficient	**SE**	**p**	**Coefficient**	**SE**	**p**
Age	0.13	0.02	**< 0.001**	-0.002	0.001	**0.02**
MAP	0.02	0.02	0.28	-0.003	0.001	**0.006**
Heart rate	0.02	0.02	0.40	0.008	0.001	**<0.001**
Gender (Male)	0.02	0.40	0.96	0.02	0.03	0.52
Height	-	-	-	0.003	0.002	0.07
Glycated Hemoglobin	0.32	0.16	**0.04**	-	-	-
	R^2= 28%			**R^2= 45%**		

PWV, pulse wave velocity; PP, pulse pressure; MAP, mean arterial pressure;
Glycated Hemoglobin level was not significantly correlated with PP amplification in multivariate analysis (p=0.55).

Table 5: Determinants of the presence of previous cardiovascular events in the study population (N=351).

Previous cardiovascular events	OR	95% CI	P-value
Age	0.96	0.93 – 1.03	0.32
Gender (Male)	**13.16**	2.34 – 74.01	**< 0.001**
Dyslipidaemia	**2.82**	1.10 – 8.10	**0.04**
Carotid Plaque	**3.57**	1.33 – 10.77	**0.016**
Smoking	1.02	0.43 – 2.40	0.97
MAP	**0.94**	0.90 – 0.99	**0.012**
Heart rate	**0.93**	0.88 – 0.97	**0.013**
Diabetes-HTN Status*			
• **Diabetes only**	0.31	0.01 – 2.79	0.35
• **HTN only**	1.12	0.29 – 4.81	0.87
• **Both HTN & Diabetes**	1.92	0.48 – 8.63	0.37
Pulse pressure amplification	**0.02**	0.001 – 0.62	**0.03**
Aortic Pulse Wave Velocity	**1.2**	1.01– 1.44	**0.04**
AIC= 197			

MAP, mean arterial pressure; HTN, hypertension; * "neither diabetes nor hypertension" is considered as the reference group.

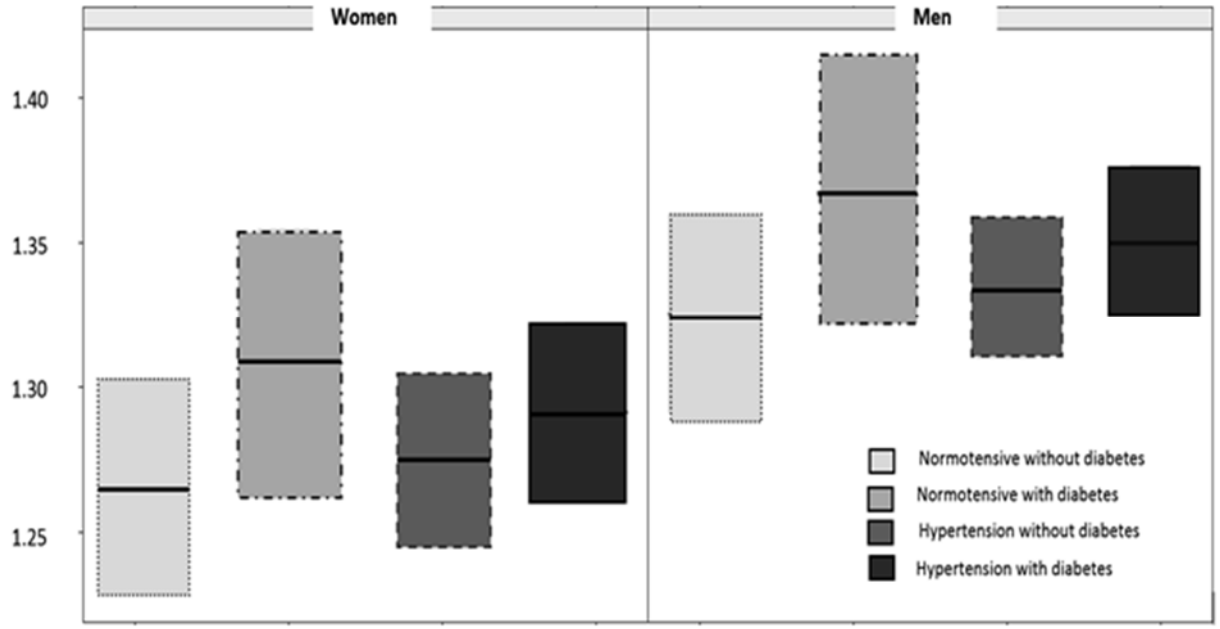
Table S1: Multivariate linear regression: PP amplification and drug treatment in hypertensive diabetic patients.

PP amplification	Coefficients	SE	P-value
Age	-0.002	0.001	**0.05**
MAP	-0.003	0.001	**0.005**
Heart rate	0.007	0.001	**< 0.001**
Gender (Male)	0.02	0.03	0.42
Height	0.003	0.002	0.10
Drug treatment			
ACE or ARBS	0.06	0.04	**0.07**
Beta blockers	-0.05	0.02	**0.04**
Statin	-0.06	0.02	**0.02**
R^2= 49%			

MAP, mean arterial pressure; PP, pulse pressure; ARBs, Angiotensin II receptor blockers; ACE inhibitors, angiotensin- converting-enzyme inhibitors.

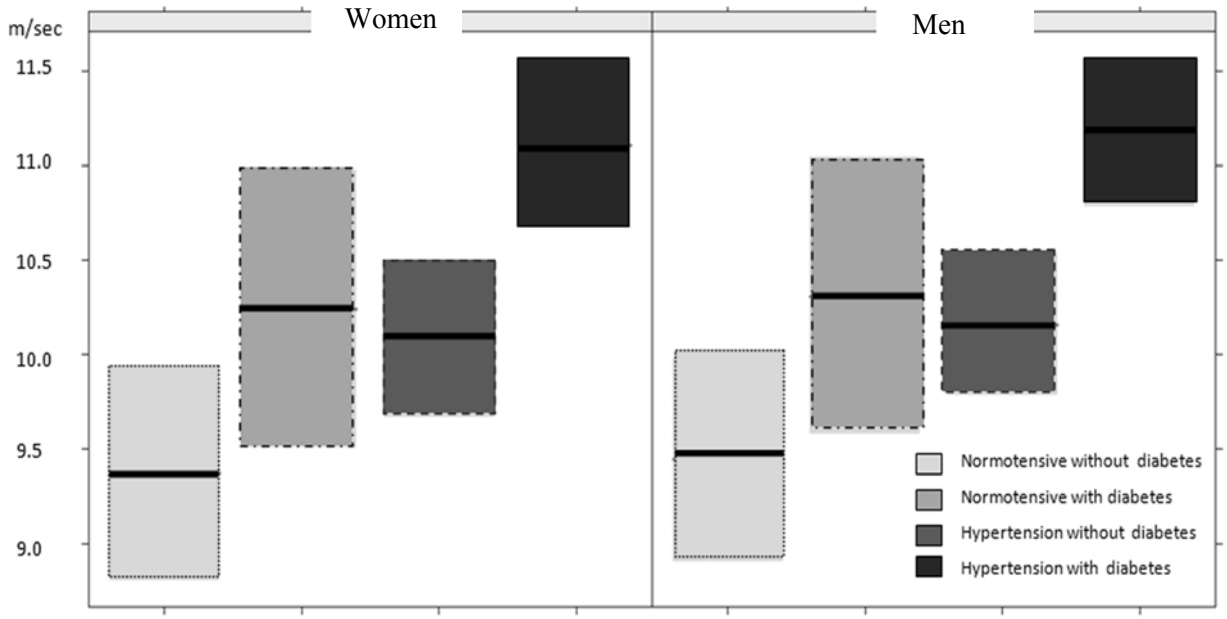
Figure 1: Pulse pressure amplification and aortic pulse wave velocity, in women and men.

Pulse pressure amplification



In overall cohort: p status = 0.28, p gender < 0.001; Mean values are presented with 95% confidence interval, after adjusting for age, height, mean arterial pressure and heart rate.

Aortic Pulse wave velocity



In overall cohort: p status < 0.001, p gender = 0.75; Mean values are presented with 95% confidence interval, after adjusting for age, mean arterial pressure and heart rate.

3.2.3 Conclusion de l'article 6

Les deux paramètres hémodynamiques artériels, rigidité aortique et amplification de la pression pulsée, n'étaient pas corrélés aussi bien dans la population d'étude que dans le groupe des patients hypertendus diabétiques. Ces deux paramètres hémodynamiques étaient associés de manière indépendante à la présence d'une maladie cardiovasculaire établie dans un modèle multivarié prenant en compte l'âge, la pression moyenne, la fréquence cardiaque et les facteurs de risque cardiovasulaire. La rigidité aortique et l'amplification de la pression pulsée ne doivent donc pas être considérés comme des paramètres hémodynamiques interchangeables pour l'estimation du risque cardiovasculaire. Dans notre population d'étude, l'association hypertension artérielle et maladie diabétique était définie par un profil hémodynamique particulier. Malgré la présence d'une rigidité aortique majorée, le phénomène d'amplification de la pression pulsée n'apparaissait pas atténué en comparaison aux patients non hypertendus non diabétiques. La fréquence cardiaque plus élevée en présence d'un diabète pourrait rendre compte du maintien du phénomène d'amplification, limitant ainsi le niveau de pression pulsée centrale. En accord avec les données de la littérature, le sexe représentait un paramètre fortement corrélé au phénomène d'amplification dans la population totale d'étude, au-delà des différences de taille entre hommes et femmes. L'amplification de la pression pulsée était plus atténuée chez les femmes. Cependant, dans le groupe des patients hypertendus diabétiques, cette différence n'était plus significative. En présence d'un diabète, le rôle de la fréquence cardiaque dans le maintien du phénomène d'amplification reste à étudier, chez les hommes et les femmes.

Dans la population d'étude, la rigidité aortique a été corrélée positivement, de manière attendue, à l'âge, à la pression artérielle moyenne, à la fréquence cardiaque, à la maladie hypertensive et à la maladie diabétique de manière indépendante. Chez les patients

hypertendus diabétiques seuls l'âge et le niveau d'hémoglobine glyquée, et non la pression artérielle moyenne ou à la fréquence cardiaque, étaient corrélés de manière indépendante à la rigidité aortique. Les mécanismes physiopathologiques entraînant un vieillissement accéléré des gros troncs artériels apparaissent donc différents chez les patients hypertendus avec et sans diabète (151). Un niveau avancé de rigidité aortique, secondaire au retard à l'initiation du traitement antidiabétique ou au retard du contrôle glycémique, peut expliquer en partie le risque majoré d'événements cardiovasculaires malgré un traitement médicamenteux optimal (141-145). De plus, le taux de glycémie pourrait rester un déterminant important de la rigidité aortique au cours du vieillissement. De nouvelles stratégies thérapeutiques, ciblant les paramètres glycémiques et instaurées de manière plus précoce, avant le diagnostic biologique de diabète, devraient être étudiées parallèlement à l'évolution de la rigidité aortique et à l'incidence des événements cardiovasculaires (152).

L'absence d'atténuation du phénomène d'amplification de la pression pulsée chez les patients hypertendus diabétiques, malgré une rigidité aortique majorée, pourrait être rapportée à une fréquence cardiaque plus élevée chez ces patients. En effet, les patients hypertendus diabétiques présentaient une amplification de la pression pulsée plus importante en comparaison aux patients non hypertendus non diabétiques (groupe contrôle) après ajustement sur l'âge, le sexe et la pression artérielle moyenne. Cette différence pour le phénomène d'amplification n'était plus significative après ajustement sur la fréquence cardiaque. Celle-ci était plus élevée chez les hypertendus diabétiques, en comparaison au groupe contrôle, indépendamment de l'âge, du sexe, de la pression artérielle moyenne et de la prise d'un traitement bétabloquant. La fréquence cardiaque pourrait alors représenter un mécanisme adaptatif en réponse à une rigidité aortique majorée, pour le maintien d'un couplage optimal entre le ventricule gauche et l'aorte.

Concernant les stratégies antihypertensives chez les patients hypertendus diabétiques, aucune corrélation n'a été retrouvée entre la rigidité aortique et les différentes classes thérapeutiques. Le phénomène d'amplification apparaissait modulé par la présence d'inhibiteur du système rénine-angiotensine, de bétabloquant et de statine. Bien que restant à la limite de la significativité, un traitement par IEC ou ARA 2 était associé positivement au phénomène d'amplification, indépendamment du niveau de pression artérielle moyenne. Une corrélation négative a été observée entre la prise d'un traitement par bétabloquant et l'amplification de la pression pulsée, indépendamment de la fréquence cardiaque. Ces résultats restent en accord avec ceux de la littérature soulignant l'effet de classe des molécules antihypertensives sur le phénomène des ondes de réflexion (100). A l'exception de la maladie coronaire, la relation inverse entre traitement bétabloquant et amplification devrait être prise en considération dans la stratégie thérapeutique antihypertensive en présence d'un diabète.

Le traitement par statine a également été associé dans la littérature à des effets pléiotropiques sur les paramètres artériels (153, 154). Une relation inverse a cependant été mise en évidence entre la prise de ce traitement et l'amplification de la pression pulsée chez les patients hypertendus diabétiques de notre étude. Ce résultat ne préjuge pas de l'existence d'une relation de cause à effet. Et plus particulièrement, la prescription d'un traitement par statine peut être le reflet d'une maladie artérielle évoluée ou d'une prévention cardiovasculaire secondaire. Cependant, la question du bénéfice d'un traitement par statine sur les paramètres hémodynamiques artériels devrait rester d'actualité, en particulier lorsque le traitement est débuté ou la dose majorée tardivement (155).

La rigidité aortique et la disparition du phénomène d'amplification sont des facteurs prédictifs de mortalité (92,101). Dans notre population d'étude, les deux paramètres hémodynamiques, amplification de la pression pulsée et VOP carotido-fémorale, étaient corrélés de manière

indépendante aux antécédents cardiovasculaires, alors que l'âge, la présence d'un diabète ou d'une hypertension artérielle n'ont pas atteint la significativité statistique. Ces résultats suggèrent d'une part que l'amplification de la pression est un puissant marqueur de la présence d'une maladie artérielle établie. De plus, la rigidité aortique et l'amplification de la pression ne sont pas des paramètres hémodynamiques interchangeables et peuvent donc fournir des informations complémentaires pour le risque cardiovasculaire. L'amplification de la pression pulsée est un paramètre hémodynamique multifactoriel pouvant être plus facilement modulable sous traitement, indépendamment de la baisse tensionnelle périphérique.

3.3 Paramètres hémodynamiques artériels et infection VIH (Article 7)

3.3.1 Introduction de l'article 7

L'introduction de la thérapie antirétrovirale combinée a permis une baisse importante de la morbidité et de la mortalité liée au sida. Cependant, les patients avec infection VIH présentent toujours un excès de mortalité par rapport à la population générale. Les maladies cardiovasculaires sont l'une des principales causes de décès dans cette population (156). L'enquête nationale française, décrivant les causes de décès chez les patients avec infection VIH en 2010 et leur évolution depuis 2000, a mis en évidence une augmentation de la proportion des causes cardiovasculaires dans la tranche d'âge moyenne, entre 40 et 59 ans (157). La réplication virale, le nadir des cellules T CD4 et la restauration immunitaire incomplète sont corrélées au risque d'infarctus du myocarde (158). L'association fréquente aux autres facteurs de risque cardiovasculaire, en particulier le tabagisme, et l'exposition prolongée aux effets dysmétaboliques des thérapies antirétrovirales rendent également compte du risque cardiovasculaire majoré (159).

Les résultats d'études de cohorte prospectives récentes mettent en évidence une espérance de vie comparable entre les patients conservant une charge virale indétectable et un taux de cellules T CD4 ≥ 500 cellules/mm^3 sous thérapie antirétrovirale et la population générale (160). Par contre, les patients ayant un compte de T CD4 inférieur à 500 cellules/mm^3 présentent un taux de mortalité plus élevé, même si la réplication virale est contrôlée. Les causes les plus fréquentes de décès sont les maladies cardiovasculaires et la mort subite. Il est donc nécessaire d'améliorer l'estimation du risque cardiovasculaire et la stratégie de prévention dans cette population. En pratique clinique, l'estimation du risque cardiovasculaire chez les patients avec infection VIH fait appel à des modèles classiques de prédiction du risque. Ces derniers ne prennent pas en compte les marqueurs spécifiques de l'infection, en particulier la charge virale et le taux de CD4. De plus, en raison de leur incapacité à intégrer l'intensité et le niveau d'exposition aux facteurs de risque, ces modèles peuvent sous-estimer le risque chez les patients jeunes et d'âge moyen ou les patients présentant un syndrome métabolique (161).

Plusieurs études antérieures ont mis en évidence une rigidité aortique significativement plus élevée en présence d'une infection VIH (162,163). L'association entre maladie artérielle et infection VIH pourrait cependant ne plus être significative après ajustement aux facteurs de risque classiques, en particulier le tabagisme et l'hypertension artérielle (164). Des résultats parfois contradictoires existent au sujet de la relation entre paramètres immuno-virologiques, rigidité artérielle et ondes de réflexion.

Notre objectif a été d'étudier la relation entre paramètres immuno-virologiques et hémodynamiques artériels chez des patients présentant une charge virale indétectable mais potentiellement à risque cardiovasculaire. De plus, le déficit en vitamine D, anomalie

biologique fréquente chez ces patients, est associée à la morbidité cardiovasculaire et à la mortalité toutes causes et cardiovasculaire aussi bien dans la population générale qu'en présence d'une infection VIH (165,166).

Afin de mieux évaluer les altérations artérielles et leurs déterminants, une étude observationnelle transversale a été menée à l'Hôpital Hôtel-Dieu. Les corrélations entre la VOP carotido-fémorale, l'AIx carotidien et l'amplification de la pression pulsée avec les paramètres liés à l'infection VIH et le statut en vitamine D ont été étudiées. Entre septembre 2010 et juillet 2011, 178 patients (143 hommes et 35 femmes) régulièrement suivis à l'Hôtel-Dieu, en prévention primaire cardiovasculaire, ont été consécutivement inclus dans cette étude après avoir donné leur consentement. Les explorations hémodynamiques ont été réalisées lors de l'hôpital de jour pour bilan immuno-virologique et cardiovasculaire.

3.3.2 Article 7

Yannoutsos A, Agnoletti D, Peroz-Froz J, Ly C, Lelong H, Topouchian J, Gilquin J, Boucly S, Rostane H, Safar M.E, Viard JP, Blacher J.

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Structural and Functional Arterial Parameters, Immunovirological Control and Vitamin D in HIV-Infected Patients

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Abstract

Objective: HIV-infected patients still experience higher Cardiovascular (CV) mortality rates, even if an adequate viral suppression is achieved. In addition, vitamin D insufficiency, a common condition in HIV-infected patients, is increasingly associated with CV risk. We therefore aim to investigate relationships between immunological parameters, antiretroviral therapy, plasma vitamin D and arterial parameters, including aortic stiffness and wave reflections, in HIV-infected patients who achieved viral suppression but possibly remain at increased CV risk.

Methods: We conducted a cross-sectional study including 178 middle-aged HIV-infected patients. HIV infection was controlled in a large number of participants, representative of a real-world setting. In addition to carotid Intima Media Thickness (IMT), central hemodynamic parameters involved aortic Pulse Wave Velocity (PWV), carotid Augmentation index (AIx) and Pulse Pressure Amplification (PPA) measured noninvasively using applanation tonometry.

Results: Aortic PWV was slightly but unsignificantly higher than the theoretical values obtained in general population according to age and blood pressure, and was independent of HIV-related parameters. In univariate and multivariate analyses, carotid AIx was positively correlated with current CD4 T-cell count and PPA was positively correlated with vitamin D, independently of other confounders. No HIV-related parameters or vitamin D entered the multivariate analysis of carotid IMT / plaque.

Conclusion: In our chronically treated population, HIV infection was not associated with increased aortic stiffness but with a positive correlation between current CD4 T-cell count and degree of AIx, suggesting that patients with higher CD4 T-cell count may have higher wave reflections. The positive correlation between vitamin D and PPA suggests that vitamin D deficiency may be independently associated with altered central hemodynamics in well controlled HIV-infected patients. These findings should be confirmed in prospective studies.

Keywords: HIV infection; Aortic stiffness; Pulse wave velocity; Arterial wave reflections; Pulse pressure amplification; Cardiovascular disease risk factors; Plasma vitamin D

Introduction

Combined antiretroviral therapy has led to a substantial decline in AIDS-related morbidity and mortality [1,2]. Mortality and overall incidence of opportunistic infections declined markedly in 1996 and early 1997 with the introduction of combination therapy including protease inhibitor (PI) [1]. In the mid-2000s, despite a near-normal life expectancy, HIV-infected patients presented excess mortality rates compared to the general population; the estimated median remaining lifetime of a 25-year-old HIV-infected individual was 39 years compared to 51 years for a 25-year-old HIV-uninfected person [3]. Patterns of co-morbidities and causes of death have changed. More specifically, cardiovascular (CV) diseases became one of the leading causes of death in this population [2]. The French national survey, describing the causes of death among HIV-infected patients in France in 2010 and their evolution since 2000, has highlighted an increase in the proportion of CV deaths in middle-aged patients, between 40 and 59 years [4]. HIV replication and incomplete immune restoration or persistent immune activation (as reflected by a high CD8 cell count or a CD4/CD8 ratio<1) were independently related to the risk of myocardial infarction [5]. High burden of traditional risk factors and cumulative exposure to Highly Active Antiretroviral Therapy (HAART), especially to PI, may also account for increased CV risk [5,6].

Recently, evidence from large prospective cohort studies has highlighted that HIV-infected patients with viral suppression and who maintained or had recovered CD4 T-cell counts of at least 500 cells/mm^3 in the HAART era, had no evidence for a raised risk of death compared with the general population [7]. In contrast, patients with CD4 T-cell counts less than 500 cells/mm^3 still experienced

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higher mortality rates, even if viral suppression was achieved [7]. The commonest causes of death were CV disease and sudden death, highlighting the need for improved CV risk prediction and prevention in this population [7].

Routine CV risk prediction in HIV-infected patients is estimated with conventional risk prediction models but these tools do not include HIV-specific markers. Furthermore, because of their inability to integrate individual levels of intensity and exposure to all CV risk factors, such models of risk stratification may underestimate CV risk in young and middle-aged HIV-infected patients or those with the metabolic syndrome [8]. Nevertheless, several previous studies have highlighted greater structural and functional arterial damage in HIV-infected patients compared to uninfected individuals [9,10]. Rather than increased carotid intima-media thickness (IMT) [11,12], carotid to femoral pulse wave velocity (PWV), a measure of aortic stiffness, has allowed to gather the largest amount of evidence regarding added predictive value for CV risk, over and above traditional risk factors, and persisting even after adjustment for carotid IMT and carotid stiffness [13-15]. Central augmentation index (AIx), which is considered a transit time-dependent marker of intensity of arterial wave reflections, and pulse pressure (PP) amplification, also bring independent predictive value for CV events and mortality [16,17]. However, such parameters may be difficult to interpret in HIV-infected patients because the association between HIV infection and greater arterial stiffness or wave reflections may be no longer significant after adjustment for classical risk factors, especially smoking and hypertension [18].

Little and inconsistent evidence exists about the relationship between virological and immunological parameters and arterial stiffness and wave reflections in HIV-infected patients [19-21]. Our aim was to investigate the relationships between immune status and arterial parameters, including aortic stiffness and wave reflections, in middle-aged HIV-infected patients who achieved viral suppression but possibly remain at increased CV risk.

In addition, vitamin D insufficiency is a common condition [22] and has been associated with CV morbidity [23] and increased all-cause and CV mortality in the general and HIV-infected populations [24,25]. In order to better assess CV damage and its determinants in HIV-infected patients, we therefore investigated cross-sectional correlations between structural and functional arterial parameters, HIV-related factors and vitamin D status.

Methods

Study population

Among HIV-infected persons routinely followed up for immunovirological, CV, metabolic, and bone health parameters at the Paris Hôtel-Dieu hospital, 178 consecutive HIV-1-infected patients in primary CV prevention, 143 men and 35 women, were included in this cross-sectional study, between September 2010 and July 2011. Exclusion criteria were age under 18, acute medical conditions and atrial fibrillation. No patient had any active AIDS-related condition at inclusion in the study. No patient had a past or present history of endocarditis and no patient had any active bacterial infection at the time of study. No active intravenous drug user was included in the study. Patients provided informed consent for additional hemodynamic measurements and data collection. The study was approved by our institutional review board.

Clinical and laboratory parameters

We recorded data on HIV clinical classification, comorbidities, CV risk factors, current medications including statin and antihypertensive therapy, past and present ART regimens, duration of ART and nadir CD4 T-cell count. Laboratory parameters, including plasma glucose and HbA1C, cholesterol (total, LDL and HDL) and triglycerides, renal function, 25-hydroxyvitamin D (25OHD), CD4 and CD8 T-cell counts, and viral load (HIV RNA copies/ml) were determined on the day of hemodynamic measurements.

The metabolic syndrome was defined by the presence of at least three out of the five following criteria according to the Third Report of the National Cholesterol Education Program: 1) SBP above 130 mmHg and/or DBP above 85 mmHg, or treated hypertension, 2) waist circumference over 102 cm in men and 88 cm in women, 3) triglyceride concentration above 1.69 mmol/l, 4) HDL-cholesterol concentration below 1.04 mmol/l in men and 1.29 mmol/l in women, and 5) fasting plasma glucose concentration above 6.1 mmol/l.

Central and peripheral arterial parameters

Hemodynamic measurements were performed in the morning after an overnight fast, in supine position. Peripheral Systolic BP (SBP) and diastolic BP (DBP) were measured at both arms using an automatic BP monitor (OMRON 705 CP II IT) after 5 minutes of rest. Five measurements 2 minutes apart were averaged. Heart rate was recorded.

After BP determination, structural and functional parameters of the arterial wall were performed noninvasively by applanation tonometry: this measure provides an accurate profile of intra-arterial BP curves, with a continuous beat-to-beat monitoring, by applying a piezoelectric sensor, the tonometer, over an artery. The reproducibility of these measurements, in our group and in others, has been previously published in detail [26,27].

Carotid-femoral PWV is considered as the gold standard direct and non invasive test for aortic stiffness assessment [28]. The aortic PWV measurement was performed using an automatic device, the SphygmoCor, which allowed on-line pulse wave recording and automatic calculation of PWV. Aortic PWV was calculated as the distance between carotid and femoral arteries, divided by the time interval between the feet of the pressure waves at the recording sites. Pulse waveforms were obtained transcutaneously using applanation tonometry over the common carotid and femoral arteries. The carotid-femoral pathway was the direct distance measured using a standard compass system between the carotid and femoral measurement sites. Direct distance was multiplied by a scaling factor of 0.8 to obtained "real PWV" as previously described [29]. Transit time was assessed as the time difference between two characteristic points ('foot of the wave') on carotid and femoral waveforms at the measurement sites.

Central BP components (SBP, DBP and PP), were estimated by the pulse wave analysis of the common carotid artery. Pulse pressure amplification was defined as the brachial PP-to-carotid PP (B/C) ratio. Amplification of systolic and pulse pressures from central to peripheral sites depends on the timing and amplitude of the reflected waves. Normal values of PPA vary from 1.7 at less than 20 years of age to 1.2 at more than 80 years of age [16].

Augmentation index is estimated from the pulse waveform measured directly at the carotid artery. This index is defined as the pressure augmentation (which is the difference between the second

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and first systolic peaks) expressed as a percentage of PP. AIx is frequently used to assess wave reflection, and is affected by both timing and amplitude of the reflected waves. Carotid and aortic AIx are known to be strongly and positively correlated [30]. There is a non-linear relationship between normal vascular ageing and enhanced AIx, more marked in individuals under 50 [31]: in out-of-hospital community-based population considered to represent the normal population, AIx values vary from 1.6% at less than 10 years of age to 24.1% at more than 60 years of age [32].

Carotid IMT was determined ultrasonographically, in supine position, using Sigma 110 KONTRON and a 7.5-13 MHz linear array probe. Carotid arteries, abdominal aorta and limb arteries were scanned ultrasonographically for the detection of plaques and stenosis. Echocardiography was performed for left ventricular systolic and diastolic function study.

Statistical analysis

Statistics were performed with SAS software version 9.0 (SAS Institute, Cary, NC). A $p \leq 0.05$ was considered as statistically significant. We represented quantitative variables as mean ± standard deviation (±SD), or median (interquartile range, IQR) for non-normal variables. Qualitative variables are expressed as frequency and percentage.

Theoretical aortic PWV values in our study population were calculated by age category on the basis of Mean Arterial Pressure (MAP) according to The Reference Values for Arterial Stiffness' Collaboration study [29]. Mattace-Raso et al. provided normal and reference values for aortic PWV based on a large European population of 11092 non diabetic subjects without overt CV disease and without current treatment for hypertension or for dyslipidemia. The reference value population included subjects with a mean age of 50 years, with high normal or high BP, with dyslipidemia and/or smoking [29]. To test whether aortic PWV measured values in our study population are different from calculated theoretical values, we used the Mann-Whitney U test.

For regression analysis non-normal variables were log transformed. Multiple regression analyses were performed on PWV, AIx, PPA, and IMT; logistic regression was done for the presence of carotid plaques. Regressions models were obtained by stepwise selection, containing all variables that were significantly correlated in univariate analysis and based on their physiopathological plausibility. Variables that entered the stepwise selection were age, MAP, heart rate, gender, diabetes, smoking status, waist circumference, plasma 25OHD level, PI treatment, nadir CD4 T-cell count and current CD4 T-cell count. For hemodynamic parameters, age and MAP were forced into the models. For AIx and PPA, heart rate and gender were also forced into the multivariate models [33-34].

Results

Clinical, biological and HIV-related parameters

Characteristics of the study population are summarized in Table 1. Patients were mostly men (80%), with a mean (± SD) age of 49 ± 9 years, and 49% were smokers (only 13% current smokers). More than a half (52%) presented with the metabolic syndrome. 5% of patients were diabetic, 22% were on antihypertensive therapy and 20% on a statin. Median (IQR) value for plasma 25 (OH) D level was 24 (15-34) ng/ml. 18% of patients had a history of AIDS-defining events and 76% were treated with PIs. 90% of patients had a viral load below 50 copies/ml and only 6% had a viral load of 400 copies/ml or more, which led to a very skewed distribution. Thus, we could not incorporate this variable in the statistical analysis. CD4 T-cell count was ≥500/mm^3, between 200-500/mm^3 and <200/mm^3 in 55%, 39% and 6% of patients, respectively.

Variables	N	Mean ± SD	Minimum	Maximum
Clinical and biological parameters				
Age, years	178	49 ± 9	21	79
Male gender, n (%)	178	143 (80)		
[a]BMI, kg/m^2	178	25 ± 4	16	42
Waist circumference, cm	178	91 ± 11	64	131
Metabolic syndrome, n (%)	148	77 (52)		
Current smokers, n (%)	162	21 (13)		
Former smokers, n (%)	162	59 (36)		
Anthihypertensive therapy, n (%)	176	39 (22)		
Statin therapy, n (%)	175	35 (20)		
Diabetics, n (%)	178	9 (5)		
Total cholesterol, mmol/L	145	5.33 ± 1.01	2.85	8.55
[b]HDL cholesterol, mmol/L	145	1.26 ± 0.44	0.50	4.40
25-hydroxyvitamin D*, ng/mL	153	24 (15-34)	5	68
HIV-related parameters				
[c]Duration of PI treatment, months*	120	84 (44-171)	0	361
Number of patients treated with PI, n (%)	157	120 (76)		
Nadir CD4 count*	169	236 (90-325)	0	889
Current CD4 count*	174	560 (402-740)	49	2174
Current CD8 count*	172	692 (549-914)	75	2101
CD4/CD8	131	0.88 ± 0.43	0.06	2.78
Nadir CD4 / current CD8*	167	0.339 (0.107-0.553)	0	.55
HIV classification: A or B, n (%)	141	116 (82)		
HIV classification: C, n (%)	141	25 (18)		

Continuous variable are presented as mean ± standard deviation (SD); discrete variables as number (percent)

*For skewness distribution, median (interquartile range) is presented;

[a]BMI: Body Mass Index; [b]HDL: High-density Lipoprotein; [c]PI: Protease Inhibitor.

Table 1: Clinical, biological and HIV-related parameters.

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Central and peripheral arterial parameters

Arterial parameters of the study population are summarized in Table 2. Concerning peripheral hemodynamic parameters, median values (IQR) for brachial SBP, DBP, PP and MAP were 125.5(118-135) mmHg, 81(74-88) mmHg, 45.5(40-50) mmHg and 95(88-103) mmHg, respectively. Concerning central hemodynamic parameters, median values (IQR) for carotid SBP, DBP and PP were 113(105-124) mmHg, 81(75-88) mmHg and 33(28-38) mmHg, respectively. Median value (IQR) for carotid-femoral PWV in our study population was 8.3(7.5-9.5) m/sec, which was slightly higher than the theoretical carotid-femoral PWV calculated by age category on the basis of MAP [median (IQR): 8.0(7.4-9.1) m/sec]. However, the difference between measured and calculated theoretical aortic PWV did not reach significance (Mann-Whitney U test, p=0.09). The mean value (±SD) for carotid AIx and PPA were 1.0 ± 18.6% and 1.38 ± 0.20%, respectively. Concerning ultrasonographic measurement, the mean value (±SD) for carotid IMT was 0.738 ± 0.152 mm and 11% of patients had at least one carotid plaque.

Variables	N	Mean ± SD	Minimum	Maximum
Brachial SBP*[a], mmHg	174	125.5(118-135)	95	198
Brachial DBP*[b], mmHg	174	81(74-88)	61	121
Brachial PP*[c], mmHg	174	45.5(40-50)	25	91
Heart rate, bpm	177	69 ± 12	42	107
MAP*[d], mmHg	161	95(88-103)	73	146
Carotid SBP*, mmHg	161	113(105-124)	89	205
Carotid DBP*, mmHg	161	81(75-88)	61	120
Carotid PP*, mmHg	161	33(28-38)	21	97
cf-PWV*[e] †, m/s	173	8.3 (7.5-9.5)	5.8	16.9
Theoretical PWV *‡, m/s	174	8.0 (7.4-9.1)	5.6	13.5
Carotid AIx[f], %	161	1.0 ± 18.6	-50.0	42.6
Pulse pressure amplification, %	156	1.38 ± 0.20	1.02	1.96
Carotid plaque, n (%)	158	18(11)		
IMT[g], mcm	173	738 ± 152	460	1405

Continuous variable are presented as mean ± standard deviation (SD); discrete variables as number (percent);

*For skewness distribution, median (interquartile range) is presented;

†Calculated as direct distance divided by transit time multiplied by 0.8;

‡Calculated by age category on the basis of mean blood pressure; test for difference between cf-PWV and Calculated Theoretical PWV: Mann-Whitney U test; p=0.09; [a]SBP: Systolic Blood Pressure; [b]DBP: Diastolic Blood Pressure; [c]PP: Pulse Pressure; [d]MAP: Mean Arterial Pressure; [e]cf-PWV: Carotid-femoral Pulse Wave Velocity; [f]AIx: Augmentation Index; [g]IMT: Intima-media thickness.

Table 2: Central and peripheral arterial parameters.

Determinants of central arterial parameters

Multivariate regression models analysing factors independently correlated with central arterial parameters are summarized in table 3. Age (p<0.0001), MAP (p<0.0001) and diabetic status (p=0.021) were positively correlated with carotid-femoral PWV. Age (p<0.0001), gender (p<0.0001), MAP (p<0.0001), and CD4 T-cell count (p=0.012) were positively correlated with carotid AIx, whereas heart rate (p<0.0001) was negatively correlated. A positive and linear correlation between vitamin D and PPA (n=133, r=0.18, p=0.04) (Figure 1) persisted in the multiple regression analysis independently of the other cofactors as shown in Table 3. Gender (p<0.0001) and MAP (p=0.001) were negatively correlated with PPA, whereas vitamin D (p=0.042) and heart rate (p<0.0001) were positively correlated. Age was not independently associated with PPA in our study population.

		coefficient	SE	partial R^2	P value
PWV*[a]					
	Age	0.006	0.001	0.090	<0.0001
	Mean arterial pressure*	0.745	0.099	0.266	<0.0001
	Diabetes	0.139	0.060	0.033	0.021
	Adjusted R^2			0.371	
AIx[b]		coefficient	SE	partial R^2	P value
	Age	0.487	0.121	0.099	<0.0001
	Mean arterial pressure*	63.941	9.289	0.244	<0.0001
	Heart rate	-0.744	0.085	0.341	<0.0001
	Gender	18.913	2.644	0.258	<0.0001
	Current CD4 count*	15.559	6.133	0.042	0.012
	Adjusted R^2			0.537	
PPA[c]		coefficient	SE	partial R^2	P value
	Age	-0.003	0.002	0.016	0.157
	Mean arterial pressure*	-0.445	0.133	0.081	0.001
	Heart rate	0.006	0.001	0.148	<0.0001
	Gender	-0.196	0.041	0.153	<0.0001
	25-hydroxyvitamin D*	0.059	0.029	0.032	0.042
	Adjusted R^2			0.283	

*Log-transformed; [a]PWV: Pulse Wave Velocity; [b]Aix: Augmentation Index; [c]PPA: Pulse Pressure Amplification; SE: Standard Error. Variables in the selection models were age, mean arterial pressure, heart rate, gender, diabetes, smoking status, waist circumference, 25-hydroxyvitamin D level, protease inhibitor treatment, nadir CD4 count, and current CD4 count.

Table 3: Determinants of aortic PWV, carotid AIx, and PPA.

Multivariate regression models analysing factors independently correlated with carotid IMT and carotid plaque are summarized in table 4. Age (p<0.0001), waist circumference (p<0.0001) and brachial SBP (p=0.031) were positively correlated with carotid IMT.

Age (p=0.013) and active or past smoking (p=0.027) were positively correlated with carotid plaques.

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Discussion

Our study population included middle-aged patients with controlled HIV infection in a large number of participants. Nearly all patients were virologically suppressed at the time of enrollment. Aortic PWV was slightly but unsignificantly higher than the reference values found in the general population according to age and BP. To the best of our knowledge, it is the first time that better immune status, as reflected by the CD4 T-cell count, was independently associated with a transit time-dependent marker of intensity of wave reflections. Plasma vitamin D and PPA were positively and independently correlated, suggesting that vitamin D deficiency may be associated with altered central hemodynamic parameters in well controlled HIV-infected patients.

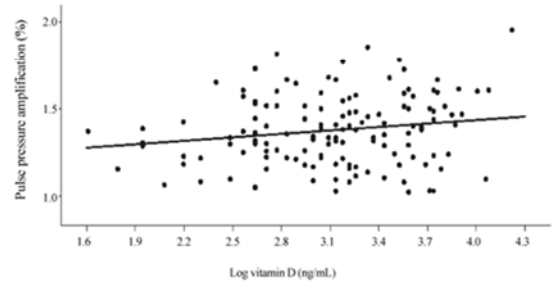

Figure 1: Correlation between 25-hydroxyvitamin D and pulse pressure amplification.

IMT[a]		Coefficient	SE	partial R^2	P value
	Age	0.006	0.002	0.076	<0.0001
	Waist circumference	0.005	0.001	0.079	<0.0001
	Brachial SBP[b]	0.002	0.001	0.028	0.031
	Adjusted R^2			0.206	
PLAQUE		**OR**	**95% CL**		**P value**
	Age	1.091	1.018	1.168	0.013
	Active or past smoking	2.245	1.096	4.598	0.027

[a]IMT: Intima-media Thickness; SBP[b]: Systolic Blood Pressure. Variables in the selection models were age, gender, brachial SBP, brachial DBP, diabetes, smoking status, waist circumference, 25-hydroxyvitamin D level, protease inhibitor treatment, nadir CD4 count, current CD4 count

Table 4: Determinants of carotid IMT and carotid plaque, respectively by multivariate linear and logistic regression.

Central arterial parameters and HIV infection

Aortic PWV: In our study population, mean ± SD age was 49 ± 9 years and the median (IQR) for carotid-femoral PWV was 8.3(7.5-9.5) m/s, which was slightly, but not significantly higher than the theoretical value which was 8.0(7.4-9.1) m/s according to the same age category, on the basis of MAP. Gold standard of normal and reference values for carotid-femoral PWV have been established previously based on an extensive data set obtained from 13 centers distributed across Europe, taking into account different methodological approaches for the determination of PWV [29]. Advancing age and distending pressure appear to be the most important determinants of altered buffering function resulting from aortic wall stiffening [33]. Aortic PWV reference values represent reliable estimates according to age and BP, allowing comparison with carotid-femoral PWV in our study population.

Consistent with our results, similar values of aortic PWV in HIV-infected patients in the HAART era compared to uninfected individuals were recently described [18,34]. Age, MAP and diabetic status were independent factors associated with increased aortic PWV in our study, with a strong correlation with age and MAP, findings highly consistent with the literature [33,35]. Contribution of other CV risk factors was nonsignificant and, interestingly, the presence of the metabolic syndrome, found in more than half of patients, did not enter the multiple regression analysis. In diabetic patients, longer past exposure to metabolic abnormalities may have a more marked impact on arterial stiffness.

A relationship between increased aortic stiffness and PI treatment in HIV-infected patients has been described in many observational studies, independently of conventional CV risk factors [9,20,36,37]. In our study population, neither HIV-related parameters or PI treatment entered the explicative model of aortic PWV, consistent with recently published results [32]. It should be noted that there is some controversy on whether PIs or other antiretroviral classes are indeed associated with CV risk [38]. Furthermore, interruption of ART has been associated with an increased risk of death and CV diseases comparatively to continuous treatment [39], suggesting that immunological benefits of drugs exceed the CV risk of metabolic side effects. In addition, we studied a group of middle-aged patients with extremely good virological control in a large number of participants and significant CV prevention implementation (only 13% were active smokers, 20% and 22% were on a statin and anti-hypertensive drugs, respectively). This may contribute to explain the discrepancy with previous studies showing higher PWV values in HIV-positive than in HIV-negative persons [9,36,37]. As age (in association with MAP) is the major determinant of aortic stiffness, the longitudinal follow-up of our study population would provide further evidence about early vascular aging and its determinants in HIV-infected patients with viral suppression.

Carotid AIx: CD4 T-cell count was the only independent HIV-related factor modulating carotid AIx, with a positive relation: increased carotid AIx was significantly associated with higher CD4 T-cell counts. The other independent factors modulating positively carotid AIx were age, MAP and female gender, consistent with the literature [34,40]. As expected, heart rate was negatively correlated with AIx [16].

The positive correlation found with current CD4 T-cell count seems in contrast with previous studies linking increased arterial stiffness with HIV infection. Little evidence and inconsistent results exist about the relationship between immunological parameters and arterial wave reflections among heterogeneous study populations. Ho et al. found, in a cross-sectional study of 134 middle-aged HIV-infected men, that increased aortic stiffness and wave reflections were independently related in multivariate models to a nadir CD4 T-cell count <350/mm^3 at HAART initiation [19]. In a cohort of 32 young HIV-infected

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patients treated with PIs and 32 HIV-uninfected subjects, Schillaci et al. [20] found that HIV infection was independently associated with increased aortic PWV and central AIx in multiple regression models. The authors suggested that immunodeficiency may account for vascular damage with earlier return of reflected waves at central level. However, the number of studied subjects was small. In contrast, Lazar et al. reported no association between HIV infection and increased arterial wave reflections in a homogeneous group of 276 HIV-infected and 67 HIV-uninfected Rwandan young women. In addition, current CD4 T-cell count among HIV-infected women did not correlate with central AIx or central PP [21].

In the present study, we found a strong positive association between carotid AIx and current CD4 T-cell count which persisted in multiple regression analysis independently of age, MAP, gender and heart rate. From a physiopathological viewpoint, AIx is a dependent measure of reflected wave transit time which may be related either to the compliance of the aorta or to increased heart rate. Increased heart rate is associated with a reduction in the time required for the backward pressure wave to return toward the heart without any change in aortic stiffness. Furthermore, central AIx may be an unreliable indicator of aortic stiffness in middle-aged or even older patients, relative wave reflections remaining unchanged or even reduced in elderly individuals whereas aortic stiffness is increased [41]. This positive and independent correlation between CD4 T-cell count and a transit time-dependent marker of intensity of wave reflections does not imply a causal relationship between higher CD4 T-cell counts and altered wave reflections. In HIV-infected patients without overt increased aortic stiffness, this positive correlation, which persisted independently of heart rate, might suggest that patients with higher CD4 T-cell count have simply a more distensible aorta. Indeed, impedance mismatch at the junction between a normally compliant aorta and carotid artery represents a protective mechanism which facilitates pressure wave reflection and limits the transmission of excessive pulsatile energy into the microcirculation. Of course, this interpretation must be confirmed in longitudinal follow-up with a matched control group. Finally, differences in clinical characteristics between our study population and the previously published cohorts have to be considered: we studied a group of middle-aged HIV-infected men and women, chronically treated and virologically suppressed at the time of enrollment, and without overt increased aortic stiffness.

Carotid IMT and carotid plaque

Carotid plaque is a marker of the presence and extent of coronary artery disease and an independent predictor of CV events and mortality. Prevalence of ultrasonographic carotid plaque was 11% in our study population of middle-aged patients. A similar prevalence of carotid atherosclerosis has been observed in the general population [42] although a direct comparison with our results is difficult, because of the absence of an age-matched control group. Consistent with a recent meta-analysis of observational studies [43], we found that parameters of HIV infection or PI exposure were not independently associated with carotid plaque. Age and smoking have emerged as leading risk factors of carotid atherosclerosis in the literature [42,44]. As expected, age and smoking status were independently and positively correlated with the prevalence of carotid plaque in our study population.

A number of studies in HIV-infected patients used carotid IMT as a screening tool for risk assessment but this marker of early vascular aging may fail to identify patients at increased CV risk [11,12]. Carotid IMT represents a structural quantitative analysis but does not account for qualitative components. The IMT reflects both intima damages (related to the atherosclerotic process) and media damages related to an adaptive process associated with age and distending pressure [45]. As expected, age and BP were independently associated with carotid IMT. No HIV-related parameters or PI treatment were independently associated with carotid IMT in our study population. We found that waist circumference, which is widely applied to estimate visceral obesity, was positively and independently associated with carotid IMT in our study population. In accordance with the present results, previous studies in middle-aged HIV-infected patients have highlighted that exposure to PI therapy or HIV infection might not be associated with an increased carotid IMT [46,47]. Indeed, in young and middle-aged individuals, traditional risk factors may overshadow impact of HAART exposure and HIV-infection in determining premature vascular lesions.

Pulse pressure amplification and plasma vitamin D

In our study population, vitamin D insufficiency (25OHD<30 ng/ml), and deficiency (25OHD<20 ng/ml) were prevalent. Plasma vitamin D level was positively associated with PPA in our study population, and persisted in multiple regression analysis independently of MAP, gender and heart rate. Age was not independently related to PPA, although age and female gender are considered the most important non-modifiable determinants of decreased PPA [16]. However, the independent value of age may be minimized in the present study: in our population, gender may represent a stronger predictor than age (since the age range was quite narrow), which could possibly attenuate the independent value of aging. As expected, heart rate was positively correlated with PPA [16].

Amplification of systolic and pulse pressures from central to peripheral sites depends on the timing and amplitude of the reflected waves and is thus closely related to aortic PWV and AIx. The decrease or disappearance of PPA has been shown to be predictive of an increased risk of all-cause and CV mortality in large community-based cohorts [48,49]. Although the strength of the correlation between vitamin D and PPA may appear weak in our study population, this positive relation did persist in the multiple regression analysis independently of the other cofactors. Our findings suggest that higher vitamin D levels may be associated with better central hemodynamic profile in HIV-infected patients, which is consistent with epidemiological evidence in healthy individuals. In fact, vitamin D levels have been inversely related to aortic stiffness, central AIx, central aortic systolic and diastolic BP, independently of age [50,51]. Mortality has been inversely and independently related to vitamin D deficiency in large prospective cohort studies [24,52]. In HIV-infected patients, vitamin D deficiency has been associated with endothelial dysfunction [53], and coronary lesions [54]. Recently, low vitamin D level has been shown to predict short term mortality in HIV-positive persons, in relation with exacerbated inflammation [55].

Mechanisms underlying the link between vitamin D status and CV disease may be related to central hemodynamic profile associated with aortic stiffness and/or wave reflections. However, these associations are derived from observational and cross-sectional studies and do not necessarily imply a causal relationship. Nevertheless, the growing body of observational data linking vitamin D insufficiency with the risk of mortality and consistent findings of high rates of low vitamin D levels in HIV-infected patients warrant further interventional studies to

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investigate the relationship between vitamin D, arterial parameters and CV health.

Our study has limitations common to cross-sectional design, especially in establishing cause-effect relationships between central hemodynamics, immunological parameters and vitamin D status. As our population was made mainly of well controlled infected patients, we could not investigate relationship between central hemodynamic parameters and overt viral replication, poorer immune status or poorer immune restoration. Immune restoration was fairly good in this population with a median of current CD4 T-cell count approaching 500/mm^3 and with 94% of patients having a CD4 T-cell count above 200/mm^3. Virological control is demonstrated by the fact that 90% of patients had a plasma viral load below the technique's detection limit, 4% had a viral load that was detectable below 400 RNA copies/ml (400 copies being the threshold for defining virological failure) and only 6% had a viral load above 400 copies/ml. The variable "viral load" showed a very skewed distribution. Thus, we could not incorporate this variable in the statistical analysis because of the small number of patients with a viral load of 400copies/ml or more.

The relatively small size of our study population may have limited the strength of the correlations between HIV-related parameters, vitamin D status and central hemodynamics. Finally, the lack of HIV-negative control group may weaken some of our conclusions on the impact of immune status on arterial parameters. However, we believe that European reference values established for PWV in an extremely large population represent an important step towards the definition of normal and reference values, to which our population can be compared. Mattace-Raso et al. noted that diabetic subjects and subjects treated for hypertension and dyslipidaemia had significantly elevated PWV values, compared with untreated patients, even after correction for age and MAP and this is why the authors decided not to include these patients [29]. In our study population, 5% of patients were diabetics and 20% and 22% were on statin and anti-hypertensive drugs, respectively. Statistical analysis comparing measured values and calculated theoretical values for aortic PWV has included all patients of our study population, which may strengthen our results. In the absence of reference and widely used values for PPA and carotid AIx, comparisons between HIV-infected and uninfected populations could not be undertaken and only determinants of these vascular parameters could be assessed in our study population.

In contrast to previous studies, our group of well-controlled HIV-infected patients did not show overtly increased aortic stiffness, when compared to the theoretical values. To the best of our knowledge, it is the first time that better immune status was associated with a transit time-dependent marker of intensity of wave reflections, in relation with the fact that patients under treatment with higher CD4 T-cell count may have unaltered buffering function. The positive correlation between vitamin D and amplification of PP suggests a possible beneficial impact of adequate vitamin D level on central hemodynamic parameters. Amplification of PP, which is modulated by vascular properties and inversely related to large artery stiffness and increased wave reflections, may provide further information about the relationship between vitamin D, arterial parameters and CV health in HIV-infected patients.

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References

1. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338: 853-860.
2. Lewden C, May T, Rosenthal E, Burty C, Bonnet F, et al. (2008) Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalité 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr 48: 590-598.
3. Lohse N, Hansen AB, Gerstoft J, Obel N (2007) Improved survival in HIV-infected persons: consequences and perspectives. J Antimicrob Chemother 60: 461-463.
4. Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, et al. (2014) Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 28: 1181-1191.
5. Lang S, Mary-Krause M, Simon A, Partisani M, Gilquin J, et al. (2012) HIV replication and immune status are independent predictors of the risk of myocardial infarction in HIV-infected individuals. Clin Infect Dis 55: 600-607.
6. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, et al. (2010) Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS Cohort CO4. Arch Intern Med 170: 1228-1238.
7. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, et al. (2013) Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS 27: 973-979.
8. Friis-Møller N, Worm SW (2007) Can the risk of cardiovascular disease in HIV-infected patients be estimated from conventional risk prediction tools? Clin Infect Dis 45: 1082-1084.
9. Lekakis J, Ikonomidis I, Palios J, Tsiodras S, Karatzis E, et al. (2009) Association of highly active antiretroviral therapy with increased arterial stiffness in patients infected with human immunodeficiency virus. Am J Hypertens 22: 828-834.
10. Monsuez JJ, Charniot JC, Escaut L, Teicher E, Wyplosz B, et al. (2009) HIV-associated vascular diseases: structural and functional changes, clinical implications. Int J Cardiol 133: 293-306.
11. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, et al. (2012) Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 308: 796-803.
12. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, et al. (2012) PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet 379: 2053-2062.
13. Blacher J, Asmar R, Djane S, London GM, Safar ME (1999) Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 33: 1111-1117.
14. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, et al. (2006) Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 113: 657-663.
15. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, et al. (2014) Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 63: 636-646.
16. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, et al. (2009) Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension 54: 375-383.

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17. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, et al. (2010) Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 31: 1865-1871.
18. Echeverría P, Bonjoch A, Moltó J, Jou A, Puig J, et al. (2014) Pulse wave velocity as index of arterial stiffness in HIV-infected patients compared with a healthy population. J Acquir Immune Defic Syndr 65: 50-56.
19. Ho JE, Deeks SG, Hecht FM, Xie Y, Schnell A, et al. (2010) Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals. AIDS 24: 1897-1905.
20. Schillaci G, De Socio GV, Pirro M, Savarese G, Mannarino MR, et al. (2005) Impact of treatment with protease inhibitors on aortic stiffness in adult patients with human immunodeficiency virus infection. Arterioscler Thromb Vasc Biol 25: 2381-2385.
21. Lazar JM, Wu X, Shi Q, Kagame A, Cohen M, et al. (2009) Arterial wave reflection in HIV-infected and HIV-uninfected Rwandan women. AIDS Res Hum Retroviruses 25: 877-882.
22. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, et al. (2011) Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D Levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. Clin Infect Dis 52: 396-405.
23. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, et al. (2008) Vitamin D deficiency and risk of cardiovascular disease. Circulation 117: 503-511.
24. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, et al. (2008) Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 168: 1340-1349.
25. Viard JP, Souberbielle JC, Kirk O, Reekie J, Knysz B, et al. (2011) Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. AIDS 25: 1305-1315.
26. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, et al. (1998) Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 16: 2079-2084.
27. Lieber A, Millasseau S, Bourhis L, Blacher J, Protogerou A, et al. (2010) Aortic wave reflection in women and men. Am J Physiol Heart Circ Physiol 299: H236-242.
28. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, et al. (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27: 2588-2605.
29. Mattace-Raso F, Hofman A, Verwoert GC, Wittemana JC, Wilkinson I, et al. (2010) Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 31: 2338-2350.
30. Segers P, Rietzschel E, Heireman S, De Buyzere M, Gillebert T, et al. (2005) Carotid tonometry versus synthesized aorta pressure waves for the estimation of central systolic blood pressure and augmentation index. Am J Hypertens 18: 1168-1173.
31. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, et al. (2005) Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 46: 1753-1760.
32. Kelly R, Hayward C, Avolio A, O'Rourke M (1989) Noninvasive determination of age-related changes in the human arterial pulse. Circulation 80: 1652-1659.
33. Cecelja M, Chowienczyk P (2009) Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 54: 1328-1336.
34. Monteiro P, Miranda-Filho DB, Bandeira F, Lacerda HR, Chaves H, et al. (2012) Is arterial stiffness in HIV-infected individuals associated with HIV-related factors? Braz J Med Biol Res 45: 818-826.
35. Kimoto E, Shoji T, Shinohara K, Inaba M, Okuno Y, et al. (2003) Preferential stiffening of central over peripheral arteries in type 2 diabetes. Diabetes 52: 448-452.
36. van Vonderen MG, Smulders YM, Stehouwer CD, Danner SA, Gundy CM, et al. (2009) Carotid intima-media thickness and arterial stiffness in HIV-infected patients: the role of HIV, antiretroviral therapy, and lipodystrophy. J Acquir Immune Defic Syndr 50: 153-161.
37. Schillaci G, De Socio GV, Pucci G, Mannarino MR, Helou J, et al. (2008) Aortic stiffness in untreated adult patients with human immunodeficiency virus infection. Hypertension 52: 308-313.
38. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL (2011) Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. J Acquir Immune Defic Syndr 57: 245-253.
39. Strategies for Management of Antiretroviral Therapy (SMART) Study Group1, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, et al. (2006) CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 355: 2283-2296.
40. Hayward CS, Kelly RP (1997) Gender-related differences in the central arterial pressure waveform. J Am Coll Cardiol 30: 1863-1871.
41. Vyas M, Izzo JL Jr, Lacourcière Y, Arnold JM, Dunlap ME, et al. (2007) Augmentation index and central aortic stiffness in middle-aged to elderly individuals. Am J Hypertens 20: 642-647.
42. Prati P, Vanuzzo D, Casaroli M, Di Chiara A, De Biasi F, et al. (1992) Prevalence and determinants of carotid atherosclerosis in a general population. Stroke 23: 1705-1711.
43. Hulten E, Mitchell J, Scally J, Gibbs B, Villines TC (2009) HIV positivity, protease inhibitor exposure and subclinical atherosclerosis: a systematic review and meta-analysis of observational studies. Heart 95: 1826-1835.
44. Dempsey RJ, Moore RW (1992) Amount of smoking independently predicts carotid artery atherosclerosis severity. Stroke 23: 693-696.
45. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, et al. (1992) Parallel cardiac and vascular adaptation in hypertension. Circulation 86: 1909-1918.
46. Currier JS, Kendall MA, Zackin R, Henry WK, Alston-Smith B, et al. (2005) Carotid artery intima-media thickness and HIV infection: traditional risk factors overshadow impact of protease inhibitor exposure. AIDS 19: 927-933.
47. Bongiovanni M, Casana M, Cicconi P, Pisacreta M, Codemo R, et al. (2008) Predictive factors of vascular intima media thickness in HIV-positive subjects. J Antimicrob Chemother 61: 195-199.
48. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, et al. (1997) Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 30: 1410-1415.
49. Benetos A, Thomas F, Joly L, Blacher J, Pannier B, et al. (2010) Pulse pressure amplification a mechanical biomarker of cardiovascular risk. J Am Coll Cardiol 55: 1032-1037.
50. Alvarez JA, Gower BA, Calhoun DA, Judd SE, Dong Y, et al. (2012) Serum 25-hydroxyvitamin D and Ethnic Differences in Arterial Stiffness and Endothelial Function. J Clin Med Res 4: 197-205.
51. Al Mheid I, Patel R, Murrow J, Morris A, Rahman A, et al. (2011) Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. J Am Coll Cardiol 58: 186-192.
52. Melamed ML, Michos ED, Post W, Astor B (2008) 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 168: 1629-1637.
53. Shikuma CM, Seto T, Liang CY, Bennett K, DeGruttola V, et al. (2012) Vitamin D levels and markers of arterial dysfunction in HIV. AIDS Res Hum Retroviruses 28: 793-797.
54. Lai H, Gerstenblith G, Fishman EK, Brinker J, Kickler T, et al. (2012) Vitamin D deficiency is associated with silent coronary artery disease in cardiovascularly asymptomatic African Americans with HIV infection. Clin Infect Dis 54: 1747-1755.
55. Shepherd L, Souberbielle JC, Bastard JP, Fellahi S, Capeau J, et al. (2014) Prognostic value of vitamin D level for all-cause mortality, and association with inflammatory markers, in HIV-infected persons. J Infect Dis 210: 234-243.

3.3.3 Conclusion de l'article 7

Notre population d'étude comprenait des patients d'âge moyen (49 ± 9 années) avec une infection VIH contrôlée. La grande majorité de patients avaient une charge virale indétectable le jour de l'inclusion. La prévalence de la maladie diabétique était de 5 % et 22 % des patients étaient sous traitement antihypertenseur. La pression artérielle était dans les valeurs de la normale dans la population d'étude (la valeur médiane de la systolique et de la diastolique était respectivement de 125 mm Hg et 81 mm Hg).

La rigidité aortique, estimée par la VOP carotido-fémorale, n'était pas significativement plus élevée chez ces patients (médiane de VOP 8,3 (7,5-9,5) m/s), par rapport aux valeurs théoriques de référence selon l'âge et le niveau de pression artérielle moyenne (médiane de VOP 8,0 (7,4-9,1) m/s) (75). L'âge, la pression artérielle moyenne et le statut diabétique étaient les facteurs indépendants associés à la rigidité aortique dans notre population d'étude. Les paramètres immuno-virologiques ou le traitement antirétroviral n'étaient pas associés à la rigidité aortique. Il est à noter que notre population d'étude était composée de patients présentant pour la majorité d'entre eux un bon contrôle virologique associé à la mise en œuvre d'une prévention cardiovasculaire (seulement 13 % des patients étaient des fumeurs actifs). Cela peut contribuer à expliquer l'écart avec les études précédentes mettant en évidence une rigidité aortique plus élevée dans un contexte d'infection VIH. L'âge (en association avec la pression artérielle) étant le principal déterminant de la rigidité aortique, le suivi longitudinal de notre population d'étude apportera des preuves supplémentaires quant au vieillissement vasculaire prématuré et ses déterminants chez les patients avec charge virale indétectable.

Les résultats mettent également en évidence une corrélation positive entre le statut immunitaire, illustré par le nombre de cellules T CD4, et l'AIx carotidien, marqueur de

l'amplitude des ondes de réflexion. Les autres paramètres corrélés positivement avec l'AIx étaient l'âge, la pression artérielle moyenne et le sexe féminin, alors qu'une corrélation négative était notée avec la fréquence cardiaque, résultats en accord avec la littérature (73). La corrélation positive mise en évidence entre l'AIx et le taux actuel de lymphocytes T CD4 semble en contraste avec les données épidémiologiques antérieures associant rigidité aortique et déficit immunitaire. Cependant, peu d'études, avec des résultats discordants, se sont intéressées à la relation entre les paramètres immunologiques et le phénomène des ondes de réflexion. L'association entre taux de CD4 et AIx, persistant après ajustement à la fréquence cardiaque, n'implique pas une corrélation positive entre taux de CD4 et rigidité aortique. Ce résultat pourrait suggérer que les patients ayant un taux plus élevé de cellules CD4 présentent une paroi aortique plus compliante (97). Le mismatch d'impédance à la jonction entre l'aorte et l'artère carotide est considérée comme un mécanisme de protection qui facilite la réflexion des ondes de pression et limite la transmission de l'énergie pulsatile à la microcirculation d'aval (97). Cette hypothèse doit être confirmée par le suivi longitudinal de notre cohorte de patients en comparaison à un groupe témoin.

Enfin, le taux de vitamine D plasmatique était corrélé positivement à l'amplification de la pression pulsée. Ce résultat suggère que la carence en vitamine D est associée à une altération des paramètres hémodynamiques centraux indépendamment des critères immuno-virologiques dans un contexte d'infection VIH bien contrôlée. Dans notre population d'étude, la carence en vitamine D était fréquente et la corrélation avec l'amplification est restée significative indépendamment de la pression artérielle moyenne, du sexe et de la fréquence cardiaque. Nos résultats suggèrent que des taux plasmatiques normalisés de vitamine D pourraient être associés à un meilleur profil hémodynamique central chez les patients avec infection VIH. Cette hypothèse est cohérente avec les données épidémiologiques chez les

individus sains. En effet, les taux plasmatiques de vitamine D ont été inversement corrélés à la rigidité aortique et la pression centrale indépendamment de l'âge (167, 168). La mortalité a été corrélée à la carence en vitamine D dans de grandes études de cohortes prospectives (165,169) et plus récemment dans une population de patients avec infection VIH (166,170). Les mécanismes sous-jacents rendant compte de l'association entre le statut en vitamine D et la mortalité cardiovasculaire peuvent être liés à un profil hémodynamique central altéré. Cependant, ces observations proviennent d'études transversales et ne permettent pas d'établir une relation de causalité. Des études interventionnelles apparaissent nécessaires pour étudier la relation entre correction d'une carence en vitamine D, paramètres artériels et prévention cardiovasculaire chez les patients avec infection VIH.

Chapitre 4
Rigidité aortique et dépistage de la maladie artérielle

4.1 Rigidité aortique et dépistage de la maladie artérielle chez le patient diabétique type 2 (Article 8)

4.1.1 Introduction de l'article 8

Le diabète de type 2 est souvent considéré comme un très haut risque cardiovasculaire, équivalent de maladie coronaire. Cependant, une hétérogénéité de risque a été démontrée dans la population diabétique, en particulier chez les jeunes patients nouvellement diagnostiqués et sans facteur de risque cardiovasculaire associé ou atteinte d'organes cibles (171). Les équations de risque ne permettent pas au clinicien d'intégrer la durée d'évolution et la persistance du contrôle de la maladie diabétique et ne fournissent pas des estimations fiables du risque cardiovasculaire individuel chez les patients diabétiques (172). L'évaluation de la rigidité aortique, considérée comme un marqueur d'atteinte artérielle infra-clinique, permettrait de distinguer une population de patients diabétiques à plus haut risque requérant un traitement préventif optimal et un suivi rapproché pour le dépistage d'une maladie cardio ou cérébro- vasculaire encore asymptomatique. En particulier, il a été montré que la rigidité aortique était corrélée à la présence d'ischémie myocardique chez des patients diabétiques asymptomatiques (173). Ce paramètre hémodynamique artériel permettrait donc de cibler une population ayant une forte probabilité de maladie coronaire infra-clinique. Les recommandations européennes pour la prise en charge de l'hypertension artérielle incluent la mesure de la VOP carotido-fémorale dans le bilan d'atteinte d'organes cibles (174). Ce marqueur artériel permet d'identifier les patients hypertendus à risque cardiovasculaire élevé. La maladie diabétique est associée à une rigidité aortique majorée, indépendamment d'une maladie antihypertensive associée (175). Cependant l'utilité clinique de la rigidité aortique en

termes de prédiction du risque cardiovasculaire a été peu étudiée chez les patients diabétiques.

Le diabète de type 2 et l'hypertension artérielle représentent des problèmes de santé émergents en Algérie (176, 177). En collaboration avec l'équipe de médecine interne de l'hôpital de Tizi Ouzou en Algérie, nous avons étudié la rigidité aortique en tant que marqueur indépendant de maladie cardiovasculaire chez des patients diabétiques de type 2. De 2005 à 2009, une étude observationnelle transversale a été menée sur une cohorte de 618 patients diabétiques de type 2 dans le service de médecine interne de l'hôpital de Tizi Ouzou. Les patients ont été inclus de manière consécutive lors de leur consultation de suivi, après avoir donné leur consentement. La cohorte de l'étude était alors composée de 618 patients, 260 hommes et 358 femmes, d'âge moyen 59,4 ± 11,5 ans. Cent vingt- sept patients présentaient un antécédent d'événements cardiovasculaires, impliquant au moins un site vasculaire :
79 (62 %) patients présentaient une maladie coronarienne, 36 (28 %) patients présentaient une maladie vasculaire périphérique et 32 (25 %) patients, une maladie cérébro-vasculaire. L'objectif de l'étude était : (1) d'étudier les paramètres modulant la rigidité aortique ; (2) de démontrer que la rigidité aortique peut être considérée comme un marqueur indépendant de maladie cardiovasculaire ; (3) de démontrer que la prise en compte de la rigidité aortique chez les patients diabétiques améliore le modèle explicatif de la présence de maladie cardiovasculaire au-delà des facteurs de risque traditionnels.

4.1.2 Article 8

Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar M.E, Ouerdane S, Blacher J.

Aortic stiffness and cardiovascular risk in type 2 diabetes.

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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 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: $P = 0.189$).

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.

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

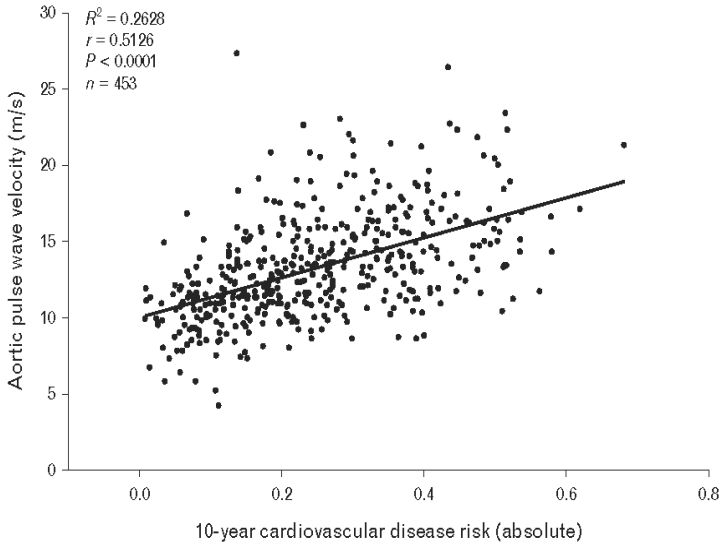

FIGURE 1 Relationship between 10-year cardiovascular disease risk and aortic pulse wave velocity.

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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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.

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Conflicts of interest

There is no conflict of interest for any of the authors.

REFERENCES

1. Safar ME, Temmar M, Kakou A, Lacolley P, Thornton SN. Sodium intake and vascular stiffness in hypertension. *Hypertension* 2009; 54:203–209.
2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339:229–234.
3. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, *et al.* Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000; 102:1014–1019.
4. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men. Influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med* 2011; 171:404–410.
5. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321:405–412.
6. Bailey CJ, Day C. Glycaemic memory. *Br J Diabetes Vasc Dis* 2008; 8:242–247.
7. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.*, Collaborative Group ADVANCE. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358:2560–2572.
8. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group; Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358:2545–2559.
9. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al.* VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; 360:129–139.
10. Nilsson PM, Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Gudbjörnsdóttir S. Swedish National Diabetes Register (NDR). Pulse pressure strongly predicts cardiovascular disease risk in patients with type 2 diabetes from the Swedish National Diabetes Register (NDR). *Diabetes Metab* 2009; 35:439–446.
11. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 2007; 30:1292–1293.
12. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation* 2009; 119:243–250.
13. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, *et al.* Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007; 50:197–203.
14. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* European Network for Noninvasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605.
15. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, *et al.* Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010; 121:505–511.
16. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37:1236–1241.
17. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002; 39:10–15.
18. Laurent S, Katsahian S, Fassot C, Tropeano AI, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003; 34:1203–1206.
19. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; 99:2434–2439.
20. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H, *et al.* Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 2001; 12:2117–2124.
21. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects > 70 years of age. *Arterioscler Thromb Vasc Biol* 2001; 21:2046–2050.
22. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, *et al.* Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well functioning older adults. *Circulation* 2005; 111:3384–3390.
23. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, *et al.* Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006; 113:657–663.
24. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, *et al.* Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles Hiroshima study. *Circ J* 2005; 69:259–264.
25. Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; 113:664–670.
26. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007; 25:1751–1762.
27. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; 26:485–490.
28. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; 33:1111–1117.
29. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. *Circulation* 2002; 106:3143–3421.
30. American Diabetes Association. Peripheral arterial disease in people with diabetes (consensus statement). *Diabetes Care* 2003; 26:3333–3341.
31. Pencina MJ, D'Agnostino RB Sr, D'Agnostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; 27:157–172.
32. SAS. Nonparametric comparison of areas under correlated ROC curves. http://support.sas.com/kb/25/017.html. [Accessed 14 June 2011].
33. Berglund L. Nonparametric comparison of areas under correlated ROC curves. Uppsala Clinical Research Center. www.ucr.uu.se/en/index.php/epistat/program-code [Accessed 7 June 2011].
34. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; 121:293–298.
35. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008; 51:527–539.
36. Chen Y, Huang Y, Li X, Xu M, Bi Y, Zhang Y, *et al.* Association of arterial stiffness with HbA1c in 1000 type 2 diabetic patients with or without hypertension. *Endocrine* 2009; 36:262–267.
37. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, *et al.* Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002; 105:1202–1207.
38. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension* 2009; 54:1328–1336.
39. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55:1318–1327.
40. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; 106:2085–2090.
41. Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, *et al.* Guidelines on diabetes, prediabetes, and cardiovascular diseases. The Task Force on Diabetes and Cardiovascular Diseases

of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; 28:88–136.
42. Safar ME, Blacher J, Pannier B, Guerin A, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; 39:735–738.
43. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, *et al.* CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113:1213–1225.
44. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, *et al.* Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005; 45:980–985.
45. Vlachopoulos C, Aznaouridis K, Stefanadis C. Clinical appraisal of arterial stiffness: the Argonauts in front of the Golden Fleece. *Heart* 2006; 92:1544–1550.
46. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; 103:987–992.
47. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.* ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; 366:895–906.

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.

4.1.3 Conclusion de l'article 8

La prévalence de l'hypertension artérielle dans la cohorte de patients diabétiques était de 82%. L'âge, la pression artérielle moyenne, la fréquence cardiaque, la durée de la maladie diabétique et la glycémie à jeun ont été positivement et indépendamment corrélés à la rigidité aortique dans cette étude. La rigidité aortique était positivement et indépendamment corrélée à la présence d'une maladie cardiovasculaire. Ce paramètre hémodynamique artériel améliorait le modèle explicatif de la présence de maladie cardiovasculaire au-delà de la prise en compte des facteurs de risque traditionnels. Une méta-analyse récente évaluant la valeur prédictive de la rigidité aortique, a souligné qu'une augmentation de la VOP carotido-fémorale d'une déviation standard a été associée à une augmentation du risque de morbi-mortalité cardiovasculaire de 47 % (91). Ces résultats sont très similaires à l'odds ratio (OR = 1,47) de la VOP carotido-fémorale dans le modèle explicatif de la présence de maladie cardiovasculaire dans notre étude. Ce marqueur d'atteinte artérielle représente donc un indicateur du risque cardiovasculaire chez les patients diabétiques de type 2. Des données récentes prospectives soutiennent ce dernier point, indiquant que la mesure de la rigidité aortique chez des patients diabétiques à haut risque aide à mieux prédire la survenue d'événements cardiovasculaires (178).

Le suivi prospectif des paramètres hémodynamiques artériels, parallèlement aux données de morbi-mortalité, de la cohorte de patients diabétiques de cette première étude permettrait de confirmer ces résultats. La mise en évidence des facteurs impliqués dans l'évolutivité des lésions artérielles permettrait de proposer de nouvelles stratégies thérapeutiques chez ces patients à très haut risque.

4.2 Rigidité aortique et dépistage de la maladie coronaire (Article 9)

4.2.1 Introduction de l'article 9

La pathologie cardiovasculaire reste au premier rang des causes de mortalité, la maladie coronaire étant responsable d'environ 20 % de tous les décès chez les adultes en Europe (179). En matière de dépistage, la maladie coronaire représente une cible primordiale, l'ischémie myocardique symptomatique ou silencieuse étant un facteur prédictif du risque d'événements coronariens et de mort subite (180, 181). L'épreuve d'effort couplée à la scintigraphie myocardique représente un outil diagnostic de premier niveau dont dépend la décision de réalisation de la coronarographie, examen invasif à visée diagnostique et thérapeutique. Cet examen invasif est considéré comme justifié lorsque l'évaluation clinique pré-test associée au test de dépistage non invasif suggère un risque élevé de lésions coronaires obstructives symptomatiques. Cependant, la coronarographie diagnostique élective ne met en évidence des lésions obstructives que chez un tiers des patients (182).

L'objectif de notre étude a été d'évaluer l'amélioration de la valeur prédictive positive du dépistage de la maladie coronaire par la prise en compte de la rigidité aortique. Pour des raisons de disponibilité locale et d'expertise au sein de l'hôpital Hôtel- Dieu, l'épreuve d'effort couplée à la scintigraphie de perfusion myocardique a représenté l'examen de dépistage chez les patients à risque lors de leur hôpital de jour programmé. Les valeurs prédictives positive et négative de la scintigraphie myocardique d'effort pour le dépistage d'une maladie coronaire obstructive sont considérées respectivement à 53 % et 83 % (183). Des résultats faussement positifs peuvent entraîner l'exposition inutile du patient aux risques de l'angiographie invasive. Des résultats faussement négatifs ou douteux risquent de sous-estimer la présence d'une maladie coronaire et entraîner une prise en charge médicale

inadaptée. L'examen anatomique des coronaires par angioscanner aurait le potentiel de réduire le nombre de procédures invasives, comme il a été récemment mis en évidence sur une large cohorte de patients pour lesquels une maladie coronaire était suspectée (184). Cependant sur une durée moyenne de suivi de 2 ans, une stratégie initiale de dépistage par examen anatomique ne permet pas de réduire le taux d'événements coronariens en comparaison à une stratégie initiale faisant intervenir un test fonctionnel.

En considérant la variabilité des symptômes, des caractéristiques cliniques de chaque patient ainsi que des résultats du test de dépistage, la décision de réalisation d'un examen invasif à visée diagnostique est prise en concertation pluridisciplinaire. En raison de l'imperfection des tests de dépistage non invasifs, l'apport de mesures complémentaires de l'état artériel pourrait en améliorer la puissance diagnostique. La rigidité aortique représente un marqueur artériel candidat dans l'amélioration de la prise en charge diagnostique des patients à risque.

L'apport de la mesure de la rigidité aortique dans l'amélioration du dépistage de la maladie coronaire a été étudié en termes de réduction d'examens invasifs inappropriés. Cette étude observationnelle transversale a été réalisée au sein de la cohorte précédemment décrite (article 6). Celle-ci était constituée de 399 patients inclus consécutivement de décembre 2012 à septembre 2014 lors de leur bilan cardiovasculaire en hôpital de jour à l'Hôtel-Dieu. La mesure de la VOP carotido-fémorale a pu être réalisée de manière adéquate chez 367 patients (219 hommes et 148 femmes). Les antécédents de maladie coronaire étaient présents chez 55 (15 %) patients, parmi lesquels un antécédent d'infarctus du myocarde était présent chez 22 patients.

L'âge, la pression artérielle et le sexe sont des facteurs corrélés à la fois à la rigidité aortique et au risque de maladie coronaire. Par conséquent, un index de VOP a été calculé

pour évaluer la pertinence à l'échelle individuelle de la mesure de la rigidité aortique. Le calcul de cet index a été précédemment proposé pour évaluer la puissance prédictive de la rigidité aortique en termes de mortalité cardiovasculaire et toutes causes dans une population de patients avec insuffisance rénale terminale (185). Cet index a été évalué dans notre étude par [(VOP mesurée-VOP théorique)/VOP théorique] pour identifier les hommes et les femmes présentant une rigidité aortique majorée par rapport à leur âge et leur niveau de pression artérielle moyenne.

Les objectifs de cette étude rétrospective ont été : (1) d'évaluer la valeur prédictive positive de l'épreuve d'effort couplée à la scintigraphie myocardique chez les patients de la cohorte ayant eu une coronarographie élective ; (2) d'évaluer la corrélation entre l'index VOP et la sévérité de la maladie coronaire lors de la coronarographie ; (3) de déterminer si l'index VOP améliore la précision diagnostique de l'épreuve d'effort couplée à la scintigraphie myocardique dans notre population d'étude.

4.2.2 Article 9

Yannoutsos A, Ahouah M, Dreyfuss Tubiana C, Topouchian J, Safar M.E, Blacher J. Aortic stiffness improves the prediction of both diagnosis and severity of coronary artery disease. Submitted.

Aortic stiffness improves the prediction of both diagnosis and severity of coronary artery disease

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ABSTRACT

Aims. Myocardial ischemia represents a crucial target of coronary artery disease (CAD) screening. Nevertheless, elective coronography presents a low diagnostic yield for obstructive CAD. The purpose of this study was to determine whether non invasive aortic stiffness assessment improves diagnostic accuracy of obstructive CAD screening. ***Methods.*** A cross-sectional study was conducted from January 2013 to September 2014 in our medical center. Electrocardiogram (ECG) stress test coupled with nuclear imaging was performed in 367 consecutive patients routinely followed-up, for myocardial ischemia screening. Aortic pulse wave velocity (PWV) was assessed by applanation tonometry in overall population. Forty-two patients underwent elective coronography because of ischemia. Theoretical PWV was calculated according to age, blood pressure and gender. Results were expressed as an index [(measured PWV – theoretical PWV) / theoretical PWV] for each patient. ***Results.*** Ten patients presented with obstructive CAD, 16 patients had non-obstructive CAD and 16 patients had normal coronary angiography. PWV index and severity of CAD were positively correlated (p=0.001). Glomerular filtration rate (GFR) was negatively associated with severity of CAD (p=0.014). Diagnostic accuracy of stress test coupled with nuclear imaging was improved when using PWV index in case of discordant clinical/nuclear results (performance index without versus with PWV index: 0.41 versus 0.69). ***Conclusion.*** Aortic PWV index should be considered as clinically useful to rule out the presence of obstructive CAD and to reduce the rate of unnecessary angiographies. Prospective studies, taking into account renal function, shall have the potential to further evaluate PWV index as a marker of CAD.

KEYWORDS: coronary artery disease, cardiovascular screening, aortic stiffness, pulse wave velocity, myocardial perfusion scintigraphy.

INTRODUCTION

Although the survival rate of patients with coronary heart disease (CHD) has been steadily improving (1), ischemic heart disease remains a worldwide public health problem (2). Symptomatic coronary artery disease (CAD) or silent myocardial ischemia are both predictive of the risk of myocardial infarction and sudden death and therefore represent a crucial target of cardiovascular (CV) screening (3, 4). Invasive coronary angiography is considered to be justified when clinical evaluation associated with non-invasive cardiac testing suggests a high risk of obstructive coronary lesions. However, only slightly more than one third of patients without known CAD who underwent elective cardiac catheterization had obstructive coronary artery lesions (5). Better strategies for CAD screening are required to reduce unnecessary angiography rate with the intension of improving patient care.

Because of local availability and expertise, myocardial perfusion scintigraphy by single-photon emission computed tomography (SPECT) coupled with electrocardiogram (ECG) stress test was used in this study as a screening test for the assessment of inducible myocardial ischemia in at-risk patients. A large body of evidence supports the prognostic value of stress functional imaging with SPECT (6) regarding future cardiac events. However, positive and negative predictive values for obstructive CAD are considered to be 53% and 83%, respectively (7). False positive results of non invasive cardiac imaging may result in patient exposure to unnecessary risk during invasive angiography whereas inconclusive or false negative results may lead to an underestimation of CAD and subsequent inadapted medical management. In particular, significant multivessel CAD may lead to uniform tracer uptake due to “balanced” ischemia (8).

Because of the variability in symptoms, clinical characteristics among patients and results obtained from noninvasive cardiac tests with substantial imperfections, there is often no single correct diagnosis approach to any given patient. Anatomical testing with the use of

coronary computed tomographic angiography (CTA) has the potential to reduce unnecessary invasive procedures as recently highlighted in a large cohort of patients with suspected CAD. However, over a median follow-up of 2 years, the authors concluded that a strategy of initial anatomical testing did not improve clinical outcomes as compared with functional testing (9). Non-invasive complementary measure of subclinical arterial disease may improve the diagnostic accuracy of cardiac stress test and subsequent patient management in at-risk populations. In particular, aortic stiffness is increasingly considered as a functional and structural marker of cumulative exposure to all CV risk factors and a surrogate CV end point (10, 11, 12). Carotid-femoral pulse wave velocity (PWV) is considered as the gold standard for direct non-invasive assessment of aortic stiffness and presents an independent predictive value for primary coronary events (11, 12). Previously, in a population of patients with advanced chronic kidney disease, aortic PWV has been correlated with the extent and severity of coronary atherosclerosis (13). We aimed to explore relationships between aortic stiffness and CAD in a cohort of patients without end-stage-renal disease, routinely followed-up for cardiovascular screening.

Since age, gender and blood pressure (BP) are strong determinants of both aortic stiffness (14) and CAD (3), a PWV index was calculated to determine the individual relevance of aortic stiffness assessment for CAD screening. This index was calculated as [(measured PWV–theoretical PWV) / theoretical PWV] (15) to identify those patients with increased aortic stiffness independently of age, BP and gender. The purpose of the present cross-sectional study was: to assess retrospectively the diagnostic accuracy of ECG stress test coupled with myocardial functional imaging by SPECT (called as cardiac stress test) in patients, with known or suspected CAD, who underwent elective coronary angiography in our medical unit; to assess the correlation between aortic PWV index and the severity of CAD reported by coronary angiography; to determine whether aortic PWV index improves the

diagnostic accuracy of non-invasive cardiac testing for CAD screening.

METHODS

Overall population cohort

From January 2013 to September 2014, 399 consecutive patients, men and women, with or without previously identified CV events, were eligible in this cross-sectional study during their routine follow-up at the Paris Hôtel-Dieu University Hospital. All patients were recruited after visit in the Diagnosis and Therapeutics Center at Hôtel-Dieu University Hospital. The majority of patients had routine CV follow-up in our medical center, and the others were referred by their general practitioner for a CV check-up. Patients provided informed consent for additional noninvasive hemodynamic measurements and data collection during the day hospital for CV screening. Exclusion criteria were age under 18, atrial fibrillation and medical conditions that contraindicated exercise stress test (16). Thirty-two patients were excluded due to PWV missing data (aortic PWV measurement has not been performed successfully because of frequent extrasystoles or poor quality waveform). The overall population cohort was then composed of 367 patients. The study complies with the Declaration of Helsinki. Each subject provided informed consent. The study was registered in the French National Agency for Medicines and Health Products Safety (No. 2013-A00227-38) and was approved by the locally appointed ethics committee, the Advisory Committee for Protection of Persons in Biomedical Research.

Study cohort

From the overall population cohort, 42 patients underwent elective coronary angiography. Multidisciplinary decision for coronary angiography was proposed for each of

the 42 patients according to the probability of CAD based on age, gender, symptoms, and results of cardiac testing (17). Patients with a history of myocardial infarction or percutaneous coronary intervention were not excluded because non-invasive cardiac imaging was part of their routine follow-up as a guiding decision for a new invasive coronary angiography. No patient had a history of surgical coronary revascularization. Three from the 42 patients included in the study cohort underwent CTA instead of invasive coronary angiography because of relatively low likelihood of CAD associated with inconclusive cardiac stress test. This multidisciplinary decision was based on the main clinical advantage of CTA related to its high negative predictive value allowing the exclusion of obstructive coronary lesion (18).

Clinical and hemodynamic parameters

Information compiled from the questionnaire filled out at inclusion during the day hospital for CV screening included gender, age, body mass index (BMI, weight in kilograms divided by the square of the height in meters), family history of premature CV events, personal history of dyslipidaemia, hypertension, diabetes, smoking habits, medications and previous diseases. Hypertensive patients were all receiving antihypertensive drug treatment. Dyslipidaemia was defined as a total/HDL cholesterol ratio > 5 or the presence of a hypocholesterolemic drug. Previous CHD was defined as past medical history of documented myocardial infarction, coronary revascularization or epicardial CAD diagnosed during coronary angiography for patients with symptoms or typical electrocardiographic modifications. Previous cerebro-vascular disease and peripheral arterial disease were defined as scan imaging-documented stroke for cerebrovascular disease, ankle-brachial pressure index value less than 0.90, imaging-documented atherosclerotic vascular disease including asymptomatic severe carotid artery stenosis, peripheral vascular disease and abdominal aortic aneurysm or arterial revascularization.

Laboratory parameters, including plasma glucose and glycated hemoglobin,

cholesterol (total, LDL and HDL) and triglycerides, plasma creatinine and creatinine clearance rate were determined on the day of hemodynamic measurements.

Hemodynamic measurements were performed in the morning after an overnight fast, in supine position. Brachial systolic BP and diastolic BP were measured at both arms using an automatic BP monitor (OMRON 705 CP II IT) after 5 minutes of rest. Five measurements 2 minutes apart were averaged. Heart rate was recorded.

After BP determination, aortic PWV was performed noninvasively by applanation tonometry using an automatic device (SphygmoCor AtCor, Sydney, Australia), with simultaneous three-lead orthogonal ECG as previously described (19). The reproducibility of these measurements, in our group and in others, has been previously published in detail (20, 21). Aortic PWV was calculated as the direct distance between carotid and femoral arteries, divided by the time interval between the feet of the pressure waves at the recording sites. Pulse waveforms were obtained transcutaneously using applanation tonometry over the common carotid and femoral arteries. Direct distance was multiplied by a scaling factor of 0.8 (22).

A nomogram of aortic PWV was constructed, as previously described (15), based on clinical characteristics of the overall population cohort of 367 patients, in order to determine multiadjusted theoretical aortic PWV values according to age, gender and mean BP. The equation derived from the multivariate analysis was then applied to the subgroup of patients who underwent elective coronary angiography in order to obtain a theoretical aortic PWV value. The results were finally expressed as a PWV index defined as [(measured PWV– theoretical PWV) / theoretical PWV] adjusted on these three parameters for each of the 42 patients.

Coronary heart disease screening

Electrocardiogram stress test (during upright bicycle exercise) coupled with

myocardial functional imaging by SPECT (cardiac stress test) was performed during 1-day protocol for stress and rest studies (16). Symptoms, 12-lead ECG, heart rate and BP were monitored continuously during the exercise test and for at least 5 minutes into the recovery phase (23). The radiotracer injection (technetium-99m labeled perfusion agent sestamibi) was performed intravenously at the peak of exercise. Electrocardiogram gating of the perfusion SPECT acquisition allowed quantitative assessment of the left ventricular function simultaneously with the evaluation of the left ventricular perfusion (24). Perfusion abnormalities derived from the accepted 17-segment model for SPECT was used to evaluate the extent and severity of myocardial hypoperfusion and reversibility. Hybrid imaging modality with SPECT/ computed tomography was used for attenuation correction (25).

In patients who could not exercise adequately, a pharmacologic vasodilator stress test with dipyridamole was performed according to ASNC guidelines (16). Discontinuation of antihypertensive medication with antianginal properties such as b-blocker or calcium channel blocker was left to the discretion of the referring physician. However, these medications were not discontinued in patients with known CHD.

Referring physicians reported stress test results as normal, equivocal/nondiagnostic, or abnormal. Normal test was defined as normal clinical and electrical stress test and uniform tracer uptake with normal regional wall motion. Abnormal ECG stress test was defined as clinically and/or electrically abnormal results. Abnormal myocardial perfusion SPECT was defined as inducible or fixed perfusion defects between the rest and stress images.

Obstructive coronary artery disease diagnosis

Elective invasive angiography was performed within 30 days of non invasive cardiac testing. Results included location and degree of CAD as reported by the performing physicians. Consistent with prior studies (5, 26), CAD was defined by the degree of stenosis

which was classified as:

- No apparent CAD: no stenosis >20%;
- Non-obstructive CAD: ≥1 stenosis ≥20% but less than 70% (or less than 50% in the left main coronary artery);
- Obstructive CAD: any stenosis ≥70% or left main coronary artery stenosis ≥50%.

Statistical analysis

Data were analyzed using R 3.1.3 software package. The characteristics of the study population were described as means plus or minus standard deviation (±SD) for continuous variables. Categorical variables were described as numbers and proportions. Comparisons between groups were performed using non parametric tests because of the skewed distribution of the variables. Alpha levels for significance were set at less than 5%. In order to determine multiadjusted theoretical PWV values, an equation of aortic PWV derived from a multivariate analysis was constructed based on the overall population cohort (N=367). The factors included in the analysis are patient's age, mean BP and gender (male=1 and female=0). The following equation, derived from the multivariate analysis, was then applied to the patients who underwent coronary angiography in order to obtain a theoretical PWV value according to their age, BP and gender:

*Theoretical PWV = - 4.63 + 0.12 * age + 0.07 * mean BP - 0.01* gender.*

A PWV index was calculated as [(measured PWV–theoretical PWV) / theoretical PWV]. This index was considered to be abnormal when positive.

We analyze screening performance of cardiac stress test by assessing sensitivity, specificity and Youden's index (defined as the sum of sensitivity and specificity minus 1). The latter gives equal weight to false positive and false negative results. The value of this performance index ranges from 0 to 1: zero value indicates that the test gives the same

proportion of positive results for groups with and without obstructive CAD (the test is useless) whereas a value of 1 indicates that there are no false positives or false negatives (the test is perfect).

RESULTS

Overall population cohort

Clinical, biological and hemodynamic parameters of the overall population cohort are given in table 1. Patients who underwent elective coronary angiography were more frequently men, past or current smokers compared to patients who did not underwent elective angiography. They had more frequently known CHD, carotid atherosclerosis and presented with lower heart rate. Age, peripheral hemodynamic measurements, aortic PWV and PWV index did not differed significantly between the two groups.

Study cohort

A minority of patients who underwent coronary angiography had obstructive CAD. Ten patients (24%) presented with obstructive CAD. Thirty-two patients (76%) presented with non-obstructive coronary artery lesions from which 16 patients (38% of the study cohort), including the three patients who underwent CTA, had normal coronary angiography.

Clinical, biological and hemodynamic parameters of the patients who underwent elective coronary angiography are given in table 2. Presence of hypertension and diabetes was associated with the severity of coronary artery lesions. Previous diagnosed CHD and peripheral arterial disease were more frequent in patients with obstructive coronary lesions. Estimated glomerular filtration rate (GFR) was negatively correlated with the severity of coronary artery lesions ($p=0.014$). Observed aortic PWV and PWV index were positively correlated with the severity of coronary artery lesions ($p=0.003$ and $p=0.001$, respectively) (Figure 1). Aortic PWV index was significantly increased in the 10 patients with obstructive

CAD in comparison with the others (p=0.004). Aortic PWV index and GFR were not correlated (p=0.24). After adjusting for estimated GFR, aortic PWV index and presence of obstructive and non obstructive coronary artery lesions remained significantly and positively correlated (p=0.006 and p=0.011, respectively).

Performance of screening tests

The results of ECG stress test coupled with myocardial functional imaging by SPECT were studied to evaluate retrospectively the diagnostic accuracy of cardiac stress test for obstructive coronary lesions in the study cohort and the added value of aortic PWV index. Overall, 8 patients had abnormal ECG stress test associated with abnormal myocardial perfusion SPECT and 34 patients presented with discordance between nuclear and clinical responses to stress.

The sensitivity and specificity of cardiac stress test was given in Table 3 and performance index was calculated. In case of discordance between nuclear and clinical responses to stress, the performance of PWV index as a screening test was studied (Table 3). Cardiac stress test accuracy without and with aortic PWV index was calculated with a performance index of respectively 0.41 and 0.69. This result indicated that aortic PWV index should be considered as clinically relevant to rule out the presence of obstructive coronary lesions (negative predictive value of 100%) and to reduce the rate of unnecessary angiographies (22 procedures may have been avoided in the present study cohort).

DISCUSSION

The salient finding of this study was that, in patients with known or suspected CAD, routinely followed-up, aortic PWV index may improve the diagnostic accuracy of non-invasive cardiac testing by reducing unnecessary invasive angiography rate without underestimating the presence of obstructive coronary artery lesions. Furthermore, aortic PWV

index was strongly correlated with the severity of CAD, according to the degree of stenosis, independently of renal function. Thus, aortic stiffness may also be considered as a marker of the presence of non obstructive atherosclerotic coronary lesions which represent a potential target for pharmaceutical interventions to prevent acute coronary syndrome.

Clinical relevance of aortic stiffness as a decision-making tool for the diagnostic use of coronary angiography

In our study cohort, a minority of patients who underwent coronary angiography (24%) had obstructive coronary lesions. No CAD was reported in 38% of the patients. These results are in line with previously published data highlighting the low diagnostic yield of elective coronary angiography (5). Stress myocardial perfusion scintigraphy has emerged as one of the most commonly used functional imaging modality for CHD screening (27). The performance of SPECT in this study was comparable to that in others, and our results pointed out its imperfect level of accuracy in obstructive CAD screening (7). Diagnostic application of SPECT is based on the ability to detect myocardial perfusion abnormality which may be related to a hemodynamically significant and thus flow-limiting epicardial coronary stenosis. However, impaired myocardial perfusion during SPECT may also be related to microvascular dysfunction in patients with angiographically normal or minimally diseased coronary arteries (28, 29). In the present study cohort, 39% of patients presented left ventricular hypertrophy which may be associated with impairment of perfusion reserve independently of the presence of obstructive CAD (30). Furthermore, our results highlighted the fact that clinicians are often confronted with marked discordance between nuclear and clinical responses to stress in patients with suspected CAD.

In the present study, the clinical relevance of aortic stiffness was studied as a noninvasive decision-making tool for further coronary angiography in patients with

discordant results between nuclear and clinical responses to stress. Aortic PWV index was significantly increased in patients with obstructive coronary lesions and was positively correlated with the severity of coronary artery stenosis. The diagnostic accuracy of non invasive cardiac imaging associated with PWV index was substantially improved. In the present study, PWV index may be considered as clinically useful to rule out the presence of obstructive coronary lesions and to reduce the rate of unnecessary angiographies (22 procedures may have been avoided in the study cohort).

Aortic stiffness is increasingly considered as a structural and functional marker of the integrated arterial damage caused by CV risk factors. This arterial marker may also reflect individual susceptibility for atherosclerotic disease which cannot be captured on the basis of known traditional risk factors. Carotid to femoral PWV, as a direct measure of aortic stiffness, is considered as a marker of severity of CAD (31) and thus may be a useful index for CAD screening. Pathophysiological and observational evidence support the clinical relevance of aortic stiffness as a decision-making tool for the diagnostic use of coronary angiography. Aortic wall stiffening leads to increased PWV which is considered as the most important determinant of increased central systolic and pulse pressures in patients with preserved left ventricular ejection fraction (32). Pathogenesis and progression of atherosclerotic damage appear to be driven by pressure pulsatility (33) which is related to expression of adhesion molecules in the endothelium (34) and lipid arterial wall infiltration (35). Observations from cross-sectional studies highlighted the correlation between central pulse pressure and presence, extent and severity of coronary artery plaque (36, 37, 38).

Clinical implications and perspectives

Epidemiological and pathophysiological evidence support the relationship between aortic stiffness and the severity of coronary atherosclerosis. Large prospective data support the

predictive value of aortic PWV for coronary events. In our study population, aortic stiffness assessment improves the diagnostic accuracy of non invasive cardiac imaging and increased PWV index may also be considered as a marker of the presence of coronary atherosclerosis, obstructive or non-obstructive. These considerations have potential clinical implications. Firstly, to be clinically useful for CAD screening, non invasive assessment of aortic stiffness must be relevant at the individual level. In the present study, theoretical PWV was defined on a population of patients routinely followed-up in our Cardiovascular Prevention Unit. This population was representative of the cohort of patients who underwent coronary angiography. In each individual patient who underwent coronary angiography, the equation used to estimate theoretical PWV was based on patient's age, mean arterial pressure and gender which are considered as the most important determinants of aortic wall stiffening (22). The calculation of a PWV index for each patient allows the estimation of the attributable part of aortic stiffness as a marker of CAD, adjusted on these three clinical parameters. We also observed that patients with obstructive coronary artery lesions presented with lower GFR. It has been previously underlined that the incidence and severity of CAD increases as GFR declines (39). Furthermore, the degree of aortic stiffness is known to be negatively correlated with GFR in subjects with mild-to-moderate renal insufficiency (40). In our study population, impaired renal function may have represented a confounding factor in the correlation between aortic PWV index and severity of coronary atherosclerosis. However, after adjusting for GFR, the correlation between aortic PWV index and obstructive and non obstructive coronary lesions remained significant.

Secondly, with the exception of acute coronary syndromes, it remains unclear if percutaneous angioplasty of severe coronary artery stenosis, in association with optimal medical therapy, improves outcomes in patients with stable CAD (41). These results pointed out the concept of vulnerable plaque which is considered as a major precursor of acute

coronary syndrome (42, 43). The severity of coronary stenosis evaluated during angiography appears inadequate to accurately predict the time or location of a future myocardial infarction (44). Pending further methods to identify those coronary plaques that are on the evolution toward a vulnerable state for targeted therapeutic interventions, the pan arterial approach may serve as an aid to identify at-risk patients. The degree of pulsatile stress, which is closely related to aortic stiffness, appears to be associated with the risk of plaque disruption (45). Central pulsatility is considered as the most powerful hemodynamic predictor of CV risk in coronary patients (46). Aortic PWV may therefore represent a candidate marker of arterial damage which may be indicative of the presence of vulnerable plaque prone to rupture.

Thirdly, the clinical importance of non-obstructive CAD in primary prevention was recently highlighted in a large cohort of patients who underwent elective coronary angiography. Compared with patients with no apparent CAD, patients with non-obstructive lesions exhibited significantly greater 1-year risk of myocardial infarction and all-cause mortality (47). In primary prevention, medical management of patients with non-obstructive coronary lesions should warrant further consideration. Presence of non-obstructive CAD in association with increased aortic stiffness may be indicative of a vulnerable population exposed to the risk of cardiovascular events.

Limitations

The present study has limitations common to cross-sectional design, especially in establishing cause-effect relationships between aortic PWV index and severity of CAD or for considerations regarding coronary plaque vulnerability. Most patients with obstructive coronary lesions had more frequently known CHD which may explain the observed increased PWV values. The study cohort was only representative of the patients followed-up in our medical unit. Results have to be confirmed in other populations of patients, in primary prevention.

The definition of the patient population is critical for the evaluation of the clinical relevance of aortic PWV. Calculation of an index is dependent on the theoretical PWV evaluation which is expected to be different based on another patient group. Estimation of theoretical PWV value has included a representative population of patients routinely followed-up for CHD screening in the present medical unit, which may strengthen the individual relevance of aortic stiffness assessment. The small number of patients who underwent elective coronary angiography may represent a principal limitation in this study. Impaired renal function may also represent an important confounding factor of the relation between PWV index and CAD. However, our results underlined that aortic PWV index and severity of CAD remained significantly correlated even after adjusting for GFR. This result may alleviate the problem of the small number of patients included. In fact, renal function always has to be taken into account in the decision to perform angiography, as pre-existing renal disease is considered as the most important risk factor for radiocontrast-induced nephropathy.

The present results call for a prospective study about the relevance of aortic PWV index in CAD screening in association with the current recommended clinical practice. Pathophysiological and epidemiological evidence suggest that this marker of arterial damage may have the potential to improve patient care. This approach is expected to aid the physician in invasive angiography decision in the CAD diagnostic pathway.

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REFERENCES

(1) Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50:2128-2132.

(2) Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014; 35:2950.

(3) Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.

(4) Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Hansen JF. Prevalence and prognostic significance of daily-life silent myocardial ischaemia in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2005;26:1402-1409.

(5) Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG,

Douglas PS. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-895.

(6) Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, Pohost GM, Williams KA. ACCF/ASNC/ACR/AHA/ ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging. Circulation 2009;119:e561-587.

(7) Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguadé-Bruix S, Pizzi MN, Todiere G, Gimelli A, Schroeder S, Drosch T, Poddighe R, Casolo G, Anagnostopoulos C, Pugliese F, Rouzet F, Le Guludec D, Cappelli F, Valente S, Gensini GF, Zawaideh C, Capitanio S, Sambuceti G, Marsico F, Perrone Filardi P, Fernández-Golfín C, Rincón LM, Graner FP, de Graaf MA, Fiechter M, Stehli J, Gaemperli O, Reyes E, Nkomo S, Mäki M, Lorenzoni V, Turchetti G, Carpeggiani C, Marinelli M, Puzzuoli S, Mangione M, Marcheschi P, Mariani F, Giannessi D, Nekolla S, Lombardi M, Sicari R, Scholte AJ, Zamorano JL, Kaufmann PA, Underwood SR, Knuuti J. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015;8(3). pii: e002179. doi: 10.1161/CIRCIMAGING.114.002179.

(8) Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: an update. JACC Cardiovasc Imaging 2011;4:1305-1319.

(9) Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015; 372:1291-1300.

(10) Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999;33:1111-1117.

(11) Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll

Cardiol 2010; 55:1318-1327.

(12) Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014; 63:636-646.

(13) Covic A, Haydar AA, Bhamra-Ariza P, Gusbeth-Tatomir P, Goldsmith DJ. Aortic pulse wave velocity and arterial wave reflections predict the extent and severity of coronary artery disease in chronic kidney disease patients. J Nephrol 2005;18:388-396.

(14) Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

(15) Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. Kidney Int 2003;63:1852-1860.

(16) Henzlova MJ, Cerqueira MD, Mahmarian JJ, Yao SS. Quality Assurance Committee of the American Society of Nuclear Cardiology. Stress protocols and tracers. J Nucl Cardiol 2006;13:e80-90.

(17) Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-1358.

(18) Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed J Am Coll Cardiol 2008 ;52:1724-1732.

(19) Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. Hypertension 1995; 26:485-490.

(20) Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079-2084.

(21) Lieber A, Millasseau S, Bourhis L, Blacher J, Protogerou A, Levy BI, Safar ME. Aortic wave reflection in women and men. Am J Physiol Heart Circ Physiol 2010;299:H236-242.

(22) Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 2010;31:2338-2350.

(23) Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, Balady GJ. Recommendations for clinical exercise laboratories: a scientific statement from the american heart association. Circulation 2009;119:3144-161.

(24) Paul AK, Nabi HA. Gated myocardial perfusion SPECT: basic principles, technical aspects, and clinical applications. J Nucl Med Technol 2004;32:179-187.

(25) Shaw LJ, Berman DS, Bax JJ, Brown KA, Cohen MC, Hendel RC, Mahmarian JJ, Williams KA, Ziffer JA. Computed tomographic imaging within nuclear cardiology. J Nucl Cardiol 2005;12:131-142.

(26) Bradley SM, Maddox TM, Stanislawski MA, O'Donnell CI, Grunwald GK, Tsai TT, Ho PM, Peterson ED, Rumsfeld JS. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (veterans affairs clinical assessment reporting and tracking). J Am Coll Cardiol 2014;63:417-426.

(27) Berman DS, Hachamovitch R, Shaw LJ, Friedman JD, Hayes SW, Thomson L, Fieno DS, Germano G, Slomka P, Wong ND, Kang X, Rozanski A. Roles of nuclear cardiology,

cardiac computed tomography, and cardiac magnetic resonance: assessment of patients with suspected coronary artery disease. J Nuc Med 2006;47:74-82.

(28) Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Freitas A, Habib G, Kitsiou A, Petersen SE, Schroeder S, Lancellotti P, Camici P, Dulgheru R, Hagendorff A, Lombardi M, Muraru D, Sicari R. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging 2015;16:280.

(29) Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular outcome. Coron Artery Dis 2004; 15:259-264.

(30) Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, Selvanayagam JB, Neubauer S, Watkins H. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation 2007;115:2418-2425.

(31) Alarhabi AY, Mohamed MS, Ibrahim S, Hun TM, Musa KI, Yusof Z. Pulse wave velocity as a marker of severity of coronary artery disease. J Clin Hypertens (Greenwich) 2009;11:17-21.

(32) Laurent S, Boutouyrie P. The structural factor of hypertension: large and small artery alterations. Circ Res 2015;116:1007-1021.

(33) Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure – Its role in the pathogenesis of atherosclerosis. Blood Press 2007;16:238-245.

(34) Cheng JJ, Wung BS, Chao YJ, Wang DL. Cyclic strain enhances adhesion of monocytes to endothelial cells by increasing intercellular adhesion molecule-1 expression. Hypertension 1996;28:386-391.

(35) Kiefer CR, McKenney JB, Trainor JF, Snyder LM. Pulse pressure-driven neutral lipid

accumulation and correlative proinflammatory markers of accelerated atherogenesis. Atherosclerosis 2005; 183: 17-24.

(36) Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, Eber B. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184-189.

(37) Waddell TK, Dart AM, Medley TL, Cameron JD, Kingwell BA. Carotid pressure is a better predictor of coronary artery disease severity than brachial pressure. Hypertension 2001; 38: 927-931.

(38) Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Styczkiewicz M, Pośnik-Urbańska A, Bryniarski L, Dudek D. Ascending aortic, but not brachial blood pressure-derived indices are related to coronary atherosclerosis. Atherosclerosis 2004; 176: 151-155.

(39) Chonchol M, Whittle J, Desbien A, Orner MB, Petersen LA, Kressin NR. Chronic kidney disease is associated with angiographic coronary artery disease. Am J Nephrol 2008;28:354-360.

(40) Mourad JJ, Pannier B, Blacher J, Rudnichi A, Benetos A, London GM, Safar ME. Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. Kidney Int 2001;59:1834-1841.

(41) Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-1516.

(42) Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani

Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies. Circulation 2003;108:1664-1672.

(43) Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56-62.

(44) Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157-1166.

(45) Lovett JK, Howard SC, Rothwell PM. Pulse pressure is independently associated with carotid plaque ulceration. J Hypertens 2003; 21: 1669-1676.

(46) Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badełek M, Wiliński J, Curyło AM, Dudek D. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension 2008;51:848-855.

(47) Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, Patel MR, Sandhu A, Valle J, Magid DJ, Leon B, Bhatt DL, Fihn SD, Rumsfeld JS. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA 2014;312:1754-1763.

Table 1: Clinical, biological and hemodynamic parameters of the overall cohort (N=367)

	Patients who did not underwent coronography (N=325)	Patients who did underwent coronography (N=42)	P-value
Gender/ female (%)	141 (43)	7 (17)	**0.002**
Age (years)	61.7 ± 10.8	62.7 ± 10.3	0.55
Body Mass Index (Kg/m^2)	28.6 ± 4.8	27.7 ± 4.1	0.20
Smoking* (%)	135 (42)	25 (60)	**0.04**
Dyslipidemia (%)**	175 (54)	26 (62)	0.34
Hypertension (%)	244 (75)	30 (71)	0.75
Diabetes (%)	147 (45)	19 (45)	0.99
Coronary heart disease §	43 (13)	12 (29)	**0.017**
Previous myocardial infarction	17 (5)	5 (12)	0.17
Carotid plaque (%)	181 (56)	31 (76)	**0.03**
Left ventricular hypertrophy(%)	78 (24)	16 (39)	0.09
Previous Stroke (%)	10 (3)	3 (7)	0.37
Peripheral arterial disease (%)	18 (6)	6 (14)	0.09
Glycated Hemoglobin (%)	6.54 ± 1.46	6.57 ± 5.85	0.88
Creatinine clearance (ml/mn) §§	78 ± 21	83 ± 23	0.22
Heart rate (bpm)	71 ± 11	66 ± 10	**< 0.001**
Brachial systolic BP (mm Hg)	136 ± 15	135 ± 14	0.69
Brachial diastolic BP (mm Hg)	79 ± 9	80 ± 11	0.54
Brachial PP (mm Hg)	57 ± 13	55 ± 11	0.29
Mean arterial pressure (mm Hg)	98 ± 10	98 ± 11	0.82
Aortic PWV (m/sec)	10.49 ±2.50	10.72 ± 3.14	0.65
Aortic PWV index (%)	2.80 ± 19.63	3 ± 22.30	0.95

Continuous variables are presented as mean ± standard deviation. BP, blood pressure; PP, pulse pressure; PWV, pulse wave velocity; * Past and current smokers; ** Patients receiving lipid lowering medication or classified as dyslipidemic; § Coronary heart disease: previous documented myocardial infarction, coronary revascularization or epicardial coronary artery disease diagnosed during coronography for patients with symptoms or typical electrocardiographic modifications. §§ creatinine clearance estimated using MDRD formula. Aortic PWV index (Median value with 95% confidence interval) defined as the difference between observed and theoretical PWV divided by theoretical PWV for each subject.

Table 2: Clinical, biological and hemodynamic parameters of the study cohort (N=42)

	Normal coronary angiography (N=16)	Non Obstructive coronary lesions (N=16)	Obstructive coronary lesions (N=10)	P-value
Gender/ female (%)	6 (37.5)	0 (0)	1 (10)	0.99
Age (years)	61 ± 7	61 ± 14	68 ± 8	0.14
BMI (Kg/m^2)	28.6 ± 4.5	27.3 ± 4.1	27.0 ± 3.4	0.64
Smoking* (%)	9 (56)	8 (50)	8 (80)	0.16
Dyslipidemia (%)**	7 (54)	10 (63)	9 (90)	0.12
Hypertension (%)	8 (50)	12 (75)	10 (100)	**0.04**
Diabetes (%)	4 (25)	7 (44)	8 (80)	**0.03**
Coronary heart disease §	0 (0)	5 (31)	7 (70)	**0.002**
Previous MI	0 (0)	2 (13)	3 (30)	0.08
Carotid plaque (%)	11 (69)	11 (69)	9 (90)	0.53
LVH (%)	5 (31)	5 (31)	6 (60)	0.15
Previous Stroke (%)	1 (6)	1 (6)	1 (10)	0.99
Peripheral arterial disease (%)	1 (6)	1 (6)	4 (40)	**0.02**
Glycated Hemoglobin (%)	5.96 ± 0.85	6.87 ± 1.52	7.00 ± 1.29	**0.05**
Creatinine clearance (ml/mn) §§	81 ± 20	91 ± 22	68 ± 17	**0.014**
Heart rate (bpm)	66 ± 10	64 ± 9	69 ± 10	0.69
Brachial SBP (mm Hg)	133 ± 12	134 ± 13	140 ± 19	0.75
Brachial DBP (mm Hg)	80 ± 13	80 ± 10	78 ± 9	0.81
Brachial PP (mm Hg)	53 ± 8	53 ± 9	62±17	0.27
MAP (mm Hg)	98 ± 12	98 ± 10	98 ± 10	0.99
Aortic PWV (m/sec)	9.09 ± 2.07	10.98 ± 3.40	12.94 ± 2.88	**0.003**
Aortic PWV index (%)	-10.63 ± 19.69	7.44 ±22.33	15.78 ± 15.87	**0.001**

Continuous variables are presented as mean ± standard deviation. BMI, Body Mass Index; MI, Myocardial Infarction; LVH, Left Ventricular Hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; PWV, pulse wave velocity; * Past and current smokers; ** Patients receiving lipid lowering medication or classified as dyslipidemic; § Coronary heart disease defined as previous documented myocardial infarction, coronary revascularization or epicardial coronary artery disease diagnosed during coronography for patients with symptoms or typical electrocardiographic modifications. §§ creatinine clearance estimated using MDRD formula. Aortic PWV index (Median value with 95% confidence interval) defined as the difference between observed and theoretical PWV divided by theoretical PWV for each subject.

Table 3: Performance of cardiac stress test without and with aortic pulse wave velocity (PWV) index for obstructive coronary artery disease (CAD) screening in the study cohort (N=42). Performance index (ranged from 0 to 1) is defined as the sum of sensitivity and specificity minus 1.

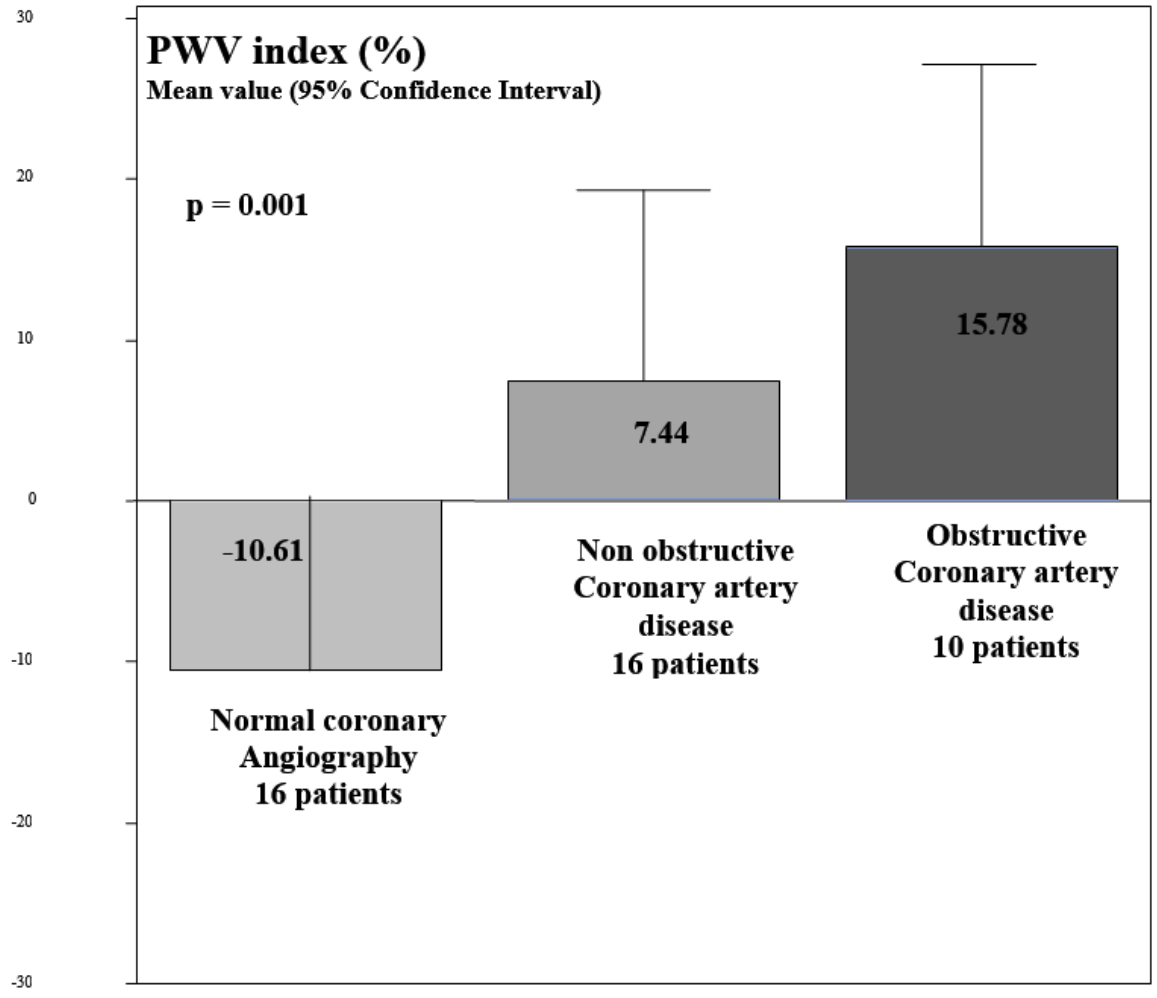
	Presence of obstructive CAD		Sensitivity (%)	Specificity (%)	Performance index
	Yes (n=10)	No (n=32)			
Cardiac stress test without PWV index §					
Abnormal	**5***	**3****	50 [19-81]	91 [80-100]	**0.41**
Discordant	**5**	**29**			
Cardiac stress test with PWV index §§					
Abnormal	**10**	**10**	100	69 [53 –85]	**0.69**
Normal	**0**	**22**			

*: All patients had positive Pulse wave velocity index, **: One patient had negative pulse wave velocity index.

§ Abnormal test was defined as abnormal ECG stress test and abnormal scintigraphy; Discordance between nuclear and clinical results was defined as discordant test.

§§ Abnormal test was defined as abnormal ECG stress test and abnormal nuclear imaging or discordance between nuclear and clinical results associated with positive PWV index.

Figure 1: Aortic pulse wave velocity (PWV) index and severity of coronary artery disease.



4.2.3 Conclusion de l'article 9

La conclusion principale de cette étude est que l'index VOP peut améliorer la précision des tests de dépistage chez des patients avec ou sans maladie coronaire connue, sans insuffisance cardiaque, en réduisant le taux de coronarographies inappropriées sans sous-estimer la présence de lésions obstructives. De plus, l'index VOP est corrélé à la présence et à la gravité de la maladie coronaire, évaluée par le degré de sténose. La rigidité aortique peut ainsi être considérée comme le marqueur de la présence de lésions coronaires, obstructives ou non obstructives, cibles thérapeutiques potentielles pour la prévention des syndromes coronariens aigus.

Dans cette étude, seuls 24 % des patients ayant eu une coronarographie élective avaient effectivement des lésions coronaires obstructives. L'absence d'athérome coronaire lors de l'angiographie concernait 38 % des patients. De plus, 80 % des patients ayant eu une coronarographie avaient des résultats discordants entre test clinique et imagerie nucléaire.

La pertinence clinique de l'index VOP a été étudiée de manière rétrospective comme outil de décision pour la réalisation d'une coronarographie en cas de discordance entre l'épreuve d'effort et la scintigraphie myocardique. Evaluée selon l'index de Youden (sensibilité + spécificité - 1), la performance du test de dépistage couplé à l'index VOP a été sensiblement améliorée. La performance de l'épreuve d'effort couplée avec la scintigraphie myocardique était évaluée avec un index à 0.41. Lorsque la mesure de la VOP était prise en compte, la performance du test de dépistage était évaluée à 0.69. Un index VOP négatif ou nul permettait d'exclure la présence de lésions coronaires obstructives (22 procédures auraient pu être évitées dans la cohorte étudiée).

La rigidité aortique est considérée comme le principal déterminant de l'augmentation de la pression pulsée centrale en présence d'une fraction d'éjection du ventricule gauche

conservée (186, 187). La pathogénèse et la progression des lésions athéromateuses apparaissent corrélées à la pulsatilité de la pression artérielle (188). Des données observationnelles transversales ont mis en évidence une corrélation entre la pression pulsée centrale et la présence, l'étendue et la sévérité de l'athérome coronaire (189). De plus, la contrainte pulsatile est corrélée au risque de rupture de plaque (190) et pourrait donc être considérée comme le marqueur de plaque vulnérable.

A l'exception du syndrome coronarien aigu, le bénéfice d'une angioplastie d'une lésion coronaire obstructive, en association au traitement médicamenteux optimal, reste toujours très discuté chez le patient coronarien stable. Cette stratégie invasive de prise en charge ne paraît pas supérieure au traitement médicamenteux optimal en termes d'incidence d'événements coronariens (191). De plus, il a été montré que la sévérité d'une sténose coronaire observée lors de l'angiographie est un critère insuffisant pour prédire avec précision le moment et le territoire de survenue d'un syndrome coronarien aigu (192). Ces données mettent en avant le concept de vulnérabilité de la plaque, indépendamment du degré de sténose. La présence de lésions coronaires non obstructives associées à une rigidité aortique majorée pourrait être représentative d'une population vulnérable exposée au risque d'événements coronariens aigus.

La définition de la population d'étude est essentielle pour l'évaluation de la pertinence clinique de l'index VOP. La valeur théorique de la VOP a été estimée pour chaque patient ayant eu une coronarographie d'après les données de VOP d'une population représentative suivie en hôpital de jour. Les patients de cette population étaient majoritairement hypertendus et/ou diabétiques, ce qui peut renforcer la pertinence de l'évaluation de cet index à l'échelle individuelle. Cependant, parmi les 42 patients ayant eu une coronarographie, la présence de maladie coronaire obstructive concernait une population hypertendue avec une prévalence plus élevée de maladie diabétique, d'antécédent de coronaropathie et de maladie artérielle

périphérique, qui peuvent représenter des facteurs confondants dans la relation entre maladie coronaire obstructive et index VOP. De plus, ce groupe de patients présentait également un débit de filtration glomérulaire significativement plus bas (68 ± 17 ml/mn) par rapport au groupe de patients avec lésions coronaires non obstructives (87 ± 22 ml/mn). La maladie rénale pourrait également représenter un important facteur confondant dans la relation entre index VOP et sévérité de la maladie coronaire. Cependant, après ajustement sur le débit de filtration glomérulaire, la corrélation positive entre index VOP et présence de lésions coronaires non-obstructives et obstructives reste significative.

Une population d'étude plus large est essentielle pour déterminer l'utilité de l'index VOP dans le dépistage de la maladie coronaire en association aux recommandations de bonne pratique actuelles. Cette approche peut aider le praticien dans la décision de réalisation d'une coronarographie diagnostique et dans la prise en charge médicamenteuse préventive des patients.

Chapitre 5
Perspectives

5.1 Prévention cardiovasculaire

La rigidité aortique est considérée comme un facteur prédictif indépendant du risque de survenue d'événement cardiovasculaire (91, 92), étudié dans différentes populations de patients présentant des facteurs de risque (1, 2, 3, 178) et dans la population âgée sans maladie cardiovasculaire et non institutionnalisée (90, 193, 194). La rigidité des gros troncs artériels est en majeure partie déterminée par le vieillissement physiologique à partir de l'âge de 50 ans. Cette relation est modulée par le niveau de pression artérielle : l'effet de l'âge sur la rigidité aortique est amplifié par le niveau de pression artérielle moyenne (75). L'existence de valeurs de référence pour la VOP carotido-fémorale en fonction de l'âge et de la pression artérielle moyenne dans une large population en Europe permettrait d'utiliser cette mesure en pratique clinique. Le haut risque cardiovasculaire d'un patient serait ainsi identifié en raison d'une rigidité aortique majorée au-delà du vieillissement physiologique et du niveau de pression artérielle moyenne. Cependant, il est noté que les différences inter-individuelles de VOP carotido-fémorale pour un âge et un niveau de pression moyenne donnés, sont plus marquées que les différences entre les classes d'âge ou de pression artérielle (75). D'autres facteurs, métaboliques, inflammatoires ou épigénétiques, interviennent donc également dans l'atteinte structurale de la paroi aortique. Ce marqueur artériel est intégré dans les recommandations européennes pour l'évaluation de l'atteinte des organes cibles chez le patient hypertendu (174). Très récemment, les recommandations américaines ont également souligné l'importance de la mesure de la VOP carotido-fémorale dans l'estimation du risque cardiovasculaire (195).

Une récente méta-analyse de données individuelles regroupant 17 635 participants au sein de 16 études a confirmé la valeur prédictive de la VOP carotido-fémorale dans la reclassification du risque cardiovasculaire (92). Le pouvoir prédictif de la rigidité aortique est particulièrement souligné dans les tranches d'âge les plus jeunes (<50 ans et <60 ans). La mesure de la VOP carotido-fémorale apparaît donc comme un outil utile en pratique clinique pour identifier précocement les patients les plus à risque, avant que l'altération structurale de la paroi aortique ne soit devenue potentiellement irréversible.

Dans un contexte de rigidité aortique majorée à un tel degré du fait d'un âge avancé ou de l'exposition prolongée à des facteurs de risque, la capacité discriminative pour le risque cardiovasculaire de ce paramètre hémodynamique apparaît être limitée (89, 103, 196). Dans ce contexte de rigidité aortique majorée, l'amplification de la pression pulsée peut rendre compte du maintien d'un couplage optimal entre le cœur et l'aorte, en limitant ainsi le niveau de pression pulsée centrale (197).

Cette hypothèse a des conséquences en termes de stratégies de réduction du risque (198). Le patient à haut risque cardiovasculaire étant individualisé, la question d'une cible thérapeutique précise se pose, au-delà du contrôle des facteurs de risque cardiovasculaire. La rigidité aortique peut être considérée comme un marqueur intermédiaire potentiel. L'amélioration de la compliance aortique sous traitement médicamenteux et règles hygiéno-diététiques (199) pourrait être associée à l'amélioration du pronostic cardiovasculaire au-delà de la baisse tensionnelle. Cependant, bien que la composante fonctionnelle de la rigidité aortique soit très corrélée au niveau de pression artérielle, le traitement d'une hypertension artérielle n'entraîne pas toujours une baisse de la VOP (200). Le traitement ciblé des anomalies structurales de la paroi aortique, au-delà de la prise en charge de l'hypertension artérielle, pourrait ne pas être adapté et potentiellement délétère dans un contexte de rigidité aortique majorée. Cette

situation pathologique est fréquemment rencontrée en pratique clinique, en particulier chez les patients âgés, les patients avec maladie rénale chronique, avec maladie diabétique ou hypertensive évoluant depuis plusieurs années ainsi que chez les patients en prévention secondaire. Deux études menées sur des populations en prévention secondaire (patients avec insuffisance rénale terminale (115) et patients coronariens (201)) ont démontré que l'absence de diminution de la rigidité aortique sous traitement antihypertenseur optimale était prédictive du risque de survenue d'événements cardiovasculaires majeurs.

La stratégie de réduction du risque devrait donc être pensée en individualisant les patients en prévention primaire, les patients avec maladie cardiovasculaire ou rénale établie et en tenant compte de l'âge. Chez les patients les plus jeunes, en prévention primaire, l'objectif de la prise en charge est de corriger de manière stricte tous les facteurs de risque afin de prévenir la survenue précoce d'un événement. La rigidité aortique représente alors un marqueur intermédiaire et une cible thérapeutique potentielle (202). Chez les patients âgés ou avec maladie artérielle évoluée, l'objectif du traitement est double : dans un contexte de rigidité aortique avancée, il est nécessaire d'éviter la survenue ou la récidive d'un événement mais sans que le traitement ne devienne délétère. Les anomalies structurales de la paroi aortique pourraient être peu ou pas réversibles sous traitement antihypertenseur à des valeurs de pression artérielle périphérique considérées comme optimales. Deux principales questions se posent alors : quel délai doit-on attendre pour évaluer l'efficacité du traitement sur la VOP au-delà de l'obtention de chiffres de pression artérielle optimaux, avant de majorer les posologies médicamenteuses ? Comment évaluer de façon objective la tolérance de l'escalade progressive des traitements antihypertenseurs ? La baisse excessive des niveaux de pression artérielle périphérique au cours d'une stratégie de réduction des anomalies structurales de la paroi aortique, pourrait avoir des conséquences délétères en termes d'évènements cardiovasculaires chez certains patients. Une réduction marquée de la pression centrale systolique et plus

particulièrement de la pression diastolique est associée au phénomène de courbe en J (203) principalement mis en évidence pour le risque coronaire. Inversement, pour le risque d'accident vasculaire cérébral, cette relation de courbe en J entre baisse excessive de la pression artérielle et événement ischémique ne semble pas documentée (203, 204).

La pression centrale représente une cible thérapeutique potentielle, en particulier chez les patients âgés ou en prévention secondaire, dans l'objectif de corriger le risque résiduel et d'éviter un phénomène de courbe en J pour les patients à risque coronarien. La prise en considération de la pression centrale serait d'autant plus logique que les molécules antihypertensives proposées dans les stratégies de réduction de la rigidité aortique ont un impact différent sur le phénomène d'amplification. A même niveau de pression périphérique, certaines molécules antihypertensives seraient donc associées à une baisse plus marquée de la pression centrale (100, 105).

L'étude du bénéfice clinique de la baisse de la pression pulsée centrale chez le patient hypertendu, indépendamment du niveau de pression artérielle périphérique, est la première étape dans la confirmation de l'utilité de ce paramètre hémodynamique en pratique clinique. La reproductibilité et la fiabilité de sa mesure non invasive est un prérequis indispensable. Plusieurs dispositifs existent dont la tonométrie d'aplanation, opérateur-dépendant, ainsi que des dispositifs automatisés opérateur-indépendants permettant la mesure ambulatoire des paramètres hémodynamiques centraux (205). Les dispositifs sur le marché n'ont cependant pas tous été validés en comparaison à la mesure invasive (de référence) de la pression aortique. De plus, les méthodes de calibration et les sites de mesure de l'onde de pouls diffèrent (tonométrie d'aplanation radiale ou carotidienne, mesure oscillométrique automatisée au niveau brachiale). Ces différentes méthodes de mesure apparaissant non interchangeables (206). Un accord professionnel est donc nécessaire sur la méthode d'évaluation non

invasive de la pression centrale. L'appareil Sphygmocor, considéré comme une méthode de mesure comparative de référence dans plusieurs études (205), permet d'estimer la pression aortique par tonométrie radiale associée à une fonction de transfert. La forme de l'onde de pouls obtenue au niveau radial est calibrée avec les valeurs de pressions brachiales systolique et diastolique mesurées au brassard. Cette calibration ne prend pas en compte l'amplification, non négligeable, de la pression systolique entre l'artère brachiale et radiale (207). Les valeurs de pression centrale apparaissent par conséquent sous-estimées avec cette méthode de mesure. La valeur de l'amplification de la pression systolique et pulsée entre artère carotide et radiale peut être surestimée. Afin d'éviter les erreurs de calibration, il apparaît donc nécessaire de calibrer la forme de l'onde de pression mesurée au niveau radial par la pression artérielle moyenne et diastolique brachiales, considérées comme constantes sur l'arbre artériel. Cette méthode de calibration est également utilisée lors de la mesure directe de la pression centrale par tonométrie carotidienne. Une méthode de mesure automatisée serait la prochaine étape dans l'estimation de la pression centrale (208). La forme de l'onde de pression peut être directement obtenue et calibrée au niveau brachial par méthode oscillométrique, évitant ainsi les erreurs de calibration associée à l'amplification brachio-radiale. Cependant, une des principales limites dans l'estimation non invasive de la pression centrale reste la mesure oscillométrique de la pression artérielle périphérique, sous- estimant la valeur systolique et surestimant la valeur diastolique (209).

Les méthodes de mesure automatisées pourront permettre à terme l'évaluation des paramètres hémodynamiques centraux de manière plus fiable et reproductible dans les protocoles de recherche clinique ainsi que leur étude en ambulatoire. Les mesures de la pression centrale, de l'amplification de la pression pulsée et de la rigidité aortique devront être réalisées en parallèle de la mesure conventionnelle brachiale au début de la prise en charge du patient

hypertendu et au cours du suivi. La prise en charge médicamenteuse, le choix des molécules et l'escalade thérapeutique se fera en fonction des recommandations françaises pour la prise en charge d'une hypertension essentielle (35) ou résistante (210). La valeur pronostique de la modulation des paramètres hémodynamiques centraux sous traitement antihypertenseur, indépendamment du niveau de pression artérielle périphérique, devra être étudiée pour le risque coronaire et cérébrovasculaire. Les molécules antihypertensives modulant le niveau de pression pulsée, indépendamment de la baisse de la pression artérielle moyenne pourront être individualisées et leurs mécanismes d'action précisés (211). En particulier, les molécules et combinaisons antihypertensives entraînant une atténuation de l'amplitude de l'onde de pression incidente et des ondes réfléchies seront précisées. La modulation de la rigidité de l'aorte ascendante (212, 213), l'allongement du temps de transit des ondes de réflexion (113, 214), le raccourcissement du temps d'éjection systolique, la baisse de la pré-charge du ventricule gauche et l'augmentation de la relaxation ventriculaire (215) pourraient rendre compte du bénéfice de certaines molécules, indépendamment de la baisse de la pression artérielle moyenne, en termes de survenue d'événements chez le patient hypertendu. Une attention particulière devrait être portée sur l'effet des molécules ayant une action vasodilatatrice au niveau artériolaire. L'hypothèse relevée serait l'effet délétère de la transmission de l'énergie pulsatile à la microcirculation, facilitée par la baisse des résistances vasculaires périphériques (202).

5.2 Dépistage de la maladie coronaire

Une des principales conclusions de ce travail est que la prise en compte de la rigidité aortique peut améliorer la valeur prédictive positive des tests de dépistage de la maladie coronaire, réduisant le taux de coronarographies inappropriées sans sous-estimer la présence

de lésions coronaires obstructives.

La compréhension des mécanismes physiopathologiques reliant les paramètres hémodynamiques centraux et la survenue d'événements coronariens permettra d'améliorer le dépistage chez les sujets à risque et de préciser les indications de coronarographie (216, 217). En raison de la nature multifactorielle de la maladie coronaire, il est nécessaire de prendre en compte des paramètres intégrateurs des facteurs de risque cardiovasculaire. Pour être validée et utilisable en pratique clinique, la valeur prédictive de la rigidité aortique devra s'ajouter à celle de l'épreuve d'effort associée au bilan cardiovasculaire standard de tout patient à risque. Une reclassification du risque coronarien est attendue à l'aide de cette mesure non invasive en plus de la prise en charge diagnostique conventionnelle. L'évaluation prospective permettra de préciser le bénéfice à la fois en termes de réduction d'examens invasifs inappropriés et aussi d'amélioration du pronostic coronaire.

Récemment, une stratégie de dépistage par angioscanner coronaire n'a pas montré d'amélioration du pronostic en termes de réduction d'évènements coronariens en comparaison au dépistage fonctionnel (ECG d'effort, échocardiographie de stress ou imagerie nucléaire) (184). Ces résultats mettent en avant le concept de plaque vulnérable, obstructive ou non obstructive, considérée comme le précurseur d'un syndrome coronarien aigu (218). Ainsi, la sévérité d'une lésion coronarienne évaluée en angiographie n'est pas un facteur prédictif du site d'un futur syndrome coronarien aigu (192, 218). La limite principale des stratégies actuelles de dépistage tient au fait que seules les lésions sévères hémodynamiquement significatives sont dépistées et traitées de manière interventionnelle. Les lésions athéromateuses récentes avec peu de débord endoluminal du fait du remodelage premier excentrique adaptatif de la coronaire ne sont pas dépistées par l'épreuve d'effort car non hémodynamiquement significatives. Elles ne sont pas non plus détectées ou traitées lors de la

coronarographie car non sténosantes. Ces plaques athéromateuse ne sont donc pas ciblées par les stratégies de dépistage. Ce sont pourtant ces lésions coronariennes précoces, sans chape fibreuse stable, qui semblent être les plus vulnérables et par conséquent les plus dangereuses en termes d'événements cliniques, entraînant une thrombose artérielle aiguë en cas de brèche endothéliale (218).

Une plus large population d'étude permettrait de confirmer l'amélioration du dépistage de la maladie coronaire par la mesure de la rigidité aortique. Dans un premier temps, la valeur prédictive de la rigidité aortique pour la présence de lésions obstructives doit être évaluée rétrospectivement, comme dans le cas de la présente étude, sur une plus large cohorte de patients, en prévention primaire. La décision de réalisation d'une coronarographie sera prise en fonction des caractéristiques cliniques et du résultat de l'épreuve d'effort en concertation pluridisciplinaire. La sensibilité et la spécificité de l'index VOP devront être évaluées chez les patients ayant eu une coronarographie. Il est attendu une amélioration du modèle prédictif de la présence de lésions coronaires obstructives. Une stratégie de dépistage prenant en compte la mesure de l'index VOP, en comparaison aux recommandations de bonnes pratiques actuelles, doit être étudiée par la suite chez les patients à risque en prévention primaire. Un premier objectif sera l'étude de l'amélioration du dépistage des lésions coronaires obstructives, responsables d'une ischémie, et susceptibles donc d'être traitées spécifiquement. Un deuxième objectif sera l'étude de l'amélioration du pronostic cardiovasculaire des patients au cours du suivi prospectif.

La stratégie de dépistage consisterait à proposer un deuxième test d'ischémie aux patients ayant un premier test fonctionnel négatif (ou non concluant) associé à un index VOP positif. La décision de réalisation de la coronarographie pourrait alors être prise en fonction des critères cliniques et du résultat de ce deuxième test fonctionnel. L'index VOP aiderait dans ce

cas à pallier au risque de faux négatifs de l'épreuve d'effort. Pour les patients ayant un premier test d'ischémie positif associé à un index VOP nul ou négatif, un complément d'examen morphologique non invasif serait alors proposé avant la décision d'une exploration coronaire invasive. Dans ce cas, l'angioscanner coronaire représenterait un choix d'imagerie approprié en raison de sa forte valeur prédictive négative. L'index VOP pourrait aider dans ce cas à préciser les indications de coronarographie afin d'éviter les examens invasifs inutiles.

Dans l'objectif d'améliorer le pronostic coronaire des patients, la mise en place d'un traitement médicamenteux préventif serait discutée sur la positivité de l'index VOP, même en l'absence de lésions coronaires angiographiquement détectables. Le traitement de la maladie coronaire ne peut pas être limité à la seule revascularisation de lésions serrées. Les syndromes coronariens aigus sont souvent concomitants de rupture de plaques instables non serrées. De plus, l'analyse quantitative de la maladie coronaire lors de l'angiographie reste limitée, seule la lumière du vaisseau, et non sa paroi, étant analysable. Un index VOP positif pourrait être le témoin de la présence et de l'étendue d'une maladie coronaire (avec ou sans sténose angiographiquement détectable). La pulsatilité de la pression artérielle a été corrélée à la présence, l'étendue et la sévérité de l'athérome coronarien (189, 219) ainsi qu'au risque de rupture de plaque athéromateuse (190). Ainsi, la rigidité aortique peut représenter un marqueur artériel candidat dans l'amélioration du dépistage de la maladie coronaire. La mise en place d'un traitement médicamenteux préventif en présence d'une rigidité aortique majorée au-delà de l'âge et du niveau de pression artérielle peut également présenter un bénéfice en termes de pronostic cardiovasculaire.

Conclusion

Une meilleure compréhension des mécanismes physiopathologiques reliant la maladie artérielle infra clinique et la survenue d'événements cardiovasculaires permettrait d'adapter la prise en charge thérapeutique préventive des patients. Le bénéfice attendu de cette stratégie de prise en charge est la correction du risque résiduel persistant malgré le bon contrôle des facteurs de risque classiques. Ce risque résiduel est d'une part expliqué par des cibles thérapeutiques (pression artérielle périphérique ou dosage ponctuel de paramètres biologiques) insuffisamment adaptées à l'échelle individuelle, chez le patient hypertendu, diabétique ou avec maladie rénale chronique. Il peut d'autre part être le reflet de l'existence de facteurs de risque « non traditionnels » que sont les maladies infectieuses chroniques. La maladie artérielle infra-clinique doit être ainsi considérée comme le témoin d'une plus grande susceptibilité individuelle à la survenue d'un événement.

Concernant notre premier objectif, nous avons montré que l'association hypertension artérielle et maladie diabétique est définie par un profil hémodynamique particulier. Malgré la présence d'une rigidité aortique majorée, le phénomène d'amplification de la pression pulsée n'apparaît pas atténué en comparaison aux patients non hypertendus non diabétiques. La fréquence cardiaque majorée chez les patients hypertendus diabétiques pourrait rendre compte du maintien du phénomène d'amplification, limitant ainsi le niveau de pression pulsée centrale. En présence d'une rigidité aortique majorée, le rôle de la fréquence cardiaque dans le maintien du phénomène d'amplification reste à étudier, chez les hommes et les femmes. La glycémie apparaît être un déterminant important du niveau de rigidité aortique au cours du vieillissement, indépendamment du niveau de pression artérielle moyenne. Nos résultats soulignent également le fait que l'amplification de la pression pulsée est un puissant marqueur de la présence d'une maladie artérielle établie, indépendamment de la rigidité aortique et de la

présence d'une hypertension artérielle ou d'un diabète. La rigidité aortique et l'amplification de la pression pulsée ne sont pas des paramètres artériels interchangeables. Ces paramètres fournissent donc des informations complémentaires pour le risque cardiovasculaire. L'amplification de la pression pulsée représente un paramètre hémodynamique multifactoriel modulable sous traitement, indépendamment de la baisse tensionnelle périphérique. Dans la cohorte de patients avec infection VIH d'âge moyen traités et contrôlés sur le plan virologique, nos résultats soulignent que le niveau de rigidité aortique n'est pas majoré par rapport aux valeurs théoriques en fonction de l'âge et du niveau de pression artérielle moyenne. Nos résultats soulignent également que le taux de vitamine D plasmatique est corrélé à l'amplification de la pression pulsée chez ces patients. Des études interventionnelles apparaissent nécessaires pour étudier la relation entre correction d'une carence en vitamine D, paramètres artériels et prévention cardiovasculaire chez les patients avec infection VIH. Concernant le deuxième objectif de notre travail, nous avons montré que la rigidité aortique représente un marqueur indépendant de maladie cardiovasculaire chez des patients diabétiques de type 2. Le suivi de l'évolution des paramètres hémodynamiques artériels sous traitement en parallèle avec les données de morbidité et de mortalité cardiovasculaire permettra de préciser de nouvelles cibles thérapeutiques.

Enfin, la prise en compte de l'atteinte artérielle infra-clinique peut améliorer le dépistage de la maladie coronaire et préciser les indications de coronarographie. En réponse au troisième objectif, nos résultats soulignent le fait que la rigidité aortique est un marqueur candidat permettant de corriger le risque de faux positifs et de faux négatifs des examens de dépistage coronaire. Il sera de plus nécessaire de démontrer de manière prospective que la prise en compte de ce marqueur artériel dans le dépistage de la maladie coronaire est associée à une amélioration du pronostic des patients.

Bibliographie

1. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999; 99(18):2434-2439.

2. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic Pulse Wave Velocity as a Marker of Cardiovascular Risk in Hypertensive Patients. Hypertension 1999; 33(5):1111-1117.

3. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37(5):1236-1241.

4. Debbabi H, Uzan L, Mourad JJ, Safar M, Levy BI, Tibiriçà E. Increased Skin Capillary Density in Treated Essential Hypertensive Patients. Am J Hypertens 2006; 19(5):477-483.

5. De Ciuceis C, Porteri E, Rizzoni D, Rizzardi N, Paiardi S, Boari GE, Miclini M, Zani F, Muiesan ML, Donato F, Salvetti M, Castellano M, Tiberio GA, Giulini SM, Agabiti Rosei E. Structural Alterations of Subcutaneous Small-Resistance Arteries May Predict Major Cardiovascular Events in Patients With Hypertension. Am J Hypertens 2007; 20(8):846-852.

6. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, Struijker-Boudier HA. Impaired Tissue Perfusion: A Pathology Common to Hypertension, Obesity, and Diabetes Mellitus. Circulation 2008; 118(9):968-976.

7. Serné EH, de Jongh RT, Eringa EC, IJzerman RG, Stehouwer CD. Microvascular Dysfunction: A Potential Pathophysiological Role in the Metabolic Syndrome. Hypertension 2007; 50(1):204-211.

8. Safar ME, Levy BI, Struijker-Boudier H. Current Perspectives on Arterial Stiffness and Pulse Pressure in Hypertension and Cardiovascular Diseases. Circulation 2003; 107(22):2864-2869.

9. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 2006.

10. Safar ME., O'Rourke M, Frohlich ED (Eds.). Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases. Publisher Springer, ISBN: 978-1-4471-5197-5, 2014.

11. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985) 2008; 105(5):1652-1660.

12. McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe CV, Cockcroft JR, Wilkinson IB; on Behalf of the Anglo-Cardiff Collaborative Trial Investigators. Central Pressure: Variability and Impact of Cardiovascular Risk Factors. The Anglo-Cardiff Collaborative Trial II. Hypertension 2008; 51(6):1476-1482.

13. Avolio A, Van Bortel L, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension 2009; 54(2):375-383.

14. Albaladejo P, Copie X, Boutouyrie P, Laloux B, Déclère AD, Smulyan H, Bénétos A. Heart Rate, Arterial Stiffness, and Wave Reflections in Paced Patients. Hypertension 2001; 38(4):949-952.

15. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001; 103(9):1245-1249.

16. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, Wang JG, Fagard RH, Safar ME. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000; 160(8):1085-1089.

17. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. Hypertension 2001; 38(6):1461-1466.

18. Cooper LL, Rong J, Benjamin EJ, Larson MG, Levy D, Vita JA, Hamburg NM, Vasan RS, Mitchell GF.Components of hemodynamic load and cardiovascular events: the Framingham Heart Study. Circulation 2015; 131(4):354-361.

19. Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Arterial Stiffness and Wave Reflection: Sex Differences and Relationship with Left Ventricular Diastolic Function. Hypertension 2012; 60(2):362-368.

20. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med 2009; 169(19):1767-1774.

21. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000; 86(10):1090-1096.

22. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME.Comparative effects of aging in men and women on the properties of the arterial tree. J Am Coll Cardiol 2001; 37(5):1374-1380.

23. Torjesen AA, Wang N, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Forward and backward wave morphology and central pressure augmentation in men and women in the Framingham Heart Study. Hypertension 2014;64(2):259-265.

24. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360 (9349):1903-1913.

25. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure. The Framingham Heart Study. Circulation 2002; 106(24):3068-3072.

26. Fesler P, Safar ME, du Cailar G, Ribstein J, Mimran A. Pulse pressure is an independent determinant of renal function decline during treatment of essential hypertension. J Hypertens 2007;25(9):1915-1920.

27. Staessen JA, Richart T, Birkenhäger WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension 2007; 49(3):389-400.

28. Lawes CMM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke. An overview of published reviews. Stroke 2004; 35(4):1024-1033.

29. Hackam DG, Duong-Hua ML, Mamdani M, Li P, Tobe SW, Spence JD, Garg AX. Angiotensin inhibition in renovascular disease: A population-based cohort study. Am Heart J 2008; 156(3):549-555.

30. Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, Casiglia E, Kerlikowske K, Coope J. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. Lancet 1999; 353(9155):793-796.

31. Systolic Hypertension in Elderly Patients Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; 265(24):3255-3264.

32. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358(18):1887-1898.

33. Balkau B, Vernay M, Mhamdi L, Novak M, Arondel D, Vol S, Tichet J, Eschwège E. The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. Diabetes Metab 2003; 29(5):526-532.

34. Zhang Y, Lelong H, Kretz S, Agnoletti D, Mourad JJ, Safar ME, Blacher J. Characteristics and future cardiovascular risk of patients with not-at-goal hypertension in general practice in France: the AVANT'AGE study. J Clin Hypertens (Greenwich) 2013; 15(4):291-295.

35. Blacher J, Halimi JM, Hanon O, Mourad JJ, Pathak A, Schnebert B, Girerd X; French Society of Hypertension. Management of hypertension in adults: the 2013 French Society of Hypertension guidelines. Fundam Clin Pharmacol 2014; 28(1):1-9.

36. Blacher J, Evans A, Arveiler D, Amouyel P, Ferrières J, Bingham A, Yarnell J, Haas B, Montaye M, Ruidavets J-B, Ducimetière P, on behalf of the PRIME study group. Residual cardiovascular risk in treated hypertension and hyperlipidaemia: The PRIME study. J Hum Hypertens 2010; 24(1):19-26.

37. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL, The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28(12):1462-1536.

38. Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. Lancet 1979; 1(8121):861-865.

39. Messerli FH, and Panjrath GS. The J-Curve Between Blood Pressure and Coronary Artery Disease or Essential Hypertension, Exactly How Essential? J Am Coll Cardiol 2009; 54(20):1827-1834.

40. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation 2009; 119(2):243-250.

41. Franklin SS, Gokhale SS, Chow VH, Larson MG, Levy D, Vasan RS, Mitchell GF, Wong ND. Does low diastolic blood pressure contribute to the risk of recurrent hypertensive cardiovascular disease events? The Framingham Heart Study. Hypertension 2015; 65(2):299- 305.

42. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A. European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009; 27(11):2121-2158.

43. Stacy DL, Prewitt RL. Effects of chronic hypertension and its reversal on arteries and arterioles. Circ Res 1989; 65(4):869-879.

44. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, Thomas F, Pannier B, Asmar R, Zureik M, Safar M, Guize L. Determinants of Accelerated Progression of Arterial Stiffness in Normotensive Subjects and in Treated Hypertensive Subjects Over a 6- Year Period. Circulation 2002; 105(10):1202-1207.

45. Humphrey JD. Mechanisms of Arterial Remodeling in Hypertension: Coupled Roles

of Wall Shear and Intramural Stress. Hypertension 2008; 52(2):195-200.

46. Safar ME, Peronneau PA, Levenson JA, Toto-Moukouo JA, Simon AC. Pulsed Doppler: diameter, blood flow velocity and volumic flow of the brachial artery in sustained essential hypertension. Circulation 1981; 63(2):393-400.

47. Westerhof BE, Westerhof N. Magnitude and return time of the reflected wave: the effects of large artery stiffness and aortic geometry. J Hypertens 2012; 30(5):932-939.

48. Safar ME, Toto-Moukouo JJ, Bouthier JA, Asmar RE, Levenson JA, Simon AC, London GM. Arterial dynamics, cardiac hypertrophy, and antihypertensive treatment. Circulation 1987; 75(1 Pt 2):I156-161.

49. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/ Environment Susceptibility – Reykjavik Study. Brain 2011; 134(Pt 11):3398-3407.

50. Wang KL, Cheng HM, Chuang SY, Spurgeon HA, Ting CT, Lakatta EG, Yin FC, Chou P, Chen CH. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertens 2009; 27(3):461-467.

51. O'Rourke MF, Safar ME. Relationship between Aortic Stiffening and Micro vascular Disease in Brain and Kidney. Cause and Logic of Therapy. Hypertension 2005; 46(1):200-204.

52. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women. The Framingham Heart Study. Hypertension 2004; 43(6):1239-1245.

53. Allen SP, Wade SS, Prewitt RL. Myogenic tone attenuates pressure induced gene expression in isolated small arteries. Hypertension 1997; 30(2 Pt 1):203-208.

54. Ono Z, Prewitt RL, Stacy DL. Arteriolar changes in developing and chronic stages of two-kidney, one clip hypertension. Hypertension 1989; 14(1):36-43.

55. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation. 2010; 122(14):1379-1386.

56. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol 2008; 51(14):1377-1383.

57. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA 2012; 308(9):875-881.

58. Mitchell GF, De Stefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, Vita JA, Levy D. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. Circulation 2005; 112(2):194-199.

59. Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, Levy BI, Smulyan H. Hypertension and vascular dynamics in men and women with metabolic syndrome. J Am Coll Cardiol 2013; 61(1):12-19.

60. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008; 51(4):527-539.

61. Blacher J, Demuth K, Guerin AP, Safar ME, Moatti N, London GM. Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. Arterioscler Thromb Vasc Biol 1998; 18(4):535-541.

62. Townsend RR. Pathogenesis of drug-resistant hypertension. Semin Nephrol 2014; 34(5):506-513.

63. Hedman A, Reneland R, Lithell HO. Alterations in skeletal muscle morphology in glucose-tolerant elderly hypertensive men: relationship to development of hypertension and heart rate. J Hypertens 2000; 18(5):559-565.

64. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, Struijker-Boudier HA. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. Circulation 2008; 118(9):968-976.

65. Debbabi H, Uzan L, Mourad JJ, Safar M, Levy BI, Tibiriçà E. Increased skin capillary density in treated essential hypertensive patients. Am J Hypertens 2006; 19(5):477-483.

66. Vilar J, Waeckel L, Bonnin P, Cochain C, Loinard C, Duriez M, Silvestre JS, Lévy BI. Chronic hypoxia-induced angiogenesis normalizes blood pressure in spontaneously hypertensive rats. Circ Res 2008; 103(7):761-769.

67. Czernichow S, Greenfield JR, Galan P, Bastard JP, Charnaux N, Samaras K, Safar ME, Blacher J, Hercberg S, Levy BI. Microvascular dysfunction in healthy insulin-sensitive overweight individuals. J Hypertens 2010; 28(2):325-332.

68. Frisbee JC. Hypertension-independent microvascular rarefaction in the obese Zucker rat model of the metabolic syndrome. Microcirculation 2005; 12(5):383-392.

69. Jonk AM, Houben AJ, de Jongh RT, Serné EH, Schaper NC, Stehouwer CD. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology (Bethesda) 2007; 22:252-260.

70. Gongora MC, Qin Z, Laude K, Kim HW, McCann L, Folz JR, Dikalov S, Fukai T, Harrison DG. Role of extracellular superoxide dismutase in hypertension. Hypertension 2006; 48(3):473-481.

71. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating

ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001; 38(4):932-937.

72. Rajzer MW, Wojciechowska W, Klocek M, Palka I, Brzozowska-Kiszka M, Kawecka-Jaszcz K. Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. J Hypertens 2008; 26(10):2001-2007.

73. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR; ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 2005; 46(9):1753-1760.

74. Segers P, Mahieu D, Kips J, Rietzschel E, De Buyzere M, De Bacquer D, Bekaert S, De Backer G, Gillebert T, Verdonck P, Van Bortel L; for the Asklepios investigators. Amplification of the Pressure Pulse in the Upper Limb in Healthy, Middle-Aged Men and Women. Hypertension 2009; 54(2): 414-420.

75. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 2010; 31(19):2338-2350.

76. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27(21):2588-2605.

77. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Ménard J, Mallion J.M. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004; 291(11):1342-1349.

78. Kario K, Shimada K, Pickering TG. Clinical implication of morning blood pressure surge in hypertension. J Cardiovasc Pharmacol 2003; 42 Suppl 1:S87-91.

79. Mena LJ, Maestre GE, Hansen TW, Thijs L, Liu Y, Boggia J, Li Y, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Filipovsky J, Lmai Y, Wang J, O'Brien E, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. How many measurements are needed to estimate blood pressure variability without loss of prognostic information? Am J Hypertens 2014; 27(1): 46-55.

80. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximal systolic blood pressure, and episodic hypertension. Lancet 2010; 375 (9718):895-905.

81. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship Between Short-Term Blood Pressure Variability and Large-Artery Stiffness in Human Hypertension. Findings From 2 Large Databases. Hypertension 2012; 60(2): 369-377.

82. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badełek M, Wiliński J, Curyło AM, Dudek D; Aortic Blood Pressure and Survival Study Group. Pulsatile but Not Steady Component of Blood Pressure Predicts Cardiovascular Events in Coronary Patients. Hypertension 2008; 51(4): 848-855.

83. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central Pressure More Strongly Relates to Vascular Disease and Outcome Than Does Brachial Pressure The Strong Heart Study. Hypertension 2007; 50(1): 197-203.

84. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002; 39(3):735-738.

85. Pini R, Cavallini MC, Palmieri V, Marchionni N, Di Bari M, Devereux RB, Masotti G, Roman MJ. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population. The ICARe Dicomano study. J Am Coll Cardiol 2008; 51(25):2432-2439.

86. Roman MJ, Devereux RB, Kizer JR, Okin PM, Lee ET, Wang W, Umans JG, Calhoun D, Howard BV. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. J Am Coll Cardiol 2009; 54(18):1730-1734.

87. Kolh P, D'Orio V, Lambermont B, Gerard P, Gommes C, Limet R. Increased aortic compliance maintains left ventricular performance at lower energetic cost. Eur J Cardiothorac Surg 2000; 17(3):272-278.

88. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C. Central Blood Pressure Measurements and Antihypertensive Therapy: A Consensus Document. Hypertension 2007; 50(1):154-160.

89. Protogerou AD, Safar ME, Papaioannou TG, Zhang Y, Agnoletti D, Papadogiannis D, Blacher J. The combined effect of aortic stiffness and pressure wave reflections on mortality in the very old with cardiovascular disease: the PROTEGER Study. Hypertens Res 2011; 34(7):803-808.

90. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar M. Aortic pulse wave velocity predicts cardiovascular mortality in subjects with >70 years of age. Arterioscler Thromb Vasc Biol 2001; 21(12):2046-2050.

91. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55(13):1318-1327.

92. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang S, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014; 63(7):636-646.

93. London GM, Blacher J, Pannier B, Guérin AP, Marchais SJ, Safar ME. Arterial Wave Reflections and Survival in End-Stage Renal Failure. Hypertension 2001; 38(3):434-438.

94. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, Perez G, Mendez AJ. Aortic Pressure Augmentation Predicts Adverse Cardiovascular Events in Patients With Established Coronary Artery Disease. Hypertension 2005; 45(5):980-985.

95. Millasseau SC, Patel SJ, Redwood SR, Ritter JM, Chowienczyk PJ. Pressure Wave Reflection Assessed From the Peripheral Pulse Is a Transfer Function Necessary? Hypertension 2003; 41(5):1016-1020.

96. Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA, Ting CT, Najjar SS, Lakatta EG, Yin FC, Chou P, Chen CH. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension 2010; 55(3):799-805.

97. Vyas M, Izzo JL Jr, Lacourcière Y, Arnold JM, Dunlap ME, Amato JL, Pfeffer MA, Mitchell GF. Augmentation index and central aortic stiffness in middle-aged to elderly individuals. Am J Hypertens 2007; 20(6):642-647.

98. Protogerou AD, Safar ME. Dissociation between central augmentation index and carotid-femoral pulse-wave velocity: when and why? Am J Hypertens 2007; 20(6):648-649.

99. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial Stiffness and Cardiovascular Events: The Framingham Heart Study. Circulation 2010; 121(4):505-511.

100. Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: evidence for specific class-effects of antihypertensive drugs on pressure amplification. Curr Pharm Des 2009; 15(3):272-289.

101. Benetos A, Thomas F, Joly L. Pulse pressure amplification: a mechanical biomarker of cardiovascular risk. J Am Coll Cardiol 2010; 55(10):1032-1037.

102. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Pośnik-Urbańska A, Styczkiewicz K. Ascending aortic blood pressure-derived indices are not correlated with the extent of coronary artery disease in patients with impaired left ventricular function. Atherosclerosis 2006; 184(2):370-376.

103. Benetos A, Gautier S, Labat C, Salvi P, Valbusa F, Marino F, Toulza O, Agnoletti D, Zamboni M, Dubail D, Manckoundia P, Rolland Y, Hanon O, Perret-Guillaume C, Lacolley P, Safar ME, Guillemin F. 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. J Am Coll Cardiol 2012; 60(16):1503-1511.

104. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention

of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009; 338:b1665.

105. Boutouyrie P, Lacolley P, Briet M, Regnault V, Stanton A, Laurent S, Mahmud A. Pharmacological modulation of arterial stiffness. Drugs 2011; 71(13):1689-1701.

106. Simon AC, Safar ME, Levenson JA, Bouthier JE, Benetos A. Action of vasodilating drugs on small and large arteries of hypertensive patients. J Cardiovasc Pharmacol 1983; 5(4):626-631.

107. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342(3):145-153.

108. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359(9311):995-1003.

109. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366(9489):895-906.

110. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113(9):1213-1225.

111. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000; 525 Pt 1:263-270.

112. Boutouyrie P, Achouba A, Trunet P, Laurent S, for the EXPLOR Trialist Group. Amlodipine-Valsartan Combination Decreases Central Systolic Blood Pressure More Effectively Than the Amlodipine-Atenolol Combination The EXPLOR Study. Hypertension 2010; 55(6):1314-1322.

113. London GM, Asmar RG, O'Rourke MF, Safar ME; REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J Am Coll Cardiol 2004; 43(1):92-99.

114. Mitchell GF. Does Measurement of Central Blood Pressure have Treatment Consequences in the Clinical Praxis? Curr Hypertens Rep 2015; 17(8):573.

115. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001; 103(7):987-992.

116. Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M; BP GUIDE (value of central Blood Pressure for GUIDing managEment of hypertension) study investigators. Randomized Trial of Guiding Hypertension Management Using Central Aortic Blood Pressure Compared With Best-Practice Care: Principal Findings of the BP GUIDE Study. Hypertension 2013; 62(6):1138-1145.

117. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17(7):2034-2047.

118. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011; 79(12):1341-1352.

119. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351(13):1296- 1305.

120. Muntner P, Bowling CB, Gao L, Rizk D, Judd S, Tanner RM, McClellan W, Warnock DG. Age-specific association of reduced estimated glomerular filtration rate and albuminuria with all-cause mortality. Clin J Am Soc Nephrol 2011; 6(9):2200-2207.

121. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol 2007; 50(3):217-224.

122. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, Eckardt KU, Kasiske BL, McCullough PA, Passman RS, DeLoach SS, Pun PH, Ritz E. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011; 80(6):572-586.

123. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005; 16(2):520-528.

124. Mehrotra R, Kermah DA, Salusky IB, Wolf MS, Thadhani RI, Chiu YW, Martins D, Adler SG, Norris KC. Chronic kidney disease, hypovitaminosis D, and mortality in the United States. Kidney Int 2009; 76(9):977-983.

125. Georgianos PI, Sarafidis PA, Liakopoulos V. Arterial Stiffness: A Novel Risk Factor for Kidney Injury Progression? Am J Hypertens 2015; 28(8):958-965.

126. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K, London AM. Aortic and large artery compliance in end-stage renal failure. Kidney Int 1990; 37(1):137-142.

127. Makita Z, Bucala R, Rayfield EJ, Friedman EA, Kaufman AM, Korbet SM, Barth RH, Winston JA, Fuh H, Manogue KR. Reactive glycosylation endproducts in diabetic uraemia and treatment of renal failure. Lancet 1994; 343 (8912):1519-1522.

128. Karras A, Haymann JP, Bozec E, Metzger M, Jacquot C, Maruani G, Houillier P, Froissart M, Stengel B, Guardiola P, Laurent S, Boutouyrie P, Briet M. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. Hypertension 2012; 60(6):1451-1457.

129. Blood Pressure Lowering Treatment Trialists, C., T. Ninomiya, V. Perkovic, F. Turnbull, B. Neal, F. Barzi, A. Cass, C. Baigent, J. Chalmers, N. Li, M. Woodward, and S. MacMahon, Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ 2013; 347:f5680.

130. Verbeke F, Lindley E, Van Bortel L, Vanholder R, London G, Cochat P, Wiecek A, Fouque D, Van Biesen W. A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in non-dialysis-dependent chronic kidney disease: an endorsement with some caveats for real-life application. Nephrol Dial Transplant 2014; 29(3):490-496.

131. Sarafidis PA, Ruilope LM. Blood pressure targets for patients with chronic kidney disease. Blood Press 2013; 22(6):395-396.

132. Kashiwagi M, Shinozaki M, Hirakata H, Tamaki K, Hirano T, Tokumoto M, Goto H, Okuda S, Fujishima M. Locally activated renin-angiotensin system associated with TGF-beta1 as a major factor for renal injury induced by chronic inhibition of nitric oxide synthase in rats. J Am Soc Nephrol 2000; 11(4):616-624.

133. Boffa JJ, Lu Y, Placier S, Stefanski A, Dussaule JC, Chatziantoniou C. Regression of renal vascular and glomerular fibrosis: role of angiotensin II receptor antagonism and matrix metalloproteinases. J Am Soc Nephrol 2003; 14(5):1132-1144.

134. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 2003; 139(4):244-252.

135. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, Esmatjes E, Gilbert RE, Hunsicker LG, de Faria JB, Mangili R, Moore J Jr, Reisin E, Ritz E, Schernthaner G, Spitalewitz S, Tindall H, Rodby RA, Lewis EJ. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005; 16(10):3027-3037.

136. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345(12):861-869.

137. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999; 354 (9176):359-364.

138. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int 2004; 65(6):1991-2002.

139. Griffin KA, Picken MM, Bakris GL, Bidani AK. Class differences in the effects of calcium channel blockers in the rat remnant kidney model. Kidney Int 1999; 55(5):1849- 1860.

140. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, Cutler JA, Evans GW, Gerstein HC, Grimm RH Jr, Lipkin EW, Narayan KM, Riddle MC Jr, Sood A, Goff DC Jr. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014; 37(6):1721-1728.

141. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362(17):1575-1585.

142. Tandon N, Ali MK, Narayan KM. Pharmacologic prevention of microvascular and macrovascular complications in diabetes mellitus: implications of the results of recent clinical trials in type 2 diabetes. Am J Cardiovasc Drugs 2012; 12(1):7-22.

143. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24):2560-2572.

144. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-2559.

145. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360(2):129-139.

146. De Ciuceis C, Porteri E, Rizzoni D, Rizzardi N, Paiardi S, Boari GE, Miclini M, Zani F, Muiesan ML, Donato F, Salvetti M, Castellano M, Tiberio GA, Giulini SM, Agabiti Rosei D. Structural Alterations of Subcutaneous Small-Resistance Arteries May Predict Major

Cardiovascular Events in Patients With Hypertension. Am J Hypertens 2007; 20(8):846-852.

147. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse- wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002; 106(16):2085-2090.

148. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321(7258):405-412.

149. Protogerou AD, Blacher J, Mavrikakis M, Lekakis J, Safar ME. Increased pulse pressure amplification in treated hypertensive subjects with metabolic syndrome. Am J Hypertens 2007; 20(2):127-133.

150. Vergnaud AC, Protogerou AD, Li Y, Czernichow S, Vesin C, Blacher J, Safar ME. Pulse pressure amplification, adiposity and metabolic syndrome in subjects under chronic antihypertensive therapy: The role of heart rate. Atherosclerosis 2008; 199(1):222-229.

151. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008; 51(4):527-539.

152. van Popele NM, Elizabeth Hak A, Mattace-Raso FU, Bots ML, van der Kuip DA, Reneman RS, Hoeks AP, Hofman A, Grobbee DE, Witteman JC. Impaired fasting glucose is associated with increased arterial stiffness in elderly people without diabetes mellitus: the Rotterdam Study. J Am Geriatr Soc 2006; 54(3):397-404.

153. Orr JS, Dengo AL, Rivero JM, Davy KP. Arterial destiffening with atorvastatin in overweight and obese middle-aged and older adults. Hypertension 2009; 54(4):763-768.

154. Takagi H, Umemoto T. A low-density lipoprotein-dependent effect of atorvastatin upon the systolic blood pressure reduction: meta-regression analyses of randomized trials. Int J Cardiol 2013; 170(1):e14-16.

155. Safar ME, Protogerou AD, Blacher J. Statins, central blood pressure, and blood pressure amplification. Circulation 2009; 119(1):9-12.

156. Lewden C, May T, Rosenthal E, Burty C, Bonnet F, Costagliola D, Jougla E, Semaille C, Morlat P, Salmon D, Cacoub P, Chêne G. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalité 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr 2008; 48(5):590-598.

157. Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, Georget A, Aouba A, Rosenthal E, May T, Chauveau M, Diallo B, Costagliola D, Chene G; ANRS EN20 Mortalité 2010 Study Group. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 2014 ; 28(8):1181-1191.

158. Lang S, Mary-Krause M, Simon A, Partisani L, Gilquin J, Cotte L, Boccara F, Costagliola D. HIV replication and immune status are independent predictors of the risk of

myocardial infarction in HIV-infected individuals. Clin Infect Dis 2012 ; 55(4):600-607.

159. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, Boccara F, Costagliola D. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS Cohort CO4. Arch Intern Med 2010; 170(14):1228-1238.

160. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, Gilson R, Paredes R, Bakowska E, Engsig FN, Phillips A; INSIGHT SMART, ESPRIT Study Groups. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS 2013; 27(6):973-979.

161. Friis-Moller N, Worm SW. Can the risk of cardiovascular disease in HIV-infected patients be estimated from conventional risk prediction tools? Clin Infect Dis 2007; 45(8):1082-1084.

162. Lekakis J, Ikonomidis I, Palios J, Tsiodras S, Karatzis E, Poulakou G, Rallidis L, Antoniadou A, Panagopoulos P, Papadopoulos A, Triantafyllidi H, Giamarellou H, Kremastinos DT. Association of highly active antiretroviral therapy with increased arterial stiffness in patients infected with human immunodeficiency virus. Am J Hypertens 2009; 22(8):828-834.

163. Monsuez JJ, Charniot JC, Escaut L, Teicher E, Wyplosz B, Couzigou C, Vignat N, Vittecoq D. HIV-associated vascular diseases: structural and functional changes, clinical implications. Int J Cardiol 2009; 133(3):293-306.

164. Echeverría P, Bonjoch A, Moltó J, Jou A, Puig J, Ornelas A, Pérez-Álvarez N, Clotet B, Negredo E. Pulse wave velocity as index of arterial stiffness in HIV-infected patients compared with a healthy population. J Acquir Immune Defic Syndr 2014; 65(1):50-56.

165. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med 2008; 168(12):1340-1349.

166. Viard JP, Souberbielle JC, Kirk O, Reekie J, Knysz B, Losso M, Gatell J, Pedersen C, Bogner JR, Lundgren JD, Mocroft A. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. AIDS 2011; 25(10):1305-1315.

167. Alvarez JA, Gower BA, Calhoun DA, Judd SE, Dong Y, Dudenbostel T, Scholl J, Ashraf AP. Serum 25-hydroxyvitamin D and Ethnic Differences in Arterial Stiffness and Endothelial Function. J Clin Med Res 2012; 4(3):197-205.

168. Al Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, Kavtaradze N, Uphoff I, Hooper C, Tangpricha V, Alexander RW, Brigham K, Quyyumi AA. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. J Am Coll Cardiol 2011; 58(2):186-192.

169. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk

of mortality in the general population. Arch Intern Med 2008; 168(15):1629-1637.

170. Shepherd L, Souberbielle JC, Bastard JP, Fellahi S, Capeau J, Reekie J, Reiss P, Blaxhult A, Bickel M, Leen C, Kirk O, Lundgren JD, Mocroft A, Viard JP; EuroSIDA in EuroCOORD. Prognostic Value of Vitamin D Level for All-cause Mortality, and Association With Inflammatory Markers, in HIV-infected Persons. J Infect Dis 2014; 210(2):234-243.

171. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of Diabetes on Cardiovascular Disease Risk and All-Cause Mortality in Older Men. Influence of Age at Onset, Diabetes Duration, and Established and Novel Risk Factors. Arch Intern Med 2011; 171(5):404-410.

172. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007; 30(5):1292-1293.

173. Roos CJ, Djaberi R, Schuijf JD, de Koning EJ, Rabelink TJ, Smit JW, Pereira AM, Al Younis I, van der Hiel B, Scholte AJ, Bax JJ, Jukema JW. Relationship between vascular stiffness and stress myocardial perfusion imaging in asymptomatic patients with diabetes. Eur J Nucl Med Mol Imaging 2011; 38(11):2050-2057.

174. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34(28):2159-2219.

175. Tedesco MA, Natale F, Di Salvo G, Caputo S, Capasso M, Calabró R. Effects of coexisting hypertension and type II diabetes mellitus on arterial stiffness. J Hum Hypertens 2004; 18(7):469-473.

176. Lamri L, Gripiotis E, Ferrario A. Diabetes in Algeria and challenges for health policy: a literature review of prevalence, cost, management and outcomes of diabetes and its complications. Global Health 2014; 10:11.

177. Temmar M, Labat C, Benkhedda S, Charifi M, Thomas F, Bouafia MT, Bean K, Darne B, Safar ME, Benetos A. Prevalence and determinants of hypertension in the

Algerian Sahara. J Hypertens 2007; 25(11):2218-2226.

178. Cardoso CR, Ferreira MT, Leite NC, Salles GF. Prognostic impact of aortic stiffness in high-risk type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetes Care 2013; 36(11):3772-3778.

179. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014; 35(42):2950-2959.

180. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013; 34(38):2949-3003.

181. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Hansen JF. Prevalence and prognostic significance of daily-life silent myocardial ischaemia in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2005; 26(14):1402-1409.

182. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010; 362(10):886-895.

183. Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguadé-Bruix S, Pizzi MN, Todiere G, Gimelli A, Schroeder S, Drosch T, Poddighe R, Casolo G, Anagnostopoulos C, Pugliese F, Rouzet F, Le Guludec D, Cappelli F, Valente S, Gensini GF, Zawaideh C, Capitanio S, Sambuceti G, Marsico F, Perrone Filardi P, Fernández-Golfín C, Rincón LM, Graner FP, de Graaf MA, Fiechter M, Stehli J, Gaemperli O, Reyes E, Nkomo S, Mäki M, Lorenzoni V, Turchetti G, Carpeggiani C, Marinelli M, Puzzuoli S, Mangione M, Marcheschi P, Mariani F, Giannessi D, Nekolla S, Lombardi M, Sicari R, Scholte AJ, Zamorano JL, Kaufmann PA, Underwood SR, Knuuti J; EVINCI Study Investigators. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015; 8(3). pii: e002179. doi: 10.1161/CIRCIMAGING.114.002179.

184. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015; 372(14):1291-1300.

185. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse

wave velocity index and mortality in end-stage renal disease. Kidney Int 2003; 63(5):1852-1860.

186. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis 2012; 1(4).

187. Ioannou CV, Stergiopulos N, Katsamouris AN, Startchik I, Kalangos A, Licker MJ, Westerhof N, Morel DR. Hemodynamics induced after acute reduction of proximal thoracic aorta compliance. Eur J Vasc Endovasc Surg 2003; 26(2):195-204.

188. Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure – Its role in the pathogenesis of atherosclerosis. Blood Press 2007; 16(4):238-245.

189. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Styczkiewicz M, Pośnik-Urbańska A, Bryniarski L, Dudek D. Ascending aortic, but not brachial blood pressure-derived indices are related to coronary atherosclerosis. Atherosclerosis 2004; 176(1):151-155.

190. Lovett JK, Howard SC, Rothwell PM. Pulse pressure is independently associated with carotid plaque ulceration. J Hypertens 2003; 21(9):1669-1676.

191. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007; 356(15):1503-1516.

192. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988; 78(5Pt1):1157-1166.

193. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlick R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, for the Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005; 111(25):3384-3390.

194. Mattace-Raso FUS, van der Cammen TJM, Hofman A, vam Popele NM, Bos ML, Schalekamp ADH, Asmar R, Reneman RS, Hoeks APG, Witteman B, Witteman JCM. Arterial stiffness and risk for coronary heart disease and stroke: The Rotterdam Study. Circulation 2006; 113(5):657-663.

195. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension 2015; 66(3):698-722.

196. Protogerou AD, Safar ME, Iaria P, Safar H, Le Dudal K, Filipovsky J, Henry

O, Ducimetière P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. Hypertension 2007; 50(1):172-180.

197. O'Rourke MF, Yaginuma T, Avolio AP. Physiological and pathophysiological implications of ventricular/vascular coupling. Ann Biomed Eng 1984; 12(2):119-134.

198. Protogerou AD, Papaioannou TG, Lekakis JP, Blacher J, Safar ME. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part I: (Patho)-physiology, rationale and perspective on pulse pressure amplification. Curr Pharm Des 2009; 15(3):267-271.

199. Hawkins M, Gabriel KP, Cooper J, Storti KL, Sutton-Tyrrell K, Kriska A. The impact of change in physical activity on change in arterial stiffness in overweight or obese sedentary young adults. Vasc Med 2014; 19(4):257-263.

200. Triantafyllidi H, Trivilou P, Ikonomidis I, Kontsas K, Tzortzis S, Pavlidis G, Lekakis J. Is Arterial Hypertension Control Enough to Improve Aortic Stiffness in Untreated Patients With Hypertension? A 3-Year Follow-Up Study. Angiology 2015; 66(8):759-765.

201. Orlova IA, Nuraliev EY, Yarovaya EB, Ageev FT. Prognostic value of changes in arterial stiffness in men with coronary artery disease. Vasc Health Risk Manag 2010; 6:1015-1021.

202. Mitchell GF. Arterial stiffness: insights from Framingham and Iceland. Curr Opin Nephrol Hypertens 2015; 24(1):1-7.

203. Tanna MS, Bangalore S. Antihypertensive therapy and the J-curve: fact or fiction? Curr Hypertens Rep 2015; 17(2):6.

204. Verdecchia P, Reboldi G, Angeli F, Trimarco B, Mancia G, Pogue J, Gao P, Sleight P, Teo K, Yusuf S. Systolic and diastolic blood pressure changes in relation with myocardial infarction and stroke in patients with coronary artery disease. Hypertension 2015; 65(1):108- 114.

205. Narayan O, Casan J, Szarski M, Dart AM, Meredith IT, Cameron JD. Estimation of central aortic blood pressure: a systematic metaanalysis of available techniques. J Hypertens 2014; 32(9):1727-1740.

206. Kips JG, Schutte AE, Vermeersch SJ, Huisman HW, Van Rooyen JM, Glyn MC, Fourie CM, Malan L, Schutte R, Van Bortel LM, Segers P. Comparison of central pressure estimates obtained from SphygmoCor, Omron HEM-9000AI and carotid applanation tonometry. J Hypertens 2011; 29(6):1115-1120.

207. Segers P, Mahieu D, Kips J, Rietzschel E, De Buyzere M, De Bacquer D, Bekaert S, De Backer G, Gillebert T, Verdonck P, Van Bortel L; Asklepios investigators. Amplification of the pressure pulse in the upperlimb in healthy, middle-aged men and women. Hypertension 2009; 54(2):414-420.

208. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, Kropf J, Eber B. Validation of a brachial cuff-based method for estimating central systolic

blood pressure. Hypertension 2011; 58(5):825-832.

209. Shih YT, Cheng HM, Sung SH, Hu WC, Chen CH. Quantification of the calibration error in the transfer function-derived central aortic blood pressures. Am J Hypertens 2011; 24(12):1312-1317.

210. Recommandations de la Société Française d'Hypertension Artérielle sur la prise en charge de l'hypertension artérielle résistante, décembre 2013. http://www.sfhta.eu/recommandations/les-recommandations-de-la-sfhta/

211. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. Curr Opin Nephrol Hypertens 1999; 8(3):335-342.

212. Mitchell GF, Izzo JL Jr, Lacourcière Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. Circulation 2002; 105(25):2955-2961.

213. Safar ME, van Bortel LM, Struijker-Boudier HA. Resistance and conduit arteries following converting enzyme inhibition in hypertension. J Vasc Res 1997; 34(2):67-81.

214. Asmar RG, London GM, O'Rourke ME, Safar ME; REASON Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension 2001; 38(4):922-926.

215. Fok H, Guilcher A, Li Y, Brett S, Shah A, Clapp B, Chowienczyk P. Augmentation pressure is influenced by ventricular contractility/relaxation dynamics: novel mechanism of reduction of pulse pressure by nitrates. Hypertension 2014; 63(5):1050-1055.

216. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003; 108(14):1664-1672.

217. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to

vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003; 108(15):1772-1778.

218. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12(1):56-62.

219. Khoueiry G, Azab B, Torbey E, Abi Rafeh N, Atallah JP, Ahern K, Malpeso J, McCord D, Chemaly ER. Aortic pulse pressure is associated with the localization of coronary artery disease based on coronary flow lateralization. Am J Hypertens 2012; 25(10):1055-1063.

TITRE en français Paramètres hémodynamiques artériels : approche du risque cardiovasculaire individuel et apport diagnostique dans la maladie coronaire

RÉSUMÉ Le traitement combiné des facteurs de risque, notamment d'une hypertension artérielle et d'un diabète, reste insuffisant pour obtenir une réduction substantielle de la morbidité et de la mortalité cardiovasculaire. Ce risque résiduel peut être considéré comme le reflet d'une maladie artérielle infra clinique. La rigidité aortique et l'amplification de la pression pulsée sont des marqueurs hémodynamiques de l'atteinte artérielle et peuvent être étudiés de manière non invasive. L'objectif de ce travail a été dans un premier temps de décrire la maladie artérielle infra clinique et ses déterminants au sein de deux cohortes de patients à risque cardiovasculaire, hypertendus et/ou diabétiques et patients suivis pour une infection au virus de l'immunodéficience humaine (VIH). L'apport de la mesure non invasive de la rigidité aortique dans l'estimation du risque chez des patients diabétiques de type 2 a été évalué au sein d'une troisième cohorte. La deuxième partie de ce travail a été orientée vers le dépistage de la maladie coronaire. L'apport de la rigidité aortique dans l'amélioration de la valeur prédictive positive des examens de dépistage a été étudié dans le cadre d'un bilan cardiovasculaire réalisé en hôpital de jour. La conclusion principale de ce travail est que la maladie artérielle infra clinique permet d'une part de cibler le patient à haut risque et, d'autre part, d'améliorer le dépistage de la maladie coronaire à l'échelle individuelle. Le suivi de l'évolution, sous traitement, du degré de rigidité aortique et du niveau de pression pulsée centrale, en parallèle avec l'incidence des événements cardiovasculaires, doit permettre désormais de préciser l'importance de ces paramètres dans la prise en charge thérapeutique au-delà du contrôle des facteurs de risque « traditionnels ».

TITRE en anglais
Arterial hemodynamic parameters in risk assessment strategies and coronary artery disease screening

ABSTRACT The combined treatment of risk factors, in particular hypertension and diabetes, appears insufficient to achieve a substantial reduction in cardiovascular morbidity and mortality. This residual risk may be indicative of adverse responses of subclinical, structural and functional arterial damage, illustrated by aortic stiffness and pressure wave reflection. These hemodynamic parameters are considered to be associated with central pulse pressure level. Central blood pressure appears closely related to the development and complications of atherosclerosis as well as microvascular organ damage. Firstly, the objective of this work was to study subclinical arterial damage by non-invasive measurement of aortic stiffness and pressure wave reflection, and their determinants, in two cohorts of patients with increased cardiovascular risk, hypertensive and / or diabetic patients and patients with HIV infection. In a third cohort, composed of patients with type 2 diabetes, we studied aortic stiffness as an independent marker of cardiovascular disease. Secondly, we investigated whether non invasive aortic stiffness assessment improves diagnostic accuracy of coronary artery disease screening. The contribution of aortic stiffness in improving the detection of coronary artery disease was studied as part of a complete cardiovascular evaluation. The main conclusion of this work is that assessment of subclinical arterial damage provide a clinically useful tool to individualize high-risk patients and to improve coronary artery disease screening. Prospective evaluation of aortic stiffness and central pulse pressure level in parallel with the incidence of cardiovascular events would clarify the importance of these hemodynamic parameters in the management of the residual risk, over and above the control of "traditional" risk factors.

DISCIPLINE Santé et Santé Publique

MOTS-CLÉS Rigidité aortique, vitesse de l'onde de pouls, amplification, pression pulsée, pression centrale, maladie coronaire, hypertension artérielle, maladie diabétique.

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