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COMMENTARY

Lower-limb pulse wave velocity: correlations and clinical value

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Although the objective recording of arterial pulse as a tool for estimating vascular stiffness was developed about 150 years ago, many years before the measurement of arterial pressure became possible,[1] clinical and scientific interest in sphygmography tapered off by the end of the nineteenth century and remained negligible throughout most of the twentieth century. The reasons for this declining fortune were clearly recognized in 1931 by Paul Dudley White, who wrote in his classic cardiology textbook that 'the difficult and bothersome technique and the obscurity concerning interpretation in the minds of most physicians prevented a wide adoption of the method'.[2] The situation has changed substantially in the last few decades, when a renewed and growing interest into vascular stiffness has been mainly driven by the availability of devices able to measure noninvasively pulse wave velocity (PWV), a direct measure of arterial stiffness.

PWV is a simple and direct way to assess the stiffness of a given arterial segment, provided that the arterial path is included between two palpable pulses, and path length and transit time are both measurable. To date, most of the published data on the clinical and prognostic significance of arterial stiffness have been based on carotid-femoral PWV,[3–6] which is basically a measure of the stiffness of aorta, an elastic artery. Some studies have also shown the adverse prognostic significance of brachial-ankle PWV,[7–9] although this parameter is a combination of both elastic and muscular arterial segments and does not differentiate between central and peripheral arteries. The clinical significance of PWV in muscular arterial segments, including the lower limbs, has been less studied so far.

In the present issue of *Hypertension Research*, Wohlfahrt *et al.*[10] further report on the stiffness of muscular arteries and its correlates by examining the predictors of carotid-femoral and lower-limb PWV. Compared with a previous study by the same group,[11] this paper examines a larger and more heterogeneous population of 911 individuals from the Czech post-MONICA study, a cross-sectional survey at the general population level. In both cases, PWV was evaluated by using an electrocardiogram-gated tonometric approach. Lower-limb PWV was found to be higher than carotid-femoral PWV especially at younger ages, and the PWV gradient between the aorta and lower-limb territories was progressively reduced by aging. Moreover, whereas femoral-ankle PWV was higher in men, the effects of age on lower-limb PWV were weaker and significantly less pronounced in men than in women. The impact of traditional cardiovascular risk factors on PWV was also investigated. Whereas diabetes, hypertension, dyslipidemia, waist circumference and chronic kidney disease had an independent relationship with carotid-femoral PWV, high blood pressure was the only cardiovascular risk factor to be independently related to lower-limb PWV. Finally, ankle systolic blood pressure was more closely related to carotid-femoral PWV than to femoral-ankle PWV, and the latter was lower in subjects with a low ankle-brachial blood pressure index (ABI) than in those with a normal ABI.

It is generally accepted that stiffening of the peripheral arteries is less of an age-dependent process than stiffening of the central arteries such as the aorta; therefore, lower-limb PWV is a less reliable marker of arterial aging than is carotid-femoral PWV.[12–15] The divergent effects of aging on the peripheral and central arteries might be related to the different structural characteristics of these arteries. Peripheral arteries such as the brachial, femoral and tibial arteries are classified as muscular arteries and are composed mainly of smooth muscle cells with small amounts of extracellular matrix. Central arteries such as the aorta and carotid and subclavian arteries are examples of elastic arteries, which are composed of smooth muscle cells with larger amounts of elastin, collagen and other extracellular matrix proteins forming multiple layers of elastic lamellae.[16] Thus, elastin depletion and collagen deposition with advancing age are more prominent in elastic arteries and explain the greater age-dependent stiffness increase in central arteries.

The paper by Wohlfahrt *et al.*[10] also confirms that lower-limb PWV has no strong relationship with major cardiovascular risk factors. Diabetes mellitus has been associated with preferential stiffening of the large elastic arteries, and an independent influence of diabetes has been reported on carotid-femoral, but not on lower-limb PWV.[17,18] More importantly, at variance with the carotid-femoral PWV, the PWV of muscular arterial segments has not been shown to predict adverse cardiovascular prognosis or to correlate with the global atherosclerotic burden.[19,20]

What are the clinical implications of an elevated lower-limb arterial PWV? A reduced glomerular filtration rate has been accompanied by a parallel increase in both elastic (aortic) and muscular (upper limb) arterial stiffness, probably as a result of

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common inflammatory mechanisms, as well as the development of arterial calcifications and sodium-related alterations in extracellular matrix composition.[21] However, the renal resistive index, a widely accepted ultrasonographic marker of renal microvascular damage, was independently correlated with aortic-, but not femoral-dorsalis pedis, PWV. This finding suggests that aortic stiffness may cause renal microvascular damage possibly through increased central pulse pressure, which in turn may be transmitted toward and across glomeruli, and initiate glomerulosclerosis and/or tubulointerstitial damage.[22] Similar to aortic PWV, lower-limb PWV may be reduced by treatments for major cardiovascular risk factors, such as statins[23–25] and blood pressure-lowering drugs.[26]

Muscular-artery PWV also shows significant gender-related differences. The physiological determinants of femoral PWV were evaluated by Vermeersch *et al.*[27] in a large healthy population by means of the Bramwell–Hill formula. They found that PWV in the femoral artery is higher in men, whereas characteristic impedance (Z_c), a measure related directly to PWV and inversely to arterial cross-sectional area, is higher in women. In both genders, aging was accompanied by a decrease in local Z_c, despite unchanged values of PWV. These findings indicate that both body size and stroke volume may be important determinants of arterial stiffness, and their effects on PWV are higher in the peripheral muscular arteries than that in the aorta. These and other differences are important to keep in mind when investigating PWV in different arterial territories.

In the study by Wohlfahrt *et al.*,[10] a small proportion of the examined population (6%) was affected by peripheral arterial disease, manifested as a low or high ABI. In both cases, independently of age and brachial blood pressure, carotid-femoral PWV was higher than in people with a normal ABI. By contrast, lower-limb PWV was lower in subjects with a reduced ABI and was not significantly different in people with a normal ABI and those with a high ABI. Interestingly, for any given level of brachial blood pressure, carotid-femoral PWV was independently related to high values of ankle blood pressure, whereas this relationship was not found for lower-limb PWV. Thus, lower-limb PWV had less power to predict lower-limb arterial disease than did carotid-femoral PWV.

In contrast to the upper limbs, lower-limb arteries are highly prone to developing both atherosclerosis and arteriosclerosis. The former includes intima-media thickening and the formation of the atherosclerotic plaque, whereas the latter is characterized by the progressive degeneration and calcification of the arterial media. A low ABI is the result of the presence of an atherosclerotic plaque with a consequent downstream blood pressure fall, whereas a high ABI is generally assumed to reflect arterial incompressibility due to extended calcification that generates artifactually higher values of ankle blood pressure. Thus, the low values of lower-limb PWV observed by Wohlfahrt *et al.*[10] in individuals with peripheral artery disease and a low ABI are likely to be 'falsely' low values, attributable to the stenosis reducing blood flow and distending pressure downstream. The absence of an association between high ABI and high lower-limb PWV when brachial mean arterial pressure is accounted for as a confounding factor confirms the evidence that PWV in a given arterial segment is a function of invasive distending pressure, which in turn may not necessarily be mirrored by externally measured pressure.

Another important aspect derived from the combined evaluation of carotid-femoral PWV and femoral-ankle PWV is the critical role of arterial stiffness as a determinant of lower-limb perfusion. Increased stiffness of the arteries of the lower limbs has indeed been associated with impaired arterial blood flow,[28] subclinical hypoxia of the foot[29,30] and ischemic symptoms of the lower extremities.[31] Physiologically, the resistance to flow in a given arterial segment is generally composed of two elements: a constitutive component, which is related to the vasoconstrictor tone of arterioles, and a phasic component, the above mentioned Z_c, which determines the relationship between pulsatile pressure and pulsatile flow in the arterial segment.[32] Although it is well established that peripheral resistance is inversely related to blood flow in the lower limbs, less data are available on the relationship between arterial stiffness and blood flow. Suzuki *et al.*[28] investigated the relationship between lower-limb PWV and popliteal flow in diabetic patients without peripheral arterial disease. They found that patients in the highest tertile of lower-limb PWV had decreased total popliteal inflow volumes compared with subjects in the lower tertile, particularly for the lower late diastolic component. However, their method for lower-limb PWV was indirectly derived from brachial-ankle transit time and was somewhat questionable as a real measure of lower-limb PWV. Other authors found a significant relationship between peripheral circulation and symptoms of arterial insufficiency, and an indirect measure of local artery stiffness, namely β-index.[29,31] More recently, Hashimoto *et al.*[33] have analyzed the relationship of lower-limb blood flow evaluated by Doppler ultrasound profile with carotid-femoral and lower-limb PWV, evaluated by applanation tonometry in 138 hypertensive patients without peripheral arterial disease. They found that, independently of distending blood pressure, augmented pressure and other determinants, increased carotid-femoral PWV was associated with a decreased reverse femoral flow, a decreased diastolic forward flow and a disappearance of diastolic forward flow. By contrast, lower-limb PWV was not related to any of the above findings but showed an independent inverse relationship with the acceleration time of forward systolic flow.[33]

Therefore, for a given blood pressure, an increased femoral stiffness generates a reduction in the time to the peak of incident flow wave and an early transition from acceleration to deceleration, whereas increased aortic stiffness leads to decreased accumulation of reverse flow caused by a reduction in the aortic 'windkessel effect', which translates into a decreased diastolic lower-limb blood flow. It is noteworthy that modifications of flow waveform profile, such as the decrease in the flow pulsatility index, have been proposed as a contributing factor in the development of arteriosclerosis.[34]

Overall, carotid-femoral and lower-limb PWV may interfere with lower-limb perfusion through different pathways, and their combined evaluation might be of clinical utility. Direct measurement of the two parameters is quick, simple and reproducible. A thorough assessment of the factors that affect lower-limb PWV, including blood pressure values and an abnormal ABI, is necessary to fully appreciate the physiological and practical value of lower-limb PWV in different research and clinical settings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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