Reduced Myocardial Flow Reserve Is Associated with Subendocardial Infarction and Coronary Stenosis in Patients with Coronary Artery Disease: A Perfusion MRI Study

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Objective: Although the relationship between coronary stenosis and myocardial perfusion is well established, little is known regarding the contribution of subendocardial infarction to this relationship. The purpose of this study was to evaluate the effects of obstructive coronary stenosis and subendocardial infarction on myocardial flow reserve (MFR).

Materials and Methods: Fifty-four patients with suspected and known coronary artery disease (CAD) who underwent perfusion 3T-MRI and invasive angiography were studied. The time-intensity curves of the left ventricle tissue and cavity were fitted by a single-compartment model to compute myocardial blood flow (MBF). Global MFR and regional MFR were calculated by dividing stress MBF by rest MBF. Myocardial infarction lesions were assessed by late gadolinium enhancement. The effects of obstructive coronary stenosis and subendocardial infarction on the regional MFR were evaluated.

Results: Obstructed vessels ($\geq 70\%$ diameter stenosis for main vessels or $\geq 50\%$ for left main) were observed in 65 out of 162 vessels. Further analysis demonstrated that MFR in obstructed vessels was significantly lower than that in non-obstructed vessels [1.48 [the interquartile range (IQR) : 1.31–2.03] vs. 1.84 (IQR: 1.44–2.46), $p=0.01$]. After excluding vessels with transmural infarction ($n=19$), the MFR for vessels with subendocardial infarction ($n=20$) was significantly lower than the MFR for non-infarction vessels ($n=123$) [1.48 (IQR: 1.40–1.79) vs. 1.88 (IQR: 1.41–2.48), $p=0.02$].

Conclusion: Subendocardial infarction in addition to obstructive coronary atherosclerosis might be associated with an impairment of regional MFR in patients with CAD.

Key words Myocardial perfusion imaging · Flow reserve · Magnetic resonance imaging · Perfusion · Coronary artery disease.

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INTRODUCTION

Cardiac magnetic resonance (CMR) is a well-established, noninvasive modality for assessing patients with coronary artery disease (CAD). CMR provides a multitude of pathological information—not only information on anatomy and function—in a single examination using high spatial resolution [1]. A contrast agent can be used to perform late gadolinium enhancement (LGE) and myocardial perfusion imaging (MPI), and LGE with CMR is known to detect myocardial infarction [2]. Infarction burden is associated with reduced cardiac function, myocardial viability, and cardiac events [3]. Additionally, CMR can detect subendocardial infarctions due to its high spatial resolution [4]. The LGE distribution is strongly correlated with myocardial viability and predicts recovery of function after revascularization [5]. The differentiation between transmural and sub-endocardial infarctions by LGE is important for assessing myocardial viability in the setting of chronic ischemic heart disease [6]. Adenosine or an adenosine triphosphate (ATP) stress CMR has been established as an accurate method for the detection of obstructive epicardial CAD [7]. Dynamic CMR perfusion images can estimate the myocardial blood flow (MBF) and the myocardial flow reserve (MFR). The quantification of MBF using MRI could improve the diagnosis of CAD [8] and the evaluation of microcirculatory dysfunctions such as diabetes mellitus [9] and smoking [10].

Although the relationship between coronary stenosis and myocardial perfusion is well established, little is known about the effects of subendocardial infarction on myocardial perfusion. Repeated severe myocardial ischemia due to chronically low MFR could cause myocardial injury in the subendocardial layer supplied by obstructed vessels or diffuse atherosclerosis. Accordingly, there seems to be a significant association between low MFR and the infarction burden in the left ventricle (LV) tissue. In this study we evaluated the effects of obstructive coronary stenosis and subendocardial infarction on the regional MFR.

MATERIALS AND METHODS

Study population

This was a single-center retrospective study that included patients with CAD or suspected CAD between August 2010 and February 2014. Sixty-six patients with suspected or known stable CAD that were referred for both CMR and invasive catheterization within a 1-month period were included in this analysis. Patients were excluded if they had coronary artery bypass grafting, valvular heart disease, or severe renal dysfunction (e-GFR <30 mL/min). Of the 66 patients, seven patients were excluded due to poor images in which a region of interest (ROI)

could not be determined for LV tissue. Additionally, five patients with time intensity curves from the dynamic MRI scans that could not be used to calculate the quantitative MBF were also excluded.

For each of the remaining 54 patients included in the study, information about his or her past medical history, coronary risk factors, and medication use was collected. The study was approved by the Institutional Review Board, and all study procedures were in accordance with institutional guidelines (IRB No. 014-202).

CMR protocol

Cardiac MRI was performed using a 3T whole-body scanner (Achieva Tx; Philips Medical Systems, Best, The Netherlands) with a 32-channel phased-array receiver torso-cardiac coil. A fully flexible dual-source RF transmission system for patient-adaptive local radiofrequency shimming was used. Each MRI sequence was obtained using the electrocardiography (ECG)-triggered and breath-hold technique in three short-axis planes (basal, mid-ventricular, and apical) for dynamic perfusion. Scanning was repeated every two cardiac cycles with 160-ms temporal resolution. Gd-DTPA (Magnevist, Bayer, Wayne, NJ, USA) was administered at 0.03 mmol/kg with a flow rate of 4.0 mL/s, followed by a 20 mL saline flush at 4.0 mL/s. The patients were instructed to hold their breath for as long as possible and take shallow breaths thereafter. Dynamic perfusion MRI was performed 3 min after ATP infusion (160 µg/kg/min) to induce stress. MRI was performed using the turbo field-echo technique with saturation recovery (SR) magnetization preparation under the following conditions: repetition time/echo time (TR/TE) of 4.0/1.9 ms; flip angle of 18; slice thickness of 8 mm; field of view (FOV) of 380×380 mm; matrix of 224×224; SR delay time of 200 ms; and sensitivity encoding parallel imaging (SENSE) factor of 2 [11]. The perfusion sequence was initiated concurrently with Gd-DTPA administration and obtained during the diastolic phase using the ECG-triggering.

After performing MPI under stress and at rest additional Gd-DTPA was administered up to a total concentration of 0.1 mmol/kg for LGE, which was then performed approximately 10 min after the additional Gd-DTPA. An inversion-recovery-prepared fast field echo pulse sequence was used to obtain LGE images for the localization of the infarct region in the short axis. The imaging parameters for LGE were as follows: slice thickness of 5 mm; FOV of 380×380 mm; matrix size of 256×256 (512×512 reconstructed matrix); TR/TE of 3.0 ms/0.96 ms; flip angle of 10°; and number of signals averaged (NSA) of 1. The inversion time to nullify the signal from the normal myocardium was adjusted for each patient, and the typical inversion time was 250–290 ms.

Analysis of CMR

The MBF quantifications and left ventricular ejection fraction (LVEF) calculations were performed by an investigator (M.N.) who was blinded to the results of all other investigations. To compute a semi-quantitative summed LGE score, we used a standard 16-segment (after subtracting the apical cap of the 17-segment model), 5-point scoring system: 0=no delayed enhancement (0% transmural); 1=1–24% transmural; 2=25–49% transmural; 3=50–74% transmural; and 4=75–100% transmural [12]. Lesions with a score of 0–2 were defined as sub-endocardial infarctions and lesions with a score of 3–4 were defined as transmural infarctions [6]. Two physicians (Y.K. and M.N.) independently evaluated the LGE images, and discordant interpretations were evaluated by a third observer (N.M.).

Commercially available software was used to estimate left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and LVEF (the Extended MR WorkSpace; ver. 2.6.3.4; Philips Medical Systems). Trabeculated and papillary muscles were excluded from the volume measurements. The LVEDV index (LVEDVI) and the LVESV index (LVESVI) were calculated as LVEDV/body surface area (BSA) and LVESV/BSA, respectively. The MBF and MFR were quantified using dedicated software with high inter-observer reproducibility as previously described [11]. For accurate quantification of the MBF by myocardial first-pass perfusion, a relationship between the signal and the concentration of the contrast agent was assumed from a phantom study as described previously [11]. Global and regional MFR values were calculated by dividing the stress MBF value by the rest MBF value. The territory of coronary arteries was assigned to each of the 17 myocardial segments by the American Heart Association [13].

Angiographic assessment

All patients underwent coronary angiography using the standard technique. Coronary stenosis was assessed by a cardiologist blinded to the CMR results following invasive angiography (M.O. or T.A.). The percent luminal narrowing of the stenosed arterial segment and the adjacent reference segments were evaluated at end diastole. Coronary vessels were grouped according to their most severe stenosis into the following categories: angiographically normal vessels (<50% stenosis), non-obstructive CAD (50–69% stenosis), and obstructive CAD ($\geq 70\%$ stenosis in the native proximal to mid-left anterior descending (LAD), proximal to mid-left circumflex, or proximal to distal right coronary arteries and $\geq 50\%$ in the left main coronary artery]. To quantify the extent and severity of CAD on a per-patient level, we used the Duke CAD prognostic index integrating the number of affected vessels and the location of disease with $\geq 50\%$ stenosis [14]. For the comparison of MFR values between groups, the Leaman score [15] and the Pryor risk score [16] were

also calculated as previously described.

Statistical analysis

Continuous variables are presented as medians with the inter-quartile range (IQR). Differences between groups were evaluated using the Wilcoxon rank sum test followed by the Steel-Dwass test for continuous data. Categorical variables are presented as absolute numbers with percentages. The Mann-Whitney U-test or Fisher's exact test was used for intra-group comparisons of dichotomous variables as appropriate. A linear regression analysis was performed to examine the association between the MFR and the Leaman, Duke, and Pryor scores. A p-value <0.05 was considered significant. Statistical calculations were carried out using SAS software (JMP ver. 13.0, SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. The patients with CAD had significantly higher frequencies of dyslipidemia and aspirin intake compared to the patients without CAD. The Leaman score ($p < 0.0001$) and Duke score ($p < 0.0001$) were significantly higher in the patients with CAD compared to those without CAD. The global MFR was negatively correlated with the Leaman score ($R = -0.27$, $p = 0.04$). Among the 54 patients, 17 (31.5%) had at least one LGE lesion. MRI parameters including LVEF, LGE score, rest MBF, stress MBF and MFR showed no significant differences between the patients with and without significant stenosis (Table 2). A negative correlation was found between MFR and LGE score ($R = -0.24$, $p = 0.0026$).

Per-vessel analysis

Significant stenosis was observed in 65 of 162 vessels (40.1%). The per-vessel analysis demonstrated that the regional MFR of the obstructed vessels was significantly lower than that of the non-obstructive vessels: 1.48 (IQR 1.31–2.03) vs. 1.84 (IQR 1.44–2.46; $p = 0.01$) (Table 3). However, the regional MFR of normal vessels was not significantly different from the MFR in patients with non-obstructive CAD [1.81 (IQR 2.46–1.47) vs. 1.82 (IQR 2.35–1.36), $p = 0.72$]. The at-rest MBF was comparable across the entire spectrum of stenosis severity.

Correlation between MFR and LGE

The regional MFR in an LGE-positive region ($n = 39$) was lower than the regional MFR of an LGE-negative region ($n = 123$) [1.41 (IQR 1.29–2.58) vs. 1.88 (IQR 1.41–2.48), $p < 0.0001$]. After excluding vessels with transmural infarction ($n = 19$), the per-vessel MFR in the subendocardial infarction group ($n = 20$) was significantly lower than that in the non-infarction group ($n = 123$)

[1.48 (IQR 1.40–1.79) vs. 1.88 (IQR 1.41–2.48), $p=0.046$] (Fig. 1). A representative case is shown in Fig. 2.

DISCUSSION

This study revealed several important findings. First, on a per-

Table 1. Predictors of patients with significant coronary artery disease

Patient characteristics	All (n=54)	CAD (+) (n=36)	CAD (–) (n=18)	p-value
Age, yrs	69.0 (64–73)	69.5 (63.3–73.0)	68.5 (64.8–73.3)	0.96
Male	31 (57.4)	20 (55.6)	11 (61.1)	0.78
BMI, kg/m ²	23.7 (21.9–26.4)	23.2 (21.0–26.0)	25.3 (22.2–28.5)	0.15
Hypertension	37 (68.5)	25 (69.4)	12 (66.7)	1.00
Diabetes	25 (46.3)	18 (50.0)	7 (38.9)	0.57
Dyslipidemia	42 (77.8)	32 (88.9)	10 (55.6)	0.01
Family history of CAD	7 (13.0)	4 (11.1)	3 (16.7)	0.67
Smoker	32 (59.3)	22 (61.1)	10 (55.6)	0.77
Prior myocardial infarction	9 (16.7)	5 (13.9)	4 (22.2)	0.46
Prior PCI	11 (20.4)	7 (19.4)	4 (22.2)	1.00
Medications				
Angiotensin inhibitors	28 (51.9)	18 (50.0)	10 (55.6)	0.78
β -blocker	35 (64.8)	26 (72.2)	9 (50.0)	0.14
Calcium channel blocker	29 (53.7)	20 (55.6)	9 (50.0)	0.78
Statin	42 (77.8)	33 (91.7)	9 (50.0)	0.54
Aspirin	47 (87.0)	34 (94.4)	13 (72.2)	0.03
Insulin	3 (5.8)	3 (8.8)	0 (0.0)	0.54
Nitrates	15 (27.8)	13 (36.1)	2 (11.1)	0.06
Angiographic severity				
Leaman score	2.8 (0.0–9.5)	5.5 (2.5–11.5)	0.0 (0.0–1.0)	<0.0001
Duke score	23 (23–37)	23 (23–37)	23 (0–23)	<0.0001
Pretest probability				
Pryor score	0.7 (0.3–0.9)	0.7 (0.3–0.9)	0.7 (0.4–0.9)	0.62

Data are median (interquartile range) or number (%). BMI: body mass index, CAD: coronary artery disease, PCI: percutaneous coronary intervention

Table 2. MRI parameters in the patients with and without significant stenosis

	All (n=54)	CAD (+) (n=36)	CAD (–) (n=18)	p-value
LVEF	65.2 (57.7–71.7)	67.0 (62.1–72.1)	60.1 (50.5–70.1)	0.13
LVEDV, mL	85.9 (67.0–111.8)	79.7 (66.9–99.8)	94.6 (66.4–128.8)	0.26
LVEDVI, mL/m ²	53 (43.3–65.7)	51.6 (43.1–60.7)	56.8 (42.6–74.4)	0.52
LVESV, mL	26.2 (22.7–44.0)	25.9 (22.2–34.2)	32.8 (23.7–72.4)	0.14
LVESVI, mL/m ²	16.4 (14.1–29.6)	16.4 (13.8–23.7)	19.8 (14.0–37.3)	0.24
LGE score	0.0 (0.0–6.0)	0.0 (0.0–7.8)	0.0 (0.0–6.3)	0.63
Global MBF at rest, mL/min/g	0.96 (0.71–1.16)	1.00 (0.79–1.13)	0.93 (0.68–1.18)	0.81
Global MBF at stress, mL/min/g	1.64 (1.23–2.25)	1.58 (1.20–2.25)	1.68 (1.35–2.33)	0.46
Global MFR	1.59 (1.35–2.27)	1.53 (1.31–2.21)	1.95 (1.45–2.47)	0.21

Data are median (interquartile range). CAD: coronary artery disease, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVEDVI: left ventricular end-diastolic volume index, LVESV: left ventricular end-systolic volume, LVESVI: left ventricular end-systolic volume index, LGE: late gadolinium enhancement, MBF: myocardial blood flow, MFR: myocardial flow reserve

Table 3. Per-vessel analysis between patients with and without stenosis

	Stenosis (+) (n=65)	Stenosis (–) (n=97)	p-value
MBF at rest, mL/min/g	1.01 (0.79–1.17)	0.97 (0.70–1.19)	0.88
MBF at stress, mL/min/g	1.57 (1.18–2.08)	1.79 (1.31–2.35)	0.08
MFR	1.48 (1.31–2.03)	1.84 (1.44–2.46)	0.01

MBF: myocardial blood flow, MFR: myocardial flow reserve

Fig. 1. Correlation between MFR and the LGE scores. MFR values are plotted by the region without LGE, subendocardial, and transmural LGE scores. MFR: myocardial flow reserve, LGE: late gadolinium enhancement.

vessel basis, we observed a statistically significant but clinically modest relationship between the degree of stenosis severity and its downstream effect on coronary artery physiology as assessed by regional MFR. Second, there appears to be widespread variability in regional stress MBF and MFR values, even in coronary territories supplied by angiographically normal vessels or those with non-obstructive disease. Third, the regional MFR showed a significant relationship with the extent of transmural and subendocardial infarction observed by LGE.

CMR is a well-established and noninvasive technique in widespread clinical use. Stress MR perfusion provides information about the functional severity of CAD [17]. CMR can also detect the myocardial fibrosis or scar formation with LGE, which can be related to the clinical outcome of CAD [18,19]. In addition, dynamic perfusion MRI has the potential to estimate the MBF from time–intensity curves for the LV tissue and LV cavity using a single-tissue compartment model. In this study we used the Renkin-Crone model to estimate an accurate MBF to calculate MFR from dynamic perfusion MRI [11]. The quantitative MBF using CMR was well correlated to the microsphere measurements in animals [20] and has been validated against PET data [11,21,22]. Slart et al. [23] reported that the combination of myocardial perfusion data derived from PET and functional assessments by MRI was a powerful tool for evaluating the functional integrity of the injured myocardium. Therefore, MRI could provide a comprehensive assessment of the MBF and regional wall motion in relation to simultaneously acquired LGE data.

The quantification of MFR is a reliable method for evaluating the functional severity of CAD and is also influenced by microvascular disease [24]. The MFR is therefore affected by micro-

vascular function even in the absence of underlying obstructive epicardial CAD [25]. Measurements of MBF were acquired to identify patients at increased risk of cardiac death or myocardial infarction who might benefit most from coronary revascularization [26]. Our present results demonstrate a significant but clinically modest relationship between the degree of coronary stenosis severity and the per-vessel MFR. In addition, widespread variability in stress MBF and MFR values was observed, even in non-obstructive territories. These results are in accordance with previous studies using the PET method [25], suggesting that MFR derived from CMR could be used to assess CAD and its downstream effect on coronary artery physiology.

The MFR had a significant relationship with the LGE lesion scores in our analyses. The MFR could be influenced by scarring or fibrosis, which would be reflected in the MR imaging sequence of LGE, as LGE is capable of detecting a broad range of infarctions with or without clinical knowledge of a prior myocardial infarction [27,28]. Several coronary risk factors such as diabetes, dyslipidemia, hypertension and smoking are known to adversely affect microvascular function [29,30], which could have contributed to the widespread variability in stress MBF and MFR even without LGE positive territories.

Study limitations

There are several limitations in this study. First, this patient population was relatively small. In addition, only three short-axis slices were obtained to quantify the MBF. Theoretically, the gap between the slices might miss a perfusion decrease. However, a significant correlation between coronary artery stenosis and the MFR was observed, which is in accordance with previous studies' findings. Since the number of patients was relatively small, we could not assess the effect of coronary risk factors on the variability of MFR in segments without stenosis or LGE lesions. Therefore, further investigation on a larger number of patients is necessary.

Conclusion

The quantification of the regional MFR by 3T-MRI is a feasible and reliable method to assess functional significance in patients with obstructive coronary artery stenosis. The presence of subendocardial infarction in addition to obstructive coronary atherosclerosis might be associated with an impairment of regional MFR in patients with CAD.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Fig. 2. Representative case: a male in his 60s. Angiographic images at the left coronary artery (A) and RCA (B), short-axis (C) and long-horizontal images (D) of LGE, and polar maps of the rest MBF (E), stress MBF (F) and MFR (G) are displayed. Significant stenosis was observed in the proximal LAD (A; red arrow) and the left circumflex artery (A; yellow arrow). There was no significant stenosis in the RCA (B). Cardiac magnetic resonance images showed subendocardial LGE in the LAD territory (C, D; red arrows). The estimated whole MFR was decreased at 1.2. RCA: right coronary artery, MFR: myocardial flow reserve, LGE: late gadolinium enhancement, MBF: myocardial blood flow, LAD: left anterior descending artery.

REFERENCES

- Motwani M, Swoboda PP, Plein S, Greenwood JP. Role of cardiovascular magnetic resonance in the management of patients with stable coronary artery disease. *Heart* 2018;104:888-894.
- Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J* 2005;26:1461-1474.
- Kwon DH, Halley CM, Carrigan TP, Zysek V, Popovic ZB, Setser R, et al. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyper-enhancement cardiac magnetic resonance study. *JACC Cardiovasc Imaging* 2009;2:34-44.
- Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003;361:374-379.
- Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, et al. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation* 2004;110:1535-1541.
- Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445-1453.
- Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;379:453-460.
- Mordini FE, Haddad T, Hsu LY, Kellman P, Lowrey TB, Aletras AH, et al. Diagnostic accuracy of stress perfusion CMR in comparison with quantitative coronary angiography: fully quantitative, semiquantitative, and qualitative assessment. *JACC Cardiovasc Imaging* 2014;7:14-22.
- Larghat AM, Swoboda PP, Biglands JD, Kearney MT, Greenwood JP, Plein

- S. The microvascular effects of insulin resistance and diabetes on cardiac structure, function, and perfusion: a cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2014;15:1368-1376.
10. Fairbairn TA, Motwani M, Mather AN, Biglands JD, Larghat AM, Radjenovic A, et al. Cardiac MR imaging to measure myocardial blood flow response to the cold pressor test in healthy smokers and nonsmokers. *Radiology* 2014;270:82-90.
11. Tomiyama Y, Manabe O, Oyama-Manabe N, Naya M, Sugimori H, Hirata K, et al. Quantification of myocardial blood flow with dynamic perfusion 3.0 Tesla MRI: validation with (15) O-water PET. *J Magn Reson Imaging* 2015;42:754-762.
12. Bratis K, Henningsson M, Grigoratos C, Omodarme MD, Chasapides K, Botnar R, et al. Clinical evaluation of three-dimensional late enhancement MRI. *J Magn Reson Imaging* 2017;45:1675-1683.
13. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539-542.
14. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;118:81-90.
15. Mark DB, Nelson CL, Califf RM, Harrell FE Jr, Lee KL, Jones RH, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation* 1994;89:2015-2025.
16. Pryor DB, Harrell FE Jr, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. *Am J Med* 1983;75:771-780.
17. Vincenti G, Masci PG, Monney P, Rutz T, Hugelshofer S, Gaxherri M, et al. Stress perfusion CMR in patients with known and suspected CAD: prognostic value and optimal ischemic threshold for revascularization. *JACC Cardiovasc Imaging* 2017;10:526-537.
18. Catalano O, Moro G, Perotti M, Frascaroli M, Ceresa M, Antonaci S, et al. Late gadolinium enhancement by cardiovascular magnetic resonance is complementary to left ventricle ejection fraction in predicting prognosis of patients with stable coronary artery disease. *J Cardiovasc Magn Reson* 2012;14:29.
19. Klein C, Gebker R, Kokocinski T, Dreyse S, Schnackenburg B, Fleck E, et al. Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. *J Cardiovasc Magn Reson* 2008;10:45.
20. Hsu LY, Groves DW, Aletras AH, Kellman P, Arai AE. A quantitative pixel-wise measurement of myocardial blood flow by contrast-enhanced first-pass CMR perfusion imaging: microsphere validation in dogs and feasibility study in humans. *JACC Cardiovasc Imaging* 2012;5:154-166.
21. Morton G, Chiribiri A, Ishida M, Hussain ST, Schuster A, Indermuehle A, et al. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. *J Am Coll Cardiol* 2012;60:1546-1555.
22. Fritz-Hansen T, Hove JD, Kofoed KF, Kelbaek H, Larsson HB. Quantification of MRI measured myocardial perfusion reserve in healthy humans: a comparison with positron emission tomography. *J Magn Reson Imaging* 2008;27:818-824.
23. Slart RH, Glauche J, Golestani R, Zeebregts CJ, Jansen JW, Dierckx RA, et al. PET and MRI for the evaluation of regional myocardial perfusion and wall thickening after myocardial infarction. *Eur J Nucl Med Mol Imaging* 2012;39:1065-1069.
24. Manabe O, Naya M, Tamaki N. Feasibility of PET for the management of coronary artery disease: comparison between CFR and FFR. *J Cardiol* 2017;70:135-140.
25. Naya M, Murthy VL, Taqueti VR, Foster CR, Klein J, Garber M, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. *J Nucl Med* 2014;55:248-255.
26. Gewirtz H. PET measurements of myocardial blood flow post myocardial infarction: relationship to invasive and cardiac magnetic resonance studies and potential clinical applications. *J Nucl Cardiol* 2017;24:1883-1892.
27. Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, et al. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circulation* 2009;120:1390-1400.
28. Van Herck PL, Paelinck BP, Haine SE, Claeys MJ, Miljoen H, Bosmans JM, et al. Impaired coronary flow reserve after a recent myocardial infarction: correlation with infarct size and extent of microvascular obstruction. *Int J Cardiol* 2013;167:351-356.
29. Tsukamoto T, Morita K, Naya M, Katoh C, Inubushi M, Kuge Y, et al. Myocardial flow reserve is influenced by both coronary artery stenosis severity and coronary risk factors in patients with suspected coronary artery disease. *Eur J Nucl Med Mol Imaging* 2006;33:1150-1156.
30. Manabe O, Naya M, Aikawa T, Obara M, Magota K, Kroenke M, et al. PET/CT scanning with 3D acquisition is feasible for quantifying myocardial blood flow when diagnosing coronary artery disease. *EJNMMI Res* 2017;7:52.