The Clinical Significance and Application of Vascular Stiffness Measurements

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Abstract

Increasing evidence points out at vascular stiffness (and in particolar aortic stiffness measured by pulse wave velocity) as a reliable biomarker of vascular aging, able to integrate in a single measure the overall burden of cardiovascular risk factors on the vasculature over time; furthermore it may be per se a mechanism of disease, by inducing microcirculatory damage and favouring cardiovascular events. Increased aortic stiffness has been shown to predict future cardiovascular events and improve risk reclassification in those at intermediate risk. However, several questions in this field are still open, limiting the wide use of these tools in the clinical practice. This article will review the basic aspects of physiology of large artery stiffness, as well as current evidence about its possible clinical applications.

Keywords: vascular stiffness, arterial stiffness, clinical significance, vascular aging, blood pressure

Introduction

Cardiovascular (CV) disease is the first cause of mortality and morbidity worldwide [1]. Prevention of this condition, which is responsible of more than 2200 deaths per day only in United States, is a public health priority [2]. Thus in the last decades great efforts have been made in the search of non-invasive biomarkers, able to identify the individual at risk for CV events in the asymptomatic, subclinical stage [3]. Some biomarkers are currently recommended in order to improve stratification of CV risk, whereas other are considered useful only for research purposes[4].

Increasing evidence points out at vascular stiffness as a reliable biomarker of vascular aging, able to represent an integrated marker of the overall burden of CV risk factors on the vasculature over time; furthermore it may be per se a mechanism of disease, by inducing cardiac, renal and brain microcirculatory damage and favouring CV events (Figure 1) [5]. Increased aortic stiffness has been shown to predict future CV events [6] and improve risk reclassification in those at intermediate risk [7]. However, several questions in this field are still open, limiting the wide use of these tools in the clinical practice. This article will review the basic aspects of physiology of large artery stiffness, as well as current evidence about its possible clinical applications.

Arterial stiffness in cardiovascular physiology and how to measure it

Any material is elastic. Even diamonds strain as they are stressed, though their deformation is very small. Any organ tissue is subjected to stress during normal and pathological events, and is characterized by its own resilience to stress. However the cardiovascular system has peculiar characteristics, related to its functions (conduit and cushion), for which elasticity is a key property for reconciling opposite aspects: a beating heart providing intermittent propulsion to blood and the necessity to provide a permanent blood flow to organs for dispatching nutrients. At each heart contraction, pressure and flow pulsatility are transmitted to the arterial tree, which thus is permanently exposed to oscillating stresses, additive to the tensile stress imposed by mean blood pressure (BP). Arteries are also longitudinally stressed

by being 10/20% elongated in the body even in the absence of pressure. The ratio between tensile stress and corresponding strain defines the elastic modulus (should be called stiffness modulus since higher stress and lower strain imply stiffer material). From the abovementioned definition, it is easy to measure arterial stiffness in different arterial segments by measuring strain (through ultrasound or magnetic resonance) and stress (through blood pressure and ultrasound for thickness and diameter). This constitutes a direct assessment of the cushion properties of an artery at a local level [8].

However, the most validated and used method to assess vascular stiffness is based on the measurement of the velocity of pulse waves (generated by heart contractions) travel along the arterial tree between two sites (Figure 2). Indeed, according to the Moens-Korteweg equation, the propagation of the pulse wave is inversely related to the square root of the distensibility of the arterial tube. Measurement of pulse wave velocity (PWV) is the oldest method to evaluate arterial stiffness: the first reports in humans were published nearly one century ago [9]. This method is robust, extensively validated and, depending on the segment studied, may provide very useful measures of arterial stiffness.

Finally, the currently accepted model of the arterial system assumes that the propagation of the pulse wave from the heart to the periphery (forward) along arteries induces reflections phenomena and retrograde waves (from the periphery to the heart - backward) on a number of sites along the arterial tree: passages from low-resistance to high-resistance arteries, changes in diameter and elastic properties, bifurcations [10]. Indeed, the arterial tree has a reflection profile characteristic of distributed and diffuse reflections, rather than from discrete reflections [11]. Forward and backward wave summation occurring in any arterial site results in modification of the shape and amplitude of the original wave, with a continuous change in the morphology of the wave along the arterial tree. When the characteristic impedance (the ratio of pressure and flow in the absence of wave reflections) is known at a particular arterial site, it is possible to decompose the pressure (and flow) wave into a forward and backward component [12]. Wave reflection is a crucial determinant of central hemodynamic, a major player in the cross-talk between micro- and macrocirculation [5] and a possible predictor of CV events [13], thus providing information additive to PWV assessment.

The arterial system acts thus as resonant system. The energy generated by the heart is transmitted to blood (flow) and arteries (strain); the more elastic the arteries, the more energy will be stored by the system during systole and released during diastole. This leads to less

systolic work for the left ventricle and more diastolic flow, advantageous for coronary perfusion. This pulsatile tensile stress leads to adaptation of the arterial wall in term of structure designed to withstand oscillating pressure. However, the excellent cushioning properties of the aorta are progressively lost over years, as a consequence of the mechanical wear-and-tear of the wall constituents (and in particular the fracture of elastic lamellae), due to the repeated exposition to the oscillating stress of blood pressure and incomplete healing [14]. This is considered as the basic phenomenon leading to age-induced remodeling (Figure 1).

In younger individuals, arteries close to the heart are the more elastic and distal, smaller size arteries are stiffer. This stiffness gradient has a very important role in physiology. More elastic proximal arteries will enhance the stiffness gradient and hence reinforce the filtering of high amplitude high energy pressure waves to reach the small arteries and capillaries, resulting in attenuated pulse pressure transmission to small arteries, protecting the microcirculation. However, aging and risk factors tend to reverse this gradient, with less distal reflection and less attenuation of the forward pressure wave which is transmitted with higher energy to the microcirculation, potentially leading to increased organ damage (Figure 1) [15].

Molecular and cellular determinants of arterial stiffness

The physical substrate of arterial stiffness is the extracellular matrix composition, vascular smooth muscle cells and their tridimensional and dynamic behavior [16]. Collagen (III>I) is the stiffest component. Its wavy disposition within the wall leads to a non-linear behavior, i.e. stiffness increase accelerates with distensions as collagen fibers straighten. This limits the dilatation of arteries at very high pressures, which can be reached during extreme physiological conditions (weight lifting, jumping, falls etc). Elastin carries a quasi-pure elastic behavior similar to natural rubber and carries most of the elastic properties at usual blood pressure. Other fibers (fibronectin, collagen subtypes, fibrillin etc, and other substances) (ground matter, proteoglycans) play important roles by connecting stiff elements together and with vascular smooth muscle cells (VSMC). Many of the fibrillary proteins have powerful biological properties. VSMC are embedded in the matrix and densely attached to extracellular matrix (ECM) by dense plaques, and the intracellular fibers, contractile or not, may distribute stress to stiffer or more elastic ECM components. The mechanical role of VSMC has long being neglected and is now reassessed [16]. Similarly, the dynamics of ECM in the arterial wall

has long being considered as very slow. This is now reconsidered and the 3D organization of ECM and cells can change very quickly, as do fibers [17].

Arterial stiffness: effect of age and blood pressure

The two strongest factors inducing arterial stiffening are aging and high blood pressure; both acting synergistically to increase arterial stiffness [9,18-21]. With aging, large arteries dilate, thicken and get stiffer. Any increase in blood pressure at a given age will enhance these phenomena. Other classical risk factors act similarly on arterial remodeling. Large arteries act as long term memories of the combined effect of time and intensity of risk factors. Thus, arterial stiffness (and/or remodeling) represents an ideal integrated biomarker of vascular aging.

Outside wartime, in the last century life expectancy has steadily increased worldwide, not only in Western Europe, USA and Japan, but also in many of the former developing countries, which achieved a dramatic reduction of global health inequality [22]. However, other countries such as former Soviet Union countries have experienced a dramatic decrease in life expectancy from 1990 to 2000. In the same line, when looking at the recently published reference values for PWV, one can see that the dispersion of values in healthy individuals increases with age, as if some individuals, despite not presenting risk factors, have a propensity to have stiffer arteries as age progresses [23]. At this stage, it is important to repeat that chronological age IS NOT synonymous of aging. Age in fact represents at the same time a true aging process (i.e. time-associated tear-and-wear of arterial wall material), AND the duration of exposure to factors accelerating the aging process, such as oxidative stress or high blood pressure etc. With measurement of arterial stiffness, it is possible to identify subjects with arterial stiffness largely exceeding the normal values of population of same chronological age, thus defining early vascular aging (EVA) [24]. However, age-related arterial stiffness might not be entirely physiological even in apparently healthy subjects: a healthy lifestyle and the absence of classical CV risk factors is associated with abnormally lower PWV and reduced risk of CV events, a condition that has been recently described as “healthy vascular aging” [25] and that lies at the opposite side of the Gaussian distribution than EVA.

Indeed, arterial aging is not inevitable. This observation was first made by Avolio and coauthors, back in the 80s, by comparing two Chinese populations, one living in a big city, Beijing, the other one in a rural area. The main finding of this seminal paper was that the

relation of PWV to age was steeper for urban Chinese than for rural Chinese [20]. This finding, which was independent of major confounders, such as PB and heart rate, was confirmed by subsequent studies, showing that the relation of PWV to age in general population was curvilinear, accelerated for advanced age. The reference value paper, performed in more than 10,000 subjects and patients in Europe confirmed the quadratic association of PWV with age [23]. These observations from cross-sectional data were confirmed by longitudinal follow-up of cohorts. Benetos published a 6-year follow-up of hypertensive subjects, confirming an acceleration of vascular aging with age and high blood pressure [19]. The cumulative effect of age and BP on PWV trajectories over time was further demonstrated in the Baltimore study of aging, with waist circumference as the only additional factor playing a significant role in women [26]. Significant sex differences have also been shown, with diverging trajectories of BP and PWV with aging in men [27]. Furthermore, the genetic component is conceivably relevant. In the Twin-UK study, predictors of progression in carotid-femoral PWV in 762 female twins over around 5 years included age, mean BP, heart rate and body mass index, whereas its heritability was 55% [28].

The availability of reference values for arterial stiffness allowed to identify specific populations. For instance, some intriguing information come from the Guimaraes study, a population-based survey recruiting around 3,000 subjects in Northern Portugal. This study revealed that a significant proportion of younger subjects had abnormally high PWV. Up to 40% of the subjects less than 30 years were above the 90th percentile, 26% were above the 97,5 percentiles of age and BP-specific reference values. This inappropriately high PWV in young adults might explain the high incidence of stroke in this population [29].

Risk stratification using arterial stiffness

Increased arterial stiffness is predictive of outcome. This has been demonstrated for carotid-femoral PWV in hypertensive subjects [30,31], further confirmed with numerous epidemiological trials and 2 subsequent metaanalyses [7,32]. Some evidence also come from alternative measures of PWV such as brachial-ankle PWV [33]. A recent collaborative paper demonstrated that carotid distensibility coefficient was predictive of cardiovascular and all-cause mortality, and that this prediction was independent from (and additive to) PWV[34]. This shows that techniques are complementary, and that different arterial territories may provide additive risk

prediction, as suggested also by the association of carotid and aortic stiffness with cardiac and renal organ damage in hypertensive patients respectively [35]. In the same line, we have shown that although aortic stiffness increases with age, carotid stiffness has a blunted increase with age [36], more peripheral, muscular arteries stiffness (such as carotid-radial or femoral-pedis PWV do not increase and in some cases decreases with age [21,37], thus inducing a reduction in the stiffness gradient. This has been interpreted as a mechanism for compensating the loss of compliance proximal arteries, but may promote microvascular damage per se. A prospective study in dialysis patients demonstrated that a reduced stiffness gradient is associated with increased CV events [15], though this was not confirmed in the general population [38]. However this discrepancy might be related to the extreme severity of vascular damage in dialysis patients.

The first study demonstrating an improvement in integrated discrimination by adding PWV to a standard risk factor assessment was performed on the general population sample of the Framingham cohort [39]. Later, an individual participant meta-analysis of prospective observational data from 17,635 subjects from 17 cohorts confirmed that PWV was a predictor of coronary heart disease, stroke and CV events on top of conventional Framingham CV risk factors [7]. Reclassification indices showed that the addition of PWV improved risk prediction, especially in intermediate risk individuals [7]. Furthermore, PWV was a stronger risk factor amongst younger individuals [7]; in older individuals, the reclassification power of PWV appears to be less strong, though still significant [40]. Sehestedt et al demonstrated in a general population sample that PWV is associated with cardiovascular prognosis independent of SCORE; a stronger prognostic importance of PWV was demonstrated in particular in low-risk subjects (those with SCORE<5%) [41]. Furthermore, in a cohort of patients with chronic kidney disease, PWV improved by 29% the net reclassification index for all-cause mortality in comparison to a panel of CV and renal risk factors [42]. Finally, in the general population sample of Glostrup County, Copenhagen, the role of multiple organ damage assessment in risk reclassification was assessed prospectively [41]. This paper demonstrated that subclinical organ damage, assessed by PWV, left ventricular hypertrophy, albuminuria and carotid plaques, taken separately, predicted cardiovascular death independently of SCORE. The combination of albuminuria and PWV appears to be broadly superimposable to the 4-organ damage approach [41] and more feasible and cost-effective. Although none of these papers specifically addressed the issue of reclassification power of PWV in hypertensive patients, in

particular in patients under stable antihypertensive treatment, which is known to cause relevant long-term reductions in PWV [43,44].

When assessing the role of biomarkers in cardiovascular risk prediction, it is crucial to demonstrate that they add incremental information to traditional CV risk factors [45]. Thus, the biomarker needs not only to be independently associated with outcomes, but also to improve discrimination, calibration and net reclassification. As developed before, arterial stiffness fulfils these requirements. Finally, the biomarker assessment should affect clinical management and be cost-effective. PWV already fulfills almost entirely the aforementioned requirements, [4], nevertheless it cannot be considered yet as a surrogate endpoint, since studies that address its ability to monitor and guide therapy and eventually improve outcomes are not available at the moment [44] (see below). Accordingly, PWV is still marginally positioned among possible risk modifiers of calculated total cardiovascular risk in current Joint ESC Guidelines on CV prevention [46]. Furthermore, in the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension, measurement of PWV has been given a level of evidence IIb for the assessment of vascular hypertensive organ damage [47].

Demonstrating vascular involvement in non-cardiovascular diseases

One intriguing issue is that arterial stiffness is predictive of cardiovascular events and mortality in primarily non-cardiovascular diseases. This is true especially for diseases characterized by chronic inflammation, which is able to induce molecular changes in the vessel wall leading to increased stiffness. Inflammation is associated with arterial stiffening in healthy individuals [48], hypertensive patients [49] and in patients with several chronic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, [50], systemic vasculitis [51], and inflammatory bowel diseases [52]. These diseases are characterized by an observed risk of coronary artery disease and cerebrovascular accidents that is disproportionately high in comparison to the observed burden of classical CV risk factors [53,54]. The use of vascular stiffness biomarkers might be useful to achieve a more accurate CV risk stratification in chronic inflammatory diseases.

Monitoring of treatment

Whether arterial stiffness can be used for monitoring the efficacy cardiovascular treatments and guiding therapy is plausible but not demonstrated yet. It is tempting to consider that arterial stiffness better represents the damage on target organs than BP itself, because less variable. Among different BP-lowering drug classes, blockers of the renin-angiotensin system are able to improve arterial stiffness independent of BP [55,56]. However, the fact that regression of hypertensive organ damage is associated with better outcome has been demonstrated by now only for left ventricular hypertrophy and microalbuminuria [47]. Up to now, only one small clinical study has shown, in end-stage renal disease patients, that patients who improve arterial stiffness in parallel with improvement in BP have a better outcome than those who do not [57]. The ongoing Strategy for Preventing Cardiovascular and Renal Events Based on ARTErial Stiffness (SPARTE) trial (NCT02617238) is designed to demonstrate whether monitoring antihypertensive treatment intensity using PWV may affect outcome compared to classical monitoring, mainly based on BP [44]. The study is ongoing and its first results are expected in 2020. One limit will be that due to the protocol, patients are closely monitored and BP control is excellent in both groups, which might decrease the power of the trial.

We have also shown that some treatments like antiangiogenic drugs, used in cancer treatment induce BP-independent increase in arterial stiffness, and that this increase in arterial stiffness truly represents a toxic effect since it is not associated with improved survival [58]. In a similar line, Zanoli et al showed that different treatment lines used in inflammatory bowel disease have differential effects on arterial stiffness, independent of BP, and that newer drugs with improved efficacy on inflammatory symptoms are also the most efficient on arterial stiffness [52]. Adverse effect on large arteries could be taken into account to judge the long-term effect of medications on CV outcomes.

Finally, central hemodynamics might also be an appealing target to guide therapy in hypertensive patients. The ongoing Targeted LOWering of Central Blood Pressure in patients with hypertension (LOW CBP) study (ACTRN12613000053729) will ascertain the role of central versus brachial BP for predicting changes in left ventricular mass index in patients with controlled brachial BP but elevated central BP by using spironolactone [59].

Unmet needs in a technological perspective

As already stated, the main method for measuring arterial stiffness is carotid to femoral PWV. This technique, introduced nearly one century ago, is still the gold standard for arterial stiffness assessment, thanks to the availability of reference values for European patients [23], and of a standardized way of measuring, especially for estimating path length [60]. However some technical limitations need to be acknowledged. Although non invasive, this technique is demanding in term of training, and takes approximately 10 min to be performed (including rest), which is a strong limitation to its everyday use [47]. Alternative techniques using pulse transit time use alternative arterial paths using cuffs or oximeters, such as brachial-ankle [33] and finger-to-toe PWV [61], respectively are deemed to be more applicable in routine. These techniques have been compared with reference methods with usually good agreement and some were also validated in term of epidemiology. They nevertheless provide different metrics, which cannot be directly translated into carotid to femoral PWV metrics. Techniques based on single-site measures using oscillometric BP cuffs have been proposed [62,63]. They have major advantages since brachial and central BP are measured at the same time, and estimation of arterial stiffness only requires modest increase in measurement time. They also allow 24-h monitoring of central BP and arterial stiffness, which could provide additional information. Their limits have nevertheless to be taken into account. The theory behind estimation of arterial stiffness from single brachial measurement has been questioned, since it is based on a mathematical model combining several parameters from pulse wave analysis and wave separation analysis together with age and BP. The added value of such measurement beyond age of BP is a matter of debate. Nonetheless, these novel, simpler techniques for PWV assessment have the potential of being applied to large numbers of individuals. The UK-Biobank project has included arterial stiffness measurements in the phenotyping the recruited population [64]. More than 200,000 patients have been investigated by Arterial Stiffness Index (ASI) derived from finger photoplethysmography. Unfortunately, the validity of this technique is not strongly demonstrated, the huge number of patients is supposed to compensate (at least partially) the lower quality of measurements, though the first results released showed relevant inconsistencies with previous findings obtained by carotid-femoral PWV, i.e. lack of prognostic value of ASI independent of BP [65]. A novel, non-contact direct measurement of pulse transit time using laser vibrometers is currently under

validation (http://www.cardis-h2020.eu, ClinicalTrials.gov Identifier: NCT03446430). If successful, it would provide a very fast and reliable measurement of arterial stiffness, which could be of great utility for stratifying intervention, especially in low-middle income countries [66].

We have now to consider the proliferation of alternative techniques based on smartphones [67,68]. The ARTERY society has published guidelines for the validation of arterial stiffness devices [69]. Those guidelines should be mandatorily applied before these techniques are launched and used in clinical practice or for personal use. A system based on a bathroom weighting scale, using ballistocardiography as cardiac activity landmark and foot impedance as index of pulse propagation, has been recently proposed and validated [70]. The clinical significance of this kind of multiple self-measurements is an open issue that will raise a large debate in the era of big data.

Conclusions

Measuring arterial stiffness non-invasively is possible and provides information about CV risk additional to classical risk factors. Reference values and methods standardization are available, at least for carotid-femoral PWV, which effectively reclassifies patients, especially in individuals at low-to-intermediate risk. The two main drawbacks of carotid-femoral PWV are: 1) its relative complexity and 2) lack of demonstration of whether its modification by treatment is associated with a better outcome. For the first issue, the wider use of vascular stiffness measurement is still hampered by the heterogeneity of methods and different metrics, and the absence of consensus on simpler alternative methods. A reliable, direct technique applicable by general practitioners or paramedics (or even self-measurements) is still awaited. For the second issue, no specific intervention targeting arterial stiffness is available, though several interventions such as physical activity, dietary supplementations, antihypertensive drugs, antidiabetic and lipid lowering drugs, anti-inflammatory drugs etc have shown blood pressure-independent reduction in arterial stiffness. The final demonstration that prognosis is improved in those who correct arterial stiffness is still awaited for.

Disclosure :
Pierre Boutouyrie has participated to the development of many devices. He has not received personal honorarium for this. Research grants have been obtained, together with investigation devices for the purpose of technique validation (CAVI Fukuda, ABI Omron, Popmetre Axelife, Sphygmocor ATCOR, Artlab ESAOTE). Academic grants have been obtained for the CARDIS device (H2020 European grant)
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Figure legends

Figure 1. Aortic stiffness: interaction with age and blood pressure and its role in cardiovascular pathophysiology.

PP: pulse pressure; BP: blood pressure.

Figure 2. Carotid-femoral pulse wave velocity.

PWV: pulse wave velocity; ΔL : path length ; Δt : transit time. Images are modified, from Servier Medical Art (https://smart.servier.com), and licensed under a Creative Commons Attribution 3.0 Unported License.

Figure 1