DOI: https://doi.org/10.24297/jab.v16i.95469546

When Microvasculature Rules: microvascular assessment in invasive coronary angiogram

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Abstract

Patients with symptoms of ischaemia without obstructive coronary artery disease present a diagnostic and therapeutic challenge. Microvascular angina (MVA) was called before syndrome X. Invasive coronary angiography used commonly to assess those patients. This article provides a common pathway to diagnose MVA using different invasive and non-invasive tests. In addition, it provides insights for treatment and management of patients in this common clinical scenario.

Keywords

MVA**:** microvascular angina

IHD: ischemic heart disease

CMD: coronary microvascular dysfunction

CFR: coronary flow reserve

CAD: coronary artery disease

VSA: vasospastic angina

ECG: electrocardiogram

ACS: acute coronary syndrome

MBF: myocardial blood flow

MPR: myocardial perfusion reserve

PET**:** Positron emission tomography

LAD: left anterior descending artery

FFR: fractional flow reserve

LCA: left coronary arteries

RCA: right coronary artery

CFVs: coronary flow velocities

IMR: index of microvascular resistance

INOCA: ischaemia with non-obstructive coronary arteries

ASCVD: atherosclerotic cardiovascular disease.

GTN: glyceryl trinitrate.

Introduction

Angina is the most common presenting symptom of ischemic heart disease (IHD) which affects approximately 112 million people globally (1). According to the American College of Cardiology (ACC) and American Heart Association (AHA) 2021

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guidelines for coronary revascularization, the definition of significant coronary artery stenosis is an estimated diameter stenosis severity of 70% for non-left main disease and 50% for left main disease (1).

Invasive coronary angiography is the gold standard of care in patients with angina who are not responsive to medical therapy – however up to 70% of patients undergoing invasive coronary angiography have non-obstructive coronary arteries or insignificant coronary stenosis and most of them are women (2). In addition, almost 40% of patients referred for evaluation of anginal symptoms and evidence of myocardial ischemia on non-invasive testing have angiographically normal coronary arteries or mild atherosclerotic disease (3)(4)(5). This was previously named as syndrome X; however, it is now called microvascular angina to reflect the underlying pathogenesis of coronary microvascular dysfunction (CMD), an abnormal vasodilatory capacity or intense vasoconstriction affecting smaller coronary arteries. CMD is characterized by reduced coronary flow reserve (CFR), microvascular spasm, and/or coronary endothelial dysfunction. CFR refers to the magnitude of increase in coronary flow (per unit of time) that can be achieved between basal coronary perfusion to maximum coronary vasodilation. It is expressed as the ratio of blood flow during hyperaemia to blood flow at rest (6).

- **Microvascular angina (MVA):** is the clinical disease of coronary microvascular dysfunction which is described in patients who have angina with evidence of ischaemia in non-invasive tests and normal or mild disease in coronary angiogram (2)(7). It can be subdivided to:

1. **Primary MVA: r**efers to MVA in the absence of any underlying cardiac risk factors like diabetes or HTN. Microvascular vasoconstriction is included in this category.
2. **Secondary MVA** – Refers to MVA secondary to coexisting conditions such as hypertension or diastolic dysfunction (6).

The Coronary Vasomotion Disorders International Study Group (COVADIS) has proposed the following clinical criteria for suspecting MVA (definitive MVA diagnosed if all four criteria are present):

- Symptoms of myocardial ischemia. Effort and/or rest angina or angina equivalent.
- Objective evidence of myocardial ischemia. Ischemic ECG changes during an episode of chest pain, stress-induced chest pain, and/or ischemic ECG changes, and/or presence of transient/reversible abnormal myocardial perfusion or wall motion abnormality.
- Absence of obstructive coronary artery disease (CAD) (<50 percent stenosis or fractional flow reserve >0.8) by coronary computed tomography angiogram or invasive coronary angiography.
- Evidence of impaired coronary microvascular function:
  - Impaired coronary flow reserve (CFR) (<2 to <2.5).
  - Coronary microvascular vasoconstriction. Reproduction of symptoms; ischemic ECG changes but no epicardial vasospasm during acetylcholine testing.
  - Abnormal coronary microvascular resistance indices (eg, index of microcirculatory resistance >25).
  - Coronary slow flow phenomenon. TIMI frame count >25 (2)(3)(8).

Pathogenesis of Primary MVA

Angina in non-obstructive coronary artery disease is thought to be caused by a reduced ability to increase blood flow to meet the demand due to coronary microvascular dysfunction (CMD)(9)(10). Epicardial coronary spasm or vasospastic angina is part of ischemia with non- obstructive coronary arteries (INOCA) which can include epicardial or microvascular disease. The prevalence of Vasospastic angina (VSA) varies with ethnic origins: More prevalent in Japan (24%), 19% in Taiwan, and 5% in the USA. VSA is more common among men between the ages of 40 and 70 years old and decreases with age >70 years. Smoking is a risk factor for vasospastic angina, while diabetes and hypertension are not (11).

The focus here will be on microvasculature and MVA.

Microvascular **endothelial dysfunction** in the form of poor vasodilatation and or abnormal **vasoconstriction** are key disease mechanisms. Anxiety was shown to be associated with microvascular endothelial dysfunction as well (6).

Other possible mechanisms for primary MVA:

- **Viral illness:** presentation of MVA after a viral infection is a relatively common scenario.
- **Hormonal mechanisms** – there is a higher proportion of females, especially postmenopausal, this suggests hormonal mechanisms, possibly estrogen deficiency.

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- **Inflammation**
  - ★ In patients with MVA, biomarkers of systemic inflammation are related to lower coronary flow reserve (CFR).
  - ★ High sensitivity C-reactive protein correlates with a greater number of MVA symptoms and ECG changes.
  - ★ MVA is associated with inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis.
  - ★ Ectopic fat depots that exert paracrine inflammatory effects on adjacent tissues may be involved in MVA pathogenesis.
  - ★ Coronary microvascular dysfunction is associated with proinflammatory markers in women with MVA (6).

Pathogenesis of secondary MVA

Mechanisms for conditions that cause secondary MVA include the following:

Microembolization in acute coronary syndrome

In the initial event or with recanalization, there can be microembolization causing luminal obstruction.

Left ventricular hypertrophy (LVH) – Extramural compression can be present in conditions with LVH, such as aortic valve stenosis and arterial hypertension and hypertrophic cardiomyopathy. Abnormal CFR has been demonstrated in patients with left ventricular hypertrophy despite presence of angiographically normal coronary arteries. An imbalance between supply and demand is also an important determinant of myocardial ischemia in these patients (7)(11).

Heart failure with preserved ejection fraction (HFpEF) – The majority of patients with HFpEF have CMD and this most likely due to associated comorbidities in these patient categories.

Infiltrative heart disease

Deposition of amyloid material in the heart causes severely reduced CFR. Likewise, in Anderson-Fabry disease, where glycosphingolipid deposition leads to low CFR and MVA.

Rheumatologic disease

Both systemic lupus erythematosus and rheumatoid arthritis are more prevalent in patients with angina and coronary microvascular dysfunction.

Hyperalgesia Syndrome

Low pain threshold may cause severe chest pain with very mild evidence of ischaemia at the microvascular level. That might be due to decreased opioid level (6).

Epidemiology

Prevalence of MVA is around 40% in patients referred for invasive angiogram (3). The following demographic and clinical risk factors for MVA have been identified:

- **Younger age**

Patients with MVA are younger at the time of diagnosis (mean age 49 years) and are more often female than those with atherosclerotic cardiovascular disease in most series.

- **Female sex**

Coronary microvascular dysfunction (CMD) is present in 20 to 50 percent of females with chest pain and normal coronary arteries. Effects of fluctuating estrogen levels on epicardial vessels and arteriolar vasomotion have been postulated as explanations for a higher frequency of symptoms in premenopausal women without obstructive CAD (2).

- **Traditional cardiovascular risk factors**

These are found more often in patients with MVA than in the general population. Diabetes mellitus, smoking and hypercholesterolemia are often associated with microvascular disease (CMD) and reduction in CFR.

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- **Anxiety**

Among patients with anxiety, there was a higher prevalence of coronary endothelial dysfunction. After stratifying by sex, anxiety was related to coronary endothelial dysfunction in females but not in males (6).

Clinical Presentation

History

- **Angina characteristics** – Most often, patients present with a chronic pattern of recurrent episodes of chest pain on effort that is similar to classic angina pectoris and others (less commonly) with angina at rest suggestive of coronary artery spasm. Some patients have atypical chest pain that is interpreted to be noncardiac. In some patients, chest pain may be severe and debilitating to a point where it affects daily activities. The duration of chest pain episodes is often prolonged compared with that with effort angina. Some patients have dyspnoea on exertion as the only manifestation of microvascular angina(6).

There are four common clinical patterns of MVA that have different treatment approaches:

•Effort-related angina

This occurs in about half of the patients with MVA.

•Rest angina

Often episodes occur in the early morning. Importantly, if rest angina is present (with or without effort angina), vasoconstriction is likely involved.

•Mixed effort and rest angina.

•In a minority of patients, MVA is precipitated by an acute illness such as a viral infection. After resolution of the illness, the angina symptoms usually (but not always) become less troublesome.

- **Reduced exercise tolerance**

Several studies have found that exercise capacity is reduced in patients with microvascular disease, perhaps in part related to deconditioning.

- **Acute myocardial infarction**

Some patients with MVA can present with an acute myocardial infarction. Support for the possible role of MVA as a cause of acute coronary syndrome (ACS) is the observation that normal coronary vessels or no vessel with ≥50 percent stenosis have been reported in approximately 9 to 14 percent of patients with a non−ST elevation ACS (6).

Physical examination

There are no findings that are specific for MVA. During an episode, tachycardia, hypertension, diaphoresis, and an S3 or S4 may be heard.

Electrocardiogram

ECG is usually normal between episodes. Transient ECG changes, including ST-segment depression with anginal pain, are common, but the absence of ECG changes does not exclude a cardiac etiology. ST-segment elevation that is the hallmark of vasospastic angina is not a feature of MVA.

Ambulatory ECG monitoring for 24 hours may be helpful for documenting ST-segment changes.

Investigations

The ACC/AHA guidelines recommend local availability and expertise to choose a diagnostic test whereas the ESC CCS 2019 guidelines recommend non-invasive methods as first-line tests (12)(13).

Initial noninvasive evaluation

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If an exercise ECG is used, the typical finding in patients with MVA is horizontal or downsloping ST-segment depression, as seen in patients with obstructive coronary artery disease (CAD). Exercise stress myocardial perfusion scintigraphy may demonstrate regional myocardial perfusion defects during exercise. However, some reports have demonstrated neither perfusion defects nor regional wall motion abnormalities after dobutamine or transesophageal atrial pacing, despite the frequent provocation of chest pain (6).

Finally, some patients are evaluated at the time of an anginal episode and are given sublingual nitroglycerin both as a diagnostic and therapeutic test. In MVA, as the small arterioles are less directly affected by the vasodilatory effects of GTN compared with the epicardial arteries, the drug may not be reliably effective. Thus, when a patient is felt to have angina but does not respond rapidly to GTN, MVA should be considered.

Additional Non-invasive testing

The following non-invasive tests may be used in patients who are not able to undergo the invasive tests or who do not have a clear diagnosis after completion of an invasive evaluation:

- **Positron emission tomography coronary flow reserve (PET-CFR)**

Positron emission tomography images can provide an estimate of coronary flow reserve by comparing myocardial blood flow (MBF) at rest with blood flow acquired during stress (1)(3)(6).

These measurements then allow for the calculation of the myocardial perfusion reserve (MPR), defined as the ratio of stress MBF to rest MBF. An MPR <2.0, in the absence of obstructive CAD, is widely accepted as the diagnostic threshold for CMD. In addition, use of MPR improves risk stratification in patients with suspected CMD. Another advantage of PET scan over invasive tests is assessing all cardiac territories as it is well known that CMD can be patchy and not global in the myocardium (14)(15).

- **Cardiovascular magnetic resonance imaging coronary flow reserve**

Cardiovascular magnetic resonance imaging provides a measure of coronary flow reserve by comparing perfusion at rest with perfusion during vasodilator or dobutamine stress (16) .

- **Echocardiographic coronary flow reserve**

Echocardiographic coronary flow reserve is measured by comparing velocities obtained from the left anterior descending artery (LAD) at rest with velocities obtained during stress. It has a limitation of single artery assessment which is LAD; hence missing heterogeneous CMD. Echocardiographic myocardial perfusion reserve is measured by comparing contrast echocardiography-derived myocardial replenishment curves obtained at rest with curves obtained with peak adenosine infusion. Also, this has a limitation of operator experience and acoustic windows (6).

Diagnostic coronary angiography

In patients with MVA, the coronary angiogram will show normal epicardial coronary arteries or mild coronary artery disease (<30 percent stenosis). In patients with lesions between 30 and 50 percent, further evaluation with fractional flow reserve (FFR) should be carried out to make sure that the lesion(s) is not hemodynamically significant (17). FFR is a ratio of distal coronary pressure (Pd) to aortic Pressure (Pa) during maximal hyperaemia induced by IV adenosine and used to estimate the physiological significance of epicardial coronary artery stenosis. It is considered significant if epicardial FFR is ≤0.80 (18)(19).

Additional invasive testing

Additional testing, usually performed at the time of coronary angiography, may be helpful. Invasive diagnostic testing using CFR is found to be superior in improving the burden of angina and guiding therapy in patients with MVA (20).

1- Coronary flow reserve on angiography

CFR is the ratio of maximal hyperaemic coronary blood flow measured after infusion of a coronary vasodilator, such as adenosine to resting, or basal coronary blood flow. Normal CFR ranges from 2.5 to 5. Maximal coronary blood flow should be at least two and a half times the resting blood flow. When there is no significant epicardial coronary artery disease, CFR shows the degree of resistance to blood flow in the microcirculation. It can be measured invasively using a Doppler wire placed into the coronary artery, and then infusing adenosine either intravenously or directly into the coronary artery. CFR values below or equal to 2 or 2.5, depending on methodology used, are indicative of coronary microvascular dysfunction (21).

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1- **Coronary microvascular vasoconstriction**

Acetylcholine causes coronary vasodilation in presence of healthy endothelium and vasoconstriction in the presence of endothelial dysfunction (6).

In an Ach test for MVA, 36.4 mcg given over 2 minutes then 72.8 mcg given over 2 minutes in LCA. Similarly, 18.2 mcg and 36.4 mcg are given over 2 minutes each in RCA (3).

- Positive response for epicardial coronary spasm is >90 percent focal or diffuse coronary artery diameter reduction. A bolus dose of intracoronary 100 mcg over 20 seconds in LCA and 50 mcg over 20 seconds in RCA to test for epicardial coronary artery spasm. Patients who have angina and ischemic ECG changes, considered to have vasospastic angina, not MVA (3). This is more common in men than in women (8).

- When patients have angina during the test with ECG changes without epicardial coronary artery spasm, this is considered MVA.

Limited vasodilatation during the test, reduction of blood flow like in cases of no reflow and spasm of distal epicardial are features of microvascular vasoconstriction (6).

2- **Adenosine test**

Patients who have a "negative" response to Ach should be evaluated with intracoronary adenosine. In adenosine test, bolus adenosine doses (18 micrograms in the left coronary artery and 12 micrograms in right coronary artery) are given. Coronary flow velocities (CFVs) are measured using sensor-tipped guidewire. CFR is calculated from CFVs (ratio of peak CFV to baseline CFV). CFR <2.5 indicates endothelium-independent coronary microvascular dysfunction. These patients with abnormal CFR will be considered to have MVA.

The index of microvascular resistance (IMR) is calculated as the product of distal coronary pressure at maximal hyperaemia multiplied by the hyperaemic mean transit time. An IMR > 25 is highly diagnostic of CMD (15)(22)(23)(24).

TIMI frame count provides a semi-quantitative method of assessing microvascular resistance. In the absence of obstructive CAD, a corrected TIMI frame count >27 (images acquired at 30 frames -1) suggests MVA due to impaired resting flow (coronary slow-flow phenomenon). While this technique is low cost and easy to perform, it is less sensitive than other invasive techniques (15).

The procedure begins with intravenous heparinization followed by engagement of guide catheter, intracoronary nitrate and positions the wire in the selected artery and zero both guide and guide wire pressures. Then advance the guide wire distally (about two-thirds of the artery. The sensor should be 6-10 cm from the guide tip). Flush the guide with saline. Thermo-dilution (Tmn) technique is used to obtain a CFR value which is the ratio between resting and hyperaemic temperature arrival time. 3 mls of heparinized saline is injected vigorously following computer prompts and closes the injection port to monitor pressure. Repeat this 3 times at rest and 3 times after maximum hyperaemia induced by IV adenosine. The software will interpret and give the final value of FFR, CFR and IMR (19).

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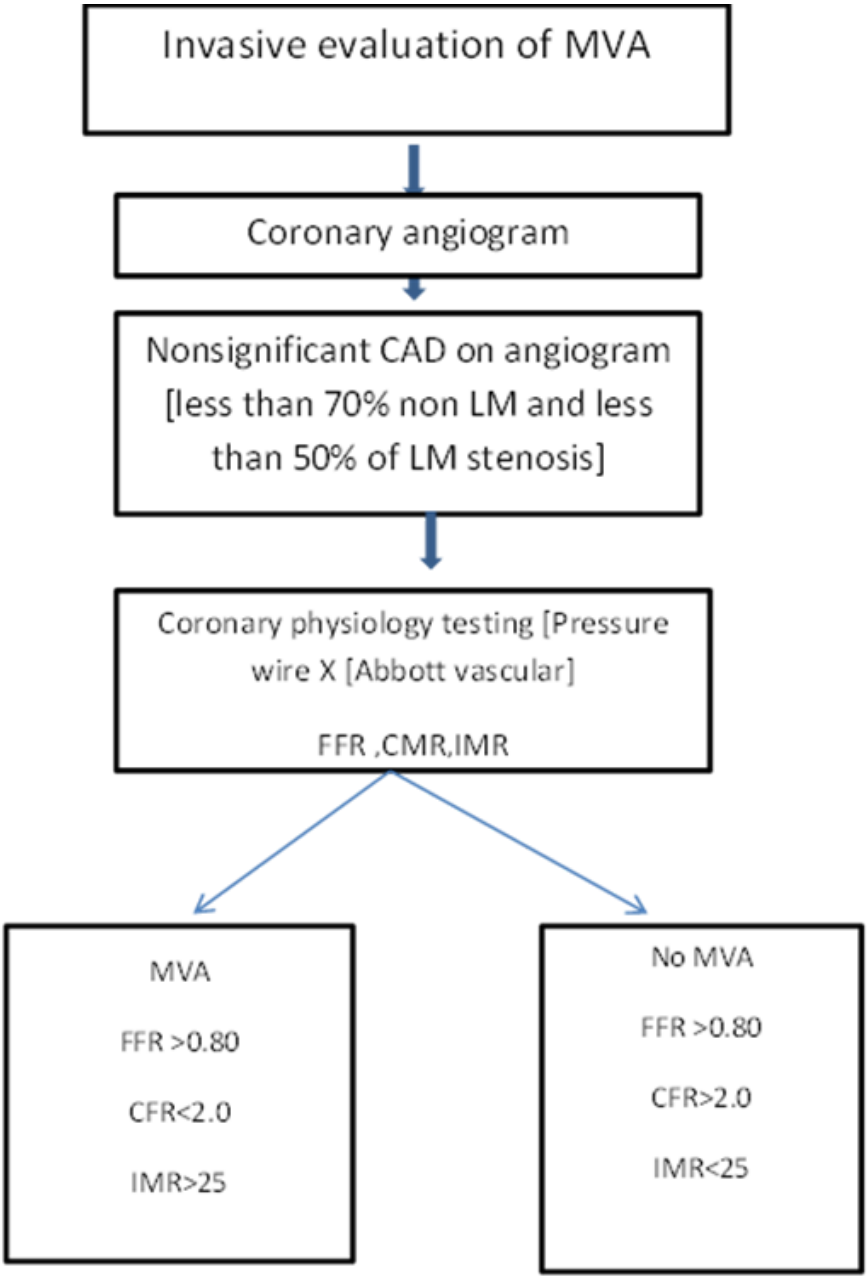
Invasive evaluation of MVA
Coronary angiogram
Nonsignificant CAD on angiogram [less than 70% non LM and less than 50% of LM stenosis]
Coronary physiology testing [Pressure wire X [Abbott vascular]
FFR ,CMR,IMR
MVA
FFR >0.80
CFR<2.0
IMR>25
No MVA
FFR >0.80
CFR>2.0
IMR<25

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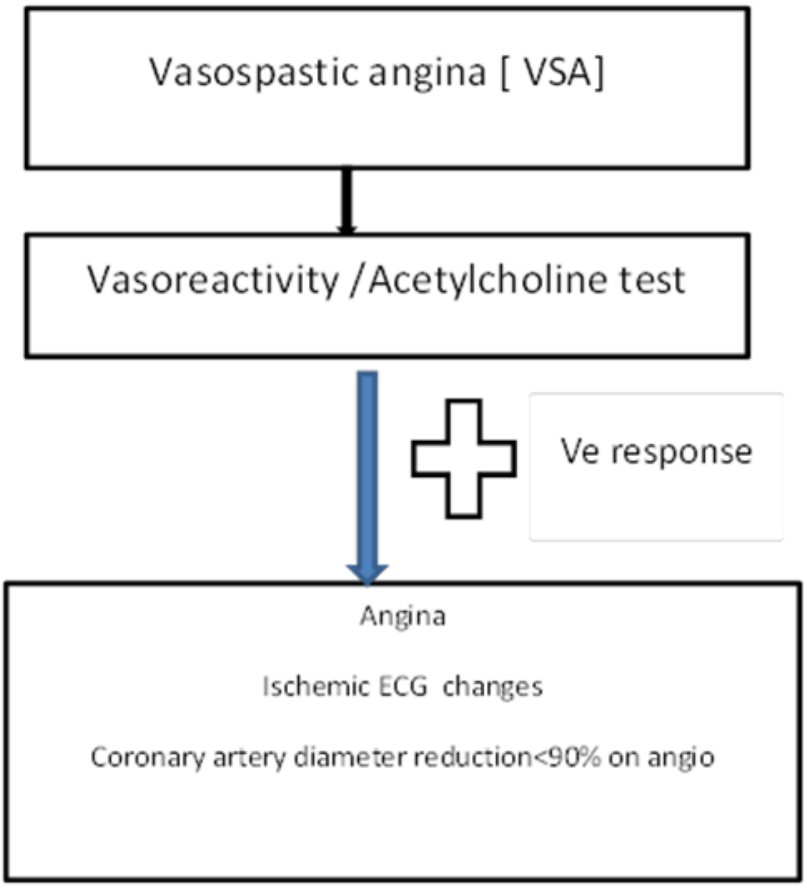

Figure 1 : Invasive evaluation of MVA.

PROGNOSIS

The prognosis of MVA is far from benign. It was considered a non-serious condition earlier (2)(25)(26, 27). For most patients, primary MVA is a chronic condition that can be managed with lifestyle changes and pharmacotherapy but does not completely resolve. It affects quality of life and has a high morbidity and mortality. Females with MVA are more affected by chest pain and have lower quality of life compared with men with MVA (2).

MANAGEMENT

Prior studies demonstrate less than half of patients are appropriately treated with anti-ischemic agents (25).

Patients who underwent invasive tests and diagnosed INOCA were referred more (40% vs. 16%) to cardiac rehabilitation which helped to improve functional capacity of patients (23)(28).

•Primary ASCVD prevention

Patients with MVA who have risk factors (ie, hypertension, diabetes, dyslipidemia, obesity, smoking) should be treated aggressively to control these factors with lifestyle modifications as symptom-limited exercise with gradual increase in duration as well as medications as per guidelines (19).

•Secondary ASCVD prevention

While there is no clear evidence for the benefit of aspirin in patients with CMD, many of these patients have multiple cardiovascular risk factors, and it is reasonable to prescribe aspirin 81 mg daily (6).

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Initial therapy for effort angina

Nitrates:

Patients should be given a prescription for sublingual GTN, which can be used to relieve or prevent angina. Sublingual GTN is not effective for all patients with MVA due to the steel phenomenon (2). It might be beneficial in 40% of patients with MVA.

If long-acting nitroglycerin therapy is effective, then it should be continued otherwise to switch to beta blocker and other antianginal medications (6).

Beta blockers

Beta blockers can be used for initial treatment of persistent effort-induced angina. Metoprolol succinate can be started at 50 mg and up titrated to 200 mg daily if needed. Also, bisoprolol is an alternative with an initial dose of 2.5 mg daily and an increase to 10 mg daily if required. Beta blockers seem to be most effective in reducing the frequency and severity of angina and in improving exercise tolerance.

If beta blockers cannot be tolerated, calcium channel blockers are viable alternatives (2).

Initial therapy for rest or mixed angina

Calcium channel blockers are the initial therapy in patients with underlying microvascular vasoconstriction/vasospasm. Extended release diltiazem180 mg daily and increase the dose at two- to four-week intervals to a maximum dose of 540 mg daily, as necessary. Short-acting calcium channel blockers should not be used, because of safety concerns.

A study compared patients with documented coronary epicardial vasospasm with patients with microvascular dysfunction and found that half the patients with microvascular dysfunction showed symptomatic improvement with calcium channel blockers while almost all patients who were given a combination of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors showed substantial relief of angina.

Combination therapy for persistent symptoms

If MVA symptoms persist, we add ranolazine and/or ivabradine.

- Ranolazine is a late sodium current inhibitor. It can be started at 375 mg twice a day and increased according to the response.
- Ivabradine is a selective I_f channel blocker that causes sinus bradycardia by inhibiting I_f current in the sinus node. It has no negative inotropic or vasoconstriction effect as beta blockers. The starting dose is 2.5 mg twice a day which can be up titrated as per symptoms improvement.
- Imipramine: in hyperalgesia syndrome when more therapy is needed, adding imipramine might help decrease symptoms. It is started at 25 mg at night and can be increased to 100 to 300 mg daily. Imipramine is a tricyclic antidepressant medication, which has been used successfully in the management of chronic pain syndromes (6).

Other therapy

In other groups of patients when symptoms persist despite the above medications, other treatments can be used which have little evidence to support.

- Sildenafil: 25 mg daily has been used for relief of symptoms in patients with MVA when all other therapies have failed. It was seen to improve CFR when used at higher doses 100 mg. That needs a randomized controlled trial to prove it at long term (29).
- **Hormone replacement therapy**

Studies of hormone replacement therapy (HRT) have shown no definite cardioprotective effect, and, overall, HRT appears to increase the risk of coronary disease, stroke, venous thromboembolism, and breast cancer.

Due to increased incidence of MVA in postmenopausal women, it seems that might be related to estrogen deficiency (6)(29).

Cilostazol as a phosphodiesterase type 3 (PDE-3) inhibitor increases intracellular cyclic adenosine monophosphate with anti-inflammatory, antiplatelet, and vasodilatory effects and showed to improve MVA due to vasoconstriction (29).

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Vitamin D. It was noticed low vitamin D levels in patients with MVA can cause endothelial dysfunction and some improvement when replacing it (29).

Management of refractory angina

- **Spinal cord stimulation**

For patients in whom the diagnosis of MVA is confirmed and who have persistent unacceptable angina, Patients should be referred for spinal cord stimulation. Spinal cord stimulation has been successful in the treatment of refractory angina due to coronary heart disease. Spinal cord stimulation also improves angina and increases exercise tolerance in patients with refractory angina and normal coronary arteries(6)(19).

- **Coronary sinus reduction**

This surgical device has been studied for relief of refractory angina in patients with obstructive coronary disease; however, it has not been extensively tested in MVA. In a preliminary study of eight patients, coronary sinus reduction was effective in reducing angina, increasing exercise tolerance, and improving ischemia on myocardial perfusion imaging tests. However, larger randomized studies are needed prior to recommending this therapy for patients with MVA and refractory angina (6).

Conclusion:

MVA is a challenge in the current era of ischemic heart disease and coronary intervention. It is associated with a huge burden on cost management including recurrent hospitalization, recurrent angiogram, and sick leave for morbidity.

Chronic coronary artery disease patients who undergo conventional angiograms and are found to have non-obstructive coronary artery disease should have coronary functional assessment to diagnose MVA so that early diagnosis will help to treat the patient appropriately. It will ultimately have a huge positive impact on management of large group patients who have non-obstructive CAD and contribute to improving the health economy in the long run.

Conflict of interest:

Authors have no conflict of interest and have nothing to disclose.

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