

Reappraisal of Ischemic Heart Disease - The fundamental role of coronary microvascular dysfunction in the pathogenesis of angina pectoris

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ABSTRACT

In recent years, it has become apparent that coronary microvascular dysfunction plays a pivotal pathogenic role in angina pectoris. Functional and structural mechanisms can affect the physiological function of the coronary microvasculature and lead to myocardial ischemia in people without coronary atheromatous disease and also in individuals with obstructive coronary artery disease. Abnormal dilatory responses of the coronary microvessels, coronary microvascular spasm and extravascular compressive forces have been identified as pathogenic mechanisms in both chronic and acute forms of ischemic heart disease. The condition characterized by anginal symptoms and evidence of myocardial ischemia triggered by coronary microvascular dysfunction, in the absence of obstructive coronary disease, is known as “microvascular angina”. The concept of microvascular angina however, may extend further to include patients with obstructive coronary artery disease and individuals with angina post coronary revascularization or heart transplantation, since coronary microvascular dysfunction contributes to myocardial ischemia in many such patients. Patients with microvascular angina constitute a sizeable proportion of all cases of stable angina undergoing diagnostic coronary angiography and of those with persisting angina after successful coronary revascularization. Coronary microvascular dysfunction is also often responsible for angina in individuals with cardiomyopathy and heart valve disease as well as acute coronary syndrome cases such as Takotsubo syndrome and MINOCA (myocardial infarction with no obstructive coronary artery disease). Patients with stable microvascular angina present typically with effort and/or rest chest pain and a reduced coronary flow reserve or microvascular spasm. This condition, which affects women and men, can markedly impair quality of life and prognosis, and represents a substantial cost burden to healthcare systems and individuals alike. In recent years, progress in the diagnosis of myocardial ischemia and the use of tests to investigate functional and structural causes for a reduced coronary flow reserve and microvascular spasm have allowed the identification of an increased number of cases of microvascular angina in everyday clinical practice. Although some of the available anti-anginal drugs may be helpful, treatment of coronary microvascular dysfunction remains a major challenge. The present article discusses the fundamental role that coronary microvascular dysfunction plays in the pathogenesis of ischemic heart disease, the clinical characteristics of patients presenting with microvascular angina, and possible diagnostic and therapeutic strategies.

Key words: Coronary circulation; Microvascular angina – Coronary microvascular dysfunction – Ischemic heart disease – Cardiac imaging

INTRODUCTION

The term “angina pectoris”, proposed over two centuries ago, is commonly considered to be synonymous with obstructive atherosclerotic epicardial coronary artery disease (CAD). The frequently reported association between “angina pectoris” (central chest pain), myocardial ischemia and coronary atherosclerosis has reinforced the concept that “anginal” pain and myocardial ischemia are almost exclusively caused by obstructive CAD.¹ Diagnostic and therapeutic strategies for angina pectoris in its two main forms of presentation, namely chronic stable angina and acute coronary syndrome (ACS), have been and continue to be, based upon the obstructive CAD paradigm. Current recommendations in international angina management guidelines are informed by the notion that coronary atheromatous plaques are the main cause for myocardial ischemia.²⁻⁴ Nonetheless, the latest ESC guidelines⁴ acknowledge the pathogenic role of coronary artery spasm and coronary microvascular dysfunction (CMD) in myocardial ischemia and the 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guidelines for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease mention that microvascular disease, with vascular reactivity related to abnormalities in microvascular and endothelial function, contributes to ischemia to a greater extent in women than in men.

Although strategies based on the “classical” pathophysiological concepts are useful for the management of a substantial proportion of patients with chronic stable angina and the majority of ACS patients, the paradigm that obstructive CAD is synonymous with myocardial ischemia needs to be revised, as it is not universally applicable to individuals presenting with chronic stable angina⁵ or to a proportion of ACS patients.⁶ Indeed, functional mechanisms have been documented that can cause myocardial ischemia in the absence of obstructive CAD. Epicardial coronary artery spasm, as initially proposed by Prinzmetal et al⁷ and further documented and characterized by Maseri et al.,⁸ are striking examples. Evidence gathered over the past 30 years has made it clear that functional and/or structural mechanisms affecting pre-arterioles, arterioles and capillaries, represent yet another major cause for myocardial ischemia (Figure 1) in the absence of obstructive CAD⁹⁻¹³ and can also contribute to trigger ischemia in patients with CAD.¹⁴

The initial descriptions of angina developing in the absence of CAD gave rise to the rather ill-defined concepts of “chest pain with normal coronary arteries” or “cardiac syndrome X”.¹⁵⁻¹⁷ The term “microvascular angina” (MVA) was originally proposed by Cannon and Epstein in 1988 to describe patients with normal coronary arteriograms and evidence of myocardial ischemia “caused by a disorder of the coronary microvasculature”.¹⁶ The term MVA has gained acceptance over other denominations to define patients with angina despite non-obstructive CAD or with completely normal coronary angiograms. It could be argued however - as it will be elaborated throughout the manuscript - that the term MVA should be applicable to all forms of angina/ischemia triggered by CMD, irrespective of the absence or the presence of CAD, rather than restricting the term to conditions characterized by myocardial ischemia in the absence of obstructive CAD.

Progress in the understanding of MVA was slow, as studies were usually underpowered, used either very restrictive inclusion criteria or included rather heterogeneous groups of patients. Moreover, tools for the assessment of the microcirculation were not available until recently in clinical practice. Probably as a result of the above, chest pain with normal coronary arteries was considered to be an infrequent condition, often non-cardiac in origin, and with a benign prognosis.¹⁷ Studies in the past decade, however, have shown that angina in the absence of obstructive CAD is more common than initially thought^{5, 18} and also that CMD is associated with myocardial ischemia and adverse clinical outcomes.¹⁹⁻²¹ Importantly, as proposed by Camici and Crea,²² CMD can be the underlying pathogenic mechanism in a large proportion of angina cases, with and without CAD. (Table 1) CMD may result from functional and/or structural abnormalities occurring at the site of the coronary microcirculation and the relative roles these mechanisms play may vary across different clinical settings and also among patients. The present article discusses the fundamental role of CMD in the pathogenesis of ischemic heart disease (IHD), the clinical characteristics of patients presenting with microvascular angina, and possible diagnostic and therapeutic strategies. We also discuss how CMD can lead to chronic stable or acute forms of myocardial ischemia^{6, 23-26} and impair clinical outcomes.

MYOCARDIAL ISCHEMIA – PATHOPHYSIOLOGY – The role of CMD

Anatomy and physiological responses of the coronary circulation

The myocardium is an aerobic tissue that requires continuous perfusion with oxygenated blood to generate the energy necessary for its contraction. Under baseline conditions oxygen extraction from the arterial blood is close to 60-70% and therefore a rise in myocardial oxygen demand can only be met by an appropriate increase in coronary blood flow (CBF). Under physiological circumstances the coronary circulation provides an adequate match between myocardial oxygen demand and supply. The coronary arterial system comprises three compartments - each with a different function - whose anatomical borders cannot be clearly delineated *in vivo*. (Figure 2)

The *proximal compartment* is represented by the epicardial arteries, which have a capacitance function and offer little resistance to CBF. These are vessels ranging from 5.0 mm to 0.5 mm in diameter that run on the surface of the heart before branching off into the myocardium giving rise to intramural vessels. Epicardial coronary arteries have a thick wall with three, well demarcated layers or *tunicae*: i- the adventitia that harbors the vasa vasorum and nerves; ii- the media, with a circular array of vascular smooth muscle (that modulates vessel diameter changes); iii- the intima, on which sits the vascular endothelium. The more distal - intramyocardial - branches have thinner walls and do not possess vasa vasorum. During systole, the epicardial arteries accumulate elastic energy as they increase their blood content up to about 25%. This elastic energy is - at the onset of diastole - converted into kinetic energy that contributes to the prompt reopening of the intramyocardial vessels after having been compressed during systole. This mechanism is of particular relevance considering that 90% of CBF takes place in diastole.²⁷

The *intermediate compartment* is represented by the pre-arteriolar vessels with diameters ranging from approximately 500 μm to 100 μm , and characterized by a measurable pressure drop along their length. Their specific function is to maintain pressure at the origin of downstream arterioles within a narrow range when changes in coronary perfusion pressure and/or flow take place. The more proximal vessels (500 to 150 μm in diameter) are more responsive to changes in flow, whereas the more distal vessels (150 to 100 μm) are more sensitive to changes in pressure.²⁸ Functionally, their vasomotor actions are not under the direct control of diffusible myocardial metabolites.

The *distal compartment* is represented by the arterioles, which have diameters $<100 \mu\text{m}$ and are characterized by a considerable drop in pressure along their path. Arterioles are the site where metabolic regulation of CBF takes place, as their tone is influenced by substances produced by the surrounding cardiac myocytes.^{29, 30}

Pre-arterioles, arterioles and capillaries constitute the coronary microcirculation. Under resting conditions, the tone of the coronary microvasculature is high, but rapid changes in arteriolar diameter can take place to allow the coronary circulation to promptly increase CBF in response to increased myocardial oxygen demand, i.e. “functional hyperemia”. This initial arteriolar response, driven by the strict cross-talk that exists between these vessels and the contracting cardiomyocytes, represents the basis for “metabolic vasodilatation”.³¹ Such a drop in arteriolar resistance, to increase CBF, subsequently drives a number of vascular adaptations that involve all upstream coronary vessels. Capillaries and venules are also an important component of the coronary microcirculation and both structural and functional abnormalities at this level -i.e. capillary rarefaction or microembolization- can contribute to the development of myocardial ischemia. An in-depth discussion of the above mechanisms is beyond the scope of this article. Interested readers are referred to recently published review articles.^{28, 32}

The different causes of transient myocardial ischemia

Myocardial ischemia invariably results from an imbalance between myocardial metabolic demand and CBF. Inadequate blood supply can be caused by anatomical and/or functional abnormalities in all and each of the compartments of the coronary circulation. In addition, extravascular factors, such as decreased diastolic time and elevated extravascular pressure affecting the coronary microcirculation, can also contribute to the development of myocardial ischemia.³³ (Figures 1 and 2)

Ischemia caused by abnormalities in the epicardial circulation

Obstructive CAD - Atheromatous plaques can reduce the lumen of the vessel and lead to a progressive reduction of coronary flow reserve (CFR) and impaired myocardial perfusion. This mechanism can lead to typical exercise- or emotional stress-induced ischemic symptoms and signs, including silent ischemia.³⁴

Coronary artery spasm^{7, 8} can cause myocardial ischemia as a result of a “primary reduction” of CBF. Characteristically, coronary artery spasm patients

present with angina at rest associated with transient ST segment elevation or depression, which responds rapidly to the administration of nitrates.³⁵ Spasm may occur at the site of an atheromatous plaque and/or in angiographically normal vessels.³⁵ Intracoronary ergonovine or acetylcholine (ACh) - used for diagnosis - can provoke coronary spasm and reproduce the symptoms and ECG changes that occur “spontaneously” in patients with vasospastic angina.³⁶⁻³⁸

Ischemia caused by coronary microvascular dysfunction (CMD)

CMD can lead to myocardial ischemia by 1. impairing the ability of the coronary microcirculation to increase CBF in response to an increased myocardial oxygen demand, an effect which is equivalent to that exerted by flow-limiting epicardial coronary artery stenoses, and/or 2. resulting in coronary microvascular spasm. CMD is typically the mechanism underlying myocardial ischemia in individuals with angina despite completely normal coronary arteriograms - also known as “primary” MVA-⁹ but it can also trigger myocardial ischemia in several other clinical conditions, including systemic hypertension, cardiomyopathies and obstructive CAD.²² (Figure 1) Indeed, CMD can coexist with epicardial CAD, causing or contributing to myocardial ischemia and providing additional prognostic value over and above the presence of CAD.²⁰

Structural and functional abnormalities - CMD can result from structural and/or functional alterations of the coronary microvasculature. The relative importance of these mechanisms may vary in different clinical conditions and patient subsets. CMD due to structural changes of the microvasculature has been documented in patients with risk factors for CAD and different cardiomyopathies and is due to capillary rarefaction and adverse remodeling of intramural coronary arterioles. The latter results from medial wall thickening, mainly due to smooth muscle hypertrophy and increased collagen deposition, with variable degrees of intimal thickening and a reduced wall/lumen ratio. An important feature here is the diffuse nature of this remodeling, which generally affects the coronary microvessels in the whole of the ventricle.²² These structural changes can, even in the absence of epicardial CAD, induce progressive reductions in CFR mimicking the effects of flow limiting stenoses. (Figures 1 and 2). The difference, however, is that CFR reduction in patients with CMD rarely follows the “regional” (in the territory subtended by the stenotic artery), pattern seen in obstructive CAD patients, rather appearing as “patchy”³⁹ with small areas of ischemic tissue interspersed among otherwise normal myocardium, or diffuse, involving most of the left ventricle. Functional abnormalities leading to CMD include impaired dilatation or excessive coronary microvascular constriction. Impaired vasodilatation may be due to abnormalities in endothelium-dependent mechanisms (frequently associated with diabetes, obesity, smoking, and other cardiovascular risk factors), endothelial-independent mechanisms, or both.^{12, 40} Inflammation is another potentially important cause of CMD, as recently reviewed by Faccini et al.⁴¹ Coronary microvascular spasm, originally described by Mohri et al.¹³ can, similarly to epicardial coronary spasm, cause myocardial ischemia in the absence of increased myocardial demand and trigger rest angina. Structural and functional abnormalities can coexist in a

given individual and may modulate the patient's ischemic threshold.²⁰ In angina patients undergoing acetylcholine testing, Ong et al.^{38, 42} showed that approximately 1 out of 4 of patients had microvascular spasm, characterized by ischemic ECG changes without visible changes in the diameter of the epicardial coronary arteries. (Figure 3) Arrebola-Moreno et al reported that coronary microvascular spasm triggered by intracoronary ACh is associated with myocardial perfusion abnormalities, abnormal myocardial contractility and - in a proportion of patients - elevation of high sensitivity cardiac troponin concentrations.⁴³

Coronary microvascular ischemia, cardiomyocyte injury and stiffness are also likely to play a role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF).^{44, 45} In a recent study in over 200 symptomatic patients without overt CAD, Taqueti et al.⁴⁴ showed that impaired CFR was independently associated with diastolic dysfunction and adverse events, particularly hospitalization for HFpEF. (Figure 4).

Extravascular mechanisms contributing to CMD and myocardial ischemia (Figure 2)

Increased intramyocardial pressure. During the cardiac cycle the pulsatile pattern of CBF follows typical physiologic variations that are influenced by changes in intramyocardial and intracavitary pressures.⁴⁶ As approximately 90% of CBF occurs in diastole, CBF is vulnerable to the effect of increased extravascular pressure (e.g. in left ventricular hypertrophy)³⁰ and LV diastolic dysfunction such as that caused by increased interstitial and perivascular fibrosis.⁴⁷ CBF is also impaired when arteriolar driving pressure in diastole is lower than intracavitary pressure, as seen in patients with severe aortic stenosis and in those with flow limiting coronary stenoses. Furthermore, increased systolic intramyocardial and intracavitary pressures may negatively impact myocardial perfusion, as compression of intramural vessels during systole may hinder subendocardial vessels tone restoration in diastole, thus impairing diastolic perfusion particularly in the subendocardial layers.⁴⁸

Reduced diastolic filling time. As CBF occurs predominantly during diastole, diastolic time plays a central role in preserving myocardial perfusion. In the normal heart, both subendocardial and subepicardial perfusion are maintained even with very short diastolic times, as during intense physical exercise. In contrast, when coronary driving pressure is significantly lower than intracavitary pressure, as in patients with aortic stenosis, a reduction of diastolic time can contribute to a critical impairment of myocardial perfusion.⁴⁹

Myocardial ischemia in acute coronary syndromes

Atheromatous plaque related mechanisms- For decades, atheromatous plaque rupture with thrombus formation has been considered the main pathogenic mechanism underlying acute myocardial ischemia and myocardial infarction. Yet, current evidence suggests that a sole focus on plaque rupture oversimplifies what is actually a complex clinical syndrome. Coronary artery thrombosis due to plaque erosion and leading to ACS/NSTEMI is on the rise in the current era of intense lipid lowering treatment. Moreover, in about one third of patients ACS can occur in the absence of epicardial coronary artery

thrombosis or stenosis. In a recent review article, Crea and Libby⁵⁰ recommended a mechanistic approach to the categorization of ACS highlighting the role of plaque erosion, inflammation, epicardial spasm and microvascular disease. This approach provides a useful clinical framework for triaging patients at risk and tailoring therapy in a more personalized and precise manner.⁵⁰

Coronary microvascular obstruction- Myocardial reperfusion in STEMI may be associated with a secondary impairment of the coronary microcirculation because of endothelial swelling, microvascular spasm, external compression, and distal embolization by plaque debris and platelet-leukocyte aggregates resulting in coronary microvascular obstruction (CMVO).^{39, 40, 51} The latter prevents effective reperfusion of the ischemic region, despite successful recanalization of the culprit vessel (no-reflow).⁵² No-reflow can be diagnosed during coronary angiography using the Thrombolysis In Myocardial Infarction (TIMI) flow grade, TIMI myocardial blush grade, and TIMI frame count.⁵³ Tissue Edema. Changes in capillary permeability, favoring migration of intravascular fluid into the interstitium, can cause myocardial edema and contribute to CMD through extravascular compression. Edema results from a combination of mechanisms including increased interstitial osmolality and vascular permeability, abnormal ionic transport and inflammation.⁵⁴ Coronary microvascular compression favors both intravascular plugging by neutrophil-platelet aggregates and CMVO. Edema can further impair CBF in the setting of ST elevation myocardial infarction (STEMI).^{47, 48} Non-invasive assessment of intramyocardial hemorrhage,⁵⁵ myocardial edema and CMVO can be carried out using T2-based and Inversion Recovery cardiac magnetic resonance (CMR) imaging.²⁸

CMD of different types, as described in previous sections of this review, can trigger unstable angina, NSTEMI or STEMI (“acute MVA”). In this context, two conditions have captured the attention of physicians worldwide, i.e. MINOCA (myocardial infarction with no obstructive CAD) and Takotsubo syndrome. Both have been reviewed extensively elsewhere^{23, 25, 56} and will not be discussed in detail here. A recent large study showed that approximately 8% of all AMI patients are MINOCA cases.⁶ Other studies report a prevalence ranging from 1% to 14%.^{9, 57} It is not known, however, what proportion of MINOCA cases are due to CMD, as opposed to other mechanisms. Regarding Takotsubo syndrome, several authors have suggested that CMD and more specifically, coronary microvascular spasm, are likely to be the underlying cause in a sizeable number of cases.^{23, 24, 58} The diagnosis of acute MVA requires confirmation that no obstructive CAD is present and also documentation of CMD - in the absence of epicardial coronary spasm or acute coronary thrombosis - as the causal mechanism. The assessment of CMD, including microvascular spasm, requires the use of provocative tests with ACh or ergonovine during angiography. The high diagnostic yield of these tests, as discussed in previous sections of this manuscript, indicates that they should be performed routinely as part of the diagnostic pathways for MINOCA and Takotsubo syndrome. Recent studies have shown that these tests are safe if and when carried out by experienced teams even during the acute phase of MINOCA.^{59, 60} Clinical studies showed impaired outcomes in patients with

NSTE-ACS and normal coronary arteries with rates of death or AMI of 1.2% and recurrence of unstable symptoms of 8.4% at 1-year follow-up.⁶¹ In a more recent study in patients with MINOCA the rate of death at 2.5 year follow-up was 11.8%.⁵⁷ The causal mechanism underlying the ACS in these patients was not specifically investigated. In relatively small prospective studies comparing clinical outcomes in acute versus stable MVA, no major cardiac events were observed in either group at a mean follow-up of 36 months.⁶² Controversial results have been published regarding acute symptoms or rates of hospital re-admission with ACS-MVA.^{57, 62} In a very recent study in patients with MINOCA and documented microvascular spasm, mortality at 3-year follow-up was 7.7%.⁶⁰

Large, prospective functional studies are needed to clarify the true role of CMD in Takotsubo syndrome and MINOCA.

MICROVASCULAR ANGINA

The term MVA typically describes myocardial ischemia triggered by CMD in the absence of CAD. “Primary” MVA is a term used to describe subjects with completely normal coronary arteriograms and no clinically identifiable causes for CMD and myocardial ischemia.⁹ As discussed in previous sections of this review, MVA can occur in the presence of conditions such as diabetes mellitus, rheumatic diseases, CAD and in subjects with cardiomyopathies and heart valve disease, such as aortic stenosis.⁹

This section deals with patients who, in the absence of obstructive CAD, have stable angina or angina equivalent symptoms and documented myocardial ischemia caused by a reduced CFR or microvascular spasm.^{9, 17, 63}

Prevalence

Larger numbers of patients than previously thought are now known to have angina in the absence of obstructive CAD, with National Cardiovascular Data Registry (NCDR) and the WISE (Women’s Ischemic Syndrome Evaluation) databases leading to estimations suggesting that in the USA 3 to 4 million women and men with symptoms of angina may have no obstructive CAD.¹⁸ Moreover, data from a large USA registry,⁵ show that over 60% of 398,978 patients undergoing diagnostic coronary arteriography for the assessment of stable angina had normal coronary arteries or non-obstructive CAD (stenoses <50%). This is particularly striking given that a large proportion of individuals in the study had one or more conventional risk factors for CAD and 69% developed transient myocardial ischemia, as assessed by non-invasive diagnostic tests. It needs to be mentioned, however, that the occurrence of chest pain in the absence of obstructive CAD is not necessarily synonymous with MVA. Hence the prevalence of true MVA is likely to be lower than the prevalence of ‘angina without obstructive CAD’.

Clinical presentation and diagnosis

Stable MVA is characterized by effort-induced symptoms similar to those observed in patients with angina triggered by obstructive CAD. Very often, however, MVA patients have also angina at rest and a variable angina threshold, suggestive of dynamic coronary vasomotor changes. Other clinical differences that can help identifying patients with MVA include, among others, prolonged episodes of chest pain, and a relatively poor response to sublingual nitrates in many cases.^{9, 17, 63, 64} Primary MVA is more common in peri- and

post-menopausal women than in men, but the condition should not be considered to be one that affects women exclusively. Importantly, both atypical chest pain and effort induced dyspnea are common symptoms in MVA, particularly in women. In the latter, a history of oophorectomy and symptom exacerbation in specific phases of the menstrual cycle as seen in some patients should alert physicians as to the presence of MVA. Estrogen deficiency has been associated with the development of angina in patients with chest pain and angiographically normal coronary arteries.⁶⁵ In subjects with MVA secondary to cardiomyopathies, heart valve disease, and systemic diseases, symptoms and signs typical of these conditions are also present.

Diagnostic criteria

Recently, the Coronary Vasomotor Disorders Study Group (COVADIS) proposed the following diagnostic criteria for MVA:⁶⁶ signs and symptoms of myocardial ischemia, reduced CFR (defined as the ratio of CBF during near maximal coronary vasodilatation to baseline CBF) or microvascular spasm, and documented myocardial ischemia, which is not triggered by obstructive CAD, but by functional and/or structural abnormalities at the site of the coronary microcirculation. (Table 2). The following represent useful clues for the diagnosis of MVA:

1. Symptoms suggestive of myocardial ischemia. Typical chest pain will alert as to the possible ischemic nature of the symptoms, but chest pain can have atypical features in MVA patients. The presence of both effort and rest angina suggests a possible coexistence of reduced coronary microvascular dilatory function and microvascular (and/or epicardial) spasm.⁶⁴ Angina occurring exclusively at rest will point toward epicardial or microvascular spasm as the prevailing mechanism.

2. Absence of obstructive CAD or objective demonstration that CAD is not responsible for myocardial ischemia. Excluding angiographic atheroma and/or establishing that a stenosis has no effect on coronary physiology, i.e. normal fractional flow reserve (FFR) strongly suggests a microvascular origin of symptoms.⁶⁷

3. Objective documentation of myocardial ischemia. This includes typical ST segment changes during chest pain, as assessed by 12-lead ECG exercise stress testing or 12-lead Holter monitoring and/or ischemic findings on stress echocardiography, single photon emission tomography or CMR perfusion scanning. Of note, in a sizeable proportion of MVA patients these imaging modalities will give negative results -despite the occurrence of ischemia- because, contrary to what is seen in obstructive CAD, myocardial ischemia does not follow a regional pattern in MVA and/or ischemia may be in many cases limited to the subendocardium.^{17, 39}

3. Demonstration of coronary microvascular dysfunction. Functional CMD, i.e. reduced CFR or microvascular spasm) can be investigated during angiography using intracoronary adenosine and ACh. The latter is considered to be the gold standard for the assessment of endothelial-dependent coronary vasodilatation. Adenosine, a powerful endothelial independent dilator of the coronary microcirculation, is used to assess FFR, CFR and the index of microcirculatory resistance (IMR) in the catheterization laboratory. CFR measurements reflect CBF changes influenced by both the epicardial and microvascular compartments and - in the absence of obstructive CAD - CFR

is a good marker of CMD. IMR has been suggested to provide good reproducible assessment of CMD independently from hemodynamic changes.⁶⁸ An exhaustive description of techniques used to assess CMD is beyond the scope of this manuscript. However, recent publications highlight the ability of FFR and IMR to more specifically assess epicardial vessel and coronary microvascular responses, respectively.⁶⁹ Moreover, recent data suggest that IMR measurements may have prognostic value in both stable and ACS patients.⁷⁰ Noninvasive assessment of CMD can be carried out using PET, CMR^{69, 71} and pulsed-wave Doppler assessment of CBF on the left anterior descending coronary artery.⁷²⁻⁷⁶ In 2012, Ong et al³⁸ reported that in patients with effort induced stable angina and non-obstructive CAD (approximately 50% of the total study population) intracoronary ACh, at the time of diagnostic angiography, triggered distal epicardial spasm or microvascular spasm in over 60% of patients. Coronary microvascular spasm, however, is a challenging diagnosis, as intracoronary ACh may affect both the epicardial vessels and the microvasculature when endothelial dysfunction is present thus making it difficult to diagnose microvascular spasm in isolation. Ergonovine, an ergot alkaloid acting on serotonin receptors in the coronary artery has been also used extensively for the diagnosis of coronary artery spasm⁷⁷ with results that are similar to those of ACh.^{36, 37} Both tests have been shown to be safe when performed by experienced operators and following suitable drug administration protocols.^{36, 42, 78}

Clinical outcomes and economic impact

Contrary to prior opinion^{17, 79} more recent studies have shown that prognosis in patients with angina despite the absence of obstructive CAD is not necessarily benign.^{21, 80-82} Both men and women with angina who had impaired CFR despite non-obstructive CAD appear - in different series - to have worse clinical outcomes.^{11, 19, 44, 83-87} As recently reviewed by Bairey-Merz et al,¹⁰ almost two thirds of women undergoing clinically indicated coronary angiography for suspected CAD in the original cohort of the WISE had ischemia with no obstructive CAD^{11,18}. During follow-up, they had a risk rate for major adverse cardiac event (death, nonfatal MI, nonfatal stroke, and hospitalization for heart failure) exceeding 2.5% yearly by 5 years, as well as elevated rates of hospital readmission and repeat angiography. At 10 years, cardiovascular death or MI occurred in 6.7% of those with no evident angiographic CAD and in 12.8% of those with nonobstructive CAD.⁸⁸ In the WISE database, invasively assessed CFR <2.32 was the best predictor of adverse outcomes, with a 5-year MACE rate of 27% versus 9.3% for women with a CFR ≥ 2.32 (P=0.01) Similar outcome findings have been reported using non-invasive assessment of CFR with transthoracic echo Doppler or PET.^{19, 86, 89} One of the problems that hampers the assessment of clinical outcomes in angina patients without obstructive CAD is that studies have used broad and very different inclusion criteria, resulting in heterogeneous groups being assessed. Large, prospective studies, in well-characterized patients, are required to clarify the natural history of angina without obstructive CAD.

In addition to increased rates of adverse cardiovascular events these patients

have an impaired quality of life.^{63, 90} Moreover, they undergo multiple diagnostic investigations, a strategy that imposes a substantial financial burden on health services. In the U.S and in Europe, healthcare costs related to angiography and hospital admission in these individuals are similar to those in patients with obstructive CAD.⁹¹ Taking all of the above together, it is apparent that diagnostic strategies leading to a firm diagnosis of MVA are desirable. Albeit not as yet tested in a clinical trial we propose a diagnostic algorithm based on our own clinical practice and suggestions by other authors, aimed at identifying MVA and characterizing its pathogenic mechanisms.⁹² (FIGURE 5)

Management

The management of MVA represents a major unmet need, as the lack of large randomized studies involving homogeneous patient groups makes it difficult to generate evidence-based recommendations. Recent papers have discussed the management of patients with ischemia and non-obstructive CAD^{10, 92} and suggested potential therapies for CMD,¹⁰ These recommended therapies, however, are not always based on the pathogenesis of MVA, which would be desirable.⁹³ This section briefly discusses treatment options taking into consideration currently accepted pathogenic mechanisms of CMD and MVA. Key objectives of the proposed management strategy are: 1. To improve or abolish myocardial ischemia addressing its mechanisms/causes; 2. To improve quality of life, and 3. To improve prognosis, identifying and tackling mechanisms associated with impaired clinical outcomes. Targets to be addressed include endothelial dysfunction and risk factors, myocardial ischemia caused by impaired dilatory ability of the coronary microvessels and/or microvascular spasm, and chest pain - increased nociception.

Manage endothelial dysfunction, modifiable cardiovascular risk factors and lifestyle. A majority of patients with primary MVA and CMD have endothelial dysfunction, and studies using intravascular ultrasound have shown non-obstructive CAD to be present in a large proportion of patients.⁹⁴ Aggressive management of all modifiable conventional risk factors – hypertension, diabetes mellitus, smoking, obesity, sedentary lifestyle, hyperlipidemia, etc - is of paramount importance in most MVA patient subgroups.^{95, 96} Statins - alone or in combination with other agents - have been shown to have beneficial effects in individuals with coronary endothelial or vascular smooth muscle dysfunction despite non-obstructive CAD.⁹⁷⁻¹⁰¹ Angiotensin-converting enzyme inhibitors (ACE-I) have also been shown to improve exercise tolerance and angina symptoms.^{102, 103} Metformin improves endothelial function in patients with MVA without diabetes mellitus.¹⁰⁴ The ACC/American Heart Association chronic stable angina guidelines² recommend the use of aspirin in patients with myocardial ischemia and no obstructive CAD, but this is not a strong recommendation.

Prevent and treat myocardial ischemia acting on pathogenic mechanisms. Robust evidence for the efficacy of antianginal agents in the treatment of MVA is lacking at present. Marinescu et al¹⁰⁵ carried out a systematic review of the efficacy of current treatment strategies in CMD patients with CFR <2.5, as

assessed by PET, CMR imaging, thermodilution methods, or intracoronary Doppler. Only eight articles met the strict inclusion criteria established by the authors, and a major limitation was the small numbers of patients assessed in these studies.

Calcium channel blockers are likely to represent first line agents for patients with documented microvascular spasm and/or abnormal CFR. Despite controversial data in small studies,^{16, 106} expert consensus seems to highlight the use of calcium channel blockers as the preferred initial option when vasomotor abnormalities, particularly microvascular spasm, are suspected or documented. Nitrates do not appear to have major beneficial effects in MVA. Less than 50% of patients report improved symptoms with the use of sublingual nitroglycerin and a sizeable number have no benefit from oral nitrates. Similarly, little if any evidence exists at present for the use of L-arginine, the precursor of nitric oxide, to improve CMD.¹⁰⁷ Conversely, nicorandil, a potassium ATP channel opener with nitrate like actions has been reported to have beneficial actions in patients with MVA.^{108, 109} Fasudil, a rho-kinase inhibitor and a potent coronary dilator available in Japan for the management of epicardial coronary artery spasm, has also been shown to be effective in patients with CMD.¹¹⁰ β -blockers - alone or in combination with vasodilators - are useful in MVA patients with predominantly effort induced myocardial ischemia in whom a reduction in myocardial oxygen demand may increase exercise capacity.^{9, 111, 112} Caution however is required regarding the use of β -blockers (particularly those lacking vasodilating properties) in patients with microvascular or epicardial spasm, because these agents may increase coronary vasoconstriction by unmasking α -adrenoceptors in the coronary circulation. Another agent that reduces myocardial oxygen demand through its bradycardic effects is ivabradine, but little information exists at present regarding the efficacy of this agent in people with MVA. In small pilot studies of MVA trimetazidine, a metabolic modulator that shifts cardiac metabolism away from fatty acid oxidation improving myocardial metabolism during ischemia, was effective to improve symptoms and exercise capacity.¹¹³ Ranolazine, an inhibitor of the late sodium current,¹¹⁴ improved symptoms and CFR in women with no obstructive CAD and myocardial ischemia associated with CMD. In other studies, however¹¹⁵⁻¹¹⁷ - including a randomized trial -¹¹⁷ ranolazine had no beneficial effects on CMD,¹¹⁶ symptoms or myocardial perfusion reserve when all patients were considered, although the subgroup of MVA patients with a markedly reduced CFR showed an improved response.¹¹⁷

Addressing the problem of abnormal nociception

As abnormal cardiac nociception may be the main cause for chest pain in some patients with MVA,¹¹⁸ tricyclic antidepressants (i.e. imipramine) have been proposed for treatment. Acting centrally these agents have modulatory effects on norepinephrine uptake and anticholinergic actions that may result in analgesia. Imipramine has been shown to improve chest pain in subjects without obstructive CAD¹¹⁹ but side effects requiring discontinuation of the drug are common.¹²⁰

In patients defined as "cardiac syndrome X", xanthine derivatives such as aminophylline were suggested to have analgesic effects resulting from adenosine receptor blockade. They may also have anti-ischemic actions

through attenuation of the coronary microvascular “steal” phenomenon reported in MVA patients. Aminophylline improves exercise tolerance and exercise induced myocardial ischemia in patients with chest pain despite angiographically normal coronaries.¹²¹⁻¹²³ Non pharmacological treatments such as spinal cord stimulation, transcutaneous nerve stimulation (TENS), enhanced external counter pulsation (EECP), cognitive behavioral therapy and other psychological treatments, programmed exercise and cardiac rehabilitation have been proposed that can be effective in managing chest pain. These, however, have been generally assessed in small size studies often involving heterogeneous groups of patients making it difficult to issue strong evidence based recommendations at this point in time.

CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH OBSTRUCTIVE CAD

Three clinical scenarios have been described where CMD is the underlying mechanism of myocardial ischemia, or a major contributor, in patients with obstructive CAD. The first is represented by the fact that CFR may be abnormal not only in territories subtended by flow limiting stenoses, but also in regions supplied by arteries without stenosis,¹²⁴ suggesting that CMD and CAD can coexist and contribute, perhaps synergistically, to the development of myocardial ischemia in some individuals. The second relates to persistent or recurrent angina after successful PCI and coronary stenting. The third relates to CMVO after primary PCI

Evidence of the importance of CMD in patients with CAD has been provided by PET studies showing that the inclusion of CFR in risk prediction models resulted in more precise re-classification of risk of events at follow up.¹⁹ Furthermore, van de Hoef et al. assessed CFR invasively in non-obstructed coronary artery branches in 178 patients with obstructive CAD on diagnostic coronary angiography. After multivariable adjustment, $CFR \leq 2.7$ was associated with a 2.24-fold increase in all-cause mortality hazard.¹²⁵ Similar findings were reported by Gupta et al.¹²⁶ in 4029 consecutive patients (median age 66 years, 50.5% women) with known or suspected CAD who had been referred for rest or stress myocardial perfusion positron emission tomography scans (Figure 6). Moreover, in a prospective, multicenter, observational study in 4,313 patients with known or suspected CAD, Cortigiani et al. showed that $CFR \leq 2$ as assessed by transthoracic Doppler echocardiography, and inducible wall motion abnormalities on stress echocardiography were independent predictors of mortality. Conversely, normal stress echocardiographic results and CFR conferred an annual risk of death $<1\%$.⁸⁷ Also, Taqueti et al.¹²⁷ in a study involving 329 consecutive patients undergoing stress testing with myocardial perfusion PET and invasive coronary angiography that while global CFR was only modestly associated with the overall extent and severity of angiographic disease, a low CFR was strongly and independently associated with adverse clinical events. Also of interest in this study, only patients with a low CFR appeared to benefit from myocardial revascularization using CABG. Taken together these data highlight the importance of CMD as a contributor to ischemia, as a marker for

risk stratification and as guidance to devise successful treatment strategies in patients with obstructive CAD.

Although challenged by a very recent study comparing PCI with a sham procedure¹²⁸ there is general agreement that PCI has some advantages over optimal medical treatment (OMT) regarding symptom control.^{2, 4} Yet, a sizeable proportion of patients continue to experience angina after successful myocardial revascularization with PCI¹²⁹⁻¹³³ In the COURAGE trial, 47% of patients randomized to PCI had persistent angina at 3-month follow-up, and the differences in angina prevalence favoring patients randomized to PCI and OMT vs. those randomized to OMT only, decreased over time and became non-significant at three years of follow-up.¹³⁴ Similar findings were observed in other prospective trials and meta-analyses.¹³⁰⁻¹³³ Thus, angina post-PCI represents an important clinical problem, affecting approximately one fifth to 50% of patients at 1-year follow-up. Data from the FAME 2 trial, however, indicate that when FFR guidance is used to identify flow limiting stenoses the rate of residual chest pain after PCI is significantly lower.¹³⁵

The pathophysiology of angina persisting or recurring after successful PCI is complex and involves both structural and functional mechanisms. Structural causes of post-PCI angina include in-stent restenosis, stent thrombosis, progression of atherosclerotic disease in other coronary segments, incomplete revascularization, and diffuse atherosclerosis without focal stenosis. Functional causes include vasomotor abnormalities of epicardial coronary arteries and/or CMD. Regarding the latter, Ong et al⁴² showed that in 51 of 104 patients (49%) undergoing coronary angiography for recurrent post-PCI angina despite patent stents, epicardial or microvascular coronary spasm, as assessed with ACh provocation, was responsible for the patients' symptoms. Highlighting the role of CMD in post-PCI angina, Li et al.,¹³⁶ found a greater reduction of CBF and a larger IMR increase (intracoronary thermodilution method), in patients with post-PCI recurrent angina compared to patients without recurrent angina. Similar findings were reported by Milo et al.¹³⁷ using transthoracic Doppler echocardiography of the LAD coronary artery. CFR was reduced at 3 and 6 months of follow-up in patients with myocardial ischemia on stress testing after successful PCI, but not in those with normal stress test responses. It has been suggested that drug eluting stent implantation might amplify pre-existing functional abnormalities of the coronary circulation.^{138, 139}

In the primary PCI (PPCI) setting, CMVO has been shown to be associated with adverse left ventricular remodeling, a higher risk of cardiac death, recurrent MI, and heart failure-related re-hospitalization.^{140, 141} Experimental and clinical studies have shown that CMVO is caused by a combination of four pathogenic components: ischemic injury, reperfusion injury, distal embolization and individual susceptibility to reperfusion injury.⁴⁰ An individual "susceptibility" to microvascular dysfunction, i.e. genetic factors, may modulate adenosine-induced vasodilation in this setting. In particular, the 1976T.C polymorphism of the adenosine 2A receptor gene was found to be associated with a higher prevalence of CMVO.⁵¹ Further research is needed

to gain insight into the molecular mechanisms, pathophysiology, prevention and treatment of CMVO.

Summary and conclusions

The information reviewed in this manuscript suggests that CMD plays a substantial pathogenic role across the spectrum of IHD and indicates that MVA caused by CMD can affect large numbers of patients including subjects with no obstructive CAD and individuals with obstructive CAD, as well as those with persisting angina after anatomically successful coronary recanalization. Structural and functional mechanisms affecting the coronary microcirculation can lead to myocardial ischemia. Progress in the diagnosis of myocardial ischemia and the availability of tests to investigate CFR and coronary vasomotion in recent years has allowed a better identification and characterization of MVA patients in everyday clinical practice. Clinical outcome is not necessarily benign in MVA and efforts should be made to identify these individuals at an early stage of their disease. Treatment of the different forms of MVA discussed in this manuscript remains a major unmet need, but strategies exist that can help improving quality of life. Hopefully, future international guidelines on the management of angina will highlight the growing importance of CMD and MVA in the field of IHD.

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