Arterial Stiffness as an Imaging Biomarker
Are All Pathways Equal?

Stéphane Laurent, Elie Mousseaux, Pierre Boutouyrie

The article by Gosse et al7 published in the present issue of Hypertension provides an important contribution with regard to the predictive value of arterial stiffness for CV events for ≥24 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 al8 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 index8 or carotid intima-media thickness.5

The findings of Gosse et al7 are stimulating from another point of view: the method which has been used to determine arterial stiffness. Indeed, Gosse et al7 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. 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 arterial stiffness, 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 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 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, 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

<table>
<thead>
<tr>
<th>Description of the Method (Year of First Publication)</th>
<th>Device</th>
<th>Method</th>
<th>Arterial Pathway</th>
<th>Predictive Value for CV Events (Year of First Publication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Sphygmocor</td>
<td>Tonometer</td>
<td>Carotid-femoral</td>
<td>Yes (2011)</td>
</tr>
<tr>
<td>1994</td>
<td>QKD</td>
<td>ECG + Korotkoff sounds</td>
<td>Aorta + brachial</td>
<td>Yes (2005)</td>
</tr>
<tr>
<td>2002</td>
<td>Doppler probes</td>
<td>Doppler probe</td>
<td>Aortic arch + descending aorta</td>
<td>Yes (2002)</td>
</tr>
<tr>
<td>2002</td>
<td>VP-1000 Omron</td>
<td>Brachial and ankle pressure cuffs</td>
<td>Aorta + brachial + lower limbs</td>
<td>Yes (2005)</td>
</tr>
<tr>
<td>2004</td>
<td>PulsePen</td>
<td>Tonometer</td>
<td>Carotid-femoral</td>
<td>No</td>
</tr>
<tr>
<td>2006</td>
<td>CAVI-VaSera</td>
<td>ECG + Brachial and ankle pressure cuffs</td>
<td>Aorta + brachial + lower limbs</td>
<td>No</td>
</tr>
<tr>
<td>2008</td>
<td>Arteriograph</td>
<td>Arm pressure cuff</td>
<td>Aorta + brachial</td>
<td>No</td>
</tr>
<tr>
<td>2009</td>
<td>MRI-ArtFun</td>
<td>MRI</td>
<td>Aortic arch</td>
<td>No</td>
</tr>
<tr>
<td>2009</td>
<td>Vicorder</td>
<td>Cuffs</td>
<td>Carotid-femoral</td>
<td>No</td>
</tr>
<tr>
<td>2010</td>
<td>Mobil-O-Graph</td>
<td>Arm pressure cuff</td>
<td>Aorta</td>
<td>No</td>
</tr>
</tbody>
</table>

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

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