Original Article

Coronary microvascular dysfunction and myocardial area at risk assessed by cadmium zinc telluride single photon emission computed tomography after primary percutaneous coronary intervention in acute myocardial infarction patients

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Background: A high proportion of coronary microvascular dysfunction (CMD) has been observed in patients with acute myocardial infarction (AMI) who have received primary percutaneous coronary intervention (PCI), which may affect their prognosis. This study used cadmium zinc telluride (CZT) single photon emission computed tomography (SPECT) to evaluate the prevalence and characteristics of CMD and myocardial area at risk (AAR) in AMI patients who had undergone primary PCI.

Methods: We conducted a single-center cross-sectional retrospective study at TEDA International Cardiovascular Hospital from September 2021 to June 2022. A total of 83 patients received primary PCI for AMI. Subsequently, a rest/stress dynamic and routine gated myocardial perfusion imaging (MPI) were performed 1 week after PCI. The CMD group was defined as having a residual stenosis of infarct-related artery (IRA) <50% and myocardial flow reserve (MFR) <2.0 in this corresponding territory, whereas MFR ≥2.0 of IRA pertained to the normal control group. Rest-AAR of infarction (%) and stress-AAR (%) were expressed by the percentage of measured rest-defect-size and stress-defect-size in the left ventricular area, respectively. Logistic regression analyses were performed to identify significant predictors of CMD.

Results: A total of 53 patients with a mean age of 57.06±11.99 years were recruited, of whom 81.1% were ST-segment elevation myocardial infarction (STEMI). The proportion of patients with CMD was 79.2% (42/53). The time of pain to SPECT imaging was 7.50±1.27 days in the CMD group and 7.45±1.86 days among controls. CMD patients had a higher body mass index (BMI) than controls (26.48±3.26 *vs.* 24.36±2.73 kg/m^2,

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P=0.053), and a higher proportion of STEMI, thrombolysis in myocardial infarction (TIMI) 0 grade of IRA prior PCI than controls (88.1% *vs.* 54.5%, P=0.011; 61.9% *vs.* 18.2%, P=0.004, respectively). No significant difference was identified in the rest-myocardial blood flow (MBF) of IRA between the 2 groups, whereas the stress-MBF and MFR of IRA, rest-AAR, and stress-AAR in the CMD group were remarkably lowered. Higher BMI [odds ratio (OR): 1.332, 95% confidence interval (CI): 1.008–1.760, P=0.044] and stress-AAR (OR: 1.994, 95% CI: 1.122–3.543, P=0.019) were used as independent predictors of CMD occurrence.

Conclusions: The prevalence of CMD is high in AMI patients who received primary PCI. Each 1 kg/m^2 increase in BMI was associated with a 1.3-fold increase in CMD risk. A 5% increase in stress-AAR was associated with a nearly 2-fold increase in CMD risk. Increased BMI and stress-AAR predicts decreased coronary reserve function.

Keywords: Coronary microvascular dysfunction (CMD); myocardial flow reserve (MFR); acute myocardial infarction (AMI); percutaneous coronary intervention (PCI); single photon emission computed tomography (SPECT)

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Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI) (1,2). The goal is to open the infarct-related arteries (IRA) early and effectively to achieve reperfusion for tissue rescue. However, coronary microvascular dysfunction (CMD) such as slow flow or no reflow occurs in 5–50% of patients when opening the IRA (1-3). Previous studies have shown that even when thrombolysis in myocardial infarction (TIMI) test flow has reached grade 3 after primary PCI, a large proportion of patients still fail to achieve effective myocardial perfusion. The benefit of primary PCI for patients is significantly diminished by the widespread CMD, which is a significant cause of early complications, heart failure, and death (1-6).

It is estimated that nearly half of acute myocardial infarction (AMI) patients undergoing primary PCI may exhibit CMD, which reflects reduced coronary reserve and is associated with poorer long-term prognosis (1,2). Positron emission tomography/computed tomography (PET/CT)-based myocardial perfusion imaging (MPI) can determine myocardial blood flow (MBF) at rest and under stress, thereby calculating myocardial flow reserve (MFR) given by the ratio of stress-MBF to rest-MBF. PET is considered the gold standard for the noninvasive measurement of MFR; however, it is not widely applicable for clinical practice due to limitations in equipment and radiopharmaceuticals. Cardiac-specific single photon emission computed tomography (SPECT), exploiting a semi-conductor detector termed cadmium zinc telluride (CZT), is a technique that exhibits high sensitivity and good spatial and temporal resolution for the quantitative measurement of MBF. CZT-SPECT-based MFR correlates well with PET/CT findings (7). In this study, CZT-SPECT was used to assess the MFR of IRA to diagnose CMD 1 week after PCI for AMI, whether the extent of the myocardium at risk and CZT-SPECT is safe and feasible for diagnosing CMD in AMI patients, and we analyzed the risk factors for CMD, which can facilitate improving prognosis. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1260/rc).

Methods

Study population

This was a single-center cross-sectional retrospective analysis of consecutive AMI patients who had received primary PCI at TEDA International Cardiovascular Hospital from September 2021 to June 2022. *Figure 1* illustrates the flow of participants.

The inclusion criteria were as follows: patients (I) aged between 18 and 79 years; (II) who had received primary PCI successfully and the residual stenosis of IRA <50% (including the side branches which vessel diameter ≥2.0 mm); (III) who had received SPECT 1 week after onset of pain.

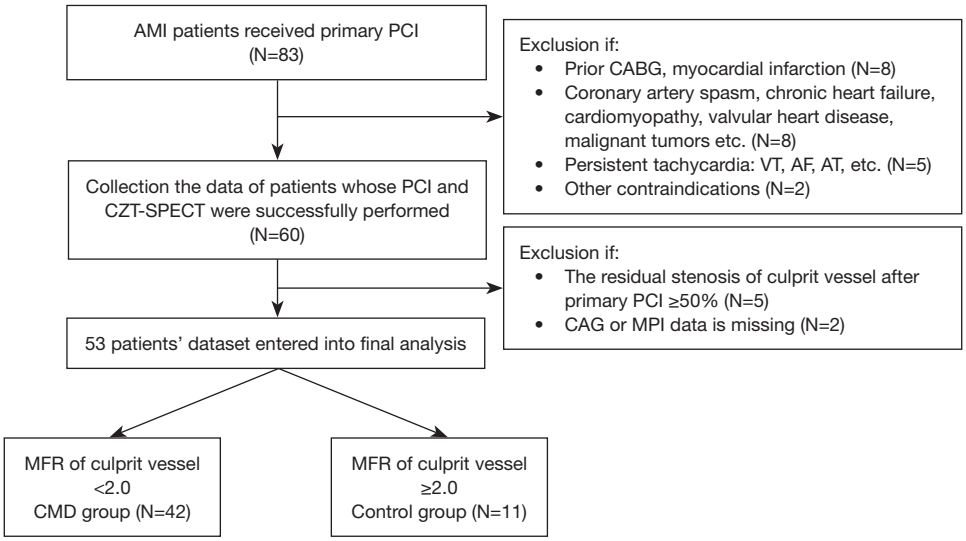

Figure 1 Inclusion flow chart. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; VT, ventricular tachycardia; AF, atrial fibrillation; AT, atrial tachycardia; CZT, cadmium zinc telluride; SPECT, single photon emission computed tomography; CAG, coronary angiography; MPI, myocardial perfusion imaging; MFR, myocardial flow reserve; CMD, coronary microvascular dysfunction.

The exclusion criteria were as follows: patients with (I) contraindications to adenosine; prior coronary artery bypass grafting (CABG); (II) old myocardial infarction; coronary artery spasm, chronic heart failure, cardiomyopathy, valvular heart disease, malignant tumors; and (III) persistent ventricular tachycardia, atrial fibrillation, atrial flutter, or atrial tachycardia.

The following clinical data were collected: body mass index (BMI), past medical history, smoking history, cardiac troponin I (cTnI; initial and peak values), pain to reperfusion (h), coronary angiography (CAG) parameters, TIMI of IRA prior and post primary PCI, SPECT parameters of IRA: rest-MBF, stress-MBF and MFR, summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS), rest-defect-size (cm^2), stress-defect-size (cm^2), rest-area at risk (AAR) of infarction (%), stress-AAR (%), rest-left ventricular ejection fraction (LVEF) (%), stress-LVEF (%); electrocardiographic (ECG) parameters 1 hour after PCI.

CZT-SPECT: imaging equipment, methods, and image analysis

All patients underwent SPECT to evaluate the MFR and AAR 1 week after primary PCI. The imaging device was equipped with a CZT detector with 19 pinhole collimators (NM530c; GE Healthcare, Milwaukee, WI, USA). The imaging agent applied was ^{99m}Tc-methoxy isobutyl isonitrile (MIBI), which was provided by Beijing Senke Pharmaceutical Co., Ltd. (Beijing, China) or Atomic Hi-Tech Tianjin Pharmaceutical Co., Ltd. (Beijing, China).

Imaging was performed using the 1-day method: Adenosine load imaging was performed after resting. MyoFlowQ 1.0.2 (Beijing Larkcloud Biomedical, Beijing, China) workstation was used to quantify perfusion and functional parameters, with which rest-MBF, stress-MBF, MBF, SSS, SRS, SDS, rest-defect-size (cm^2), stress-defect-size (cm^2), rest-AAR (%), stress-AAR (%), rest-LVEF (%), and stress-LVEF (%) were calculated. The dynamic list mode data were transferred to MyoFlowQ workstation and automatically re-binned into 18 frames consisting of 10×10, 5×20, 2×60, and 1×280 s frames. The regions of interest (ROIs) for input function and myocardial radioactivity sampling were automatically or manually set to obtain the dynamic curve and fitting curve of the left ventricular blood pool and left ventricular myocardium, and to calculate the rest-MBF and stress-MBF of the left ventricle (LV). MFR was calculated by the ratio of stress-MBF to rest-MBF. Myocardial perfusion defect on SPECT images were used to delineate the AAR as previously described (8-10).

The stress blood flow of vasodilating drugs was not required to be corrected, whereas the rest blood flow measurement

method was corrected according to RPP (the product of heart rate and blood pressure, i.e., the effect of the heart at rest, when RPP ≥1,000, the coefficient of 10,000/RPP was used for correction). For specific methods, please refer to the references (8-10). All patients discontinued vasoactive drugs, calcium antagonists, dipyridamole, adenosines, theophylline, as well as tea, coffee, or caffeinated beverages at least 24 hours before the test. Then, 2 fully blinded operators, using an offline dedicated workstation, performed all measurements. In order to avoid bias, manual intervention was performed only when the automatic LV alignment was incorrect, as assessed by 2 nuclear medicine physicians. In case of conflicting opinions, a third nuclear medicine physician was invited for an independent evaluation. Each physician had been actively employed in this field more than 10 years and could perform independent assessments.

Diagnostic criteria: CMD, AMI, rest-AAR, stress-AAR

The diagnostic criteria of the CMD group were defined as follows: the residual stenosis of IRA <50% (including the side branches which vessel diameter ≥2.0 mm) and MFR <2.0 in this corresponding territory was considered to microvascular dysfunction (1,11); MFR ≥2.0 of IRA pertained to the normal control group.

Patients were diagnosed with AMI as previously described (1,2). AMI was divided into STEMI and NSTEMI, depending on the existence of ST-segment elevation in 2 contiguous leads on the presenting ECG. Our team implemented the following strategies in STEMI: primary PCI should be done within 90 minutes; the patients with NSTEMI recruited were all high-risk, for whom urgent CAG (<2 h) and primary PCI was recommended (12). Rest-AAR and stress-AAR were expressed by the percentage of measured rest-defect-size and stress-defect-size in the left ventricular area, respectively.

Statistical analysis

The software SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Shapiro-Wilk test was utilized to confirm the normal distribution of data. Continuous data were expressed as mean ± standard deviation (SD) or medium values; independent sample *t*-test or Mann-Whitney method was used to compare the 2 groups. Categorical data were expressed as a percentage, and comparison between groups was performed by χ^2 test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify significant predictors of CMD. A P value <0.05 (2-sided) was considered statistically significant.

Ethical statement

This study was approved by Institutional Ethics Board of TEDA International Cardiovascular Hospital, China (No. 2022-1118-6), and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (as was revised in 2013). All patients provided informed consent.

Results

Comparison of baseline characteristics (Tables 1,2)

A flow diagram of the identification, inclusion, and exclusion of participants is shown in *Figure 1*. A total of 83 patients were initially identified. After exclusion, 53 patients with a mean age of 57.06±11.99 years were finally recruited, of whom 79.2% (42/53) were male, 81.1% were STEMI patients, and 79.2% (42/53) showed evidence of CMD. No significant difference was identified in age, sex, hypertension, diabetes, smoking history, emergency cTnI value and peak cTnI, myocardial infarction area, time of pain to reperfusion, proportion of complete revascularization, TIMI grade of IRA post PCI, and first ECG parameter post PCI between the CMD group and non-CMD group. However, peak cTnI, the percentage of Q-wave and ST-segment elevation in the first ECG after PCI was slightly higher in patients with CMD. CMD patients had a higher BMI than controls (26.48±3.26 *vs.* 24.36±2.73, P=0.053), and a higher proportion of STEMI patients (88.1% *vs.* 54.5%, P=0.011) and TIMI 0 grade of IRA prior to PCI (61.9% *vs.* 18.2%, P=0.004).

Comparison of SPECT imaging parameters between CMD patients and controls (Table 3)

The duration from chest pain onset to SPECT imaging was 7.50±1.27 days in the CMD group and 7.45±1.86 days among controls. No significant difference was identified in the rest-MBF of IRA between the 2 groups, whereas the stress-MBF and MFR of IRA in the CMD group were remarkably lowered [CMD *vs.* control: 0.80±0.31 *vs.* 1.93±0.44 mL/g/min, 1.16±0.46 *vs.* 2.49±0.45, respectively

Table 1 Baseline characteristics of CMD and control patients

Variable	Overall (N=53, 100%)	CMD group (N=42, 79.2%)	Control group (N=11, 20.8%)	t or χ^2	P value
Age (years)	57.06±11.99	55.85±11.93	61.55±11.67	–1.411	0.164
Male	42 (79.2)	33 (78.6)	9 (81.8)	0.056	0.813
Hypertension	15 (28.3)	12 (28.6)	3 (27.3)	0.017	0.897
Diabetes mellitus	17 (32.1)	15 (35.7)	2 (18.2)	1.335	0.248
Smoking	32 (60.4)	26 (61.9)	6 (54.5)	0.288	0.591
BMI (kg/m^2)	26.04±3.25	26.48±3.26	24.36±2.73	1.979	0.053
STEMI	43 (81.1)	37 (88.1)	6 (54.5)	6.410	0.011

Values were given as number of patients (%) or mean ± SD. CMD, coronary microvascular dysfunction; BMI, body mass index; STEMI, ST-elevation myocardial infarction; SD, standard deviation.

Table 2 Coronary angiography and electrocardiogram characteristics of CMD and control group

Variable	CMD group (N=42)	Control group (N=11)	t or χ^2	P value
Pain to reperfusion (h)	3.70±4.55	2.64±1.68	0.757	0.453
cTnI in emergency (ng/mL)	3.28±6.92	3.49±4.47	–0.098	0.922
Peak of cTnI (pg/mL)	15,323.95±7,887.12	11,801.27±8,948.84	1.283	0.205
Myocardial infarction area			0.287	0.866
Anterior	20 (47.6)	6 (54.5)		
Inferior	19 (45.2)	4 (36.4)		
Lateral	3 (7.1)	1 (9.1)		
TIMI of IRA prior PCI			13.44	0.004
TIMI 0	26 (61.9)	2 (18.2)		
TIMI 1	3 (7.1)	0 (0)		
TIMI 2	4 (9.5)	6 (54.5)		
TIMI 3	9 (21.4)	3 (27.3)		
TIMI of IRA post PCI			1.446	0.229
TIMI 0	0 (0)	0 (0)		
TIMI 1	0 (0)	0 (0)		
TIMI 2	5 (11.9)	0 (0)		
TIMI 3	37 (88.1)	11 (100)		
Proportion of complete revascularization	21 (50.0)	7 (63.6)	1.879	0.391
First electrocardiogram post PCI				
Q wave	29 (69.0)	5 (45.5)	2.110	0.146
ST-segment elevated ≥0.05 mV	33 (78.6)	6 (54.5)	2.589	0.108
T wave inversion	34 (81.0)	8 (72.7)	0.359	0.549

Values were given as number of patients (%) or mean ± SD. CMD, coronary microvascular dysfunction; cTnI, cardiac troponin I; TIMI, thrombolysis in myocardial infarction; IRA, infarct-related artery; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 3 Comparison of SPECT imaging parameters between CMD and control group

Variable	CMD group (N=42)	Control group (N=11)	*t* or z*	P value
Pain to SPECT imaging (d)	7.50±1.27	7.45±1.86	0.095	0.924
Rest-MBF of IRA (mL/g/min)	0.72±0.18	0.785±0.15	–1.116	0.270
Stress-MBF of IRA (mL/g/min)	0.80±0.31	1.93±0.44	–9.688	<0.001
MFR of IRA	1.16±0.46	2.49±0.45	–8.644	<0.001
SSS score	11.0 (6.0, 18.8)	2 (1.8, 8.2)	2.875	0.004
SRS score	4.0 (1.0, 10.0)	1.5 (0.0, 3.3)	1.984	0.047
SDS score	6.0 (2.0, 8.0)	2.0 (0.0, 5.0)	2.090	0.037
Rest-defect-size (cm^2)	6.0 (1.0, 25.0)	1.0 (0.0, 4.3)	2.091	0.037
Stress-defect-size (cm^2)	16.0 (8.0, 28.0)	3.0 (0.0, 11.3)	2.993	0.003
Rest-AAR (%)	6.0 (1.0, 20.3)	1.0 (0.0, 4.0)	2.197	0.028
Stress-AAR (%)	21.5 (9.8, 35.3)	3.0 (0.0, 15.0)	3.326	0.001
Rest-LVEF (%)	50.72±9.67	60.56±6.78	–2.880	0.006
Stress-LVEF (%)	49.08±9.68	60.22±6.99	–3.251	0.002

Values were given as mean ± SD or medium values (P25, P75). **t*, grouped comparison using student *t*-test; z, grouped comparison using Mann-Whitney method. SPECT, single photon emission computed tomography; CMD, coronary microvascular dysfunction; MBF, myocardial blood flow; d, days; IRA, infarct-related artery; MFR, myocardial flow reserve; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; AAR, area at risk; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 4 Multivariate logistic regression analysis for the risk factors of CMD

Variable	β	SE	Waldχ^2	OR (95% CI)	P value
BMI (kg/m^2)	0.287	0.142	4.057	1.332 (1.008–1.760)	0.044
STEMI (yes/no)	–0.510	0.999	0.261	0.601 (0.085–4.252)	0.610
TIMI of IRA prior PCI	–0.202	0.381	0.280	0.817 (0.387–1.726)	0.597
Pain to reperfusion (h)	0.158	0.203	0.610	1.172 (0.787–1.744)	0.435
Stress-AAR (0% as reference)	0.690	0.293	5.539	1.994 (1.122–3.543)	0.019

CMD, coronary microvascular dysfunction; SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; IRA, infarct-related artery; PCI, percutaneous coronary intervention; AAR, area at risk.

(P<0.001)]. Meanwhile, the rest-AAR, stress-AAR, stress-defect-size, and SSS score were more pronouncedly enhanced in the CMD group than in the control group, and the SRS score and SDS score were relatively higher. We also found that the rest-LVEF and stress-LVEF in CMD patients were significantly decreased.

Multivariate logistic regression analysis of CMD-related factors (Table 4)

BMI, STEMI, TIMI of IRA prior to PCI, pain to reperfusion, and stress-AAR were used as input variables for logistic regression. After adjustment of the proportion STEMI, increased BMI [odds ratio (OR): 1.332, 95% confidence interval (CI): 1.008–1.760, P=0.044] and stress-AAR (OR: 1.994, 95% CI: 1.122–3.543, P=0.019) were used as independent predictors of CMD occurrence. Each 1 kg/m^2 increase in BMI was associated with a 1.3-fold increase in CMD risk, and each 5% increase in stress-AAR was associated with a nearly 2-fold increase in CMD risk. Increased BMI and stress-AAR predicts decreased coronary reserve function.

Discussion

AMI is a common life-threatening and serious cardiovascular disease (13,14) for which primary PCI is currently the preferred treatment option (1,2,14). In recent years, the aim has been shortening the door-to-balloon time to open the IRA as early as possible for achieving myocardial horizontal reperfusion, but this is hindered by CMD (1,2). CMD is increasingly recognized to play a crucial role in the pathogenesis of myocardial ischemia, and predicts a poor prognosis (1-5,15-17). A study showed that after successful reperfusion with primary PCI in STEMI patients, the absolute risk of mortality remained 12–18% at 28 days and 53–58% at 5 years (18). Despite the successful revascularization of epicardial coronary artery, actual optimal myocardial reperfusion is difficult to achieve due to CMD. Extensive CMD leads to suboptimal reperfusion, which predicts greater infarct size and increased risk of adverse remodeling (1-4,15,19). Scarsini *et al.* (4) examined 198 STEMI patients who underwent primary PCI, assessed CMD using the pressure-wire-based index of microcirculatory resistance (IMR) and/or by the presence of microvascular obstruction (MVO) by cardiovascular magnetic resonance (CMR). The results showed that post-PCI CMD predicts a more than 4-fold increase in long-term risk of adverse outcomes, mainly driven by the occurrence of heart failure. CMD by either invasive IMR >40 U or by CMR-assessed MVO showed a similar risk of adverse outcomes. Identifying, reducing, and potentially reversing CMD in STEMI is an unmet clinical need. In addressing this challenge, assessing the status of the coronary microvasculature is critical, as it is likely to benefit patients receiving additional therapy (2).

The coronary vasculature consists of subepicardial coronary arteries and coronary microvessels (small arteries and microarteries), with the primary role of the subepicardial coronary arteries being blood transmission. The coronary microvessels assume the role of myocardial perfusion and peripheral blood supply. Primary PCI should not only relieve the obstruction of the subepicardial coronary artery, but also protect the function of the coronary microvasculature in order to achieve myocardial level perfusion for effective myocardial cell salvage. Since CAG can only show vessels >200 μm in diameter, it is difficult to observe coronary microvessels, thus making the diagnosis of CMD more difficult. CAG is currently used to assess parameters related to microcirculation based on TIMI flow grading, corrected TIMI frame count, and TIMI myocardial perfusion grading (1). Although epicardial vessel blood flow has reached TIMI grade 3, there is a wide variation in peripheral coronary microcirculatory perfusion, and thus TIMI grading does not accurately reflect tissue-level myocardial reperfusion. Numerous studies (1-5) have demonstrated that epicardial vascular flow has reached TIMI grade 3, and still 25–30% of patients' myocardial tissue is not effectively reperfused. CZT-SPECT has the unique advantage of good accuracy in quantitatively assessing MBF and the extent of myocardium at risk in the IRA and corresponding blood supply regions (6,20).

In this study, CZT-SPECT was used to identify CMD after AMI primary PCI, aiming to further improve the detection of CMD. MFR <2 was used as a criterion for the diagnosis of CMD in 79.2% of patients with CMD. This suggests that close to 80% of patients fail to return to normal coronary reserve function 1 week after primary PCI for AMI. Indeed, Succar *et al.* (21) reported on a patient with typical CMD, where stress and rest myocardial perfusion images showed a large perfusion defect in the anterior wall that was mostly reversible. Similar findings were observed for our study (*Figure 2*).

Among the risk factors associated with CMD, we found that STEMI in the CMD group accounted for 88.1% (54.1% in the control group), preoperative TIMI grade 0 accounted for 61.9% (18.2% in the control group), time of pain to reperfusion was 3.70±4.55 hours (2.64±1.68 h in the control group), and the peak of cTnI was 15,323.95±7,887.12 pg/mL (11,801.27±8,948.84 pg/mL in the control group). Compared to NSTEMI, CAG in STEMI patients showed more complete occlusive lesions in IRA, with a longer time of pain to reperfusion, accompanied by a greater extent of myocardial necrosis (22). An important indicator of ischemia-related injury is the length of time from symptom onset to reperfusion, with longer times implying a higher incidence and degree of CMD (22,23). Mechanistically, STEMI patients with IRA may have a higher burden of thrombosis and are more likely to have combined distal microvascular embolism after primary PCI. Together with reperfusion injury after primary PCI, these factors increase the risk of developing CMD.

Post-procedure ECGs showed a higher percentage of ST elevation >0.5 mv (78.6% *vs.* 54.5%), and STR (degree of ST-segment regression). This is also the criteria used in previous clinical studies (24,25). Less than 50% or 70% ST-segment regression on the admission ECG is a marker for CMD, although the sensitivity is not as good as that of imaging methods.

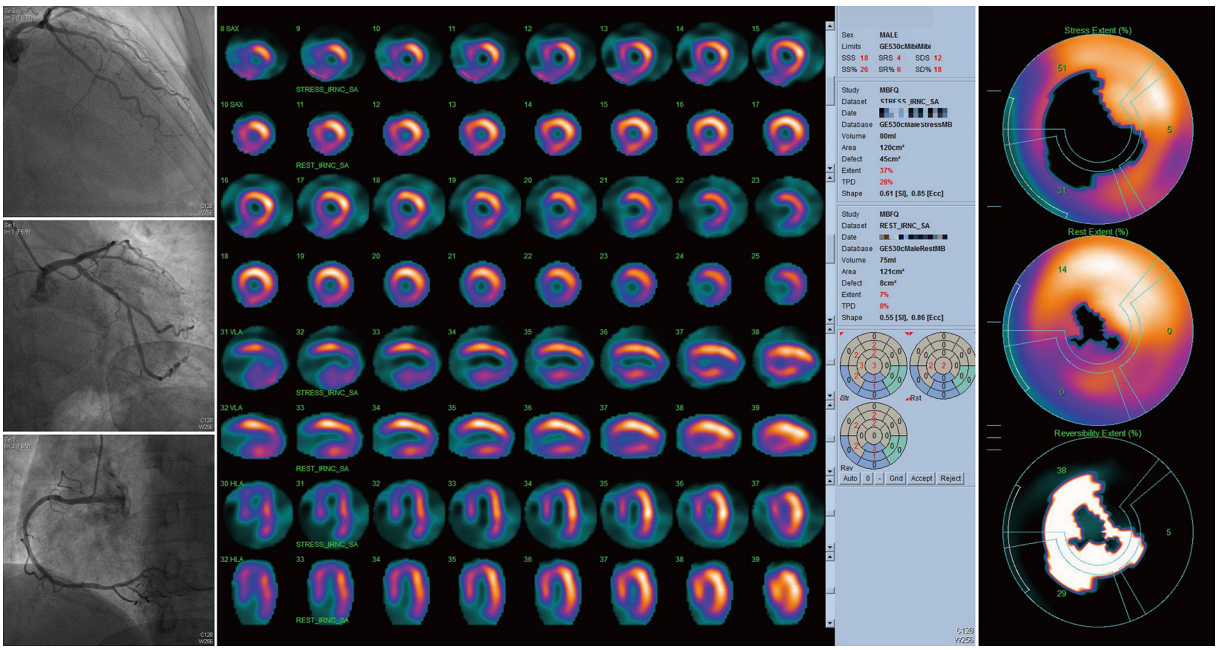

Figure 2 A 65-year-old male patient with the chief complaint of persistent angina attack received primary PCI in TEDA International Cardiovascular Hospital. Left figures: coronary angiography showing complete occlusion of the LAD with no significant coronary stenosis and no significant spasm on left circumflex branch and right coronary artery. Central figure: routine adenosine stress plus rest serial tomographic images (row 1/3/5/7 for stress images, and row 2/4/6/8 for rest images) indicating a large perfusion defect in the anterior wall that is mostly reversible. Right figures: myocardial AAR at rest was 7%, Stress AAR 37%, showing that 30% area in the left ventricular area is reversible. Quantitative diagnosis with dynamic data is very definitive of the abnormal results and showed a significant reduction in MFR in the large LAD and a severe reduction in stress-MBF in the LAD (rest-MBF of LAD =0.90 mL/g/min; stress-MBF of LAD =1.11 mL/g/min; LAD-MFR =1.20), meeting the diagnostic criteria for CMD. SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; SS%, summed stress%; SR%, summed rest%; SD%, summed difference%; MBFQ, myocardial blood flow quantitation; TPD, total perfusion defect; PCI, percutaneous coronary intervention; LAD, left anterior descending branch; AAR, area at risk; MFR, myocardial flow reserve; MBF, myocardial blood flow; CMD, coronary microvascular dysfunction.

SPECT

At 1 week after primary PCI for AMI, we used CZT-SPECT to quantify resting and loading MBF and thus MFR to diagnose CMD, as well as to assess the myocardial extent at risk. CMD represents reduced coronary reserve function. Rest-MBF did not differ between the 2 groups and stress-MBF of IRA was significantly decreased in the CMD group (0.80±0.31 *vs.* 1.93±0.44 mL/g/min), which is an indication of elevated distal microvascular resistance, SSS score, SRS score, and SDS score. MPI revealed that rest-AAR and stress-AAR were significantly higher in the CMD group than in the control group, with the difference in stress-AAR being more pronounced. Rest-LVEF, and stress-LVEF were significantly lower in the CMD group than in the control group, however, this is not unexpected and is even an inevitable direction of disease progression in CMD patients, predicting a higher risk of myocardial remodeling with concomitant poor prognosis in CMD patients. Such results provide ample evidence that reperfusion to the myocardial cell level is particularly important and can influence the size of myocardial infarction as well as the recovery of coronary reserve capacity in patients.

AAR

Assessment of stress-AAR using adenosine-loaded MPI imaging allows a clearer identification of the extent of myocardium at risk than resting MPI imaging applied alone. We found that in a large proportion of patients without abnormal rest-AAR, stress-AAR showed a larger range of myocardial perfusion defects. Moreover, stress-AAR was

more closely related to CMD, more representative of the extent of damaged myocardium, and more indicative of the predicted decrease in a coronary reserve capacity.

Association of CMD with BMI, lipids, and inflammation

According to existing studies (26), every 10 kg/m^2 increase in BMI is correlated with a 20% increase in cardiovascular events. Although the relationship between the increase in BMI and CMD is not well-established, BMI is directly proportional to blood levels of lipids, glucose, and inflammatory factors. Indeed, our previous study showed that BMI is an independent predictor of CMD in obstructive coronary artery disease (27). Previous studies using PET have shown that MFR is reduced in patients with normal CAG and asymptomatic hypercholesterolemia (28), but can be reversed by lipid-lowering medications (29). Notably, the results of *in vitro* studies suggest that endothelial dysfunction is due to decreased nitric oxide (NO) release or increased superoxide anion radical production due to low-density lipoprotein cholesterol (LDL-C) oxidation, rather than to an increase in total cholesterol (30). Kaufmann *et al.* (31) showed a significant negative correlation between MFR and LDL-C in the lipid fraction, thereby supporting a direct pathogenic role of LDL-C in the development of CMD. There is increasing evidence suggests that the inflammatory response within atherosclerotic plaques is important in the pathogenesis of AMI (32,33). Pro-inflammatory responses can mediate CMD severity (34,35). Neutrophil counts are associated with microvascular injury after primary PCI and can effectively predict CMD (36).

However, whether CMD status is improved in patients with AMI and how long it takes for IRA coronary reserve function to return to normal is not fully established (1). Galiuto *et al.* used continuously measured myocardial sonography and found that approximately 50% of MVO present 24 hours after successful PCI improves spontaneously, classifying it into persistent or reversible (37). Persistent MVO is caused by irreversible coronary microcirculatory injury, whereas reversible MVO is caused by reversible changes in microcirculatory function (37). Interestingly, there is negative LV remodeling in patients with persistent MVO and ventricular volumes remain unchanged in patients with reversible MVO (38,39). Indeed, similar results were obtained by Hoffman *et al.* (40) who analyzed myocardial staining grading changes. In our few patients with follow-up, at the 3-month review by SPECT, IRA coronary reserve function had partially or completely returned to normal: most of the improvement were in stress-MBF, whereas rest-AAR and stress-AAR were significantly reduced, predicting that the myocardial AAR is related to the blood supply status of the microcirculation.

Limitations

Several limitations of this study should be recognized. Firstly, the relatively small sample size is related to a retrospective study that failed to fully reflect the exact incidence of CMD in patients with obstructive AMI and the relevance of various risk factors. Secondly, certain bias in patient selection may be present, with a higher positive rate of abnormal blood flow quantification after patient self-reporting and physician screening. Thirdly, methods of eliminating coronary spasms (acetylcholine tests) were not available. Therefore, the involvement of coronary microvascular spasm could not be excluded, and its possible impact on the diagnosis of CMD was unknown.

Conclusions

The prevalence of CMD is high in AMI patients who received primary PCI. Each 1 kg/m^2 increase in BMI was associated with a 1.3-fold increase in CMD risk. A 5% increase in stress-AAR was associated with a nearly 2-fold increase in CMD risk. Increased BMI and stress-AAR predicts decreased coronary reserve function.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1260/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1260/coif). The authors have no conflicts of interest to declare.

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