JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 4, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.02.015

EDITORIAL COMMENT

Vascular Function Tests in Women With no Obstructive CAD

A Few Pieces of the Puzzle*

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Endothelium plays a critical role in maintaining healthy homeostatic properties of the vasculature. Endothelial dysfunction promotes atherosclerosis by creating a vasospastic, prothrombotic, and proinflammatory milieu. Therefore, the assessment of endothelial function as a surrogate marker of arterial health has gained significant interest for clinical risk assessment beyond the risk conveyed by a structural impediment to flow (1). Furthermore, the observation that cardiovascular events may occur remotely from the site in which the endothelial dysfunction is detected prompted clinical studies in search for peripheral vascular endothelial dysfunction as a predictor of cardiovascular events.

Endothelial dysfunction is characterized by a paradoxical vasoconstriction or attenuated dilation due to reduced endothelium-dependent nitric oxide (NO) release. In earlier studies, the response of the epicardial arteries to infused acetylcholine was measured invasively to assess endothelial function in the coronary circulation. Later on, a number of noninvasive methods has been introduced for this purpose including forearm flow-mediated dilation (FMD) of the brachial artery and, more recently, pulse amplitude tonometry (PAT), which measures flow-mediated volumetric changes in the fingertip.

Despite the association of FMD with traditional atherosclerotic risk factors and cardiovascular risk (1,2), its integration into clinical practice has been limited due to a number of technical difficulties. Digital pulse amplitude tonometry (PAT) is a promising technique that quantifies pulse amplitude and measures volumetric changes in response to reactive hyperemia in the fingertip. Simultaneous measurements of the signals from the contralateral arm not experiencing hyperemia serve as control for systemic vascular tone. Thereby, a reactive hyperemia index (RHI) in relation to the control arm is obtained. Nohria et al. (3) have shown that approximately 60% of the PAT-RHI response is mediated by NO release. Subsequently, PAT was shown to correlate with coronary endothelial function (4), showed decrement with obstructive and nonobstructive coronary artery disease (CAD) (5) and cardiovascular risk factors (6), although no correlation was found between FMD and PAT (7), one being a marker of macrovascular and the other a microvascular endothelial function. In addition, PAT and FMD had differing patterns in risk factor associations (7).

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In this issue of *iJACC*, Michelsen et al. (8) examined whether peripheral vascular function assessed by PAT-RHI is associated with coronary microvascular function measured by coronary flow velocity reserve (CFVR) in women with angina-like chest pain and no obstructive CAD in a medium sized population randomly selected after systematic screening of all women referred to coronary angiography. The study population is relevant for several reasons: angina is more prevalent in women despite lower rates of acute coronary syndromes yet higher rates of hospitalizations for angina and death after myocardial infarction (9–11). Microvascular dysfunction and nonobstructive CAD are highly prevalent in women with chest pain (9). Furthermore, women with persistent angina, despite nonobstructive CAD have higher risk of cardiac events if there is evidence of microvascular dysfunction (12,13). Accordingly, reliance upon

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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identifying patients at risk by means of alternative strategies rather than detecting obstructive lesions is important to minimize diagnostic imprecision and therapeutic indecision in women. Noninvasive stress tests remain insensitive for the diagnosis of nonobstructive or microvascular CAD in women. Perfusion imaging with positron emission tomography or cardiac magnetic resonance are of value but have limited access and high cost. Vascular wall imaging by intravascular ultrasonography or coronary computerized tomography angiography are also viable options that provide information about the structure and composition of atherosclerotic plaques. However, thinking simply, a clinically applicable test for vascular function would be of great value if it helps to improve early diagnosis, risk stratification and therapeutic interventions in symptomatic women over and above the detection of coronary obstructive lesions. Assessment of CFVR is an already well-established tool for evaluation of both epicardial and microvascular CAD. Its relation to conventional risk factors and its predictive value for CAD have been tested in various patient populations including women with normal appearing coronary angiograms (14).

The findings presented by Michelsen et al. (8) are clinically important. They show that PAT-RHI and CFVR, 2 relevant noninvasive vascular function parameters, are not interchangeable, do not correlate with each other, differ significantly in their relation to traditional risk factors, and clearly provide different information about distinct aspects of vascular biology. Of note, Matsuzawa et al. (5) previously assessed coronary endothelial function by using acetylcholine and CFVR by adenosine provocation tests invasively in women with chest pain undergoing coronary angiography. In that study, RHI-PAT was significantly associated with coronary endothelial function and predicted nonobstructive CAD, however their finding of no correlation between RHI-PAT and CFVR assessed by adenosine provocation cannot completely negate the potential relationship between RHI-PAT and non-endothelium-dependent coronary microvascular disease as adenosine test results were comparable between nonobstructive CAD and no ischemic disease groups in their study. This leaves a gap of knowledge about the association between RHI-PAT and endothelial independent coronary microvascular function which is presently addressed by Michelsen et al. (8). Several reasons may help to understand the differing aspects of these 2 functional tests: CFVR is regarded as a measure of mainly endothelium independent function of the coronary microvasculature. CFVR as assessed by dipyridamole is mediated by the inhibition of adenosine reuptake and catabolism, thereby reflects the smooth muscle cell relaxation in the coronaries. In contrast, PAT-RHI is a measure of inadequate microvascular vasodilator capacity in response to reactive hyperemia mainly mediated by endothelial NO bioactivity. In addition, PAT hyperemic responses at the digital microvessel level should be considered in the context of anatomically complex fingertip vasculature, consisting of a dual circulation with arteriovenous anastomoses and distinct physiology. Also, both pathological and nonpathological conditions, including temperature in the environment, autonomic nervous system tone, blood pressure, valvular calcifications, immune activation, and many others can potentially interfere with PAT-RHI and CFVR measurements, respectively. Finally, atherosclerosis may have different manifestations in vascular bed depending on stages of disease process, risk factor profile, and site specific predilection for vascular involvement. This study underlines the importance of assessing vascular functions in more than one vascular bed and the need to define which testing modalities give the best clinical and prognostic information in different patient populations. Of note, the regulation of vascular tone is only one aspect of the complex endothelial function.

Although PAT has several technical advantages as a simple, automated, repeatable test, there is still much work to be done before it can be integrated into clinical practice. Standardization among laboratories, population normal data, additive risk predictive value (particularly in intermediate-risk subjects), alteration of the measurements with therapeutic interventions, and the relation of this alteration to change in the risk need further exploration and evidence. Meanwhile, recent data demonstrated that PAT-RHI is an independent and additive risk marker to Framingham risk score for adverse cardiac events (6,15).

In conclusion; the assessment of vascular function seems to be valuable to capture pathobiological effects of unmeasured risk factors and deserves further investigation. Elucidating the inferences from different vascular function tests for diagnosis, cardiovascular risk prediction and gauging response to therapy is an attractive goal awaiting further studies.

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JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 4, 2016
APRIL 2016:418–20

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KEY WORDS coronary flow velocity reserve, coronary microvascular function, microvascular angina pectoris, peripheral microvascular function, reactive hyperemia index