

EDITORIAL COMMENT

Predicting Ischemic Heart Disease in Women

The Value of Endothelial Function*

Bill Q. Lian, MD, PHD, John F. Keaney, JR, MD

Worcester, Massachusetts

Since the discovery in 1980 that acetylcholine elicits vasodilation in an endothelium-dependent manner (1), it has become evident that the endothelium plays a crucial role in vascular homeostasis by regulating vasodilation, smooth muscle cell proliferation and migration, platelet and leukocyte adhesion, and thrombosis. Endothelial dysfunction is characterized by the impairment of endothelium-dependent vasodilation due to reduced vasodilator bioactivity, particularly nitric oxide (NO), and/or an increase in contracting factors (2). In addition to its vasomotor manifestations, endothelial dysfunction extends to other endothelial properties, resulting in a proinflammatory and prothrombotic endothelial phenotype that promotes atherosclerosis, plaque progression, and the occurrence of clinical events.

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Early studies of endothelial dysfunction focused on the coronary circulation, demonstrating paradoxical vasoconstriction to acetylcholine in patients with mild as well as advanced atherosclerosis (3). Subsequent studies showed that endothelial dysfunction is also present in both coronary and peripheral arteries in patients with risk factors, but without angiographic or ultrasound evidence of structural coronary artery disease (4,5). Indeed, almost all known cardiovascular risk factors, including hypercholesterolemia, hypertension, hyperglycemia, smoking, and aging, are associated with endothelial dysfunction (6–10). These findings suggest that endothelial dysfunction contributes to the development of atherogenesis. There is also considerable evidence that endothelial dysfunction contributes to clinical events. Many studies in both the coronary and

peripheral circulation indicate that endothelial dysfunction is an independent predictor for the development of cardiac events (11).

A major issue with assessment of endothelial function is the choice of test. In clinical settings, endothelial function has been assessed primarily via vasomotion in response to agonists (e.g., acetylcholine, flow) in the coronary or peripheral circulation that induce endothelial NO release. Because coronary events are the principal source of morbidity and mortality from atherosclerosis, one might argue that the gold standard for endothelial function evaluations should be in the coronary circulation. However, the invasive nature of intracoronary studies makes their broad application difficult. As a consequence, alternative methods that assess peripheral vascular endothelial function have been developed. Among these techniques, the high-resolution ultrasonographic measurement of brachial artery flow-mediated dilatation (FMD) has been used extensively (12). This technique involves induction of post-ischemic reactive hyperemia to elicit shear-induced endothelial NO release and vasodilation. This indirect measurement of endothelial function is correlated with coronary endothelial function (13), consistent with the notion that precipitants of endothelial dysfunction act systemically. Nevertheless, FMD use is limited to research settings owing to the technical demands required for consistent measurements.

Findings that abnormal patterns of pulse wave amplitude were associated with atherosclerosis prompted new interest in developing simpler measurements of endothelial function (14). Accordingly, Kuvin et al. (15) used a specially designed finger plethysmograph for peripheral arterial tonometry (PAT) to show that changes in pulse wave amplitude during reactive hyperemia are correlated with brachial artery FMD. Subsequently, digital reactive hyperemia was found to be attenuated in patients with coronary endothelial dysfunction (16). These findings were supported by observations in the Framingham Heart Study that digital reactive hyperemia-induced PAT (RH-PAT), as an index of vasodilator function, is correlated with multiple traditional and metabolic cardiovascular risk factors (17). Collectively, these data suggest that RH-PAT could prove useful in the prediction of coronary artery disease.

In this issue of the *Journal*, Matsuzawa et al. (18) have demonstrated that impaired RH-PAT indices were predictive of ischemic heart disease in women. A similar decrement in RH-PAT indices was observed in both obstructive (demonstrable coronary lesions) and nonobstructive coronary artery disease, defined as epicardial coronary spasm, microvascular spasm, or microcirculatory insufficiency in the absence of significant epicardial obstruction. Consistent with previous studies, this study also found that the RH-PAT index is correlated with

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Divisions of General Internal Medicine and Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts. The work in Dr. Keaney's laboratory is supported by National Institutes of Health grants AG027081, HL081587, and HL092122.

coronary artery endothelial dysfunction as determined by an acetylcholine infusion study.

As with any study claiming a new test for the prediction of ischemic heart disease, one must ask whether there is any additive information compared with previously published data. In this regard, Matsuzawa et al. (18) compared RH-PAT with the Reynolds Risk Score. They found that both the Reynolds Risk Score and the RH-PAT index predicted ischemic heart disease. However, only RH-PAT was significantly associated with nonobstructive coronary artery disease, and this index was a superior predictor of nonobstructive coronary artery disease in women with angina-like symptoms lacking angiographic coronary artery disease. This is not surprising, as vasomotor dysfunction is a prominent source of symptoms in nonobstructive coronary artery disease, and RH-PAT is a measurement of vasomotor function.

The increase in digital pulse amplitude with reactive hyperemia is a complex response that reflects changes in digital blood flow and microvessel dilation. Because endogenous NO is important for the control of resistance artery tone (19), it is not surprising that digital reactive hyperemia-induced pulse amplitude is mediated, in part, by NO. However, the NO-mediated component totals ~60% of digital artery dilation, whereas the remainder represents other vasodilator components (20). In contrast, brachial artery FMD is primarily a reflection of NO, as it is largely blocked by inhibitors of nitric oxide synthase (21). Thus it is possible that RH-PAT may measure components of vasodilation not reflected in FMD, providing at least a theoretical basis for a more comprehensive assessment of vascular function. From a technical viewpoint, RH-PAT also has clear advantages over the established methods of coronary angiography or ultrasound used to measure endothelial function. It is completely noninvasive, simple to perform, and less prone to operator error and is thus more reproducible. These features hold promise for allowing wider application of endothelial function testing in clinical settings.

It is important to remember that the current study has several limitations. First, there were only 42 patients in this study, significantly fewer than that in the Framingham Reynolds Risk Score study, with which the current study is intended to compare. Second, the study was conducted in a single medical center. To validate the true value of RH-PAT in women, a second independent study applying the same criteria is needed. Most importantly, to establish the usefulness of the test, prospective evaluation of future cardiac events, rather than correlation with angiographic findings, will be crucial.

Thus, the study of Matsuzawa et al. (18) indicates that RH-PAT may serve as a simple measure to integrate risk factor burden and to reflect overall conduit and microvascular endothelial function. Consequently, RH-PAT has the

potential for wide clinical application, should it be found to predict risk of future cardiac events. Continued investigation will be needed to extend the findings of the current study to more diverse populations and provide the necessary linkage to clinical outcomes.

Reprint requests and correspondence: Dr. John F. Keaney, Jr., Division of Cardiovascular Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, S3-855, Worcester, Massachusetts 01655. E-mail: john.keaney@umassmed.edu.

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Key Words: myocardial ischemia ■ endothelium ■ women.