

Review Article

Women's Heart Disease: A Review of the Current Testing Modalities for Coronary Microvascular Dysfunction

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California, Irvine, Orange, USA**Received:** March 17, 2015; **Accepted:** September 10,
2015; **Published:** September 25, 2015**Abstract**

Up to 40% of female patients with chest pain syndromes are found to have non-obstructive coronary artery disease. Of these patients, studies have shown, an increase risk of poor cardiovascular outcomes, adverse prognosis and increased mortality. Coronary microvascular dysfunction has been proposed as the etiology to explain such symptoms and increased risks, especially in the female population. Several non-invasive and invasive techniques of assessing coronary microvascular dysfunction have been studied and have been shown to be safe. The use of coronary microvascular dysfunction testing in the cardiac catheterization laboratory by measuring coronary flow reserve (CFR) has been proven to be both sensitive and specific measure for microvascular disease, although it is not used on routine basis. This review of the literature describes the various microvascular disease testing available in current practice (especially in the female population). Such testing includes various protocols used in the cardiac catheterization lab to measure CFR. CFR, defined as the ratio of maximal coronary flow with hyperemia to baseline flow can be a routine testing modality in the cardiac catheterization laboratory. These types of protocols play an important component in the diagnosis of coronary microvascular dysfunction, and can be a routine testing protocol in cath labs that are willing to embrace such testing modalities.

Keywords: Heart disease; Microvascular disease; CFR; Microvascular dysfunction

Introduction

Coronary physiology dictates that coronary arterial vessels constantly adapt through vasomotor tone in response to changes in myocardial oxygen demand [1]. Lack of this ability to adapt to increasing myocardial oxygen requirements results in a mismatch between myocardial oxygen supply and demand, and can sometimes lead to myocardial ischemia. To prevent such ischemia the coronary arterial tree has blood flow reserve. This coronary blood flow reserve is defined as increase in blood flow in response to metabolic or pharmacological stimulations. Normal coronary blood flow reserve increases 2.5-5 fold in response to increases in oxygen demands [1].

In order to evaluate chest pain syndromes many patients undergo coronary angiogram in order to investigate for coronary artery disease. Patel et al, found that 39.2% of a study population of almost 400,000 patients, to have normal angiograms defined by <20% stenosis in coronary artery vessels. This study population was comprised of 47.3 % females. The percentage of patients who were female with obstructive coronary artery disease and non-obstructive coronary disease were 33.9% and 55.4% respectively [2]. Of these patients, studies have shown, women with impaired glucose tolerance or diabetes presenting with angina, regardless of angiographic findings, were found to have increased mortality [3]. The National Heart, Lung, and Blood Institute sponsored WISE (Women's Ischemic Syndrome Evaluation) has shown that of symptomatic women (with normal angiograms after abnormal cardiac stress testing), up to one half have no obstructive coronary artery disease [4]. As a follow up to the WISE study population, Johnson et al found women with

persistent chest pain with non-obstructive coronary artery disease predicted adverse cardiovascular outcomes [5]. Therefore, suggesting that undiagnosed disease likely contributes to anginal symptoms, adverse outcomes and mortality despite non-obstructive coronary artery disease by angiogram. Review of different methods to evaluate coronary flow reserve, concluded a reduction in coronary blood flow reserve in absence of obstructive flow-limiting coronary stenosis suggests vascular dysfunction as etiology of chest pain syndromes [6].

In 1985, Cannon and Epstein introduced a concept of "microvascular angina". They proposed small vessel dysfunction might play a role in pathogenesis leading to chest pain syndromes [7]. Further studies have shown both coronary artery spasm and endothelial dysfunction to be predictors of morbidity and mortality in patients with angina [8, 9],

The combination of these findings led to several studies to evaluate the possibility of microvascular disease in symptomatic women with normal coronary arteries disease. In addition to microvascular disease as a diagnosis for angina in women with normal coronary anatomy, microvascular disease has been shown to be possibly present in patients diagnosed with takotsubo cardiomyopathy [10]. The distinction of cause-and-effect relationship has not be proven, alternative theories of microcirculation abnormalities as a result of wall stress from apical ballooning have been suggested [11].

Microvascular Disease Testing

Over a 20-year period several invasive and non-invasive techniques have been used for assessment of coronary microvascular

dysfunction specifically with respect to impaired coronary blood flow reserve.

Coronary blood flow is regulated by different factors influencing both macrovascular and microvascular vasomotor tone. These include endothelium-dependent and independent factors [1]. The endothelium regulates vasomotor tone by stimulating release of vasoactive factors, specifically, nitric oxide, originally identified as endothelium-derived relaxing factor [12]. Various techniques have been used to replicate or simulate vasomotor tone in an effort to evaluate for microvascular dysfunction as a function of reduction of coronary flow reserve.

Useful non-invasive methods for diagnosis microvascular dysfunction as a reduction in coronary flow reserve include using positron emission tomography [13], cardiac magnetic resonance [14] and transthoracic Doppler echocardiography [15]. Invasive coronary vasomotor testing as shown by Wei et al, involves macrovascular and microvascular evaluation with both endothelium dependent and independent tests involving intracoronary injections of adenosine, acetylcholine and nitroglycerine [16]. Currently, invasive coronary vasomotor testing with acetylcholine remains the gold standard for diagnosis of coronary microvascular dysfunction with a well-described risk and benefit record [9, 16]. Furthermore, patients with a diagnosis of microvascular dysfunction are at increased risk for adverse outcomes over time [16].

Coffman and Gregg, in 1960, first introduced the idea of coronary arterial reactive hyperemia, which serves as the basis for many of these tests [17]. It has been established that vasodilator responses to acetylcholine occurs in normal coronary arteries through the release of endothelium-derived relaxing factors including nitric oxide [18]. Paradoxically the response was reversed to constriction of vessels in patients with evidence of coronary artery disease [19]. Intracoronary acetylcholine is considered the gold standard for detection of coronary endothelial function [20]. The safety of using intracoronary acetylcholine for the purpose of diagnosing microvascular disease has shown to have few adverse effects [9]. Most of these reactions were related to the effects of acetylcholine's paradoxical constriction and spasm of the coronary arteries. Sueda et al showed 1.7% major adverse reaction out of 1000 patients tested, these ranged from non-sustained ventricular tachycardia, ventricular fibrillation, shock and cardiac tamponade [21]. Ong et al, in 2008, showed 86 patients with acute coronary syndrome, who underwent intracoronary acetylcholine infusion, had no adverse events documented [9]. As a result, many studies follow doses of acetylcholine with nitroglycerine to ensure dilatation of these vessels post vasoreactivity testing. The clinical measures for diagnosis of microvascular dysfunction following intracoronary acetylcholine have included coronary diameter reduction as well as coronary blood flow measurements derived from Doppler peak velocities.

Doppler of peak velocity with regards to coronary blood flow was evaluated post acetylcholine infusion using flow and pressure measurements using Doppler flow wires. Coronary blood flow changes < 50% at highest dose of acetylcholine was defined as an abnormal test result suggesting endothelial-dependent microvascular disease. This was followed by measurements of coronary artery dilation as a function of Doppler-derived velocity defined by

< 5% changes as abnormal suggesting endothelial-dependent macrovascular disease. Coronary flow reserve (CFR) is defined as the ratio of maximal coronary flow with hyperemia to baseline flow. CFR tests the ability of epicardial stenosis and microcirculatory resistance to maintain flow. In the WISE study, 159 women with chest pain and non-obstructive coronary artery disease a coronary reserve velocity of 2.24 provided a 90% sensitivity and 89% specificity for the diagnosis of microvascular dysfunction based on a CFR of < 2.516.

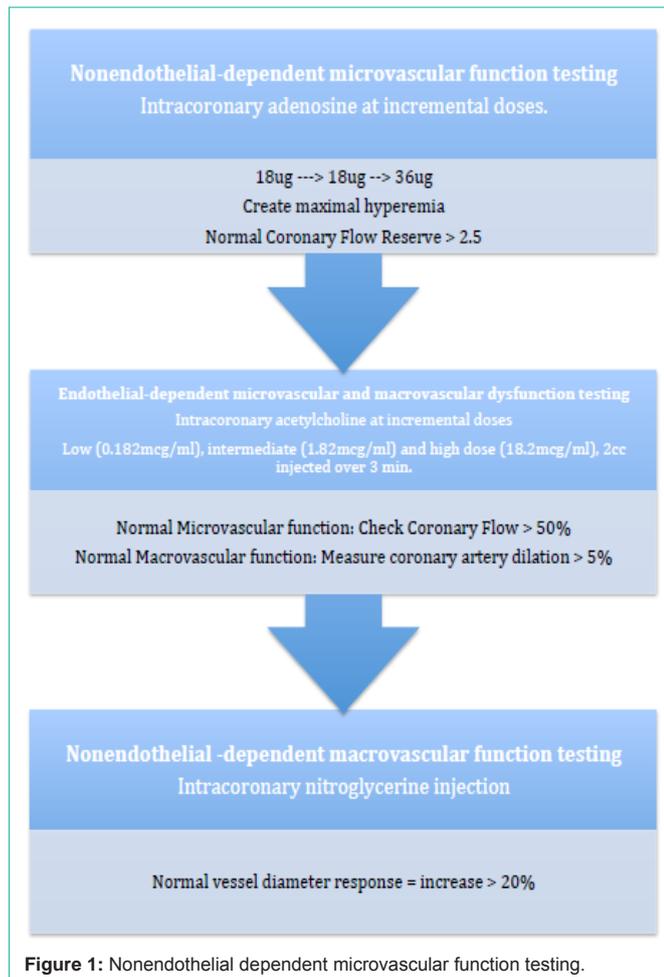
Discussion

Evaluation of patient with chest pain syndromes typically involves possible stress test evaluation with definitive diagnosis of coronary artery disease by coronary angiogram to evaluate for obstructive macrovascular disease. Up to 40% of these patients have normal angiograms however this same subset has been shown to have higher risk for adverse cardiac events despite a normal angiogram [2-4]. These patients are told they have normal coronary arteries and advised further evaluation for non-cardiac etiologies for their symptoms.

Invasive testing to measure microvascular dysfunction includes CFR testing in the cath lab using intracoronary acetylcholine, adenosine and nitroglycerine. Coronary arterial blood flow velocity and coronary flow reserve are assessed using a 0.014-inch Doppler coronary wire with a piezoelectric ultrasound transducer at the wire tip to determine volumetric flow. The position of the Doppler sensor is in the proximal to mid portion of the vessel and manipulated until an optimal and stable blood flow velocity signal is obtained. The sensors are positioned at the same location for all measurements obtained throughout the procedure. Coronary flow reserve relates to the ability, in response to oxygen demands, of coronary vessels to increase blood flow to supply myocardium [22]. It is a ratio of maximal coronary blood flow to resting coronary blood flow. Bradley et al described the use of intracoronary Doppler flow meters to measure coronary blood flow velocity, which is proportional to flow [23]. Coronary flow reserve can be calculated as the ratio of resting compared to maximal blood flow velocity with the assumption that the cross sectional area of vessel remains constant between measurement.

The institutional use of IC acetylcholine requires a team effort from physicians, nurses and pharmacy staff. Our own protocol, modeled from Wei et al, uses intracoronary adenosine is administered to create maximal hyperemia with incremental doses of 18 micrograms, 18 micrograms then 36 micrograms. Intracoronary acetylcholine was prepared by the pharmacy 4 hours prior to the procedure following a specific dilution protocol [16]. The dosing protocol consisted of low, intermediate and high doses defined as 0.182mcg/ml, 1.82mcg/ml and 18.2mcg/ml respectively. Each dose is infused for a total of 2ml over 3 minutes using a syringe pump (Figure 1). Each dose is infused for a total of 2ml over 3 minutes using a syringe pump. Coronary Flow Reserve (CFR) is then measured using a 0.014-inch Doppler coronary wire. Using a CFR velocity of < 2.50 provides a 90% sensitivity and 89% specificity for the diagnosis of microvascular dysfunction [16].

Non-invasive methods for diagnosis microvascular dysfunction as a reduction in coronary flow reserve include using positron emission tomography [12], cardiac magnetic resonance [24], and transthoracic Doppler echocardiography [14]. We have also introduced these



methods into our patient care practices, and use this testing in conjunction to more invasive testing. The use of transthoracic Doppler echocardiography for assessment of measured velocities under hyperemic conditions of adenosine infusion has been used to evaluate for microvascular dysfunction. Using the short-axis view of the left ventricle, diastolic flow can be examined in the anterior groove. Under color Doppler flow mapping, using second harmonic technology, one can identify the distal left anterior descending artery [25]. Bartel et al, found the echocardiographic model comparable to the invasive measurements for microvascular dysfunction assessment [26]. Using an optimal cut off point for coronary flow velocity reserve of 2.84 cm/s they found a sensitivity of 80% and specificity of 88%. This matched previous study data of coronary flow velocity reserve sensitivity and specificity for detection of coronary artery disease [27].

Magnetic resonance myocardial perfusion imaging has been reported to have similar specificity and sensitivity in detecting obstructive CAD compared to conventional radionuclide imaging [24]. Several papers have suggested the utility of Magnetic resonance myocardial perfusion imaging for detection of microvascular dysfunction, however these have been small study populations and sensitivity and specificity data is not available at this time.

Office based testing includes endothelial vasodilator function testing using ENDO-PAT 2000 [28]. This is based on testing done

by Gould et al with regards to simulated hyperemia by restriction of maximal flow by temporary occlusion to an artery [22]. Though several methods have been evaluated to diagnose microvascular disease, as mentioned previously the use of intracoronary acetylcholine has proven to be a safe option for evaluation in the cardiac catheterization laboratory. In the follow up to the WISE study, they found in 159 women with chest pain and non-obstructive coronary artery disease, microvascular dysfunction in one-half of the patients on the basis of reduced coronary flow reserve velocities. They found that a coronary reserve velocity of 2.24 provided a 90% sensitivity and 89% specificity for the diagnosis of microvascular dysfunction based on a CFR of < 2.516.

Summary

It is important that we do not overlook the patient population with microvascular dysfunction (especially women), as they have been shown to have higher risk for adverse events and mortality. Through routine testing with coronary angiography bundled with coronary microvascular dysfunction testing, we can give these patients an accurate diagnosis and appropriate management to prevent long-term adverse outcomes. Using CFR testing with a 0.014-inch Doppler coronary wire to determine volumetric flow, any (CFR) velocity measurement of < 2.50 provides a 90% sensitivity and 89% specificity for the diagnosis of microvascular dysfunction. This protocol has been an important component in the development of our Women's Heart Disease Program, and plays an important role in the diagnosis of coronary microvascular disease. Ultimately, through routine CFR testing for coronary microvascular dysfunction, we can change management for patients with chest pain syndromes for both symptom relief as well as improved outcomes.

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