

Coronary microvascular dysfunction in stable ischaemic heart disease (non-obstructive coronary artery disease and obstructive coronary artery disease)

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Abstract

Diffuse and focal epicardial coronary disease and coronary microvascular abnormalities may exist side-by-side. Identifying the contributions of each of these three players in the coronary circulation is a difficult task. Yet identifying coronary microvascular dysfunction (CMD) as an additional player in patients with coronary artery disease (CAD) may provide explanations of why symptoms may persist frequently following and why global coronary flow reserve may be more prognostically important than fractional flow reserve measured in a single vessel before percutaneous coronary intervention. This review focuses on the challenges of identifying the presence of CMD in the context of diffuse non-obstructive CAD and obstructive CAD. Furthermore, it is going to discuss the pathophysiology in this complex situation, examine the clinical context in which the interaction of the three components of disease takes place and finally look at non-invasive diagnostic methods relevant for addressing this question.

Keywords

Coronary microvascular dysfunction • Non-obstructive coronary artery disease • Obstructive coronary artery disease • Pathophysiology • Index of microvascular resistance • Fractional flow reserve

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1. Introduction

Recently, it has become increasingly obvious that diffuse and focal epicardial coronary disease and coronary microvascular abnormalities may exist side-by-side.^{1,2} Identifying the contributions of each of these three players in the coronary circulation is a difficult task. However, looking at the problem of coronary microvascular dysfunction (CMD) as an adjunct to diffuse and focal plaque and stenosis formation in the coronary arteries makes sense in the context of the vexing challenges of proving the symptomatic and prognostic value of percutaneous coronary interventions (PCIs).^{3,4} Identifying CMD as an additional player in patients with coronary artery disease (CAD) may provide explanations of why symptoms persist so frequently following PCI⁵ and why global coronary flow reserve (CFR) may be more

prognostically important⁶ than fractional flow reserve (FFR) measured in a single vessel before PCI. The term CMD focuses on the functional aspect of microvascular disease. However, we should not forget that, especially in patients with epicardial coronary plaque formation or stenoses morphological changes, such as occlusive microvascular lesions⁷ (Figure 1) or microvascular rarefaction,⁸ may also be found in the resistance vessels of the coronary tree.

In this review, we take a closer look at the challenges of identifying the presence of CMD in the context of diffuse non-obstructive CAD (NOCAD) and obstructive CAD (OCAD). Furthermore, we are going to discuss the pathophysiology in this complex situation, examine the clinical context in which the interaction of the three components takes place and finally look at the non-invasive diagnostic methods relevant for addressing this question.

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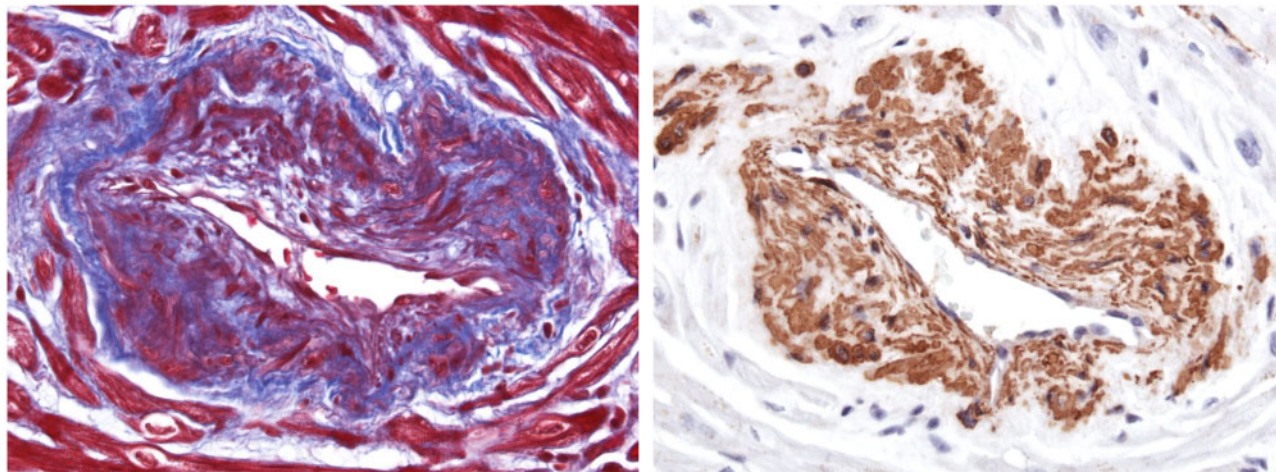


Figure 1 Intramural arteriole of a 59-year-old male patient with ischaemic cardiomyopathy. Left: haematoxylin–eosin staining. Fibrosis is blue and smooth muscle cells are violet. White spaces represent fat accumulation. There is diffuse narrowing of the vessel by a process which resembles vaguely plaque formation in the larger epicardial vessels. Right: same vessel with actin staining. Actin is a marker of smooth muscle cells and shows the irregular proliferation of these cell in the arteriolar wall. Courtesy of Professor Karin Klingel, MD, Director of Cardiac Pathology, Institute of General and Molecular Pathology and Pathologic Anatomy, University of Tübingen, Germany.

2. How to identify microvascular abnormalities in the presence of diffuse non-stenotic coronary epicardial plaque formation or coronary epicardial stenosis?

There are several clinical scenarios in which the identification of CMD existing in addition to NOCAD or OCAD would be helpful. Let us have a look at a common situation in the catheterization laboratory: a patient is lying on the catheterization table because his general practitioner felt that clarity regarding the patient's symptoms is needed: does this man have an epicardial stenosis or not? There has been no testing for myocardial ischaemia. The coronary arteries of the patient show diffuse disease and some of the irregularities may represent stenoses of 50% severity. The interventional cardiologist performs a measurement of the FFR which is 0.81. Fortunately, the interventional cardiologist used a dual-purpose wire which also carries a thermistor at its tip which allows temperature measurements over time (alternatively the colleague might have also used a dual-purpose catheter equipped with a pressure sensor for FFR measurements and a Doppler probe for measurements of the velocity of coronary blood flow). Using this wire,⁹ CFR is measured and returns a value of 1.9 which is abnormal in this laboratory. What is the interpretation of this finding of a normal FFR value and low CFR value? FFR has been designed as a surrogate measure of impairment of coronary flow to the myocardium. The pressure drop across a coronary stenosis is proportional to the magnitude of coronary flow through the stenosis which is the essence of Ohm's law. Thus, a low coronary flow through a stenosis is usually associated with a normal FFR value even if the stenosis is tight, whereas a high coronary flow through the same stenosis will result in a low FFR. An increase of flow through a coronary stenosis can be achieved by administration of vasodilator drugs such as adenosine. But what determines the amount of flow through the stenosis once

adenosine has been applied? It is the degree of vasodilatation in the periphery of the coronary artery, the microvasculature! Therefore, CMD resulting in very little vasodilatation in response to adenosine will as a consequence result in a rather normal FFR value whereas—in the presence of the same stenosis—a normally functioning microvasculature by inducing a much larger increase in coronary flow will result in a low FFR value.

The thermodilution catheter used in our patient does not measure coronary flow but measures how quickly a bolus of 3 mL of room temperature saline passes the thermistor at its tip. This value is called the transit time. When coronary flow is high, transit time will be low and vice versa. Using this technique, CFR is determined by dividing the transit time at rest by the transit time during maximal vasodilatation of the microvasculature after adenosine stimulation. Coming back to our patient: a low CFR of 1.9 may mean one of two things: (i) resting flow is elevated resulting in a short mean transit time at rest¹⁰; thus, even if flow after adenosine would rise to levels regarded as almost normal and mean transit time would shorten further as compared to the value at rest, CFR would be low. Under these circumstances, the normal FFR value is reliable (due to the near-normal flow following adenosine) and the epicardial stenosis is not significant; and (ii) flow at rest is normal, whereas maximal flow following adenosine is low; in this case, FFR will underestimate the significance of the stenosis.¹¹ One way of deciding whether resting flow is abnormally high is to compare mean transit time of the afflicted vessel with a normal vessel although this increases the complexity of the procedure. Unfortunately, indeed, there are no absolute normal values for mean transit times due to the complexity of the measurement and the variability of parameters influencing mean transit times.

A partial solution is measuring the index of microvascular resistance (IMR) which in contrast to CFR is a measure independent of stenosis severity.¹² IMR is calculated as the product of distal coronary pressure times hyperaemic mean transit time.⁹ Although IMR measurements

suffer from similar limitations as those of mean transit times a value $>25 \text{ mmHg} \times \text{seconds}$ has been agreed upon to indicate abnormally high microvascular resistance.^{13,14} A somewhat worse clinical course has recently been demonstrated, however, for values above only $18 \text{ mmHg} \times \text{seconds}$.¹⁵

Possible combinations of FFR and CFR measurements fall into four main categories^{11,16} (Figure 2) allowing one to better distinguish between the epicardial and microvascular parts contributing to ischaemia and symptoms. Measurements of hyperaemic microvascular resistance (HMR) using intracoronary Doppler wires or IMR may further help in interpreting the extent of microvascular involvement¹⁷ (Figure 3). Obviously, such measurements are time-consuming and need meticulous attention to detail. However, clarifying the haemodynamic situation in the coronary artery by measuring FFR plus CFR coupled with HMR or IMR may avoid useless interventions and direct attention to necessary medical treatment.¹⁸

3. Pathophysiology of CMD

Accumulating evidence has demonstrated that CMD plays an important role in the pathophysiology of myocardial ischaemia in patients with stable ischaemic heart disease (IHD).^{2,19} Although structural and functional abnormalities of epicardial coronary arteries in IHD patients have been the main focus of interest, those of coronary microvasculature have attracted growing attention in view of their unexpectedly high prevalence and their potential prognostic impact on clinical outcomes in various clinical settings.^{20–22} The aetiologies of CMD may be heterogeneous; several structural (e.g. vascular remodelling, vascular rarefaction, extramural compression, etc.) and functional [e.g. endothelial dysfunction, vascular smooth muscle cell (VSMC) dysfunction, and microvascular spasm, etc.] alterations have been proposed for the pathophysiological mechanisms of CMD.^{19,23} As structural alterations may also play an important part in the ultimate consequences of microvascular abnormalities it may also be justified to summarize the entire complex of abnormalities as coronary microvascular disease. Herein, we will briefly summarize the current knowledge on coronary vasomotor abnormalities relevant to CMD in patients with stable IHD with a special reference to endothelial modulation of vascular tone and coronary microvascular spasm (CMS). Further discussions on the coronary microcirculation physiology are available elsewhere.^{2,23–26}

3.1 Endothelial modulation of vascular tone

The endothelium plays crucial roles in modulating vascular tone by synthesizing and releasing endothelium-derived relaxing factors including vasodilator prostaglandins (e.g. prostacyclin), nitric oxide (NO), and endothelium-derived hyperpolarizing factor(s) (EDHF) in a distinct vessel size-dependent manner (Figure 4).^{24,27} Endothelium-derived NO mainly mediates vasodilatation of relatively large, conduit vessels (e.g. epicardial coronary arteries), while EDHF-mediated responses are the predominant mechanisms of endothelium-dependent vasodilatation of resistance arteries (e.g. coronary microvessels). This vessel size-dependent contribution of NO and EDHF to endothelium-dependent vasodilatation is well-preserved from rodents to humans, making a physiological balance between them.²⁷ EDHF cause hyperpolarization and subsequent relaxation of underlying VSMCs with resultant vasodilatation of small resistance vessels and thus finely regulate blood pressure and organ perfusion in a moment to moment manner in response to

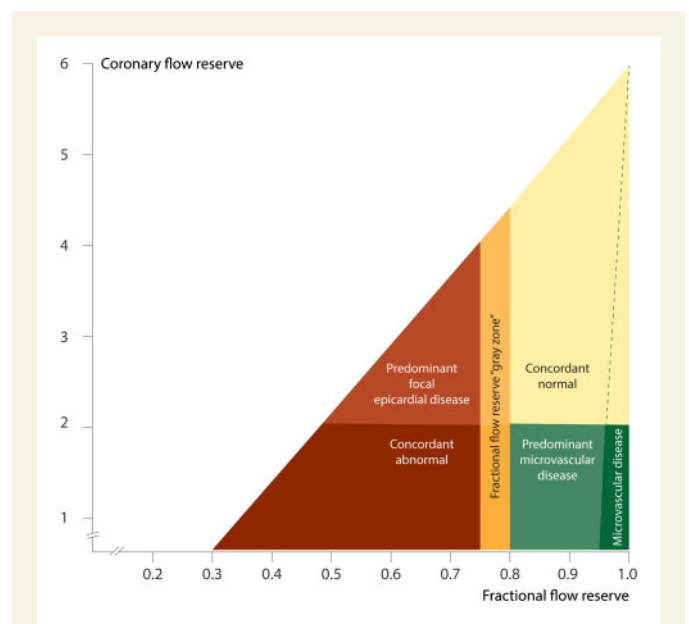


Figure 2 Conceptual plot of the fractional flow reserve (FFR)–coronary flow velocity reserve (CFR) relationship. Four main quadrants can be identified by applying the clinically applicable cut-off values for FFR–CFR indicated by the dotted lines. Patients in the upper right blue area are characterized by concordantly normal FFR and CFR, and patients in the red lower left area are characterized by concordantly abnormal FFR and CFR. Patients in the upper left orange area and lower right light green area are characterized by discordant results between FFR and CFR where the combination of an abnormal FFR and a normal CFR indicates predominant focal epicardial but non-flow-limiting coronary artery disease and the combination of a normal fractional flow reserve and an abnormal CFR indicates predominantly microvascular involvement in coronary artery disease. The small dark green region in the lower right is characterized by an FFR are near one and low CFR indicating sole involvement of the coronary microvasculature. The FFR grey zone indicates the equivocal 0.75–0.80 FFR range. Reproduced with permission from van de Hoef et al.¹¹

diverse physiological demands.²⁷ Although the nature of EDHF probably varies depending on the vascular bed, vessel size, and species of interest,²⁷ endothelium-derived hydrogen peroxide (H_2O_2) is one of the major EDHF in human,^{28,29} porcine,³⁰ and canine coronary arteries.^{31–33} The estimated normal concentrations of H_2O_2 as an EDHF are in micromolar order ($<50 \mu\text{mol/L}$),^{30,31} which are much lower than those observed in various pathological conditions.³⁴ In the canine coronary microcirculation *in vivo*, endothelium-derived H_2O_2 exerts cardioprotective effects, including myocardial protection against ischaemia/reperfusion injury,³¹ coronary autoregulation,³² and metabolic coronary vasodilatation.³³ Given that H_2O_2 has potent vasodilator properties in coronary resistance vessels, impaired endothelial H_2O_2 production, or impaired H_2O_2 -mediated vasodilatation may lead to CMD. Coronary vascular resistance is predominantly determined by pre-arterioles ($>100 \mu\text{m}$ in diameter) and arterioles ($<100 \mu\text{m}$) where EDHF-mediated responses become more prominent than NO-mediated relaxation. Thus, for an adequate treatment of CAD, it would be essential to maintain a physiological balance between NO and EDHF. This notion is supported by the fact that significant negative interactions exist between NO and several EDHF^{35–37} and that nitrates as NO donors are

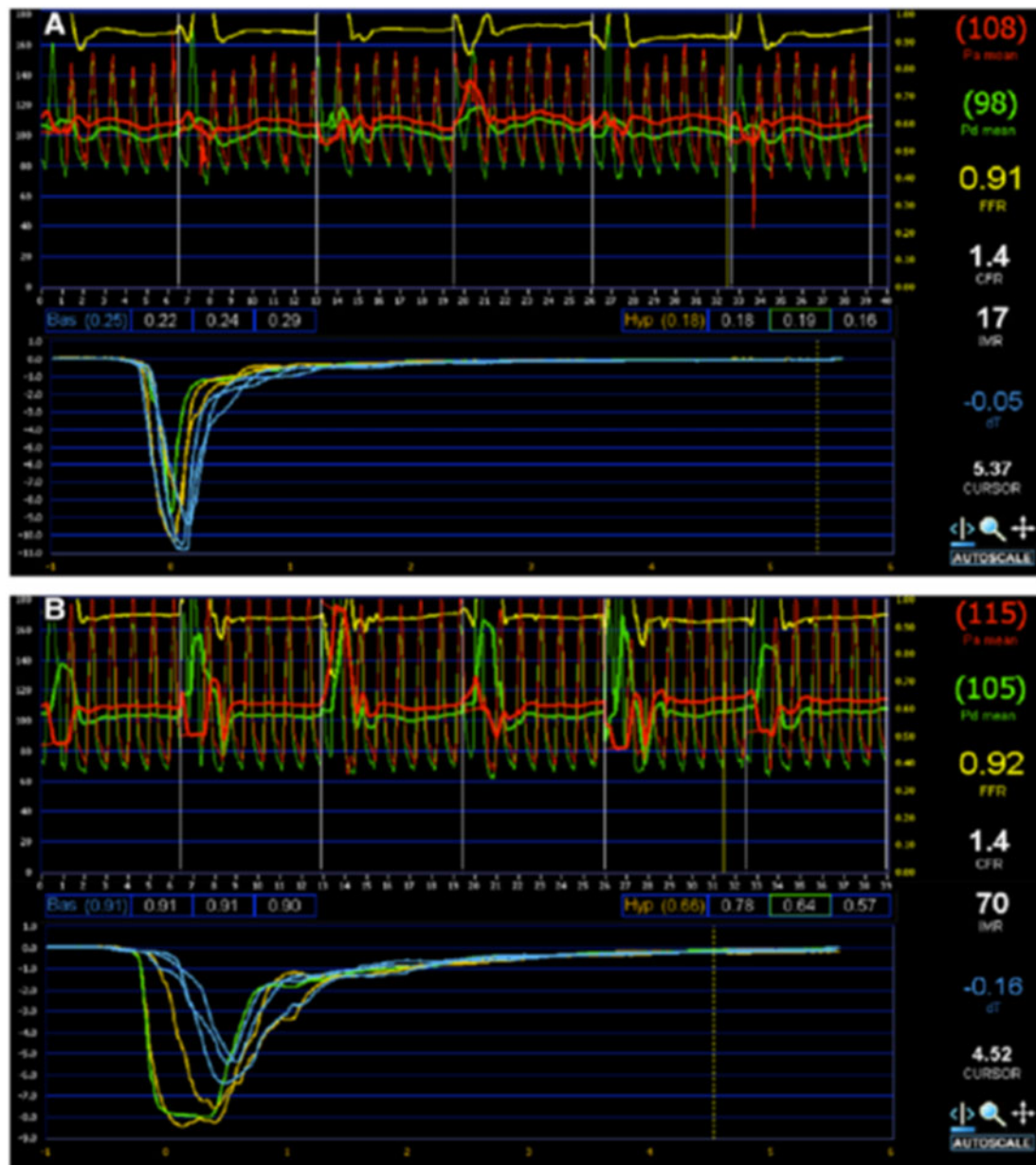


Figure 3 Representative cases of vessels with normal fractional flow reserve (FFR) and abnormal coronary flow reserve (CFR). These two tracings illustrate the separate contribution of diffuse atherosclerotic narrowing (DAN) or microcirculatory dysfunction (MCD) to abnormal coronary haemodynamics in some vessels with normal FFR. (A) Vessel with normal FFR and reduced CFR located in the lower right green quadrant of Figure 1. The index of microvascular resistance (IMR) is 17 mmHg \times seconds which is normal. The theoretical explanation is that DAN is the dominant cause of abnormal haemodynamics. (B) Another vessel with normal FFR and reduced CFR also located in the lower right green quadrant of Figure 1. FFR and CFR values are virtually identical to the ones in A. However, IMR value is very high (70 mmHg \times seconds) suggestive of CMD. Reproduced with permission from Echavarría-Pinto et al.¹⁷

ineffective for the chronic treatment of CMD.^{38,39} However, clinical observations also suggest that intracoronary nitrate may quickly relieve microvascular spasm elicited by acetylcholine (ACh) provocation in some patients.

Recent studies have highlighted the association of CMD with advanced coronary plaque characteristics beyond conventional coronary risk factors.⁴⁰⁻⁴² For example, Siasos et al.⁴¹ demonstrated that endothelium-dependent CMD is associated with low endothelial shear stress and larger plaque burden in the epicardial coronary artery. Steady

laminar or pulsatile shear stress exerts antiatherogenic effects on the vascular wall, whereas conversely, altered oscillatory or low shear stress with disturbed flow promotes atherogenesis through endothelial and VSMC proliferation, inflammation, lipoprotein uptake, and leucocyte adhesion.⁴³ Indeed, altered shear stress on the coronary artery wall has been implicated in the local progression of atherosclerotic coronary plaque.⁴⁴ Another possible explanation for the link between CMD and epicardial coronary atherosclerosis comes from a novel mechanism of CMD in human CAD, which has been proposed by the Gutterman's

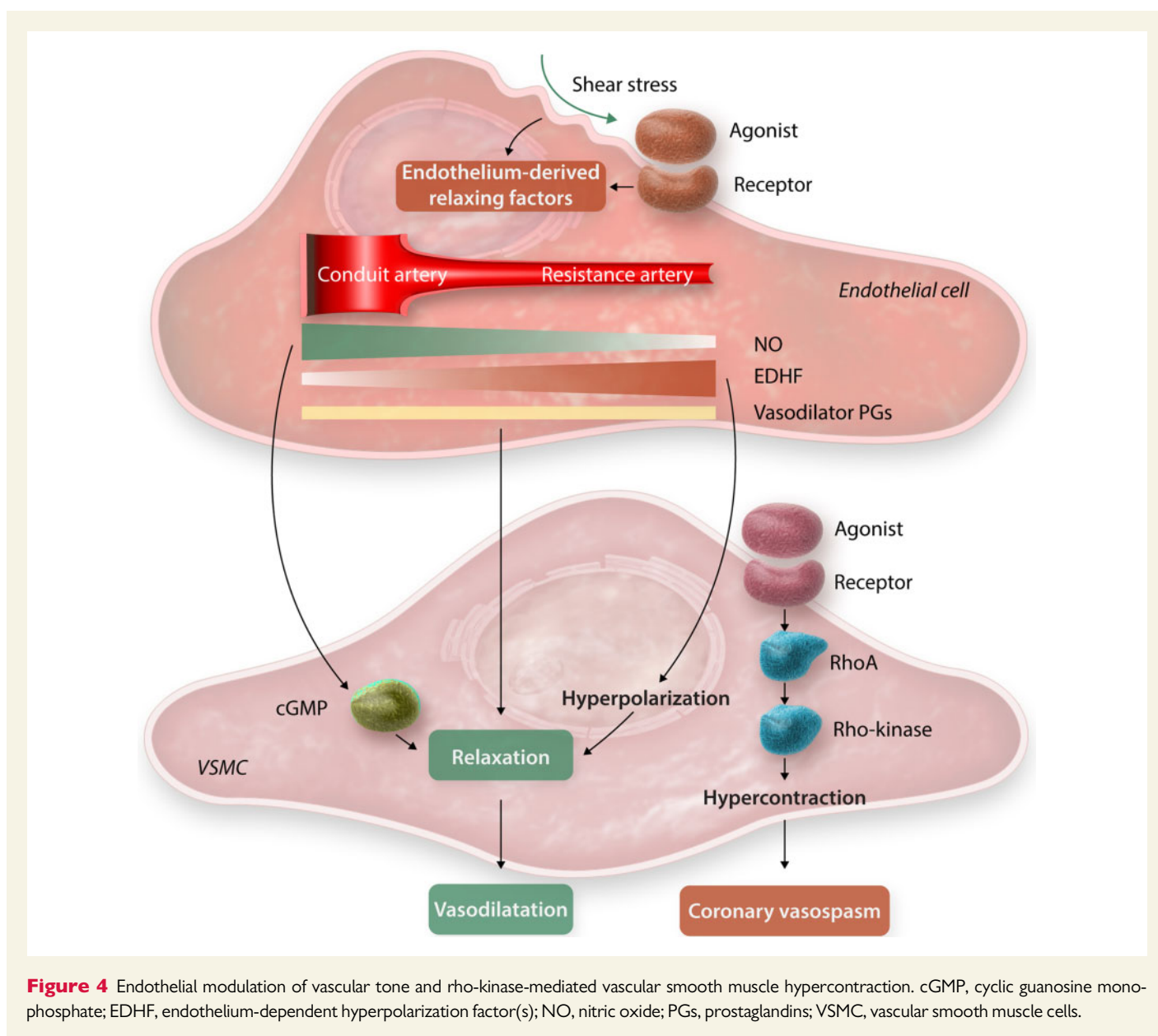


Figure 4 Endothelial modulation of vascular tone and rho-kinase-mediated vascular smooth muscle hypercontraction. cGMP, cyclic guanosine monophosphate; EDHF, endothelium-dependent hyperpolarization factor(s); NO, nitric oxide; PGs, prostaglandins; VSMC, vascular smooth muscle cells.

laboratory.^{45,46} In brief, as stated above, the healthy human coronary circulation is regulated by NO and low physiological levels of H₂O₂ as an EDHF. However, various atherosclerotic risk factors (e.g. ageing, hypertension, obesity, and smoking) can cause a switch from NO to H₂O₂ as the mediator of endothelium-dependent vasodilatation in human coronary arteries. The resultant impaired production of NO and pathologically elevated levels of H₂O₂, both favour vasoconstrictor, pro-inflammatory, pro-proliferative, and pro-thrombotic states, thus contributing to the development of coronary atherosclerosis.^{45,46} Taken together, these observations may provide insight into the underlying mechanisms by which CMD contributes to the development of epicardial coronary atherosclerosis, even though these focal lesions are located upstream to the microcirculation.

3.2 Coronary microvascular spasm

CMD comprises both impaired coronary microvascular dilatation and enhanced coronary microvascular constriction.⁴⁷ Coronary artery

spasm at both epicardial and microvascular levels has been implicated in a wide variety of IHD endotypes.²⁴ Mechanistically, rho-kinase-induced myosin light chain phosphorylation with resultant VSMC hypercontraction is a major mechanism in the pathogenesis of coronary artery spasm, whereas the role of endothelial dysfunction may be minimal (Figure 4).²⁴ Intracoronary administration of the rho-kinase inhibitor, fasudil, is indeed effective not only for relieving coronary spasm resistant to nitrates or calcium-channel blockers but also for suppressing CMS in most patients with the disease.⁴⁸ In addition, enhanced epicardial and CMSs are associated with increased production of vasoconstrictive mediators, such as endothelin⁴⁹ and serotonin⁵⁰ in patients with CMD.

Intracoronary ACh provocation testing is useful in inducing coronary artery spasm with high sensitivity and specificity in susceptible patients. A high prevalence (around 33%) of ACh-induced CMS has been reported in patients with stable chest pain and NOCAD.^{51,52} Recently, the Coronary Vasomotion Disorders International Study Group (COVADIS) proposed a consensus set of standardized diagnostic

criteria for microvascular angina, i.e. angina attributable to CMD, including ACh-induced CMS.⁵³ The diagnostic value of these criteria has been demonstrated by a recent randomized clinical trial.¹⁸

3.3 Clinical implications: CMD as a manifestation of systemic small artery disease

CMD may be a cardiac manifestation of systemic small artery disease⁵⁴ which supports the concept of 'primary coronary microcirculatory dysfunction'⁵⁵ and provides important implications for practice and research. Identifying CMD in patients with stable IHD may provide physicians with useful information for decision-making and risk stratification beyond conventional coronary risk factors. A comprehensive and invasive assessment of coronary physiology is feasible and may have both prognostic and therapeutic implications.¹⁸ Further research is warranted to address how to modulate CMD to improve clinical outcomes of patients with this condition.

4. CMD in patients with stable IHD

In the absence of coronary obstruction, CFR, the ratio of coronary flow achieved at maximal coronary vasodilation to flow under baseline conditions, reflects coronary microvascular function such that a reduced CFR indicates CMD.⁵⁶ CFR may be measured invasively as an adjunct to coronary angiography, or non-invasively, using positron emission tomography (PET) cardiac magnetic resonance (CMR) imaging or transthoracic Doppler echocardiography of the left anterior descending coronary artery.⁵⁷ Thus, the assessment of CMD requires technology and skills that are not widely available.

CMD may exist in two varieties: first, impaired microvascular conductance ('classical' CMD) and second, arteriolar dysregulation (microvascular spasm). Procedural details of how these two entities can be diagnosed is nicely described in the new European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes.⁵⁸ It is important to think of the possibility that the patient may have microvascular angina in order to avoid a useless invasive exclusion of epicardial stenoses without concomitant comprehensive invasive coronary function testing.^{18,58} If microvascular angina is clinically considered it makes sense to send the patient to a catheterization laboratory where the recommendation given by the ESC new guidelines can and will be put into practice. Unfortunately, CMD in the presence of OCAD or following revascularization is almost never assessed outside of research protocols. For these reasons, data regarding the outcomes and prognosis of patients with CMD come from clinical trials and registries based in referral centres and therefore may not be generalizable to the population at large. Nevertheless, the currently available data suggest that a fundamental paradigm shift in the understanding of stable IHD is indicated.⁵⁹

IHD has long been the leading cause of death in the developed world⁶⁰ but the nature of IHD is changing. Although angina remains a common presenting symptom, unlike in previous eras, angiography now frequently fails to detect OCAD.^{20,61,62} Furthermore, contrary to the reassurance that these patients have been historically offered that their condition is not serious, the prognosis of some subgroups of these individuals may not be benign.^{20,61} The increasing numbers of patients presenting with ischaemic symptoms but without OCAD has led to the gradual recognition that abnormalities of the entire coronary circulation, including the microcirculation, should be considered in the assessment

of the symptoms and treatment of patients with angina. In 2007, Camici and Crea⁵⁶ proposed four categories of CMD: Type 1—CMD in the absence of myocardial disease and OCAD; Type 2—CMD in myocardial disease; Type 3—CMD in OCAD; and Type 4—iatrogenic CMD. However, there is growing evidence that many of these conditions overlap in their clinical manifestations and pathogenesis. For example, Types 1 and 3 CMD exist on a spectrum defined by an arbitrary and imprecise definition of the extent of 'obstructive' atherosclerosis. Furthermore, Type 1 patients may develop myocardial disease and Type 4 CMD that is caused by distal embolization during PCI may be influenced by the presence of pre-existing CMD. There also appears to be a relationship between the extent and severity of epicardial CAD and CMD and the clinical risk of major adverse cardiac events, where coronary atherosclerosis interacts with CMD to influence outcomes. It is conceivable that the diffuse morphologic alterations of the vessel wall observed in severe CAD may extend into the arterioles as depicted in *Figure 1*. Taqueti and Di Carli⁶² recently proposed a simplified classification of CMD in which the clinical spectrum of CMD is conceptualized as a function of the degree of atherosclerosis (none, non-obstructive, or obstructive), the severity of CMD, and factors that amplify clinical risk such as metabolic syndrome, obesity, diabetes, female sex, and chronic kidney disease (CKD). Only well-designed and prospective studies, however, may clarify the clinical implications of CMD in this complex clinical scenario.

4.1 CMD without atherosclerosis

CMD is prevalent in a number of clinical conditions where atherosclerosis plays little or no role in its pathogenesis including hypertension,^{63–65} aortic stenosis,⁵⁷ and non-ischaemic cardiomyopathies including idiopathic,^{66,67} hypertrophic,^{68,69} infiltrative,⁷⁰ and stress^{71,72} cardiomyopathies. It is unknown if CMD in non-ischaemic cardiomyopathies is a cause or effect of the underlying myopathic process.⁶² However, in all of these conditions, severe CMD has been implicated in the pathophysiology of subendocardial ischaemia, subclinical myocardial injury, and diffuse interstitial fibrosis⁷³; worsening systolic and diastolic function, heart failure, and arrhythmias,⁷⁴ which may result in adverse cardiac events.^{62,66,67,69–72}

4.2 CMD with NOCAD

As many as 80% of patients with chest pain and NOCAD have evidence of diffuse atherosclerosis by intravascular ultrasound.^{75,76} The presence of CMD appears to be associated with more extensive atherosclerosis.⁷⁷ CMD in combination with NOCAD represents the largest cohort of CMD patients with CAD.⁷⁸

The association of non-obstructive atherosclerosis with CMD has important clinical and prognostic implications. First, diffuse atherosclerosis may generate a longitudinal pressure gradient in more than half of atherosclerotic coronary arteries without focal obstructive lesions⁷⁹ reducing coronary blood flow and myocardial perfusion⁷⁹ that can result in myocardial ischaemia and symptoms.⁶² Second, since coronary plaque rupture and thrombosis commonly occur at sites of NOCAD, CMD with NOCAD is a more ominous condition than CMD with normal coronary arteries because of the coexistence of CMD and extensive substrate for plaque rupture.

The subgroup of patients with the combination of CMD and NOCAD includes patients with obesity, diabetes, metabolic syndrome, CKD, and heart failure with preserved ejection fraction (HFpEF), and a predominance of females.⁶² In obese patients, CMD is frequently present,^{80,81} increases in severity with increasing body mass index, and may

serve as a better predictor of adverse clinical events than body mass index or traditional risk factors.⁸² Although patients with diabetes and metabolic syndrome are at a markedly increased risk of future atherosclerotic and heart failure adverse events, this excess risk is incompletely explained by OCAD or left ventricular dysfunction and is significantly higher in women with diabetes than in men.^{62,83}

Mounting evidence suggests that diabetes and prediabetic states contribute to important alterations in the regulation of coronary vascular tone before they present with OCAD.^{62,84,85} Patients with diabetes show a range of structural and functional microvascular abnormalities which vary in extent and severity across cardiometabolic states. Symptomatic patients with diabetes, even without known CAD, demonstrate a variable risk of events when stratified by the severity of coronary vasomotor dysfunction,⁸⁶ and those with metabolic syndrome and diabetes, respectively, demonstrate a stepwise increase in rates of CMD and cardiac events.⁸⁷

IHD is highly prevalent in patients with CKD, is responsible for more than one-half of their associated mortality, and is not fully explained by the presence of OCAD.⁶² The severity of CMD increases with decreasing glomerular filtration rate^{88,89} beginning in the early stages of CKD and is associated with increased cardiovascular mortality across the spectrum of kidney function.⁸⁸

Recent evidence suggests that CMD likely plays an important role in the pathophysiology of HFpEF that is mediated through cardiomyocyte injury.^{62,90,91} Chronic elevation in high-sensitivity troponin levels is common in patients with left ventricular hypertrophy, diabetes, and CKD and is associated with an increased risk of cardiovascular death and heart failure.⁹² In otherwise low-risk patients with ischaemic symptoms and minimally elevated troponin, only those with CMD have a significantly increased risk of major adverse cardiac events.⁹⁰ Moreover, CMD is independently associated with worsening diastolic dysfunction and, only in the presence of CMD, is a mild troponin elevation associated with diastolic dysfunction.⁹¹ Strikingly, patients with CMD and diastolic dysfunction experience a >5-fold risk of HFpEF hospitalization.⁹¹ With increased oxygen demand, factors tipping the balance towards cardiomyocyte injury in patients with existing CMD may worsen myocardial mechanics and increase the risk of HFpEF, even without OCAD.^{62,91,93–95}

The pathophysiology of stable IHD in women is different from that in men.^{22,62,96–99} Women present with a higher burden of symptoms and comorbidities compared with men and experience similar or worse outcomes⁶⁰ but are less likely to manifest OCAD, regardless of whether they present with stable IHD⁹⁹ or acute coronary syndromes.⁹⁸ A major contributor to this apparent paradox is CMD, which often coexists with diffuse, non-obstructive atherosclerosis.^{21,22,99} CMD increases cardiovascular risk in both women and men,²¹ but may constitute an especially malignant phenotype in a subset of severely affected women.⁹⁹ Sex-specific factors may promote the development of CAD in a diffuse pattern with a greater propensity for CMD than focal obstruction.¹⁰⁰ Although not a uniquely female disorder, this pattern of abnormalities may be more prognostically important in women.¹⁰¹

4.3 CMD with obstructive atherosclerosis

Although underdiagnosed, CMD also occurs in patients with OCAD. This finding is not surprising because endothelial and coronary vasomotor dysfunction represent early manifestations of atherosclerosis, which may long precede the development of obstructive stenosis. In patients with stable CAD, reductions in microcirculatory reserve exacerbate the functional significance of upstream coronary stenosis and may magnify

the severity of inducible myocardial ischaemia. From a clinical perspective, the presence of CMD in patients with stable OCAD has several important prognostic implications.

First, depending on its severity, CMD may have a significant effect on the evaluation of the physiological significance of a coronary stenosis using trans-stenosis pressure gradients or non-invasive imaging for ischaemia. In the presence of CMD, values of FFR measured for any given stenosis are higher (and potentially pseudonormal) than when coronary microvascular function is normal, which can lead to underestimation of the severity of a stenosis.¹⁰² This may help, in part, to explain discrepancies observed between obstructive lesion severity as defined by FFR and the extent and severity of myocardial ischaemia. Second, some studies suggest that reduced CFR as determined by PET, reflecting the combined haemodynamic effects of obstructive stenosis, diffuse atherosclerosis, and CMD, may identify patients at higher risk of adverse events, independent of the severity of angiographic disease.^{6,103–105} Third, in OCAD patients the severity of CMD may have prognostic implications. For example, patients with normal FFR but abnormal CFR who have revascularization deferred on the basis of FFR have been reported to experience an increase in adverse events, suggesting a significant role for CMD in their outcomes.¹⁰⁶ The prevalence of severe CMD in patients who have revascularization deferred based on FFR, however, is unknown. Some studies have estimated that this phenomenon may affect up to one-third of patients with normal FFR.^{106,107} This suggests that interrogation of CMD in patients with OCAD could potentially identify circumstances in which mixed abnormalities from upstream stenoses and the microcirculation synergize to alter the apparent functional significance of a focal stenosis. A recent study found that measurement of global CFR modified the effect of revascularization such that only patients with severely reduced global CFR appeared to benefit from revascularization, and only if the revascularization was with coronary artery bypass graft surgery.⁶ This finding suggests that sensitive measures of diffuse atherosclerosis and downstream CMD may be able to determine if greater therapeutic benefit will result from more complete revascularization with coronary artery bypass grafting. Furthermore, residual CMD may account for the high frequency of persistent angina following successful PCI in patients with stable IHD^{108,109} even in those with normalization of previously abnormal stress tests.³

Thus, CMD represents a combination of structural and functional abnormalities in the coronary microcirculation, is prevalent across a broad spectrum of cardiovascular risk factors and diseases and may be associated with increased risk of adverse outcomes. Contemporary evidence indicates that most patients with CMD have coexisting obstructive or non-obstructive atherosclerosis that has important implications for their prognosis.

4.4 Patients with angina post-PCI—role of CMD

While the exact contribution to myocardial ischaemia and angina of CMD in OCAD patients is difficult to demonstrate due to the presence of flow-limiting stenosis, the clinical relevance of CMD can become evident after the removal of the epicardial obstruction by PCI. CMD is indeed a major cause of angina and myocardial ischaemia on non-invasive stress tests after successful PCI.¹¹⁰

The persistence/recurrence of angina after PCI has been reported in 20–40% of patients and is independent of the type of procedure applied.⁵ The mechanisms of chest pain in these patients are, in fact, heterogeneous, and include restenosis, the development of new critical coronary

lesions, diffuse non-critical atherosclerosis, coronary dissection, thromboembolism and, possibly, myocardial bridging. Moreover, among patients in whom no cause of chest pain can immediately be identified at angiography, a significant epicardial constriction or spasm at the level of or distal to the treated stenosis is a further possible cause of angina. Induction of epicardial spasm by provocative tests, resulting in myocardial ischaemia and angina, has indeed been reported in up to about 50% of these patients.^{111,112} In addition, CMD may be present in these patients and potentially explain ongoing or recurrent symptoms.¹¹² Li et al.¹¹³ found a reduced CFR (2.62 ± 0.98 vs. 3.01 ± 1.13 in a control group without angina, $P=0.029$) and a higher IMR (29.3 ± 11.7 vs. 24.9 ± 9.7 , $P=0.008$) in response to adenosine in patients with recurrent angina but no restenosis after 6–12 months from PCI; of note, CMD was associated with evidence of myocardial ischaemia on exercise stress testing. More recently, Hokimoto et al.¹¹⁴ found evidence of CMD in 59% (62/105) of patients with and without angina who had undergone PCI with drug-eluting stents 9 months previously. Of those, 37% showed an impaired coronary blood flow response to both adenosine and ACh, thus suggesting an impairment of both endothelium-independent and endothelium-dependent coronary microvascular dilatation.

There is conflicting evidence on whether the prevalence of CMD is higher in patients with OCAD as compared to those with NOCAD. One reason for this is that data on angiographic or intracoronary imaging features of the arterial wall regarding the presence of plaques is often not reported in patients without epicardial obstruction who underwent intracoronary function testing. In Japanese patients, the prevalence of CMD was significantly higher ($P<0.001$) in those who had undergone PCI due to significant epicardial disease (59%) compared to those who were initially suspected to have functional coronary disease (29.5%).¹¹⁴ In contrast, the prevalence of epicardial spasm was similar in the two groups. The prevalence of smooth coronary arteries in the group with suspected functional coronary disease is not available from this report.¹¹⁴ Corcoran et al.,¹¹⁵ in a British cohort of patients, observed a similar prevalence of CMD in patients with suspected CAD who had NOCAD (17/25 patients = 68%) and in patients with OCAD (23/28 = 61%). Again, the prevalence of patients with smooth coronary arteries in the NOCAD group has not been reported.

An impaired coronary microvascular dilatation in post-PCI patients has also been demonstrated using non-invasive methods. Thus, Milo et al.¹¹⁶ found reduced dilator responses to both adenosine and cold pressor test (representing endothelium-independent and endothelium-dependent vasodilatation) by transthoracic Doppler echocardiography of the left anterior descending in patients who had undergone PCI of this vessel 1 day before. Of note, these alterations persisted at 3- and 6-month follow-up and correlated with persistence of exercise-induced myocardial ischaemia [by exercise electrocardiogram (ECG) testing]. Importantly, a greater impairment of CFR was associated with restenosis during 3-year follow-up.¹¹⁷

The studies listed above clearly show that obstructive epicardial coronary disease and microvascular dysfunction may coexist. However, several groups have also observed that reversible microvascular abnormalities may be associated with the haemodynamic situation of a proximal epicardial stenosis.^{118,119} These observations are consistent with the hypothesis that the microvasculature distal to a tight stenosis may not be able to immediately adjust its tone to the level required to maintain normal resting flow. This inability to return to normal autoregulation may be related to anatomic remodelling or functional readjustment in response to the haemodynamic effects of the stenosis.¹²⁰ The findings by Verhoeff et al.¹¹⁹ suggest that a functional contraction of the

microvasculature seems to exist distal to a tight stenosis. They observed an increased HMR which dropped impressively once the stenosis was removed by PCI. HMR in the intervened vessel dropped to values lower than those measured before PCI in a reference vessel.¹¹⁹ However, baseline microvascular resistance was also reduced in the intervened vessel resulting in an increase of basal myocardial blood flow (MBF) post-PCI. Such an increase of basal MBF was also found non-invasively in the perfusion bed of the intervened vessel using PET at 1 and 7 days following PCI.¹¹⁸ The increased basal MBF coupled with a still reduced hyperaemic MBF led to a persistently reduced dipyridamole-CFR in the PCI region of patients at 1 and 7 days after the procedure. However, CFR was normalized in these patients when PET was repeated after 3 months¹¹⁸ indicating the potential reversibility of the microvascular abnormalities developing distal to a tight proximal coronary stenosis.

The inability of the microvasculature in the first days following PCI to fully relax may also explain the persistence of pathologic exercise stress test in some patients shortly after PCI. el-Tamimi et al.¹²¹ found that 50% of patients successfully treated by balloon angioplasty continued to have a pathologic exercise stress test 1 week after the procedure. Interestingly, the test became normal after sublingual nitrates administration suggesting nitrate-induced improved relaxation of the microvasculature during exercise. Spastic involvement of the epicardial coronary vessel was excluded by a normal intracoronary ergonovine test. Thus, exercise-induced ischaemia persisting early after coronary intervention seems to be related to microvascular rather than epicardial constriction and may have the potential to be reversible in some patients.

Microvascular dysfunction may come in two varieties: firstly, there may be an inability to appropriately relax when stimulated by adenosine and secondly, there may be an inappropriate spastic reaction of the microvasculature when stimulated by ACh. The latter mechanism may also explain some of the persistent anginal symptoms in patients after PCI. Ong et al.¹¹² found evidence of ACh-induced CMS in 18 (17%) of 104 patients with angina and previous PCI but no restenosis. Moreover, 28 of the 51 patients who showed ACh-induced epicardial spasm developed symptoms and ischaemic ECG changes before the angiographic appearance of epicardial spasm. This observation suggests that CMS develops first and is initially responsible for myocardial ischaemia followed by epicardial spasm with subsequent intensification of symptoms and signs of ischaemia. Overall, 46/104 (45%) patients in this study had at least parts of their symptoms potentially related to CMS.¹¹²

The mechanisms responsible for post-PCI CMD are poorly known but are likely multiple and heterogeneous. Microvascular changes in response to the reduced perfusion pressure distal to a critical stenosis¹²⁰ might negatively affect coronary microvascular dilatation, with microvascular dysfunction persisting for a variable time after restoration of a normal epicardial flow.^{118,119,122,123} CMD, however, might be present together with, but independently of, coronary stenosis in some patients and become the sole source of persisting angina after removal of the epicardial stenosis. Furthermore, at least in some patients, CMD might depend on mechanisms related to PCI itself, including microvascular damage by coronary microembolization of debris material and reactive inflammation consequent to the procedure,¹²⁴ and, in patients with drug-eluting stent, negative effects on both endothelial and smooth muscle cell function of the active stent drugs released downstream.^{125–127}

In clinical practice, the diagnosis of a microvascular origin of angina in post-PCI patients is difficult to achieve on the basis of clinical features and results of non-invasive stress tests, as they usually do not allow a distinction between the various mechanisms of myocardial ischaemia. However, similar to patients with primary microvascular angina,⁵⁵ some

findings may suggest a microvascular origin of symptoms, including: (i) a slow or delayed response of angina pain to short-acting nitrates; (ii) lack of regional wall motion abnormalities during echocardiographic stress test, despite the induction of angina and ischaemic ECG changes¹²⁸; (iii) absence of OCAD at coronary computed tomography (CT) angiography in patients with evidence of myocardial ischaemia or abnormal CFR on non-invasive testing¹²⁹; (iv) a diffuse, rather than regional, impairment of MBF on PET¹³⁰ or CMR stress tests¹³¹; and (v) failure of calcium-antagonists therapy to prevent angina attacks, which makes epicardial spasm an unlikely cause of symptoms.

While clinical findings and non-invasive assessment of patients may give important clues to the origin of symptoms, a full invasive assessment may still be required in many patients in order to make the exact diagnosis and direct appropriate management of these patients. The COVADIS group has recently proposed an algorithm to distinguish between the various causes of chest pain in patients post-PCI (Figure 5).⁵ Thus, CMD is present in most patients with obstructed coronary arteries and is responsible for persistent angina in several patients treated by successful PCI. Further research, however, is required to determine whether routine assessment of CMD may lead to improved clinical management of these patients.

5. Non-invasive diagnosis of CMD in patients suspected to have OCAD

Up to 50–60% of patients undergoing elective coronary angiography for suspected CAD have NOCAD.¹³² These patients are often reassured regarding the test result and no further diagnostic or therapeutic steps are undertaken. However, the prognosis of these patients depends on the extent of plaque formation as seen by coronary angiography⁶¹ or coronary CT angiography.^{133,134} Retrospective analysis of all US veterans undergoing elective coronary angiography for CAD over a period of 5 years showed that 45% of patients had no OCAD. Half of those had entirely normal coronary arteries by coronary angiography, whereas the other half showed plaque (NOCAD in the definition of this review paper).⁶¹ The prognosis of patients with entirely normal coronary arteries was good with an annual incidence of death or myocardial infarction of around 1.2%.⁶¹ In another study, patients without plaque by coronary CT angiography have an even lower annual event rate of only 0.4%.¹³⁴ Depending on the number of angiographically affected vessels with plaque, this annual incidence increases gradually.⁶¹ Patients with plaque in all three major coronary vessels experience events at a rate of approximately 2.9% annually which closely approximates the event rate of patients with obstructive single-vessel disease (3.0%).⁶¹ Similar data were obtained based on the information from coronary CT angiography when patients were followed for a median of 3.6 years.¹³⁴ Extensive diffuse non-obstructive coronary atherosclerosis involving >4 of 18 coronary segments on coronary CT angiography carried a similar prognosis with respect to death (annual death rate of 2.3%) as the same extent of affected segments with obstructive disease.¹³⁴

Although the population of patients with chest pain is heterogeneous, many may have CMD.¹³⁵ In order to avoid invasive coronary angiography done for the sole purpose of excluding epicardial stenoses patients should be investigated for evidence of myocardial ischaemia prior to coronary angiography.¹³⁶ This is in keeping with current clinical ESC guidelines for the diagnosis and management of patients with chronic coronary syndromes.⁵⁸ Patients with a low clinical likelihood of OCAD

may also undergo coronary CT angiography in order to exclude obstructive plaque. Patients without ischaemia are recommended to undergo carotid ultrasound to exclude arterial plaque, whereas the presence of plaque is simultaneously revealed in those undergoing only CT angiography. The consequence of finding plaque is to initiate secondary preventive measures. Depending on the type of chest pain antianginal treatment may be justified. Coronary angiography is recommended for patients with a high clinical likelihood of obstructive disease and symptoms refractory to medical therapy.⁵⁸

In a patient with chest pain, the diagnosis of definitive microvascular angina (i.e. angina caused by microvascular disease) can be made if the following criteria are met: (i) symptoms consistent with angina, (ii) absence of OCAD, (iii) objective evidence of myocardial ischaemia, and (iv) evidence of abnormal coronary microvascular function (defined as abnormal CFR, abnormal IMR, microvascular spasm, or coronary slow flow phenomenon).⁵³ Thus, the diagnosis can be made non-invasively based on a careful clinical history, a coronary CT angiogram demonstrating absence of stenoses, pathologic exercise stress ECG, and an abnormally low CFR measured by transthoracic Doppler echocardiography. Alternatively, one can rely on the invasive coronary angiogram enriched by invasive coronary function testing.¹⁸ However, the invasive path to the diagnosis of microvascular angina requires that ischaemia should be demonstrated beforehand.

5.1 Absence of OCAD demonstrated by anatomical imaging

As outlined above, the diagnosis of CMD requires, firstly, the exclusion of OCAD as a cause of the anginal symptoms. With recent guidelines^{58,137} placing emphasis on CT coronary angiography (CTCA) as a first-line investigation for patients presenting with suspected angina, fewer patients can be expected to undergo invasive coronary angiography for excluding OCAD. In patients in whom CTCA has excluded OCAD, symptoms suggestive of angina should prompt clinicians to consider CMD as a potential mechanism for ischaemia and proceed to functional testing in the first instance. Combining an exercise stress ECG (demonstration of ischaemia) with transthoracic Doppler echocardiography of the left anterior descending coronary artery before and after intravenous adenosine (measurement of CFR) would be a good approach to rule in or rule out the diagnosis of CMD.

5.2 Functional tests to prove the presence of ischaemia and an abnormal CFR

Most stress tests are widely available in the clinical setting and should be utilized when assessing a patient with suspected angina. There are also several other modalities that are specific to CMD, with the caveat that OCAD has been excluded prior to functional testing.

The treadmill stress test remains the most accessible form of functional testing. However, no specific features diagnostic of CMD have been identified. Many women with 'false positive' stress ECGs (because of the absence of epicardial stenoses at subsequent coronary angiography) will have CMD as the underlying abnormality causing symptoms.¹³⁸ However, a negative treadmill stress test does not exclude the possibility of CMD which only involves non-exercise dependent abnormal vasoconstrictor activity of the microvasculature (microvascular spasm).

CMD will usually not produce echocardiographically detectable dysfunction despite the occurrence of symptoms, ECG changes, and perfusion abnormalities.¹²⁸ This contrasts to the good sensitivity of stress

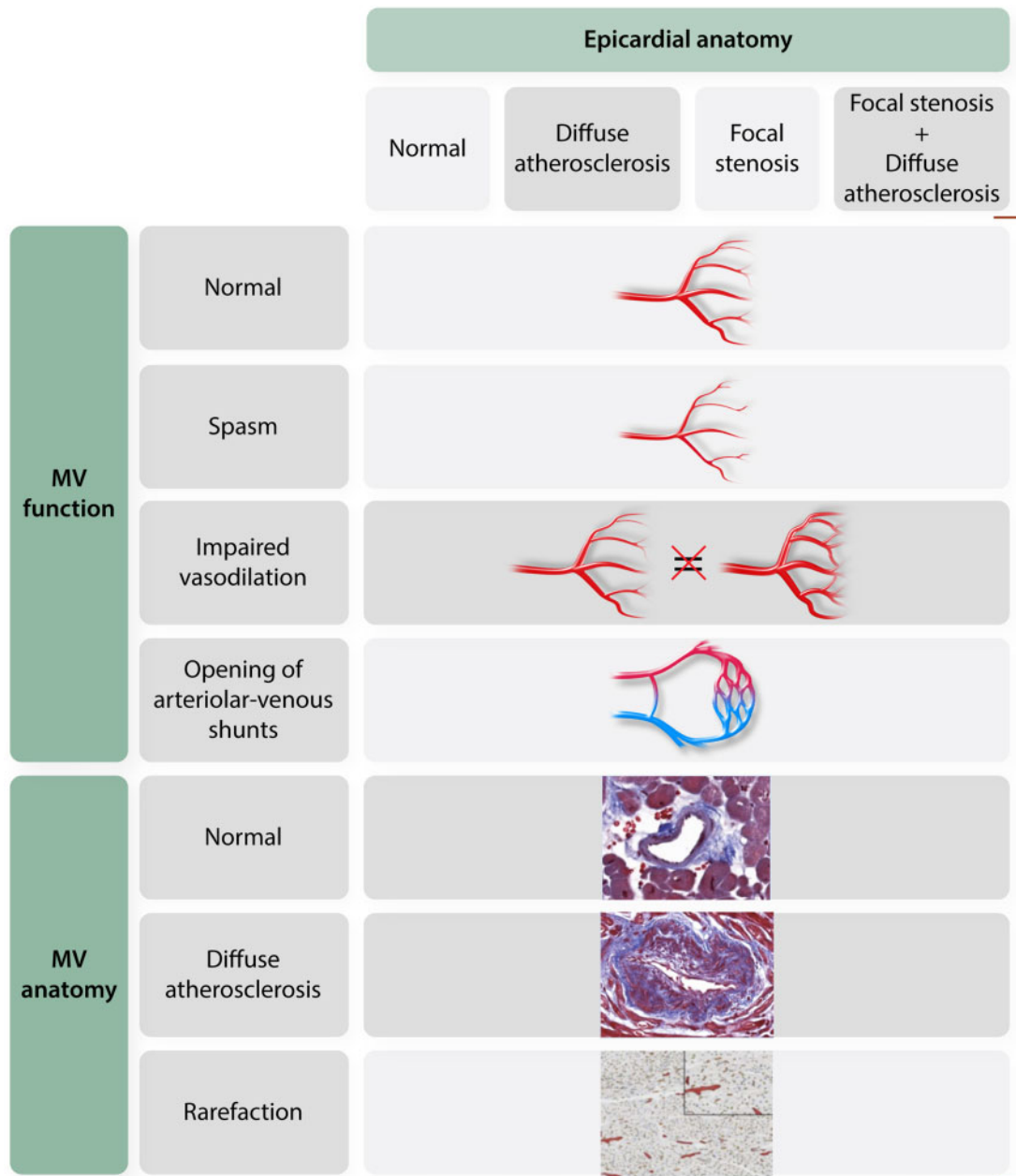


Figure 5 Possible combinations of epicardial coronary anatomy and microvascular abnormalities. For the purpose of clarity, functional epicardial abnormalities which may be present in addition to the conditions shown were left out. The comb-like structures shown in the three illustrations on the left are schematic representations of the microvasculature. The drawing of the arteriolar-venous shunt (shown in red in the centre of the seven illustrations) is reproduced with permission from Pries and Reglin.²³ The two images of a normal arteriole and a diffusely diseased arteriole from a patient with OCAD shown in the left and middle panel under MV anatomy were kindly provided by Professor Karin Klingel, MD, Director of Cardiac Pathology, Institute of General and Molecular Pathology and Pathologic Anatomy, University of Tübingen, Germany. The image shown in the right panel demonstrates diffuse rarefaction of capillaries (yellow), precapillary arterioles (orange), and larger intramyocardial arteries (red) in a patient with heart failure with preserved ejection fraction. This image was reproduced with permission from Mohammed *et al.*⁸ *Any combination of these conditions.

contrast echocardiography if perfusion in a sizeable territory of an epicardial artery or a major branch is significantly decreased.¹³⁹ Patchy involvement, which is common in CMD, is likely to be missed.

Diffuse mild involvement across the myocardium may also fail to produce an area of localized reduction in stress contrast echocardiography. However, in patients with intermediate coronary stenoses with normal

FFR values stress contrast echocardiography may demonstrate ischaemia. This may be related to an inability to increase flow sufficiently through the stenosis due to associated severe CMD.¹⁴⁰

Transthoracic Doppler echocardiography has been used to evaluate flow in the left anterior descending artery. Coronary flow velocity is measured at baseline and at maximal hyperaemia in response to

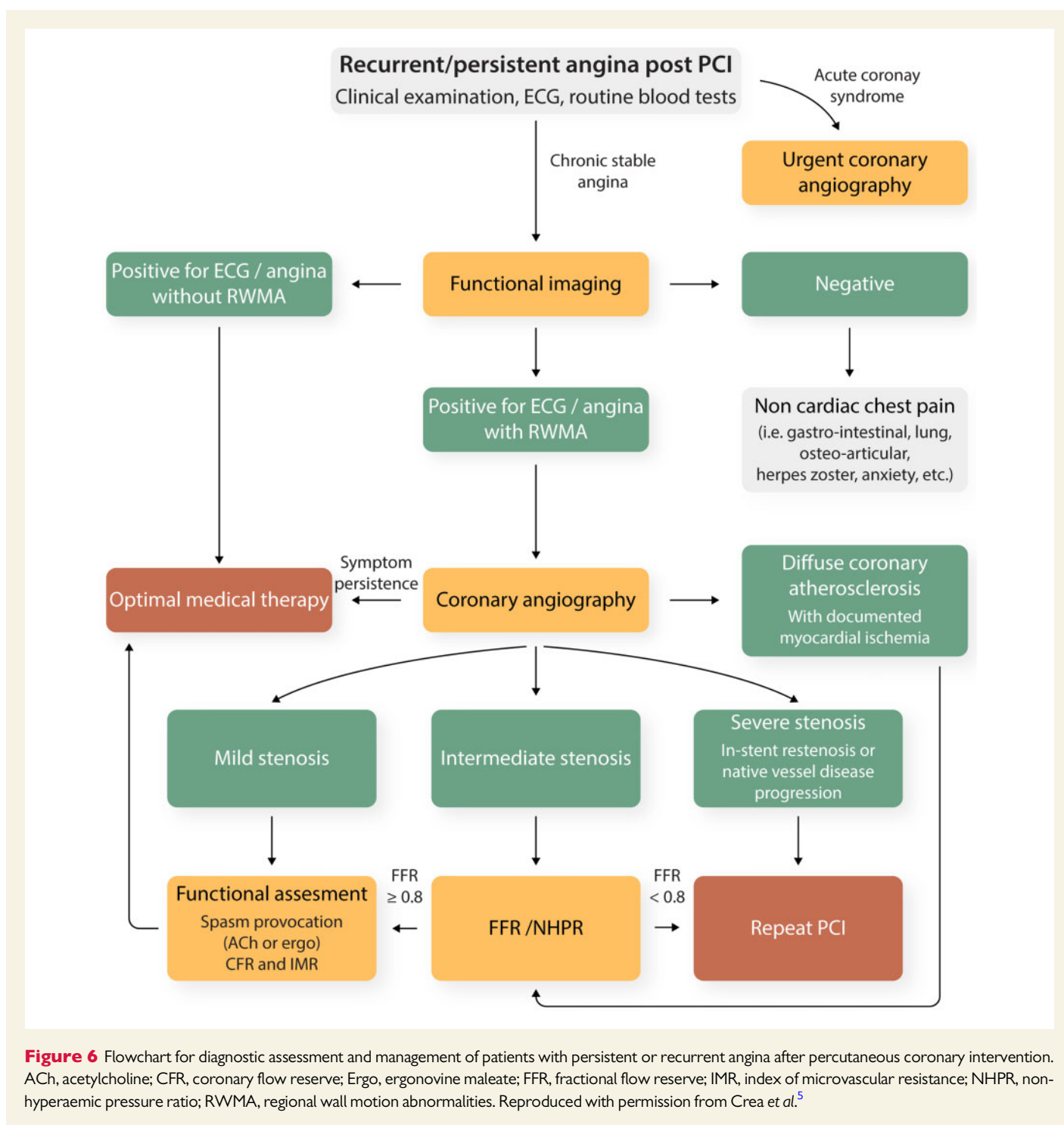


Figure 6 Flowchart for diagnostic assessment and management of patients with persistent or recurrent angina after percutaneous coronary intervention. ACh, acetylcholine; CFR, coronary flow reserve; Ergo, ergonovine maleate; FFR, fractional flow reserve; IMR, index of microvascular resistance; NHPR, non-hyperaemic pressure ratio; RWMA, regional wall motion abnormalities. Reproduced with permission from Crea *et al.*⁵

adenosine, and the ratio between the latter and the former is taken as representative of CFR.¹⁴¹ This test requires a high-frequency transducer and highly sensitive and dedicated equipment and is significantly dependent on an appropriate acoustic window. Interpretation of a negative test in a patient with typical anginal symptoms and a pathologic exercise stress ECG in the absence of an epicardial coronary stenosis is challenging. Such a patient would not fulfil the current diagnostic requirements for making a diagnosis of CMD.⁵³ Nevertheless, if the patient suffers from intense symptoms especially at rest, proceeding to invasive diagnosis including an ACh provocation test may be appropriate.

Single-photon-emission computed tomography (SPECT) nuclear perfusion scans may show relative overall reduction in technetium uptake and reduced washout in CMD. SPECT may also show regional ischaemia in patients with severe, regionally accentuated CMD.¹⁴² However, recent systematic studies studying SPECT in patients with invasively proven CMD do not exist. In the past, overall sensitivity of demonstrating ischaemia in CMD (formerly called syndrome X) was shown to be low.^{143,144}

PET has been shown to be a reliable tool to quantify MBF,¹⁴⁵ which has good correlation with invasively measured CFR (see above). It remains the current reference standard for non-invasive quantification of

myocardial ischaemia, with or without OCAD. Unfortunately, cardiac PET is not widely available and reimbursement may be difficult in some countries.

Stress CMR is an alternative to PET and can also be used to measure MBF and myocardial perfusion reserve, both of which correlate with CFR. Liu et al.¹³¹ recently showed that patients with NOCAD and IMR invasively measured to be <25 U also had normal values for the myocardial perfusion reserve index (MPRI) which is a non-invasive correlate of CFR. In contrast, patients with IMR \geq 25 U had significantly reduced MPRI values similar to ischaemic myocardium downstream of OCAD. Highly selected patients with severe CMD (typical exertional angina, pathologic exercise ECG, completely normal coronary arteries by invasive coronary angiography, and absence of inducible spasm by ergonovine-provocation testing) may demonstrate circumferential subendocardial ischaemia on CMR perfusion imaging which is associated with provocation of intense chest pain.¹⁴⁶ This is in contrast to the pattern seen in patients with epicardial disease, where the transmural and segmental perfusion defects would correspond with the distribution of an epicardial coronary artery.

A new CMR technique, gadolinium-free CMR stress T1-mapping seems to be able to distinguish epicardial from microvascular disease non-invasively.¹⁴⁷ This technique makes use of the fact that the water content of ischaemic myocardium will not increase in response to adenosine, whereas that of non-ischaemic myocardium does. The higher water content leads to a higher T1 relaxation time. Therefore, T1 during adenosine is approximately 4–6% higher in normal myocardium compared to the measurement of T1 at rest. In contrast, T1 only increases up to 1.5% in ischaemic myocardium distal to a high-grade epicardial coronary stenosis. Patients with CMD exhibit differences between rest and stress T1 of 1.5–4%. Although these differences are rather small correlation with invasive indices of CMD seems to be excellent.¹⁴⁷ In this first prospective validation of the technique with invasive confirmation, the authors did not look at patients who had epicardial disease and CMD. Moreover, these results await confirmation by other groups.

Although combinations of non-invasive tests can be used efficiently to identify patients with symptoms commonly ascribed to stenosing CAD yet without epicardial stenosis, it will need a major change of mainstream thinking to apply them broadly instead of resorting to coronary angiography as a panacea for the patients with angina. The combination of epicardial plaque formation resulting in various degrees of luminal narrowing with CMD will be a continuing clinical challenge. In these patients, conventional thinking will always strive to see whether it is not a stenosis in disguise causing the symptoms. Moreover, coronary CT angiography with its tendency to overestimate the degree of narrowing caused by plaques may be instrumental in perpetuating the enamoured fixation on epicardial stenoses as the sole cause of anginal symptoms. A sharp clinical eye will be helpful to look beyond the visible and the obvious and consider CMD as the main or additional substrate of the patient's problems. A masterful command of non-invasive testing will also be necessary to come to the right diagnosis of CMD with having to resort to additional invasive support of that diagnosis.

6. Summary

CMD is a complicating factor in many patients with NOCAD and OCAD. The microvasculature may be affected by anatomic and functional derangements and combinations of those. Diagnosing the additional presence of CMD is difficult and often requires invasive diagnostic

testing. However, establishing a diagnosis of CMD has important consequences for therapy and prognosis. CMD may explain why angina persists in a substantial portion of patients after successful revascularization. Non-invasive diagnosis of CMD is also possible. Ideally, the absence of OCAD should be established using coronary CT angiography, whereas the presence of CMD can be ascertained using imaging methods such as PET, CMR, or Doppler echocardiography to demonstrate a reduced myocardial perfusion or CFR. However, CMD may also manifest itself as an abnormal tendency for vasoconstriction (vasospasm) which can only be proven by invasive provocation testing.

Conflict of interest: none declared.

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