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EDITORIAL COMMENT

A Novel Technique to Assess Flow-Mediated Vasodilation*

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In this issue of the *Journal*, Dupuis et al. (1) report on a novel technique of assessing flow-mediated vasodilation (FMD) in the brachial artery by scintigraphic hyperemic reactivity (SHR). This technique, which has the potential to be integrated into the resting myocardial perfusion scan, allows noninvasive measurements of endothelial function of the peripheral vasculature.

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The hyperemia induced by re-establishing flow in the brachial artery after temporary occlusion increases luminal shear, resulting in the opening of calcium-activated potassium channels and hyperpolarization of the endothelial cells (2). The augmented electric gradient drives calcium entry into the endothelial cell that results in endothelial nitric oxide synthase (eNOS) activation and nitric oxide (NO) elaboration, causing vasodilation (3–8). Endothelial denudation or treatment with a NO synthase inhibitor abolishes FMD. However, blood vessels from mice that lack the eNOS gene still respond to shear stress by dilating, most likely by a prostanoid-dependent pathway (9). Although neuronal regulation of vasomotor tone also has been implicated in FMD, cardiovascular investigators have focused on FMD as an indirect measurement of endothelial function.

The rationale for gauging endothelial function is to gauge the propensity of the vasculature to undergo atherosclerosis. (10). The new paradigm of atherosclerosis links oxidative stress, inflammation, thrombosis, and endothelial dysfunction (11,12). Endothelium may be a target that integrates damaging effects of traditional and unknown risk factors and may function as a "barometer" that gauges the magnitude of atherosclerotic forces (13). For instance, known risk factors of atherosclerosis have been associated with endothelial dysfunction, and endothelial dysfunction appears to become manifest before overt atherosclerosis (14,15).

Risk factor stratification is routine in the practice of the cardiovascular physician (16) and forms an important cornerstone of the "Get with the Guidelines" initiative of the American Heart Association. It is clear that aggressive pharmacologic treatment benefits patients who are in the high-risk category. However, the treatment of choice and the extent of treatment are unclear in patients who have intermediate risk. According to the National Health And Examination Survey (NHANES) III data, 40% to 50% of adults fall into the intermediate-risk group. Further risk stratification with the use of endothelial function assessment could potentially benefit the patients within this large group who have a wide range of risk. Indeed, several trials have examined the utility of vasomotor functions as a prognosticating tool for coronary artery disease (CAD) with modest success (17–25). Albeit not investigated, monitoring endothelial dysfunction may provide another readout to which cardiovascular therapies also may be titrated, as has been suggested for C-reactive protein (CRP) (26).

Although coronary endothelial function, and not necessarily peripheral endothelial function, is the most appropriate point of evaluation, the difficulty in noninvasively monitoring coronary endothelial function prohibits its routine use. Whether endothelial function in the forearm reflects coronary endothelial function is debated. On the one hand, investigators argue that endothelial dysfunction is widespread. Risk factors for coronary atherosclerosis are systemic risk factors and should affect all vascular trees. For instance, the new biomarker of atherosclerosis, systemic CRP (27,28), also partakes in lesion formation by a variety of mechanisms. C-reactive protein leads to endothelial dysfunction by destabilizing eNOS messenger ribonucleic acid and decreasing NO production (29–32). Because these experiments were performed on endothelial cells isolated from human saphenous veins, it also is very likely that CRP exerts similar effects on other endothelial cells both in the peripheral as well as in the coronary circulation. Such evidence is consistent with the assertion that endothelial function in the forearm may relay information about the atherosclerotic propensity within the coronary vasculature.

On the other hand, even in patients with extensive atherosclerosis within the coronary circulation, arteries in the arm frequently appear to be free of atherosclerosis. In fact, the latter observation has lead some surgeons to adopt the radial artery as the bypass conduit of choice after the internal mammary arteries (33–36). Furthermore, the endothelial function of the brachial artery does not always correlate with endothelial function of the coronary circulation (37). Thus, the brachial artery reactivity may not always be directly correlated with coronary endothelial function.

Because of the technical challenges of ultrasonographic brachial artery evaluation (38) and the invasiveness of strain-gauge venous impedance plethysmography (39,40), other methods to measure endothelial function in the brachial artery would be a welcome addition. The report by Dupuis et al. (1) presents a noninvasive alternative that may be incorporated into the resting myocardial perfusion scan. There are several issues to discuss concerning the Dupuis et al. (1) report. First, the new technique of SHR has not been

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compared with other more accepted methods of FMD measurement such as by ultrasonography. For validation of the proposed new test, direct comparison with a gold standard is helpful. Second, the intrapatient variability of SHR is not reported. The precision of a new biomarker must be evaluated to provide the readers with confidence in the proposed new test. Third, the authors reported a sensitivity of 0.7 and specificity of 0.6 in discriminating between patients with CAD versus those without CAD. The modest discriminatory attribute of the test suggests significant limitations in applying the test for further risk stratification. Fourth, the authors compared patients with CAD who were taking multiple medications to patients without CAD. It is well known that several cardiovascular drugs, such as the statins, improve endothelial function (41–43). Thus, the authors may have diminished the discriminatory power of their study. Last, the other arm of each patient served as control. Considering that vasodilators were used exclusively in all patients with CAD, the resultant FMD may have been minimal in comparison with the control arm because of supranormal vasodilation at baseline caused by drugs. These considerations notwithstanding, the ease with which SHR may be incorporated into clinical practice and clinical trials may significantly add to our risk-stratification capability and post-diagnosis monitoring of patients with CAD.

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