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EDITORIAL COMMENT

# Can Advanced Physiological Testing Bridge the Gap Between Chest Pain and Nonobstructive Coronary Atherosclerosis?*

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Evaluation of chest pain can be one of the most challenging scenarios faced by cardiologists. The differential diagnosis of chest pain includes myocardial ischemia and pericardial, musculoskeletal, gastrointestinal, pulmonary, or psychologically related syndromes. Our current diagnostic pathway includes the clinical history in the context of the cardiovascular risk factors, noninvasive stress testing, or computed tomography angiography, followed by invasive coronary angiography when these tests indicate significant ischemia. Yet 30% to 50% of patients who undergo angiography are found to have nonobstructive epicardial disease (1). This high rate of nonobstructive disease seen on angiography is often attributed to false-positive stress test results and is sometimes considered a failure of our clinical processes. For some patients, the "negative" angiography allows reassurance and pursuit of nonischemic causes of chest pain. Other patients with persistent chest pain and nonobstructive disease frequently present to emergency departments, requiring recurrent evaluation.

Among patients with persistent chest pain and nonobstructive disease, those with compelling clinical syndromes may have underlying myocardial ischemia. Those with exercise-induced angina may have diffuse unappreciated epicardial atherosclerosis, myocardial bridging, coronary microvascular disease, or exercise-induced vasospasm (2,3). Patients with rest or mental stress–induced angina pain may have severe endothelial dysfunction or coronary vasospasm, and those with mixed chest pain syndromes may have any combination of these conditions. There is confusion over the nomenclature of these latter syndromes, which have been variably called syndrome X, vasospastic angina, variant angina, Prinzmetal angina, microvascular angina, endothelial dysfunction, and coronary microvascular disease. Although the diagnosis and management of these patients are often difficult for patient and physician, an accurate diagnosis can be extremely important to definitively exclude identifiable ischemic disease or, conversely, to vindicate the patient's symptoms when pathology is identified and help guide medical therapy.

So where are we with advanced functional or physiological testing for the diagnosis of coronary microvascular and endothelial dysfunction in 2015? Advances in our understanding of the vascular biology of coronary atherosclerosis and physiology, in concert with technological advances in our equipment, have been leveraged to develop new diagnostic tests. Noninvasive imaging techniques, including cardiac magnetic resonance imaging, cardiac positron emission tomography, single-photon emission computed tomography, and contrast echocardiography, can provide an aggregate of baseline and hyperemic flow within the myocardial bed; however, only invasive diagnostic testing can tease out the

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relative contribution of endothelium-dependent and endothelium-independent pathways within the epicardial vessels and microvasculature. Hemodynamically significant unappreciated epicardial disease can be excluded by a fractional flow reserve >0.80, an instantaneous wave-free ratio >0.90, or hyperemic stenosis resistance <0.8 mm Hg/cm/s. Coronary flow reserve (CFR) <2.5 in the context of nonobstructive epicardial disease signifies reduced aggregate epicardial and microvascular flow. Novel indexes of microvascular function include the index of microcirculatory resistance and hyperemic microvascular resistance. To evaluate epicardial and microvascular endothelial dysfunction or coronary vasospasm, provocative testing using acetylcholine (off-label in the United States) or ergonovine (ergometrine may be an alternative in the United States) may be performed.

Because these patients have persistent symptoms, an adverse prognosis similar to those with obstructive disease require additional attention and experience, few specialized centers of advanced physiological testing have emerged for their management. Yet the literature supporting such testing is sparse (4).

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In this issue of *JACC: Cardiovascular Interventions*, Sara et al. (5) report on the largest experience of invasive microvascular and endothelial function testing in symptomatic patients with nonobstructive atherosclerosis to date. In total, 1,439 patients with nonobstructive angiographic disease (<40% diameter stenosis by angiography) underwent physiological testing over 20 years. All patients underwent evaluation of endothelium-dependent function using intracoronary acetylcholine infusions and endothelium-independent function using intracoronary bolus injections of adenosine. Impairment of endothelium-dependent microvascular function was defined as a maximal percentage increase in coronary blood flow in response to any dose of acetylcholine compared with baseline of ≤50%. Impaired endothelium-independent microvascular function was defined as a CFR of ≤2.5. Patients were divided into 4 groups: patients with *normal* microvascular function; patients with *abnormal* endothelium-dependent and *normal* endothelium-independent function; patients with *abnormal* endothelium-independent and *normal* endothelium-dependent function; and patients with both *abnormal* endothelium-dependent and endothelium-independent function. They found coronary microvascular abnormalities in 63.9%, with more female than male patients (65.7% vs. 60.4%, p = 0.043). However, after adjusting for other traditional cardiovascular risk factors, age was the only independent predictor of abnormal microvascular function. Aging is known to be associated with functional changes of the coronary microvasculature by reducing synthesis/release and increasing the breakdown of nitric oxide in the endothelium. Another interesting finding of this study is that the microvascular status of the patient correlated poorly with conventional cardiovascular risk factors and was dissociated from the findings of noninvasive functional testing. The authors conclude that their study supports the role of invasive coronary pharmacological provocation testing to comprehensively assess coronary microvascular function in patients with chest pain and nonobstructive coronary artery disease.

Several limitations of this study should be pointed out. First, the 63.9% incidence of physiological abnormality should be interpreted in light of the referral bias for advanced physiological testing and likely represents a selected group of patients. The authors provide limited data on the details of patient symptomatology. What percentage of patients had typical exertional angina, atypical angina, mental stress-induced chest pain, or noncardiac sounding chest pain? The true prevalence of microvascular or endothelial dysfunction among all patients with persistent chest pain and nonobstructive disease is likely <63.9%. One could evaluate this more accurately by performing invasive testing in consecutive patients with ischemic sounding chest pain and not selected patients as performed in this study. Second, only 24% of all study patients had documented myocardial ischemia. Although conventional stress testing may have limited diagnostic power in this population, recent advances in noninvasive assessment including measurement of CFR with positron emission tomography or cardiac magnetic resonance imaging, 6-lead ambulatory electrocardiographic monitoring, or a steepening of the heart rate-to-oxygen consumption ($V_{O_2}$) uptake slope on cardiopulmonary stress testing may provide evidence of myocardial ischemia. Other promising noninvasive tests include pulsatile arterial tonometry, forearm blood flow vasodilation studies, as well as some novel vascular biomarkers.

In this study, CFR was measured using intracoronary bolus injections and not intravenous or intracoronary infusion of adenosine, which is considered the gold standard. Both CFR and endothelial function are continuums, and any dichotomous cutoffs, albeit reasonable based on the limited available literature, are arbitrary. In addition, the

value of CFR and endothelial function reserve for every patient may vary over time. It is therefore difficult to interpret a single value without the context of the patient's baseline value. Few serial data exist on patient-specific changes in these measures with aging other than they likely deteriorate over time. Another methodological issue is that the potential role of endothelium-derived hyperpolarizing factor (EDHF) was not explored in this study. EDHF is believed to play an important role in the regulation of coronary blood flow and to have an important role, even when the nitric oxide pathway is impaired. Endothelial vasodilator functions are heterogeneous depending on the vessel size, with a relatively greater role of nitric oxide in conduit arteries and a predominant role of EDHF in resistance arteries (6). Finally, this investigation would have been strengthened by providing serum biomarker or intravascular imaging data linking symptoms to physiological response in the cath lab. Clearly, prospectively relating these biological responses in the cath lab to clinical outcomes is necessary.

Nevertheless, this study represents a detailed and comprehensive evaluation of a large number of patients undergoing detailed invasive physiological testing by experienced investigators and clinicians. The paper makes an important contribution to our understanding of the substantial prevalence and predictors of coronary microvascular and endothelial dysfunction. The lack of correlation with cardiovascular risk factors and noninvasive stress testing underscores the value of invasive physiological testing in appropriately selected patients. Large multicenter registries with prospectively collected clinical, biochemical, genetic, and invasive physiological data are warranted to further our understanding of this challenging patient population. Functional coronary angiography will likely have an integral role in the diagnosis of patients with chest pain and nonobstructive coronary atherosclerosis.

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**KEY WORDS** coronary microvascular dysfunction, coronary nonobstructive disease, endothelial dysfunction, nonobstructive coronary artery disease