Coronary microvascular dysfunction and flow reserve: an update

Paolo G. Camici · Ornella E. Rimoldi

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Abstract Non-invasive imaging techniques (positron emission tomography and cardiovascular/cardiac magnetic resonance) provide accurate and reproducible measurements of global and regional myocardial blood flow (MBF) in absolute units of ml/min/g of tissue, thus providing unique pathophysiological and diagnostic insights into the functioning of the coronary microcirculation. There is compelling evidence suggesting that, in many instances, in the absence of angiographically demonstrable stenosis of the epicardial coronary arteries, significant abnormalities of global myocardial perfusion can be demonstrated in individuals with either risk factors for coronary artery disease or different cardiomyopathies accompanied by alteration of the structure of the microvasculature. In this context, measurement of MBF gives unique diagnostic information regarding the functioning of the coronary microcirculation and provides a quantitative surrogate endpoint against which the efficacy of treatments can be established. In this review article, we discuss the more recent advances regarding the non-invasive measurement of MBF and flow reserve and their clinical applications for the detection of coronary microvascular dysfunction.

Keywords Microcirculation · Myocardial perfusion · PET · CMR

Background

Obstructive disease of the epicardial coronary arteries has been recognized as the cause of myocardial ischemia and angina pectoris for more than two centuries. Therefore, these arteries have been the focus of both diagnostic and therapeutic attention. In the late 1950s, Sones introduced coronary angiography, which provided a “road map” of the epicardial coronary arterial tree [1, 2]. This was followed by the development, first of coronary artery bypass grafting, in 1970 [3], and then of percutaneous coronary angioplasty, in 1977 [4].

In the past three decades, however, several studies have shown that abnormalities in the coronary microcirculation may also cause or contribute to myocardial ischemia in several conditions. It has been suggested that in a number of patients admitted with angina attacks but no apparent cardiac or systemic disease, coronary microvascular dysfunction (CMD) could represent the sole cause of the symptoms [5]. Myocardial blood flow (MBF) abnormalities and the consequent CMD-related myocardial alterations may differ substantially from those caused by flow-limiting stenoses in epicardial coronary arteries. In the latter case, the impairment of MBF is generally regional and distributed within the territories subtended by the stenosed artery, resulting in detectable segmental impairment of contractile function. In the case of CMD, on the other hand, the abnormality may not necessarily involve the territory subtended by a major coronary branch; indeed, it may involve the whole left ventricle (LV) diffusely or be distributed in a scattered manner [5].

Color figures online at <http://link.springer.com/article/10.1007/s40336-013-0037-8>.

P. G. Camici
San Raffaele Scientific Institute, Vita Salute University,
Milan, Italy

O. E. Rimoldi (✉)
C.N.R., Istituto di Bioimmagini e Fisiologia Molecolare, Centro
PET, Istituto Scientifico Universitario San Raffaele, Settore C,
piano -2, Via Olgettina, 60, 20132 Milan, Italy
e-mail: rimoldi.ornella@hsr.it

Camici and Crea [5] have proposed a clinical classification of CMD, dividing it into four main types on the basis of the clinical setting in which it occurs [1]: (1) CMD in the absence of myocardial diseases and obstructive coronary artery disease (CAD), (2) CMD in myocardial diseases, (3) CMD in obstructive CAD, and (4) iatrogenic CMD.

CMD may be underlain by several pathogenetic mechanisms including structural, functional and extravascular alterations that can contribute to the condition in different ways. The importance of these mechanisms varies in different clinical conditions, although several of them may coexist in a single condition.

Structural alterations

Structural abnormalities responsible for CMD have, in particular, been consistently documented in patients with hypertrophic cardiomyopathy (HCM) and in those with arterial hypertension. In both these conditions, morphological changes are characterized by an adverse remodeling of intramural coronary arterioles consisting of vessel wall thickening, due mainly to hypertrophy of smooth muscle cells and increased collagen deposition in the tunica media, with variable degrees of intimal thickening [2, 5]. This thickening of the vascular wall leads to an increase in the medial wall area, and a relative reduction of the size of the lumen that correlates with the increase in minimal coronary resistance and the reduction of coronary flow reserve (CFR). Although qualitatively similar in the two conditions, these anatomical changes are usually quantitatively more severe in patients with HCM.

An important feature shared by patients with arterial hypertension and those with HCM is the diffuse nature of the microvascular remodeling, which involves the entire LV independently of the distribution of the ventricular hypertrophy (i.e., symmetrical vs asymmetrical), and may also involve portions of the right ventricle [6]. The functional counterpart of this phenomenon is the maximum MBF and CFR blunting in the whole LV that has been demonstrated in most of these patients [7]. Interestingly, similar changes have been described in the spontaneously hypertensive rat, which is, therefore, a good model of coronary microvascular remodeling associated with hypertension [8, 9].

Functional alterations

Functional CMD may be caused by a variable combination of mechanisms leading to impaired coronary microvascular dilatation and mechanisms resulting in increased microvascular constriction.

Endothelial cells play a major role in the regulation of blood flow in the coronary microcirculation, particularly at the level of the pre-arteriolar vessels, both in resting conditions and during increased myocardial oxygen consumption. Accordingly, alterations in endothelial function may impair MBF both at rest and in the event of an increased myocardial workload, as typically seen during exercise [10].

Impairment of endothelium-independent dilatation has been shown to be a cause of CMD in several experimental and clinical conditions characterized by a significant reduction of the MBF increase in response to direct arteriolar/pre-arteriolar vasodilators (e.g., adenosine, dipyridamole, papaverine). Despite the large amount of data documenting the role of endothelium-independent dilatation in CMD, the cellular mechanisms involved remain incompletely understood [10, 11].

Evidence to support the notion that coronary microvascular constriction may cause myocardial ischemia has been found both in experimental models and in man. Some vasoconstrictor substances, indeed, cause selective intense microvascular constriction with minimal effects on the epicardial coronary arteries [11].

Extravascular mechanisms

The pulsatile pattern of blood flow shows typical physiological variations, linked to the variations in intramyocardial and intraventricular pressure occurring during the systolic and diastolic phases of the cardiac cycle. MBF mainly occurs in diastole and, therefore, diastolic abnormalities particularly affect myocardial perfusion. Nevertheless, increased systolic intramyocardial and ventricular pressure, as typically seen in primary and secondary left ventricular hypertrophy, can also negatively impact on myocardial perfusion [12]. Indeed, an increase in microvascular compression generated during contraction makes subendocardial vessels less able to promptly regain their tone in diastole, a circumstance that results mainly in diastolic impairment of microvascular blood flow in subendocardial layers [13]. Diastolic blood flow is impaired by all conditions that increase intraventricular diastolic pressure. Thus, it is impaired in the presence of left ventricular hypertrophy and also in the presence of diastolic dysfunction related to increased collagen content in the myocardial tissue. Of note, conditions that make arteriolar driving pressure during diastole significantly lower than intraventricular pressure, such as aortic stenosis, critical coronary stenoses, prearteriolar constriction or merely hypotension, may facilitate diastolic impairment of MBF in this setting. The detrimental effects of increased systolic intramyocardial pressure and of diastolic intraventricular

Fig. 1 In the absence of coronary stenosis (in the *right panel* angiography shows a patent left coronary artery) maximum MBF and CFR (maximum MBF/Rest MBF) reduction during adenosine infusion reflects the impairment of microvascular function (color figure online)

pressure on MBF are more pronounced in subendocardial than in subepicardial layers.

Methods for studying coronary microvascular function

Unlike epicardial coronary arteries, the coronary microcirculation cannot be directly imaged *in vivo* either with coronary angiography or intracoronary imaging techniques. Indeed, small coronary arteries are below the spatial resolution of coronary angiography (about 0.5 mm) and cannot be reached by the catheters utilized for intravascular imaging or optical coherence tomography.

Assessment of coronary microvascular function, therefore, relies on the measurement of parameters that reflect its functional status, such as MBF and CFR. This latter is the ratio of MBF during pharmacologically induced arteriolar vasodilatation, achieved by means of intravenous or intracoronary vasodilators, to baseline resting MBF. Adenosine, because of its safety profile, is the vasodilator most widely used to assess hyperemic blood flow. However, some limitations must be taken into consideration. When it is administered systemically, hypotension and reflex tachycardia alter the coronary blood flow response and coronary vasomotor tone mediated by α -receptors is not fully eliminated resulting in “near” maximal vasodilatation [14].

CFR is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation [15]. In the absence of obstructive stenoses of the epicardial arteries, a reduced CFR is a marker of CMD (Fig. 1). Although a single cutoff value of CFR (e.g., ≤ 2.0) below which microvascular function is deemed abnormal would be useful clinically, it must be noted that, in normal humans, CFR varies according to age and gender [16]. Therefore, it is essential to compare CFR data obtained in patients with those obtained in age- and sex-matched normal subjects. In addition, resting MBF is linearly related to cardiac workload. Therefore, when comparing different

patients, it is important to correct resting MBF for the main determinants of external cardiac workload, i.e., blood pressure and heart rate (rate-pressure product; RPP). A corrected CFR can then be calculated by dividing hyperemic flow by RPP-corrected resting flow [17–19]. More complex, on the other hand, is the assessment of CMD in territories subtended by stenotic coronary arteries, where the evaluation of microvascular function depends on the clinical context.

Hajjiri et al. [20] proposed that maximum MBF (i.e., the flow measured during pharmacological vasodilatation) might be superior to CFR. Their data are consistent with previous reports indicating that the degree of impairment of MBF flow bears important prognostic information [21]. In fact, it has been demonstrated that both in hypertrophic [22] and dilated [23] cardiomyopathies, the severity of impairment of peak MBF measured during dipyridamole stress is predictive of major adverse cardiac events at follow-up. In patients affected by these conditions, in whom there is no overt evidence of CAD, the curtailment of MBF is due to dysfunction of the coronary microcirculation. This could be explained, at least in part, by the fact that CFR is a ratio and factors that influence either the numerator or the denominator may affect its calculation. Therefore, a reduced CFR does not necessarily reflect a reduction of maximum flow, but may be due to an abnormally elevated resting flow in the face of a normal hyperemic flow. This problem can be overcome, at least in part, by normalizing resting flow for the external cardiac workload [17, 18].

Although much of the excess of CAD risk can be accounted for by the presence of diabetes-associated coronary risk factors such as obesity, dyslipidemia and hypertension, a significant proportion of it remains unexplained. A direct deleterious effect of diabetes on vascular and, in particular, endothelial function has been suggested, which would increase the potential for vasoconstriction and thrombosis. There is consistent evidence that CFR is impaired in patients with diabetes and that this may be an early marker of atherosclerosis. A positron emission

tomography (PET) study found marked CMD in response to adenosine (reflecting primarily endothelium-independent vasodilatation) and a cold pressure test (reflecting primarily endothelium-dependent vasodilatation) in young subjects with uncomplicated diabetes. The findings were very similar in type 1 and type 2 diabetes [24]. This provides further support for a key role of hyperglycemia in the pathogenesis of vascular dysfunction in diabetes [5].

Positron emission tomography

PET has been shown to allow non-invasive and accurate quantification of regional MBF, providing suitable tracers are used and appropriate mathematical models applied. These PET measurements of MBF, for which the symbol F/W is also used, are expressed as units of volume per time per unit weight of myocardium (i.e., ml/min/g) [15, 19].

Different tracers can be used for measuring MBF using PET, including oxygen-15-labeled water ($H_2^{15}O$) [25–27], $^{13}NH_3$ [28–31] and the cationic potassium analog rubidium-82 (^{82}Rb) [32, 33]. $^{13}NH_3$ and ^{82}Rb are given intravenously as boluses. In the case of $H_2^{15}O$, the tracer can be administered as an intravenous bolus injection [34–36] or an intravenous slow infusion [36, 37]. ^{82}Rb is produced by a Strontium-82/ ^{82}Rb generator that generally needs replacing once a month. ^{82}Rb is a very appealing MBF tracer because it does not require a cyclotron on site and has a very short $t_{1/2}$ (78 s) [33]. The high positron energy of ^{82}Rb results in a relatively inferior image quality and reduced spatial resolution due to its long positron track (4 mm). Kinetic models have been proposed for quantification of MBF using ^{82}Rb [38–40]; however, these are limited by the dependence of myocardial extraction of this tracer on the prevailing flow rate and myocardial metabolic state. Nevertheless, in the past few years, both semi-quantitative [41] and fully quantitative measurements [42] of myocardial perfusion with ^{82}Rb have proven feasible on a large scale and provide incremental prognostic information both in patients with suspected and in those with known CAD.

Because of its ability to provide non-invasive regional absolute quantification of MBF, PET has been widely used to assess CFR in healthy volunteers. Chareonthaitawee et al. [16] investigated the range of resting and hyperemic MBF in a large population ($n = 160$) of healthy males and females with a broad age range (21–86 years). They found baseline and hyperemic MBF to be heterogeneous both within and between individuals. Furthermore, baseline and hyperemic MBF exhibited a similar degree of spatial heterogeneity, which appeared to be temporally stable. Resting myocardial perfusion ranged from 0.59 to 2.05 ml/min/g (average 0.98 ± 0.23 ml/min/g) and adenosine-induced

hyperemic perfusion ranged from 1.85 to 5.99 ml/min/g (average 3.77 ± 0.85 ml/min/g). Significant differences within subjects were found when comparing different segments with each other, except for anterior versus lateral regions. MBF was significantly higher in females than in males. A significant linear association was found between age and baseline MBF, partly related to changes in external cardiac workload with age. Hyperemic MBF declined after the age of 65 years.

Different studies have tested the short-term reproducibility of MBF measurements using PET with $^{13}NH_3$, $H_2^{15}O$ and ^{82}Rb [27, 43, 44]. Repeated measurements of resting and hyperemic MBF using intravenous dipyridamole and adenosine during the same study session were not significantly different, demonstrating the validity of the technique. The variability of hyperemic flow was larger, as indicated by a greater repeatability coefficient, and was paralleled by a greater variability of the RPP. This could mean that the greater variability of MBF during stress is more likely due to a variable response to vasodilators rather than to a larger measurement error. The feasibility and reproducibility of MBF measurement during supine bicycle exercise have been tested as well. The study results demonstrated the feasibility of this protocol, which was found to be at least as repeatable as using adenosine stress [45]. More recently, Jagathesan et al. [46], using PET with $H_2^{15}O$, tested the long-term reproducibility of MBF measurement at rest and following dobutamine stress in patients with stable CAD. Dobutamine induced reproducible changes in both global and regional MBF and flow reserve over a time interval of 24 weeks. The reproducibility of MBF and CFR with dobutamine was comparable with the short-term repeatability reported for adenosine and physical exercise in healthy subjects.

Clinical perspective

Myocardial perfusion imaging and CFR have a predictive value with regard to long-term prognosis in patients with suspected myocardial ischemia. In patients with normal perfusion, abnormal CFR is independently associated with a higher annual event rate over 3 years compared with normal CFR [21] (Fig. 2). A hybrid multislice CT system can provide comprehensive assessment of cardiac and coronary morphology in addition to assessment of inducible ischemia [42] in suspected CAD [47]. Both the coronary calcium content and the presence of coronary vascular dysfunction are associated with an increased risk of adverse cardiac events. However, in a large cohort of 901 patients, Naya et al. [48] found that in symptomatic patients without obstructive CAD, after adjustment for clinical risk, only coronary vascular dysfunction improved

Fig. 2 Left panel PET scan with $^{13}\text{NH}_3$ in a young patient showing a perfusion defect in the apex, but apparently normal flow in the rest of the myocardium. Quantification of absolute myocardial blood flow (right panel) and flow reserve (middle panel) demonstrated diffuse

impairment of hyperemic (dipyridamole stress) myocardial blood flow and flow reserve. Courtesy of Dr. L. Gianolli, Dr. V. Bettinardi and Dr. E. Busnardo (color figure online)

risk assessment, thus confirming that the total burden of coronary calcium deposits is only modestly associated with impaired vascular function.

PET is particularly effective in those circumstances in which the CFR is diffusely (and not regionally) blunted, e.g., in patients with balanced ischemia [49] and with hypertrophic or dilated cardiomyopathy [7].

In primary cardiomyopathies, postmortem studies on patients who died suddenly, or at transplant have provided compelling evidence for the occurrence of myocardial ischemia in HCM, despite normal coronary angiograms, showing frequent and often extensive areas of myocardial damage exhibiting all stages of ischemic injury [50]. Myocardial ischemia is often silent in HCM patients, and standard techniques employed over the years to assess hypoperfusion or ischemia, such as standard exercise testing, stress echocardiography and thallium-201 scintigraphy, have proven neither sensitive nor specific in this disease [51]. Our group, using PET, first demonstrated the occurrence of severe CMD in HCM patients not only in the hypertrophied septum, but also in the non-hypertrophied LV free wall. Subsequent studies using PET and, more recently,

cardiovascular/cardiac magnetic resonance (CMR), have confirmed that CMD is a diffuse phenomenon in HCM hearts [7, 11, 51]. Nevertheless, the absolute degree of microvascular impairment remains partly related to the extent of LVH, with the most severe blunting generally occurring at the septal level, where maximum wall thickening is usually present [51].

In patients with systemic hypertension, myocyte hypertrophy is accompanied by structural and functional alterations of coronary arterioles [2, 52], whereas larger intramyocardial arterioles do not show significant wall thickening. The reduction of CFR in hypertrophied hypertensive hearts is caused both by a concomitant increase in resting MBF, due to increased workload and oxygen consumption, and by a reduction of the hyperemic response to endothelial-dependent [53, 54] and independent stressors [53]. Interestingly, in a pre-clinical model, spontaneously hypertensive rats treated with perindopril, alone or in combination with indapamide, showed evidence of reverse remodeling of the coronary microvasculature, paralleled by an increased coronary flow, yielding an inverse relationship between hyperemic coronary flow and

arteriolar medial area [9]. The improved spatial resolution of the latest generation of 3D PET scanners [55] has allowed the quantification of the transmural distribution of MBF in patients with LV hypertrophy secondary to aortic stenosis, demonstrating a more significant reduction of subendocardial CFR, which was directly related to the reduction of the aortic valve area [56].

Non-nuclear techniques: cardiovascular/cardiac magnetic resonance

Assessment of myocardial perfusion by means of CMR exploits the first pass kinetics of T1-enhancing extra-cellular gadolinium chelates. During the first pass, the contrast medium diffuses in the interstitial space from the microvasculature resulting in increased signal intensity, proportional to the perfusion and blood volume of the tissue, extravascular compartment size, and capillary permeability [57]. Gadolinium chelates do not cross intact cell membranes and the volume of distribution is restricted to approximately 20 % in normal viable myocardium [58]. Different extravascular, extracellular contrast medium doses, administration protocols and pulse sequences have been tested and validated in animal experiments [59–61] which have subsequently been translated into human studies [62–65]. The main issue in the design of CMR perfusion pulse sequences is the trade-off between spatial and temporal resolution, linearity between signal intensity and contrast agent concentration, acquisition time and signal-to-noise ratio. Over time, different solutions to the above problems have been proposed by several groups to optimize performance [66]. The need for standardization of protocols and of image artifacts is a factor limiting clinical performance. The time signal intensity curves may be degraded and this prevents accurate analysis. The worst artifacts are subendocardial dark rims, which can be visually misdiagnosed as perfusion defects.

In everyday clinical practice, qualitative analysis consisting of visual examination of the homogeneous increase in signal during the first pass followed by contrast washout is generally employed. The detection of a delayed signal increase and persistently hypointense regions indicates that the blood supply is reduced by a high-grade stenosis [67, 68]. Interpretation of the data can be semi-quantitative, using the signal intensity index and/or the up-slope rate [65, 69], or fully quantitative [70, 71]. Fully quantitative perfusion analysis is not yet widely used in clinical practice and is performed in highly specialized centers, either calculating various parameters of the tissue enhancement curves and correcting them by subtracting or scaling the arterial input function derived from the LV [59, 65] or using a model-independent deconvolution [72].

Two main approaches are currently under consideration for widespread clinical application: a hyperemic stress only protocol and a stress–rest protocol for the assessment of CFR. The stress–rest protocol offers the advantage of improving the discrimination of dark rim artifacts from truly impaired perfusion in regions without prior myocardial infarction. However, the issue of residual ischemia in an infarcted region remains incompletely addressed [67].

There is accruing evidence of the diagnostic performance of CMR stress perfusion with adenosine in patients with overt CAD (stenosis >50 %) and in patients with a lower likelihood of disease or risk factors. A multicenter [73] study has shown good sensitivity (range 90–84 %) and specificity (range 89–58 %) for CAD detection on a per-patient basis in comparison with conventional coronary X-ray angiography. In the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective study designed to evaluate risk factors and progression of cardiovascular disease, myocardial perfusion was assessed in 222 subjects [74]. In 28 subjects, the reproducibility and repeatability over an average of 1 year were comparable with PET with relative repeatability coefficients of 30 % of mean at rest and 41 % during hyperemia in the whole heart [75, 76].

In 18 centers in Europe and the USA, the diagnostic performance of CMR perfusion assessed qualitatively has been compared head to head, for the detection of CAD, with more established non-invasive techniques such as SPECT using conventional coronary angiography as the standard of reference. CMR perfusion proved equivalent to gated SPECT with 85 % sensitivity and 67 % specificity, and the receiver-operator characteristic curve analysis favoured CMR perfusion over gated and non-gated SPECT [73]. A recent meta-analysis confirmed the diagnostic performance of stress myocardial perfusion CMR in the detection of significant CAD [77]. The data were derived from studies employing 1.5 Tesla magnets and invasive coronary angiography as the reference standard for diagnosing significant obstructive CAD. Hamon and colleagues [77] combined data from more than 11,000 patients in 26 different studies to demonstrate an overall patient-based sensitivity of 0.89 and specificity of 0.80 for the detection of CAD. Out of 26 studies, 20 were evaluated qualitatively and six semi-quantitatively. It has to be noted that high heart rate, motion artifacts due to breathing and low differences in contrast enhancement between normal and underperfused myocardium represented a limitation in the interpretation of the images. Scanners with higher magnetic field strength (e.g., 3 T) have increased signal-to-noise ratio and contrast enhancement, which can be used to improve spatial resolution and image quality [78].

In summary, PET has been shown to provide accurate and reproducible measurements of MBF and the availability of non-cyclotron-dependent tracers might increase

its clinical use. CMR, on the other hand, is more readily available and has lower costs, although MBF quantification is not yet fully validated.

Conclusions

Pathophysiological mechanisms, assessments, clinical relevance and therapeutic implications vary in different types of CMD [5, 19]. CMD can be the functional counterpart of traditional coronary risk factors. In this setting, CMD can be assessed by non-invasive measurement of CRF and a number of studies have demonstrated that PET is the ideal technique for measuring MBF and CFR, even though its clinical application continues to be rather limited in Europe for a number of reasons, including tracer availability, costs and awareness among referring clinicians. As this type of CMD is, at least in part, reversible, its assessment might be used to guide interventions aimed at reducing risk factor burden. Likewise, PET has been the main technique used to investigate CMD in cardiomyopathies. In hypertrophic and dilated cardiomyopathies, MBF and CFR measured by PET can be useful in risk stratification.

In CAD patients, CMD should be suspected in cases whose symptoms are worse than anticipated on the basis of the severity and extent of angiographic findings. In these patients, CMD might become a new therapeutic target. CMD can be assessed invasively by measuring TIMI frame count and TIMI blush grade, while CFR can be assessed invasively by intracoronary flow wires and non-invasively by contrast echocardiography, PET or CMR.

Conflict of interest Paolo G. Camici: no conflict to declare. Ornella Rimoldi: no conflict to declare.

Human and Animal Studies This article does not contain any studies with human or animal subjects performed by any of the authors.

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