Since the description of the classical cardiovascular risk factors by the Framingham group some 50 years ago, more recent efforts have explored the utility of biomarkers to further refine risk stratification. Although vascular imaging and biochemical markers have shown considerable promise, assessment of vascular function has particular appeal. Endothelial dysfunction is an attendant feature of established atherosclerosis and a precursor when only risk factors for atherosclerosis are present. It is thought in large part to reflect decreased nitric oxide bioavailability in the vasculature. As such it has been suggested that endothelial dysfunction plays a central pathophysiological role in the development and clinical expression of cardiovascular disease, making it well suited as a surrogate marker of risk.

Assessment of Endothelial Function
Endothelial function has been generally assessed by measuring vasomotion of conduit vessels or regional increases in blood flow, reflecting microvascular/resistance vessel function, in the coronary or peripheral circulation. Although coronary endothelial function remains a “gold standard,” its complexity and invasive requirements do not permit extensive use. Flow-mediated dilation of the peripheral circulation (FMD) has evolved as a popular marker because of the relative simplicity, a belief that it largely reflects nitric oxide–dependent endothelial function, its correlation with coronary reactivity, and modulation by risk factors or their treatment. What is often underappreciated, however, is that the relationship between vascular risk factors and FMD is rather poor. In addition, the correlation between measures of conduit vessel and microvascular function is weak and ultimately it is microvascular function that controls blood flow and oxygen transport.

Can Endothelial Function Testing Predict Outcomes?
Impaired coronary reactivity has been shown to predict subsequent cardiac events in several small studies. Attenuated FMD has been associated with complications after coronary angioplasty and vascular surgery, long term events in subjects with atherosclerosis, and in patients without overt cardiovascular disease. In the recently published Cardiovascular Health Study the association was weak but was maintained independent of traditional cardiovascular risk factors. Finally, microvascular dysfunction assessed by forearm plethysmography predicts long term outcomes in patients with cardiovascular disease.

Mechanism of Endothelial Function Testing
Assessment of FMD in humans typically involves the induction of a shear stress stimulus in the conduit brachial artery after ischemia induced by occlusion of the forearm vessels for 5 minutes. This shear stress is generated by dilation of the microvasculature, thereby producing increased flow (reactive hyperemia) in the conduit vessel. This can be measured by Doppler ultrasound after the release of the blood pressure cuff. FMD has been shown to produce a largely NO-dependent FMD response, depending on study conditions. Pyke et al also suggest that the FMD measure could be improved if corrected for variability in the shear stimulus.

As part of the exploration of the appropriate vascular end point, components of FMD, namely shear stress and reactive hyperaemia, were compared with traditional risk factors. Risk factors were more closely related to diastolic shear stress and hyperaemic velocity than FMD. This suggested that endothelial dysfunction detected by FMD may be in greater part attributable to a reduced microvascular stimulus (via reduced reactive hyperemia) rather than impaired conduit vessel response (via brachial artery dilatation). The prognostic importance of these measures of microvascular function had not been previously evaluated.

Current Study
In the current issue, Huang and colleagues report data providing support for the hypothesis that the stimulus for FMD, reactive hyperaemia, as well as FMD itself both provide prognostic information. This was the first study to associate reactive hyperaemia velocity with cardiovascular outcomes. The study involved 267 stable patients with peripheral vascular disease in whom an assessment of vascular function was undertaken within the month before vascular surgery. The group included the cohort (n = 199) that were originally reported to demonstrate an association between FMD and perioperative events.

After a median follow-up of nearly 1 year and 50 cardiovascular events (representing 19% of the study population), lower hyperemic flow velocity (75 ± 39 versus 95 ± 50 cm/s, P = 0.009) and lower FMD (4.5 ± 3.0 versus 6.9 ± 4.6%, P < 0.001) predicted patients with an event. Cox proportional hazards models including both reactive hyperaemia and FMD revealed that both predicted cardiovascular events (OR 2.7, 95% CI 1.2 to 5.9, P = 0.018, and OR 4.2, 95% CI: 1.8 to 9.8, P = 0.001, respectively) after adjusting for other risk factors. It should be noted that although a subanal-
Analysis revealed that this association remained significant for events occurring after 30 days, the majority of the events occurred during or soon after surgery, and as such it could be argued that the principal message from the study pertains to the link between reactive hyperemia and perioperative risk.

Interestingly, despite the independent association of reactive hyperemia with outcomes, FMD remained a stronger measure of risk in this population. This may suggest that conduit function is more important than microvascular stimulus in this population with advanced disease. In light of the recent Framingham data, which showed a stronger association between cardiovascular risk factors and reactive hyperemia than with FMD, it could be speculated that microvascular dysfunction may be more sensitive to the early stages of atherosclerosis, whereas conduit function may better reflect overt cardiovascular disease. Comparative analysis of these 2 markers in upcoming large population studies with more diverse risk may provide some clarification.

**Mechanism of Reactive Hyperemia**

Reactive hyperemia is a consequence of the reduction in vascular resistance after temporary interruption of blood flow, and likely results from the combined effects of flow and ischemia-induced vasodilators as well as a local myogenic response.\(^\text{21}\) The relative contribution of these factors to reactive hyperemia, particularly NO, but also ATP-sensitive potassium channels, adenosine, and endothelium-derived hyperpolarizing factor has been the subject of some debate and may depend on some extent on the testing conditions and vascular territory.\(^\text{22}\) Several authors have described diminution of reactive hyperemia in the presence of the nitric oxide synthase inhibitor L-NMMA suggesting a role for NO in this process.\(^\text{23,24}\) although this result is not replicated in all studies.\(^\text{22}\) It would be fair to say, however, that peak hyperaemic velocity or flow changes after occlusion release may be more endothelium-dependent but is generally not measured simultaneously with diameter changes. Peak hyperaemic velocity likely provides an integrated measure of vascular function not confined to endothelium-derived products.

Recent analysis of data from the Framingham study found that reactive hyperemia and the related measure shear stress were more strongly related to cardiovascular risk factors in that population than was FMD.\(^\text{20}\) Previously, small studies have shown that reactive hyperemia is impaired in the presence of hypertension, and the nitric oxide dependency of reactive hyperemia indicated by L-NMMA has been shown to be diminished in this setting, suggesting a causative role for NO in reduced RH in the presence of this cardiovascular risk factor. With the current study of Huang et al, we perhaps see the translation of this microvascular dysfunction into long-term cardiovascular outcomes.

**Conclusions and Future Perspectives**

This study is the first to investigate and report an independent association between impaired reactive hyperemia and subsequent cardiovascular outcomes. It is in agreement with previous studies that assessed outcomes related to a different measure of microvascular function using the more invasive technique of forearm plethysmography.\(^\text{14,15}\) The results speak to the importance of the microvascular stimulus in addition to the conduit response and provide impetus for further exploration of the mechanisms of vascular dysfunction and its assessment. The most appropriate measure of vascular health has yet to be established. As the hyperaemic velocity measure should be relatively easily derived from existing data within the several large population studies investigating long-term outcomes and FMD, answers on general applicability of these results may not be far away.

**Sources of Funding**

T.J.A. is a Senior Scholar of the Alberta Heritage Foundation for Medical Research (Edmonton, AB, Canada).
Disclosures
None.

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Reactive Hyperemia and Cardiovascular Risk
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Arterioscler Thromb Vasc Biol. 2007;27:2065-2067
doi: 10.1161/ATVBAHA.107.149740
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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