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Coronary microvascular dysfunction- a closer look

Zakariye Ashkir

Introduction

Microvascular angina or 'Cardiac syndrome X' are diagnostic terms used to describe angina in patients with non-obstructive epicardial coronary artery disease and hint at underlying coronary microvascular dysfunction (CMD). It is becoming increasingly recognised that a significant proportion of patients (20-30%) with angina fall into this category[1], necessitating a change in our understanding of ischaemic heart disease - it is no longer synonymous purely with obstructive epicardial coronary artery disease (CAD).

We have known of these patients for decades (the term cardiac syndrome X was coined in the 1970s[2]) yet they remain a poorly characterised group. There are significant gaps in our knowledge and clinical studies have delivered conflicting or disappointing results. We have found that CMD is not always present in patients with 'microvascular angina', functional assessments can be hit or miss, and to add insult to injury there is no treatment that has been proven to have a significant and consistent benefit across this patient group. Consequently, the ESC angina guidelines have few strong recommendations for the investigation and management of microvascular angina[3].

On a more positive note however, our understanding of this condition has certainly improved in recent years. Progress has been made to piece together potential underlying mechanisms[4] and identify risk factors (primarily female sex, diabetes, hypertension and renal impairment[5]), and diagnosis has been bolstered by new techniques assessing coronary physiology using different imaging modalities particularly CMR and PET.

Take Home Messages

- Coronary microvascular dysfunction (CMD) is common, especially in women. Most patients with CMD also have some epicardial CAD.
- CMD can be due to different structural and functional abnormalities affecting the coronary microvasculature.
- A diagnosis of 'microvascular angina' i.e. caused by CMD relies on the exclusion of obstructive epicardial CAD.
- Functional tests are not sensitive or specific for CMD and therefore are not diagnostic.
- CMD can be diagnosed by measuring physiological surrogates of microvascular function such as coronary flow reserve (CFR) using Invasive and non-invasive (PET, CMR, Echo) techniques.
- A CFR value of <2 is highly suggestive of CMD.
- There is no proven and validated treatment for CMD. Current strategies involve optimising management of risk factors such as diabetes, hypertension and hyperlipidaemia and trialling anti-anginal therapies for symptom control.

Using the correct terminology

In daily practice, 'microvascular angina' is used as an umbrella term for patients with angina in the context of non-obstructive CAD- this is somewhat of an oversimplification.

Firstly, it is important to remember that there are alternative causes for such a presentation other than microvascular dysfunction such as flush origin occlusions, epicardial vasospastic angina as well non-cardiac chest pain and abnormal cardiac pain perception[7].

Secondly, 'true' microvascular angina i.e. angina due to CMD can be caused by different pathophysiological processes[8], and patients may have a combination of these mechanisms occurring simultaneously. To complicate matters even further, most patients with coronary microvascular dysfunction also have a degree of epicardial CAD[9]. It is this complex heterogeneity which is likely responsible for inconsistent diagnostic results and treatment effects in this patient group.

Currently there is no universally agreed classification of CMD.

Understanding the pathophysiology

The coronary arterial tree consists of epicardial vessels, pre-arterioles (100-400 μm in diameter), arterioles (40-100 μm) and capillaries (<10 μm). Arterioles are resistance vessels which regulate flow and capillaries are the interface with cardiac myocytes where delivery of nutrients and removal of waste products occurs.

A recent JACC review[10] divided the different pathological mechanisms in each of these vessel types elegantly into structural and functional causes (see figure 1).

Macrovascular dysfunction
In the case of epicardial vessels the most common structural pathology is, of course, atherosclerotic disease which results in gradual obstruction and/or plaque rupture. Other important structural abnormalities which could cause angina include myocardial muscle bridge formation and anomalous coronary arteries. Vasospastic (Prinzmetal) angina is the main example of functional epicardial disease.

Microvascular dysfunction
In arterioles, structural abnormalities such as intimal thickening caused by smooth muscle cell hypertrophy and proliferation and perivascular fibrosis increase microvascular resistance and compromise coronary microvascular blood flow. Such remodelling is commonly seen with hypertension, hypertrophic cardiomyopathy and aortic stenosis. Endothelial dysfunction and smooth muscle dysfunction resulting in impaired vasodilatation are functional phenomena which may occur separately but can also cause structural abnormalities and also result in a deleterious effect on myocardial perfusion.

Interestingly the main risk factors beyond female gender for coronary microvascular dysfunction -both structural and functional - are not only similar but are also those

implicated in atherosclerotic epicardial coronary artery disease: namely hypertension, diabetes, smoking, hyperlipidaemia, obesity and metabolic syndrome.

Furthermore CMD has also been linked with HF-PEF and it is thought that the underlying structural mechanisms of CMD may play a key role in diastolic dysfunction[11]. As previously mentioned, patients with CMD often also have epicardial CAD. This is important to bear in mind because the combination of CMD and epicardial disease is associated with difficult to treat angina[12] (think of your last diabetic, hypertensive patient who had ongoing angina despite stenting of their epicardial lesion), which can be less responsive to medical therapy and also carries a poorer prognosis in terms of MACE outcomes[13]. Another potential consequence of dual pathology is suboptimal treatment of epicardial CAD - CMD can cause pseudo-normalisation of FFR measurements[14] and therefore be responsible for underestimation of the significance epicardial stenoses.

How to investigate suspected microvascular angina

The diagnostic pathway relies on the confirmation of non-obstructive epicardial CAD which may be done with CT coronary angiography or with invasive coronary angiography.

In addition to this, imaging modalities such as transthoracic echocardiography and cardiac MR should be used to exclude alternative causes for chest pain such as structural (e.g. hypertrophic cardiomyopathy) and inflammatory (e.g. pericarditis) conditions.

Functional testing using echocardiography, CMR, or MPS performed either before or after negative coronary angiography traditionally is how many clinicians eventually reach a diagnosis of microvascular angina. The problem with conventional functional tests is that they can often be inconclusive[10] as they are not sensitive or specific for microvascular dysfunction.

Patients with angina who have had a negative coronary angiogram but a positive functional test and those with risk factors for microvascular angina especially women (with or without a positive functional test), should be considered for further non-invasive or invasive investigation of CMD.

<u>Diagnosing coronary microvascular dysfunction</u>
As we do not yet have the ability to directly visualise the coronary microvasculature, diagnosis of CMD is based on invasive and non-invasive assessment of myocardial perfusion and microvascular resistance which are surrogate markers of microvascular function.

Non-invasive diagnosis can be achieved with PET and CMR imaging and is primarily done by determining coronary flow reserve (CFR), with PET being the more accurate and more validated modality[10]. CFR is the ratio of myocardial blood flow at maximal hyperaemia compared to rest. A CFR value of <2 in the absence of obstructive epicardial CAD is indicative of microvascular dysfunction[15]. The main limitations of both

of these techniques are cost and availability of requisite expertise. Lesser used non-invasive modalities include echocardiography and CT. Doppler echocardiography can diagnose CMD by assessing doppler flow velocities in the left anterior descending artery[10] (only vessel in which it is validated), disadvantages of this technique are that it is operator dependent and only characterises flow in a single coronary territory.

Invasive coronary angiography is not only instrumental in the diagnosis of CMD by excluding significant epicardial CAD, but is also very useful in confirming microvascular dysfunction by allowing the measurement of several different physiological surrogates of microvascular function. A doppler tipped guidewire can be used to determine coronary blood flow (CBF) and CFR by employing techniques such as thermodilution or gas washout[16]. Vasodilators used to achieve maximal hyperaemia include adenosine (endothelium independent vasodilatation) and acetylcholine (endothelium dependent vasodilatation). Index of microvascular resistance or IMR is another surrogate of microvascular function[17] which can be assessed both invasively and non-invasively.

How to treat patients with suspected coronary microvascular dysfunction

There is currently no validated treatment which has been proven to be widely effective for CMD. A lack of a universal definition of CMD and difficulty in recruiting suitable subjects and designing appropriate trials in this heterogeneous patient group has resulted in a paucity of high quality studies.

Despite the lack of evidence, the treatment strategy employed by most clinicians and supported by the ESC are based on a) management of recognised risk factors and b) symptomatic treatment with anti-anginal therapy.

The ESC stable angina guidelines from 2013 strongly recommend all patients with microvascular angina receive secondary prevention medications including aspirin and statins (Class 1, Level B)[3]. They admit that symptomatic treatment with anti-anginal medication in microvascular angina is empirical. Nevertheless, they favour the use of beta blockers or calcium blockers as a first line treatment (Class 1, Level B). Several other treatments including ACE inhibitors, nicorandil, xanthine derivatives and non-pharmacological treatments such as transcutaneous electrical nerve stimulation (TENS) are recommended for refractory cases (Class 2 Level B).

Unfortunately, a more recent systematic review of different treatments options (including beta-blockers, nitrates, calcium channel blockers, ACE/ARBs, anti-hypertensives, nitrous oxide modulators, xanthine derivatives, oestrogens as well as TENS) concluded that there was "little data to support therapies for CMD"[18].

Although symptomatic relief may prove challenging, optimising blood pressure, glycaemic control and lipid profile of patients with microvascular angina is achievable and highly advisable. Even if this strategy has not been shown to directly improve symptoms, it could theoretically inhibit progression of CMD and of course it is beneficial against concomitant epicardial CAD. Statins may be of particular benefit in this regard because of their anti-inflammatory and anti-atherosclerotic effects- but once more they lack the evidence to support the theory.

Conclusion

Microvascular angina is defined as angina caused by coronary microvascular dysfunction (CMD) in patients with no significant epicardial coronary artery disease (CAD).

It is thought to be responsible (fully or in part) for a large proportion of angina cases and is significantly more common in women[19]. Other risk factors include diabetes, hypertension, hyperlipidaemia, smoking and obesity. CMD is also seen in certain cardiac conditions which result in left ventricular hypertrophy such as hypertensive heart disease, hypertrophic cardiomyopathy and aortic stenosis.

The conventional diagnostic pathway for epicardial CAD is not suitable for the diagnosis of CMD. Although (CT or invasive) coronary angiography to exclude obstructive epicardial CAD is essential, the diagnosis of CMD is made by measuring physiological surrogates of microvascular function such as coronary flow reserve (CFR) using Invasive and non-invasive (PET, CMR, Echo) techniques.

There is no proven and validated treatment for CMD. Current strategies involve optimising management of risk factors such as diabetes, hypertension and hyperlipidaemia and trialling anti-anginal therapies.

Figure 1. Pathophysiology of coronary microvascular disease (CMD)

	Role	Structural abnormalities	Functional abnormalities
Epicardial arteries	Conduit vessels	Focal atheroma Diffuse atherosclerosis Coronary remodelling	Epicardial coronary vasospasm -SMC dysfunction -Endothelial dysfunction
Pre-arterioles Arterioles	Metabolic control and regulation of flow distribution	Intimal thickening Smooth muscle cell (SMC) hypertrophy SMC hyperplasia Perivascular fibrosis	Impaired vasodilatation -SMC dysfunction -Endothelial dysfunction
Capillaries	Exchange vessels	↓Capillary density ↓Capillary diameter Capillary obstruction	Endothelial dysfunction

Adapted from: *Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options. J Am Coll Cardiol 2018; 72: 2625-2641*

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