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# The Coronary Microcirculation – from the Basic Research to CMR Imaging – Part II

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## Abstract

The dysfunction of the coronary microcirculation came to light as a significant contributing and/or leading mechanism of myocardial ischaemia with important prognostic implications. The function of the coronary microcirculation (CMC) can be assessed in humans by applying several non-invasive and invasive techniques. This part of the review (Part II) focuses on the utility of positron emission tomography (PET) and computed tomography (CT) for the evaluation of the coronary microvascular function in different disease states. It also summarizes insights into the pathophysiology of the coronary microvascular dysfunction that can invasively be discovered by a Doppler-derived coronary blood flow velocity reserve and microcirculatory resistance indexes.

**Keywords:** coronary microcirculation, PET scan, CT, coronary flow reserve, microcirculatory resistance indexes

## An Assessment of the Coronary Microcirculatory Function by PET Scan

Positron emission tomography (PET) is a non-invasive technique based on the radiotracers that decay by positron emission [1]. A positron is a positively charged electron emitted from the nuclei of unstable isotopes during radioactive decay. Using dedicated flow tracers, PET enables the imaging of regional myocardial perfusion with a high spatial resolution (down to the secondary or tertiary coronary branches) and the quantification of myocardial blood flow (MBF) in absolute units (ml/min/kg) at rest and at stress (hyperaemia). The most frequently used stressor is adenosine, an endothelium-independent vasodilator. The intravenous administration of adenosine produces near-maximal vasodilatation and hyperaemia. The ratio of hyperaemic to rest absolute perfusion represents myocardial flow reserve (MFR), the analogue to the coronary flow reserve (CFR) obtained by transthoracic Doppler echocardiography or the intracoronary Doppler wire.

Coronary flow reserve is an integrated measure of flow both through the large epicardial arteries and the coronary microcirculation (CMC). In the absence of flow limiting epicardial stenosis, reduced CFR is a marker of coronary microcirculatory dysfunction. However, obstructive epicardial disease and the dysfunction of CMC often coexist, making the distinction between these two based on myocardial perfusion challenging. Hybrid

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PET/CT scanners allow a non-invasive evaluation of the coronary anatomy and functional information in one setting. They are valuable options with a higher diagnostic accuracy compared to dedicated PET scanners alone [2, 3]. Furthermore, the perfusion abnormalities detected by this methodology are based on the CT-derived anatomy without the standard assumptions of the vascular distribution, which are frequently inaccurate.

## Myocardial Perfusion by PET: the Basic Principle and Technical Aspects

There are several cyclotron- (15O-labelled water (H215O) and 13N-labelled ammonia (13NH3)) and generator- (82Rb (cationic K+ analogue)) produced radiotracers for the assessment of myocardial blood flow by PET. Each of these radiotracers displays different characteristics, with both their respective advantages and disadvantages. Apart from 13N-ammonia, 82Rb is the most widely used radionuclide for the assessment of myocardial perfusion with PET [4, 5]. The myocardial uptake of 82Rb requires active transport via the sodium/potassium adenosine triphosphate transporter, which is dependent on coronary blood flow. Accurate data are available in the literature, linking 82Rb myocardial perfusion imaging and clinical outcomes [6, 7, 8]. The total-body effective dose from a stress-rest myocardial perfusion study performed with 82Rb is approximately 4 mSv [5].

Myocardial blood flow measurement by using PET is achieved by the continuous monitoring of the radioactivity emitted by an intravenously administered tracer, in the circulation and the myocardium. The kinetics of the radiotracer uptake in the myocardium are derived from the time–activity curves in the left ventricular cavity (the input function) and the myocardium; fitting these time–activity curves with an operational equation provides the accurate estimates of MBF (in ml/min/gof tissue) [9].

The advantages of PET over single-photon emission computed tomography (SPECT) include a lower radiation exposure, fewer artefacts and an improved spatial resolution. PET continues to be the most accurate non-invasive modality for the MBF quantification which other emerging techniques are compared to. Its accuracy and reproducibility are well-established [10, 11, 12, 13].

## The Clinical Application of PET-derived CFR

A large number of PET studies have significantly contributed to our understanding of coronary microcirculatory dysfunction in patients with classical risk factors for atherosclerosis (hypertension, diabetes mellitus, hyperlipidemia), overt epicardial coronary artery disease, the heart failure of different etiology, LV hypertrophy, and valve disease.

### Arterial hypertension

In patients with systemic hypertension, impaired CFR due to both elevated resting MBF and reduced hyperaemic MBF was demonstrated [14, 15]. Interestingly, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers reversed coronary microvascular remodelling, consequently improving both resting and hyperaemic MBF [16].

### Diabetes mellitus

Coronary microvascular dysfunction is a significant determinant of cardiovascular morbidity and mortality in patients with diabetes mellitus (DM), and its correlation with insulin resistance has been extensively demonstrated [17, 18, 19]. Furthermore, coronary vasodilatory dysfunction, as assessed by impaired CFR measured by PET in patients with DM (and in non-diabetics as well) provided significant incremental risk stratification beyond comprehensive clinical data [20]. The diabetic patients without known coronary artery disease (CAD), but with impaired CFR, experienced a cardiac death rate comparable to the non-diabetic patients with known CAD, whereas the diabetics without known CAD and preserved CFR had cardiac mortality similar to the patients without known CAD or DM and the normal stress perfusion and systolic function. The inability to appropriately augment myocardial blood flow in response to stress can be normalized by insulin infusion [21], euglycaemic control with glyburide and metformin [22], or insulin-sensitizer [23].

### Hyperlipidemia

CFR was reduced in the asymptomatic individuals with hypercholesterolemia and without overt coronary stenosis [24]. Interestingly, CFR correlated with the LDL cholesterol levels, but not with the total cholesterol levels, emphasising the pathogenic role of LDL particles [25]. Additionally, treatment with pioglitazone plus the conventional lipid-lowering therapy in the patients with familial combined hyperlipidemia caused significant increases in myocardial glucose utilization and hyperaemic MBF [26].

## PET-derived CFR for the Diagnosis of Coronary Artery Disease, Prognosis and a Revascularisation Strategy

PET enables the determination of the myocardial blood flow threshold for stress-induced perfusion defects with severe angina and/or significant ST-segment depression during dipyridamole hyperaemia [27]. A vasodilator stress perfusion cut-off of 0.91 ml/min/g optimally separated definite from no ischemia with a CFR cut-off of 1.74 [27].

Non-invasive CFR by PET was validated against invasively derived CFR for the functional diagnosis of CAD [28]. PET can reduce the procedure time and costs, and simultaneously simplify the diagnostic protocol for assessing CAD, augmenting both the functional and anatomical diagnosis of CAD.

Diffuse coronary atherosclerosis and coronary microvascular dysfunction are not only highly prevalent among the patients with known or suspected (epicardial) coronary artery disease, but they also increase the severity of inducible myocardial ischemia and identify the patients at high risk for serious adverse events, including cardiac death [29].

The additional prognostic value of attenuated CFR in the patients with known or suspected CAD was proven in a large number of the patients by several investigators [30, 31, 32, 33]. A global CFR<2 (measured by using 13NH3-PET) permitted advance risk stratification in these patients. Abnormal perfusion was associated with increases in major adverse cardiac events and cardiovascular mortality throughout the 10 years of follow-up, whereas in the patients with normal perfusion, a normal global CFR predicted a low risk of major adverse cardiac events during the following 3 years [30]. The incremental prognostic value of CFR was also confirmed by using 82Rb-PET in the study in which CFR values were divided into tertiles. The lowest tertile of the CFR values (<1.5) was associated with a 5.6-fold increase in the risk of cardiac death versus that in the highest tertile (>2) [31]. The independent predictive value of 82Rb-PET-measured CFR over the standard, semi-quantitative parameters, such as the summed stress score, was also documented [32].

Whether the coronary microcirculatory dysfunction detected by PET-derived CFR can help or even guide a revascularisation strategy or not remains to be answered. However, it was shown that PET-derived CFR was associated with the outcomes independently of angiographic CAD and that it modified the effect of early revascularization [29]. The subjects with a low CFR experienced the rates of the events similar to those of the subjects with high angiographic scores, whereas those with a low CFR or a high CAD prognostic index (the measure of the extent and severity of angiographic disease) showed the highest risk of events. Interestingly, the patients with a low CFR who underwent coronary artery bypass grafting, but dd not undergo percutaneous coronary intervention, experienced the event rates comparable to those with preserved CFR, independently of revascularization [29].

## PET-derived CFR in Heart Failure and LV Hypertrophy

The accurate characterization of the etiology of heart failure (HF) (i.e. ischaemic vs non-ischaemic) is important for risk stratification and a therapeutic strategy. However, the severity of left ventricular (LV) dysfunction and remodelling is often out of proportion to the severity of angiographic CAD, pointing to the importance of the structural and/or functional abnormalities of CMC. Abnormal CFR is found in patients with cardiomyopathy even in the presence of the angiographically normal coronary arteries and is associated with an increased risk of adverse ventricular remodelling independent of the clinical severity of HF [34, 35, 36, 37].

The comparison between PET-derived CRF in the patients with ischaemic (ICM) and those with

non-ischaemic (NICM) cardiomyopathy showed that the mean CFR was significantly lower among the patients with ICM [38]. Although impaired CFR (i.e. CFR <2.0) occurred in the majority of both groups, it was more prevalent in the patients with ICM (85.1%) than in those with NICM (71.9%). The patients with ICM had lower stress MBF and CFR, but not resting MBF. Among those patients with dyspnoea, CFR was abnormal in 84.3%. Overall, the patients with CFR≤1.65 experienced the higher annualized rates of MACE, cardiac death, HF hospitalization, and late revascularization. Future work should be focused on investigating whether and how the quantitative measurements of CFR can direct therapy in patients with HF.

Left ventricular hypertrophy (LVH) is an independent predictor of morbidity and overall mortality in a wide range of diseases, including hypertension [39], hypertrophic cardiomyopathy, aortic stenosis, as well as in the general population [40]. The functional and structural alterations of CMC in the patients with pathological LVH were documented by PET [41, 42]. The main mechanism in the patients with hypertrophic cardiomyopathy is blunted maximal MBF and consequently impaired CFR [43, 44]. Even more important is its strong predictive power [45]. In the patients with hypertrophic cardiomyopathy, the hyperaemic flow value <1.1 ml/min g–1 measured by PET was the most powerful independent predictor of the long-term adverse outcome, and was associated with a 9.6-fold increase in the age-adjusted relative risk of death [45].

In the patients with aortic stenosis, an increase in the intramyocardial pressure caused by raised extravascular compressive forces is considered to be the main cause of CMC dysfunction [41]. Although resting MBF increases proportionally with left ventricular mass in patients with aortic stenosis, (suggesting that the demand of the hypertrophied myocardium is met by the increased baseline MBF), CFR is severely reduced and inversely correlated with the valve orifice area [46].

## The Limitation of PET-derived CFR

PET technology is complex and has not yet been completely standardized into widely available hardware, software algorithms, or protocols [13]. The availability of scanners, an increased cost, and reimbursement issues also limit its widespread clinical application.

The knowledge of the optimal cut-off values for absolute perfusion needs to be studied in large populations and for various tracers. The potential sources of errors in measurement, including the effect of high driving pressure and high resting flow rates, are still being characterized. Still unexplored is whether PET-derived CFR/MFR can differentiate the patients with epicardial stenosis from the patients with abnormalities within subendocardial microvascular perfusion only or not [4]. Another point is that the axial spatial resolution of modern PET scanners ranges from 5 to 6.3 mm full width at half maximum (FWHM), depending on the scanner configuration and a location in the field of view. This is poorer than the spatial resolution of cardiac magnetic resonance (CMR) imaging and CT, and allows the reporting of only the transmural distribution of myocardial perfusion, i.e. subendocardial versus epicardial versus mid-ventricular wall perfusion defects cannot be differentiated [5]. Also, the technical limitations of PET during physical exercise (as a means to increase cardiac workload) involve the body movements that degrade the quality of PET [9].

## An Assessment of the Coronary Microcirculatory Function by CT: the Basic Principle and Technical Aspects

Computed tomography (CT) enables a non-invasive anatomical assessment of coronary stenosis. In the last several years, however, much effort has been made to investigate the role of CT in the physiological evaluation of the coronary circulation and myocardial perfusion. This could be done by dynamic CT myocardial perfusion imaging (CTMPI), a technique providing quantitative perfusion measurements by analysing changes in contrast enhancement and contrast distribution in a tissue in time.

This technique is based on the detection of the first pass of iodine-based contrast and the estimates of the maximum slope of the time–attenuation curve in the target tissue divided by the maximum arterial input function. CT-measured attenuation is converted to the iodine concentration and the time activity curves are converted to the time-iodine concentration curves. A

two-compartment model of the vascular and extravascular spaces is used to correspond the time-attenuation curves – this approach being called the deconvolution technique [47]. CTMPI is able to differentiate cellular viability with a single acquisition [48] and with a higher diagnostic accuracy for fixed defects [49]. If a perfusion defect is fixed, it is interpreted as a scar or necrosis, whereas if it is reversible – it is interpreted as viable.

By using the sequential CT acquisitions of the myocardial tissue while applying dypiridamole intravenously over a defined period of time, CTMPI quantifies MBF expressed in mL/min/100 g. Myocardial blood flow is assessed in all of the three vascular territories by selecting a region of interest (ROI). CFR is then calculated as the $MBF_{stress}/MBF_{rest}$ ratio. According to Ho et al., baseline MBF should be corrected for the rate pressure product (RPP), an index of myocardial oxygen consumption, by using the formula: $MBF_{corr}=(MBF_{baseline}/RPP)$ and consequently, the corrected CFR is then calculated as $CFR_{corr}$=MBFdipyridamole /$MBF_{corr}$[50].

## The Clinical Application of CT-derived MPI

The CORE 320 multicenter study that was carried out at 16 hospitals in eight countries and involved 381 patients found that the accuracy of CT angiography was significantly increased by the addition of CT-derived MPI at both the patient and the vessel levels, correctly identifying the patients with flow limiting CAD defined as ≥50% stenosis by coronary angiography [51]. Many studies have shown that CT-derived MPI has a good diagnostic accuracy compared to the other techniques previously used to assess coronary flow.

Ho et al. studied the use of vasodilator-stress CTMPI in detecting myocardial flow reserve and found it to be comparable to SPECT (52). The same group showed that global hyperaemic and CFR values were significantly lower in the population with a documented CAD than in the low-risk population [50]. In another study, George et al. found the excellent diagnostic accuracy (the overall sensitivity and specificity) of CTMPI in detecting myocardial ischemia compared with the reference standard of CTA+SPECT [53].

The main advantage of this technique is its ability to simultaneously assess the coronary anatomy, myocardial flow reserve, as well as tissue viability. The examination is rather quick and has a high spatial resolution, a high diagnostic accuracy in detecting (transmural) infarcted myocardial segments, as well as a good diagnostic accuracy in detecting any other perfusion defects, compared to CMR and SPECT.

## The Limitation of CT-derived MPI

The limitations of this technique are as follows: radiation (the effective radiation dose is around 11 mSv), a requirement for the optimal timing of the contrast, a limited use in the patients with arrhythmia or a high heart rate, and a limited/contraindicated application in the patients with the impaired renal function. Motion and beam hardening artefacts are the limiting factors; however, they can be partly overcome by excluding the 1 mm subendocardial zone directly adjacent to the contrast-filled left ventricle, and the 1 mm subepicardial zone when selecting ROI. The insufficient coverage of the heart, due to the limited width of the detector, can be partly overcome by using CT scanners of a new generation [47, 50, 54, 55].

Despite being widely accepted as a measure of the CMC function, CFR has an inherent limitation reflected in its inability to make a difference between the focal stenosis of the epicardial coronary artery, diffuse epicardial atherosclerosis, and microvascular dysfunction. In real life, all these alterations frequently coexist (with mutual interactions), often with a heterogeneous spatial distribution. For example, high resting flow (global or regional) often causes a low CFR, which may be misinterpreted as a consequence of epicardial stenosis or a low CFR due to microvascular disease. Conversely, low resting flow frequently produces an adequate CFR, which might conceal the diagnosis of reduced stress flow due to microvascular disease, leading to a false negative CFR. In order to overcome these limitations, in addition to CFR, the *coronary flow capacity (CFC)* has recently been introduced [56]. CFC simultaneously integrates regional resting flow, hyperaemic flow, and CFR. CFC has been validated by invasive pressure and Doppler flow velocity measurements.

It should distinguish microvascular vs diffuse vs focal CAD by accounting for the perfusion heterogeneity that mimics these deferent pathophysiologies. Although this concept is physiologically based and a promising one, it still requires further research.

### CT-derived Fractional Flow Reserve (FFRCT)

Advances in imaging techniques, mathematics, and computer science provide us with the ability to accurately measure fractional flow reserve (FFR) from coronary computed tomography angiography datasets ($FFR_{CT}$) [57]. Generally, FFR represents the ratio of the maximal blood flow through the coronary artery distal to a stenotic lesion and the normal maximal blood flow. It is traditionally measured in the cardiac catheterization lab by using a pressure wire and allowing an intracoronary or intravenous vasodilator to produce maximal hyperaemia. For example, an FFR value of 0.70 means that the stenosis is causing a 30% drop in pressure across the lesion, which means that the maximal hyperaemic flow is equally reduced by 30%. The major clinical utility of FFR is to estimate the hemodynamic significance of (epicardial) coronary stenosis.

Based on the standard CT angiography image acquisition, a quantitative 3D anatomical model is first generated, after which a physiological model of the coronary microcirculation is derived from an individual patient's data by using the three main assumptions: that resting coronary flow is proportional to myocardial mass; that microvascular resistance is inversely proportional to the vessel size; and that the mathematical model simulates maximal hyperaemia, reducing microvascular resistance at any point in the vascular tree [9]. The application of fluid dynamics CBF is computed, and $FFR_{CT}$ can be calculated for each point in the coronary tree [57]. In one study with the patients who had low calcium scores, $FFR_{CT}$ appeared as a promising tool to assess the microvascular function in the patients with CT-angiography-defined intermediate stenosis [57]. Nevertheless, in order to become an alternative to the established non-invasive techniques for the assessment of the microvascular function, further studies need to be conducted regarding $FFR_{CT}$.

### An Assessment of the Coronary Microcirculatory Function by Applying Invasive Methods

There are a variety of methods to assess the microcirculation and myocardial perfusion in the catheterization laboratory.

The *thrombolysis in myocardial infarction (TIMI)* score grading system is a semi-quantitative subjective, categorical description of the penetration and exit of the dye in a coronary artery. The values of TIMI can be between no perfusion i.e. no flow (Grade 0) to a normal flow rate (Grade 3). Although it is the basic, robust and most widely used technique for quantifying coronary flow, it is yet limited since it predominately reflects epicardial vessel disease, thus preventing us from gaining a more profound insight into the CMC function. Nevertheless, acute microvascular obstruction (MVO) after the successful opening of the infarct-related epicardial artery by primary percutaneous intervention (pPCI) in STEMI patients is associated with angiographic TIMI flow ≤2, or TIMI=3 and myocardial blush grade=0 or 1 [58]. In general, TIMI 1 and TIMI 2 in STEMI patients following pPCI [59], as well as in those following elective PCI, are associated with worse outcomes [60]

Since post-pPCI MVO may even occur in the patients with TIMI flow 3 [61], in order to improve the stratification of these patients, the *corrected TIMI frame count (TFC)* was developed. Defined as the number of the frames required for the contrast medium to reach the standardized distal landmarks, this index correlated well with invasively assessed CFR [62].

In order to shift the assessment of reperfusion in STEMI patients from the epicardial to the myocardial level, the two angiographic methods based on the kinetics of the dye penetration within the myocardium were further proposed, namely the *myocardial blush grade (MBG),* and the *TIMI myocardial perfusion grade (TMPG)* [62, 63]. The myocardial blush grade is a densitometric method assessing the maximum intensity of the contrast medium in the microcirculation on a scale scored from 0 to 3. The TMPG assesses the microvascular clearance of the contrast medium on a scale from 0 to 3, too. Higher scores indicate

better perfusion. Both MBG and TMPG are able to stratify the patients with TIMI flow 3 at the end of pPCI according to the risk of a further adverse event.

All of the foregoing methods for the angiographic assessment of perfusion are qualitative metrics, potentially with a significant interobserver variability. Because of that, more quantitative, invasive, coronary wire-based techniques for the assessment of CMC have emerged. They include the use of intracoronary *pressure* and *Doppler flow wires* or their combination [64], *invasive CFR* and the *index of microcirculatory resistance (IMR)* being most commonly used in clinical practice.

**Invasive CFR**

One of the most reliable assessments of the CMC function is to directly measure coronary blood flow velocity by using the *intracoronary (IC) Doppler wire*. An ultrasound is emitted from the tip of the guidewire in a pulsed wave manner and coronary flow velocity or average peak velocity is measured. Developments in wire technology have significantly improved the reliability and reproducibility of this technique. The profile of blood flow velocity (i.e. the Doppler spectra) under the resting condition can be very informative. For example, a typical coronary blood flow pattern associated with post-pPCI MVO is characterized by systolic retrograde flow, diminished systolic anterograde flow, and the rapid deceleration of diastolic flow [65]. More importantly, by means of the IC Doppler wire, invasive CFR can be determined by usually using intracoronary adenosine to achieve maximal hyperaemia. In daily clinical practice, Doppler-derived cross-sectional peak flow velocity is used to compute CFR from hyperaemic and resting coronary blood flow velocity measurements. Beside the IC Doppler wire technique, invasive CFR can be determined by using the temperature and pressure sensing guidewire that incorporates the thermodilution principle [66].

Whereas FFR (FFR = the *resting distal coronary pressure to aortic pressure* ratio [Pd/Pa] during hyperaemia) estimates the haemodynamic i.e. functional severity of epicardial coronary stenosis (i.e. lesion-level ischaemia with the ischaemic threshold ≤0.80), CFR depends on the functional integrity of both the epicardial and microcirculatory compartments. Only in the absence of a flow limiting epicardial stenosis does the increment in the flow velocity induced by adenosine (i.e. CFR) predominately depend on the functional integrity of the microcirculation.

Given the fact that they give different insights into coronary physiology, CFR and FFR might be discordant. In a study van de Hoef et al. conducted among the patients with the borderline stenosis of the epicardial coronary artery, those with normal FFR, but an abnormally impaired CFR, had a worse outcome in the 10 years of follow-up, suggesting the predominant effect of microvascular dysfunction, whereas the patients with abnormal FFR and preserved CFR had the same prognosis as the individuals with the normal values for both parameters [67].

The predictive value of post-PCI CFR was evaluated for future cardiovascular events [68]. In the DEBATE study [69], after the single-vessel balloon angioplasty with a residual stenosis ≤35%, the Doppler-wire derived CFR>2.5 identified the lesions with a lower incidence of the recurrence of the symptoms during the mid-term follow-up, a lesser need for re-intervention, and a lower restenosis rate. Furthermore, Doppler-wire derived CFR predicted long-term cardiac mortality after pPCI done for STEMI. In another study carried out by van de Hoef et al. [70], CFR was assessed in both the infarct-related and the reference coronary arteries immediately after pPCI. The CFR<2.1 in the reference vessel predicted a fourfold increased risk of long-term (the median 11 years) cardiac mortality, whereas the infarct-related artery CFR<1.5 was associated with an increase in a short-, but not in a long-term risk of cardiac mortality. These data point to the fact that the rather general functional status of the microvasculature, not only the changes induced by the acute effects of ischemia and reperfusion, is more important for a long-term outcome in pPCI-treated STEMI patients.

The prognostic relevance of the CMC function as assessed by invasive CFR was also demonstrated among the patients with INOCA (ischemia with non-obstructive coronary artery disease). In the WISE study, 81% of the nearly 200 women with suspected ischemia and risk factors for coronary

artery disease referred for coronary angiography had either normal findings at angiography or epicardial coronary stenosis <50% [71]. The CFR<2.32 was the best predictor of major adverse outcomes (death, nonfatal myocardial infarction, nonfatal stroke, and heart failure requiring hospitalization), with a sensitivity of 62% and a specificity of 65%, during the follow-up of more than 5 years. This association between the impaired CFR and the major adverse outcomes remained after the adjustment for obstructive CAD and multiple risk factors. Furthermore, by using the same methodology, the same authors tested the benefit of the therapy with ACE inhibitors in the women with microvascular dysfunction in a randomized trial [72]. They revealed a reduction in angina and the improvement of CFR under the ACE-I treatment, however with a beneficial response of the coronary microvasculature to this therapy only in the women with a low baseline CFR.

However, as noted before, CFR is not microvascular-specific and is significantly affected by resting hemodynamics.

## The Index of Microvascular Resistance (IMR)

The **index of microvascular resistance (IMR)** is calculated as the product of distal pressure and the mean transit time of a saline bolus during maximum hyperaemia by using a dual temperature and pressure wire [73]. This technique is based upon thermodilution. The mean transit time (Tmn) of a bolus of saline at room temperature is inversely correlated with invasively measured flow velocities. Maximal hyperaemia is usually induced by using either a single bolus of 10 to 15 g of intracoronary papaverine or (more frequently) 140 g/kg/min of intravenous adenosine via a central venous catheter. IMR is a more specific metric for the microcirculation than CFR and is less dependent on hemodynamic parameters. Unlike CFR, IMR is not affected by the epicardial arteries, but reflects the minimal resistance during hyperaemic flow independently of the variations in the resting vascular tone or heart rate [74].

In the case of the present epicardial stenosis, a correction for coronary wedge pressure (Pw) is proposed to offset the hemodynamic effect of the stenosis. Therefore, the basic formula used to calculate IMR in the absence of epicardial stenosis IMR=Pd Tmn (where Pd is distal coronary pressure) is corrected for IMR=Pd Tmn[(Pd–Pw)/(Pa–Pw)]), where Pa is the aortic pressure measured by the guiding catheter [75]. It seems that several factors might influence Pw predominately including collateral flow, but also the other factors related to the intramural compressive forces that might be especially important in the patients with left ventricular hypertrophy. Which equation best describes microvascular resistance is still a topic under debate. It is also important to notice that IMR is a relative index and that its validity is limited to the same patient in the same myocardial territory.

IMR has been introduced as a method for evaluating the coronary microvascular circulation at the time of the primary percutaneous intervention (pPCI) [76]. Generally, an IMR<25 is accepted as a cut-off for the normal microvascular function [77]. However, in STEMI, a post-stenting IMR>40 reflects severe microvascular impairment and is associated with poorer left ventricular functional recovery, a higher incidence of death, a myocardial infarction and readmission for heart failure [78, 79]. Despite the fact that IMR has been validated against CMR, not all studies have shown a perfect concordance between the increased post-procedural thermodilution-derived IMR and MVO detected by CMR [80, 81]. However, in the patients with MVO and higher IMR, a larger IS was observed than in those in whom MVO was associated with IMR≤40. Those with MVO but IMR<40 experienced the significant regressions of IS after 6 months, whereas no significant change in IS was observed in the patients with MVO and higher IMR [81].

In the patients with stable angina, the pre-PCI measured IMR was predictive of a periprocedural myocardial infarction, suggesting that the baseline impairment of the CMC function was relevant for peri-PCI outcomes [82, 83]. Furthermore, Luo et al. demonstrated that IMR was higher in the selected patients with the cardiac syndrome X [84].

The development of the dual-sensor catheters that simultaneously measure intracoronary pressure and flow velocity by the Doppler technique enables the introduction of a novel parameter: **hyperaemic microvascular resistance (HMR)**. This index

is calculated according to the following formula: HMR= Pd/pAPV, where Pd is the pressure downstream of the stenosis and pAPV is the average hyperaemic peak flow velocity expressed in cm/s [85]. It has recently been compared with conventional thermodilution-derived IMR. The correlation was only modest. However, in the STEMI population, hMR had a clinically superior sensitivity over IMR in predicting the MVD determined by CMR, but it was not statistically significant [86]. Hyperaemic microvascular resistance significantly correlated with the degree of the anatomical alterations in the endomyocardial sampling in the cardiac allografts, albeit with a strong contribution of capillary density.

The other invasively determined parameters of the CMC function were investigated, including the **instantaneous hyperaemic diastolic velocity–pressure slope** (calculated from the acquired electrocardiogram, aortic pressure, and the peak flow velocity signals of the same beat, and plotted as a pressure flow–velocity loop). Representing the slope of the linear portion of the loop during the diastolic interval, this index turns to be the physiological index that best correlated with the structural changes in the microcirculation evaluated in the endomyocardial sampling from the cardiac allografts [87].

## Conclusion

The assessment of the CMC function and the understatement of its role in different disease states in humans still remain a challenge. Although modern technologies continuously increase the number of clinical studies, experts opine that no profound breakthrough in the field will be achieved without the substantial improvements of experimental (animal) pathophysiological studies [88]. Only the gathering and translation of this knowledge will enable us to better understand the old and define new nosological entities, the stratification of affected patients, and the development of the effective therapeutic strategies that have the coronary microcirculation in focus.

## Conflict of interest

The authors confirm that there are no conflicts of interest

## References


1. Ziadi MC. Myocardial flow reserve (MFR) with positron emission tomography (PET)/computed tomography (CT): clinical impact in diagnosis and prognosis. Cardiovasc Diagn Ther. 2017;7(2):206–218. doi: 10.21037/cdt.2017.04.10.
2. Javadi MS, Lautamäki R, Merrill J, Voicu C, Epley W, McBride G, Bengel FM. Definition of vascular territories on myocardial perfusion images by integration with true coronary anatomy: a hybrid PET/CT analysis. J Nucl Med. 2010;51(2):198–203. doi: 10.2967/jnumed.109.067488.
3. Gaemperli O, Saraste A, Knuuti J. Cardiac hybrid imaging. Eur Heart J Cardiovasc Imaging 2012;13:51–60. doi:10.1093/ehjci/jer240.
4. Nakazato R, Heo R, Leipsic J, Min JK. CFR and FFR assessment with PET and CTA: strengths and limitations. Curr Cardiol Rep. 2014;16(5):484. doi: 10.1007/s11886-014-0484-5.
5. Di Carli MF, Murthy VL. Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. Radiographics. 2011;31(5):1239–54. doi: 10.1148/rg.315115056.
6. Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol. 2006;48(5):1029–39. doi: 10.1016/j.jacc.2006.06.025.
7. Lertsburapa K, Ahlberg AW, Bateman TM, Katten D, Volker L, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. J Nucl Cardiol. 2008;15(6):745–53. doi: 10.1007/bf03007355.
8. Dorbala S, Hachamovitch R, Curillova Z, Thomas D, Vangala D, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging. 2009;2(7):846–54. doi: 10.1016/j.jcmg.2009.04.009.
9. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. Nat Rev Cardiol. 2015;12(1):48–62. doi: 10.1038/nrcardio.2014.160.
10. El Fakhri G, Sitek A, Guérin B, Kijewski MF, Di Carli MF, Moore SC. Quantitative dynamic cardiac 82Rb PET using generalized factor and compartment analyses. J Nucl Med. 2005;46(8):1264–71.

11. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA. Quantification of myocardial blood flow with 82Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging. 2007;34(11):1765–74. doi: 10.1007/s00259-007-0478-2.
12. Efseaff M, Klein R, Ziadi MC, Beanlands RS, deKemp RA. Short-term repeatability of resting myocardial blood flow measurements using rubidium-82 PET imaging. J Nucl Cardiol. 2012;19(5):997–1006. doi: 10.1007/s12350-012-9600-3.
13. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013;62(18):1639–1653. doi: 10.1016/j.jacc.2013.07.076.
14. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. J Nucl Med. 2011;52(9):1369 77. doi: 10.2967/jnumed.110.082883.
15. Prior JO, Quiñones MJ, Hernandez-Pampaloni M, Facta AD, Schindler TH, et al. Coronary circulatory dysfunction in insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus. Circulation. 2005;111(18):2291–8. doi: 10.1161/01.cir.0000164232.62768.51.
16. Neglia D, Fommei E, Varela-Carver A, Mancini M, Ghione S, et al. Perindopril and indapamide reverse coronary microvascular remodelling and improve flow in arterial hypertension. J Hypertens. 2011;29(2):364–72. doi: 10.1097/hjh.0b013e328340a08e.
17. Iozzo P, Chareonthaitawee P, Rimoldi O, Betteridge DJ, Camici PG, Ferrannini E. Mismatch between insulin-mediated glucose uptake and blood flow in the heart of patients with Type II diabetes. Diabetologia. 2002;45(10):1404–9. doi: 10.1007/s00125-002-0917-3.
18. Momose M, Abletshauser C, Neverve J, Nekolla SG, Schnell O, et al. Dysregulation of coronary microvascular reactivity in asymptomaticpatients with type 2 diabetes mellitus. Eur J Nucl Med Mol Imaging 2002;29, 1675–1679. doi: 10.1007/s00259-002-0977-0.
19. Yokoyama I, Yonekura K, Ohtake T, Yang W, Shin WS, et al. Coronary microangiopathy in type 2 diabetic patients: relation to glycemic control, sex, and microvascular angina rather than to coronary artery disease. J Nucl Med. 2000;41(6):978–85.
20. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation. 2012;126(15):1858–68. doi: 10.1161/circulationaha.112.120402.
21. Lautamäki R, Airaksinen KE, Seppänen M, Toikka J, Härkönen R, et al. Insulin improves myocardial blood flow in patients with type 2 diabetes and coronary artery disease. Diabetes. 2006;55(2):511–6. doi: 10.2337/diabetes.55.02.06.db05-1023.
22. Schindler TH, Facta AD, Prior JO, Cadenas J, Hsuehet WA et al. Improvement in coronary vascular dysfunction produced with euglycaemic control in patients with type 2 diabetes. Heart. 2006;93(3):345–9. doi: 10.1136/hrt.2006.094128.
23. Quiñones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenez X, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med. 2004;140(9):700–8. doi: 10.7326/0003-4819-140-9-200405040-00009.
24. Yokoyama, I. Ohtake T, Momomura S, Nishikawa J, Sasaki Y, Omata M. Reduced coronary flow reserve in hypercholesterolemic patients without overt coronary stenosis. Circulation. 1996;94:3232–3238. doi: 10.1161/01.cir.94.12.3232.
25. Kaufmann PA, Gnecchi-Ruscone T, Schäfers KP, Lüscher TF, Camici PG. Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. J Am Coll Cardiol. 2000;36(1):103–9. doi: 10.1016/s0735-1097(00)00697-5.
26. Naoumova RP, Kindler H, Leccisotti L, Mongillo M, Khan MT, et al. Pioglitazone improves myocardial blood flow and glucose utilization in nondiabetic patients with combined hyperlipidemia: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 2007;50, 2051–2058. doi: 10.1016/j.jacc.2007.07.070.
27. Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. JACC Cardiovasc Imaging. 2011;4(9):990–8. doi: 10.1016/j.jcmg.2011.06.015.
28. Peelukhana SV, Kerr H, Kolli KK, Fernandez-Ulloa M, Gerson M, et al. Benefit of cardiac N-13 PET CFR for combined anatomical and functional diagnosis of ischemic coronary artery disease: a pilot study. Ann Nucl Med. 2014;28(8):746–60. doi: 10.1007/s12149-014-0869-y.
29. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect

 

of early revascularization. Circulation. 2015;131(1):19–27. doi: 10.1161/circulationaha.114.011939.

30. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol. 2009;54(2):150–6. doi: 10.1016/j.jacc.2009.02.069.
31. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011;124(20):2215–24. doi: 10.1161/ circulationaha.111.050427.
32. Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. J Nucl Med. 2011;52(5):726–32. doi: 10.2967/jnumed.110.081828.
33. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol. 2011;58(7):740–8. doi: 10.1016/j.jacc.2011.01.065.
34. Neglia D, Michelassi C, Trivieri MG, Sambuceti G, Giorgetti A, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation. 2002;105:186–93.2. doi: 10.1161/hc0202.102119.
35. Rigo F, Gherardi S, Galderisi M, Pratali L, Cortigiani L, et al. The prognostic impact of coronary flow-reserve assessed by Doppler echocardiography in nonischaemic dilated cardiomyopathy. Eur Heart J. 2006;27:1319–23.3. doi: 10.1093/eurheartj/ehi795.
36. Rigo F, Gherardi S, Galderisi M, Sicari R, Picano E. The independent prognostic value of contractile and coronary flow reserve determined by dipyridamole stressechocardiography in patients with idiopathic dilated cardiomyopathy. Am J Cardiol. 2007;99:1154–8. doi: 10.1016/j.amjcard.2006.11.049.
37. Rigo F, Ciampi Q, Ossena G, Grolla E, Picano E, Sicari R. Prognostic value of left and right coronary flow reserve assessment in nonischemic dilated cardiomyopathy by transthoracic Doppler echocardiography. J Card Fail. 2011;17:39–46. doi: 10.1016/j.cardfail.2010.08.003.
38. Majmudar MD, Murthy VL, Shah RV, Kolli S, Mousavi N, et al. Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. Eur Heart J Cardiovasc Imaging. 2015;16(8):900–9. doi: 10.1093/ehjci/jev012.
39. Schillaci G, Verdecchia P, Porcellati G, Cuccurullo O, Cosco C, Perticone F. Continuous relation between left ventricular mass and cardiovascularrisk in essential hypertension. Hypertension. 2000;35:580–586. doi: 10.1161/01.hyp.35.2.580.
40. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. Stroke. 2003;34(10):2380–4. doi: 10.1161/01.str.0000089680.77236.60.
41. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. Circulation. 2002;105(4):470–6. doi: 10.1161/hc0402.102931.
42. Akinboboye OO, Idris O, Goldsmith R, Berekashvili K, Chou RL, Bergman SR. Positron emission tomography, echo-doppler, and exercise studies of functional capacity in hypertensive heart disease. Am J Hypertens. 2002;15:907–910. doi: 10.1016/s0895-7061(02)02985-0.
43. Choudhury L, Elliott P, Rimoldi O, Ryan M, Lammertsma AA, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. Basic Res Cardiol. 1999;94(1):49–59. doi: 10.1007/s003950050126.
44. Knaapen P, Germans T, Camici PG, Rimoldi OE, ten Cate FJ, et al. Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy. Am J Physiol Heart Circ Physiol. 2008;294(2):H986–93. doi: 10.1152/ajpheart.00233.2007.
45. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003;349(11):1027–35. doi: 10.1056/nejmoa025050.
46. Garcia D, Camici PG, Durand LG, Rajappan K, Gaillard E, et al. Impairment of coronary flow reserve in aortic stenosis. J Appl Physiol (1985). 2009;106(1):113–21. doi: 10.1152/japplphysiol.00049.2008.
47. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. Nat Rev Cardiol. 2015;12(1):48–62. doi: 10.1038/nrcardio.2014.160.
48. Bamberg F, Klotz E, Flohr T, Becker A, Becker CR, et al. Dynamic myocardial stress perfusion imaging using

fast dual-source CT with alternating table positions: initial experience. Eur Radiol. 2010;20(5):1168–73. doi: 10.1007/s00330-010-1715-9.

49. Bamberg F, Marcus RP, Becker A, Hildebrandt K, Bauner K, et al. Dynamic myocardial CT perfusion imaging for evaluation of myocardial ischemia as determined by MR imaging. JACC Cardiovasc Imaging. 2014;7(3):267–77. doi: 10.1016/j.jcmg.2013.06.008.
50. Ho KT, Ong HY, Tan G, Yong QW. Dynamic CT myocardial perfusion measurements of resting and hyperaemic blood flow in low-risk subjects with 128-slice dual-source CT. Eur Heart J Cardiovasc Imaging. 2015;16(3):300–6. doi: 10.1093/ehjci/jeu200.
51. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. Eur Heart J. 2014;35(17):1120–30. doi: 10.1093/eurheartj/eht488.
52. Ho KT, Chua KC, Klotz E, Panknin C. Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT. JACC Cardiovasc Imaging. 2010;3(8):811–20. doi: 10.1016/j.jcmg.2010.05.009.
53. George RT, Arbab-Zadeh A, Miller JM, Vavere AL, Bengel FM, et al. Computed tomography myocardial perfusion imaging with 320-row detector computed tomography accurately detects myocardial ischemia in patients with obstructive coronary artery disease. Circ Cardiovasc Imaging. 2012;5(3):333–40. doi: 10.1161/circimaging.111.969303.
54. Blankstein R, Shturman LD, Rogers IS, Rocha-Filho JA, Okada DR, et al. Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. J Am Coll Cardiol. 2009;54(12):1072–84. doi: 10.1016/j.jacc.2009.06.014.
55. Waller AH, Blankstein R, Kwong RY, Di Carli MF. Myocardial blood flow quantification for evaluation of coronary artery disease by positron emission tomography, cardiac magnetic resonance imaging, and computed tomography. Curr Cardiol Rep. 2014;16(5):483. doi: 10.1007/s11886-014-0483-6.
56. Gould KL, Johnson NP. Coronary Physiology Beyond Coronary Flow Reserve in Microvascular Angina. J Am Coll Cardiol. 2018;72:2642–62. doi: 10.1016/j.jacc.2018.07.106.
57. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, et al; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145–1155. doi: 10.1016/j.jacc.2013.11.043.
58. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119–77. doi: 10.1093/eurheartj/ehx393.
59. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol. 2009;54:281–92. doi: 10.1016/j.jacc.2009.03.054.
60. Montalescot G, Ongen Z, Guindy R, Sousa A, Lu SZ, et al; RIVIERA Investigators. Predictors of outcome in patients undergoing PCI. Results of the RIVIERA study. Int J Cardiol. 2008;129(3):379–87. doi: 10.1016/j.ijcard.2007.07.127.
61. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. Eur Heart J. 2016;37(13):1024–33. doi: 10.1093/*eurheartj*/ehv484.
62. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002;105:1909–13. doi: 10.1161/01.cir.0000014683.52177.b5.
63. Van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation. 1998;97:2302–06. doi: 10.1161/01.cir.0000065221.06430.ed.
64. Niccoli G, Cosentino N, Spaziani C, Fracassi F, Tarantini G, Crea F. No-reflow: incidence and detection in the cath-lab. Curr Pharm Des. 2013;19:4564–75. doi: 10.2174/1381612811319250005.
65. De Waha S, Patel MR, Granger CB, Ohman ME, Maehara A, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment

 

elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J. 2017;38:3502–10. doi: 10.1093/eurheartj/ehx414.

66. Layland J, Nerlekar N, Palmer S, Berry C, Oldroyd K. Invasive assessment of the coronary microcirculation in the catheter laboratory. Int J Cardiol. 2015;199:141–9. doi: 10.1016/j.ijcard.2015.05.190.
67. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. Circ Cardiovasc Interv. 2014;7(3):301–11. doi: 10.1161/circinterventions.113.001049.
68. Yamamuro A, Akasaka T, Tamita K, Yamabe K, Katayama M, et al. Coronary flow velocity pattern immediately after percutaneous coronary intervention as a predictor of complications and in-hospital survival after acute myocardial infarction. Circulation. 2002;106:3051–56. doi: 10.1161/01.cir.0000043022.44032.77
69. Serruys PW, di Mario C, Piek J, Schroeder E, Vrints C, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). Circulation. 1997;96(10):3369-77. doi: 10.1161/01.cir.96.10.3369.
70. van de Hoef TP, Bax M, Meuwissen M, Damman P, Delewi R, et al. Impact of coronary microvascular function on long-term cardiac mortality in patients with acute ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv. 2013;6(3):207–15. doi: 10.1161/circinterventions.112.000168.
71. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55(25):2825–32. doi: 10.1016/j.jacc.2010.01.054.
72. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: A double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2011;162(4):678–84. doi: 10.1016/j.ahj.2011.07.011.
73. Pijls NH, De Bruyne B, Smith L, Aarnoudse W, Barbato E, et al. Coronary thermodilution to assess flow reserve: validation in humans. Circulation. 2002;105(21):2482–6. doi: 10.1161/01.cir.0000099521.31396.9d.
74. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. Circulation. 2006;113(17):2054–61. doi: 10.1161/circulationaha.105.603522.
75. Aarnoudse W, Fearon WF, Manoharan G, Geven M, van de Vosse F, et al. Epicardial stenosis severity does not affect minimal microcirculatory resistance. Circulation. 2004;110(15):2137–42. doi: 10.1161/01.cir.0000143893.18451.0e.
76. Bulluck H, Foin N, Cabrera-Fuentes HA, Yeo KK, Wong AS, et al. Index of microvascular resistance and microvascular obstruction in patients with acute myocardial infarction. JACC Cardiovasc Interv. 2016;9(20):2172–74. doi: 10.1016/j.jcin.2016.08.018.
77. Bajrangee A, Collison D, Oldroyd KG. Resistance to flow in the coronary microcirculation: we can measure it but what does it mean? EuroIntervention. 2017;13:901–3. doi: 10.4244/eijv13i8a133.
78. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, et al. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2008;51:560–565. doi: 10.1016/j.jacc.2007.08.062.
79. Carrick D, Haig C, Ahmed N, Carberry J, Yue May VT, et al. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. Circulation. 2016;134(23):1833–1847. doi: 10.1161/circulationaha.116.022603
80. Payne AR, Berry C, Doolin O, McEntegart M, Petrie MC, et al. Microvascular resistance predicts myocardial salvage and infarct characteristics in ST-elevation myocardial infarction. J Am Heart Assoc 2012;1:e002246. doi: 10.1161/jaha.112.002246
81. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, et al. Index of microcirculatory resistance as a tool to characterize microvascular obstruction and to predict infarct size regression in patients with STEMI undergoing primary PCI. JACC Cardiovasc Imaging. 2018 pii: S1936-878X(18)30217-1. doi: 10.1016/j.jcmg.2018.02.018.

82. Ng MK, Yong AS, Ho M, Shah MG, Chawantanpipat C, et al. The index of microcirculatory resistance predicts myocardial infarction related to percutaneous coronary intervention. Circ Cardiovasc Interv. 2012;5(4):515–22. doi: 10.116/circintervention.112.969048.
83. Layland JJ, Whitbourn RJ, Burns AT, Somaratne J, Leitl G, et al. The index of microvascular resistance identifies patients with periprocedural myocardial infarction in elective percutaneous coronary intervention. Heart. 2012;98(20):1492–7. doi: 10.1136/heartjnl-2012-302252.
84. Luo C, Long M, Hu X, Huang Z, Hu C, et al. Thermodilution-derived coronary microvascular resistance and flow reserve in patients with cardiac syndrome X. Circ Cardiovasc Interv. 2014;7(1):43–8. doi: 10.1161/circinterventions.113.000953.
85. Meuwissen M, Siebes M, Chamuleau SA, van Eck-Smit BL, Koch KT,et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. Circulation. 2002;106(4):441–6. doi: 10.1161/01.cir.0000023041.26199.29.
86. Williams RP, de Waard GA, De Silva K, Lumley M, Asrress K, et al. Doppler versus thermodilution-derived coronary microvascular resistance to predict coronary microvascular dysfunction in patients with acute myocardial infarction or stable angina pectoris. Am J Cardiol. 2018;121(1):1–8. doi: 10.1016/j.amjcard.2017.09.012.
87. Escaned J, Flores A, García-Pavía P, Segovia J, Jimenez J, et al. Assessment of microcirculatory remodeling with intracoronary flow velocity and pressure measurements: validation with endomyocardial sampling in cardiac allografts. Circulation. 2009;120(16):1561–8. doi: 10.1161/circulationaha.108.834739.
88. Pries AR, Reglin B. Coronary microcirculatory pathophysiology: can we afford it to remain a black box? Eur Heart J. 2017;38(7):478–88. doi: 10.1093/eurheartj/ehv760.