

## Aortic Stiffness and Disease Location is Key

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**I**ncreased risk of cardiovascular disease and events associated with aortic stiffening has been attributed both to the hemodynamic consequences of stiffening and to this being a marker for an age-related degeneration of the arterial wall predisposing to arterial disease.<sup>1</sup> There are several measures of arterial stiffness. Indeed, the term stiffness, which does not have a physical definition, was coined to encompass properties of arteries that tend to lead to an increase in many biomechanical measures of stiffness, particularly the speed of propagation of the pulse wave, pulse-wave velocity (PWV). For any individual segment of an idealized artery, PWV is determined not only by the intrinsic stiffness of the arterial wall as represented by its Young elastic modulus (E, the ratio of stress to strain) but also by the effective thickness of the arterial wall, and PWV is inversely related to (the square root of) arterial diameter.<sup>2</sup> PWV measured between accessible points in the arterial tree such as the carotid and femoral arteries provides an average measure of stiffening over the whole of this carotid-femoral pathway but is a simple robust measure of large-artery stiffening that is closely related to major adverse cardiovascular events.<sup>3</sup> E is also inversely related to the distensibility of the artery: the fractional change in arterial diameter produced by a given pressure change. This provides a measure of stiffness at a single location but requires knowledge of the local pulse pressure, which is often difficult to obtain. Although E is the property most closely related to the behavior of the arterial wall, it represents the behavior of a composite material comprising individual elements that each have differing elastic properties and thus behaves in a very different fashion from a homogeneous elastic material. One consequence is the pressure dependence of stiffness: As the arterial wall is stretched by an increasing distending pressure, load is transferred to stiffer elements so that E and hence PWV increase with increasing blood pressure.<sup>4</sup>

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In this issue of *Circulation*, Raaz and colleagues<sup>5</sup> examine the role of aortic stiffness in abdominal aortic aneurysm (AAA) formation. As with other cardiovascular conditions,

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this is a pathology in which aortic stiffness could act as a marker for aortic wall pathology predisposing to aneurysm or could be implicated in the pathogenesis of AAA through mechanical forces imposed by the stiffening. In an elegant series of experiments, they show that stiffening is causally related to aneurysm formation and that, to fully understand the impact of aortic stiffening, we need to go beyond simple integrative measures and examine regional variation in stiffening. Raaz and colleagues first show that, in a mouse model of elastase-induced AAA, stiffening of the aneurysm-prone segment precedes aneurysm growth. They measure distensibility rather than PWV but are able to ignore the distending pressure by measuring distensibility relative to adjacent segments of the aorta. Stiffening of the aneurysm-prone aortic segment after elastin degradation can be conceptualized in terms of the redistribution of the load onto stiffer collagen components. Using finite-element analysis, they show that this leads to axial (longitudinal) wall stress generated by cyclic (systolic) tethering of adjacent, more compliant wall segments. In *ex vivo* studies, cyclic pressurization of segmentally stiffened aortic segments increased the expression of genes related to inflammation and extracellular matrix remodeling. The key experiment to demonstrate a causal effect of stiffening of the aneurysm-prone segment relative to adjacent segments was to equalize the axial gradient of stiffness along the abdominal aorta by stiffening aortic segments adjacent to the aneurysm-prone segment through external application of surgical adhesive. This significantly reduced aneurysm growth. Reduced growth correlated with reduced axial wall stress, decreased the production of reactive oxygen species, attenuated elastin breakdown, and decreased the expression of inflammatory cytokines and macrophage infiltration, as well as attenuated apoptosis within the aortic wall.

In a cross-sectional sample of healthy humans between 36 and 71 years of age, Raaz and colleagues used ultrasound to demonstrate that aging, one of the most powerful risk factors for AAA, is accompanied by segmental infrarenal aortic stiffening. This is consistent with studies using magnetic resonance that demonstrate that age-related stiffening (as measured by PWV) increases with progression from the thoracic to abdominal aorta.<sup>6</sup> This observation represents something of a paradox because the ratio of elastin to smooth muscle decreases with distance from the aortic valve and muscular conduit arteries show little age-related stiffening.<sup>2</sup> One explanation may be that calcification, a process driven by differentiation of smooth muscle cells to an osteogenic phenotype,<sup>7</sup> may contribute to arterial stiffening (especially in older humans),<sup>8</sup> is more prevalent in the abdominal compared with the thoracic aorta, and is associated with AAAs that are more prone to rupture (Figure).<sup>9</sup>

The study of Raaz and colleagues undoubtedly demonstrates that axial gradients in stiffness may contribute to AAA formation. However, the most notable finding from this study is the demonstration that transduction of local mechanical forces increases the expression of genes that accelerate AAA formation. In this respect, it is worth considering whether such forces could be generated in other ways. Calcification is a highly heterogeneous process (Figure) that may lead to both axial and circumferential gradients in stiffening. As with axial gradients, circumferential gradients may lead to tethering of more compliant regions, generating stresses that may be transduced into the expression of genes inducing or accelerating AAA formation. In the absence of AAA formation, such gradients may generate a vicious circle of functional stiffening of the aorta with adverse hemodynamic effects contributing to hypertension and predisposing to heart failure.

Regardless of the exact role of biomechanical transduction of stress in AAA formation, the study of Raaz and colleagues demonstrates that, to understand how mechanical forces lead to disease in the arterial wall, we need to move beyond integrative measures such as carotid-femoral PWV. It should also be noted that because of the inverse relationship between PWV and arterial diameter, even segmental measures of stiffness such as PWV will not reflect the stiffness of the aortic wall in an established AAA.<sup>10</sup> Although PWV has proven value in predicting risk, we need to evaluate the regional distribution of stiffening to fully assess its potential impact. This applies not only to AAA but also to other pathologies within the aorta and other arteries, for example, dissection and plaque rupture. A better understanding of the relative distribution of stiffening within the components of wall at the microscopic level may also be important. Both may be achieved by coupling imaging technology with appropriate mathematical analysis,



**Figure.** Sagittal maximal-intensity projection image from a computed tomography scan showing the heterogeneous nature of calcification in the abdominal aorta and in an abdominal aortic aneurysm. Reproduced from Buijs et al.<sup>9</sup>

although partitioning stiffness into individual components requires additional information such as how stiffness varies with load.<sup>11</sup>

Therapeutic options for decreasing arterial stiffness through a specific action on the arterial wall remain limited. Promising results have been obtained with anti-inflammatory drugs such as tumor necrosis factor- $\alpha$  inhibitors, matrix metalloproteinase inhibitors, elastase inhibitors, and collagen cross-link breakers in preclinical studies.<sup>12,13</sup> However, experience in humans is limited, and results from human trials have been mixed.<sup>12</sup> Reducing blood pressure is proven to reduce arterial stiffening, and some antihypertensive drugs acting on the renin-angiotensin-aldosterone axis may have specific blood pressure-independent antistiffening effects.<sup>14,15</sup> However, the study of Raaz and colleagues adds further complexity. In regions of the aorta where there is loss of elastin, the aortic wall may behave more like a homogeneous material, with blood pressure reduction having relatively little effect on reducing stiffness.<sup>11</sup> Conversely, in regions with preserved elastin, a reduction in blood pressure may transfer stress onto the more elastic elastin and hence reduce stiffness. Antihypertensive drugs may thus have differential effects on stiff and less stiff segments of the aorta and could potentially exacerbate segmental gradients in stiffness despite having an overall effect of reducing stiffness. If the findings of Raaz and colleagues turn out to translate to human AAA, then an intervention that specifically targets the stiffest area of the aorta may be required to prevent AAA. Given the potential role of calcification as a relatively late process in the stiffening of the abdominal aorta and its association with AAA progression, halting or reversing vascular calcification is an attractive intervention. Because calcification may be induced/accelerated by elastin degradation, protecting elastin may be important.<sup>13</sup> Bisphosphonates show promising effects in preventing vascular calcification in animal models. Studies in humans have been both positive and neutral, but the intervention should not be dismissed because long-term effects have not been sought in trials with sufficient power.<sup>16</sup>

Raaz and colleagues are to be congratulated for applying an integrated biophysical approach to aortic disease. They start a new chapter in which regional variation in arterial stiffening will need to be evaluated in identifying drug targets and assessing the effects of interventions to prevent or treat aortic disease that may yield some surprising findings.

## Disclosures

None.

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