

# Arterial Stiffness, Vascular Disease, and Risk of Cardiovascular Events

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**M**ost cardiovascular morbid events are the consequence of a progressive vascular disease called atherosclerosis. This disease begins at an early age, probably initially with a defect or injury of the arterial endothelial protective function, and progresses with structural remodeling in the microcirculation and cellular and lipid accumulation in conduit arteries complicated by calcification, plaque formation, and, ultimately, plaque rupture as a precipitating factor for clot formation and acute morbid events.<sup>1</sup> The rate of progression of this process is highly variable but may extend over many decades. Furthermore, aging changes, pressure effects, and atherosclerotic changes become inextricably intertwined.

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Because it is now possible to slow progression of this vascular disease with a number of pharmacological agents and possibly with lifestyle alterations, the discovery of markers that can identify the disease in asymptomatic individuals could facilitate appropriate intervention. The wall of the artery is the primary site of the disease process and has therefore become an attractive target for demonstrating functional or structural alterations that may precede the morbid events.

Noninvasive assessment of the arterial vasculature suitable for screening has been practiced since the development of the blood pressure cuff. Unfortunately, the ease of blood pressure measurement and the demonstration of its correlation with morbid events inhibited for many years the development of methods to more directly assess the arteries. Recently, there has been growing recognition that the disease of interest is in the arteries and that elevated blood pressure, although it may serve as a crude surrogate for arterial disease, is neither a sensitive nor a specific guide to its presence.<sup>2</sup> Therefore, a number of noninvasive methods have been introduced to gain better insight into the abnormalities in the wall of the artery that can define the atherosclerotic process. It is important to begin with the recognition that atherosclerosis is a systemic vascular disease that results in functional and structural abnormalities in the entire arterial vasculature. Certain vas-

cular areas, particularly the coronary and cerebral circulations, precipitate most morbid events, and the rate of progression may vary in different vascular beds in different individuals. The relative role of genes and environment in this variability is unclear, but abnormalities that mark the disease are usually discernible in any vascular area studied.

In this issue of *Circulation*, 2 European groups, the Rotterdam Study<sup>3</sup> group and the Danish participants in the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) health survey,<sup>4</sup> report that aortic pulse-wave velocity (PWV), a measure of aortic wall stiffness, provides prognostic information above and beyond that from traditional risk factors, including age, gender, blood pressure, cholesterol, diabetes mellitus, and smoking. These data provide further support for the concept that the biological process in the artery wall is a better guide to future cardiovascular morbid events than standard risk factors that epidemiologists have identified as statistically related to such events. These publications therefore raise important questions that must be addressed.

### What Are the Determinants of PWV?

PWV as measured in these studies represents the velocity of the pulse wave transit from the carotid artery (equivalent to the aortic arch) to the femoral artery. Thus, it is a measure of stiffness of the aorta, an elastic artery with muscular contributions to its compliance. PWV is dependent not only on structural changes that alter stiffness or elastic modulus of the wall, which influences wave propagation, but also on caliber increases, which slow velocity, and on aortic pressure, which has a powerful direct relationship to stiffness.<sup>5</sup> In general, thickening of the wall should reduce compliance, increase stiffness, and accelerate wave velocity. Thickening of the wall is characteristic of aging, of systolic hypertension, and of the increased intimal-medial thickness associated with atherosclerosis.<sup>6</sup> Decreased compliance of the aorta results in higher systolic pressure, wider pulse pressure,<sup>7</sup> and more rapid return of reflected waves to the root of the aorta, where they may further augment late systolic pressure.<sup>8</sup>

The relationship between PWV and morbid cardiovascular events in these studies, therefore, could at least in part reflect the older age and higher blood pressure associated with increased PWV. The authors have attempted to correct for these influences and conclude that the PWV is an independent predictor of morbid events. Does that mean that aortic stiffness is contributing to the disease, as suggested by the Rotterdam Study group?<sup>3</sup> Or does it merely imply that the vascular abnormality detected in the aorta is also present in other vascular beds and that its magnitude identifies the disease process better than chronological age, blood pressure,

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cholesterol, and other factors shown to be statistically associated with disease?

### Is PWV the Best Measurement of Arterial Stiffness?

Structural changes in the aorta are probably a late manifestation of atherosclerotic disease, just as obstructive plaques in conduit arteries represent advanced disease that should be detected earlier. Because the vascular disease may have its origin in endothelial dysfunction, which has a profound influence on the microvasculature and on smaller muscular conduit arteries,<sup>9,10</sup> evaluation of the arterial vasculature distal to the aorta would be likely to better detect early disease.

A number of noninvasive methods have been developed, and some are in wide use. Most depend on arterial pulse contour analysis that uses a piezoelectric transducer placed over an accessible artery, usually the radial artery. The recorded pulse wave provides a “window” into the arterial system, thus requiring the assumption that the vascular abnormality being sought is a systemic process that influences the function and structure of the entire vasculature. Stiffening of the small arteries, as a consequence of either vasoconstriction or structural change, alters the magnitude and timing of reflected waves that can often be identified visually in late systole and more reliably by computer analysis of the diastolic pressure decay.<sup>11</sup> Some of these methods are so user-friendly that analysis can be completed in 5 to 10 minutes, which makes the technique suitable for large-scale screening. Preliminary studies have demonstrated the predictive value of small-artery compliance or elasticity independent of age and blood pressure.<sup>12</sup>

A decision about the best method for measuring arterial stiffness is dependent on the clinical question. Because aortic stiffening is a marker for advanced disease, it may serve, as it did in the European cohorts,<sup>3,4</sup> as a predictor of morbid events in the next 5 to 10 years. If one's goal is early identification of vascular abnormalities to initiate preventive therapy, however, one would prefer a smaller-artery assessment that serves as an earlier marker for vascular disease, recognizing that its predictive value may be delayed. If one were interested in a measurement of stiffness that might respond to effective drug treatment, independent of blood pressure, one would certainly choose a measure of small-artery function, which is modifiable over weeks to months, rather than PWV, which is pressure-dependent and influenced by long-term structural changes that may be slowed but not necessarily reversed by pharmacotherapy.

### Are Measures of Stiffness Useful Clinically?

Epidemiological evidence for a measurement to be significantly predictive of morbid events does not necessarily render that measurement a useful clinical tool in managing individual patients. Usefulness depends on the sensitivity and specificity of the measurement and the magnitude of the hazard ratio detectable. Indeed, age is the most powerful predictor of short-term events, and blood pressure provides incremental prognostic information. Does the magnitude of incremental information from measurements of stiffness jus-

tify their widespread clinical use, as suggested by the MONICA authors?<sup>4</sup>

The Rotterdam Study calculated receiver-operating characteristic curves using various traditional risk markers and found that the addition of PWV increased the area under the curve from 0.69 or 0.70 to 0.72. The MONICA investigators observed that hazard ratios were increased by approximately 13% to 15% when PWV was added to traditional markers of risk. Is that magnitude of improved risk stratification useful clinically? Would one alter diagnostic or therapeutic strategies on the basis of that measurement?

Our approach at the University of Minnesota has been to utilize more comprehensive screening to identify early disease in asymptomatic individuals in whom aggressive preventive therapy might slow the trajectory of disease progression and delay events more effectively than later intervention. The appropriate target for such preventive intervention would not be 5- or 10-year event reduction but rather reduction of events before a certain age, such as 80 or 90 years old. Demonstration of efficacy of interventions in such a population could not practically be dependent solely on event reduction but should include a demonstration of slowing of the progression of the vascular or cardiac abnormalities. Our screening approach utilizes a scoring system based on measurement of small- and large-artery elasticity, treadmill exercise blood pressure, carotid intimal-medial thickness, retinal vascular photography, microalbuminuria, electrocardiography, echocardiography, and plasma  $\beta$ -type natriuretic peptide assay.<sup>13,14</sup> The hypothesis is that this global assessment to detect early vascular and cardiac abnormalities will be more sensitive and specific than single measurements such as PWV. Data to confirm this hypothesis are required. If such screening techniques are shown to identify more precisely the at-risk population and allow targeted intervention to slow progression, then this approach to build on the data from the European populations by monitoring disease progression rather than relying on risk factors could become standard clinical practice.

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### Disclosures

None.

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