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Clinical assessment of endothelial function- ready for prime time?

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The vascular endothelium plays a critical role in the regulation of arterial function through the synthesis and elaboration of a number of anti-atherogenic factors such as nitric oxide (NO). "Endothelial dysfunction" represents a pathophysiological state where normal homeostatic properties of the vasculature are impaired or lost, thereby supporting a vasospastic, prothrombotic, and proinflammatory atherogenic milieu.[1] Impaired arterial function is associated with multiple cardiac risk factors and is detectable early in the progression of atherosclerosis, thus making it an ideal target for primary preventive intervention. It is also fundamental to mechanisms of advanced disease playing a critical role in the pathophysiology of acute cardiovascular syndromes such as myocardial infarction and stroke. The concept that endothelial phenotype serves as an overall barometer of vascular health and may shape clinical disease has prompted significant interest in its clinical assessment.[2,3]

Clinical measurement of endothelial function is challenging owing to its heterogeneous functions, as no single test provides a comprehensive physiological thumbprint of the entire vascular tree. As such, most studies have focused primarily on the regulation of arterial tone as a means of assessing vasoreactivity via interrogation of NO-mediated, endothelium-dependent vasodilator responses to specific agonists such as acetylcholine or shear stress that normally provoke vasodilation. Paradoxical constriction or attenuated dilator responses develop in disease states, reflecting impaired vasomotor function and reduced NO bioactivity. While such studies were initially performed in coronary arteries, the technique has migrated to the surrogate forearm circulation which permits more practical studies that are non-invasive and repeatable.[4]

A number of non-invasive techniques are now available for assessment of forearm vascular reactivity, and presently the most frequently utilized method involves flow-mediated dilation (FMD) of the brachial artery using ultrasound imaging. In this method, brachial diameter is measured at baseline and following an increase in arterial shear stress induced by inflation then deflation of a sphygmomanometric arm cuff that elicits reactive hyperemia and brachial vasodilation, predominantly due to endothelium-derived NO release.[4] Brachial artery FMD measured in this fashion correlates with endothelial function in the coronary circulation, relates to traditional risk factors, improves with targeted treatment, and predicts risk of future cardiovascular events.[1] As such, this technique available since 1992 is presently viewed as the gold standard for non-invasive interrogation of peripheral conduit artery vasoreactivity. Despite its clinical relevance, several limitations have precluded its integration into clinical practice, partly owing to technical limitations that require extensive

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sonographer training, expensive equipment, labor-intensive image analysis, and lack of methodological standardization that have prompted a search for techniques inherently faster and easier to perform. One such newer methodology involves digital pulse amplitude tonometry (PAT) which measures volumetric changes in the fingertip using a probe that quantifies pulse amplitude in response to reactive hyperemia using a commercially available device (EndoPAT, Itamar Medical, Ltd). Signals in the contralateral hand not experiencing hyperemia are simultaneously recorded, controlling for systemic effects. Proprietary software provides a reactive hyperemia PAT ratio in relation to the control arm that is expressed after natural log transformation owing to skewed variable distribution. The potential advantage of this technique relates to use of an automated computerized analysis system that minimizes operator dependency and inter-observer variability. Small-scale preliminary studies show that PAT hyperemic responses depend on NO and are reduced in the presence of coronary artery disease (CAD) or its risk factors, suggesting that clinically important group differences can be detected using this method.[5] Another device that is fairly quick and simple to use involves fingertip infrared light transmission photoplethysmography (PulseTrace, Micro Medical, Ltd) which performs digital pulse volume waveform analysis and generates an automated reflection index (RI). The response shows decrement with cardiac risk factors but exhibits somewhat low reproducibility and its ability to detect changes with intervention is unknown.[6,7]

In this issue of *Circulation: Cardiovascular Imaging*, Schnabel and colleagues report their findings in 5000 individuals followed in the community-based Gutenberg Heart Study, examining the associations between the these three contemporary non-invasive methods described above (FMD, PAT, and RI) and their relation to classic cardiovascular risk factors.[8] The authors are to be commended as this represents the largest comparative study to date of differing methodologies in endothelial function assessment. In this gender balanced, unselected cohort aged 34–74 years, the primary novel findings were that different techniques correlated weakly with each other, differed significantly in their relation to traditional risk factors, and response profiles were influenced by gender, particularly for PAT and FMD. While in general all techniques related to age and sex, FMD also correlated with body mass index, hypertension, dyslipidemia, and C-reactive protein. PAT ratio was additionally associated with smoking status, plasma glucose, and diabetes but unexpectedly correlated positively with blood pressure. Reflection index demonstrated the weakest relationship with measured risk factors with a model R^2 of only 3.2%. Overall, hyperemic parameters correlated more weakly than baseline variables such as brachial artery size. As such, for the entire study, measured risk factors explained only a fraction (<16%) of the variability in hyperemic responses for any of the three techniques, demonstrating that traditional risk factors were more predictive of anatomical changes than physiologic responses.

The overall findings of the present study by Schnabel and coworkers are similar to data published very recently by the Framingham Heart Study group demonstrating lack of correlation between PAT and FMD and differing patterns in risk factor associations.[9] The findings from both studies are clinically important because they show that fingertip and brachial measures of endothelial function are not interchangeable and clearly provide different information about distinct aspects of vascular biology. This is not surprising since brachial FMD examines macrovascular conduit artery vasodilator capacity whereas fingertip changes measure microvascular function in a terminal vascular bed. Additionally, different stages of disease processes may have disparate effects on different vascular beds. As such, the closer association of glycemic parameters with PAT may reflect microvascular impairment in early phases of metabolic vascular disease.

So, which method do we use and where do we go from here? As with any new biomarker or test that stands to gain clinical acceptance, a number of key criteria need to be met, which include ease of use, standardization, low cost, reproducibility, firm relation to disease pathophysiology, and ability to predict cardiovascular risk and improve existing stratification tools. Additionally, interventions should alter the marker and alterations in the marker should ideally predict change in risk. At the present time, none of the three above mentioned techniques of endothelial function assessment meet all these benchmarks. Brachial artery FMD has been most subject to analytical scrutiny since it has been around longer and investigated most extensively. As such, prospective outcome studies in varying populations by and large show that brachial FMD independently predicts risk of future cardiovascular events.[10–16] We now also recognize that measures of resistance vessel function such as forearm reactive hyperemia may provide incremental prognostic information.[10,17] Recent outcome studies using these endpoints are summarized in table 1. Despite its predictive value, brachial reactivity testing has not been adopted into the clinical arena. The technique remains operator dependent, is highly variable between centers (i.e. cuff positioning, software analysis) and without established gender-specific normal values or cutoff points that define increased risk. Nevertheless, clinical studies with these methods continue to accrue, and there is also growing evidence that combining markers of vascular structure and function may provide complementary information.[16,18] Recent data also demonstrate that both forearm FMD and RH correctly reclassify up to a third of patients with intermediate Framingham Risk Scores providing incremental discriminatory power beyond existing algorithms.[13,17] Perhaps most interesting are data demonstrating that endothelial interrogation may identify patient responses and gauge treatment efficacy. For example, in hypertensive women, failure to restore endothelial function with blood pressure lowering was strongly associated with increased cardiovascular risk.[15] Similarly, lack of improvement in FMD with antiatherosclerotic treatment identified CAD patients prone to future events.[14] The notion that endothelial phenotype may capture the biological effects of unmeasured risk factors is an evolving concept that deserves further investigation, and serial vascular assessments with targeted therapy may prove useful in monitoring treatment effects. Nevertheless, these proof of principle studies need confirmation in larger and varying cohorts as these types of investigations are likely to move the field forward.

The prognostic and clinical value of more novel fingertip-based methodologies such as pulse amplitude tonometry and photoplethysmography has not been well examined to date. One recent study showed that a reduced PAT index was associated with higher hospitalization rates for cardiovascular symptoms but not risk of myocardial infarction or stroke.[19] The fingertip vasculature is anatomically complex consisting of a dual circulation with arteriovenous anastomoses and distinct physiology. As such, PAT hyperemic responses at the digital microvessel level may not be equivalent to brachial hyperemia which reflects mostly forearm microvascular responses, nor brachial FMD that reflects conduit artery dilation. As such, which vascular measures are most clinically relevant remain to be determined and much information will eventually be gained as the Gutenberg and Framingham Heart Study databases continue to mature.

The 2010 American College of Cardiology Foundation/American Heart Association Task Force guidelines for assessment of cardiovascular risk in asymptomatic adults did not recommend brachial/peripheral flow-mediated dilation studies for clinical use at the present time.[20] While brachial reactivity testing is further along the path of potential clinical utility, it remains affected by several limitations mentioned above. Even less is known about the utility of fingertip PAT and RI methodologies which lack outcome data. Nevertheless, the ability to measure endothelial function non-invasively remains a valuable tool for identification of novel risk factors, elucidating mechanisms of vascular dysfunction, and use as a surrogate of cardiovascular risk for intervention studies using novel therapies in groups

of patients. Reversal of endothelial dysfunction represents an attractive goal for therapeutic intervention, and whether any of these non-invasive measures of vascular health will eventually carve a clinical niche remains to be seen.

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Table 1

Summary of outcome studies using non-invasive methodologies

Author	N	Mean follow-up duration	Number of events	Event rate	FMD predictive	RH predictive
Modena 2002 [15]	400	67 months	47	11.7%	+	
Brevetti 2003 [16]	131	23 months	39	29.8%	+	
Gokce 2003 [11]	199	1.2 years	35	17.6%	+	
Chan 2003 [18]	152	34 months	22	14.5%	+	
Fathi 2004 [21]	444	24 months	70	15.8%	−	
Frick 2005 [22]	398	39 months	44	11.1%	−	
Yeboah 2007 [12]	2792	5 years	674	24.1%	+	
Huang 2007 [10]	267	309 days	50	18.7%	+	+
Yeboah 2009 [13]	3026	5 years	182	6%	+	
Kitta 2009 [14]	251	36 months	42	16.7%	+	
Anderson 2011 [17]	1574	7.2 years	111	7.1%	−	+