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Current Diagnostic and Therapeutic Strategies in Microvascular Angina

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Abstract

Microvascular angina is common among patients with signs and symptoms of acute coronary syndrome and is associated with an increased risk of cardiovascular and cerebrovascular events. Unfortunately, microvascular is often under-recognized in clinical settings. The diagnosis of microvascular angina relies on assessment of the functional status of the coronary microvasculature. Invasive strategies include acetylcholine provocation, intracoronary Doppler ultrasound, and intracoronary thermodilution; noninvasive strategies include cardiac positron emission tomography (PET), cardiac magnetic resonance, and Doppler echocardiography. Once the diagnosis of microvascular angina is established, treatment is focused on improving symptoms and reducing future risk of cardiovascular and cerebrovascular events. Pharmacologic options and lifestyle modifications for patients with microvascular angina are similar to those for patients with coronary artery disease.

Keywords

Microvascular angina; Cardiac syndrome X

Introduction

Acute coronary syndromes account for over one million hospital admissions each year in the United States.[1] Coronary angiography, considered the “gold standard” to diagnose and treat patients with acute coronary syndromes, evaluates for obstructive disease in the coronary macrovasculature. While myocardial ischemia is often caused by obstruction of coronary blood flow in the macrovasculature, it can also be caused by abnormalities in the microvasculature. A substantial proportion of patients with signs and symptoms of myocardial ischemia who undergo coronary angiography do not have obstructive disease,

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with estimates ranging from 14% to ~40%.[2-6] and an even higher proportion have microvascular spasm that is likely the source of their symptoms.[7-9] This microvascular dysfunction is present in both sexes but more common in women.[7, 10-12]

Microvascular angina is one type of coronary microvascular dysfunction that is broadly defined as angina or angina-equivalent with coronary angiography showing no coronary artery stenosis >50%. While several diagnostic criteria have been proposed, most criteria include the following elements.[13-15]

- Exertional angina or angina equivalent
- Cardiac stress test positive for myocardial ischemia
- Normal coronary angiography (no coronary artery stenosis >50%)
- Absence of coronary artery spasm

Microvascular angina is characterized by abnormal coronary vasodilation[8, 16-18] and impaired coronary flow reserve[13] due to endothelial dysfunction. It carries a poor prognosis with regards to both mortality and morbidity, and the severity of microvascular disease correlates with both cardiovascular and cerebrovascular adverse events.[12, 19-28] Despite the frequency and significance of microvascular angina, this condition is under-recognized in clinical practice.[9] Early identification and treatment of patients with microvascular angina is important for reducing morbidity and mortality.[10, 29] This review focuses on the diagnostic and therapeutic strategies for patients with suspected microvascular angina.

Clinical Features

Patients with microvascular angina may present with symptoms similar to those of typical angina due to macrovascular disease. Risk factors for microvascular angina are similar to those for other cardiovascular diseases and include diabetes, hypertension, hyperlipidemia, obesity, and tobacco use.[14, 18, 30, 31] Microvascular angina is more common in women than men.[7, 10, 11] Clinical features that may aid in the diagnosis include angina at rest, angina that lingers after cessation of exercise, and angina that does not respond or worsens with short-acting nitrates during exercise or stress testing.[11, 14, 32, 33] In the setting of exertional angina or angina equivalent with normal coronary angiography and no epicardial coronary artery spasm, abnormal myocardial blood flow and/or coronary blood flow are strongly suggestive of microvascular angina.

Laboratory Testing

Patients who present with angina or angina equivalents should initially receive cardiac troponin testing to evaluate for myocardial infarction. [34] Additional laboratory testing to evaluate for other causes of the patient's symptoms should be performed at the discretion of the treating physician. No specific laboratory tests for the diagnosis of microvascular angina exist. Elevations in C-reactive protein and other inflammatory markers are more frequently present in patients with microvascular angina than in controls.[35-37] However, these elevations are nonspecific and cannot be used to confirm or rule out microvascular angina. A

suggested approach to patients with suspected acute coronary syndrome is shown in Figure 1.

Diagnostic Imaging

Due to the small size of the microvasculature, it cannot be directly visualized *in vivo* using current imaging techniques. Accordingly, the diagnosis of microvascular angina relies on assessment of the functional status of the coronary microvasculature. Evaluation for evidence of myocardial ischemia and calculation of parameters that reflect vasodilator function are the two primary approaches to assessing the functional status of the coronary microvasculature.[14] Myocardial blood flow (MBF) or coronary flow reserve (CFR), parameters that reflect the functional status of the coronary circulation,[38] are commonly used in the diagnosis of microvascular angina. Myocardial blood flow is defined as blood flow per gram of myocardium, with values less than 2.0 mL/min/g considered abnormal.[39] Coronary flow reserve, also termed myocardial flow reserve, reflects the vasodilator response of the microvasculature. It can be measured following pharmacologic or nonpharmacologic vasodilation. It is expressed as the ratio of near- maximal myocardial blood flow to resting myocardial blood flow, with ratios less than 2.0-2.5 considered to be abnormal and associated with increased morbidity and mortality.[12, 18, 20, 21, 28, 40, 41] Both invasive and noninvasive diagnostic tests can measure coronary flow reserve and aid in establishing the diagnosis of microvascular angina (Table 1).

Both invasive and noninvasive tests require use of a pharmacologic or nonpharmacologic vasodilator to induce maximal hyperemia. The most commonly used pharmacologic agents include adenosine, dipyridamole, acetylcholine, and dobutamine. The normal response of the coronary vasculature to these agents is three- to fivefold vasodilation.[31, 42] Adenosine elicits endothelium-independent vasodilation. It acts primarily via α_2 receptors to increase cyclic adenosine monophosphate (cAMP), which inhibits calcium uptake to cause smooth muscle relaxation and vasodilation. Adenosine also acts via the α_1 receptors to increase cyclic guanosine monophosphate (cGMP) production and cause vasodilation. Dipyridamole inhibits the intracellular reuptake of adenosine, increasing the adenosine concentration and its downstream actions described above. While commonly used, it is less efficacious than adenosine.[43] Acetylcholine elicits endothelium-dependent vasodilation.[44] It activates cholinergic receptors to release endothelium-derived relaxing factors and produce vasodilation.[45] Dobutamine is a β_1 receptor agonist that increases cardiac contractility and myocardial oxygen demand.

The cold pressor test is an alternative to pharmacologic stress to assess endothelial function. In this test, the patient's hand is submerged in ice water for approximately one minute, which triggers a systemic sympathetic activation and subsequent vasoconstriction, increased heart rate, and increased blood pressure. The cold pressor test is a feasible and reliable alternative to pharmacologic stress.[46]

Invasive Diagnostic Imaging

Coronary vasomotor testing is considered the invasive “gold standard” for diagnosing microvascular dysfunction.[30, 42] In this procedure, increasing doses of acetylcholine are

infused into the left coronary artery during continuous electrocardiogram recording.[7-9, 17, 47, 48] Coronary microvascular dysfunction is diagnosed when the electrocardiogram shows ischemic changes and/or the patient experiences angina without epicardial coronary artery constriction 75%.[7-9, 17, 47, 48] Acetylcholine-induced microvascular spasm has been associated with increases in myocardial lactate production.[17] More recently, it has been associated with both changes in left ventricular function on echocardiography and elevations in ultra-sensitive troponin, providing direct evidence that microvascular spasm causes myocardial ischemia and angina.[47] Coronary vasomotor testing is not widely used in clinical practice, partly due to concerns regarding its safety. However, a recent study of 921 patients undergoing coronary vasomotor testing showed that acetylcholine administration has a complication rate of one percent. The most common complication was sinus bradycardia, and no serious or fatal complications occurred.[7]

Intracoronary Doppler ultrasound, performed during cardiac catheterization, can be used to measure both absolute myocardial blood flow and coronary flow reserve. In this procedure, a miniature, tip-mounted piezoelectric ultrasound transducer with a forward-directed ultrasound beam is inserted into the coronary arteries.[49] The Doppler flow velocity spectra are analyzed, and coronary blood flow is typically calculated as the vascular cross-sectional area $\times$ average peak velocity $\times$ 0.5.[20, 42] Average coronary flow velocity and the time-velocity interval can also be used to calculate coronary blood flow.[31] Coronary flow reserve is calculated from coronary blood flow measurements at baseline and during maximal hyperemia. Adenosine and acetylcholine can be used to elicit a vasodilator response.[44, 49] Incorrect position of the Doppler wire and tortuous coronary anatomy can compromise myocardial blood flow measurements.[50] Several studies have used intracoronary Doppler ultrasound to measure coronary flow reserve and characterize microvascular function in patients with suspected myocardial ischemia.[18, 20, 21]

Intracoronary thermodilution involves the use of an intracoronary wire with a proximal temperature sensor along the wire and a distal temperature sensor at its tip.[51-53] The mean transit time for a cold saline bolus to travel from the proximal to distal temperature sensors is measured at rest and during maximal hyperemia. These data are used to calculate coronary blood flow in these two states and to determine coronary flow reserve.[51, 54] In animal and human studies, coronary flow reserve derived by thermodilution correlates with that derived by Doppler ultrasound.[51, 52] An index of microcirculatory resistance, defined as the product of distal coronary pressure and transit time at maximal hyperemia, can also be calculated using a coronary wire with both pressure and temperature sensors.[53] The index of microcirculatory resistance appears to have lower variability and higher reproducibility than coronary flow reserve because it is less affected by hemodynamic parameters.[55] It also reflects microvascular function better than coronary flow reserve because it is not affected by epicardial stenosis.[53] Microcirculatory resistance also correlates with severity of ischemia measured by the Duke treadmill score.[54]

Noninvasive Diagnostic Imaging

Cardiac positron emission tomography (PET) is considered the noninvasive “gold standard” for quantifying myocardial perfusion.[31] Following infusion of a radiolabeled

tracer, resting images are obtained using dynamic PET. Sufficient time for decay of the tracer is allowed, and the same procedure is repeated following administration of a vasodilator agent for the stress images. The images capture the extraction of the tracer from the circulation into the ventricular myocardium.[56] The images are reconstructed using one of several software programs that use time-activity curves to estimate myocardial blood flow and coronary flow reserve.[28, 56-58] During analysis, the myocardium can be divided into segments to allow for the calculation of regional myocardial blood flow in addition to global myocardial blood flow.[59] Adenosine,[28] dobutamine,[60] dipyridamole,[58, 61] and the cold pressor test have been successfully used with cardiac PET.

Tracers used with cardiac PET to quantify myocardial blood flow include ammonia (^{13}N -ammonia), rubidium ($^{82}\text{rubidium}$), and water (^{15}O -water). While ^{15}O -water and ^{13}N -ammonia have been well-studied, their use is limited to facilities with an on-site cyclotron. In contrast, $^{82}\text{rubidium}$ is produced by a generator and does not require an on-site cyclotron. $^{82}\text{Rubidium}$ has been validated against both ^{15}O -water and ^{13}N -ammonia for the quantification of myocardial blood flow and shown to be reproducible.[57-59] $^{82}\text{Rubidium}$ has a much shorter half-life than the other two agents.[62] This short half-life limits acquisition time and creates a high signal to noise ratio in the resulting images, but it also allows both rest and stress images to be obtained in a timely fashion and makes $^{82}\text{rubidium}$ attractive for clinical use.[63]

Cardiac magnetic resonance imaging can be used to characterize myocardial perfusion semi-quantitatively. In this technique, the upslopes of myocardial signal intensity curves from contrast-enhanced magnetic resonance first pass T1-weighted images are used to calculate an index of myocardial perfusion in several myocardial regions. Myocardial perfusion is calculated both at rest and following vasodilator stress. As with other tests, both adenosine and acetylcholine are commonly used to induce hyperemia. The ratio of these two measurements is the myocardial perfusion reserve index.[44, 64-66] Myocardial perfusion reserve index can be calculated separately for subendocardial and subepicardial myocardial layers[64-67] but can be limited by subendocardial image artifacts.[38] Myocardial perfusion reserve index is reproducible[65, 68] and correlates with coronary flow reserve measured by intracoronary Doppler ultrasound, suggesting that it is an adequate measure of microvascular function.[44] Because of its reproducibility and noninvasive nature, cardiac magnetic resonance imaging has been used to measure response to treatment for microvascular angina.[67]

Transthoracic and transesophageal **Doppler echocardiography** can also be used to calculate coronary flow reserve to aid in the diagnosis of microvascular angina. Following administration of intravenous echocardiography contrast, color Doppler is used to measure coronary blood velocity in the left anterior descending artery before and after a vasodilator infusion.[69-71] Dipyridamole,[69, 72-75] dobutamine,[71, 76] and adenosine[70, 77] can be used to elicit vasodilation during Doppler echocardiography. Blood flow velocity is used as a surrogate for coronary blood flow in the calculation of coronary flow reserve.[69, 71, 72] Coronary flow reserve determined by Doppler echocardiography correlates with that determined by both intracoronary Doppler ultrasound[69] and positron emission tomography.[72] Lower coronary flow reserve values have also been correlated with

myocardial perfusion deficits on cardiac magnetic resonance.[70] Advantages of Doppler echocardiography include its relatively low cost, its noninvasive approach, its lack of radiation exposure, and its availability.[78] Additionally, it can be performed during standard dobutamine stress echocardiography.[71, 76] As with standard echocardiography, image quality depends upon the operator's skill and the patient's body habitus.

Therapeutic Strategies

Primary goals of therapy are to improve quality of life through symptom control and to improve prognosis.[13, 15] Lifestyle modifications for microvascular angina are similar to those for coronary artery disease, as these diseases have similar risk factors and microvascular angina may be an early form of coronary artery disease.[6, 62] Recommendations include tobacco cessation, dietary modification, weight loss if overweight, alcohol in moderation, and physical activity as symptoms allow.[15] A cardiac rehabilitation program has been shown to improve symptoms, psychological well-being, and cardiovascular risk factors in women with microvascular angina.[79, 80]

Pharmacologic agents recommended for microvascular angina are also similar to those used in coronary artery disease. Beta blockers, particularly nebivolol, have been shown to improve markers of microvascular angina disease severity in laboratory and exercise stress test assessments.[81-83] Calcium channel blockers have also been associated improvement in microvascular angina symptoms,[10] and combination therapy with a statin appears to have greater benefit than monotherapy with either agent for improving coronary flow reserve, laboratory markers, and evidence of ischemia during stress testing.[84] Given their benefits in coronary artery disease, angiotensin-converting enzyme (ACE) inhibitors have been recommended for microvascular angina. They have been associated with improvements in both symptoms and coronary flow reserve in this population.[85] Nitrates are commonly used to relieve angina in coronary artery disease, but they may be less beneficial in microvascular angina[33] as they exert their vasodilatory effects primarily in vessels larger than 200 micrometers.[86] Ranolazine is an alternative anti-anginal agent that has been shown to improve both angina symptoms and coronary flow reserve in microvascular angina.[67, 73] Last, a randomized, controlled trial of udenafil, a phosphodiesterase-5 inhibitor, to reduce symptoms and improve ischemia in women with microvascular angina is underway.[87]

Conclusions

Clinicians should strongly consider microvascular angina in patients with exertional angina or angina equivalent with normal coronary angiography and no epicardial coronary artery spasm, particularly if they have cardiac risk factors or other features suggestive of microvascular angina. In this setting, treatment should be initiated to improve patients' symptoms and to reduce their risk of future cardiovascular events. Most diagnostic tests have limited availability, and their sensitivity and specificity for microvascular angina are not well established. Routine use of invasive tests to confirm the diagnosis of microvascular is not recommended. However, in patients who are undergoing invasive or noninvasive cardiac studies as part of their evaluation, clinicians should strongly consider assessing

coronary flow reserve during this study. Similarly, clinicians should consider assessing coronary flow reserve in patients in whom diagnostic uncertainty persists. In addition to aiding in the diagnosis of microvascular angina, these measurements add incremental prognostic value and can serve as a baseline for assessing patients' response to treatment.

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Figure 1.

Suggested approach to patients with possible acute coronary syndrome.

Table 1

Summary of diagnostic imaging tests for microvascular angina.

Test	Invasiveness	Assessment	Benefits	Limitations
Acetylcholine provocation	Invasive	ECG changes or angina	Can be performed during cardiac catheterization	1% complication rate from acetylcholine infusion
Intracoronary ultrasound	Invasive	Coronary flow reserve	Can be performed during cardiac catheterization	Inproper wire position or tortuous coronary anatomy may compromise results
Intracoronary thermodilution	Invasive	Coronary flow reserve or index of microcirculatory resistance	Can be performed during cardiac catheterization; Index of microvascular resistance less affected by hemodynamic parameters and epicardial stenosis than coronary flow reserve	Requires use of specialized wire with temperature and pressure sensors
Cardiac PET	Noninvasive	Coronary flow reserve	Both regional and global myocardial blood flow can be calculated	Requires cyclotron or generator to produce radiolabeled tracer
Cardiac MR	Noninvasive	Myocardial perfusion reserve index	Myocardial perfusion reserve index can be calculated separately for subendocardial and subepicardial layers	Artifact may compromise results
Doppler echocardiography	Noninvasive	Coronary flow reserve	Echocardiography is widely available	Image quality dependent upon operator skill and patient body habitus

PET = Positron emission tomography; MR = Magnetic resonance; ECG = Electrocardiogram