Editorial

Prognostic Significance of Brachial Flow-Mediated Vasodilation

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There is currently much research devoted to the study of vascular biology in intact humans. These efforts aim to translate findings from the basic science arena to a better understanding of the pathophysiology of atherosclerosis and its complications. Markers of vascular risk have been used as surrogate end points in treatment studies. More recently, long-term studies have emerged that speak to the prognostic significance of these novel markers with a goal of refining risk stratification approaches. C-reactive protein is an excellent example of such a marker, with many others being evaluated.1

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The vascular endothelium is in a unique position to serve as a metric of atherosclerotic risk. The healthy endothelium is antiatherogenic through favorable paracrine effects on vasodilation, inhibition of leukocyte adhesion, platelet aggregation and coagulation, and promotion of healing via progenitor cells.2 However, because of its position in the vascular wall, it is also the target of hemodynamic and biochemical perturbations. This leads to endothelial dysfunction early in the course of the disease, a property that could be exploited for risk evaluation.

Endothelial Function

Endothelium-dependent vasodilation is a nitric oxide–dependent process that has been well studied in humans. There are many methods of assessing conduit and resistance vessel function. Conduit vessel responses can be evaluated by measuring the change in vessel diameter in response to physiological (shear stress) or pharmacological (acetylcholine) stimuli. Ludmer and colleagues3 were among the first to describe the differences in coronary responses to acetylcholine between healthy subjects and those with vascular dysfunction. Although the study of the coronary circulation is probably still considered the gold standard, it is not ideally suited to large population studies because of its invasive nature and expense. Celermajer et al4 advanced the concept that the dilation of the brachial artery that occurred in response to a hyperemic shear stress stimuli after temporary flow occlusion would be a good measure of vascular health.

Brachial artery flow-mediated dilation (FMD) has emerged as the most common assessment tool of endothelial function. This response is (1) nitric oxide dependent, (2) abnormal early in the course of the disease process, (3) dysfunctional in response to various cardiovascular risk factors, (4) correlated with abnormalities of coronary endothelium–dependent vasodilation, (5) improved with interventions known to improve cardiovascular outcomes such as statin therapy, (6) relatively inexpensive, (7) noninvasive, and (8) reproducible. Although FMD is not as reproducible as biochemical markers such as cholesterol, the coefficient of variation for repeated measures is acceptable at ≈20%.

Prognostic Studies of Endothelial Function

Numerous studies have recently begun to address the prognostic significance of endothelial dysfunction. In subjects with mild coronary disease and endothelial dysfunction, several groups have demonstrated an association between attenuation of acetylcholine-mediated endothelium-dependent vasodilation or coronary blood flow and cardiovascular events.5,6 Impairment of microvascular endothelial function in the forearm also is associated with vascular risk. Heitzer et al6 followed up a group of subjects with mild coronary disease who had a plethysmographic assessment of forearm blood flow. Subjects with responses below the median to both acetylcholine and sodium nitroprusside were more likely to have cardiovascular events during medium-term follow-up.

The prognostic value of abrogated brachial flow–mediated vasodilation also has been evaluated. Brachial endothelial dysfunction has been shown to predict restenosis after percutaneous coronary intervention8 and complications after vascular surgery.9 In addition, attenuated brachial flow–mediated dilation is an independent predictor of events in the long term in subjects with established atherosclerosis.10,11 In subjects without established vascular disease, the results have been mixed to date.12,13 In the Northern Manhattan Study, 842 subjects (mean age, 67 years) without established vascular disease were followed up for 36 months. Lower FMD predicted events (n = 30), but the effect was no longer present in a multivariable model.13 This evidence, although tantalizing, is far from conclusive. Many of the above-mentioned studies have suffered from retrospective designs, variable follow-up, incomplete data, and small numbers of events.

Current Study

The article by Yeboah and colleagues14 in this issue of Circulation is the first of the ongoing large prospective

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studies of brachial endothelial function to report prognostic data. The present data provide compelling information to support the notion that peripheral artery endothelial dysfunction is associated with adverse cardiovascular events. The study consisted of 2792 individuals between 72 and 98 years of age. This brachial ultrasound substudy was undertaken at the 10th annual evaluation of the Cardiovascular Health Study. Some subjects (n=666) had preexisting vascular disease; the remainder were free of incident atherosclerotic disease. The cohort was healthier than the general population but did have risk factors associated with aging. A minority only were on medications that might affect vascular function. Prospective 5-year follow-up data were available for the following composite end point: cardiovascular death, myocardial infarction, stroke, congestive heart failure, claudication, angioplasty, or cardiac bypass graft surgery. A total of 674 events were recorded, given the advanced age of the cohort. Previous trials assessing the prognostic value of endothelial function had <100 events.

Event-free survival rates for cardiovascular events were significantly higher in subjects with FMD higher than compared with subjects with FMD less than or equal to the sex-specific medians (78.3% versus 73.6%; P<0.01). After correction for risk factors known to be associated with outcome, FMD remained an independent and significant predictor, with a hazard ratio of 0.91 (95% CI, 0.83 to 0.99) for each unit standard deviation change in FMD. The strongest predictors of an adverse outcome were increasing age, blood pressure, baseline vascular status, and male gender. Similar predictive value was present for the subgroups with and without incident cardiovascular disease at baseline. When FMD was added to the best Cox hazard model, the change in the C statistic was 0.01, suggesting that FMD added only approximately 1% to the prognostic model. Recently, the value of this type of analysis has been questioned because it may underestimate the importance of a new biomarker.

A very interesting finding of the study by Yeboah and colleagues was that subjects with baseline brachial diameter above the gender-specific median values had an increase in event rates. In fact, the predictive value was of the same magnitude as FMD. There was a trend for a similar finding in the recently reported study by Shimbo et al. The interpretation of this observation is not clear. It is well known that the strongest predictor of FMD is baseline brachial diameter as a result in part of the mathematics of its calculation but probably also the physiology of shear stress generation in different-sized vessels. This raises the question as to whether the predictive value of FMD in the present study simply reflected baseline diameter differences. Positive remodeling of arteries in response to atherosclerotic risk has been described in the peripheral circulation and may account for this observation.

**Strengths and Unanswered Questions**

The study by Yeboah et al adds greatly to the literature in this field. The major strengths include the very large number of end points and the carefully performed prospective nature of the investigation. The group is to be congratulated for the results. Conclusions can be applied to subjects without incident vascular disease, an area in which there has not been as much study to date. Elderly subjects with minimal risk except age with endothelial dysfunction are at increased risk of the development of atherosclerotic complications.

Like all good studies, the work of Yeboah and colleagues raises several important questions. First, are the results applicable to younger subjects, in whom one might argue there is greater need to identify novel methods of risk stratification? Several ongoing studies, including 1 from our group, will address this issue in younger populations. Second, what is the best measure of vascular health? Is it in fact FMD, or as suggested by Yeboah et al, is FMD simply a measure of baseline diameter? Others have suggested that it may be a measure of microvascular function such as hyperemic velocity or shear stress. Modalities other than ultrasound such as pulse arterial tonometry that assess microvascular responses in the extremities are being evaluated. Third, how does a measure of endothelium-dependent vasodilation integrate with other biomarkers or tests of structural atherosclerosis such as carotid intima-media thickness or parameters derived from computed tomography? The present study was unable to address this issue because these measures were not concurrently available. The Multi-Ethnic Study of Atherosclerosis is evaluating multiple markers and should shed further light on this question. And finally, will interventions aimed at improving endothelial dysfunction result in improved outcomes, as has been suggested in 1 small study?

**Clinical Implications**

The Yeboah et al study strongly supported the premise that endothelial dysfunction is an integral component of atherosclerotic vascular disease and that its presence is a risk factor for the development of clinical events. The study provides one of the strongest pieces of evidence to date to support this claim. However, it is unlikely that this observation will spawn the widespread implementation of brachial ultrasound testing for risk assessment. The technique of FMD acquisition is highly operator dependent, requires expensive equipment and offline analysis, is without established normal values, and may not even be the best metric. In addition, the incremental value above traditional Framingham risk factors is small at best. The sensitivity, specificity, and predictive values of various FMD cut points are unlikely to be acceptable.

However, even if tests of endothelial function are not readily incorporated into diagnostic algorithms, the results remain pivotal to clinical medicine. The study by Yeboah and colleagues will solidify measures of endothelium-dependent vasomotion as surrogate markers of disease. As such, these measures can be used to understand the potential importance of novel biochemical or emerging genetic risk factors. The dynamic nature of the measure also allows the study of interventions over a period of months, not years, allowing more rapid evaluation of the novel therapies. This study further justifies the value of the end point.

The study by Yeboah et al contributes significant evidence to the field of vascular biology. Measures of vascular health will further our understanding of the pathophysiology, investigation, and treatment of atherosclerotic vascular disease.
References


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