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REVIEW

An Invited Review for the Special 20th Anniversary Issue of MRMS

Advances in Myocardial Perfusion MR Imaging: Physiological Implications, the Importance of Quantitative Analysis, and Impact on Patient Care in Coronary Artery Disease

Hajime Sakuma[1*] and Masaki Ishida[1]

Stress myocardial perfusion imaging (MPI) is the preferred test in patients with intermediate-to-high clinical likelihood of coronary artery disease (CAD) and can be used as a gatekeeper to avoid unnecessary revascularization. Cardiac magnetic resonance (CMR) has a number of favorable characteristics, including: (1) high spatial resolution that can delineate subendocardial ischemia; (2) comprehensive assessment of morphology, global and regional cardiac functions, tissue characterization, and coronary artery stenosis; and (3) no radiation exposure to patients. According to meta-analysis studies, the diagnostic accuracy of perfusion CMR is comparable to positron emission tomography (PET) and perfusion CT, and is better than single-photon emission CT (SPECT) when fractional flow reserve (FFR) is used as a reference standard. In addition, stress CMR has an excellent prognostic value. One meta-analysis study demonstrated the annual event rate of cardiovascular death or non-fatal myocardial infarction was 4.9% and 0.8%, respectively, in patients with positive and negative stress CMR. Quantitative assessment of perfusion CMR not only allows the objective evaluation of regional ischemia but also provides insights into the pathophysiology of microvascular disease and diffuse subclinical atherosclerosis. For accurate quantification of myocardial perfusion, saturation correction of arterial input function is important. There are two major approaches for saturation correction, one is a dual-bolus method and the other is a dual-sequence method. Absolute quantitative mapping with myocardial perfusion CMR has good accuracy in detecting coronary microvascular dysfunction. Flow measurement in the coronary sinus (CS) with phase contrast cine CMR is an alternative approach to quantify global coronary flow reserve (CFR). The measurement of global CFR by quantitative analysis of perfusion CMR or flow measurement in the CS permits assessment of microvascular disease and diffuse subclinical atherosclerosis, which may provide improved prediction of future event risk in patients with suspected or known CAD. Multi-institutional studies to validate the diagnostic and prognostic values of quantitative perfusion CMR approaches are required.

Keywords: *coronary artery disease, myocardial ischemia, myocardial perfusion, contrast medium, myocardial blood flow*

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in many industrialized countries, and optimal management for CAD has become increasingly complex due to accumulation of evidence in recent trials and advances in treatment options. Coronary computed tomography angiography (CTA) demonstrates high diagnostic accuracy for the detection of obstructive CAD and is the preferred imaging test in patients with a lower range of clinical likelihood of

[1]Department of Radiology, Mie University Graduate School of Medicine, Tsu, Mie, Japan

[*]Corresponding author: Department of Radiology, Mie University Graduate School of Medicine, 2-174, Edobashi, Tsu, Mie 514-8507, Japan. Phone +81-50-231-5029, Fax +81-59-232-8066, E-mail: sakuma@med.mie-u.ac.jp

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CAD and no previous diagnosis of CAD.[1] However, stenoses of 50%–90% by visual inspection are not necessarily functionally significant. Fractional flow reserve (FFR) measured by intracoronary doppler wire is an effective tool for evaluating functional significance of stenosis in the epicardial coronary artery, and FFR-guided revascularization was shown to be superior to angiography-guided treatment. According to the 2019 JROAD report,[2] more than 490000 invasive coronary angiography (ICA) procedures were performed in Japan. However, the number of percutaneous coronary interventions (PCIs) was 271000, indicating that up to 45% of patients who underwent ICA may not have functional significant CAD. Stress myocardial perfusion imaging (MPI) using single-photon emission CT (SPECT), positron emission tomography (PET), or perfusion cardiac magnetic resonance (CMR) is the preferred test in patients with intermediate and high clinical likelihood of CAD because it can be used as a useful gatekeeper to avoid unnecessary ICA and revascularization[1].

Compared with SPECT and PET, perfusion CMR does not expose the patients to radiation. In addition, owing to a higher in-plane spatial resolution as compared with SPECT or PET, perfusion CMR can delineate balanced ischemia in multivessel lesions as subendocardial ischemia spreading throughout the left ventricular (LV) myocardium (Fig. 1). CMR also permits comprehensive assessments of global and regional cardiac function, myocardial ischemia, tissue characterization including myocardial fibrosis and edema, and morphological stenosis in the coronary artery (Fig. 2).[3] It should be noted that, however, atherosclerosis is a diffuse progressive disease, and coronary circulatory dysfunction may develop in smaller arteries in an early stage of atherosclerosis and precedes epicardial coronary arterial stenosis. Therefore, even if the spatial resolution of CMR is much higher than that of SPECT or PET, qualitative or semi-quantitative assessment of regional myocardial ischemia by CMR may fail to detect diffuse, subclinical atherosclerosis. As an increasing number of studies using PET demonstrated that quantitative measurements of global myocardial blood flow (MBF) and coronary flow reserve (CFR) have excellent prognostic value, the clinical implication of quantitative myocardial perfusion CMR has substantially increased over the past 10 years. In addition, CMR has a unique capability of quantifying global MBF and CFR with 2D phase contrast cine MR imaging of the coronary sinus (CS).

This article will summarize physiological background of MBF and CFR, the diagnostic and prognostic importance of ischemia assessment as a gatekeeper of revascularization, technical advances of image acquisition and analysis of perfusion CMR, challenges for the absolute quantification of MBF with CMR, implications of quantitative perfusion CMR for improved management of patients with CAD, and future perspective of perfusion CMR.

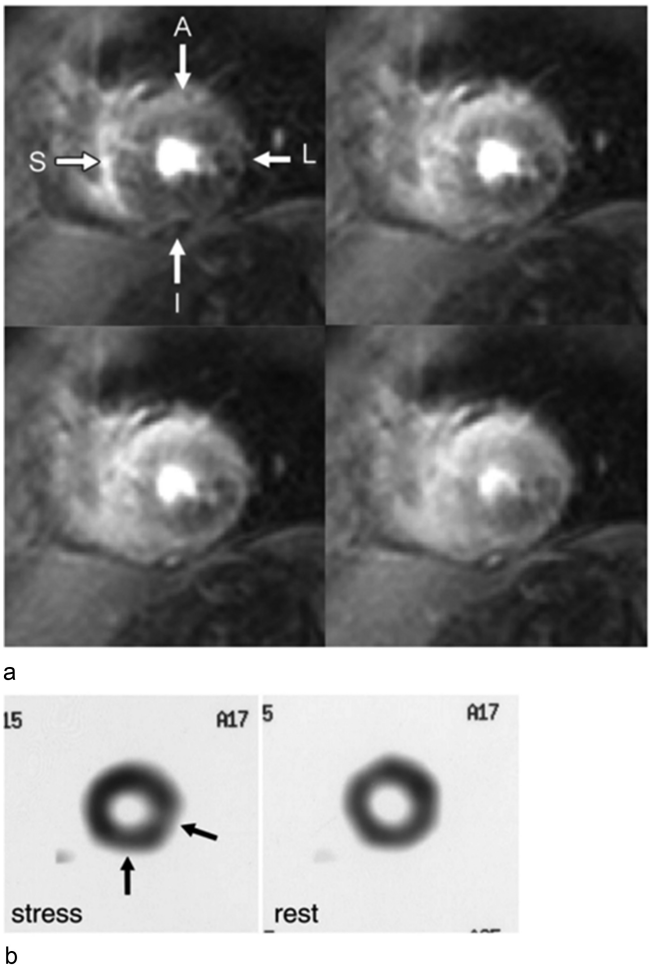

Fig. 1 First-pass contrast-enhanced multishot echo-planar stress MR images (6.7/1.4/180) (**a**) and ^{201}Tl SPECT images obtained at rest and during stress in a patient with triple-vessel stenosis (**b**). The MR images in a show lower myocardial enhancement in the inferior wall (I), lateral wall (L), and subendocardial area of the anterior wall (A) and septum (S). In b, ischemia (arrows) in the inferolateral wall is depicted; however, ischemia in the territory of the left anterior descending artery is not well visualized. Reproduced, with permission, from reference #27. SPECT, single-photon emission CT.

Assessment of Coronary Circulation

The coronary artery system consists of three compartments: large epicardial coronary arteries, prearterioles, and intramural arterioles.[4–6] Prearterioles (100–500 μm) are responsible for > 25% of total coronary artery resistance and act to maintain adequate perfusion pressure in the arteriole with an endothelium-dependent mechanism. Intramural arterioles (< 100 μm) account for > 50% of total coronary artery resistance, and the tonus of smooth muscle cells around the small arterioles is modulated by myocardial metabolic activity to match blood supply according to the oxygen consumption. Through these mechanisms in prearterioles and intramural arterioles, coronary blood flow is autoregulated to maintain

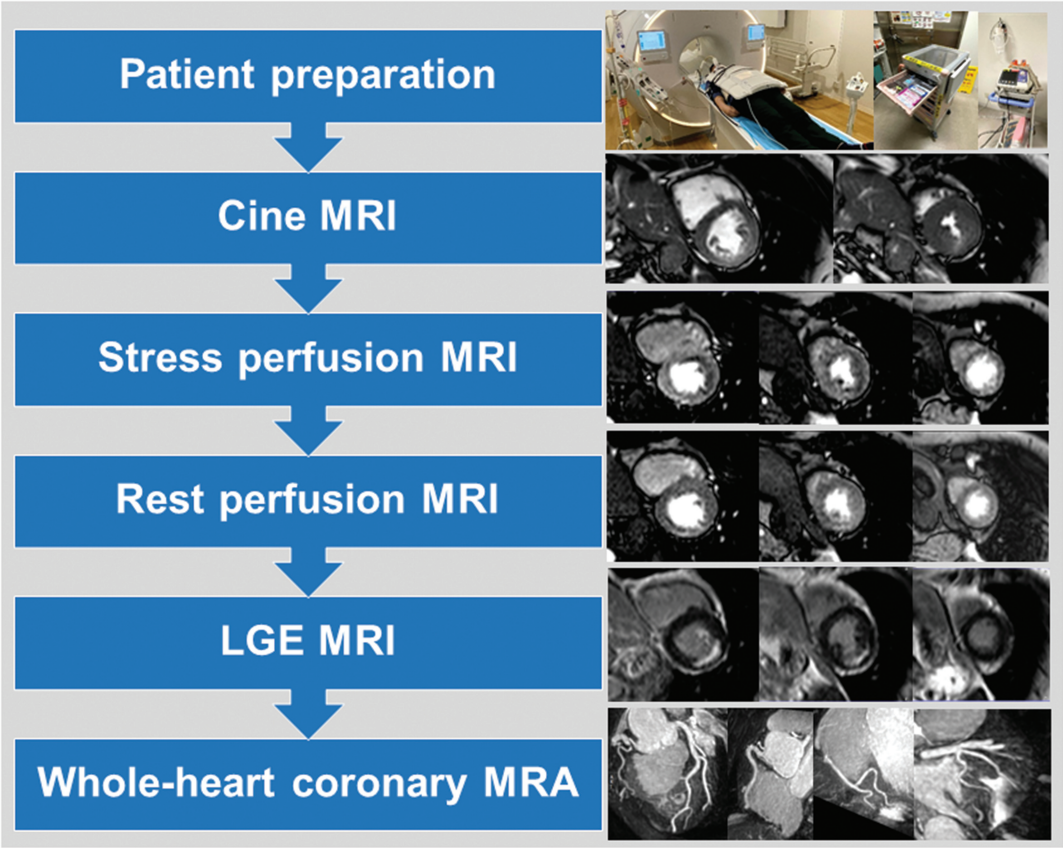

Fig. 2 Comprehensive CMR protocol with pharmacological stress. Two intravenous lines are prepared, one for gadolinium contrast medium typically in the right art and another for stress agent in the left arm. After acquisition of scout images and cine CMR images, stress perfusion CMR is acquired during adenosine or ATP stress, which is followed by rest perfusion CMR. LGE CMR is usually acquired approximately 10 min after stress perfusion CMR. Acquisition of whole-heart coronary MRA is optional but permits comprehensive assessments of morphological stenosis in the coronary artery and corresponding myocardial ischemia. ATP, adenosine triphosphate; CMR, cardiac magnetic resonance; LGE, late gadolinium enhanced.

adequate myocardial oxygen supply. In the presence of physiologically significant narrowing in the epicardial coronary artery, the resistance of prearterioles and intramural arterioles is reduced to maintain coronary blood flow.[7] Owing to this autoregulation mechanism, MBF in the resting state remains normal for up to 90% of luminal diameter stenosis in the epicardial coronary artery. In the stress condition, in contrast, maximal coronary blood flow is reduced with the luminal diameter stenosis of 50% in the epicardial coronary artery.

The main principle of stress MPI is based on the concept of CFR, i.e. the ratio of maximal hyperemic coronary blood flow divided by resting coronary blood flow. CFR is an index of the ability of the microvasculature to respond to pharmacological vasodilator stress. Because the majority of coronary circulatory resistance is at the microvascular level, administration of vasodilators such as adenosine increases coronary blood flow by 3–4 times. In the presence of flow-limiting stenosis in the epicardial coronary artery, however, the tonus of smooth muscle cells around the small arterioles is already relaxed to maintain coronary blood flow, resulting in a limited capacity of flow augmentation by vasodilator. Consequently, physiologically significant stenosis in the coronary artery can be evaluated from the distribution of MBF on stress MPI.

It is important to notice that CFR is not only reduced by stenosis in the epicardial coronary artery but also altered by coronary microvascular function.[8] FFR is a pressure-wire–based index that is invasively measured during ICA as the ratio of poststenotic intracoronary pressure divided by prestenotic pressure measured with maximal hyperemia by pharmacological stress. In contrast to CFR, FFR primarily represents the functional severity of epicardial stenosis and is relatively insensitive to microvascular function.[4] Therefore, FFR is widely used for the assessment of functional severity of the epicardial coronary artery stenosis in patients with CAD prior to revascularization, by using a typical FFR threshold of 0.8 for revascularization.[9] As mentioned above, CFR and FFR reflect different physiological aspects in the coronary artery circulation. Since dysfunction in coronary circulation may develop in smaller arteries in an early

stage of atherosclerosis and precedes epicardial coronary arterial stenosis, the use of CFR-based imaging techniques, such as PET and quantitative perfusion CMR, may have important implications to detect microvascular dysfunction when compared with FFR or FFR-CT.

Importance of Assessing Regional and Global Perfusion for the Risk Assessment and Optimal Therapeutic Decision

In patients with CAD, the assessment of the likelihood of future cardiac events is an important step in choosing medical management or revascularization.[10] The prognostic value of stress MPI has been well investigated in the field of nuclear cardiology, and the extent and severity of myocardial ischemia on SPECT were shown to be independent predictors of the prognosis in patients with known or suspected CAD.[11] In patients with myocardial ischemia on stress SPECT, the risk of adverse events increased according to the amount of ischemic myocardium. In a study by Hachamovitch et al. published in 2003, the prognosis of patients with ischemic myocardium exceeding 10% of LV myocardium is less favorable with medical therapy, and revascularization improves their prognosis.[12] On the other hand, in patients with less than 10% of ischemic myocardium, the prognosis is worsened by revascularization and medical therapy is recommended.

It should be noted that SPECT MPI evaluates relative perfusion, by assessing regional myocardial perfusion in comparison to the area exhibiting the highest perfusion tracer uptake.[13] Consequently, a global reduction in myocardial perfusion cannot be appropriately detected in patients with multivessel disease due to balanced ischemia, early stage blood flow impairment by diffuse atherosclerosis, and microvascular disease. In addition, myocardial perfusion SPECT is prone to artifacts caused by tissue attenuation of photons by the body structures around the heart such as breast and liver. These limitations associated with SPECT can be resolved by PET using tracers, such as ^{82}Rb, ^{13}N-ammmonia, and ^{15}O-water, which allow for absolute quantification of global and regional MBF in mil/min/g of the tissue.[14] The superiority of quantitative evaluation over qualitative evaluation of PET MPI was well demonstrated. Kajander et al. reported that the sensitivity, specificity, and accuracy of ^{15}O-water myocardial perfusion PET for the detection of obstructive CAD were 95%, 91%, and 92%, respectively, with absolute quantification.[15] The corresponding values were 74%, 73%, and 73% with visual assessment of PET MPI. Fiechter et al. used ^{13}N-ammonia myocardial perfusion PET and reported that the sensitivity, specificity, and accuracy of visual PET MPI for detecting significant CAD were 79%, 80%, and 79%.[16] The addition of reduced global CFR of < 2.0 to visual assessment of PET MPI improved these values to 96% ($P < 0.005$), 80%, and 92% ($P < 0.005$), respectively.

There is growing evidence demonstrating that global CFR assessed by quantitative PET has high prognostic value in predicting major adverse cardiac events (MACE) and cardiac death in patients with known or suspected CAD.[17] Ziadi et al. investigated the prognostic value of global CFR by ^{82}Rb PET in 414 patients with normal relative perfusion and 263 patients with abnormal relative perfusion.[18] In both groups, the subgroups with CFR < 2.0 showed worse prognosis than their counterparts with CFR ≥ 2.0. In addition, CFR was an independent predictor for cardiac death and myocardial infarction after adjustment for relative perfusion. In a more recent study by Murthy et al. investigating 2783 patients who underwent rest and stress ^{82}Rb PET, the patients with CFR > 2.0 (the highest tertile) showed an extremely good prognosis with cardiac death rate of < 0.5%/year.[19] In contrast, the patients with CFR < 1.5 (the lowest tertile) had a 5.6-fold increase in the risk of cardiac death compared to those with CFR > 2.0.

Characteristics of Perfusion CMR Compared to Other MPI Approaches

CMR has a number of favorable characteristics, including: (1) high spatial resolution that allows for the assessment of subendocardial ischemia (Fig. 3); (2) uniform signal from the entire LV myocardium, unaffected by attenuation artifacts; (3) tissue characterizations such as myocardial scar, edema, and infiltrating disease by using late gadolinium enhanced (LGE) CMR, and T1 and T2 mapping; (4) comprehensive assessment of morphology, global and regional cardiac functions, and coronary artery stenosis; and (5) lack of ionizing radiation.[20] Due these advantages, CMR has become indispensable for assessing the pathophysiology and co-existing myocardial ischemia in patients with heart failure and myocardial hypertrophy, and for diagnosing of myocardial diseases, such as amyloidosis and sarcoidosis.

Unlike the tracers used in nuclear cardiology, the contrast medium used in myocardial perfusion CMR is not taken up into myocardial cells. Therefore, first-pass transit of a contrast medium through the cardiac chambers and myocardium needs to be monitored to evaluate myocardial perfusion by CMR, necessitating pharmacological stress testing in the magnet. For brain perfusion imaging, dynamic susceptibility imaging is the most widespread MRI technique for evaluating cerebral perfusion parameters. During an early stage of technical development of myocardial perfusion CMR, Sakuma et al. demonstrated that magnetic susceptibility contrast medium allows for monitoring the first-pass dynamics of contrast media through the heart.[21] However, currently T1-weighted dynamic imaging sequences are widely used in myocardial perfusion CMR. In contrast to the brain with a blood-brain barrier, distribution volume of extracellular gadolinium contrast medium in the myocardial is much larger, allowing for excellent contrast enhancement with T1-weighted imaging sequences.

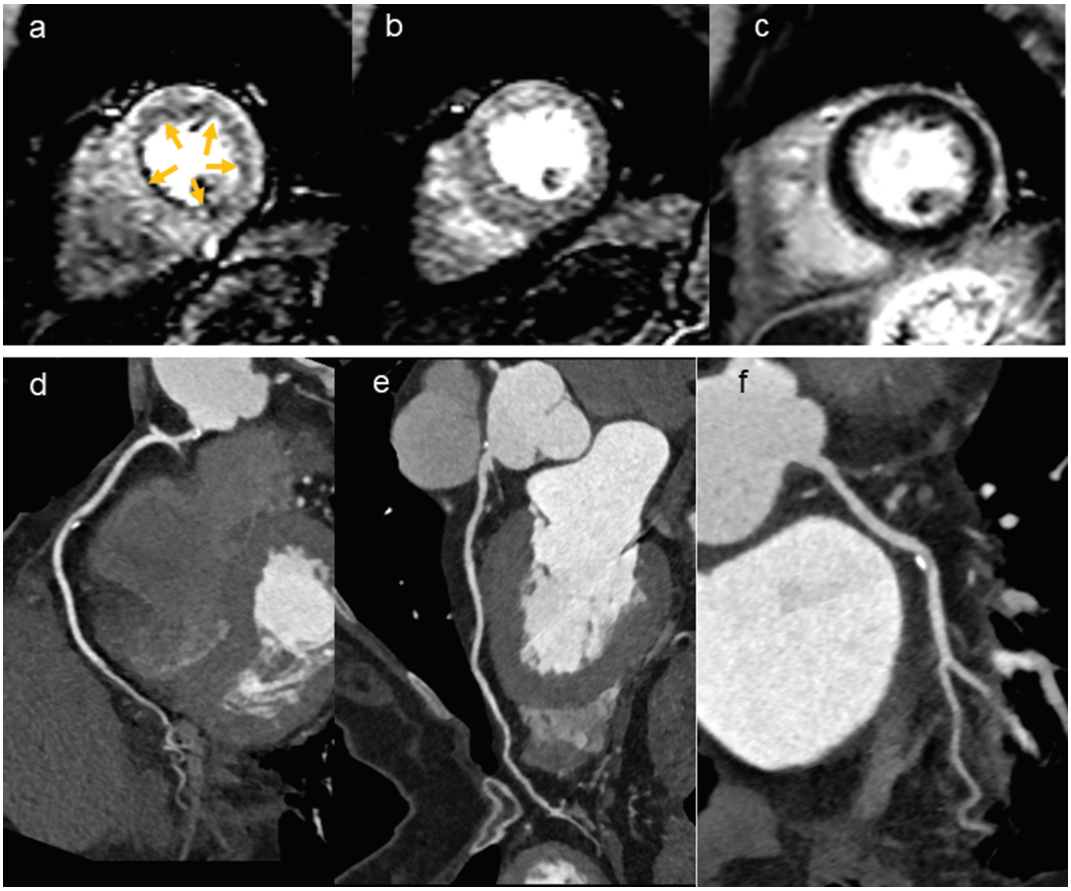

Fig. 3 69-year-old woman with multiple risk factors but no symptoms. Diffuse subendocardial perfusion abnormality was observed on stress perfusion MRI (arrows) (**a**). On rest perfusion MRI (**b**) and LGE MR (**c**), no abnormal finding was observed. On coronary CTA (**d**, RCA; **e**, LAD; **f**, LCx), no only some mild stenoses accompanied by partly calcified plaques were noted. In this patient, stress-induced diffuse subendocardial perfusion abnormality was considered due to microvascular dysfunction. CTA, CT angiography; LAD, Left anterior descending; LCx, Left circumflex; LGE, late gadolinium enhanced; RCA, Right coronary artery.

Imaging Technique for Stress Myocardial Perfusion CMR

Technical requirements in pulse sequences for myocardial perfusion CMR

First-pass perfusion CMR typically acquires multiple short-axis T1-weighted images of the LV after bolus injection of gadolinium contrast medium (typically 0.05 mmol/kg at 4 ml/s) followed by saline flush (typically 20 ml at 4 ml/s). Saturation recovery (SR) pulse is most commonly used to achieve T1-weighting and has been combined with various readout methods, such as balanced steady-state free precession (SSFP), gradient echo (GRE), and GRE echo-planar imaging (GRE-EPI) hybrid readout. There is no clear consensus regarding the sequence of choice for MPI.

Optimization of the pulse sequence is important to achieve successful myocardial perfusion CMR. Temporal resolution, spatial resolution, and spatial coverage are important, though tradeoffs between parameters are common in MRI. The duration of image data acquisition primarily determines the sensitivity of the pulse sequences to cardiac motion. Readout temporal resolution will be set preferably at 100–125 ms or shorter. A longer inversion time (TI) may result in increased SNR, while this comes at the cost of reduced linearity, which may influence the quantitative analysis. In literature, 100–150 ms is usually selected for TI. The spatial resolution should be sufficient to distinguish subendocardial ischemia and to assess transmural extent of perfusion abnormality (< 3 mm in-plane). At least 3 slices are needed to cover 16 segments of the heart (slice thickness 8–10 mm), although a larger number of slices are preferable. Image acquisition on every heartbeat is desirable, if possible, for typically at least 50–60 heartbeats. To achieve those requirements, the use of fast imaging techniques, such as parallel imaging and compressed sensing, is required

History of the imaging technique for myocardial perfusion CMR

First-pass myocardial perfusion CMR sequences have been developed by many investigators since it was firstly reported by Atkinson et al. in 1990.[22] In the 90s, most of

the studies were performed using spoiled GRE sequences with short TR and TE.[23] However, the lengthy acquisition time for each image limits the number of slices acquired in each cardiac cycle, particularly during stress. Although SR prepulse is commonly used for perfusion CMR today, inversion recovery (IR) approaches were also tested in early works.[24] Although IR approaches may provide increased dynamic range, they are susceptible to heart rate variation because incomplete magnetization recovery results in signal intensity variation. Further, IR approaches require relatively long preparation time between IR pulse and imaging acquisition, limiting the number of imaging slices per heartbeat. Segmented EPI was also applied to perfusion CMR to improve the temporal resolution.[25] In contrast to single-shot EPI, segmented EPI reads 2 to 4 lines in the k-space after each RF pulse by rapidly switching the gradient polarity for readout. Thus, the data acquisition time is greatly reduced. However, segmented EPI technique is prone to geometric and intensity distortions due to susceptibility interfaces around the heart. To overcome those problems, GRE-EPI hybrid readout technique was developed in the late 90s.[26,27] However, those techniques still suffered from suboptimal SNR and contrast-to-noise ratio (CNR), and susceptibility to magnetic field inhomogeneity around the heart.

In the early 2000s, SSFP techniques have been successfully implemented in perfusion CMR. In contrast to incoherent techniques where all transverse magnetization is destroyed before the next phase encoding step, SSFP is a coherent gradient echo technique that recycles the transverse magnetization for each data acquisition. SSFP perfusion technique demonstrated higher SNR and/or better resolution, especially for tissues with large T2/T1 values.[28,29]

Those conventional pulse sequences have been combined with parallel imaging or k-t acceleration in the mid-2000s to further improve the temporal resolution, spatial resolution, and spatial coverages.

Acceleration techniques in myocardial perfusion CMR

Parallel imaging techniques can reduce the number of k-space lines required to reconstruct an image.[30,31] Parallel imaging techniques achieve up to 2- to 3-fold acceleration without degrading the image quality and are widely used in clinical MR systems today. The amount of data required for image reconstruction can be further reduced by using the correlation between images at different times in the cardiac cycle or between different heartbeats in a dynamic perfusion acquisition. This technique is called k-t acceleration technique.[32,33] Accelerations of 12 × have been achieved using this technique. However, k-t acceleration technique is susceptible to respiratory motion.

Current techniques typically image 3 short-axis myocardial slices with an in-plane resolution of < 2 mm by using parallel imaging or k-t acceleration techniques.[34] Generally, increasing spatial coverage is associated with technical trade-offs, such as reducing spatial resolution or increasing the temporal acquisition window. Both factors could result in insufficient image quality when compared with the high-resolution 3-slice acquisitions.[35] Recently, k-t acceleration technique achieved improved spatial coverage, maintaining spatial and temporal resolution, and enabled acquiring 3D volumetric data.[36] A multicenter study showed excellent diagnostic performance for 3D whole-heart perfusion CMR for detection of functionally significant CAD defined by FFR (sensitivity and specificity, 84.7% and 90.8%, respectively).[37]

An active area of image reconstruction research involves compressed sensing, which enables reconstruction of images from significantly fewer lines of data by the sparsity. Compressed sensing has the potential to further accelerate the perfusion MRI, which may enable 3D volume acquisition with higher spatial resolution, as well as denoising.[34]

Imaging Protocol for the Stress Perfusion CMR

Pharmacological vasodilators

Stress MPI can be performed with exercise stress or pharmacological stress. Exercise stress is a physiological stress method that can induce an increase in the oxygen demand of the myocardium. Exercise tolerance is known to be an important prognostic indicator. However, inadequate exercise decreases the diagnostic performance of exercise stress MPI. Pharmacological stress induces approximately 4-fold increase in MBF, which is higher than that obtained by exercise stress. The diagnostic performance of pharmacological stress SPECT is at least equivalent to that of exercise stress SPECT for the detection of flow-limiting CAD and is not influenced by exercise tolerance.

Adenosine, adenosine triphosphate (ATP), and dipyridamole have been used as a vasodilator agent for stress myocardial perfusion CMR. Regadenoson is a newer stress agent, which has been approved in many countries in the last decade.[38] As of the end of 2020, regadenoson is not available in Japan. Those vasodilator agents have equivalent stress effects on myocardial perfusion CMR with an appropriate injection scheme or dose (Table 1). Adenosine is a nonselective adenosine receptor agonist.[39] ATP is a precursor of adenosine that is metabolized into adenosine after administration.[40] In contrast, dipyridamole indirectly induces vasodilation by blocking adenosine reuptake and increasing endogenous adenosine.[39] The vasodilator mechanisms of those agents are similar, in which the adenosine molecule binds to the adenosine A2A receptor. However, those might cause negative chronotropic, dromotropic, and inotropic effects via A1 receptors, and bronchospasm and mast cell degranulation via A3 receptors.[39] Regadenoson is a selective A2A receptor agonist, which is considered to be a safer stress agent.[39]

Table 1 Pharmacological stress agents for myocardial perfusion CMR

	Injection scheme	Dose and duration	Scan start	Half-life	Reverse
Adenosine	Slow infusion	140 mcg/kg, 5-6 min	At 3 min	< 2 s	n/a
ATP	Slow infusion	160 mcg/kg, 5-6 min	At 3 min	10 s	n/a
Dipyridamole	Slow infusion	0.56 mg/kg over 4 min	At 4 min	20-30 min	Aminophylline*
Regadenoson	Bolus injection	400 mcg dose over 10 s followed by a 10 ml saline flush	At 70 s	2-3 min	Aminophylline*

* Aminophylline 100 mg IV after acquiring stress images. ATP, adenosine triphosphate; CMR, cardiac magnetic resonance.

In the countries where regadenoson is not available, adenosine or ATP is predominantly used since they are easy to use due to their short half-lives. ATP is preferred in Asian countries including Japan due to cheaper cost. Since the duration of effect by dipyridamole and regadenoson is relatively long, those drugs are typically reversed by aminophylline. The administration of aminophylline can reduce the side effects and reverse the heart rate to baseline immediately. However, aminophylline should be carefully used because of arrhythmogenic side effects. Side effects of regadenoson are generally less significant when compared with other vasodilators.

Those stress agents may have minor side effects, including flushing, chest pain, palpitations, headache, dizziness, and breathlessness. More severe side effects, including transient heart block, transient hypotension, and bronchospasm, are reported for adenosine, ATP, and regadenoson. Dipyridamole may have severe, but rare, side effects, including myocardial infarction, ventricular tachycardia, and transient ischemic attack. Contraindications of those stress agents are as follows: 1) 2nd degree or complete atrioventricular block; 2) systolic blood pressure < 90 mmHg; 3) systemic arterial hypertension (> 220/120 mmHg); 4) sinus bradycardia (heart rate < 40 bpm) and ; 5) active bronchoconstrictive or bronchospastic disease with regular use of inhalers.[41]

Since no vasodilator agent has regulatory approved for stress CMR in Japan, it is mandatory to obtain an ethical approval in each institution to use stress agents in stress CMR study.

Patient preparation

To obtain sufficient vasodilator effects, patients need to refrain from caffeine (coffee, tea, caffeinated beverages or foods, and caffeinated medications), theophylline, and dipyridamole for 12–24 hours prior to stress CMR study to avoid antagonistic effects to the stress agent.[41] If adenosine, ATP, and dipyridamole are used, it is necessary to put two intravenous lines, one for gadolinium contrast medium and one for stress agent, one in each arm. Gadolinium contrast medium is typically injected from the right arm in our institution, similar to most contrast-enhanced CT scans, because the left brachiocephalic vein may be narrowed between the aortic arch and sternum depending on the respiratory cycle. Only one intravenous line is required for regadenoson. Fasting is not mandatory. During the examination, blood pressure, heart rate, ECG, and SaO_2 should be monitored. The blood pressure should be monitored carefully to avoid interference with gadolinium contrast media injection or vasodilator infusion. Evacuation procedures for rapid removal of the patient from the scanner need to be planned and practiced in case of emergency. An emergency cart with appropriate resuscitative medications, supplies, and equipment, such as epinephrine, ß-blockers, atropine, bronchodilators, antiarrhythmic drugs, and oxygen, has to be established outside the scanner room. Especially, ß-blocker, nitroglycerin, aminophylline, bronchodilators, and oxygen should be immediately available.

Inadequate stress effect with caffeine intake: relation to splenic perfusion

False-negative results were reported in up to 10% of the patients who underwent adenosine stress perfusion CMR. Over one-third of these false-negative cases may be related to insufficient pharmacologic stress due to drug interactions between adenosine and caffeine.[42] The main mechanism of caffeine action in humans is through the blockade of adenosine receptors masking the vasodilatation by adenosine.[43] In addition, caffeine stimulates sympathetic nerve activity, inducing capillary de-recruitment, which results in reduced MPR.[43] The current standardized protocol for adenosine stress perfusion CMR depends on the pre-specified physiological changes, such as heart rate increase by 10 bpm and drop in systolic blood pressure by 10 mmH. However, heart rate and blood pressure correlate poorly with hemodynamic changes induced by adenosine.[44]

Splenic switch-off (SSO) is an index of adenosine-induced splenic vasoconstriction, manifested as reduced brightness of the spleen during adenosine stress perfusion CMR as compared with rest perfusion CMR.[42] The prevalence of the patients without SSO was significantly higher in

those with false-negative studies as compared to those with true-negative studies in the CE-MARC study, suggesting that lack of SSO might be a possible indicator for the false-negative results. The spleen intensity ratio, the ratio between the brightest mean signal intensity and stress and rest images adjusted for baseline signal intensity, of 0.40 is an optimal cutoff for the SSO.[45] García-Baizán et al. demonstrated that SSO can be used to evaluate the adequacy of stress even in the stress perfusion CMR using ATP.[46]

Regadenoson does not induce reduction in splenic blood flow. Adenosine mediates splenic blood flow via the A1 and/or A2B adenosine receptors to maintain circulating blood volume when shock occurs. In contrast, coronary vasodilatation is mediated by the adenosine A2A receptor.[42] This might explain why regadenoson, the selective coronary A2A receptor agonist, had no discernible effect on splenic blood flow in stress perfusion CMR study.

Interpretation of Stress Perfusion CMR

How to diagnose ischemia in stress perfusion CMR

To assess the myocardial ischemia, corresponding slices of stress and rest perfusion CMR images should be displayed side by side. Then, it should be checked if there was an adequate hemodynamic response to stress by reviewing the alterations of heart rate and blood pressure during examination. Images should also be checked for SSO during stress.[42] By visual analysis of myocardial perfusion CMR, the observers need to identify relative perfusion abnormalities by comparing the contrast enhancement between myocardial regions during the first-pass passage of the gadolinium contrast medium through the LV myocardium. A stress-induced perfusion abnormality is present only on the stress, but not on the rest images. Typically, relative hypoenhancement in ischemic myocardium is observed from the time the contrast medium reaches the LV myocardium and is seen over several temporal phases as the contrast enhancement progresses. Hypoenhancement is usually most pronounced in the subendocardial area of the myocardium and often manifests as a transmural gradient in the direction of wall thickness. If perfusion defects are observed on both stress and rest perfusion CMR images, they are considered to be artifacts, myocardial scar, or fatty metamorphosis.

Subendocardial dark banding artifacts should be reminded as an important pitfall which may cause false-positive reports.[47] Dark banding artifacts are considered to be truncation artifact or ringing artifacts, and are predominantly observed when contrast medium arrives in the LV blood pool. It should be reminded that the signal intensity of the dark banding artifacts is lower than the baseline signal intensity of the myocardium, whereas the signal intensity of true myocardial ischemia is, at least, equal to or higher than the baseline signal intensity.

Multivessel CAD and microvascular disease are major pitfalls of visual analysis. Theoretically, patients with balanced multivessel CAD could demonstrate diffuse subendocardial hypoperfusion in all LV segments in all imaging slices, which is not easy to distinguish from dark bunding artifacts and could result in false-negative reading.[48] However, in patients with multivessel CAD, truly balanced myocardial ischemia is not common because the degree of physiological stenosis in the major coronary vessel is often variable. Patients with microvascular disease may lead to a global subendocardial hypoperfusion.[49] This may result in false-positive readings when ICA is used as a reference method. The differentiation between microvascular disease and multivessel CAD is challenging by using stress perfusion CMR alone, and anatomical coronary imagings, such as coronary CTA and coronary MR angiography (MRA), should be added.

How to diagnose ischemia in patients with MI

To diagnose the myocardial ischemia in case of co-existing myocardial infarction, it is required to display stress-rest perfusion and corresponding LGE images side by side. Myocardial infarction does not necessarily exhibit a perfusion defect on rest perfusion CMR, especially in chronic myocardial scar due to neovascularization. Therefore, myocardial infarction should be always evaluated on LGE images without depending on stress and rest perfusion CMR images. Presence of stress-induced perfusion abnormality is considered if the perfusion defect is observed on stress perfusion CMR in the myocardial tissue that does not exhibit LGE.

Diagnostic Performance of Stress Perfusion CMR

Improved spatial resolution of CMR permits the detection of diffuse subendocardial hypoenhancement in patients with multivessel CAD, resulting in improved diagnostic accuracy compared to SPECT in detecting flow-limiting CAD. In a study by Ishida N et al., the diagnostic accuracy of stress perfusion CMR was significantly superior to that of stress SPECT by using ICA as the reference standard, with the sensitivity of 94% by CMR and 82% by SPECT (Fig. 4).[27] In another study by Sakuma H et al., the areas under the receiver operating characteristics curve (AUC) in detecting significant CAD were 0.84–0.86 for stress perfusion CMR and 0.72–0.79 for stress SPECT.[50] CE-MARC is a large-scale prospective randomized study that compared the diagnostic accuracy of comprehensive CMR, including stress perfusion and coronary MRA with that of SPECT.[51] By receiver operating characteristic (ROC) analysis, stress CMR (AUC of 0·89) was significantly better than SPECT (0·74 $P < 0·0001$) in detecting flow-limiting stenosis on ICA. Stress CMR was significantly superior to stress SPECT for both single-vessel disease and multivessel disease.

In 2009, fractional flow reserve versus angiography for multivessel evaluation (FAME) study demonstrated that FFR-guided PCI significantly reduced the rate of death,

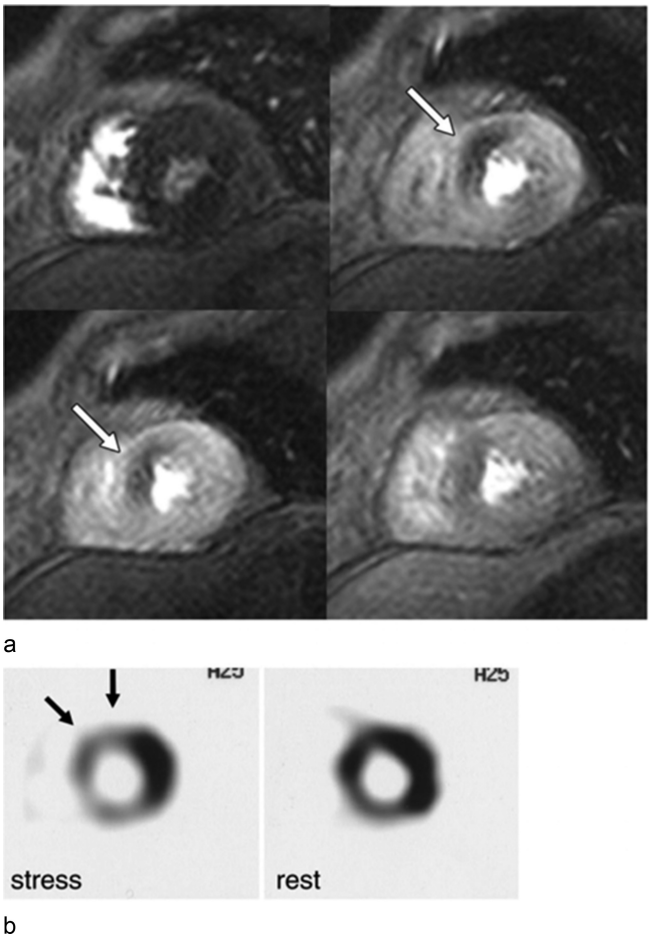

Fig. 4 First-pass contrast-enhanced multishot echo-planar stress MR images (6.7/1.4/180 [repetition time ms/echo time ms/saturation recovery time ms]) (**a**) and ^{201}Tl SPECT images obtained during stress and at rest in a patient with 70% or greater diameter stenosis of the left anterior descending artery (**b**). The hypoperfused region (arrows) in the anteroseptal wall is depicted as a region of lower enhancement in **a** and as an apparent perfusion abnormality in **b**. Reproduced, with permission, from reference #27. SPECT, single-photon emission CT.

myocardial infarction, and repeat revascularization when compared with angiography guided PCI.[52] Since then, ICA with FFR became increasingly used as a reference standard for determining the presence or absence of flow-limiting CAD. Several meta-analyses studies analyzed the diagnostic accuracy of MPI by SPECT, PET, perfusion CMR, and perfusion CT by using FFR as a reference standard. Li et al. analyzed 1073 arteries and 650 patients in 14 studies, and the sensitivity and specificity of perfusion CMR were 90% and 87%, respectively, at the patient level by using invasive FFR as the reference standard.[53] Takx et al. reported that hemodynamically significant CAD can be accurately evaluated by perfusion CMR (per-patient AUC of 0.93), perfusion CT (0.93), or PET (0.93), but less accurately with SPECT (0.82) when compared with FFR.[54]

Prognostic Value of Qualitative Assessment of Stress CMR

Stress CMR studies with either stress perfusion CMR or dobutamine stress cine CMR have been shown to exhibit excellent prognostic value. In a meta-analysis study by Lipinski et al., 11636 patients were evaluated with a mean follow-up of 32 months. The annual event rate of cardiovascular death or nonfatal myocardial infarction was 4.9% and 0.8%, respectively, in patients with positive and negative stress CMR.[55] The annual event rate was 4.6% and 1.4%, respectively, in patients with positive and negative LGE, suggesting that stress perfusion CMR may be more effective in identifying low-risk patients. In 5-year follow-up of the CE-MARC study, 104 (16.6%) of 628 patients who underwent stress perfusion CMR, SPECT, and ICA experienced MACE.[56] Both CMR (hazard ratio [HR] 2.8, $P < 0.001$) and SPECT (HR 1.62, $P = 0.014$) were shown to be strong and independent predictors of MACE. However, only CMR remained a significant predictor after adjustment for other cardiovascular risk factors, ICA result, or initial patient treatment, suggesting that stress perfusion CMR may provide more adequate risk stratification.

In SPECT, ischemic myocardium exceeding 10% of LV myocardium has been widely accepted as an ischemic threshold to stratify patients who would benefit from revascularizations in contrast to medical therapy only.[12] However, the optimal ischemic threshold for stress perfusion CMR was unknown. Vincenti et al. investigated the prognosis of 1024 patients with known or suspected CAD who referred to stress perfusion CMR.[57] Patients without ischemia had excellent outcomes that were not different from patients with < 1.5 ischemic segments (9.3% of LV myocardium) on a 16-segment model. In contrast, ischemia with ≥ 1.5 ischemic segments was a strong predictor (HR > 7) of the future cardiac events. The results in this study indicated that patients with zero or 1 ischemic segment on stress CMR can be safely deferred from revascularizations.

In patients with chronic CAD, stress MPI and FFR are widely used to determine the indication of revascularization. However, non-inferiority of a stress perfusion CMR strategy to a FFR-based strategy with respect to MACE was not known. MR-INFORM study investigated the clinical effectiveness of perfusion CMR compared to invasive ICA with FFR in patients with stable angina. A CMR-guided management was associated with a lower incidence of coronary revascularization than the invasive FFR-guided strategy. In addition, a perfusion CMR strategy was noninferior to a FFR-based strategy with regard to MACE at 12 months.[58]

According to Japanese Circulation Society 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases,[59] exercise electrocardiogram (ECG) is the first-line diagnostic test in patients with suspected stable coronary heart disease, and ICA is indicated if the risk estimated by Duke treadmill score is high. In patients with moderate risk by Duke treadmill score, nondiagnostic exercise ECG, or inability to exercise, stress MPI and coronary CTA are recommended. Stress MPI

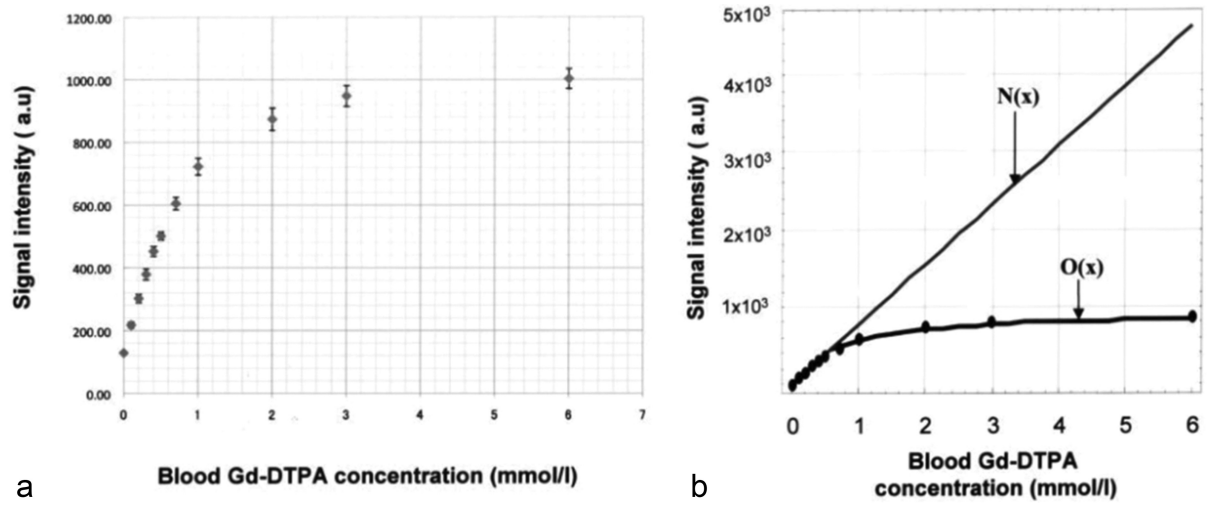

Fig. 5 The relation between the signal intensity of the blood and gadolinium concentration in human blood sample measured on saturation-recovery prepared myocardial perfusion CMR (**a**). The data point was plotted as mean ± standard deviation. O(x) represents the measured MR blood signal intensity (**b**). N(x) indicates the theoretical linear curve of the blood signal intensity versus gadolinium concentration without saturation effect, which was obtained by linearly extrapolating the low-concentration data points on O(x). (a.u. = arbitrary unit). Reproduced, with permission, from reference #60. CMR, cardiac magnetic resonance.

is suited for the evaluation in patients with moderate-to-high clinical likelihood of CAD, and ICA is indicated in patients with myocardial ischemia. Coronary CTA is an excellent imaging test to rule out CAD in patients with a lower range of clinical probability of CAD. In patients with abnormal, borderline or non-diagnostic coronary CTA, stress MPI is recommended as the next imaging test, and ICA is recommended when myocardial ischemia is observed on subsequent stress MPI. FFR-CT may be useful for the assessment of myocardial ischemia in patients with intermediate stenoses on coronary CTA. However, FFR-CT is expensive and there are only limited facilities where it is covered by health insurance at this point. At our institution, the assessment of myocardial ischemia is performed by perfusion CT (approximately 50% of the cases), perfusion CMR (40–50%), SPECT (< 10%), or FFR-CT (< 1%). The stress CT approach provides high-resolution imaging of the coronary arteries and is suited for patients with suspected CAD without initial suspicion of heart failure or myocardial disease. In contrast, stress CMR approach is suitable for ruling out coexisting CAD in patients with heart failure, cardiomyopathies, myocarditis, and other myocardial diseases.

Quantitative Assessment of Stress Perfusion CMR

Significance of quantitative assessment of stress perfusion MRI

Visual assessment has been widely used for the interpretation of stress perfusion CMR. However, visual assessment is subjective and observer-dependent, and sometimes requires a long learning curve for the observer. Absolute quantification of MBF by stress perfusion CMR can provide a more objective assessment of myocardial perfusion. In addition, quantitative assessment of myocardial perfusion CMR not only allows the objective evaluation of regional ischemia-caused epicardial CAD but also provides insights into the pathophysiology of epicardial CAD, microvascular disease, and cardiomyopathy. Further, absolute MBF and MPR determined by quantitative perfusion CMR may provide a better prognostic stratification as demonstrated by quantitative PET studies.

Relation between gadolinium concentration and signal intensity in LV blood and myocardium

Quantification of MBF by myocardial perfusion CMR relies on a linear relationship between the concentration of gadolinium contrast medium and MR signal intensity. Both arterial input function (AIF) of the LV blood pool and output function of the myocardium must behave linearly with the concentration of gadolinium contrast medium. Several studies demonstrated that while the relationship between signal intensity and gadolinium contrast concentration is linear at lower gadolinium concentration, AIF is substantially clipped at higher gadolinium concentration (Fig. 5).[60] This occurs mainly due to the T1-saturation effect, and the signal intensity may be further clipped due to T2* shortening effects at higher concentration. In contrast, the relationship between the gadolinium concentration and signal intensity is generally linear within a physiological range of gadolinium concentration in the myocardium. As a consequence, a saturation correction of the AIF is important for the accurate quantification of MBF.

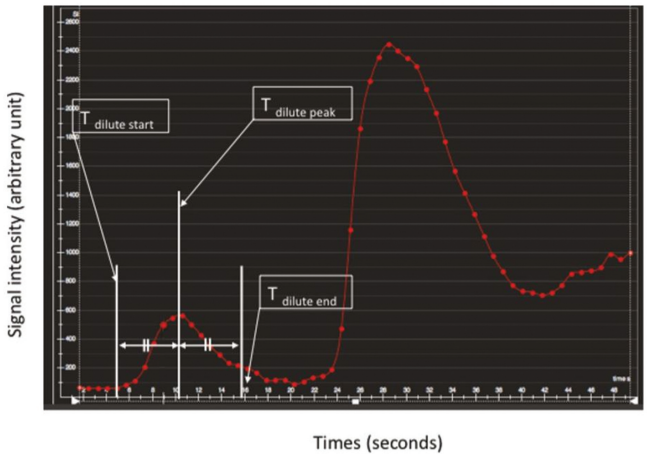

Fig. 6 Time-intensity curve in the LV blood after contrast injection with dual-bolus injection scheme (red line). Note that small peak by pre-bolus using dilute contrast medium is followed by large peak by main-bolus using non-dilute contrast medium. Clipped main-bolus was corrected for T1 saturation effect using pre-bolus data and used as arterial input function. Reproduced, with permission, from reference #61. LV, left ventricular.

AIF saturation correction: dual-bolus and dual-sequence approaches

There are two major approaches for saturation correction of AIF in perfusion CMR: dual-bolus and dual-sequence methods.

Dual-bolus method uses the pre-bolus image data to correct AIF in the main bolus. In this approach, a bolus of diluted contrast medium was injected prior to the main bolus in perfusion CMR (Fig. 6).[61] The key points of the dual-bolus approach protocol are as follows: 1) both volume and flow rate of contrast injection should be identical between the main bolus with normal contrast concentration and the pre-bolus with diluted contrast solution; and 2) both the main bolus and pre-bolus should be followed by a saline flush to maintain a compact bolus of the contrast agent through the heart. The dual-bolus protocol has shown to be robust for accurate quantification of MBF in perfusion CMR.[62,63] Ichihara et al. modified the dual-bolus method and demonstrated the utility of their approach using 1.5T MR scanner.[60]

Dual-sequence method is another promising approach for AIF correction (Fig. 7). This method uses a combination of two different types of image acquisitions in a single scan.[64–66] In this approach, short SR images with low spatial resolution for AIF correction are combined with long SR images with high spatial resolution acquisitions for myocardial signal. Dual-sequence method is an approach to solve the issue by using separate pulse sequences optimized for AIF and myocardial tissue in a single scan. Compared to the dual-bolus method, a benefit of this approach is the simultaneous measurement of the AIF and myocardial signals with a single gadolinium injection with standard concentration.

Quantification of absolute MBF

To obtain an accurate estimation of the absolute MBF by analyzing first-pass myocardial perfusion CMR, it is very important to use a mathematical model that adequately reflects the dynamics of gadolinium contrast agent. There are two major methods for the quantitative evaluation of absolute MBF: linear time-invariant model and compartmentalized model. Since detailed mathematical explanations of the quantitative models for estimating tissue blood flow are beyond the scope of this review paper, the concepts of these two mathematical models will be briefly explained.

Linear time-invariant model

The time-signal intensity curve of the tissue after contrast agent administration can be modeled with a linear time-invariant system. The impulse response of the myocardial tissue to the arterial input can be analyzed by a deconvolution method, and the MBF can be estimated directly from the impulse response.[66] The model assumes that the tissue response to arterial input can be described by a linear stationary system that has a single input and a single output.[67] To calculate the impulse response of the myocardium, either a model-dependent analytical method or a model-independent algebraic method is used to inversely convolve the input and output curves.[68] In the process of analysis, the shape of myocardial impulse response is represented by a specific analytical expression, such as the Fermi function, and the equation can be solved by using the discrete form of the convolution equation. Model-independent deconvolution methods have not been widely used so far, probably due to their complexity in the mathematical modeling and calculation.

Compartment model

Compartmental model analysis is another quantitative method of assessing tissue blood flow and has been firstly published by Ketty et al.[69] and Tofts et al.[70] In this model, the distribution and clearance of contrast medium in the myocardial tissue are analyzed from AIF and tissue time-intensity curve. The quantitative analysis of perfusion CMR using a compartment model provides K1 instead of MBF. K1 represents the one-way transfer constant from the LV blood to the myocardium and is a product of MBF and extraction fraction (E) of the perfusion tracer. In order to quantify MBF from K1, the value of E for the gadolinium contrast medium in the myocardial tissue needs to be determined. Recently, Ishida et al. established a relation between E and MBF, by determining total MBF with 2D phase contrast cine CMR of the CS and determining K1 with Patlak plot analysis of first-pass myocardial perfusion CMR.[71]

Utility of quantitative analysis of stress myocardial perfusion CMR

Quantitative assessment of myocardial perfusion CMR is considered to be a more objective approach as compared to visual assessment. Mordini et al. demonstrated that the

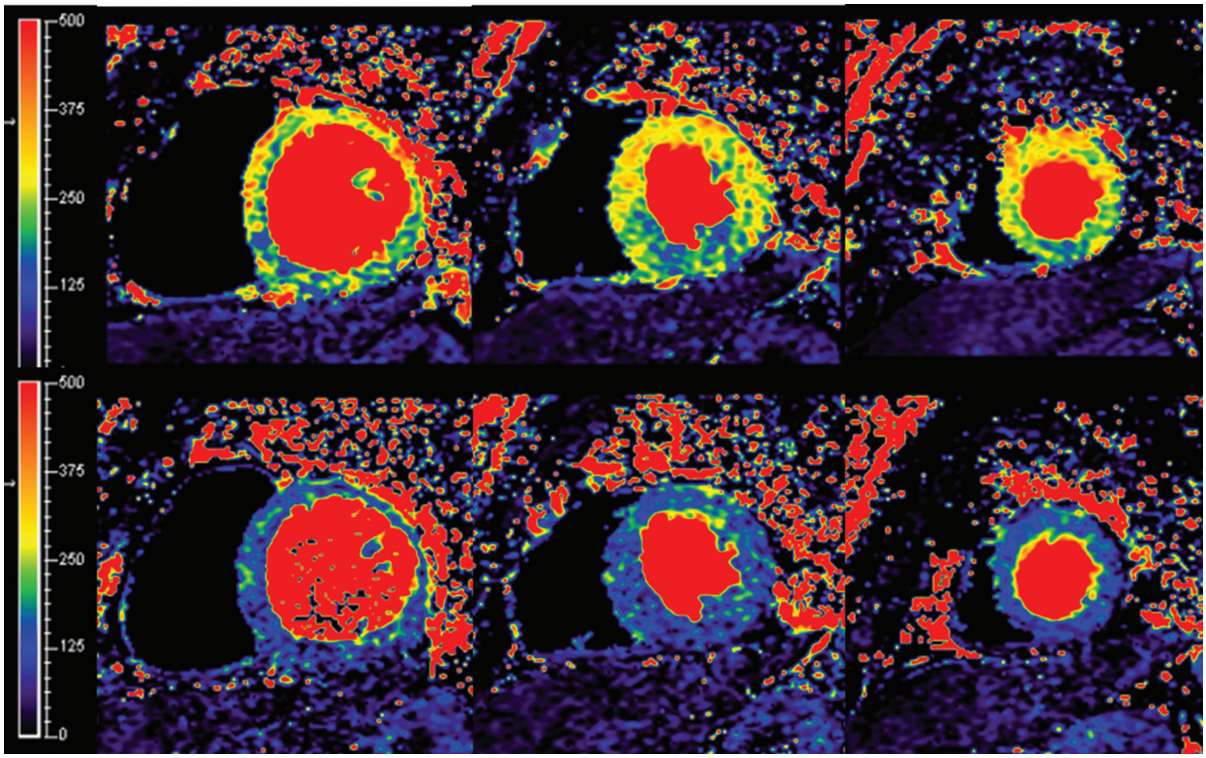

Fig. 7 MBF maps generated from the stress and rest perfusion MRI using dual-sequence approach in a 63-year-old man with the significant stenosis in RCA. ATP stress (upper row) and rest perfusion MRI (bottom row). From the left, LV basal, mid, and apical slices. Stress-induced decrease in MBF was observed in the inferior wall. ATP, adenosine tirphosphate; LV, left ventricular; MBF, myocardial blood flow; RCA, right coronary artery.

absolute MBF quantification can improve the diagnostic performance of perfusion CMR in detecting CAD as compared to visual analysis (AUC 0.92 vs. 0.78, $P < 0.001$).[72] However, in a CE-MARC sub study with larger population, Biglands et al. recently demonstrated that quantitative analysis of perfusion CMR has an excellent diagnostic accuracy (sensitivity of 87.5% and specificity of 84.5%) for detecting flow-limiting CAD but is not superior to qualitative analysis of perfusion CMR (AUC 0.89 vs. 0.88, $P = 0.72$).[73] A recent study by Kotecha et al. used quantitative myocardial perfusion CMR mapping and demonstrated that 3-vessel epicardial CAD showed the greatest reduction in global stress MBF and MPR, while the patients with microvascular disease exhibited moderate reduction.[74] Thus, quantitative analyses may help to differentiate multivessel epicardial CAD and microvascular disease because it is often difficult to distinguish between these two conditions by visual assessment. Quantitative analysis of perfusion CMR is also useful when an inadequate response to vasodilator stress due to caffeine intake, etc. is suspected. Normal MPR determined by quantitative analysis of myocardial perfusion CMR indicates adequate pharmacological stress and is superior to conventional markers, such as SSO, blood pressure, and heart rate.[75]

Quantitative analysis of perfusion CMR may play a critical role in managing patients who frequently complaint of anginal symptoms and only exhibit non-obstructive CAD. According to Rahman's study, absolute quantitative mapping with high-resolution myocardial perfusion CMR has high accuracy in detecting coronary microvascular dysfunction.[76] Kotecha et al. utilized an automated myocardial perfusion mapping and demonstrated that quantitative perfusion mapping can detect microvascular dysfunction, as well as flow-limiting stenosis in epicardial coronary arteries. In addition, this approach allows for the differentiation between microvascular dysfunction and multivessel CAD.[73] This technique has been applied to cardiomyopathy such as hypertrophic cardiomyopathy (HCM)[77] and dilated cardiomyopathy (DCM)[78] to investigate microvascular dysfunction.

Sammut et al. evaluated the prognostic value of visual and quantitative analyses of ischemic burden on perfusion CMR using accepted thresholds of > 2 segments or > 10% myocardium.[79] This study shows that quantitative analysis of myocardial perfusion CMR can provide prognostic benefit in addition to the visual assessment and other established risk factors, and these results data are considered to be important for more widespread clinical acceptance of quantitative perfusion CMR.

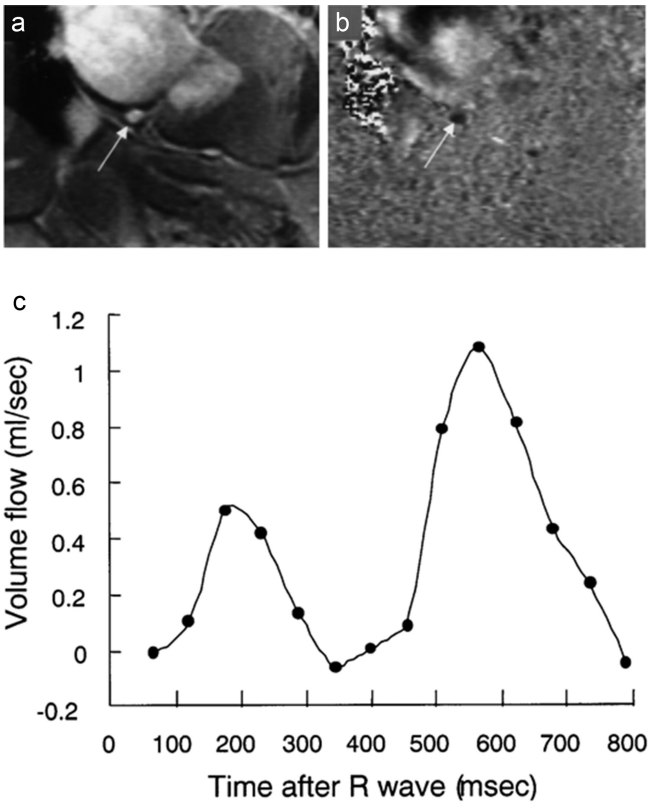

Fig. 8 Breath-hold phase contrast cine MR images obtained in the oblique coronal imaging plane from a 56-year-old man with HCM. **a**, Magnitude image and **b**, phase difference image. The blood flow velocity in the coronary sinus (arrows) is indicated as low signal intensity in **b**. Curve of volume flow in the coronary sinus measured with breath-hold phase contrast cine MR imaging in a 56-year-old man with HCM, **c**. Biphasic blood flow pattern, with a first peak during systole and a second peak during diastole, was observed. Reproduced, with permission, from reference #81. HCM, hypertrophic cardiomyopathy.

Assessment of Global CFR with Phase Contrast Cine MR Imaging of the CS

Measurement of blood flow in the CS by phase-contrast cine CMR is another technique that can quantify blood flow and flow reserve in the entire LV myocardium without using ionizing radiation or gadolinium administration.[17] Up to 96% of the venous blood from the LV myocardium returns to the right atrium via the CS. Therefore, we can estimate of the global MBF by measuring the blood flow in the CS.[80] Blood flow measurement in the CS by 2D phase-contrast cine CMR was initially performed nearly 30 years ago. Flow measurements in the CS in the resting state and during stress provide the assessment of global CFR, and have been used in patients with heart diseases, such as hypertrophic cardiomyopathy[81] and heart failure[82] (Fig. 8). Although 2D ECG-gated phase-contrast pulse sequences were not technically new, the assessment of global CFR by measuring CS flow in patients with known or suspected CAD was not commonly performed until recently. In the past decade, quantitative PET studies have shown excellent prognostic value of global CFR, and the value of CS flow measurements by CMR was recently rediscovered.

As previously explained, visual assessment of stress perfusion CMR may underestimate the severity and extent of myocardial ischemia due to diffuse myocardial hypoperfusion. In a study by Nakamori et al., qualitative perfusion CMR yielded high diagnostic accuracy with AUC of 0.93 in patients with single vessel disease by using FFR as the reference.[83] However, for multivessel disease, perfusion CMR by visual analysis underestimated flow limiting CAD, resulting in the limited AUC of 0.74. When CFR of < 2.0 by the CS flow measurement was considered as abnormal, the AUC was significantly improved to 0.88 in patients with multivessel CAD ($P = 0.002$).

The addition of global CFR measured in the CS to qualitative perfusion CMR can improve risk stratification in patients with CAD. In a study reported by Kato et al. using a 1.5-T MR scanner[84], both CFR < 2.0 by CS flow measurement and ischemia extent > 10% by perfusion CMR were significantly associated with MACE in patients with known CAD (HR: 5.2 and 5.1, respectively). The significant associations were also observed in patients with suspected CAD, with an even higher HR of 14.2 for global CFR (HR: 14.2 and 6.5, respectively). In a report by Indorkar et al. using a 3-T MR scanner,[85] 80 (16%) patients with known or suspected CAD experienced MACE during a median follow-up time of 2.1 years. After adjustment of myocardial ischemia and LGE, the risk of MACE was significantly higher in patients with median CFR < 2.2. Furthermore, the addition of CFR in a risk assessment model including extent of ischemia and size of LGE can significantly improve risk stratification.

The measurement of CS flow can be easily performed as a complemental test in stress CMR examination. As Kato and Indorkar recently demonstrated, global CFR measurement in the CS allows for more accurate prediction of future cardiovascular events in patients with known or suspected CAD, particularly in those without regional myocardial ischemia or LGE who are diagnosed as low risk by conventional stress CMR.

Limitations of Myocardial Perfusion CMR

By combining cine CMR, stress myocardial perfusion CMR, LGE CMR, T1 and T2 mapping, and whole-heart coronary MRA, CMR can provide comprehensive assessments of cardiac function, myocardial ischemia, myocardial scar, more complex tissue characterization of myocardial disorders, and anatomical stenoses in the coronary arteries. Such information is becoming increasingly important for the accurate diagnosis and risk stratification of patients with heart disease. However, the annual number of CMR examinations in Japan was approximately 45000 in 2018, which was less than one-fifth of the 226000 examinations of cardiac nuclear medicine. As

the CMR study protocol becomes more complex, the imaging time and operator dependency increase, making CMR a less profitable imaging test for the hospital. To meet the increasing demand for CMR by cardiac practitioners, it is important to make the reimbursement commensurate with the complex and time-consuming CMR examination, to standardize CMR protocols and to increase training opportunities. In addition to the general contraindications of MR imaging and safety considerations for gadolinium contrast agent, pharmacological stress is contraindicated in patients with 2nd degree or complete atrioventricular (AV) block, low systolic blood pressure, severe hypertension, sinus bradycardia, and active bronchoconstrictive or bronchospastic disease, as previously mentioned. Another limitation is that CMR cannot be performed in patients with pacemakers or implantable cardioverter defibrillators that are not MR-conditional.

Future Perspective

Stress perfusion CMR is a well-validated noninvasive imaging method that allows for the accurate assessment of the presence and extent of myocardial ischemia. In patients with intermediate-to-high likelihood of CAD, stress CMR is an excellent non-invasive imaging test as a gatekeeper for revascularization. As for revascularization, the results of the ISCHEMIA trial have received a great attention.[86] This trial investigated the outcomes of > 5000 patients who had moderate-to-severe ischemia on imaging or exercise ECG and had confirmed coronary stenosis of > 50%, and no left main CDA on coronary CTA. Patients were randomized to either an initial invasive strategy (ICA and revascularization when feasible) or an initial conservative strategy of medical therapy. The investigators found that the initial invasive strategy did not lead to a reduction in events compared to the initial conservative strategy. The results of the Ischemia trial should not be interpreted as revascularization is not necessary in patients with stable CAD or assessment of ischemia is not necessary. However, the traditional perspective of ischemia assessment for determining an indication for revascularization is no longer sufficient to provide optimal therapeutic decision for patients with CAD.

There are several important points when considering the future prospects of CMR in managing patients with stable CAD. First, CMR is a multi-parametric imaging modality that can provide comprehensive assessments of the heart, including cardiac anatomy, global and regional function, myocardial scar, and quantitative T1 and T2 mapping in addition to myocardial perfusion, which would be useful to explain patients' symptoms. Second, the measurement of global MBF and CFR by quantitative analysis of perfusion CMR and flow measurement in the CS permits assessment of microvascular disease and diffuse subclinical atherosclerosis, which will hopefully provide improved prediction of future event risk in patients with suspected or known CAD. Third, inclusion of coronary MRA in comprehensive CMR protocol permits morphological assessment of the proximal coronary arteries, including left main coronary artery, which will substantially enhance the impact of CMR on patient stratification. Further technical advances in quantitative perfusion CMR pulse sequences and analyses, utilization of artificial intelligence to minimize operator and observer dependency of quantitative perfusion CMR, and multi-institutional studies to validate the diagnostic and prognostic value of these new CMR approaches are required.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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