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Management of Microvascular Angina

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The treatment of microvascular angina [MVA] is usually challenging and not entirely effective since up to 30% of the patients continue having frequent chest pain episodes [1]. Probably it is caused by diverse and overlapping underlying mechanisms that have not been completely identified.

The main problem when approaching MVA is that until very recently it did not have universally accepted diagnostic criteria and the population included in the studies were not homogenous in the sense that an accurate diagnose had not been performed according to the actual underlying mechanism of the angina. Therefore, results of previous studies are sometimes inconsistent and difficult to apply to the clinical practice. That was also probably the case regarding clinical prognosis, where contradictorily results have also been found [2,3].

The term MVA is generally used to indicate angina episodes caused by abnormalities of resistance in the coronary artery microvessels. There is a mismatch of myocardial blood supply and oxygen consumption due to a dysfunction of the coronary microvessels with a diameter of less than 500 μm. In this case, coronary flow reserve [CFR] is impaired in the absence of epicardial artery obstruction because of non-homogeneous metabolic vasodilation that may favour the 'steal' phenomenon, or by inappropriate pre-arteriolar/arteriolar vasoconstriction, or other by causes for altered cross-sectional luminal area [4]. Although coronary microvascular disease and ischaemia cannot be confirmed in all patients previously felt to have microvascular angina, the consensus today is that coronary microvascular disease is the unifying pathogenesis mechanism in most of the patients [5]. Healthy subjects have an absolute CFR of 3.5–5, 15 whereas patients with a relevant epicardial stenosis have a CFR of 2–2.5. Patients with a CFR < 2 have an adverse prognosis, despite the absence of epicardial disease indicating severe microvascular disease [6]. Flow reserve values between 2.5 and 3.5 are difficult to interpret but may indicate milder forms of coronary microvascular dysfunction, with and without associated epicardial disease.

Doppler recordings invasive measurement of CFR using a Doppler wire is complex, time consuming, and carries a small risk. However, the acetylcholine provocation testing is a useful tool to distinguish between patients with epicardial and microvascular spasm [7], and such invasive coronary reactivity testing is safe with a reported complication rate of around 1% [8], which is comparable to the complication rate of invasive diagnostic coronary angiography.

Microvascular disease [MVD] can be evidenced non-invasively by measuring diastolic coronary blood flow in the LAD at peak vasodilatation [following intravenous adenosine] and at rest using transthoracic echocardiographic [9], however, a very good echocardiographic window is needed and mild forms of MVD can lead to false negative results. MRI and PET are good options to measure CFR and detect coronary vasomotor abnormalities but their availability is more limited [10,11].

As previously mentioned, the efficacy of the pharmacotherapy is difficult to judge because the clinical studies use a variety of definitions of study endpoints and inclusion criteria [1]. In that sense the COVADIS [Coronary Vasomotor Disorders International Study Group] was founded to establish internationally accepted criteria for patients with coronary microvascular dysfunction in order to improve the clinical diagnosis [12].

As conditions such as ventricular hypertrophy, myocardial ischaemia, arterial hypertension and diabetes can also affect the microcirculation and blunt CFR, there is a consensus that the most obvious "first step" in the management of MVA would be to appropriately control these underlying risk factors. In fact, it is not surprising that epicardial atherosclerotic coronary disease may develop later in the course of the disease [13]. Therefore, the use ACE-inhibitor for hypertension and a statins for hypercholesterolemia are good options, as both drugs have shown to improve coronary microvascular dysfunction in small-randomized studies [14,15]

Classically, beta-blockers have been stated as first line treatment in patients with MVA. However, the use of these drugs are based on early studies [16] with a few number of patients in whom the true pathophysiology was not well characterized. In first- and second-generation beta-adrenergic receptor antagonists [beta-blockers] have shown contradictory influences on microvascular function. This can be explained by the interaction of the effects on coronary blood flow at rest, generally reduced by these drugs, and after hyperaemia, when minimal coronary resistance appears to be either increased or reduced. Third-generation beta-blockers [e.g. carvedilol and nebivolol], which have vasodilating capacity, improve hyperaemic CBF [17]. This occurs as a result of a reduction in minimal resistance, which can be attributed to alpha-adrenergic blockade and/or to a nitric oxide-mediated effect. This improvement is clearly beneficial in patients with coronary artery disease and indicates an improved coronary microvascular function [18].

Albeit with weaker evidences than beta blockers, calcium antagonists, if well tolerated, are usually effective in a good percentage of patients with MVA. Diltiazem has been shown to provide amelioration of the altered coronary flow dynamics in patients with coronary artery ectasia improving both epicardial and microvascular parameters [19], and the combination with statins seems to be even more effective on endothelial function and exercise tolerance in patients with MVA [20]

Nitroglicerine [NTG] in short action forms is useful to relief symptoms in some MVA patients but the effect is usually slower and more inconsistent than in patients with CAD or epicardial spasm, mainly because NTG is an endothelial independent vasodilator that does not have effect in vessels < 200 μm, where smooth muscle with GMPc is not present [21]. Thus, long action forms of NTG are also sometimes not effective and bad tolerated in this group of patients [22].

In fact, both intracoronary diltiazem and nitroglycerin improve microvascular function in coronary slow flow phenomenon, a microvascular disorder usually observed after some percutaneous intervention. In this clinical scenario intracoronary diltiazem was superior to nitroglycerin in improving TIMI frame count [23].

The relatively new anti-ischemic drugs, ivabradine and ranolazine, nowadays also play a role in the management of patients with MVD. Both have shown to improve symptoms, but the results regarding the action in microvascular function remain controversial [24,25, 26].

To sum up, the management of MVA is currently challenging and sometimes not completely satisfactory as many patients continue experiencing symptoms despite the use of all available measures. To ensure the most optimal management available, a rigorous diagnostic approach should be performed including objective evidence of the actual pathophysiological underlying mechanism.

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