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REVIEW

Frontiers in cardiovascular medicine

Coronary microvascular dysfunction in the clinical setting: from mystery to reality

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Far more extensive than the epicardial coronary vasculature that can be visualized angiographically is the coronary microcirculation, which foregoes routine imaging. Probably due to the lack of techniques able to provide tangible evidence of its crucial role, the clinical importance of coronary microvascular dysfunction is not fully appreciated. However, evidence gathered over the last several decades indicates that both functional and structural abnormalities of the coronary microvasculature can lead to myocardial ischaemia, often comparable with that caused by obstructive coronary artery disease. Indeed, a marked increase in coronary microvascular resistance can impair coronary blood flow and trigger angina pectoris, ischaemic ECG shifts, and myocardial perfusion defects, and lead to left ventricular dysfunction in patients who otherwise have patent epicardial coronary arteries. This condition—often referred to as 'chest pain with normal coronary arteries' or 'cardiac syndrome X'—encompasses several pathogenic mechanisms involving the coronary microcirculation. Of importance, coronary microvascular dysfunction can occur in conjunction with several other cardiac disease processes. In this article, we review the pathogenic mechanisms leading to coronary microvascular dysfunction and its diagnostic assessment, as well as the different clinical presentations and prognostic implications of microvascular angina. As such, this review aims to remove at least some of the mystery surrounding the notion of coronary microvascular dysfunction and to show why it represents a true clinical entity.

Keywords Cardiac syndrome X • Coronary flow reserve • Microvascular angina • Prognosis

Introduction

Contrary to the epicardial coronary vasculature, the coronary microcirculation has remained elusive to conventional imaging techniques (*Figure 1*). For this reason, possibly, the clinical significance of coronary microvascular dysfunction (CMVD) has not been given as much attention as epicardial coronary artery disease (CAD). In particular, a condition often referred to as 'chest pain with normal coronary arteries' or 'cardiac syndrome X' (CSX) has puzzled physicians over the years and continues to represent an unsolved 'mystery' rather than a reality for many in clinical practice.[1,2] However, various lines of evidence in recent years have identified an important role for the coronary microcirculation in the clinical presentation and prognosis of patients who have typical chest pain despite a normal coronary angiogram and also in patients with other cardiac conditions. This article intends to bring this subject closer to the practising cardiologist. We will review the functional aspects of the coronary microcirculation, the diagnostic tests used for the assessment of CMVD, its clinical presentation, and prognosis. The therapeutic management of patients with CMVD, however, will not be reviewed in the present article.

Functional aspects of the coronary microcirculation

The coronary blood flow (CBF) is driven by the pressure difference between the aortic sinus and the coronary sinus (or the right atrium pressure). In the absence of obstructive stenoses, the epicardial arteries offer very little (~10%) resistance to CBF and serve mainly as conductance vessels. Capillaries and venules are likewise responsible for only 10% of CBF resistance and mainly function as capacitance vessels, holding 90% of the total myocardial blood volume. Under normal conditions and to a large extent also under pathological conditions, coronary vascular

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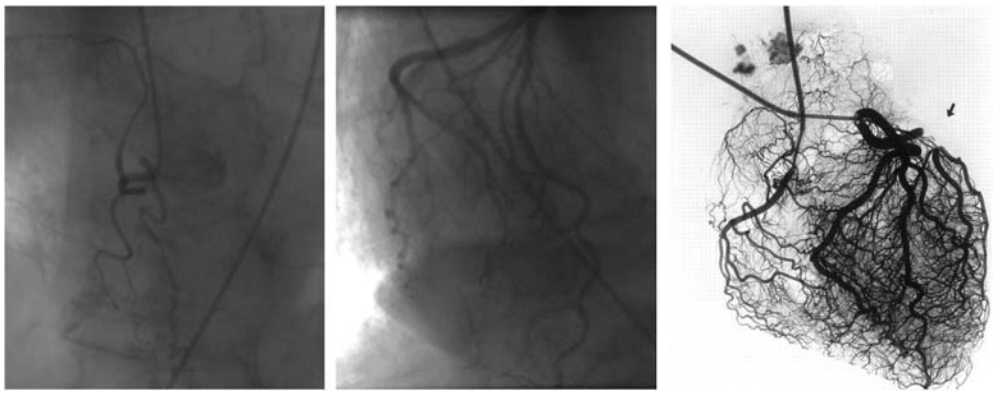

Figure 1 Angiogram of the right coronary artery (left panel) and a dominant left coronary artery system (middle panel), which do not reveal the rich microvascular network noted on an *ex vivo* arteriogram.[111]

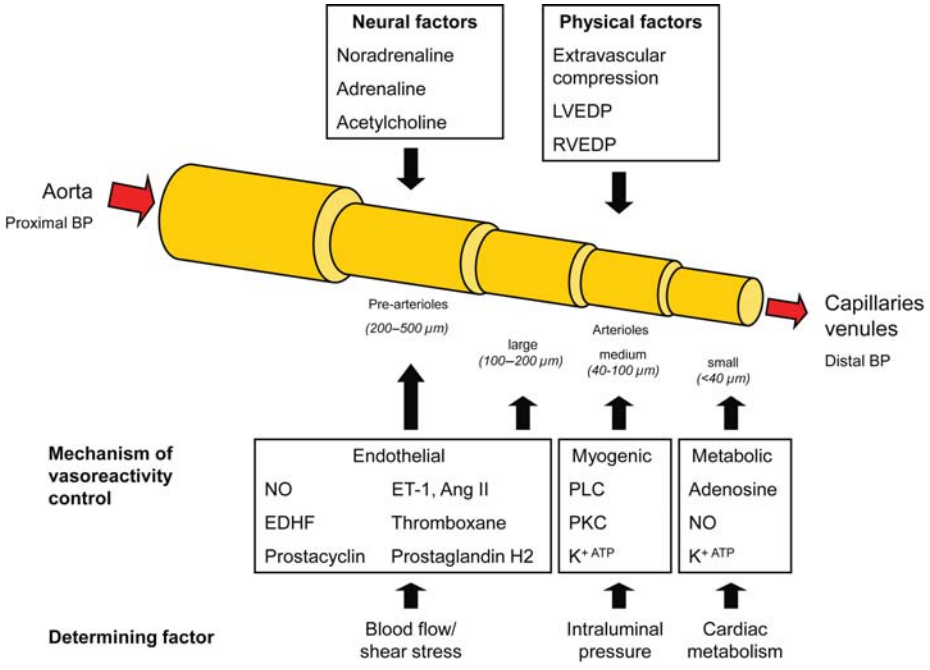

Figure 2 Coronary blood flow is driven by the pressure difference between the aorta and the capillary bed and modulated further by various physical and neural factors, which affect the microcirculation. Moreover, the different compartments of the microcirculation are influenced by one main physiological mechanism to control their vascular tone with cardiac metabolism as the final determining factor.

resistance is primarily controlled by the pre-arterioles (vessels $<500\,\mu m$ in diameter) and arterioles ($<200\,\mu m$). The pre-arterioles are epicardial (extra-myocardial) vessels that react to changes in shear stress and intravascular pressure to preserve adequate perfusion pressure in the distal arteriolar bed. They are responsible for ~25% of the total coronary vascular resistance.[3] The arterioles are the true intramyocardial regulatory component of the coronary circulation and these vessels represent the largest proportion (~55%) of the total coronary vascular resistance. Arterioles are usually subdivided in two categories, according to their diameter and the mechanism(s) that regulates their tone (*Figure 2*).[3,4] Endothelium-dependent vasoreactivity prevails in the larger arterioles ($100-200\,\mu m$ in diameter) and translates flow-related stimuli into vasomotor responses, i.e. vasodilation with increase in flow and vice versa. Medium-sized microvessels ($40-100\,\mu m$ in diameter) react predominantly to intraluminal pressure changes sensed by stretch receptors located in vascular smooth muscle cells (myogenic control), i.e. they constrict when the intraluminal

pressure increases and, conversely, dilate when the pressure decreases.[5] Finally, the tone of the smaller arterioles (vessels <40 μm in diameter) is modulated by the metabolic activity of the myocardium. As such, increased metabolic activity leads to vasodilatation of the smaller arterioles, which leads to pressure reduction in the medium-sized microvessels and myogenic dilation, which, in turn, increases flow upstream resulting in endothelium-dependent vasodilation.[3] These mechanisms effectively and efficiently allow the microcirculation to regulate myocardial perfusion both at rest and at different levels of myocardial metabolic demand.

Assessment of the coronary microcirculation: functional vs. anatomical techniques

A technique that allows an approximate 'visualization' of the microcirculation in clinical practice is the injection of dye into the coronary artery resulting in myocardial opacification—also known as myocardial blush (*Figure 3*).[6] Magnetic resonance imaging (MRI) can also outline microvascular obstruction albeit indirectly and with relatively

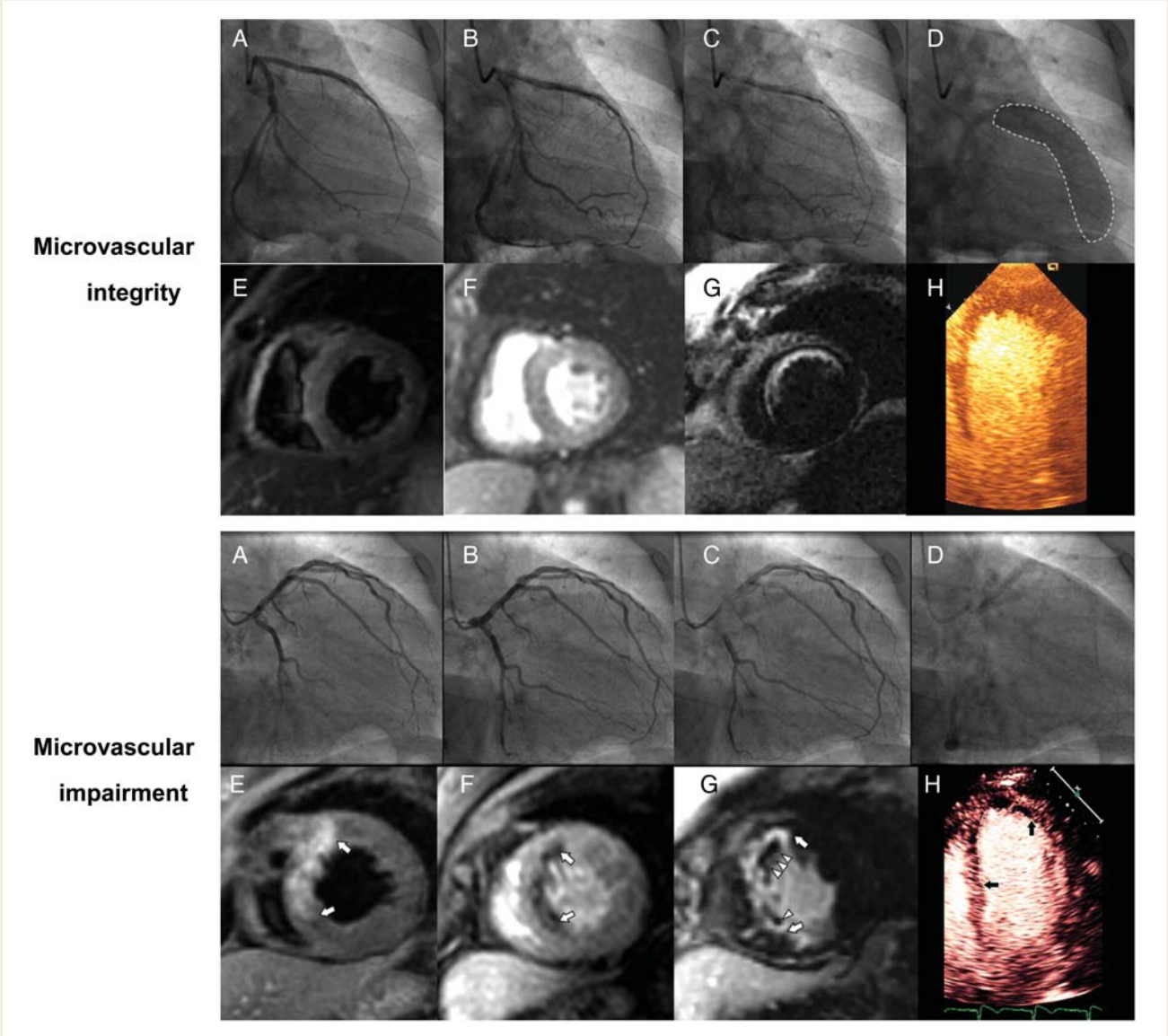

Figure 3 Illustration of two cases of anterior myocardial infarction with the restoration of blood flow in the left anterior descending artery (*A*–*C*, upper and lower panel). In the presence of microvascular integrity, the following can be seen: myocardial blush grade 3 (*D*, upper panel) a lack of oedema, homogeneous myocardial perfusion, subendocardial anteroseptal enhancement of 25–50% wall thickness on magnetic resonance imaging (MRI, *E*–*G*, upper panel) and normal perfusion on myocardial contrast echocardiography (MCE, *H*, upper panel). On the contrary, in the setting of coronary microvascular impairment, myocardial blush is poor (*D*, lower panel) along with a large area of oedema, an anteroseptal perfusion defect and extensive delayed enhancement with microvascular obstruction on MRI (*E*–*G*, lower panel), and a large perfusion defect on MCE (*H*, lower panel). Modified from Porto *et al.*[112] Used with the permission of Elsevier.

low resolution (*Figure 3*).[7] Of importance, CMVD often results from functional and not necessarily structural abnormalities, or represents a combination of both mechanisms. Hence, even if there was a technique that could clearly visualize the anatomy of the coronary microcirculation in humans *in vivo*, it would still be an incomplete evaluation. A reliable functional test, on the other hand, provides pragmatic assessment, reflecting CMVD irrespective of whether the cause is structural or functional.

Consistent with the primary haemodynamic function of the coronary microcirculation, functional techniques for the assessment of the coronary microvasculature rely on the measurement of CBF that changes mainly as a result of alterations in vascular tone (*Table 1*).[8] Positron emission tomography (PET) is the most established non-invasive technique for the assessment of CBF, as it allows the determination of absolute regional myocardial blood flow (MBF) at rest and in response to various stimuli. Importantly, however, non-invasive techniques such as PET may lack sensitivity and specificity for the diagnosis of coronary vasomotor dysfunction and, in general, are unable to differentiate between epicardial and microvascular abnormalities.[9] Thus, at present, the most definite evaluation of the coronary microcirculation remains invasive in nature. Simple angiographic techniques such a TIMI frame count can provide an approximate estimation of epicardial vs. microvascular mechanisms.[10] Intravascular ultrasound (IVUS) can be useful to identify atherosclerotic areas not necessarily visible on conventional angiography and to provide an accurate estimate of arterial cross-sectional area, which can then be used along with intracoronary Doppler-derived coronary flow velocity to calculate CBF and CBF reserve.[11] Alternatively, quantitative angiography (QCA) can be used for the determination of the cross-sectional area at the tip of the Doppler wire.

The use of a pressure–temperature sensor-tipped guidewire represents another effective mode of evaluation, allowing simultaneous measurement of the fractional flow reserve (FFR, by coronary pressure) and the coronary flow reserve (CFR, by coronary thermodilution) and calculation of the index of microvascular resistance (IMR).[12–14] IMR is defined as the distal coronary pressure divided by the inverse of the hyperaemic mean transit time.[13] This index—which is mainly used in the context of CAD—was validated in experimental models but has several limitations. For instance, it is necessary to incorporate the collateral blood flow in the calculations (accomplished by multiplying IMR by the ratio of coronary FFR and myocardial FFR), as otherwise IMR progressively increases with increasing degrees of epicardial coronary artery stenoses (as seen with studies using Doppler-derived FFR).[15]

The functional status of the coronary microcirculation can be assessed further by testing endothelium-dependent and endothelium-independent vascular responses.[16] Adenosine, dipyridamole, and papaverine are often used to trigger arteriolar vasodilation, and hence increase CBF, mainly by a direct relaxing effect on vascular smooth muscle cells. Thus, these agents are not suitable for the assessment of endothelium-dependent coronary microcirculation abnormalities.[14] Classically, intracoronary acetylcholine (ACH) has been used as a sensitive and safe test for the assessment of coronary vasomotor function in the catheterization laboratory. Its administration causes vasodilation under normal conditions but, in the absence of a functional endothelium, it leads to vasoconstriction by the unopposed stimulation of muscarinic receptors on vascular smooth muscle cells.[16] Bradykinin and substance-P are alternative agents to test the endothelium, and like ACH, also elicit a rapid vascular response.[17] Substance P has a good side effect profile and is especially useful in patients in whom the induction of coronary vasoconstriction may be undesirable. For all of these substances the mode of delivery is extremely important. Bolus injections need to be kept to the smallest volume and followed by an adequate catheter flush to allow a distinction between the vascular response to the drug from the mechanical effects of increased flow.[17] Also, bradycardia often develops with this type of administration. Graded infusions, on the other hand, allow larger dosages to be safely given over a longer period of time (e.g. 1–1000 nmol/min with infusion vs. 1–100 nmol with bolus injection for ACH). The administration of the agent through an infusion catheter minimizes inconsistencies in drug delivery and the underestimation of the drug response that may occur with the use of guiding catheters.[17] Infusion rates, however, have to be kept low at 1–2 mL/min not to affect the CBF. In part related to these considerations, atrial pacing, arm exercise, cold pressure, and mental stress testing are also used to assess endothelium-dependent, flow-related responses associated with increased myocardial oxygen demand.[16]

With regard to grading of the response, this can be based on symptoms, signs (such as ECG changes), and vascular responses.[18] Medication holiday, anxiety, and sedation can significantly influence symptomatic assessment and, on occasion, CMVD can still be present even if signs or symptoms do not develop with any given mode of challenge at any given time point. For this reason, parameters objectively reflecting the occurrence of myocardial ischaemia (i.e. biochemical or imaging variables) and functional abnormalities of the coronary microcirculation are preferred (i.e. CBF responses).

Clinical presentation of coronary microvascular dysfunction

Coronary microvascular dysfunction can present clinically primarily associated with the syndrome of chest pain despite normal coronary arteriograms (i.e. microvascular angina) or in the context of cardiac disease processes. This has been captured in the CMVD classification proposed by Camici and Crea[4] (types 1–4, *Table 2*). In agreement with this approach, one may further add CMVD after cardiac transplantation as an additional subtype (i.e. type 5, *Table 2*), which is mediated by alterations in autonomic tone, inflammation and immune mechanisms, and, possibly, defective endothelial progenitor cell recruitment.[19–23] A listing of underlying mechanisms of CMVD in disease conditions is provided in *Table 3*.

Obviously, it is quite challenging to define the clinical contribution of CMVD to any coronary or cardiac disease process. Lanza and Crea[24] advocated an additional clinical distinction for

Table 1 Modalities to assess coronary microvascular function

Method	Tracer	Primary parameter	Secondary parameter	Microvascular distinction	Endothelial assessment	Pros	Cons
PET[101]	Radioisotopes	MBF (0.6–1.3 mL/min/g)	MBF reserve (>2–2.5)	No	No	Validated and reproducibility	Limited availability, radioactivity
SPECT	Radioisotopes	Perfusion (no defect)	(Perfusion reserve)	No	No	Availability, low costs	MBF only with dynamic upgrade, radioactivity
MDCT[102]	Iodine contrast	MBF (0.9–1.3 mL/min/g)	MBF reserve (>2–2.5)	No	No	Availability	Investigational, image quality, radiation
MRI[103]	Gadolinium	MBF (0.7–1.1 mL/min/g)	MBF reserve (>2–2.5)	No	No	One-stop test, no radiation or radioactivity	Investigational, technical limitations
MCE[104]	Echo contrast	Perfusion, MBF option (0.5–2.9 mL/min/g)	MBF reserve option (>2–2.5)	No	No	One-stop test, no radiation or radioactivity	Volumetric modelling, image quality
Doppler echo [105]	Echo contrast	Flow velocity (24–36 cm/s)	Flow reserve (>2–2.5)	No	No	One-stop test, no radiation or radioactivity	No MBF option, position and image dependent
TFC[8]	Iodine contrast	Contrast flow velocity (18–24)	TFC reserve (>2–2.5)	Assumed if no epicardial dx	No	Ease of use, low cost	No CBF option, subjectivity
MBG[4]	Iodine contrast	Contrast staining (Grade 3)	None	Assumed if no epicardial dx	No	Ease of use, low cost	No CBF option, subjectivity
ICD[106]	None	Flow velocity (10–22 cm/s)	(relative) flow velocity reserve	Assumed if no epicardial dx	Yes	Direct measurement	No CBF option, invasiveness
ICD +QCA/ IVUS [107]	Iodine contrast	CBF (44–59 mL/min)	CBF reserve (>2–2.5)	Yes	Yes	Complete assessment	Costs, invasiveness
TPS[108]	Saline	IMF (15–22 U)	None	Yes	Yes	Complete assessment	Costs, invasiveness

PET, positron emission tomography; SPECT, single photo emission computed tomography; MDCT, multi-detector computed tomography; MRI, magnetic resonance imaging; MCE, myocardial contrast echocardiography; TFC, TIMI frame count; MBG, myocardial blush grade; ICD, intracoronary Doppler; QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; TPS, temperature and pressure sensor; MBF, myocardial blood flow (mL/time/myocardial mass); CBF, coronary blood flow (mL/time unit).

primary CMVD according to the mode of presentation, i.e. either as an acute (unstable) or chronic (stable) angina. This may help in distinguishing pathogenic mechanisms and perhaps identifying patients with different clinical outcomes.[25] The challenge, however, remains to identify aetiologic factors and specific triggers (*Table 4*).

Table 2 Modified clinical classification of coronary microvascular dysfunction

CMVD	Definition
Type 1	Primary, i.e. in the absence of structural heart disease
Type 2	In the presence of cardiomyopathies (incl. LVH, HCM, DCM, amyloidosis)
Type 3	In the presence of obstructive CAD (incl. ACS)
Type 4	After coronary interventions
Type 5	After cardiac transplantation
Modifiers	
Duration	Acute or chronic
Symptoms	Asymptomatic or symptomatic
Therapy	None, minimal, moderate, or maximal level

ACS, acute coronary syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.

Microvascular angina

It is conceivable that the main clinical consequence of the inability of the microvessels to match CBF to increased myocardial demand is the development of myocardial ischaemia, similar to that seen with flow-limiting epicardial stenoses. As such, patients with CMVD often present with chronic stable angina and/or dyspnoea. The term 'microvacular angina' was coined in an effort to confine and define the underlying functional abnormality in patients with chest pain and normal coronary arteries.[26] Obviously, documentation of abnormal coronary microvascular responses to functional testing with the reproduction of symptoms is of central significance for this diagnosis.[27] As CMVD is not confined to one coronary artery territory, it often leads to a patchy distribution pattern of perfusion abnormalities rather than to a condensed area of ischaemia, as typically seen in CAD patients.[28] Of interest, it has been reported that despite the occurrence of angina, dyspnoea, ECG changes, and perfusion abnormalities, a reduction in LV contractility, as assessed by echocardiography, represents a less consistent finding in patients with CMVD compared with those with obstructive CAD.[2,29]

As confirmed in recent clinical studies, ~50% of patients undergoing coronary angiography with signs and/or symptoms of myocardial ischaemia are found to have normal or 'near normal (non-obstructed)' coronary arteries.[30–32] Of note, as shown by the ACOVA study, intracoronary ACH elicits profound diffuse epicardial vasoconstriction (≥75% diameter reduction) with the

Table 3 Mechanisms of coronary blood flow alteration

	Effect on baseline CBF	Clinical example	Effect on hyperaemic CBF	Clinical example
Extravascular				
Cardiac metabolism ↑	↑	Pathological hypertrophy	↑	Physiological hypertrophy
Compressive forces ↑	↓↑		↓	Various cardiomyopathies, LVH
Diastolic perfusion time ↓	↓↑		↓	Aortic stenosis
Vascular dysfunction				
Endothelial cells	(↓)	CSY	↓	CV risk factors, CSX, heart transplantation, post-PCI
Smooth muscle cells	(↓)	CSY	↓	Hypertension, HCM, CSX
Autonomic nervous system	(↓)	CSY	↓	CSX, cardiomyopathies, heart transplantation, post-PCI
Vaso-structural changes				
Vascular plugging/ obstruction	↓	Acute coronary syndromes	↓	AMI, post-PCI
Vascular infiltration	↓↑		↓	Amyloidosis, Fabry
Vascular remodelling	↓↑		↓	Systemic hypertension, HCM
Vascular rarefaction	↓↑		↓	Aortic stenosis, LVH, DCM
Perivascular fibrosis	↓↑		↓	Aortic stenosis, LVH, HCM

AMI, acute myocardial infarction; CBF, coronary blood flow; CSX, cardiac syndrome X; CSY, cardiac syndrome Y (coronary slow flow syndrome); DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; PCI, percutaneous coronary intervention.

Table 4 Coronary microvascular dysfunction—key points

The coronary microvasculature is the primary gatekeeper for myocardial blood flow beyond the easily visible epicardial coronary arteries
Dysfunction of the coronary microvasculature can be noted under a number of clinical circumstances
Coronary microvascular dysfunction can lead to acute and chronic signs and symptoms of myocardial ischaemia and can affect ventricular remodelling and function long term
Assessment of the coronary microvasculature in clinical practice relies on its functional aspects
Currently, invasive catheterization techniques are superior to non-invasive modalities for the functional assessment of the coronary microvasculature
The functional assessment may provide important prognostic information under various clinical circumstances

reproduction of symptoms (so-called 'epicardial coronary artery spasm') in one-third of these patients.[32] In another third of patients, intracoronary ACH causes 'microvascular spasm', i.e. it reproduces angina symptoms and ischaemic ECG changes without eliciting changes in epicardial coronary artery diameter. Intriguingly, nearly half of the patients with microvascular spasm in the study also showed epicardial vasoconstriction of at least moderate degree.[32] Compared with patients with primary epicardial spasm, patients with microvascular spasm presented more frequently with ischaemic ECG changes during non-invasive testing, exertional dyspnoea, and intermittent rest angina rather than isolated exertional chest pain (which is most commonly and typically seen in obstructive CAD).[32] This is an important observation and, in fact, the occurrence of exertional angina (exclusively) is not a diagnostic requirement for 'microvascular angina' (which can presents with both exertional and rest angina).[32,33] Distinct from patients with Prinzmetal's variant angina, ST-segment elevation is extremely rare in patients with microvascular angina.[2,27] Furthermore, it has been reported that nitroglycerin may not provide quick and/or sufficient chest pain control in microvascular angina compared with Prinzmetal's variant angina, as the small arterioles can forgo the vasodilatory effect of nitroglycerin.[34] If associated with a significant drop in aortic perfusion pressure, nitroglycerin may even worsen myocardial ischaemia, as seen especially in patients with coronary slow flow syndrome, also known as 'cardiac syndrome Y'. The term cardiac syndrome Y has been chosen mainly because of the possible causal role of neuropeptide Y in this entity, which is characterized by an abnormally high microvascular resistance at rest but a normal vasodilatory response to direct vasodilators and pacing.[35–40] Patients with this condition present with rest angina rather than effort angina and abnormal stress testing results and, in fact, often have a history of multiple admissions for unstable angina. In distinction, an abnormal (ECG) stress test response is an integral criterion for CSX, which typically presents with exercise-induced angina but can also sustain episodes of angina at rest in the presence of angiographically normal coronary arteries.[1,27]

Patients with epicardial coronary atherosclerosis also have, on average, a higher microvascular resistance (even though with a noteworthy overlap in values with patients with and without epicardial CAD).[41] In particular, the impairment in endothelium-dependent dilation of the coronary microvasculature in the early stages of epicardial atherosclerosis has been viewed as evidence that the pathophysiological consequences of atherosclerosis may extend into the human coronary microcirculation.[42] However, one may also argue that the abnormalities can be first encountered in the microcirculation, i.e. before any epicardial disease. This view is supported by the fact that an impairment in the CBF reserve can be found already in patients with risk factors but without obstructive CAD.[4] Furthermore, there is evidence for progressive impairment of microvascular dysfunction involving endothelium-dependent and endothelium-independent function as the underlying disease process progresses, such as in pre-diabetes and diabetes before macrovascular disease.[43] The presence of microvascular dysfunction may also explain why at least 20% of patients with CAD continue to experience angina even after successful elimination of all haemodynamically significant lesions by revascularization procedures.[44] This holds true even in the acute post-PCI period when the signs and symptoms of myocardial ischaemia can become quite notable despite an 'otherwise successful intervention'.[45,46]

Finally, the presence of CMVD can contribute to the signs and symptoms of myocardial ischaemia in patients with other forms of structural heart disease. For instance, the CFR is markedly impaired in patients with aortic stenosis due to an increase in the baseline CBF which is to meet the increased metabolic demand.[47,48] In this patient population, reduced CFR, increased transvalvular gradient, and reduced transcoronary perfusion pressure have all been considered to mediate angina despite normal coronary arteries. More recently, decoupling of the normal regulatory mechanisms of CBF at the microvascular level has been suggested to play an important role as well.[49]

Acute coronary syndrome

Angina at rest, increasing angina, and new-onset angina are the three principal presentations of unstable angina/non-ST-segment myocardial infarction.[50] Microvascular angina may also present as an acute coronary syndrome (ACS) and should be considered a differential diagnosis in the 10% male and 25% female patients admitted to hospital with the diagnosis of ACS and found to have 'normal' coronary angiograms.[51,52] Intriguingly, ACS entails a broad spectrum of clinical presentations, and evidence of CMVD by the TIMI frame count extends beyond the presumed culprit artery in many cases.[53] These facts prompted us to postulate that the coronary microcirculation may take a more important role in ACS than traditionally thought.[54] Indeed, microvascular resistance can increase during ischaemia in patients with unstable angina, contrary to the classical concept of maximal compensatory vasodilation.[55] Moreover, CMVD may reduce the reserve of the myocardium to tolerate ischaemia. This has been highlighted in the setting of PCI, in which patients with evidence of myocardial injury and microvascular impairment have a reduced CFR preprocedurally.[56,57] Along these lines, it is noteworthy that diabetes and the metabolic syndrome, often considered to represent the

epitome of microvascular disease, are both associated with poor myocardial perfusion and larger infarcts in the setting of ACS.[58] An important (and more accepted) aspect is that CMVD can influence the clinical course following reperfusion therapies. The restoration of the CBF can (paradoxically) harm endothelial cells and myocytes further and lead to so-called reperfusion injury.[54,59] Even prior to this primarily oxidative-inflammatory (reperfusion) insult the function of the coronary microcirculation can be considerably compromised in the context of an ACS due to embolization of plaque debris and thrombus as well as the release of numerous vasoconstrictor molecules and reduced nitric oxide production and bioavailability. As a consequence, chest pain and ST-segment elevation can persist or recur despite the successful resolution of epicardial artery occlusions. Acute in-hospital complications such as heart failure, cardiac rupture, and cardiac death are also more frequent under these circumstances.[60]

In addition to these considerations, it is conceivable that acute and extensive CMVD (in terms of intensity, duration, and localization) can induce severe ischaemia that involves a larger area of the myocardium, yet not confined to a territory defined by the large epicardial coronary arteries. As a clinical example, CMVD may be responsible for cases of apical ballooning syndrome (APS), also known as stress(-induced) or takotsubo cardiomyopathy. By definition, APS patients do not have obstructive CAD; yet abnormal myocardial perfusion can be documented in 70% of patients.[61] In studies using serial echocardiography, CFR responses to dipyridamole and adenosine were found to be impaired in the acute phase of presentation and to improve thereafter, correlating with improvements in contractile function.[62,63] PET imaging studies confirmed these CFR dynamics and showed an inverse perfusion/metabolism mismatch, usually characteristic of stunning but observed here in the presence of impaired perfusion.[64,65] A yet stronger case for causality in this setting was made by the observation that myocardial perfusion, contractility, and LV function improve markedly with the administration of i.v. adenosine in patients with APS but not in those with acute myocardial infarction.[66] Moreover, in patients with a history of APS, cold pressure testing induced new regional wall motion abnormalities that were similar to those seen in the acute phase of the syndrome, in association with prominent blunting of the MBF response from a normal baseline level. [67] In addition, a study from our group pointed out increased vascular reactivity and decreased endothelial function in response to acute mental stress in patients with a history of APS.[68] Taken together, these findings suggest that the reduction in LV contractility is the consequence of a reduction in myocardial perfusion not due to epicardial disease but rather abnormal vasoreactivity at the level of the coronary microcirculation.

Chronic heart failure

Coronary microvascular dysfunction has also been considered to underlie the reduction in LV function in association with stress-induced myocardial ischaemia in women with angina and normal coronary arteries (post-stress stunning).[69,70] Repetition of such episodes could lead to hibernation and more persistent LV dysfunction. However, patients with presumed primary chronic CMVD are not at an increased risk of developing heart failure symptoms, in keeping with a functional disease process.[25] On the contrary, structural, non-reversible abnormalities of the coronary microcirculation may be associated with a greater predisposition to a persistent reduction in LV function. Indeed, several studies have demonstrated that CMVD after myocardial infarction increases the risk of congestive heart failure and heart failure hospitalizations up to six to eight times.[71,72] Similarly in patients with hypertrophic cardiomyopathy, severe microvascular dysfunction was predictive of adverse left ventricular remodelling and systolic dysfunction.[73] Furthermore, impairment of the coronary flow velocity reserve was the only independent predictor of LV systolic function dynamics in patients with hypertensive dilated cardiomyopathy over time.[74] Finally, the coronary microcirculation is considered to play an important role in the development of diabetic cardiomyopathy.[75,76] Indeed, in experimental models of diabetes, the earliest abnormality occurred in the growth factor milieu that maintains the coronary microcirculation, followed by a decrease in capillary density and impaired myocardial perfusion with subsequent cardiomyocyte apoptosis and necrosis, replacement fibrosis, and progressive diastolic and systolic dysfunction.[77] Also, experimental studies have demonstrated a reduction in systolic and diastolic function with progressive obliteration of the coronary microcirculation by repetitive injection of microemboli.[78] Collectively, these data indicate that persistent impairment of the integrity of the coronary microcirculation can lead to impairment of cardiac function and heart failure.

Prognosis of coronary microvascular dysfunction

The prognostic impact of CMVD is inherently intertwined with any concomitant coronary or cardiac disease process.

Chronic presentation with angina with or without coronary artery disease

Historically, studies in CSX indicated an overall good prognosis,[79,80] particularly in patients with chest pain and completely normal coronary arteriograms, even in the presence of abnormal exercise stress test findings. Indeed, as shown by Kaski *et al.*[81] in CSX patients with completely normal coronary angiograms, normal ventricular function, and evidence of mild ischaemia, prognosis is good, but the debate continues regarding the prognosis in CSX, particularly in relation to some patient subgroups.

More recently, and perhaps as a result of the incorporation of larger numbers of patients—therefore increasing the heterogeneity of the population—longer follow-up studies in larger sample sizes suggested a more adverse prognosis in at least some CSX subgroups.[82,83] Also, better characterization of the patients, specifically those with documented ischaemia, mild CAD, and microvascular dysfunction has resulted in the identification of at-risk subgroups. Studies have shown that coronary microvascular dysfunction and a reduced CFR predict an adverse prognosis, albeit the issue is confounded by the inclusion of patients with mild or moderate CAD in these studies.[84,85]

Of interest, patients with a reduction in the CBF to intracoronary ACH (abnormal microvascular response) appear to be at a

higher risk of developing cardiovascular events during follow-up, regardless of the presence or absence of obstructive epicardial coronary artery stenoses.[86,87] With the caveats outlined above, an abnormal CFR seems to be a marker of a worse long-term outcome including a >6-fold higher adjusted mortality risk in patients with a CFR <3.0.[84,88] In agreement, other non-invasive studies pointed CFR out as the strongest independent risk factor for non-STEMI and death in patients with coronary luminal irregularities.[89]

Among women with persistent signs and symptoms of ischaemia, a relatively higher proportion of adverse events, i.e. heart failure rather than myocardial infarction or increased mortality, has been reported in association with microvascular dysfunction. Data from the NIH-NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) and related studies implicate adverse outcomes (albeit not necessarily regarding mortality or other hard endpoints) in relation to CMVD.[85,90] Intriguingly, the event-free survival (index events including death, stroke, and hospitalization for heart failure, rather than MI) diverged more strongly after 4 years. In an unselected population of patients undergoing PET perfusion imaging, an adenosine CFR <2 was found to provide additional prognostic information, in particular for cardiac death, for which it remains the most potent independent predictor.[91] While it may be argued that the extent of CAD was not taken into consideration in these studies, an abnormal MBF response to cold pressure testing predicted a 6–8 times higher incidence of ACS and revascularization events during long-term follow-up even in patients without luminal irregularities on angiography.[92] Hence, regardless of the epicardial disease status and even in those with normal coronary arteries, the presence of CMVD indicated a significantly elevated risk for epicardial events. Of interest, this risk does not appear immediately in the follow-up but emerges during the long-term (>2 years) follow-up.

It is important to stress that most of these studies, in general, have included heterogeneous patient groups, i.e. ACS cases and patients with different degrees of CAD and LV dysfunction. Lumping together CSX patients with effort-induced angina and completely normal coronary angiograms with patients presenting with acute chest pain, coronary artery stenoses ranging from 20 to 50%, impaired LV function, conduction disturbances, and co-morbidities affecting the coronary microcirculation (and overall prognosis) is likely to confuse the issue. Future prospective studies will be required to define very specifically the different patient subgroups that are considered for analysis.

Acute myocardial infarction

The absence of the restoration of the MBF despite an open epicardial artery has been attributed to CMVD. In this setting, myocardial microvascular resistance remains high, myocardial blush and perfusion remain poor, and ST-segments remain elevated (*Figure 3*).[93,94] Clinically important is the fact that the presence of any of these parameters of inadequate tissue level perfusion (and even more so if associated with persistent abnormalities on MRI) portrays a worse prognosis (*Figure 4*).[7,71,72,95–97] Thus, there is a pathophysiological link between microvascular dysfunction and progressive LV dilation, the development of heart failure, and cardiac death after AMI and primary PCI.[72] Microvascular dysfunction is unlikely to be simply the consequence of the extent of AMI as it remains an

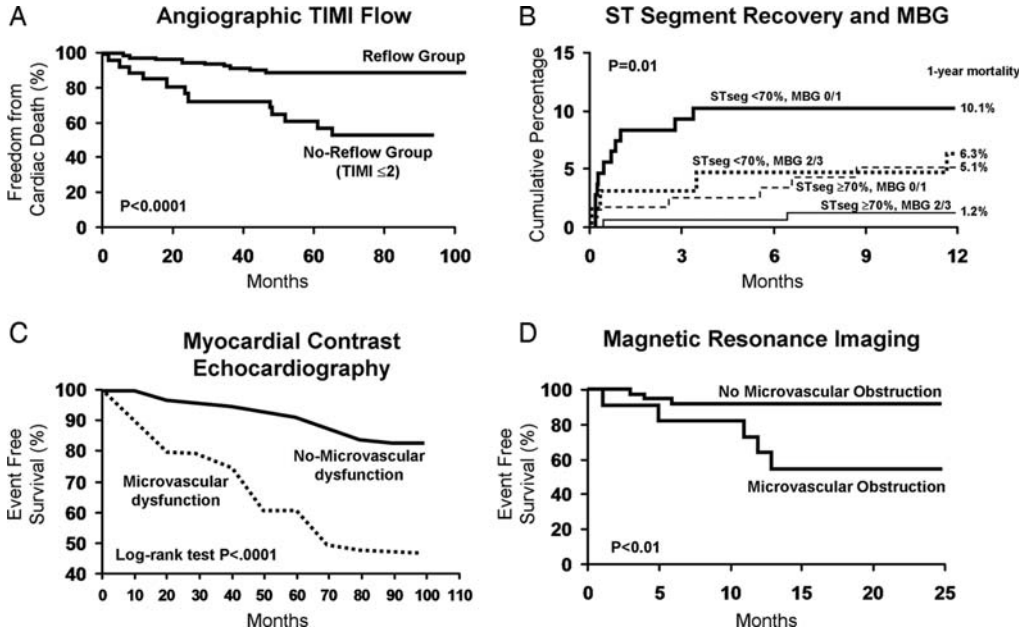

Figure 4 Illustration of the prognostic indicator function of the coronary microcirculation in acute myocardial infarction. Whether assessed by TIMI flow,[71] myocardial blush grade or ST-segment resolution,[95] myocardial contrast echocardiography,[72] or magnetic resonance imaging,[7] prognosis is significantly worse if myocardial perfusion is not restored despite an open epicardial artery. Images used with the permission of the American Heart Association.

outcome predictor even after adjustment for the infarct size. While some patients sustain microvascular injury before reperfusion and others develop it afterwards, a vital question is how much the coronary microcirculation contributes to the recovery of infarcted myocardium.[60] Most likely, the functional and structural integrity of the coronary microcirculation contributes to the recovery of stunned myocardium and limits permanent damage. This has been suggested by the observation that lesser degrees of microvascular impairment are associated with better functional recovery after an AMI.[93,94,96,98]

Percutaneous coronary intervention

One might argue that under no other circumstance can the onset and hence the impact of CMVD be more defined clinically than in the setting of elective revascularization procedures, particularly PCI. Numerous studies have provided tangible evidence for the occurrence of embolization of particulate matter and the release of vasoactive molecules into the microcirculation at the time of PCI.[56,99–101] Furthermore, the considerable reduction in no-reflow events and periprocedural myocardial infarction (PMI) with distal embolization protection devices (especially in saphenous vein graft interventions) substantiates the view that PCI-related embolic events impair the integrity of the microcirculation and the viability of myocytes.[102] Unfortunately, no long-term follow-up data are available that could provide further insight into the long-term clinical implications of microvascular dysfunction in this setting. Obviously, the extent of underlying CAD plays an important prognostic role. This holds true also for the much-debated entity of PMI, and no study so far has evaluated the differential prognostic impact of PMI due to side-branch occlusion (type I or proximal type) or microcirculatory impairment (type II or distal type).[45,46] For this reason, the prognostic implications of CMVD in the setting of PCI remain uncertain.

Cardiomyopathy

In patients with dilated cardiomyopathy, a severely (>60%) reduced hyperaemic MBF response to dipyridamole increases the relative risk of death and heart failure development or progression 3.5 times, independent of other factors such as the degree of LV dysfunction and the presence of overt heart failure.[103] Likewise, an abnormal CFR (<2) and lack of inotropic reserve in response to dipyridamole were independent predictors of survival in patients with idiopathic DCM (adjusted harzard ratios 2.8 and 2.3, respectively).[104] Importantly, the prognostic merit of severe CFR impairment in heart failure is independent of CAD and the ischaemic burden and is evident in both ischaemic and non-ischaemic cardiomyopathy.[105]

In hypertrophic obstructive cardiomyopathy, the MBF response to dipyridamole potently predicts symptomatic progression to NYHA class III and IV and life-threatening ventricular arrhythmias requiring ICD placement and is an independent mortality predictor.[106] Especially those patients with the lowest MBF response are seemingly at the highest risk (adjusted hazard ratio 10 for cardiovascular mortality and 20 for all cardiovascular events), which again becomes apparent not immediately but during long-term follow-up (i.e. 6 years). Interestingly, these patients also had a higher risk of progressive LV remodelling and systolic dysfunction.[73] Intriguingly, microvascular dysfunction colocalized with areas of late gadolinium enhancement on MRI and hence may lead to recurrent myocardial ischaemia and myocyte death, and eventually replacement fibrosis.[107]

Finally, in a study of cardiac transplant recipients, a CFR <2.5 in response to dipyridamole was found to be associated with a decline in the LVEF during exercise at the 2-year follow-up.[108] Moreover, an abnormal CBF response to ACH was found to be associated with ischaemic events and death >1 year after heart transplantation; however, only in association with angiographically significant epicardial disease (luminal diameter reduction ≥50%).[109] The central question of an independent prognostic role of CMVD was eventually answered by the finding that a CFR <2.7 in response to adenosine predicts long-term survival independent of other echocardiographic and angiographic variables, donor age, predisposition to ischaemic heart disease, and

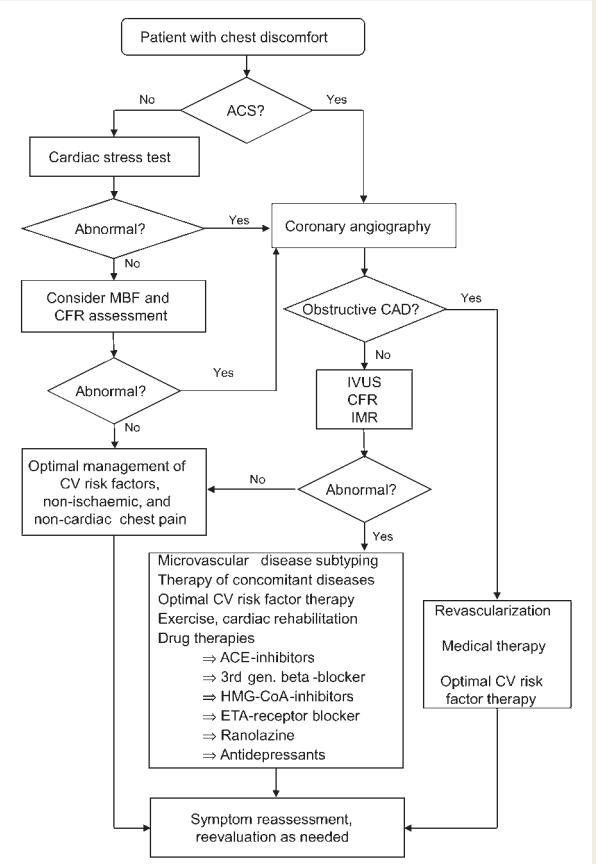

Figure 5 Although the discussion of management strategies is beyond the scope of the present manuscript, this figure shows a flow chart outlining a suggested algorithm for the management of patients with chest pain despite angiographically normal coronary arteries, in whom the underlying mechanism is coronary microvascular dysfunction. ACS, acute coronary syndrome; CAD, coronary artery disease; CFR, coronary flow reserve; CV, cardiovascular; ETA, endothelin-type A receptor; IMR, index of microvascular resistance; IVUS, intravascular ultrasound; MBF, myocardial blood flow.

treatment.[110] Hence, the status of the coronary microcirculation is an important outcome predictor in patients with cardiomyopathy and heart failure, underscoring once again, its vital role in different clinical settings (*Table 4*).

Conclusions

Over the past decades many studies have highlighted the functional significance of the coronary microcirculation in a diversity of clinical settings. Functional and/or structural coronary microvascular abnormalities often explain the signs and symptoms of myocardial ischaemia in individuals with normal coronary angiograms and can possibly contribute to the clinical presentation of patients with CAD and other cardiac conditions. As such, an assessment of CMVD should be considered in the evaluation of angina patients, particularly those with normal coronary arteries or non-obstructive CAD (*Figure 5*). Identifying the mechanisms underlying the patient's symptoms is important to provide a rational treatment that aims at both improving the quality of life and long-term prognosis when feasible. Taken together, evidence gathered in recent years has shown that CMVD is a true clinical entity rather than a mystery or an academic curiosity.

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