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EDITORIAL COMMENT

Listening to the Endothelium

A Story of Signal and Noise*

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Sensing myriad physical and chemical stimuli, the endothelium releases numerous messenger molecules that regulate local vasoactivity, inflammation, mitogenesis, and thrombosis (1,2). Nitric oxide (NO) is an important local vasodilating messenger. Blood flow shear releases NO, which underlies the phenomenon of flow-mediated dilation (FMD). Besides vasoregulation, NO has antiatherogenic effects, including inhibition of white cell activation and smooth muscle cell proliferation. The 1998 Nobel Prize for Medicine awarded to Robert Furchgott, Lewis Ignarro, and Ferid Murad acknowledged the significance of endothelial function.

See pages 1953 and 1959

The standard for assessing endothelial function remains measuring arterial diameter responses to endothelium-mediated agonists, such as acetylcholine. Such an approach, however, disregards endothelium's non–NO-mediated effects on inflammation and thrombosis (3). The evaluation of coronary artery endothelium-mediated vasomotion is an exacting, lengthy, invasive process, rarely performed for clinical reasons. An easily performed measure of endothelial function would, therefore, potentially serve as a useful biomarker of developing atherosclerosis, a means for understanding risk factors, and a monitor for antiatherogenic interventions.

In 1992, Celermajer et al. (4) demonstrated a novel, noninvasive FMD-based approach to measuring endothelial function that assesses brachial arterial dilation by ultrasound in response to the hyperemia produced by transient blood pressure cuff arterial occlusion. Numerous laboratories have experimented with this technique, including ours. Assessment of FMD has been both a rewarding and disappointing experience. Brachial artery FMD appears to be an integrative index of risk factor burden. Using the FMD technique, the relationship between established risk factors such as hypercholesterolemia and endothelial function has also been greatly clarified (5). Investigations have also demonstrated that several common activities such as eating, exercising, emotional distress, and sleep deprivation affect endothelial function (6,7).

Despite the many insights into vascular biology provided by this noninvasive approach, FMD has not proven to be clinically useful, especially for predicting cardiovascular risk. It is a biologically noisy index predominately because it is influenced by countless clinical factors. It is of greatest predictive value in low-risk individuals, but it adds little to risk assessment beyond that provided by standard factors (8,9).

Beyond its intrinsic biological variability, brachial artery FMD measurements are technical difficult. Although conceptually simple, the accurate and reproducible measurement of FMD (normal values exceed ~6% to 8%) requires skilled sonographers performing large numbers of procedures using high-frequency vascular probes with patience and care. With an average brachial artery diameter of 3 to 5 mm, each 1% increment equates to 0.03 to 0.05 mm arterial dilation measured over minutes.

In 2002, a group of experienced investigators summarized the existing standards for the performance and measurement of FMD (10). A lack of technical and interpretational standardization was evident in this summary. In this issue of the *Journal*, Donald et al. (11) in Deanfield's laboratory compare technical approaches to measuring FMD using short- and long-term reproducibility and discrimination of normal from diabetic and hypercholesterolemic subject values as the end points. This long overdue report advances the science of this technique by reducing the inherent "noise." They find that FMD is most reproducible and discriminating using a stereotactically held probe, continuous B-mode (vs. A-mode) ultrasonic imaging, automated edge detection and diameter measurement, and a maximum arterial diameter end point (vs. fixed 60-s measurement). These technical standards should be adopted by other laboratories.

This report also provides power curves that estimate cohort size required to measure specified FMD changes in crossover and parallel design studies. Their estimates underscore the difficulty in measuring small changes (1% to 2%) in FMD using a parallel design, often required for longitudinal intervention and drug studies. Multicenter studies would almost certainly be required for the performance of such trials since they estimate that 100 to 400 subjects would be needed to detect an effect.

This report has 2 important limitations. This laboratory has the most extensive experience in performing FMD measurements, calling in question whether less experienced laboratories might achieve the same 7% to 10% coefficient of variation reproducibility even using the same validated approach. Secondly, although their suggestions may reduce the noise, they do not increase the "signal." The reported difference in FMD between their normal and diabetic and hypercholesterolemic subjects was only 2% to 3% (absolute).

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In part, this small signal is due to the use of lower (as opposed to upper) arm arterial occlusion, which has been widely adopted because it is almost entirely NO dependent.

In a separate study in this issue of the *Journal*, Gori et al. (12) describe the inverse of FMD, namely brachial artery flow-mediated constriction (FMC), measured during distal arterial occlusion. They report that FMC is reduced in subjects who smoke or who have hypertension or coronary artery disease. The reduction in FMC in their smoking and hypertensive subjects was similar to their reduction in FMD, but the reduction in FMC in coronary artery disease subjects was proportionally greater (i.e., a greater signal). By summing individual FMC and FMD values, they report a 6% to 9% absolute difference between their normal and abnormal subjects compared with a 2% to 3% absolute difference in FMD as reported by Donald et al. (11). The increased signal of summed FMC and FMD with the reduced noise inherent in the described technical advances may increase brachial imaging's efficacy for clinical purposes such as predicting cardiovascular risk.

Importantly, FMC but not FMD was reduced by fluconazole, an inhibitor of endothelium-derived hyperpolarizing factor and aspirin, an inhibitor of cyclooxygenase. Inhibiting NO synthase reduced FMD, but not FMC. Thus, the FMC "signal" is dependent on a non-NO, but endothelium-mediated, process. Underscoring their different physiologies, FMC and FMD did not significantly correlate in this study. To some purists, not measuring NO availability is a disadvantage in the assessment of endothelial function. It may, however, be an advantage. It may be telling us a different, but equally interesting, story about other endothelial messenger molecules. This initial report, however, involves few subjects and at least 3 messengers, endothelium-derived hyperpolarizing factor, prostaglandins, and endothelin-1. It remains to be shown how clearly and loudly it will speak to us.

What is clear, however, is that medical science often badly falters when we exclusively focus on single mechanisms in complex diseases. For example, we might predict that hormone replacement therapy would reduce cardiovascular risk after learning that it improves endothelium-mediated dilation. At the same time, hormone replacement therapy *increases* proatherogenic factors, such as inflammation and coagulation, which are also endothelium mediated. If these FMC observations are confirmed, one might view FMD and FMC as a panel of associated tests, much like low-density lipoprotein and high-density lipoprotein cholesterol, each telling an associated but different tale. Now that we have a better understanding of how to reduce the noise, we should listen carefully to the full story the endothelium is trying to tell us.

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