The endothelium regulates vascular homeostasis by elaborating a variety of paracrine factors that act locally in the blood vessel wall and lumen. Under normal conditions, the sum total effect of these endothelial factors is to maintain normal vascular tone, blood fluidity, and limit vascular inflammation and smooth muscle cell proliferation. However, when coronary risk factors are present, the endothelium may adopt a phenotype that facilitates inflammation, thrombosis, vasoconstriction, and atherosclerotic lesion formation. In human subjects, this maladaptive endothelial phenotype manifests itself prior to the development of frank atherosclerosis and is associated with traditional risk factors such as hypercholesterolemia, hypertension, and diabetes mellitus and with emerging risk factors such as hyperhomocystinemia, obesity, and systemic inflammation.

In addition to its role in early atherosclerosis, there is growing recognition that endothelial dysfunction also contributes to the later stages of the disease when patients develop clinical symptoms. Cross-sectional studies have demonstrated the most severe impairment of endothelial function in arteries containing a culprit lesion that precipitates unstable angina or myocardial infarction. Furthermore, endothelial dysfunction promotes pathological vasoconstrictor responses in situations known to provoke ischemia, including physical and emotional stress. Another line of evidence supporting the pathophysiological role of endothelial dysfunction is provided by intervention studies. The ability to improve endothelial function is a common feature of many otherwise diverse interventions proven to reduce cardiovascular risk. For example, lipid-lowering therapy, angiotensin-converting enzyme inhibitors, smoking cessation, and physical exercise have all been shown to reduce cardiovascular risk and to improve endothelium-dependent vasodilation in the coronary and peripheral circulations.

In the past, most of the evidence suggesting a causal relation between endothelial dysfunction and clinical events from atherosclerosis was circumstantial. Recently, this evidence has been strengthened by a series of outcome studies showing that endothelial dysfunction predicts future events. For example, Suwaidi and colleagues examined 157 patients with mild coronary disease and demonstrated a greater incidence of cardiovascular events during 2.3 year follow-up in patients with impaired endothelium-dependent vasodilation of coronary resistance and conduit arteries. A similar study by Schachinger and colleagues examined coronary artery vasomotor responses to acetylcholine and nitroglycerin infusions, increased flow, and the cold pressor test in 147 patients with coronary artery disease and then followed them for a median of 7.7 years. Patients with more severe impairment of endothelium-dependent and endothelium-independent vasodilator function were more likely to suffer an event. Those two studies are limited by the relatively small number of clinical events (6 and 16, respectively) and the inclusion of coronary revascularization procedures as events. Nevertheless, they are quite important because they provided the first evidence that endothelial dysfunction has prognostic value.

In the present issue of Circulation, Halcox and colleagues provide additional information about the predictive value of coronary endothelial dysfunction. In the largest study of this type to date, they examined the coronary blood flow and epicardial coronary diameter responses to endothelium-dependent and endothelium-independent vasodilators in 308 patients undergoing cardiac catheterization. During an average 46-month follow-up period, they observed a total of 35 ischemic cardiovascular events, including sudden cardiac death, acute myocardial infarction, unstable angina, and stroke. These events were independently associated with impaired endothelium-dependent dilation of both coronary microvessels and epicardial arteries, even after controlling for other clinical variables such as the presence of coronary disease and traditional risk factors. In contrast, vasodilator responses to the endothelium-independent vasodilators sodium nitroprusside and adenosine did not predict events, providing evidence for a specific relation with endothelial dysfunction. The results were similar when an additional 21 patients who required a coronary revascularization procedure were also categorized as having an event. Very interestingly, impaired endothelium-dependent vasodilation predicted cardiovascular events even in patients with angiographically normal coronary arteries.

Thus, the study by Halcox and colleagues makes an important contribution to the literature on endothelial function. Together with the prior studies by Suwaidi and Schachinger, it makes a very strong case that impaired vascular function in the coronary circulation relates to the pathogenesis of cardiovascular disease. The strengths of the
study include its large sample size, the well-developed methodology for study of coronary endothelial function, and the focus on spontaneously occurring cardiovascular disease events. The study by Halcox and colleagues has several limitations, as acknowledged by the authors. For example, the study was retrospective in nature. The investigators apparently contacted and obtained clinical information from patients who had undergone study of coronary vascular function for other reasons in their laboratory over recent years. The study also excluded patients with relatively severe coronary disease, and thus is not applicable to all patients.

Although assessment of coronary endothelial function is clearly germane for coronary artery disease events, this methodology is limited by the risk and expense of coronary angiography and selective intracoronary agonist infusion. As a consequence, there has been considerable interest in the study of endothelial vasomotor function in more accessible vascular beds, such as the brachial circulation. Many investigators have used venous occlusion plethysmography to examine vasomotor responses of forearm resistance vessels during brachial artery infusion of acetylcholine and other endothelium-dependent vasodilators. This approach affords several advantages including the ability to examine dose-response relations and use specific agonists and antagonists. However, these studies are limited by the requirement for arterial catheterization that renders them less well suited for large-scale and intervention studies. An alternative approach involves vascular ultrasound to examine endothelium-dependent flow-mediated dilation of the conduit brachial artery. This noninvasive technique has gained popularity as an assessment of endothelial function that can safely be applied to large and varied groups of patients that may involve repeated measurement of vascular function over time. Similar to the coronary circulation, endothelial function in the brachial circulation is impaired in the setting of traditional and novel risk factors and responds to interventions known to reduce cardiovascular disease risk.

The relevance of the brachial circulation to coronary and carotid artery events is not obvious. However, the systemic nature of many risk factors makes it plausible that they might affect central and peripheral arteries in a parallel manner. Indeed, studies suggest that endothelial dysfunction detected noninvasively in the arm correlates with coronary endothelial dysfunction. Despite these findings, it is well recognized that physiological mechanisms differ importantly according to vascular bed. Although the brachial artery does develop atherosclerosis, it is clinically different from the obstructive disease that affects the coronary circulation. For these reasons, there has been a need for outcome studies demonstrating the clinical relevance of endothelial dysfunction in brachial circulation.

Several recent studies have examined this question using both the invasive and noninvasive approaches. Perticone and colleagues observed that an impaired forearm blood flow response to acetylcholine predicted future cardiovascular events in patients with hypertension. Heitzer and colleagues observed a similar relationship in patients with coronary artery disease. In regard to ultrasound-detected flow-mediated dilation, Neunteufl and colleagues observed a relation between endothelial dysfunction and need for a revascularization procedure, although their study had a relatively small number of subjects and the relation between endothelial dysfunction and events was lost after controlling for extent of coronary disease. A very recent prospective study from our laboratory demonstrated that impaired brachial artery flow-mediated dilation is an independent predictor of short-term events in high-risk patients undergoing surgery for vascular disease.

Thus, assessment of endothelial function in both the coronary and peripheral circulation of patients with cardiovascular disease and coronary risk factors provides prognostic information about future cardiovascular disease events. This body of clinical evidence fits well with current paradigms depicting the endothelium as an organ that integrates signals between the milieu of the vascular wall and the vessel lumen. In this context, endothelial function should represent an excellent "barometer" of underlying vascular health as it represents an orchestrated response to the many known and unknown processes that contribute to the development, progression, and clinical expression of atherosclerosis. Indeed, it is plausible that endothelial resistance to the adverse effects of risk factors might be determined by genetic or environmental factors that are currently difficult to quantify using traditional risk assessment models.

Although the present body of knowledge supports the notion that endothelial function has prognostic value for cardiovascular risk, several important issues remain unaddressed. Most of the published data involves selected patient populations referred for evaluation of cardiovascular disease or with established risk factors for the disease. Thus, the extent to which these data are applicable to the general population remains to be determined. Moreover, clinical studies to date have been largely retrospective and applied a variety of methods to assess endothelial function, thereby precluding consensus estimates for positive and negative predictive value. These issues are critical for any future plans to use endothelial function as a surrogate marker for cardiovascular risk to effectively target individuals for intensive primary prevention and assess potential new therapies. Further prospective studies involving large numbers of patients will be required to resolve these issues and determine the most clinically useful vascular bed and methodology for assessment of endothelial function.

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Joseph A. Vita and John F. Keaney, Jr

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