Endothelium as a Predictor of Adverse Outcomes

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Endothelial cells (ECs) play a critical regulatory role in vascular health, including vascular smooth muscle cell (SMC) relaxation and growth inhibition, inhibition of inflammatory responses, and antithrombotic actions. This is accomplished by synthesis and metabolism of numerous substances in response to chemical and mechanical stimuli (eg, shear stress). Many of these effects are mediated by nitric oxide (NO), synthesized by EC NO synthase; therefore, most consider NO-mediated effects central to endothelial function. Additionally, ECs release prostacyclin and endothelial-derived hyperpolarizing factor, which help regulate SMC activation and inhibit platelet activation synergistically with NO. When NO production is limited, endothelial-derived hyperpolarizing factor may provide some compensation.¹

Control and regional distribution of organ blood flow is an essential EC regulatory mechanism mediated via SMC contraction and relaxation at the microvascular level. Endothelial cell–derived contracting and pro-oxidant factors include endothelin and angiotensin II, which also promote SMC proliferation, contributing to plaque development as well as thrombosis.

When the balance between EC NO production and oxidant stress is disrupted, ECs become dysfunctional, leading to many unhealthy responses. Vascular SMC relaxation is impaired and its phenotype is shifted to a synthetic form that promotes growth, proinflammatory responses, and thrombotic activities. Eventually, these functional defects result in structural damage to the arterial wall with SMC proliferation in the media and subintima, creating favorable conditions for platelet and leukocyte activation and adhesion as well as cytokines that increase permeability to oxidized lipoproteins and inflammation mediators.

Hence, endothelial dysfunction is pivotal to atherogenesis (Figure 1). It is present at the earliest stages (eg, preceding angiographic or ultrasonic evidence of obstructive plaque) as well as later stages of arterial disease, contributing to clinical sequelae related to tissue damage (eg, ischemia, infarction, and organ failure).

Endothelial dysfunction is linked with levels of vascular-disease risk factors (eg, aging, elevated low-density lipoprotein cholesterol, hypertension, smoking, diabetes, male gender, family history of premature coronary artery disease [CAD]), as well as estrogen deficiency in women and

chronic inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis). Though it is established that risk scores have predictive value in populations, they also have limited predictive usefulness for a given individual and may fail to predict development of CAD-related adverse outcomes in 25%–50% of cases. However, endothelial dysfunction, because it is a manifestation of the vascular-disease process, is believed to show promise as a predictor of adverse outcomes among individuals (Figure 2).

On this background there is strong interest in assessing endothelial function in the clinical setting. Many consider assessment of coronary endothelial function the reference standard for vascular function testing, when done in the catheterization laboratory with acetylcholine (Ach). Nitric oxide is released from healthy endothelium to override direct SMC activation secondary to Ach-induced activation of muscarinic receptors. This results in SMC relaxation and dilation of the large, medium, and small (microcirculation) coronary vessels. In subjects with risk conditions or overt atherosclerosis, the diseased endothelium is deficient in NO synthesis and/or release so that Ach's direct depolarization activates SMCs, resulting in vessel constriction. A non–endothelial-dependent vasodilator like nitroglycerin is then given to assess the capacity of the SMCs to respond to assure that the failure to dilate was not due to SMC dysfunction.

Studies have suggested a relationship between microvasculature dysfunction and exercise-induced myocardial ischemia. In experimental models, endothelial cells of the microvasculature appear to be the initial cells involved in the vascular disease process. Indeed, increasing numbers of studies suggest that this may also be the case in patients. Also, there is increasing evidence to suggest that vascular SMCs interact with ECs to regulate vascular-wall homeostasis. In vivo–observed myoendothelial bridges have been proposed as the direct physical contact between ECs and SMCs, affecting cellular growth, migration, differentiation, and function in addition to paracrine regulation. We have recently found that the coronary microvascular response to adenosine, a mostly nonendothelial dilator, predicts adverse outcomes in women.²

These catheterization laboratory procedures are invasive and expensive, thus they are not applicable to large populations. Echocardiography has been used to assess left anterior descending artery flow reserve to stressors. Positron emission tomography is another tool used to assess myocardial flow reserve in response to adenosine/dipyridamole and cold pressor stress. More

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Figure 1. Atherosclerosis timeline, showing the underlying role of endothelial dysfunction in the progression of atherosclerosis from initial lesion to complicated lesion. Reprinted with permission from Pepine et al. *Am J Cardiol* 1998;82:23S-27S.

recently, cardiac magnetic resonance imaging has been used for this purpose and adds the ability to assess transmural (endocardial and epicardial) flow responses. Nevertheless, because endothelial dysfunction is a systemic disorder, less-invasive and less-expensive techniques for the assessment of peripheral vascular endothelial function have evolved.

To this end, brachial-artery ultrasound is used to measure flow-mediated dilation after occlusion release that induced ischemia-related dilation of small vessels in the hand and forearm. Recently, a constriction response to brachial occlusion release has been described,³ and we have found this response to predict adverse outcomes among women.⁴ This technique requires training to minimize variability, yet it is the most widely used noninvasive technique to assess endothelial function.

Most recently, reactive hyperemia-peripheral arterial tomography (RH-PAT) was introduced as a noninvasive tool to assess vascular function. Its responses are influenced by local, systemic, and environmental factors; moreover, sensitivity of probes to movement may result in artifacts. Nevertheless, RH-PAT responses have been suggested as a marker of endothelial function and vascular-disease risk. On the other hand, whereas the RH-PAT signal clearly reflects

NO,⁵ as a relatively new technique the number of studies is limited. Reactive hyperemia-peripheral arterial tomography has about 80%–90% sensitivity and similar specificity to predict coronary endothelial dysfunction assessed by angiographic testing. Recently it has been suggested that RH-PAT responses were an independent risk factor for adverse cardiovascular events in symptomatic patients receiving optimized therapy over follow-up as long as 7 years.

In the current issue, Toggweiler et al⁶ studied 341 consecutive patients with chest pain, and endothelial dysfunction prevalence by RH-PAT was 33% in patients without CAD, 46% in patients with chronic CAD, and 58% in patients with acute CAD. Evidence from RH-PAT for endothelial dysfunction was observed in two-thirds of patients with >3 risk factors but without CAD. However, its prevalence between patients with acute and chronic CAD seems to be lower than would be expected from a population of patients with angiographic or clinical evidence of disease. Of note, patients with chronic CAD had a lower prevalence of endothelial dysfunction than those with acute CAD, which may be explained considering that endothelial dysfunction is reversible with aggressive treatment.

Because it is a reversible condition, identifying endothelial dysfunction may have important therapeutic and

Figure 2. Forest plot of the summary relative risk for major adverse cardiac events in men and women with coronary or peripheral endothelial dysfunction. The summary relative risk for adverse outcomes is elevated approx 10.0-fold when there is evidence of coronary or peripheral endothelial dysfunction. Abbreviations: CI, confidence interval. Reprinted with permission from Bairey Merz et al.⁷

prognostic implications. Functional benefits, which result from improvement in endothelial function, include enhanced myocardial perfusion, reduced duration of transient ischemia, and plaque stabilization. Therefore, serial assessments of endothelial function could be helpful to stratify cardiovascular risk, identify at-risk individuals, and then tailor, as well as monitor, an appropriate medical strategy to prevent adverse events.

On the other hand, some patients will likely have persistent impairment of endothelial function despite optimized therapy. They may have worse cardiovascular outcomes than those whose vascular function improves in response to an intervention, but this remains to be proven prospectively. Thus, a mechanism whereby serial assessments of endothelial function could be easily obtained for optimization of therapy would be useful. As a noninvasive and sensitive tool to identify endothelial dysfunction, RH-PAT may be suitable for this purpose, but clearly more study is needed.

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