Arterial Compliance to Stratify Cardiovascular Risk: More Precision in Therapeutic Decision Making

Jay N. Cohn

The focus of attention in preventing and treating cardiovascular (CV) disease today is shifting toward the arterial wall. Evidence has been accumulating for several years that protecting the endothelium is key to reducing CV risk. Endothelial dysfunction results in reduced compliance, or increased arterial stiffness, particularly in the smaller arteries. This abnormality is characteristic of patients with hypertension but may also be seen in normotensive patients before the appearance of clinical disease. Reduced arterial compliance is also seen in patients with diabetes and in smokers, and is part of a vicious cycle that further elevates blood pressure, aggravates atherosclerosis, and leads to increased CV risk. Although other factors are involved, the damage to the endothelium results in reduced secretion of nitric oxide, which influences smooth muscle growth, migration, and contraction, as well as influencing inflammation and clotting. Arterial compliance can be measured by several techniques, most of which are invasive or otherwise not clinically appropriate. Pulse contour analysis is a newly developed noninvasive method that allows for easy, in-office measurement of arterial elasticity to identify patients at risk for CV events before disease becomes clinically apparent. Further research is needed to confirm whether this method offers a means of improving risk stratification and therapeutic decision making. Am J Hypertens 2001;14:258S–263S © 2001 American Journal of Hypertension, Ltd.

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The focus in the prevention and therapy of cardiovascular disease (CVD) in the new millennium is the blood vessel wall. It has become increasingly apparent over the past decade that when we are trying to prevent myocardial ischemia, acute myocardial infarction, and other cardiovascular (CV) events, the disease we are actually treating is that of the arterial wall (Table 1). Endothelial dysfunction and, in particular, reduced bioactivity of nitric oxide (NO), probably precedes the vascular disease that results in stroke, heart attack, and renal failure, as well as other diseases, conceivably including dementia. Alterations in the structure and function of the endothelial–vascular interface as well as elevated lipids and blood pressure (BP) initiate plaque formation, the atherosclerotic process that leads to luminal obstruction.

Methods developed over the past decade appear to make it possible to identify individuals at risk for CV events even earlier by techniques that can measure the degree of arterial wall dysfunction. That information can be used to better assess CV risk and to improve therapeutic decision making.

The Endothelium and Endothelial Dysfunction

The arterial wall consists of three layers: the intima, media, and adventitia. The endothelial layer of cells lining the lumen is the primary component of the intima. The media comprises smooth muscle cells (SMC), which cause vessel constriction, and elastin and collagen fibers. The adventitia is composed of fibrous connective tissue that maintains the shape of the vessel. The amount of smooth muscle in the media varies with the type of vessel and is present in greater proportions in the conduit arteries.

The last 15 years have seen dramatic increases in the understanding of the role of the endothelium in the maintenance of vascular tone, the modulation of inflammation and coagulation, and the inhibition and promotion of vas-
A particularly important finding was that NO, initially termed endothelial-derived relaxing factor, acts on the smooth muscle of the media to produce vasodilation. Nitric oxide also has numerous other functions, including inhibition of smooth muscle growth and platelet aggregation. In an artery such as the large femoral artery, endothelially released NO penetrates and influences smooth muscle relaxation only in layers closest to the endothelium. Nitric oxide is a more important factor in producing dilation in the smaller arteries close to arterial branch points, where the media is much thinner.

The Terminology of Arterial Hemodynamics

To grasp the importance of the arterial wall in CVD it is helpful to briefly review the hemodynamics of the vasculature. Although various terms have been used interchangeably in the literature to describe vascular hemodynamics, it should be noted that compliance is the absolute change in area for a given change in pressure, whereas distensibility is the fractional, or percentage, change. Distensibility is the preferred measure when vessels of different sizes are being compared. A large artery may have less distensibility than a smaller artery (as the percentage increase in area at a given pressure is smaller in the larger artery), but its compliance will be greater because of the larger absolute volume increase.

Compliance serves a capacitive function in the large conduit arteries, which store blood during systole. The branch points that spread into the microcirculation reflect pressure waves backward, much as a wave hits a rock; thus, compliance also fulfills a reflecting, or oscillatory, function. The term $C_1$ is used to designate compliance in the larger, proximal arteries, and $C_2$ is used to refer to distal, or oscillatory, compliance of the smaller arteries. Endothelial damage results in reduced elasticity of the smaller arteries, or decreased $C_2$, accentuating wave reflectance back toward the heart, which contributes to a rise in late systolic BP that further stresses the central arteries and left ventricle. Systemic vascular resistance is a function of the caliber of the arterioles, which is also influenced by endothelial function and maintains BP.

Several models have been developed to understand the dynamics of the arterial wall. One is the modified Maxwell model, which uses electrical terms to explain vascular hemodynamics (Fig. 1). This model represents collagen acting in parallel and in series with smooth muscle, and elastin in parallel with both. The model adequately defines the nonlinear pressure–volume relationship in a blood vessel. As the pressure rises, the incremental increase in volume decreases until all collagen is engaged and the vessel becomes stiff. If collagen is dissolved from the vessel wall, the relationship becomes linear.

Measuring Arterial Compliance

There are several methods for measuring arterial compliance, although at present there is no gold standard. Several methods are available for measuring the compliance of the large arteries, but only three are currently used.
available for measuring compliance in the smaller arteries. The condition of the endothelium in the smaller arteries, which are far more sensitive to the release of NO, is more difficult to assess.

The impedance spectra will measure compliance in the large arteries, but the methods for measuring this parameter are invasive and not useful clinically. Some other methods of assessing large arteries include calculating the ratio of the stroke volume and pulse pressure to provide an approximation of compliance; measuring pulse wave velocity by placing probes on a central and more distal artery; and using ultrasound to provide a measure of pulsatility. In the small arteries, compliance can be measured by means of late systolic pressure augmentation, biopsying of isolated small arteries, and assessing the arterial waveform. One particular technique appears to have great promise for arterial compliance in a comprehensive and clinically accessible way.

Pulse Contour Analysis

Analysis of the arterial waveform, a method that has been under study for about 20 years, is one means of estimating compliance. A recently developed noninvasive instrument based on pulse contour analysis is able to estimate both large and small arterial compliance by using a piezoelectric transducer over the radial artery.

The technique uses a modified version of the Windkessel model to predict large and small arterial compliance. The modified Windkessel is best explained in electrical terms. The simple Windkessel model is based on a mechanical device designed to smooth the intermittent spurts of water from a pump into a smooth flow through a hose (originally developed for a fire engine), but it fails to account for certain hemodynamic properties of the vasculature. In electrical terms (Fig. 2), the modified model comprises two capacitance elements (representing large and small vessel compliance), an inerterance element (representing the inertia of the blood), and a resistance element (representing peripheral vascular resistance). A computer algorithm calculates $C_1$, large artery compliance (capacitive compliance), and $C_2$, small artery compliance (oscillatory compliance) by analysis of the diastolic decay of the pulse wave. $C_2$ is particularly sensitive to the changes in the vessel wall associated with hypertension, diabetes mellitus, and atherosclerosis.

The method takes approximately 5 min to perform in a clinical setting. The output is a parameter called the small and large artery elasticity index (identical to $C_1$ and $C_2$, defined previously), along with other hemodynamic values, which can be compared with normal values in patients without peripheral vascular disease. The method holds great promise for improving risk stratification for CVD and refining therapeutic decision making.

Using pulse contour analysis, investigators have found that younger hypertensive patients (45–54 years) show remarkable decreases in small artery elasticity ($C_2$) compared with normotensive patients of the same age (Fig. 3). On average, large artery elasticity was 19% less in hypertensive versus normotensive subjects; in striking contrast, small artery elasticity was, on average, 72% less in hypertensive versus normotensive subjects. It was observed that differences in small artery elasticity were greatest in patients aged 64 years. In the oldest age group (65–75 years), however, small artery elasticity was comparably reduced in the normotensive and hypertensive groups. These results suggest that a decreased small artery compliance will be particularly useful in identifying a vascular abnormality in younger individuals.

Smoking is well known to be a major risk factor for the development of atherosclerosis and coronary events. In a study that compared the arterial pulse contours in 35 healthy long term smokers with those of 32 nonsmoking control subjects, smokers showed a statistically significant alteration in the amplitude and duration of the diastolic oscillatory wave, due to increased reflections from the peripheral arteries, an indication of decreased $C_2$ in these abnormal arteries.

In another study by McVeigh et al, patients with Type II diabetes but without hypertension ($n = 28$) showed a significant reduction in the small artery compliance ($C_2$)}
when assessed using pulse contour waveform analysis compared with age-matched healthy control subjects \((n = 22)\) (Fig. 4). In a similar patient population, endothelial dysfunction was observed in patients with Type 2 diabetes who were normotensive \((n = 29)\) and had no evidence of diabetes-related organ disease. Investigators compared the forearm blood flow in the diabetic group with that of normal age-matched controls \((n = 29)\) after infusion of acetylcholine (Fig. 5). The significantly greater blood flow increase with administration of acetylcholine in normal subjects was indicative of normal endothelial function. A further study, using pulse contour analysis, comparing patients with congestive heart failure \((n = 14)\) versus healthy controls \((n = 7)\), revealed compliance in the smaller distal arteries to be significantly diminished in the heart failure patients.

**Endothelial Dysfunction as a Central Element for Atherosclerosis and CVD**

These studies suggest that the common denominator in all patients at risk for CVD is a decrease in small artery compliance. An important finding is that these abnormalities were detectable at a preclinical stage, providing evidence that pulse contour analysis represents a potentially sensitive and specific means for early detection of impending CVD and for improved risk stratification.

Hypertension is a major risk factor for atherosclerotic events, but some normotensive persons are clearly at greater risk for CV events than are hypertensive individuals. In fact, a hypothetical analysis of the Framingham epidemiologic studies showed that more normotensive than hypertensive persons experience CV events. Thus, hypertension cannot be considered a sensitive or specific indicator of risk. Damage to the endothelium—whether caused by hypertension, diabetes, elevated cholesterol, smoking, or aging, or (as is most commonly the case) a combination of two or more of these risk factors—appears to be the key in the progression to atherosclerosis and CV events. Evidence is accumulating that the endothelium—proposed a decade ago as a central factor leading to atherosclerosis and CVD—should be the focus of therapeutic strategies to reduce risk. Endothelial dysfunction results in vasoconstriction, adhesion of blood cells to the endothelium, lipid deposition, and the proliferation, growth, and migration of SMC. In addition, endothelial damage can worsen hypertension, intensifying a vicious cycle that greatly increases the risk for atherosclerotic events.

**A New Approach to Stratifying Cardiovascular Risk**

The goal for identifying and managing hypertension should be broadened from simply initiating treatment once
an arbitrary “high” level of BP elevation has been reached. Therapeutic decision making should use a model that brings together several factors that might serve to better define the at-risk individual. This new model centers around the health of the small artery endothelium.1 Such an approach evolves from this author’s proposed redefinition of hypertension, which would define the condition as “a state of abnormal arterial function and structure associated with endothelial dysfunction, vascular smooth muscle constriction or remodeling, increased impedance to left ventricular ejection, and propensity for atherosclerosis, often but not always manifested by an elevated blood pressure.”1

In this model, the patient who ought to be treated aggressively may or may not have elevated BP. Increased risk might be identified by reduced small artery compliance, fundoscopic changes, left ventricular hypertrophy, or microalbuminuria. Appropriate therapy in these patients would include agents that are shown to have a positive therapeutic affect on the arterial wall. Other risk factors that have been clearly identified as accelerators of vascular disease (smoking, hyperlipidemia, glucose intolerance) should also be treated in an appropriate manner. The patient with mild to moderately high BP but without these other factors should be followed closely for the development of other indicators of increased risk.

Conclusion

The technique of using pulse contour recordings combined with computer analysis offers a means of screening for vascular disease before it becomes clinically apparent, or to identify earlier disease to prevent further damage.4 However, although evidence accumulates that endothelial damage precedes, and thus may be the cause and not the effect of hypertension, further research is needed to confirm this hypothesis.22 More research is also needed to determine whether antihypertensive drugs such as angio-

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tensin converting enzyme inhibitors prevent damage simply by lowering BP, or whether they have a more comprehensive effect on the arterial wall to prevent or restore the abnormal endothelial function that can lead to atherosclerosis and CV events.

References
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