

Clinical update

# Coronary microvascular dysfunction: an update

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Many patients undergoing coronary angiography because of chest pain syndromes, believed to be indicative of obstructive atherosclerosis of the epicardial coronary arteries, are found to have normal angiograms. In the past two decades, a number of studies have reported that abnormalities in the function and structure of the coronary microcirculation may occur in patients without obstructive atherosclerosis, but with risk factors or with myocardial diseases as well as in patients with obstructive atherosclerosis; furthermore, coronary microvascular dysfunction (CMD) can be iatrogenic. In some instances, CMD represents an epiphenomenon, whereas in others it is an important marker of risk or may even contribute to the pathogenesis of cardiovascular and myocardial diseases, thus becoming a therapeutic target. This review article provides an update on the clinical relevance of CMD in different clinical settings and also the implications for therapy.

## Keywords

Acute coronary syndromes • Coronary microvascular dysfunction • Myocardial diseases • Coronary microvascular obstruction • Stable angina

## Introduction

Many patients undergo coronary angiography because of chest pain syndromes believed to be indicative of coronary artery disease (CAD). A significant proportion of such patients, however, are found to have normal-appearing coronary arteries. Several published series have reported that up to 40% of patients undergoing coronary angiography fall into this category.<sup>1</sup>

In 1985, Cannon and Epstein<sup>2</sup> introduced the term 'microvascular angina' (MVA) for this patient population, in view of what appeared to be heightened sensitivity of the coronary microcirculation to vasoconstrictor stimuli associated with a limited microvascular vasodilator capacity. They proposed that dysfunction of small intramural prearteriolar coronary arteries might be the pathogenetic cause of this syndrome.<sup>3</sup> Although there was an initial attempt to group all these patients into one category, it was soon realized that they represent a spectrum from both the pathophysiological and clinical viewpoint.

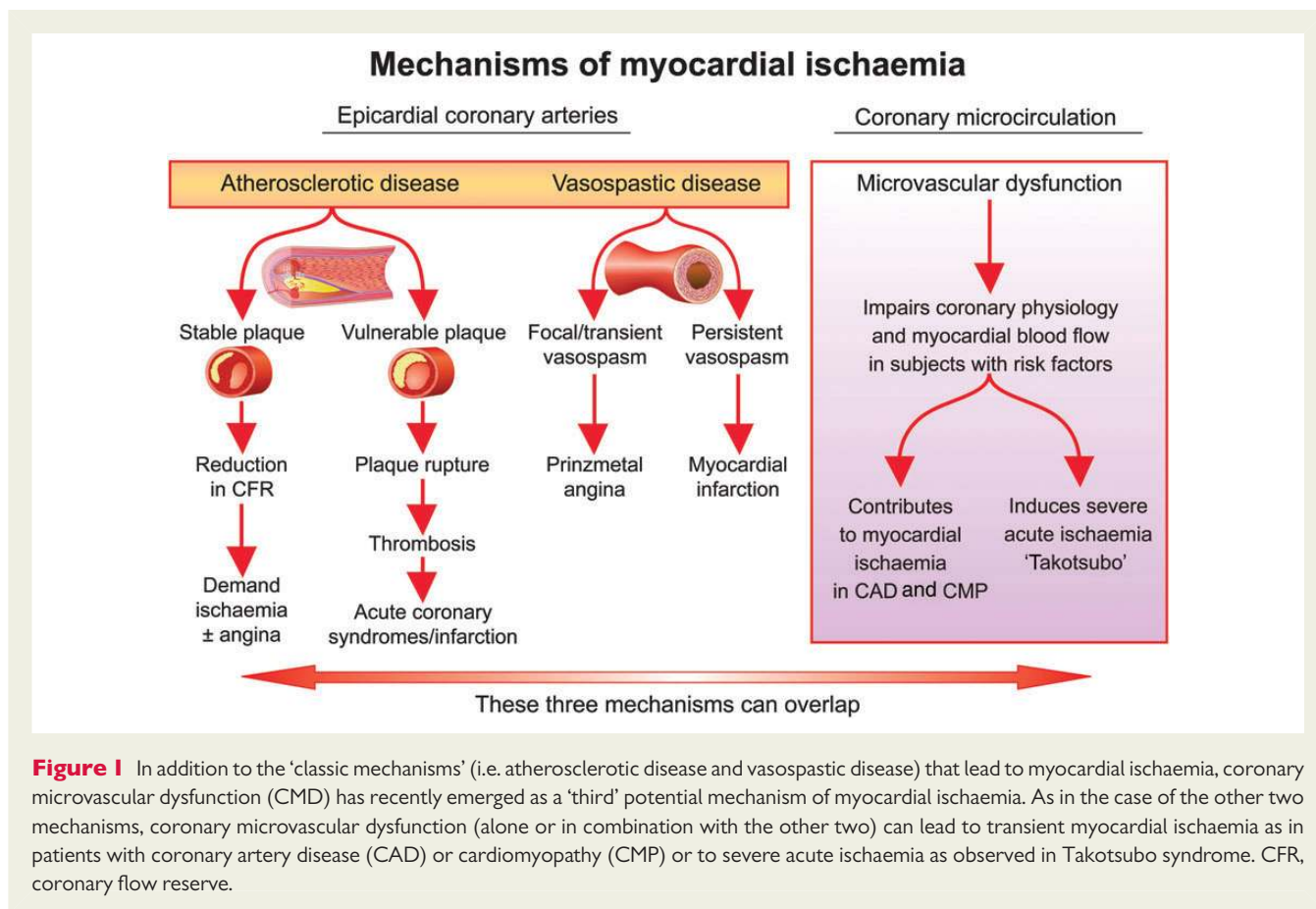
In the past 20 years, a large number of studies using both invasive and non-invasive techniques for the assessment of coronary physiology have produced a large wealth of data leading to a better understanding of coronary microvascular dysfunction (CMD) and microvascular ischaemia. Specifically, studies using positron emission

tomography (PET) have permitted to establish the normal range of absolute myocardial blood flow (MBF, mL/min/g) and of coronary flow reserve (CFR, the ratio of MBF during near maximal coronary vasodilatation to baseline MBF) in healthy volunteers of different age and gender.<sup>4</sup> The availability of normal values of MBF and CFR has allowed the investigation of coronary physiology in subjects at an increased risk of CAD and also in different categories of patients with symptoms and signs, suggestive of myocardial ischaemia despite normal coronary angiograms<sup>5</sup> (Figure 1). Of note, chest pain syndromes with normal angiography represent a wider category including, among others, MVA.

In 2007, Camici and Crea<sup>6</sup> reviewed this subject and proposed original clinical and pathogenetic classifications of CMD. Accordingly, CMD was classified into four main types on the basis of the clinical setting in which it occurs: (i) CMD in the absence of myocardial diseases and obstructive CAD, (ii) CMD in myocardial diseases, (iii) CMD in obstructive CAD, and (iv) iatrogenic CMD. Furthermore, they proposed that several pathogenetic mechanisms can contribute to CMD and their importance varies in different clinical settings, although many of them may coexist in the same condition (Table 1). The molecular pathways of CMD and, in particular of, endothelial and smooth muscle dysfunction have extensively been reviewed in previous articles.<sup>7,8</sup>

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**Table 1** Classification of coronary microvascular dysfunction

	Clinical setting	Main pathogenetic mechanisms
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	Endothelial dysfunction SMC dysfunction Vascular remodelling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Vascular remodelling SMC dysfunction Extramural compression Luminal obstruction
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Endothelial dysfunction SMC dysfunction Luminal obstruction
Type 4: iatrogenic	PCI Coronary artery grafting	Luminal obstruction Autonomic dysfunction

CAD, coronary artery diseases; SMC, smooth muscle cells; PCI, percutaneous coronary intervention.

The aim of this article was to provide an update on CMD based on the more recent literature published on this subject.

## Coronary microvascular dysfunction in patients without myocardial diseases and obstructive atherosclerosis

### Risk factors

A large body of evidence supports the role of traditional risk factors with endothelial-dependent dysfunction and the adverse prognosis associated with this finding. In addition, reports indicate that abnormal non-endothelium-dependent microvascular dilatation appears to be involved in functional and structural alterations that lead to impaired CFR with aging,<sup>9</sup> hypertension,<sup>10,11</sup> diabetes,<sup>12,13</sup> dyslipidaemia,<sup>14,15</sup> and insulin resistance.<sup>16</sup> In most of these reports, the vasodilator stimulus was adenosine, which increases blood flow mostly by non-endothelial-dependent mechanisms via receptors on microvascular smooth muscle cells that modulate intracellular calcium.<sup>17</sup>

### Diabetes

It is associated with CMD not only in the heart but also in other organs such as the eye, kidney, and brain, so deserves specific mention. Chronic hyperglycaemia is associated with significantly reduced endothelial-dependent and endothelial-independent coronary vasodilator function.<sup>18</sup> Further evidence implicates insulin resistance or hyperinsulinaemia,<sup>19</sup> and interventions aiming at improving insulin sensitivity have been shown to improve endothelial function and decrease myocardial ischaemia in patients with no obstructive atherosclerosis.<sup>20</sup> However, other studies demonstrate that hyperinsulinaemia or insulin resistance are not associated when other confounding factors are excluded.<sup>21</sup>

### Chronic inflammation

It is a relatively novel risk factor of increasing importance. High levels of C-reactive protein, as a marker of low-grade chronic inflammation, have been found associated with increased frequency of ischaemic episodes, detected by ambulatory electrocardiogram (ECG) in patients with MVA,<sup>22</sup> suggesting a role for inflammation in the modulation of coronary microvascular responses in these patients.

Accordingly, a high prevalence of CMD has recently been described in patients with systemic lupus erythematosus and rheumatoid arthritis,<sup>23,24</sup> characterized by an inverse correlation between CFR and C-reactive protein concentrations, thus confirming that chronic inflammation may contribute to microvascular abnormalities.<sup>25</sup>

### Other risk factors

Overall, risk factors were associated with CMD, but accounted for <20% of the observed variability in the WISE study.<sup>26</sup> Therefore other, as yet unidentified, factors must primarily account for non-endothelial-dependent CMD. Promising candidates include, but are not limited to, disorders of nitric oxide metabolism, dysregulation of numerous mediators including inflammatory cytokines,

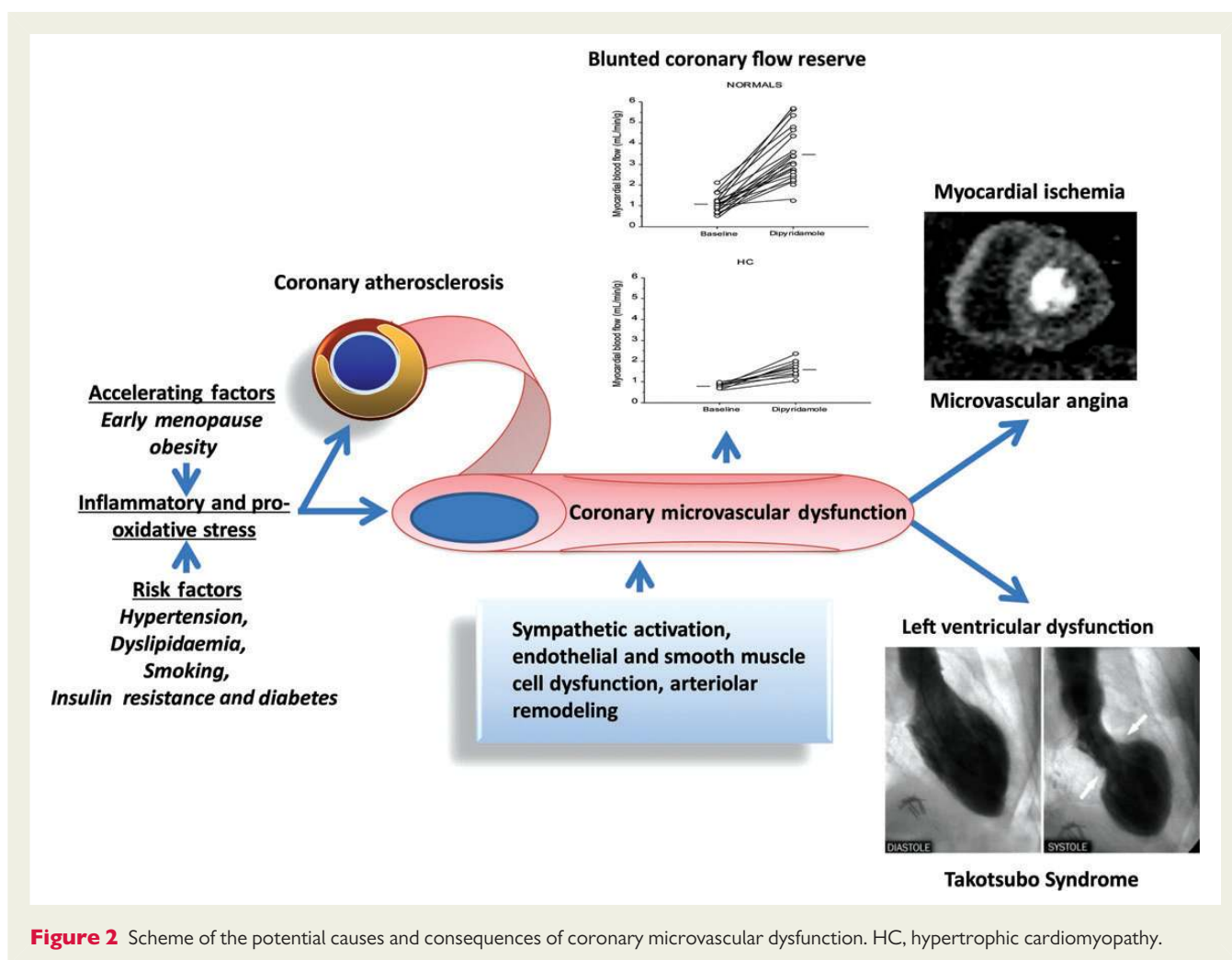
oestrogen, or adrenergic receptors, and alterations in the expression or production of local vasoactive substances such as angiotensin II and endothelin.<sup>27</sup>

### Microvascular angina

As noted above, up to 40% of patients with signs and symptoms of ischaemia undergoing coronary angiography do not have obstructive atherosclerosis.<sup>1,28</sup> Following exclusion of non-coronary causes of chest pain, the presence of coronary vascular dysfunction, ischaemia on stress testing, and chest pain persisting at 1 year of follow-up identify a subgroup at higher risk for adverse clinical outcomes.<sup>29</sup> Estimates from the WISE database show that there are at least 3–4 million patients in the USA alone with signs and symptoms of ischaemia despite no evidence of obstructive atherosclerosis,<sup>30,31</sup> with associated poor quality of life, psychological distress, and health-care costs that approximate those of patients with obstructive CAD. These contemporary data indicate that we should use the terms 'coronary microvascular dysfunction' and 'microvascular angina' for these patients rather than 'angina with normal coronary arteries'. An illustrated model of CMD in the absence of obstructive atherosclerosis is shown in *Figure 2*.

While prior studies failed to demonstrate CMD and myocardial ischaemia in this population,<sup>32</sup> contemporary studies using sensitive measures of ischaemia have documented that the majority of patients with angina and ST segment depression during exercise stress test exhibit regional myocardial underperfusion<sup>33</sup> and signs of ischaemia.<sup>34,35</sup> Accordingly, pathophysiological studies have documented frequent coronary endothelial and non-endothelial coronary dysfunction in patients with signs and symptoms of ischaemia despite the lack of obstructive atherosclerosis,<sup>36</sup> consistent with CMD. In 1991, Maseri *et al.* proposed that the abnormality may not involve all coronary microvessels of a major coronary branch uniformly, but may be distributed in the myocardium in a scattered manner. This distribution of perfusion abnormalities can provide a plausible explanation for the difficulties in obtaining objective evidence of myocardial ischaemia in most MVA patients when standard diagnostic methods are used. Indeed, a sparse distribution of myocardial ischaemia, although sufficient to produce ECG changes and also myocardial perfusion scintigraphic defects, may not result in detectable contractile abnormalities because of the normal function of the surrounding myocardial tissue. Similarly, the release into the coronary sinus of ischaemic metabolites by the sparse myocardial ischaemic foci can go undetected because of their dilution in the larger flow from normal myocardial areas.<sup>37</sup>

Patients with MVA have been considered 'low risk'.<sup>38</sup> Although this issue remains controversial, invasive angiographic data demonstrate that this group includes a spectrum of patients, more frequently women, at higher risk of adverse cardiac events.<sup>39</sup> The WISE study at 5.4-year follow-up demonstrated adverse events including cardiac death (53% being sudden cardiac death), stroke, and new onset heart failure rather than myocardial infarction, in particular in women with reduced CFR assessed by adenosine.<sup>40</sup> Recent studies based on invasive or non-invasive coronary angiography have confirmed the observation of a relatively higher prevalence in women, and extended previous findings showing a higher mortality, although they included patients with angina and normal coronary arteries without systematic exclusion of patients with non-coronary causes of chest pain.<sup>41</sup>



While the relationship between CMD and epicardial atherosclerosis is not fully understood, it has been proposed that it is a single disease process, where response to intimal atherosclerotic injury may vary related to sex differences in vascular remodelling and vascular reactivity, thereby preferentially impacting women.<sup>42,43</sup>

### Stable microvascular angina

Chest pain presentation is often reported by clinicians to differ in women with 'normal' angiograms. Although data from the WISE study indicate that typical vs. atypical angina does not discriminate between obstructive and non-obstructive coronary disease in a population of women undergoing coronary angiography,<sup>44</sup> there is often a variable threshold of physical activity that provokes angina in MVA, low heart rate activities such as mental arousal, or palpitation are more common triggers than in patients with obstructive atherosclerosis. Furthermore, in MVA, chest pain typically persists for several minutes after interrupting efforts and/or shows poor or slow response to short-acting nitrates.<sup>45</sup> Another feature which helps in the differential diagnosis is the response of ECG exercise stress testing to sublingual nitrates. Indeed, while the results of the test typically improve after sublingual nitrates in patients with obstructive atherosclerosis, they remain unchanged or may even worsen in patients with MVA.<sup>46</sup>

Chest pain persisting for many years after angiography in women with apparently 'normal' coronaries is associated with future development of coronary atherosclerosis and an adverse prognosis.<sup>47</sup>

Reduction of CFR assessed non-invasively using PET,<sup>48</sup> cardiac magnetic resonance (CMR),<sup>49</sup> or transthoracic Doppler echocardiography<sup>50</sup> can be useful for diagnosis. Furthermore, angina and ST segment depression in the absence of regional wall motion abnormalities during adenosine or dipyridamole echo-stress represent a distinctive feature of MVA.<sup>51</sup> Perfusion imaging studies have documented that about half of patients with chest pain have reduced CFR in the absence of obstructive CAD.<sup>52</sup> Resolution of chest pain spontaneously or with drugs is associated with improvement of microvascular function.<sup>53</sup>

Currently, invasive coronary vasomotor testing remains the gold standard for the diagnosis of CMD, has a described risk/benefit safety record,<sup>28,54</sup> and is associated to a worse outcome.<sup>55</sup> Diffuse coronary artery spasm pronounced in the distal epicardial coronary arteries and probably extending into the microvasculature may be provoked by intracoronary injection of acetylcholine in a substantial proportion of patients with MVA. Acetylcholine, in solution in 37°C physiological saline (concentration adjusted to obtain 5 mL of solution volume for each quantity of acetylcholine), should be injected in sequential doses (20, 50, and 100 µg into the left coronary artery and 20 and 50 µg) over a period of 20 s. Doses of acetylcholine



should be given at 5-min intervals. Coronary angiography should be performed 1 min after the start of each injection. Angiography should be performed immediately in the event of an ischaemic change on the ECG or chest pain. Nitrates should always be administered at the end of the tests or after documentation of distal spasm.<sup>56</sup>

### Unstable microvascular angina

'Normal' coronary angiograms, defined as luminal narrowing <50%, are reported relatively frequently in patients with acute coronary syndrome (ACS), including 10–25% of women when compared with 6–10% of men.<sup>57</sup> Ongoing investigation is addressing the paradox whereby women have less obstructive CAD and less severe myocardial infarctions, yet worsening clinical outcomes. The higher mortality compared with men has been attributed to advanced age, co-morbidity,<sup>58</sup> and underutilization of guideline care among women;<sup>59</sup> yet, the largest mortality gap is seen in younger women with a number of studies demonstrating persistent sex differences despite covariate adjustment.<sup>60</sup>

### Takotsubo syndrome

Coronary microvascular dysfunction may be involved in apical ballooning syndrome, also known as stress-induced or Takotsubo syndrome. By definition, patients with Takotsubo syndrome do not have obstructive CAD, yet they demonstrate abnormal myocardial perfusion,<sup>61</sup> abnormal CFR measured by echocardiography,<sup>62</sup> and abnormal PET imaging, consistent with an inverse perfusion/metabolism mismatch.<sup>63</sup> Myocardial perfusion, contractility, and left ventricular function improve markedly with the administration of intravenous adenosine in patients with Takotsubo syndrome, but not in those with acute myocardial infarction,<sup>64</sup> while patients with a history of Takotsubo syndrome demonstrate cold pressure test-induced wall motion abnormalities.<sup>65</sup> Furthermore, a long-term follow-up study demonstrated reduced endothelial-dependent response to acute mental stress in patients with a history of Takotsubo syndrome.<sup>66</sup> Taken together, these observations suggest that the syndrome is caused by intense microvascular constriction with subclinical CMD persisting over time, perhaps facilitated by endothelial dysfunction.

## Coronary microvascular dysfunction in myocardial diseases

### Hypertrophic cardiomyopathy

Myocardial ischaemia, due to severe CMD, is an established pathophysiological feature in hypertrophic cardiomyopathy (HCM) and may be associated with important disease-related complications that impact clinical outcome.<sup>67</sup> Marked structural abnormalities of the small intramural coronary arteries, including medial hypertrophy, intimal hyperplasia, and decreased luminal size, are considered the most relevant substrate producing CMD and myocardial ischaemia in HCM.<sup>6</sup> Patients with HCM and demonstrable sarcomere myofibrillar mutations are characterized by more severe CMD and increased prevalence of myocardial fibrosis, compared with genotype-negative individuals.<sup>68</sup>

There is now evidence that late gadolinium enhancement (LGE), as visualized by CMR, is representative of myocardial fibrosis in HCM.<sup>69</sup> The majority of patients demonstrate areas of LGE, and the incidence

of fibrosis was found to increase significantly across quartiles of end-diastolic wall thickness.<sup>70</sup> These findings suggest that CMD over time may lead to recurrent ischaemia and myocyte death, thus acting as a localizer of replacement fibrosis<sup>71</sup> (Figure 3). This has important clinical implications for long-term outcome in HCM patients; indeed, in one-third of the patients, the clinical course is progressive and disabling, leading to chronic limiting symptoms and complications such as atrial fibrillation and stroke, and ultimately causing heart failure-related death.<sup>72</sup> In this subgroup, consistent evidence points to CMD as a critical determinant of clinical progression and adverse outcome.

Accordingly, a recent meta-analysis in over 1000 HCM patients has shown that LGE significantly correlates, at an average follow-up of >3 years, with the development of heart failure and with all-cause and cardiac mortality, with a trend towards significance also for the prediction of sudden death.<sup>73</sup> Based on these studies, extensive LGE at CMR is now considered among the features that indicate an increased risk of sudden death in HCM, together with the classical predictors including a family history of sudden death, unexplained syncope, LV wall thickness of >30 mm, recurrent episodes of non-sustained ventricular tachycardia during ambulatory ECG monitoring, and hypotensive response or attenuated increase in blood pressure during exercise.<sup>74</sup>

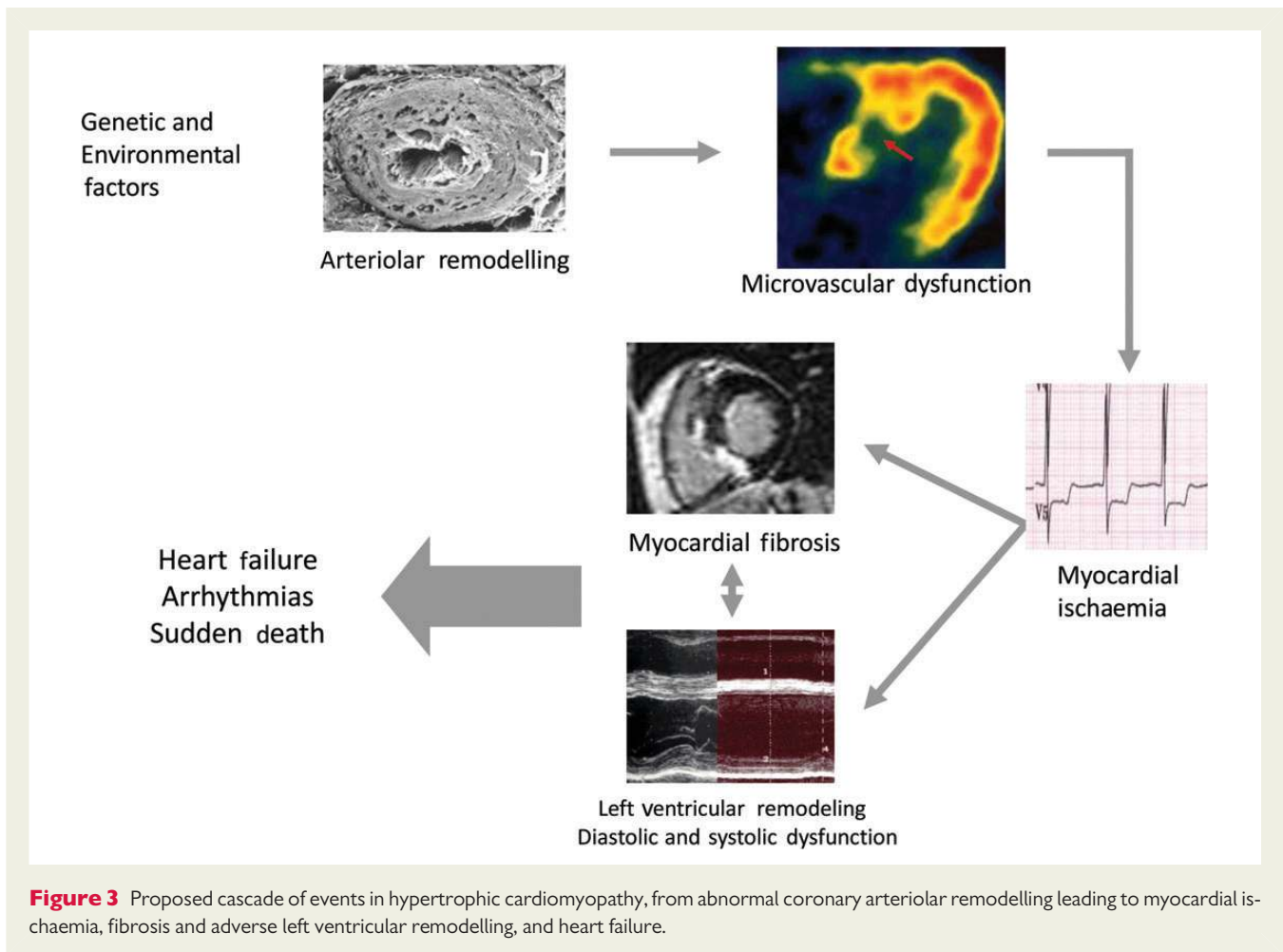
### Dilated cardiomyopathy

It has previously been assumed that myocardial ischaemia does not play a role in the pathogenesis of DCM, because a pre-requisite for the diagnosis of idiopathic DCM is the absence of significant epicardial CAD.<sup>75</sup> Yet, subsequent studies have not only shown that MBF abnormalities occur even in the early stages of the disease, but also that myocardial ischaemia attributable to CMD may have an independent role in the progression of the disease.<sup>76</sup> Although MBF abnormalities were initially attributed to extravascular mechanisms as the result of left ventricle (LV) dysfunction, structural abnormalities of the vessels and reduced capillary density, in conjunction with the abnormal endothelial function that is frequently observed in these patients, can contribute to decreased hyperaemic MBF.<sup>77</sup>

As in patients with HCM, the degree of CMD has been shown to be an independent predictor of cardiac events and is associated with an increased risk of sudden death and further progression of heart failure.<sup>78</sup> Of note, early data suggest that LGE, reflecting the presence of fibrotic areas possibly secondary to CMD, may have a relevant prognostic value in dilated cardiomyopathy, although this hypothesis needs confirmation in larger studies.<sup>79</sup>

### Myocarditis

Recent studies have shown that parvovirus B19 and human herpesvirus 6 are the most common pathogens of viral myocarditis,<sup>80</sup> and that the clinical presentation of patients with myocarditis can be related to the type of virus present in the myocardium.<sup>81</sup> Patients with myocardial parvovirus B19 infection, indeed, seem to mainly present with chest pain, whereas those with myocardial herpesvirus 6 infection or combined parvovirus B19/herpesvirus 6 infection seem to mainly show symptoms of heart failure. It is known that endothelial cells represent specific targets in parvovirus B19-associated myocarditis probably through blood group P antigen.<sup>82</sup> Thus, a causal relationship between parvovirus B19-related myocardial inflammation and/or infection of vascular endothelial cells and CMD can be



suspected. In addition, myocardial inflammation in response to viral infection was found to be associated with increased endothelial expression of human leucocyte antigen system and adhesion molecules, and to be correlated with systemic endothelial dysfunction. Taken together, these findings suggest that symptoms of chest pain in patients with parvovirus B19-associated myocarditis without significant CAD may be caused by intense coronary vasoconstriction, as a result of myocarditis-induced coronary endothelial dysfunction and/or direct infection of endothelial cells and/or smooth muscle cells. Severe vasoconstriction/spasm of microcirculation might contribute to explain ST-segment elevation in some patients, which can result from sufficiently diffuse subepicardial or transmural myocardial ischaemia.<sup>83,84</sup>

## Aortic stenosis

Angina episodes are reported by about half of the patients with a severe degree of aortic stenosis, and this occurs despite the evidence of normal epicardial coronary arteries at angiography.<sup>85</sup> Of note, the appearance of angina greatly increases the risk of sudden death, when compared with that of asymptomatic patients.<sup>86</sup>

Coronary flow reserve is reduced in aortic stenosis<sup>87</sup> due to a combination of mechanisms, including: (i) reduced time of diastolic coronary filling; (ii) increased LV diastolic filling pressure and intramyocardial pressure during diastole, both contributing to

impairment of perfusion selectively in the subendocardium;<sup>88</sup> (iii) reduced capillary density;<sup>89</sup> (iv) a low coronary perfusion pressure when compared with intra-cavitary pressure; and (v) increased intramyocardial systolic pressure and delay in myocardial relaxation at the end of systole, which further reduces time of coronary filling and perfusion.

Post-mortem studies have confirmed capillary rarefaction in aortic stenosis while, in contrast with hypertension and HCM, they failed to find additional structural alterations, which can cause CMD like medial hypertrophy or perivascular fibrosis.<sup>90</sup>

Recent studies in patients with aortic stenosis, based on the measurement of MBF by PET, have shed new light on the mechanisms of CMD. Resting total left ventricular MBF has been found to increase proportionally with left ventricular mass. As this occurs in spite of vascular rarefaction, it is likely that the increase in resting MBF is mainly sustained through metabolic vasodilatation in response to the increased myocardial oxygen demand. This is responsible for a partial exhaustion of the autoregulatory capacity of the coronary microcirculation and, therefore, contributes to limit CFR. These studies have also confirmed the experimental observation that subendocardial perfusion is severely reduced and have shown that the reduction of CFR is strictly related to aortic valve area, to haemodynamic load on the left ventricle, and to the reduced diastolic perfusion time rather than to the increase in left ventricular mass.<sup>91</sup>

## Infiltrative diseases

The role of CMD in infiltrative cardiac diseases is discussed in Supplementary material online.

## Coronary microvascular dysfunction in obstructive atherosclerosis

### Stable coronary artery disease

Several lines of evidence suggest that the direct relationship between chronic obstructive coronary atherosclerosis and angina may represent an overly simplified view. Indeed, many patients with angina and evidence of myocardial ischaemia do not have detectable coronary atherosclerosis at angiography, as highlighted in the section on MVA. Conversely, a number of patients with severe coronary atherosclerotic obstructions do not experience angina. Accordingly, in a recent study, about half of the consecutive patients with an ACS as first manifestation of CAD undergoing coronary angiography exhibited a multivessel disease.<sup>92</sup> This observation strongly suggests that pre-existing obstructive CAD had been silent probably because preserved microvascular function and, more importantly, adequate collateral development prevented angina and ischaemia in spite of obstructive CAD.

The 'plaque-centric' hypothesis can also be called into question when the impact of therapeutic strategies based on the removal of coronary atherosclerotic obstructions is considered. Most reports agree that, on a background of medical therapy, revascularization improves symptoms, but in many patients angina recurs after 2–3 years while myocardial infarction and death are not prevented, as clearly shown in a recent comprehensive meta-analysis.<sup>93</sup>

These observations certainly do not deny the usefulness of revascularization in patients with ACS, when coronary revascularization is needed to prevent an impending catastrophe, but they do raise questions about whether revascularization should continue to be regarded as the ultimate treatment for obstructive atherosclerosis in stable patients. Thus, in patients with stable angina who do not have a large area at risk of myocardial ischaemia, the main goal of treatment remains global risk factor control and anti-anginal treatment possibly targeting both large epicardial coronary arteries and coronary microcirculation.

### Acute coronary syndromes

The temporal association between events occurring in large epicardial vessels (plaque erosion or fissure associated with thrombus formation) and in the microcirculation (paradoxical vasoconstriction) does not allow to establish what is the causal relation between these two events. It is widely believed that epicardial events precede and cause microvascular events. A more extreme view is that, at least in a proportion of patients, a primary CMD might play a causal role in determining thrombus formation in epicardial coronary arteries. Several lines of evidence support this working hypothesis which has recently been proposed by Lerman *et al.*<sup>94</sup>

In the setting of ST elevation myocardial infarction (STEMI), a specific pathophysiological condition is represented by CMD, which occurs after successful recanalization of the infarct-related artery. Prompt referral for mechanical reperfusion by urgent primary

percutaneous coronary intervention (PCI) represents the pivotal step in the current management of STEMI.<sup>95</sup> Yet, in a sizable proportion of patients, primary PCI achieves epicardial coronary artery recanalization, but not myocardial reperfusion, a condition known as 'no-reflow' and currently more commonly defined as microvascular obstruction (MVO).<sup>96</sup>

In 1993, at the climax of the thrombolytic era, Lincoff and Topol<sup>97</sup> wrote a provocative editorial wondering whether reperfusion was just an illusion. At that time, they estimated that only '25% or less' of patients treated by thrombolysis had an optimal reperfusion, defined as a rapid, complete, and sustained coronary recanalization with adequate myocardial tissue perfusion. What is this figure after 15 years at the climax of primary PCI era? A reasonable estimate of the proportion of patients who get optimal myocardial reperfusion, among those without cardiogenic shock undergoing primary PCI, is ~35%.<sup>98,99</sup>

A series of consistent data have clearly shown that MVO has a strong negative impact on outcome, negating the potential benefit of primary PCI.<sup>100,101</sup>

In man, MVO is caused by the variable combination of four pathogenetic mechanisms: (i) distal atherothrombotic embolization; (ii) ischaemic injury; (iii) reperfusion injury; and (iv) individual susceptibility of coronary microcirculation to injury.

The notion that the susceptibility of coronary microcirculation to injury varies in different patients is supported by the observation that in man, MVO is occasionally observed during elective percutaneous coronary procedures,<sup>102</sup> while it can be absent following primary PCI carried out several hours after coronary occlusion. Predisposition may be acquired and/or genetic. In particular, diabetes has been associated with impaired microvascular reperfusion after primary PCI, and hypercholesterolaemia in animal models aggravates reperfusion injury by enhancing endothelial oxidative stress.<sup>103,104</sup> Of note, ischaemic pre-conditioning appears to have a beneficial effect on microvascular function.<sup>105</sup> With regard to genetic predisposition, the 1976T>C polymorphism of the adenosine 2A receptors gene was suspected to be associated with a higher prevalence of MVO, but this working hypothesis has never been proved.

## Iatrogenic coronary microvascular dysfunction

### Percutaneous interventions

The clinical relevance of distal embolization following PCI and resulting in CMD is considerable. In a recent comprehensive meta-analysis, Testa *et al.* have assessed the occurrence and prognostic impact of troponin (Tn) elevation in patients with normal baseline levels undergoing PCI. Tn elevation after PCI occurred in about one-third of patients. At 18-month follow-up, peri-procedural Tn elevation was associated with a 50% increased risk of subsequent major cardiovascular events, a two-fold increased risk of death, a three-fold increased risk of myocardial infarction, and a 50% increased risk of re-PCI.<sup>106</sup>

It is only possible to speculate as to why peri-procedural myocardial necrosis marker elevations influence long-term mortality. One potential mechanism may be related to the myocardial damage per se, which might lead to increased mortality as a result of electrical instability or of persistent myocardial ischaemia associated with CMD. Alternatively, raised necrosis marker levels after PCI may signal a

more active atherosclerotic process associated with an adverse prognosis due to a higher risk of cardiovascular events.

Finally, there is evidence that, in patients with stable CAD and exercise inducible ischaemia undergoing elective PCI, CFR does not recover immediately after the procedure despite successful recanalization, suggesting persistent functional CMD as elegantly demonstrated by Uren *et al.*<sup>107</sup> by PET.

## Surgical interventions

Surgical trauma and cardiopulmonary bypass contribute to a systemic inflammatory response, measurable by circulating cytokines, which promotes CMD.<sup>108,109</sup> This can be the result of many factors, including contact of blood with the bypass circuit, myocardial ischaemia during bypass, aortic cross clamping, and reperfusion injury. Perioperative myocardial infarction results in further elevation of inflammatory markers.<sup>110,111</sup> Spyrou *et al.* measured MBF and CFR in patients undergoing coronary artery bypass grafting (CABG) using PET. They found that hyperaemic MBF and CFR improved progressively over the 6 months following CABG, suggesting persistent CMD that recovers slowly after surgery.<sup>112</sup>

One study using LGE at CMR imaging and TnI measurement found that about one-third of the patients undergoing CABG had new myocardial infarction demonstrated by CMR, and that a cut-off of TnI of 5 µg/L (upper normal limit of 0.6 µg/L) at 1 h had 67% sensitivity and 79% specificity for detecting the new infarction. In this study, the predictive value of creatin kinase-myocardial band (CK-MB) for the diagnosis of myocardial infarction was lower than that of TnI: using a cut-off of CK-MB of 25 µg/L (upper normal limit of 4.8 µg/L) at 1 h had 44% sensitivity and 89% specificity for detecting the new infarction.<sup>113</sup> Substantial biomarker elevations after CABG have been shown to have significant prognostic implications.<sup>114</sup>

The fact that different mechanisms of injury following PCI and CABG have similar prognostic implications suggests that patient prognosis is eventually driven by the extent of necrosis regardless of the mechanisms responsible for its occurrence.

The prognostic impact of myocardial damage following CABG, assessed by enzyme elevation, is clinically relevant. Indeed, post-procedural enzyme elevation is a potentially important surrogate endpoint for clinical trials. Also of significance is the potential use of these enzyme elevations as a measure of procedure quality, including the comparison of different centres and even of individual operators. Important in this regard will be standardizing the post-procedure time when enzyme levels should be determined. Future effort should be directed to achieving a better understanding of the mechanisms that contribute to procedural myocardial necrosis, particularly those that are under the control of the operator and thus potentially amenable to easy correction.

## Treatment of coronary microvascular dysfunction

### Coronary microvascular dysfunction in the absence of myocardial diseases and obstructive coronary artery disease

Neglia *et al.* using PET demonstrated that hyperaemic MBF and CFR were significantly improved in patients with hypertension and left

ventricular hypertrophy following treatment with perindopril and indapamide for 6 months, suggesting reverse remodelling of intramural arterioles. The latter hypothesis has been confirmed in an ancillary study in spontaneously hypertensive rats, where the same drugs improved coronary flow and histology provided evidence of significant reverse remodelling of coronary arterioles.<sup>115</sup>

In patients with MVA, a first important line of treatment is represented by life style modification such as smoking cessation and weight-loss, which are known to improve endothelial dysfunction and CMD, and should therefore be strongly encouraged.<sup>116</sup> Notably, the proven benefit of exercise training in this population<sup>117</sup> suggests that adrenergic modulation may play an important role. Furthermore, statins and angiotensin converting enzyme (ACE) inhibitors, in hypertensive patients, which improve endothelial dysfunction, should represent a first line of treatment in patients with MVA.<sup>118,119</sup>

Much of the evidence of treatment in patients with CMD, however, has focused on improvement in symptoms. Many anti-ischaemic therapies have been evaluated including data that calcium antagonists do not improve CFR and show inconsistent effects on symptoms,<sup>120</sup> while beta-blockers are effective for improving chest pain symptoms.<sup>121</sup> No controlled studies are available on the effects of long-acting nitrates on health status outcomes, while the efficacy of sublingual nitrates seems less consistent than in patients with obstructive CAD.<sup>122</sup>

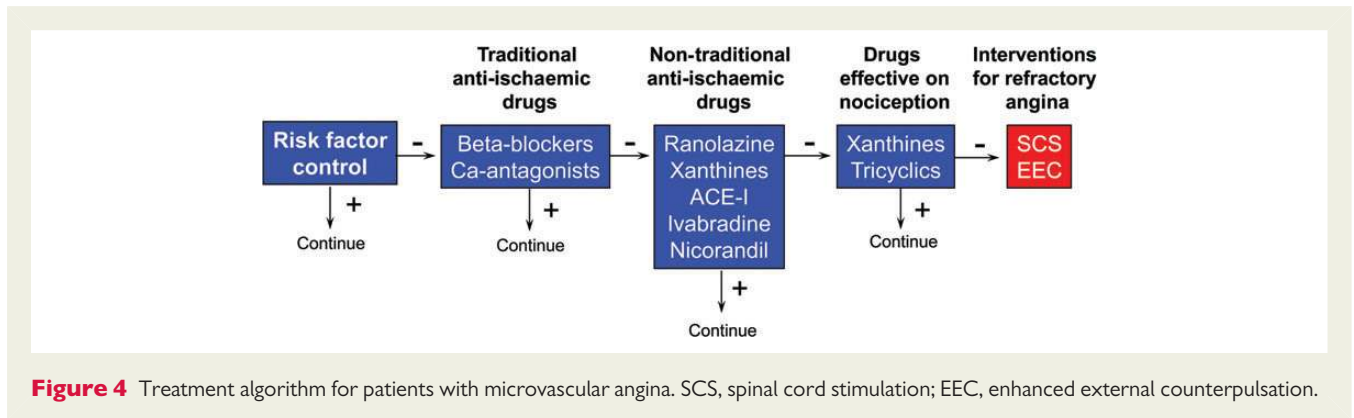
A small trial in women with CMD demonstrated angina improvement measured by the Seattle Angina Questionnaire on ranolazine compared with placebo as well as trends towards improvement in myocardial perfusion abnormalities by CMR imaging.<sup>123</sup> In a more recent study, ranolazine improved both angina status and exercise stress test results in patients with MVA, when compared with ivabradine or placebo.<sup>124</sup>

The beneficial effects of xanthines in MVA can be related to two different mechanisms.<sup>125,126</sup> First, xanthines inhibit the arteriolar dilator effects of adenosine, through antagonism of vascular A<sub>2</sub> receptors on smooth muscle cells thus favouring CBF redistribution towards myocardial areas with CMD.<sup>127</sup> Secondly, xanthines might exhibit an 'analgesic' effect, as they antagonize the stimulation of cardiac nerve pain fibres by adenosine, which is a major mediator of ischaemic pain.<sup>128</sup> Nicorandil, a nitrate and adenosine triphosphate sensitive potassium channel agonist, has been shown to improve peak exercise capacity, but failed to significantly improve exercise-induced ST changes.<sup>129</sup>

Alpha antagonists, such as doxazosin block alpha-mediated vasoconstriction, have not been shown to improve angina, exercise duration, or ischaemia by ECG.<sup>130</sup> The rho-kinase inhibitor, fasudil, has been shown to prevent acetylcholine-induced ischaemia in these patients.<sup>131</sup>

Other therapies have been evaluated in women without obstructive CAD. Imipramine improves symptoms in patients with abnormal cardiac pain perception and normal coronary angiograms; possibly through a visceral analgesic effect. Imipramine also has anticholinergic and alpha antagonist effects demonstrated in both the coronary and peripheral circulation.<sup>132</sup> Menopausal hormone therapy may improve emotional well being in postmenopausal women with angina and 'normal' angiograms; yet, there is no symptom benefit for these patients.<sup>133</sup>





**Figure 4** Treatment algorithm for patients with microvascular angina. SCS, spinal cord stimulation; EEC, enhanced external counterpulsation.

Finally, more demanding forms of treatment are spinal cord stimulation<sup>134</sup> and enhanced external counterpulsation.<sup>135</sup>

Figure 4 summarizes the proposed treatment algorithm for patients with MVA. All patients should receive optimal risk factor control. If symptoms are not well controlled, addition of traditional and non-traditional anti-ischaemic drugs is recommended. In patients in who enhanced pain perception is suspected drugs which modulate pain perception are indicated. Interventions like spinal cord stimulation, enhanced external counterpulsation, and cognitive behavioural therapy should be reserved to patients with refractory symptoms, which seriously limit life quality.

Developing strategies to provide effective prevention and treatment of CMD and angina is urgently needed. Appropriately powered, randomized, outcome trials testing management strategies have not been conducted in the 'at-risk' population. Existing guidelines focus on symptom management and current clinical practice on 'reassurance'. This appears to be insufficient because ischaemia-related symptoms frequently recur and these patients incur in relatively large health-care costs, in addition to the major adverse cardiac events. Large-scale, practical, outcome trials testing the efficacy of currently available traditional anti-atherothrombotic and anti-ischaemic therapy, as well as novel therapies in this population, are warranted.

## Coronary microvascular dysfunction in myocardial diseases

Although CMD has been demonstrated and might play a pathogenetic role in most myocardial diseases, studies specifically assessing the effect of therapy on CMD are largely lacking.

In HCM, alcohol septal ablation seems to improve CFR and septal endocardial-to-epicardial MBF,<sup>136,137</sup> while verapamil, disopyramide, and ACE inhibitors fail to improve myocardial perfusion.<sup>138–141</sup>

In patients with dilated cardiomyopathy, beta-blockers<sup>142,143</sup> but not calcium antagonists or ACE inhibitors<sup>144</sup> seem to have beneficial effects on CMD, likely as a result of improved haemodynamics. Of note, favourable effects on CMD have recently been reported by treatment with allopurinol.<sup>145</sup>

While CMD can be present and play an important role in the clinical presentation of acute myocarditis, no study has hitherto assessed the effects of any form of intervention on CMD in these patients. Thus, consequences of treatment and their clinical implications remain undefined.

As discussed above, a short diastolic time plays a significant role in causing reduction of CFR and angina in patients with aortic stenosis. Thus, drugs that increase diastolic time, like beta-blockers, might help in delaying the ominous onset of myocardial ischaemia and angina in these patients. As an alternative, in case of contraindication or intolerance to beta-blockers, ivabradine, known to selectively reduce heart rate but not blood pressure, might be of help in this setting. These considerations, however, are purely speculative, as clinical studies about the effects of these drugs on coronary microvascular perfusion and on angina and clinical outcome are lacking and should therefore be investigated in prospective randomized trials.

The treatment of infiltrative cardiac diseases is discussed in Supplementary material online.

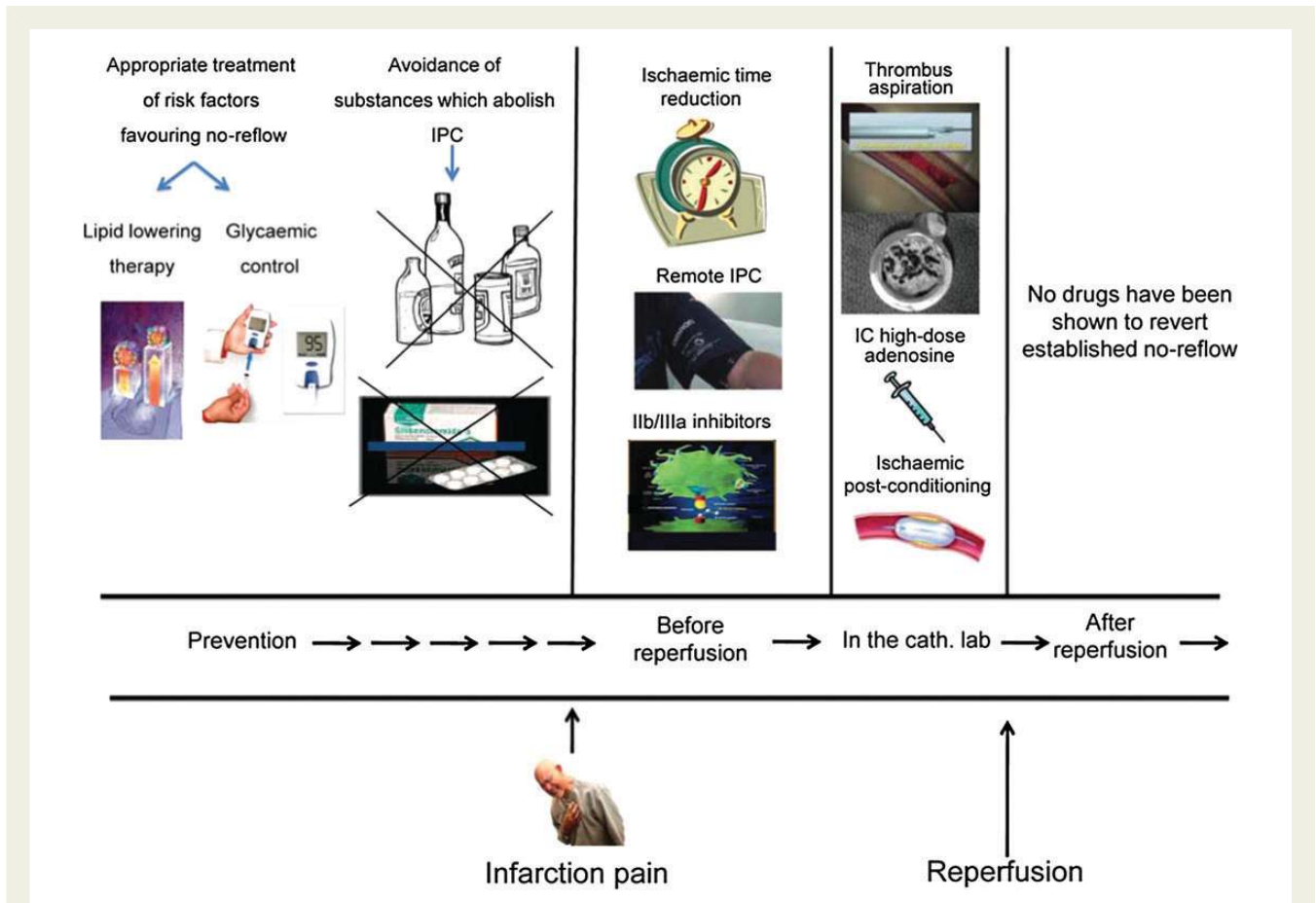
## Coronary microvascular dysfunction in obstructive coronary artery disease

Therapeutic interventions able to promote collateral growth may have an impact on outcome and also on symptoms in patients with refractory angina, i.e. those who are judged not to be candidates for revascularization procedures.

Several forms of therapy have been proposed to promote angiogenesis and collateral circulation,<sup>146</sup> but their role still waits to be definitely clarified.

Gene therapy initially appeared as the most valid approach to stimulate and enhance microcirculation and collateral growth in refractory angina, but controlled randomized studies have on the whole been disappointing with no or negligible benefit on symptoms and myocardial ischaemia, when compared with control groups.<sup>147</sup> More recently, attempts to promote collateral circulation in patients with refractory angina have been based on the intramyocardial administration of progenitor vascular cells.<sup>148</sup> The early clinical results, although promising, do not allow to establish firm conclusions about the efficacy of these form of therapy, which needs to be addressed in larger studies.

In the setting of ACS, an important, largely unmet therapeutic need is the prevention of MVO after primary PCI. Distal embolization of thrombus and debris material has been suggested to play a major role. Accordingly, two small randomized studies<sup>149,150</sup> found a beneficial effect of manual thrombus aspiration vs. the standard procedure on surrogate endpoints of myocardial reperfusion. Then, in a medium-sized trial, patients undergoing primary PCI were randomized to



**Figure 5** Prevention more than treatment has a central role in the management of microvascular angina. It starts before infarction pain occurs by targeting risk factors and by avoiding the blockage of ischaemic pre-conditioning. After the onset of infarction pain and before hospital arrival, the reduction in ischaemic time, an early administration of IIb/IIIa inhibitors, and remote ischaemic pre-conditioning have an important role. In the catheterization laboratory, the use of thrombus aspiration, high doses of intracoronary adenosine, and ischaemic post-conditioning are good opportunities to prevent microvascular obstruction (MVO). No drugs have been shown to reverse established microvascular obstruction (from Ref. <sup>110</sup>). IC, intracoronary; IPC, ischaemic pre-conditioning.

**Table 2** Diagnosis, prognostic value, and treatment of coronary microvascular dysfunction in different clinical settings

Type of CMD	Specific diseases	Diagnosis	Impact on outcome	Treatment
Type 1	RF	TTDE	Unknown*	RF control
	MVA	TTDE, CMR	Documented	RF control, see Figure 4
Type 2	HCM	CMR, PET	Documented	Alcohol septal ablation?
	COCM	CMR, PET	Unknown	Allopurinol
	PVB9 Myocarditis	A-Ch	Unknown	Unknown
	AFD	CMR, PET	Unknown	Beta-galactosidase?
	Amyloidosis	CMR, PET	Unknown	Unknown
	AS	CMR, PET	Unknown	Beta-blockers, Ivabradine?
Type 3	Stable angina	Angina after PCI	Unknown	Angiogenesis
	MVO after pPCI	BG, STR, CMR	Documented	See Figure 5
Type 4	PCI	Tn raise	Documented	Statins, alpha-blockers?
	CABG	Tn raise	Documented	Statins

A-ch, acetylcholine test; AFD, Anderson-Fabry's disease; AS, aortic stenosis; BG, blush grade; CABG, coronary aortic bypass graft; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; COCM, congestive cardiomyopathy; HCM, hypertrophic cardiomyopathy; MVA, microvascular angina; MVO, microvascular obstruction; PET: positron emission tomography; pPCI, primary percutaneous coronary intervention; PVB, Parvovirus B9; RF, risk factors; STR, ST segment resolution; Tn, troponin; TTDE, transthoracic Doppler echocardiography.

It is unknown the incremental prognostic value of coronary microvascular dysfunction in addition to that conveyed by risk factors

thrombus aspiration or standard treatment; thrombus aspiration was associated with a significant reduction of major cardiac events (death/re-infarction) at 12 months.<sup>151,152</sup> This study, however, was characterized by an unusually high rate of deaths in the control group. Furthermore, in a recent study, thrombus aspiration failed to reduce mortality at 30 days.<sup>153</sup>

With regard to pharmacological therapy, intracoronary adenosine administration appears to be the most promising approach. Accordingly, a recent medium-sized controlled randomized trial found that a high dose of intracoronary adenosine, but not nitroprusside, given immediately after thrombus aspiration in patients treated with abciximab, was associated with a lower rate of MVO when compared with placebo; the trial was not powered, however, to assess the effects on clinical endpoints.<sup>154</sup>

Finally, an attractive form of treatment is ischaemic conditioning, which is known to increase resistance of myocardial cells to ischaemic injury.<sup>155</sup> In particular, ischaemic post-conditioning<sup>156,157</sup> and remote pre-conditioning<sup>158</sup> have been found to improve MVO.

Furthermore, in small pilot studies, cyclosporine<sup>159,160</sup> and atrial natriuretic peptide,<sup>161</sup> which activate the molecular pathway triggering ischaemic pre-conditioning, have been shown to reduce infarct size. However, these promising early findings need to be confirmed in larger studies with clinical endpoints.

Figure 5 summarizes a therapeutic algorithm for the prevention of MVO.

## Iatrogenic coronary microvascular dysfunction

The treatment of iatrogenic CMD is discussed in Supplementary material online.

**Conflict of interest:** none declared.

## Future perspectives

The large body of evidence on the role of CMD in cardiovascular diseases and summarized in the current review indicates that an assessment of coronary microcirculation is frequently needed for optimal patient management. Although, in some instances, CMD represents an epiphenomenon, more frequently, it is an important marker of risk thus providing useful information in risk stratification, as it is the case in hypertrophic and dilated cardiomyopathy or may even contribute to the pathogenesis of cardiovascular and myocardial diseases, thus becoming a therapeutic target as it is the case in patients with stable angina or MVO after primary PCI. The clinical implications of the four types of CMD discussed in this review are summarized in Table 2.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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