Atherosclerosis is an inflammatory, proliferative, thrombotic arterial disease initiated by risk factor injury to the endothelium. Although obstructive plaques develop locally, the disease is always diffuse if examined by intravascular ultrasound or histology. Assessing and treating the initiating risk factors and the resulting obstructive disease has been the traditional approach to managing atherosclerosis. Our recent understanding of how the related pathophysiological processes of endothelial dysfunction and inflammation connect risk factors and disease expression has led to an interest in using these pathways to assess patient risk and determine therapies. In the future, we will also directly assess our genetic predisposition for developing and clinically manifesting atherosclerosis.

In response to physical and chemical stimuli, the endothelium regulates vascular physiology through control of vasoactivity, inflammation, vessel growth and remodeling, monocyte adhesion, platelet activation, thrombosis, and thrombolysis. Normal endothelium is associated with a vasodilatory, antiatherogenic state, whereas dysfunctional endothelium is associated with a proatherogenic state and plaque instability. The predominant endothelium-derived vasodilator, nitric oxide, has several antiatherogenic properties, including inhibition of platelet aggregation and smooth muscle cell proliferation. In experimental animals, nitric oxide availability is inversely related to disease progression. Endothelial function is impaired by all traditional risk factors. Endothelial function is thought to be a gauge of cumulative risk factor burden modified by genetic susceptibility. Conversely, improvements in endothelial function have been demonstrated with risk factor modification, such as with cholesterol and blood pressure reduction. Risk factors and risk factor modification change endothelial function very rapidly, and endothelial dysfunction is evident even before intravascular ultrasound evidence of atherosclerosis is present.

Over the past decade, endothelium-mediated vasoactivity and inflammation have evolved into clinically relevant markers of ongoing atherosclerosis. Endothelium-dependent vasodilation can be assessed in the coronary and peripheral arteries as conduit vessel diameter or blood flow (resistance vessel) responses to endothelium-mediated agonists, such as acetylcholine, serotonin, and substance P. Increased blood flow (shear) is also used as a vasoactive stimulus (flow mediated). Occasionally, the more complex cold pressor response is used to evoke endothelial responses. Endothelial dysfunction is detected as reduced vasodilation or vasoconstriction. Endothelium-mediated vasoactivity is spatially heterogeneous to a degree both within and between circulations. Flow-mediated brachial artery vasodilation correlates modestly with coronary acetylcholine responses but strongly with coronary flow-mediated responses. Endothelial function can also be assessed through measurement of soluble adhesion molecules (eg, vascular cell adhesion molecule and P-selectin), cytokines (eg, interleukins 1 and 6), inflammatory markers (eg, C-reactive protein), growth factors (eg, platelet-derived growth factor), and coagulation factors (eg, tissue plasminogen activator and plasminogen activator inhibitor-1).

Locally, inflammation can be assessed by catheter-based temperature sensors, which may convey prognostic information regarding plaque stability. Endothelium-mediated vasodilation, as measured by forearm blood flow responses to acetylcholine, has been shown to correlate modestly with C-reactive protein. Exogenous estrogen does not mediate vasodilation but worsens inflammation, as measured by C-reactive protein. Exogenous estrogen does not increase interleukin-6, another inflammatory marker.

In this issue of Circulation, Targonski et al report that abnormal coronary acetylcholine-assessed vasoactivity is associated with increased risk of cerebrovascular events, both before and after the assessment in subjects without obstructive coronary artery disease (≤30%). In multivariate analysis, cerebrovascular event risk was more strongly associated with coronary vasoactivity than with any other clinical parameter or risk factor. Several prospective and retrospective studies have previously found that abnormal endothelium-mediated vasoactivity is associated with increased risk of cardiovascular events. In these studies, vasoactivity has been assessed in the coronary, carotid, and peripheral circulations, and correlations have been noted with both coronary and cerebrovascular events. Schächinger et al found that coronary artery responses to both endothelium-mediated agonists (acetylcholine, cold pressor, and flow mediation) and nitroglycerin (endothelium independent) predicted cardiac events over a
7.7-year follow-up period. Halcox et al\textsuperscript{11} also found acetylcholine-assessed coronary vasoactivity to be predictive of cardiovascular events over 46 months of prospective follow-up in 308 subjects, both with and without coronary artery disease, although few cerebrovascular events occurred. In a 28-month study of subjects with mild coronary artery disease, AI Suwaidi et al\textsuperscript{12} found that cardiac events occurred exclusively in those subjects with the most abnormal responses to intracoronary acetylcholine. Brachial artery flow-mediated vasodilation is also predictive of cardiac risk. Cardiac events were increased 3-fold in subjects with chest pain and abnormal brachial results (<10% vasodilation) compared with those with normal vasodilation over a 5-year follow-up.\textsuperscript{13} Cardiovascular event risk was increased in coronary heart disease subjects with impaired forearm blood flow responses to acetylcholine or greater improvement in vasodilation with vitamin C coinfusion, suggesting a contribution of oxidative stress to endothelial dysfunction.\textsuperscript{14} Gokce et al\textsuperscript{15} found that preoperatively assessed brachial artery flow-mediated vasodilation <8.1% predicted postoperative cardiovascular risk in subjects undergoing noncardiac surgery.

Fewer data exist comparing cerebrovascular risk and endothelial function. Cerebrovascular events usually include thromboembolic stroke, hemorrhagic stroke, and transient ischemic attacks, the latter two of which do not generally have corresponding coronary events. Perticone et al\textsuperscript{16} found a trend toward increased cerebrovascular risk in hypertensive subjects with impaired forearm blood flow responses to acetylcholine, although cardiac risk was significantly increased. Therapy-associated changes in endothelium-mediated vasoactivity associated with risk factor modification appear to have prognostic value for both cardiac and cerebrovascular events. In a recent study, Modena et al\textsuperscript{17} found that the improvement in brachial artery flow-mediated vasodilation associated with antihypertensive therapy in postmenopausal women was significantly predictive of cardiovascular events.\textsuperscript{17} Transient ischemic attack episodes occurred less frequently in those women with greater increases in flow-mediated vasodilation, as was true for cardiac events. Conversely to the present study, Rubenfire et al\textsuperscript{18} reported that impaired cold pressor-assessed carotid vasoactivity was associated with increased risk factors and the presence of coronary artery disease, independent of carotid intima-media thickness.\textsuperscript{18} The present study reinforces the generalized nature of both atherosclerosis and endothelial dysfunction and further strengthens an association between the two entities.

The unique aspect of the present study is that both the normal and the abnormal vasoactivity groups had fairly similar risk factor burdens. Thus, the measurement of endothelial function provided an additional degree of risk prognostication. Measurements of both endothelium-dependent vasoactivity and inflammation will clinically succeed or fail depending on how much individual disease burden and event risk are conveyed by their measurement beyond that afforded by risk factors, clinical parameters, and extent of underlying atherosclerosis. The predominate reason why individuals have different endothelial responses to the same risk factor burden probably lies in genetic susceptibility. For example, although hypercholesterolemia generally reduces endothelial function at low-density lipoprotein cholesterol levels above \(\approx 50\) mg/dL, individuals have markedly different responses. Some studies have shown that African Americans have impaired brachial artery flow-mediated and endothelium-independent vasodilation, which may explain a relative increase in coronary heart disease risk. African-American women also seem to have a reduced benefit from physical fitness in terms of increased C-reactive protein. Specific polymorphisms in the reduced nicotinamide adenine dinucleotide (NADH)/NADH phosphate oxidase p22 phox gene and chemokine receptor CX3CR1 gene have been reported to be associated with, respectively, improved and impaired endothelial function.\textsuperscript{19,20} The important pathophysiological responses to risk factor burden cannot yet be used for clinical management because there are no readily available means for assessing endothelial function and genetic susceptibility. The inflammatory marker, C-reactive protein, has also been demonstrated to provide prognostic value beyond that of traditional risk factors, but it is not cardiac specific, and the prospective value of an individual determination remains to be demonstrated. Brachial artery flow-mediated vasodilation measurements are ultrasonographically demanding, and both coronary arteriography and forearm plethysmography are invasive techniques.

The study by Targonski et al\textsuperscript{9} has several limitations, mostly noted by the authors. The majority of the cerebrovascular events occurred before the assessment of endothelial function, making the study substantially retrospective. Endothelial function did predict the lesser number of subsequent events, however. The subjects studied had been specifically referred for coronary angiography, making them nonrepresentative of individuals in general. As expected, a history of myocardial infarction also predicted higher cerebrovascular event risk. Although the subjects studied did not have obstructive disease by angiography, intravascular ultrasound was not performed. Thus, the true coronary disease burden was unknown. This limitation is common to almost all of the studies comparing cardiovascular event risk and endothelial function. It is as yet unclear whether endothelial function is predictive independent of true atherosclerotic burden. The criteria of abnormal endothelial function used were a <50% increase in coronary blood flow and/or a <20% increase in mid–left anterior descending coronary diameter at peak acetylcholine concentration, values derived from prior correlations with coronary events. Whether these criteria represent the optimal cut point or not remains to be shown. Lastly, acetylcholine-assessed coronary vasodilation remains an invasive and cumbersome clinical technique. It is highly likely that noninvasive techniques for measuring endothelium-mediated vasoactivity or inflammatory markers will prove more clinically useful.

What would be an ideal marker of ongoing atherosclerosis, whether reflective of endothelium-mediated vasoactivity, inflammation, or another process? Firstly, an ideal marker would need to be low cost, noninvasive, easy to perform, reproducible, and specific for atherosclerotic risk. At present, no assays meet these requirements. An ideal assay needs to be
broadly applicable to individuals of any age, including both those with and those without vascular disease. It should provide substantial prognostic information beyond standard and evolving risk factors, clinical parameters, and atherosclerotic disease burden and be verified in prospective studies using predetermined absolute cut points. Lastly, the ideal marker should vary in proportion to the change in cardiovascular risk afforded by a therapeutic intervention. Short of having the ideal index, we now know that the same endothelial runs through both the head and the heart.

References
Heads and Hearts: The Endothelial Connection
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