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Coronary microcirculation – from basic research to cardiac magnetic resonance (CMR), imaging – part I

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Abstract

Coronary microcirculation (CMC) is the key regulator of coronary blood flow distribution in the heart. Its role is to match local blood supply to myocardial metabolic demands. This is fulfilled by continuous adaptation of coronary vessel diameter via regulation of smooth muscle tone. Both anatomical and functional integrity are necessary for normal coronary microcirculatory function.

Abnormal coronary microvascular function, i.e. coronary microvascular dysfunction is linked with several risk factors for atherosclerosis comprised cardiometabolic disorders. It is also recognized as a crucial player in the pathophysiology of the several entities with significant morbidity and mortality, including: microvascular angina pectoris and myocardial ischemia with non-obstructive coronary artery disease (INOCA), myocardial infarction with non-obstructed coronary arteries (MINOCA) and heart failure with preserved ejection fraction (HFpEF).

The mechanisms underlying coronary microvascular dysfunction in different pathological conditions are complex and still not fully elucidated. The coronary microcirculatory function can be assessed in humans by several non-invasive and invasive techniques. This review summarizes essential knowledge of physiological anatomy of CMC, key mechanisms of coronary microcirculatory dysfunction and finally focus on non-invasive methods of assessment of coronary microcirculatory function in clinical practice.

Keywords: coronary microcirculation, coronary microvascular function, diagnosis

Introduction

In the last decades, dysfunction of the coronary microcirculation (CMC) emerged as an important contributing (or in some instances crucial) mechanism of myocardial ischemia and myocardial dysfunction [1, 2]. Relevant pathological conditions where coronary microcirculatory dysfunction (CMD) has a role include microvascular angina pectoris and myocardial ischemia with non-obstructive coronary artery disease (INOCA) [3, 4], myocardial infarction with non-obstructed coronary arteries (MINOCA) [5] and heart failure with preserved ejection fraction (HFpEF) [6]. In all these

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entities coronary microcirculatory dysfunction has relevant impact on adverse cardiovascular events including cardiac death.

Although coronary microcirculation comprises of the vessels <300 μm in diameter that cannot be directly imaged in vivo, many of invasive and noninvasive techniques can be applied in different clinical scenarios to assess parameters influenced directly by coronary microvascular function.

Basic physiological anatomy of coronary microcirculation

The coronary arterial system is composed of three main compartments: large conductive vessels, (larger than 500 μm in diameter), prearterioles (diameters between 100 and 500 μm) and arterioles (less than 100 μm in diameter). Prearterioles and arterioles make up the coronary microcirculation (CMC) [1, 7].

Coronary blood flow is driven by the pressure difference between the aorta and the capillary bed. All compartments of coronary three have different regulatory mechanism to control their vascular tone, with cardiac metabolism as the final determining factor.

Epicardial arteries and proximal prearterioles contribute little to a total resistance of the coronary vasculature (approximately 10%) and their prime role is to provide adequate transport of the blood. The main mechanism of their vasomotion is **flow-dependent dilatation**, that is endothelium dependent.

Next compartments, *distal prearterioles and arterioles* (comprising CMC) are the main contributors and controllers of total resting vascular resistance. *Distal prearterioles* are most responsive to changes in intravascular pressure and are mainly in charge for so called *autoregulation* of coronary blood flow **(myogenic mechanism of control)**. They react predominantly to intraluminal pressure changes sensed by stretch receptors located in vascular smooth muscle cells, i.e. they constrict when the intraluminal pressure increases and, conversely, dilate when the pressure decreases.

Arterioles are more responsive to changes in the intramyocardial concentration of metabolites and are mainly responsible for the metabolic regulation of coronary blood flow. As such, increased metabolic activity leads to vasodilatation of the smaller arterioles, which leads to pressure reduction in the distal prearterioles causing myogenic dilation, which, in turn, increases flow upstream resulting in endothelium-dependent vasodilation.

In the most distal part of coronary circulation are *capillaries* and venules that are responsible for only 10% of CBF resistance and mainly function as capacitance vessels, holding 90% of the total myocardial blood volume. However, this is an area of intensive exchange between myocardial tissue and blood within capillaries, marked as the "business end" of the circulation, providing oxygen and nutrients to the tissue and eliminating waste products.

Abnormalities in both the function and structure of the coronary microcirculation can interfere with the control of myocardial blood flow, and contribute to the pathogenesis of myocardial ischemia.

Principles of testing coronary microcirculatory function

Currently, no technique allows direct visualization of the coronary microcirculation in vivo in humans. However, several invasive and noninvasive techniques enable the measurement of parameters that, are strongly dependent on the anatomical and functional integrity of the CMC.

Structural abnormalities of each of above-mentioned compartments of the coronary three can be estimated by specific metrics. *Fractional flow reserve* (FFR) is used to assess flow adequacy through epicardial coronary arteries and predominately tests hemodynamic significance of focal epicardial stenosis [8]. *Index of microvascular resistance* (IMR) is used to measure resistance of the small arteries and arterioles [9]. *Coronary flow reserve* (CFR) integrates flow assessment through both the large epicardial arteries and CMC, testing in that way functional integrity of all three compartments [10].

Apart from evaluating structure, another approach is to test *endothelium dependent vasomotion capacity* of coronary circulation by intracoronary

administration of acetyl choline [11]. Using specific regiments, endothelial dependent vasodilatation can be assessed separately for macro- and microvascular compartments of coronary network.

The third approach of testing CMC is visual assessment of myocardial perfusion by intravascular contrast. This principle is used for contrast echocardiography and cardiac magnetic resonance (CMR) and can be done in rest or with stressor. It should be emphasized that the final result, i.e. the speed and intensity of contrast appearance within the myocardium, depends not only on functional integrity of CMC, but also on patency of the epicardial arteries. In the presence of patent epicardial artery myocardial perfusion techniques predominately test the CMC.

When testing coronary microcirculatory function attention should be always paid to physiological variables such as heart rate, blood pressure and left ventricular inotropism, because of functional responsiveness of CMC to these parameters. For example, in cases of increased heart rate, reduced diastolic time and decreased driving blood pressure, CMF can be impaired reflecting primary at that moment contemporary hemodynamic condition.

Coronary microvascular dysfunction: basic mechanisms

Both anatomical and functional integrity are necessary for normal coronary microcirculation. Therefore, coronary microvascular dysfunction can occur due to structural and/or functional abnormalities. Methodologically they can be evaluated separately, but in vivo they are closely linked. Both are equally important, can vary across clinical settings and both can coexist in one condition.

Anatomic abnormalities of CMC

Structural changes of CMC are present in cases of external vascular compression and abnormal vascular remodeling with increased microvascular constriction. These pathoanatomical changes are documented in entities related to left ventricular hypertrophy, like in hypertensive patients, patients with DM, primary hypertrophic cardiomyopathy, aortic stenosis. [12]

In patients with hypertrophic cardiomyopathy and those with arterial hypertension, intramural arterioles undergo significant remodelling. The profound structural changes comprise medial wall thickening, predominately due to smooth muscle hypertrophy and increased collagen deposition, with variable degrees of intimal thickening. Structural remodeling is always coupled with functional impairment and makes the basis for the blunted CFR documented in these conditions. [13, 14]

Functional alteration of CMC

Generally, functional abnormality of coronary microcirculation, can be a consequence either of impaired dilatation and/or increased constriction. Abnormal vasodilatation can be consequence of abnormalities in the *endothelium-dependent* mechanisms and *endothelium independent* mechanisms. The first one occurs when endothelium is injured, mainly due to oxidative stress, such as in DM, hyperlipidemia, obesity, smoking, and other classical cardiovascular risk factors. [15] Impairment of endothelium-independent mechanisms, can be appreciated for example in case of nitrate resistance owing to reduced production of cyclic GMP. Increased vasoconstriction as a cause of coronary microvascular dysfunction can be caused by various stimuli (endothelin-1, catecholamines, etc) that are excessively produced in some pathological conditions.

There are several old as well as new clinical entities where CMD is considered as a key pathophysiological mechanism. *Microvascular angina*, i.e. angina without obstructive coronary artery disease is present in 10–30% of patients undergoing angiography, has substantial morbidity, and coronary microvascular dysfunction is documented in 50–65% of these patients [16]. Similar, if not the same is the *syndrome of myocardial ischemia with no obstructive coronary arteries – INOCA*. These patients present with the symptoms and signs suggesting ischemic heart disease, but found to have no obstructed

coronary arteries [11]. *Myocardial infarction with no obstructive coronary arteries (MINOCA)* is another recently established entity [12]. This syndrome is characterised by clinical evidence of myocardial infarction with normal or near-normal coronary arteries on angiography. Its prevalence ranges between 5% and 25% of all myocardial infarction and the prognosis is extremely variable, depending on the cause. According to recent reviews coronary microcirculatory dysfunction can be the main or significantly contributing cause of MINOCA in several clinical scenarios [5]. Furthermore, coronary microcirculatory dysfunction was recently recognized as a relevant factor in the development of heart failure with preserved ejection fraction (HFpEF) [6]. Although detailed pathophysiological mechanisms involving coronary microcirculation in all these entities is not always fully elucidated, assessment of CMC in patients having these syndrome is impinged and several non-invasive and invasive techniques are available. Each of them have advantages and limitations.

Coronary flow reserve

Coronary flow reserve (CFR) is defined as the ratio of maximal (i.e. hyperemic) to baseline coronary blood flow or ratio of maximal to baseline coronary blood flow velocities [1, 10]. It can be measured noninvasively by ultrasound transthoracic Doppler (TTD), CT and positron emission tomography (PET) and invasively using intra-coronary Doppler flow wire. TTD, CT and intra-coronary Doppler flow wire measure blood flow velocity (cm/sec) and estimate CFR of a distinctive coronary artery, whereas PET scan estimates volumetric myocardial blood flow in absolute terms, that is in ml per minute per gram of tissue [18]. Normal values for CFR are ≥ 2.0, or by some authors ≥2,5.

Basic principle and technical aspects

CFR offers two important pieces of information: information about patency and flow through the epicardial coronary artery (proximal to the site of CFR assessment when it is assessed by TTD, CT or invasively) and information about the functional integrity of coronary microcirculation (i.e. distal to the site of CFR assessment) [19].

TTD provides reliable measurements of CFR in the distal or middle LAD using pulsed wave Doppler under the guidance of color Doppler flow mapping, usually obtained by a modified apical approach [20]. Coronary flow is biphasic (systolic and diastolic), with a predominant diastolic component. The systolic and diastolic coronary flow velocity spectrum is obtained at baseline and during the peak of hyperemia. CFR is the ratio of hyperemic to basal peak diastolic flow velocities.

The feasibility of TTD CFR is improved by contrast enhancement combined with second-harmonic imaging technique, and reach 100% for LAD and 65%-80% for RCA/PD. The measurement of CFR assumes that maximal vasodilatation is achieved, usually by the endothelium-independent intravenously applied vasodilators adenosine and dipyridamole. Both of these stressors are better than exercise and dobutamine, because the latter two are submaximal to recruit CFR and more technically demanding.

Clinical application of CFR by TTD to assess CMC

In daily clinical routine, CFR by TTD is an important clinical decision-making instrument, enabling functional assessment of epicardial coronary stenosis, particularly in cases of anatomically borderline stenosis, i.e., 50%-70% [21]. Microvascular dysfunction may be announced when CFR is reduced in the absence of significant epicardial obstructive coronary artery disease, as documented by normal or near-normal coronary angiography or normal intravascular ultrasound signals [21, 22]. It should be noted that obstructive epicardial disease even with hemodynamically significant stenosis and CMD often coexist. CFR varies by age, sex and cardiac work (therefore HR and systolic blood pressure should be always reported).

Non-invasive CFR by TTD was used to estimate coronary microcirculation of the infarct related artery after primary percutaneous coronary

intervention in STEMI patients in several studies. It was proved as clinically useful to detect no-reflow Phenomenon [23] to assess microvascular integrity and myocardial viability of the infarct region [24], to predict functional recovery of the infarct area [25] and final infarct size [26], to predict left ventricular remodeling [27, 28]. Interestingly, CFR of the non IRA artery stratifies prognosis in acute coronary syndrome. These data support the concept that impaired CFR by TTE reflects CMD that is diffuse process, not limited exclusively to infarct region, reflecting global atherosclerotic burden more than just mirroring focal epicardial disease [29]. These data were also confirmed by similar invasive study [30].

CFR with different stressor agents was also used for diagnostic or prognostic purposes regarding coronary microcirculation in a plethora of conditions, including severe psoriasis, systemic hypertension, left bundle branch block, Tako-Tsubo cardiomyopathy, Chagas disease, hypertrophic cardiomyopathy, type 2 diabetes, and in patients submitted to intra-aortic counter pulsation [31-37], CFR was also tested as an additive predictor to traditional scores in septic shock or prognostic factor of long-term cardiovascular outcome in patients with chronic kidney disease [38, 39]. Finally, CFR was used to investigate the effects of the anti-ischemic agent ranolazine in patients with myocardial ischemia but without obstructive coronary artery disease and of the anti-cholesterol agent rosuvastatin in patients with severe hypertension [40]

Advantages of TTD CFR assessment are low cost and high feasibility and limitations are considerable intraobserver and interobserver variability (~10%).

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) is a non-invasive imaging technique that uses intravenous contrast agents in the form of microbubbles that enhance ultrasound signals [42, 43]. In clinical practice, MCE of the left ventricle (LV) is basically used to improve visualization of LV endocardium on 2D echocardiographic images and to assess myocardial perfusion of the LV.

Basic principle and technical aspects

Since the path of contrast microbubbles injected into circulation is the same as the path of red blood cells, MCE enables evaluation of myocardial perfusion. Microbubbles are considered as red blood cells tracers.

Myocardial perfusion is defined as a myocardial blood flow (MBF; mL x min x g-1), i.e. a flow at the capillary level, because capillaries encompass 90% of myocardial blood volume. MBF depends on two parameters: capillary blood volume and capillary blood velocity. The maximal signal intensity from the myocardium fully saturated with microbubbles under continuous contrast infusion represent the capillary blood volume. After microbubble destruction induced by high-power imaging, the rate of contrast replenishment within the myocardium reflects the blood velocity on the capillary level [44]. The product of myocardial blood volume (that can be assessed by plateau acoustic intensity) and blood velocity i.e. microbubble velocity (that can be assessed as a capillary refill after high-power imaging) equals MBF. A delayed and impaired appearance of contrast in the myocardium due to either reduced blood flow velocity or reduced contrast intensity (i.e. decreased capillary blood volume) represents the basis for coronary artery disease detection by MCE. Myocardial perfusion with MCE offers functional assessment of the complete coronary vasculature, from epicardial coronary arteries downstream to the coronary capillaries, in various clinical scenarios.

MCE offers possibility to measure myocardial perfusion reserve (MPR) as a surrogate for CFR. It can be evaluated by real-time MCE measuring myocardial blood volume in resting condition and during hyperaemia under continuous contrast infusion. Vogel et al proved that MCE-derived CFR is very similar to that derived from Positron Emission Tomography (PET) [45]. In the study of Biering et al. blood volume-derived MPR during real-rime MCE showed an excellent correlation with Doppler flow wire-derived CFR in patient without angiographic apparent coronary artery disease [46].

Importantly, Doppler flow-derived CFR correlated more closely with blood volume-derived MPR, than with MPR derived from either microbubble velocity or flow. MPR allows

the non-invasive assessment of both coronary stenosis severity and the detection of microvascular dysfunction [47]. Coronary flow reserve assessed by MCE also predicts mortality in patients with heart failure [48].

Clinical application of MCE to assess CMC

MCE was used to assess CMC and to detect *no-reflow* after myocardial infarction treated by pPCI first applying intracoronary microbubbles immediately after restoration of anterograde flow in the infarcted artery [49), then by intravenous administration of microbubbles [23]. Myocardial viability of the infarct region detected early after MI, by different modalities of MCE, predicted functional LV recovery with excellent sensitivity and specificity [50, 51]. Extent of microvascular damage, assessed by MCE one day after reperfusion therapy was the most powerful independent predictor for left ventricular remodelling compared to other indexes of post-MI reperfusion [52]. The transmurality of an infarction verified later by late gadolinium enhancement on cardiac magnetic resonance imaging, could be predicted earlier by MCE based contrast defect intensity and reduction of resting MBF [53]. Extent and intensity of myocardial perfusion defects on MCE within the risk area was an important predictor of both LV remodeling and unfavorable long-term outcome [54]. MCE was also used to estimate effects of adjunctive medical therapies to improve microvascular blood flow following STEMI [55].

Coronary microvascular dysfunction in Takotsubo cardiomyopathy was extensively evaluated in several studies by MCE. Generally, apical perfusion defect with typical apical akinesia ("apical ballooning") during acute phase of presentation was detected using quantitative and qualitative real time MCE, with normalization of perfusion during the follow up [55, 56, 57]. The primary underlying pathophysiological mechanism responsible for TC has not been entirely revealed. One of the concepts is that catecholamine-induced stunning in the affected myocardium might be the fundamental pathophysiological background. However, it is still unclear whether the cause of that stunning: hyperadrenergic state including profound arteriolar vasoconstriction and significant reduction of coronary flow or direct toxic effects of catecholamine on myocytes' metabolism. Nevertheless, echocardiography especially contrast echocardiography, by advantage of its flexibility and availability, remains the imaging modality of first choice in daily routine clinical practice to diagnose TC and also to evaluate its potential mechanisms.

Quantitative MCE was applied to reveal MVD in patients with microvascular angina ("syndrome X") and to detect its mechanism [58]. Higher mean microbubble velocity in rest with lower capability to increase microbubble velocity during dipyridamole-induced hyperemia implied that patients with syndrome X have significantly higher resting myocardial blood flow. The results indicated that coronary autoregulation is abnormal in patients with syndrome X (higher resting myocardial blood flow and lower capacity to increase it), and put in focus the coronary resistance vessels (150–300 mm in diameter) as the potential site of microvascular abnormality. Therefore, the inability of the resistance vessels to dilate in response to higher myocardial oxygen demand proved to be an important feature of abnormal coronary regulation, explaining also anginal chest pain and abnormal stress test results in these women.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) has emerging role in the assessment and management of patients with proven or suspected coronary artery disease [59]. Advances in cardiac MRI have enabled comprehensive structural and functional assessment including tissue characterization with identification of myocardial oedema and scar formation, imaging myocardial perfusion with myocardial motion and thickening at rest and stress perfusion, detection of microvascular obstruction (MVO) and intramyocardial haemorrhage (IMH). It is well validated for the quantification of left ventricular functional parameters, provides several clinical parameters of prognosis and has no radiation exposure.

Basic principle and technical aspects

Exploration of the coronary circulation by CMR is grounded on the kinetics of T1-gadolinium-based contrast media, including its "first pass kinetic" and "late enchancement". Gadolinium is a paramagnetic Gd3+ ion, which has has a long electronic relaxation time based on its totally symmetric S state making it well suited for use as an MR contrast agent. It accelerates the relaxation of the water molecules present in the tissue, giving rise to an enhanced signal on T1-weighted images and, together with appropriate sequence parameters, an improved image contrast. Gadolinium chelates are extra cellular contrast agents (i.e. cannot cross the intact/ normal myocyte cell membranes).

During the *first pass*, the contrast medium diffuses from the microvasculature into the interstitial space and is followed by contrast wash out. The increase in signal intensity is proportional to the perfusion and blood volume of the tissue, the extravascular compartment size, and capillary permeability [60]. In a normal myocardium, the signal increases homogeneously during the first pass and is followed by quick contrast wash out. However, a delayed signal increase and persistently hypointense regions during the first pass are indicative of reduced perfusion [61, 62]. Myocardial perfusion studies by CMR are performed in rest condition and under vasodilator stressor (usually adenosine, that is endothelium independent). Persistence of hypointense regions under adenosine infusion, represent hypoperfused ishaemic regions.

However, currently CMR-based fully quantitative perfusion analysis enabling measurement of myocardial blood flow (in ml/g) at rest and stress (i. e. providing parameters for CFR calculation by CMR) is not widely use. The main reason is that it requires complex calculations of various tissue enhancement curve parameters, which are corrected by subtracting or scaling the arterial input function derived from the left ventricle or by using model-independent deconvolution [63, 64]

The mechanisms of "late hyperenchancement" on CMR sequences basically represent the prolonged accumulation of the contrast media within expanded extracellular space and it is grounded on the following concept [65]. In the normal myocardium, myocytes are densely packed - myocyte intracellular space forms the majority (85%) of the volume. Therefore, the volume of distribution of gadolinium in normal myocardium is small. However, in myocardial infarction myocyte membrane rupture-additional gadolinium diffuse into increased extracellular space resulting in increased and prolonged gadolinium concentration and "hyperenhancement". Also, in chronic pathologies (chronic IM or cardiomyopathies), myocytes are replaced with collagenous scar, that causes the expansion of the interstitial space that leads to increased gadolinium concentration and "hyperenhancement".

Introduction of new CMR perfusion pulse sequences resulted in significant quality improvement in CMR images, including better spatial and temporal resolution, better linearity between signal intensity and contrast agent concentrations, and more favorable signal-to-noise ratios [66, 67].

Clinical application of CMR to assess CMC

Assessment of myocardial perfusion by cardiac MRI is currently indicated for detection of ischaemia in patients with known or suspected coronary artery disease, and for detection of MVO. Data regarding the myocardial perfusion CMR based study in patients without significant epicardial coronary diseases are limited.

In the MESA study (Multi-Ethnic Study of Atherosclerosis designed to evaluate cardiovascular risk factors), quantitative myocardial perfusion and CFR were assessed by CMR [68]. CFR values were significantly lower among male, elderly, and individuals with hypertension, fasting hyperglycaemia and hypercholesterolemia. The predicted absolute cardiovascular risk, estimated from the Framingham equation, was inversely associated with hyperaemic MBF and CFR. Furthermore, lower CFR was related to reduced regional myocardial systolic function evaluated as peak systolic circumferential strain [69]

Stress perfusion CMR proved as particularly useful in women with symptoms of myocardial

ischemia and non-obstructive CAD. In the WISE study semiquantitatively assessed MBF by CMR was predictive of adverse events beyond comprehensive clinical assessment [70].

Stress perfusion CMR also enabled assessment of CMC function in individuals with various etiology of left ventricular hypertrophy. Patients with hypertrophic cardiomyopathy was found to have markedly blunted vasodilator response in the endocardium that was proportional to the magnitude of wall hypertrophy, as well as significant reduced perfusion reserve compared to that in athletes with similar indexed left ventricular mass. [71]

CMR significantly contributes to the detection and understanding of the "no –reflow" phenomenon that is still demonstrated in certain number of patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention (PCI). The mechanisms of no-reflow are complex and encompass extravascular events (such as neutrophil infiltration), cellular injuries (endothelial swelling or myocyte oedema) and microembolisation with the debris from ruptured plaque [72, 73, 74]. Furthermore, reperfusion itself promotes multifaceted "reperfusion injury" modulated predominately by free radicals and oxidative stress, resulting finally in advanced disruption of the vascular wall cells and leaking of red blood cells into extravascular space with the accumulation of methaemoglobin. According to this pathophysiological concept microvascular obstruction (MVO) and intramural hemorrhage (IMH) within the infarct area are significant elements of no-reflow. Of the available modalities, CMR provides the most comprehensive assessment of MVO and IMH and numerous studies provided evidence that those CMR stigmata of no-reflow carry ominous prognosis.

On gadolinium-enhanced CMR, MVO is detected as delayed or absent wash-in of contrast agent into the infarct zone, "early" or "late" in reference to the timing of imaging relative to gadolinium administration. *Early* MVO is recognized as a prolonged perfusion defect on resting first-pass perfusion (FPP) imaging or as a hypointense region in the core of the infarction on T1-weighted images made 2 to 5 min after contrast administration [75]. Depending on the severity of MVO, the absence of wash-in of gadolinium may persist for >10 min, resulting in a region of persistent hypoenhancement within the core of the infarct on conventional late gadolinium enhancement images, referred to as "late MVO" [76]. Late gadolinium enhancement imaging used for late MVO assessment has high spatial and contrast resolution with full coverage of the LV myocardium. Currently, it is unidentified whether the rate of fill-in of the MVO area has prognostic importance and whether early or late MVO is a better predictor of LV remodeling or MACE. In overall pooled analysis, both early and late MVO are associated with lower EF [77], larger ventricular volumes [77] and infarct at baseline [78], and worse LV remodeling during follow- up [79]. Late MVO was demonstrated to have a stronger relationship with MACE and the individual outcomes of cardiac mortality, recurrent MI, and CHF/CHF hospitalization compared with early MVO [80]

IMH is a severe form of MVO and develops in the core of the infarct with a tendency to expand for several hours after PCI [81]. Ir order to assess for IMH most centers use T2-weighted short-tau inversion recovery (STIR) or T2*-weighted gradient echo pulse sequences. IMH appears as a hypointense region within the infarct on T2-weighted sequences. Since the paramagnetic effects of hemoglobin breakdown products more strongly affect T2* relaxation, T2*-weighted imaging is thought to be more sensitive for the detection of IMH. IMH detected by both T2 and T2* images has been correlated with the presence of hemorrhage on histopathologic analysis [82, 83]. Although intramyocardial haemorrhage is observed less frequently in patients with acute myocardial infarction than in animal models, its presence is correlated with the duration of ischaemia and infarct size, and is a predictor of adverse remodelling and outcome [84, 85] IMH also predicted MACE; however, there is a currently smaller body of literature for IMH and limited direct comparisons of IMH and MVO. Larger studies are needed.

CMR myocardial perfusion techniques are progressing rapidly. Additional improvement in diagnostic accuracy are expected to be achieved by both advanced acceleration techniques improving spatial resolution, especially of the subendocardial layer, and full 3D coverage of the whole heart.

Limitation of CMR

Apart from many clinically relevant advantages, CMR has some limitations. It is not available at all times and needs expertise for comprehensive imaging. Patients with claustrophobia, fast heart rates, severe renal impairment, high burden of ventricular ectopy, and ferromagnetic implants might not be eligible for stress CMR. Also, adequate renal function is required (eGFR >30 ml/min/1.73 m2), otherwise there is a risk of nephrogenic systemic fibrosis in case of contrast usage [86] Despite continuous technical improvements, the image artefacts, particularly "dark rim artefacts" during stress CMR, that mainly occur in the subendocardium, might be a limiting factor preventing absolute quantification of myocardial perfusion and have to be differentiated from true perfusion defects [67].

Conflict of interest

The authors confirm that there are no conflicts of interest.

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