Editorial Commentary

Arterial Stiffness as an Imaging Biomarker
Are All Pathways Equal?

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The measurement of arterial stiffness is increasingly popular among physicians and researchers mainly because its predictive value for cardiovascular (CV) events has been well demonstrated. The largest amount of evidence has been given for aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV). This has been initially reported in the late 1990s or early 2000s.[1] Currently, as many as 19 studies consistently showed the predictive value of aortic stiffness for fatal and nonfatal CV events in various populations having different levels of CV risk: general population, patients with hypertension, elderly subjects, patients with type 2 diabetes mellitus, and patients with end-stage renal disease. In a recent meta-analysis,[2] 17 longitudinal studies totalizing 15 877 subjects with a mean follow-up of 7.7 years showed, for 1 SD increase in PWV, a risk ratio of 1.47 (1.31–1.64) for total mortality, 1.47 (1.29–1.66) for CV mortality, and 1.42 (1.29–1.58) for all-cause mortality.

To be considered as a novel risk marker, arterial stiffness should add predictive information to established, standard risk markers, particularly the Framingham Risk Score or the European SCORE. This has been demonstrated with cfPWV in ≥3 studies: in patients with hypertension,[3] in elderly subjects from a general population,[4] and in middle-aged subjects from a general population.[5] Another important requirement is that the measurement of the novel risk marker changes predicted risk sufficiently to change recommended therapy. This is indeed the case because several studies showed that a substantial amount of patients at intermediate risk could be reclassified into a higher or a lower CV risk, when arterial stiffness was measured.[4–6] Aortic stiffness, measured through cfPWV, can thus be considered as a novel imaging biomarker for predicting CV events, although its value as a true surrogate end point requires a large intervention trial to demonstrate that the reduction in arterial stiffness translates into a reduction in CV events.

The article by Gosse et al[7] published in the present issue of *Hypertension* provides an important contribution with regard to the predictive value of arterial stiffness for CV events for ≥4 reasons. First, the authors reported that arterial stiffness, measured in a population of 793 patients with hypertension with a mean follow-up of 97 months, was independently related to all CV events, major CV events, and total mortality. Interestingly, the predictive value was significant in all subgroups of CV risk, defined by a low, medium, or high SCORE risk. These findings confirmed those of previous studies. Second, the authors took advantage of the simultaneous measurement of 24-hour blood pressure (BP) to include 24-hour mean BP in the multivariate Cox analysis, and this is a novelty. Thus, they were able to provide the demonstration that the predictive value of arterial stiffness is not only independent of office BP, as shown in most epidemiological studies, but also of 24-hour mean BP and pulse pressure (or alternatively 24-hour systolic and diastolic BPs) simultaneously measured. Third, among the 793 patients, 519 patients had baseline measurements of arterial stiffness before any antihypertensive treatment, and the remaining 274 patients had measurement during the follow-up period. The independent predictive value of arterial stiffness was significant whether measured before or after the administration of antihypertensive treatment. Finally, Gosse et al[7] showed, in a subgroup of 523 patients who had a measurement of left ventricular mass index, that the predictive value of arterial stiffness for major CV events was independent of left ventricular mass index. The authors thus confirmed the very few epidemiological studies which analyzed the predictive value of biomarkers of target organ damages (ie, left ventricular mass index, urinary albumin excretion rate, carotid intima-media thickness, and arterial stiffness) and found that arterial stiffness retained a significant predictive value when adjusted either to left ventricular mass index[6] or carotid intima-media thickness.[5]

The findings of Gosse et al[7] are stimulating from another point of view: the method which has been used to determine arterial stiffness. Indeed, Gosse et al[8] proposed, 2 decades ago, to take advantage of an ambulatory measurement of BP and continuous monitoring of ECG >24 hours, to calculate the QKD interval. QKD is the time between the onset of the QRS on the ECG and the detection of the last Korotkoff sound by the microphone placed on the brachial artery. It has 2 components: the pre-ejection time, which is influenced by heart rate and the pulse transmission time, which is inversely related to PWV, and arterial stiffness. BP and QKD are measured repeatedly, and a stiffness parameter is derived from the linear regression of all the measurements of QKD, heart rate, and systolic BP >24 hours. The QKD interval is calculated for a 100-mm Hg

BP, thus it gives an isobaric value of arterial stiffness, and for a 60-beats/min heart rate to reduce the influence of the pre-ejection time. Most importantly, the arterial pathway of pulse wave transmission includes the ascending aorta, the aortic arch, and muscular arteries (subclavian and brachial), and thus differs from the carotid-femoral pathway of the cfPWV measurement, considered as gold standard for arterial stiffness.[9]

Because most of the pioneering epidemiological studies used the cfPWV method, novel devices using a different method for determining arterial stiffness should also demonstrate that the stiffness parameter which they measure has an independent predictive value for CV events. This is what has been adequately done by Gosse et al[7] in the article published in the present issue of *Hypertension*. Indeed, novel devices measuring a novel stiffness parameter cannot claim a predictive value for CV events simply from data showing a significant correlation between the novel parameter and cfPWV obtained during a cross-sectional validation study. Adequate epidemiological studies should be performed. The Table shows that the well-established and novel methods have published an independent predictive value of CV events until now. This issue is of major importance at the present time because several novel apparatus, which were developed for determining arterial stiffness, claim superiority over pioneering methods through higher simplicity of use, better repeatability, or more pertinent arterial pathway.

The question of the functional substratum linking the measured parameter to events is crucial. Carotid-femoral PWV, which is considered as gold standard for determining aortic stiffness,[9] is calculated as the ratio of the transit time between the feet of the carotid and femoral pressure waveforms, and the carotid-femoral distance, a ratio which is undisputedly recognized as a stiffness parameter. Several studies and a consensus statement have determined the correction factor, which should be applied to the carotid-femoral distance, to take into account the fact that, when the pressure wave is recorded at the carotid

level, it has already reached the descending thoracic aorta. The pressure wave travels mostly along an aortic segment, including the thoracic descending aorta and the abdominal aorta, and ultimately travels along the iliac and common femoral arteries. This is well exemplified by the Figure, which superimposes the trajectory of the pressure pulse wave on a normal angiogram obtained by magnetic resonance imaging.

The method developed by Gosse et al[7,8] measures the time delay between the onset of the QRS on the ECG and the detection of the last Korotkoff sound by the microphone placed on the brachial artery. Thus, the pressure pulse wave travels first along the ascending aorta and the aortic arch (ie, a short pathway of elastic arteries) and then along the subclavian and brachial arteries (ie, a much longer pathway of muscular arteries). Because the stiffness of muscular arteries is little influenced by age and hypertension, Gosse et al[8] attributed the difference in QKD duration to ascending aorta and aortic arch. However, a closer look at the Figure shows that the length of the ascending and aortic arch pathway represents a very small part of the total pathway and casts doubt about this statement. Furthermore, in magnetic resonance imaging studies, the transit time of flow wave along the aortic arch (average 120 mm length) is often found ≈35 ms in young healthy subjects,[10] a value which is far from the mean 206 ms QKD duration found in the present study. Thus, part of that QFD duration has to be further explained by both the pre-ejection period and the transit time within muscular arteries.

The issue of the arterial pathway is also raised by other methods more recently introduced. The measurement of the brachial-ankle PWV, which includes a much longer trajectory of the pressure wave along the muscular arteries of the upper and lower limbs than along the aortic pathway, has demonstrated a predictive value for CV events in several populations. The issue of the arterial pathway is even more critical with 2 novel oscillometric devices. The arteriograph system estimates PWV from a single-site determination of the suprasystolic waveform at the brachial artery site, and measures the time elapsed between the first wave ejected from

Table. Devices and Methods Used for Determining Noninvasively Regional Arterial Stiffness Through Pulse Wave Velocity

Description of the Method (Year of First Publication)	Device	Method	Arterial Pathway	Predictive Value for CV Events (Year of First Publication)
1984	Complior	Mechanotransducer	Carotid-femoral	Yes (1999)
1990	Sphygmocor	Tonometer	Carotid-femoral	Yes (2011)
1994	QKD	ECG + Korotkoff sounds	Aorta + brachial	Yes (2005)
1997	Cardiov. Eng. Inc	Tonometer	Carotid-femoral	Yes (2010)
2002	Doppler probes	Doppler probe	Aortic arch + descending aorta	Yes (2002)
2002	VP-1000 Omron	Brachial and ankle pressure cuffs	Aorta + brachial + lower limbs	Yes (2005)
2004	PulsePen	Tonometer	Carotid-femoral	No
2006	CAVI-VaSera	ECG + Brachial and ankle pressure cuffs	Aorta + brachial + lower limbs	No
2008	Arteriograph	Arm pressure cuff	Aorta + brachial	No
2009	MRI-ArtFun	MRI	Aortic arch	No
2009	Vicorder	Cuffs	Carotid-femoral	No
2010	Mobil-O-Graph	Arm pressure cuff	Aorta	No

CAVI-VaSera indicates Cardio-Ankle Vascular Index measured with VaSera VS-1500N; and MRI, magnetic resonance imaging.
Arterial pathways and predictive values are indicated.

Figure. The trajectories of the pressure pulse waves along the arterial segments are superimposed onto an angiogram obtained by computed tomography scan (left anterior oblique). The carotid-femoral pathway is described as dotted line, and the QKD pathway is described as dashed line.

the left ventricle to the aortic root, and its reflection from the bifurcation as the second systolic wave, with subtraction of the brachial artery transit time. The Mobil-O-Graph system uses oscillometric recording of brachial artery pressure waveform and reconstructs the central pulse wave by applying a transfer function. Central pulse wave is then decomposed into forward and backward waves, and PWV is estimated from their time difference.

In conclusion, the study by Gosse et al[7] provides a valuable contribution to the ongoing research on arterial stiffness, used as an imaging biomarker of CV events. Also, results are stimulating for a better understanding of the pathophysiology of the pressure wave transmission and the role of the different arterial segments. Further studies, including magnetic resonance imaging studies,[10] are needed to determine which part of the arterial pathway contributes the most to the physiological, pharmacological, and epidemiological findings obtained with either the well-established or more recent methods measuring PWV.

Disclosures

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