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Mini-Review

Aortic-Brachial Pulse Wave Velocity Ratio: A Measure of Arterial Stiffness Gradient Not Affected by Mean Arterial Pressure

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Keywords
Aortic stiffness · Arterial stiffness · Arterial stiffness gradient · Pulse wave velocity · Blood pressure

Abstract
Background: Aortic stiffness, measured by carotid-femoral pulse wave velocity (cf-PWV), is used for the prediction of cardiovascular risk. This mini-review describes the nonlinear relationship between cf-PWV and operational blood pressure, presents the proposed methods to adjust for this relationship, and discusses a potential place for aortic-brachial PWV ratio (a measure of arterial stiffness gradient) as a blood pressure-independent measure of vascular aging. ***Summary:*** PWV is inherently dependent on the operational blood pressure. In cross-sectional studies, PWV adjustment for mean arterial pressure (MAP) is preferred, but still remains a nonoptimal approach, as the relationship between PWV and blood pressure is nonlinear and varies considerably among individuals due to heterogeneity in genetic background, vascular tone, and vascular remodeling. Extrapolations from the blood pressure-independent stiffness parameter β (β_0) have led to the creation of stiffness index β, which can be used for local stiffness. A similar approach has been used for cardio-ankle PWV to generate a blood pressure-independent cardio-ankle vascular index (CAVI). It was recently demonstrated that stiffness index β and CAVI remain slightly blood pressure-dependent, and a more appropriate formula has been proposed to make the proper adjustments. On the other hand, the negative impact of aortic stiffness on clinical outcomes is thought to be mediated through attenuation or reversal of the arterial stiffness gradient, which can also be influenced by a reduction in peripheral medium-sized muscular arteries in conditions that predispose to accelerate vascular aging. Arterial stiffness gradient, assessed by aortic-brachial PWV ratio, is

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emerging to be at least as good as cf-PWV for risk prediction, but has the advantage of not being affected by operating MAP. ***Key Messages:*** The negative impacts of aortic stiffness on clinical outcomes are proposed to be mediated through attenuation or reversal of arterial stiffness gradient. Aortic-brachial PWV ratio, a measure of arterial stiffness gradient, is independent of MAP.

Introduction

Aortic stiffness is an independent predictor of cardiovascular events and mortality in the general population, and in various pathological conditions such as hypertension, diabetes, and end-stage renal disease [1–4]. Despite its inherent pressure dependency, aortic stiffness assessed by carotid-femoral pulse wave velocity (cf-PWV) is widely used as a noninvasive and reliable clinical tool for cardiovascular risk classification [5]. With aging, the aorta loses its elasticity and its capacity to dampen the pulsatile pressure leading to increased myocardial workload. However, the stiffness of medium-sized muscular arteries was traditionally considered to be relatively unchanged over a lifetime. This knowledge has successfully been used to develop more user-friendly devices to assess vascular stiffness for large epidemiological studies. However, most of these devices rely on a global measure of arterial stiffness, which integrates a combination of both central and peripheral arterial stiffness. In light of reports stating that peripheral stiffness may decrease with age or under pathological conditions [6–8], it might be desirable to further explore this heterogeneity of the arterial tree. Indeed, a decrease in peripheral arterial stiffness could partially contribute to the attenuation or reversal of the stiffness gradient, inducing higher pulse pressure transmission into the microcirculation, causing end-organ damages. In this review, we will discuss (1) the dependency of PWV on the operating blood pressure, (2) the approaches that are proposed to adjust for blood pressure, (3) the use of aortic-brachial PWV ratio as a measure of arterial stiffness gradient, and (4) the relationship between aortic-brachial PWV ratio and blood pressure.

PWV and Operating Blood Pressure

The Bramwell-Hill variant of the Moens-Korteweg equation states that:

$$PWV = \sqrt{\frac{dP \times V}{\rho \times dV}},$$

where dP is change in pressure, dV is change in arterial volume, V is the baseline volume of the vessel, and ρ is blood density. For example, the increase in pressure from diastolic pressure to systolic pressure during a single cardiac cycle could result in a variation of 0.7–4 m/s of PWV (i.e., without any change in vascular wall property) [9, 10]. This variability is mainly caused by the organization of elastin, collagen, and vascular smooth muscle cells of the media. Due to passive mechanical properties, at low pressure the load is carried by elastin, while at high pressure the load is carried by stiffer collagen fibers [11, 12].

The pressure-diameter relationship varies greatly among individuals due to differences in genetic background, vascular smooth muscle tone [13, 14], and vascular wall remodeling related to exposure to cardiovascular risk factors. As arteries stiffen, an upward shift of the pressure-diameter relationship occurs, meaning that higher pressures are required to induce a similar change in diameter (Fig. 1). Indeed, a steeper slope in pressure-diameter rela-

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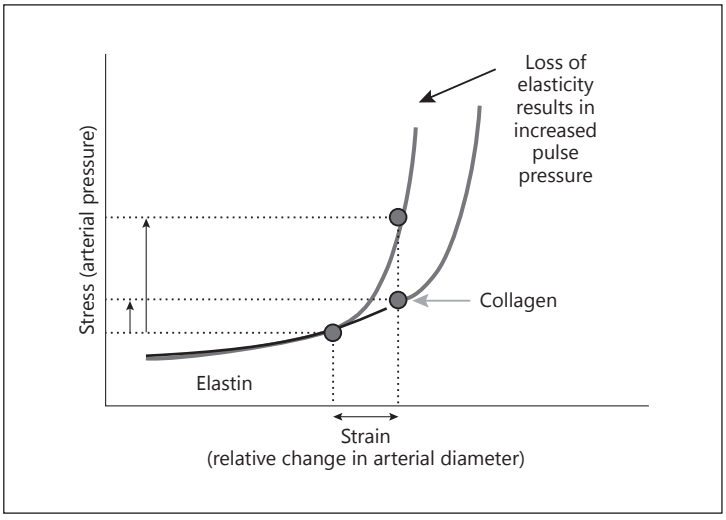

Fig. 1. Stress-strain relationship. Nonlinear relationship between arterial stress (pressure) and strain (relative change in diameter), with arterial wall components under tension according to the pressure load in normal and stiff vessels. Reprinted from McEniery et al. [40] with permission.

tionship is observed in the elderly compared to younger individuals as pressure dependence varies with age, due partly to the age-related material fatigue, fractures in the elastin lamella, and vascular fibrosis [9, 10, 15].

Adjusting Arterial Stiffness for Operating Blood Pressure

In cross-sectional studies, PWV adjustments for pressure are usually performed by a linear regression using the average mean arterial pressure (MAP) (nonpulsatile component of blood pressure) of the cohort. While this method has its merits, it also has its inherent limitations as it does not consider the interindividual differences in PWV-pressure relationship, and it does not take into account the nonlinear nature of this relationship.

Arterial stiffness index β and cardio-ankle vascular index (CAVI) theoretically consider the effect of blood pressure, since both are based on the substitution of the exponential pressure-diameter relationship to a linear relationship between the change of pressure (ln (P_s / P_d)) and relative changes in diameter (Fig. 2) [16–22]. However, stiffness index β is obtained by an approximation of the exponential pressure-diameter relationship first described experimentally by Hayashi et al. [23]

$$P = P_{ref} e^{\beta 0\left[\left(\frac{d}{d_{ref}}\right)-1\right]},$$

from which the pressure and diameter of reference (P_{ref} and d_{ref}) were substituted by diastolic pressure and diastolic diameter. Accordingly, the stiffness index β is slightly different than the proposed blood pressure-independent β_0. Indeed, Spronck et al. [24] recently demonstrated that arterial stiffness index β and CAVI are slightly blood pressure-dependent, and they proposed using a fixed reference pressure value to resolve this issue for local or segmental stiffness.

However, applying such correction to a global PWV that encompasses various heterogeneous vascular territories and treating them as homogenous does not seem to be conceptually appealing.

Indeed, this is clearly demonstrated by Shimizu et al. [25] who examined the impact of acute administration of nitroglycerin on CAVI. Their findings showed a reduction in CAVI

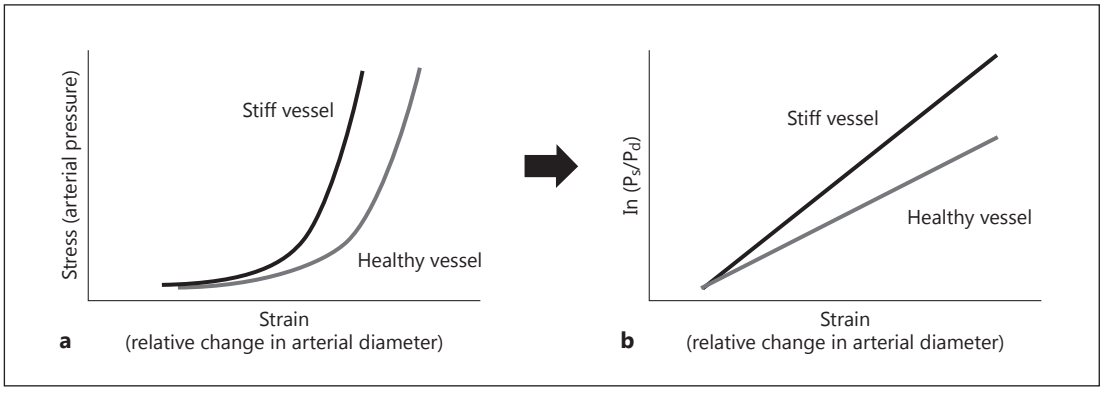

Fig. 2. Pressure-diameter relationship and stiffness index β. **a** The exponential pressure-diameter relationship in healthy and stiff vessel. **b** The transformation of this relationship into a linear model where the slope represents the proposed blood pressure-independent stiffness index β.

suggesting an improvement of vascular stiffness. Since CAVI is based on cardio-ankle PWV, it was impossible to evaluate whether this improvement was the result of a reduction in aortic stiffness, femoral-tibial stiffness, or both. Taking this idea further, the same group addressed this question by applying the stiffness index β to heart-thigh PWV and thigh-ankle PWV by utilizing Bramwell-Hill's equation in the same way as it is applied when measuring CAVI [26]. They concluded that the reduction of CAVI after nitroglycerin administration was mainly the result of a reduction in thigh-ankle stiffness index β rather than a change in the heart-thigh stiffness index β. Similarly, we observed a significant reduction in carotid-radial PWV (cr-PWV) and femoral-tibial PWV (muscular conduit vessels) without any changes in cf-PWV or MAP [27].

Taken together, these results suggest that the reduction of the stiffness of muscular conduit vessels, which link aorta to the microcirculation, results in the attenuation of arterial stiffness gradient. Given that the loss or reversal of arterial stiffness gradient is proposed to cause microvascular damage, especially to the kidneys and the brain, such effect could theoretically be undesirable.

Aortic-Brachial PWV Ratio: A Measure of Arterial Stiffness Gradient

Aorta and peripheral medium-sized muscular conduit vessels are structurally and biomechanically different, and may not be similarly affected by age, pathological conditions, and vasoactive drugs [6, 7, 26–31]. Accordingly, arterial stiffness gradient is not only affected by an increase in aortic stiffness, but also by a decrease in the stiffness of medium-sized peripheral muscular arteries [32–34]. Indeed, in a longitudinal study, we discovered that brachial PWV, as measured by cr-PWV, decreased by approximately 0.66 m/s/year, despite an accelerated increase in cf-PWV by 0.84 m/s/year. This divergent evolution of these two vascular territories led us to propose that aortic-brachial PWV ratio (cf-PWV/cr-PWV), a measure of arterial stiffness gradient, could be used to evaluate the risk of mortality. This hypothesis was tested in a cohort of 310 dialysis patients, and it was shown that aortic-brachial PWV ratio predicted mortality better than cf-PWV alone, and was the only significant hemodynamic parameter that resisted multivariable adjusted models [35].

More recently, PWV ratio was assessed in the Framingham Heart Study Offspring cohort, a large general population free of overt cardiovascular disease. It was shown that PWV ratio

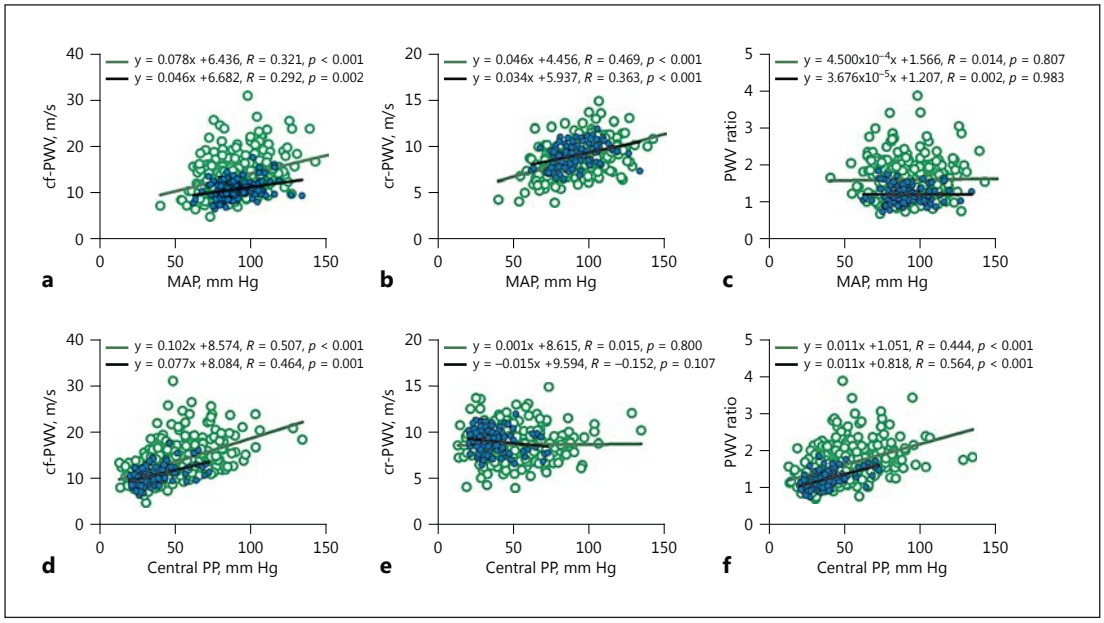

Fig. 3. Aortic stiffness, brachial stiffness and arterial stiffness gradient relationships with mean arterial pressure (MAP) and central pulse pressure (PP). There was a positive relationship between MAP and carotid-femoral pulse wave velocity (cf-PWV, **a**) and carotid-radial pulse wave velocity (cr-PWV, **b**), but no relationship between MAP and PWV ratio (**c**) for the dialysis cohort (n = 304, empty circles) and for the cohort with eGFR >45 (n = 114, filled circles). The relationship between central PP, cf-PWV (**d**) and PWV ratio (**f**) were similar in both respective cohorts, while there was no relationship between central PP and cr-PWV (**e**).

predicts cardiovascular events as well as aortic stiffness, but did not provide any additional risk information above and beyond cf-PWV [36]. This is not surprising before the fifth or sixth decade of age as stiffness of peripheral medium-sized muscular arteries are negligibly affected by age, and the main driving factor for alteration of arterial stiffness gradient is increased aortic stiffness. However, authors mentioned that they could not exclude the possibility that PWV ratio might provide an incremental predictive value over cf-PWV in the elderly, as the association between CV events and PWV ratio was greater than that of aortic stiffness in individuals over the age of 70. Moreover, other studies tend to support that arterial stiffness gradient may be better associated with target-organ damage than aortic stiffness. For example, in a cross-sectional analysis of patients with type 2 diabetes (n = 60) and age-matched controls (n = 60), aortic-brachial stiffness gradient predicted estimated glomerular filtration rate independently of age, sex, diabetes status, and cardiovascular risk factors, whereas aortic stiffness did not [37]. In addition, Lee et al. [38] observed that PWV ratio was independently associated with history of stroke and coronary artery disease in patients with a known medical history of cardiovascular disease (n = 142), while aortic stiffness did not reach a statistical level of significance.

PWV Ratio and Its Relation to Blood Pressure

Since aortic and brachial PWVs may both change in the same direction as the operating MAP, we hypothesized that PWV ratio may potentially be blood pressure-independent. We tested this hypothesis in two distinct cohorts of patients that were completely different in

terms of age, renal function, and comorbidities [7]. In the first group (n = 304), which included dialysis patients, aortic stiffness increased with age, while brachial stiffness decreased. In the second group of patients with an estimated glomerular filtration rate of >45 mL/min/1.73 m^2 (n = 114), aortic stiffness increased with age as expected, while brachial stiffness increased slightly until the fifth decade and then started to decrease thereafter. Nevertheless, aortic and brachial stiffness both increased with higher MAP (measured at the time of measurement of vascular stiffness) in the two groups, while there was no correlation between PWV ratio and MAP (Fig. 3a–c). As shown in Figure 3d–f, there was a positive and similar relationship between central pulse pressure, cf-PWV, and PWV ratio, whereas there was no significant relationship between central pulse pressure and cr-PWV.

Similar results have also been observed by other investigators [37, 39]. Picone et al. [37] assessed the determinants of PWV ratio in a diabetic group and a nondiabetic control group. They found that PWV ratio was not associated with MAP in their diabetic group, but it was associated with brachial and central pulse pressure, central augmentation pressure and augmentation index. In the nondiabetic control group of their study, there was a small correlation between aortic-brachial stiffness gradient and MAP, which was no longer significant in the multivariable model. Similarly, Bia et al. [39] did not find any associations between PWV ratio and MAP in 151 hemodialysis patients.

Perspective

Aortic-brachial PWV ratio is a simple measure of arterial stiffness gradient. Indeed, PWV ratio may potentially be more promising at least in advanced aging and conditions that predispose to accelerate vascular aging, where brachial stiffness tends to decrease with age despite an increase in aortic stiffness. Even if aortic-brachial PWV ratio does not provide additional information, its lack of relationship with operating MAP makes it more appealing than crude cf-PWV. However, these observations need further external validation in different populations. In addition, the differential impact of various classes of antihypertensive drugs on the stiffness of aorta and medium-sized muscular arteries, hence their potential impact on arterial stiffness gradient needs to be elucidated.

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Disclosure Statement

The author has no conflicts of interest to declare.

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