Predicting the Development of Atherosclerosis

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Tis easy to see, hard to foresee.
—Benjamin Franklin

Atherosclerotic vascular disease is one of the great epidemics of the 21st Century.1 Decades before its clinical manifestation, endothelial dysfunction (ED) marks the beginning of an insidious disease process, which silently progresses to a point where it can only be slowed but not reversed. ED is induced by a variety of mediators, some of which are known and related to established cardiovascular risk factors such as smoking, dyslipidemia, hypertension, diabetes mellitus, and aging, whereas others are presently unknown. As ED develops, the balance between antiatherogenic and proatherogenic factors in slowly shifted in favor of the latter. In this multifactorial process, reduced bioavailability of nitric oxide (NO) plays a pivotal role. NO, a free radical gas with an in vivo half-life of a few seconds, is synthesized primarily from endothelial NO synthase (eNOS), which is activated in response to flow-induced shear stress, cytokines, and hormones.2 In vitro, NO inhibits the expression of cell adhesion molecules such as VCAM-1, ICAM and E-selectin, as well as the secretion of proinflammatory cytokines such as interleukin 6 and interleukin 8, thus preventing monocyte attraction and adhesion.3 In line with these findings, early studies using eNOS knockout mice demonstrated an increase in atherosclerotic lesions in these animals.4,5 In contrast, however, more recent studies revealed that eNOS knockout mice may under certain circumstances also be relatively protected from the development of atherosclerosis and that transgenic overexpression of eNOS in fact may accelerate atherogenesis.6,7 Although the exact mechanism remains unclear, it is highly likely that in the inflammatory microenvironment of the dysfunctional endothelium and developing atherosclerotic lesion, increased oxidative stress leads to an immediate chemical reaction of NO with superoxide, resulting in the generation of peroxynitrite, thereby both reducing the bioavailability of NO and increasing posttranscriptional modifications of vital proteins and tyrosine residues. Together with a plethora of other mediators, the imbalance of NO and reactive oxygen species leads to the propagation of ED, which results in leukocyte adhesion and diapedesis, migration and proliferation of vascular smooth muscle cells, and enhanced platelet–vessel wall interaction. When low-density lipoprotein–laden macrophages accumulate in the vessel wall, a “fatty streak” develops that marks the first visible manifestation of atherosclerosis. Left untreated and further exposed to proatherogenic stimuli, such lesions may advance and eventually result in the development and progression of overt atherosclerotic disease with its clinical complications such as angina, acute myocardial infarction, and stroke.

Although overt atherosclerotic disease (especially when clinically symptomatic) is comparatively easy to see, its future development in an asymptomatic population is hard to foresee. Indeed, at the early stage of the cascade when solely ED is present, individuals usually do not complain of symptoms; yet identifying these potential “patients” intuitively appears important in order to interrupt the atherogenic process and prevent further vascular damage. Flow-mediated dilation (FMD) of the brachial artery was first described in the late 1980s;8 it is predominantly dependent on endothelium-derived NO9 and is therefore widely used as a readout of endothelial (dys)function, mainly in the research setting.10 For example, intravenous infusion of recombinant high-density lipoprotein cholesterol improves FMD in hypercholesterolemic patients.11 Similarly, treatment with angiotensin-converting enzyme inhibitors increased FMD in hypertensive patients.12 FMD possesses several advantages when compared with more invasive measurements such as coronary vasoreactivity testing with intracoronary infusion of acetylcholine. Indeed, FMD correlates well with coronary endothelial function,13 is noninvasive and comparatively inexpensive, and becomes abnormal early in the course of atherogenesis (ie, at the stage of endothelial dysfunction, hence long before structural changes occur). For these reasons, FMD represents an interesting candidate procedure for cardiovascular risk stratification, and several studies have been conducted in order to examine the prognostic value of FMD in patients at high risk for or with established cardiovascular disease. For example, patients with coronary artery disease (as assessed by exercise myocardial perfusion imaging) had lower FMD than those without coronary artery disease,14 and in patients with single-vascular coronary artery disease who underwent stent implantation, FMD was impaired in those who developed restenosis compared with those who did not.15 In patients undergoing vascular surgery, a low preoperative FMD was predictive of a postoperative event during the following 1.2 years.16 In a recent prospective study of 2792 elderly adults (aged 72 to 98 years), FMD predicted future cardiovascular events (without, however, adding much to the prognostic
accuracy of traditional cardiovascular risk scores or factors.17

Collectively these investigations suggest a potential prognostic value of FMD. Common to these studies, however, is the fact that they were conducted in populations at high risk for or with already established atherosclerotic disease, hence in a situation where the horse is already out of the barn. In their present study, Halcox and colleagues18 went back several years on the atherosclerotic time line and investigated the prognostic value of FMD on carotid artery intimal-media thickness (IMT) progression in a prospective cohort of middle-aged individuals at low to intermediate cardiovascular risk without clinical signs of established atherosclerotic vascular disease. Surprisingly, neither established cardiovascular risk factors nor Framingham Risk Score, but only FMD, was associated with average annual progression of IMT over an average observational period of 6.2 years. The association between FMD and IMT progression remained significant even after patients with antihypertensive drugs and statins were omitted from the analysis; this is of importance both because these patients could be considered to be at an increased risk for atherosclerosis and because of the known influence of these classes of drugs on FMD. No association was found between FMD and IMT at baseline, which, as the authors point out, is not too surprising because IMT is generally viewed as a measure of the cumulative structural atherosclerotic vascular burden; in contrast, FMD reflects both chronic and early dysfunctional changes, the latter of which most probably representing the more important part in this preclinical population.

Although these data indeed imply that FMD may predict progression of atherosclerosis, a couple of questions remain. Unexpectedly, a trend toward an inverse relationship was observed between low-density lipoprotein cholesterol and IMT progression, and patients with the most rapid progression of atherosclerosis had lower waist circumference, lower triglyceride levels, and higher high-density lipoprotein cholesterol. Given the well established association of low-density lipoprotein cholesterol and of the metabolic syndrome with the development of atherosclerotic cardiovascular disorders, these findings may indicate that the individuals studied in this trial may not represent a "normally" advancing atherosclerotic study population. The authors, in contrast, argue that this association most probably occurred through a type I error (ie, the erroneous assumption of a statistical difference [or trend] when in truth none exists). Indeed, the validity of the authors’ study population is underscored by the association of baseline low-density lipoprotein cholesterol and baseline IMT, as well as by the fact that the association between FMD and IMT progression remained significant even after adjusting for the conventional cardiovascular risk factors (both when entered separately or as Framingham Risk Score). However, the above-named discrepancies with established epidemiological findings require clarification.

A drawback of the current study and potentially of the methodology itself is the rather low positive predictive value of FMD, only 35%, for predicting rapid progression of atherosclerosis (compared with a negative predictive value of 83%). This result is in line with earlier observations of both the authors and others indicating that the negative predictive value of endothelial function testing is the most reliable (ie, a good FMD is most likely associated with less progression of atherosclerosis).14,19

Some methodological concerns also have to be taken into consideration when interpreting the data of Halcox and colleagues. Measurement of brachial artery FMD is challenging because of a variety of potential confounders, as well as an intraindividual variation to repeated measurements. In the present study, potential confounding with food intake, drugs, exercise, or ambient temperature was meticulously taken care of by the authors. One important quality criterion of FMD measurement is the observed intraexaminer difference. Halcox et al report an overall coefficient of variation for repeated measurement of <11%, which appears acceptable (especially in view of the long follow-up of the study patients) although a lower variation in the range of <5% is usually desirable.20 Furthermore, the authors found not only FMD, but also brachial artery diameter to be associated with IMT progression, which is in line with a previous prospective study in the elderly.17 This finding is important from a methodological standpoint because an increase in baseline diameter will result in a decrease in FMD (by the way FMD is calculated); it is thus tempting to speculate that the observed association of IMT progression with reduced FMD may be "artificial" and merely reflect the increase in brachial artery diameter (as a result of positive remodeling in the setting of advancing atherosclerosis). Even though the absence of an association with carotid artery diameter and IMT progression argues somewhat against this interpretation, further studies are clearly needed to address this issue.

In summary, the work of Halcox and colleagues in this issue of Circulation18 adds good-quality data to the growing evidence that brachial artery FMD measurement may be of prognostic value. As with all good studies, several open questions remain. These issues as well as the inherent limitations of the methodology itself demonstrate that FMD is not yet ready for prime time as a reliable prognostic indicator. The validity and power of this method to establish itself as a tool for risk stratification will critically depend on the ability to objectify and reproduce measurements; hence, efforts are needed to overcome the above-mentioned methodological limitations and to standardize high-quality protocols for brachial artery FMD measurement. In addition, further long-term large-scale studies are needed to substantiate the authors’ findings, to investigate whether FMD is able to truly predict the occurrence of clinical events (and not only a progression of the “surrogate” marker IMT), to demonstrate how FMD measurement integrates with other cardiovascular risk-assessment tools and biomarkers, and to focus on whether improving FMD will result in improved clinical outcome.

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