

## Original Article

# The amount of viable myocardium predicts left ventricular functional improvement and volume reduction in patients with coronary artery disease after coronary artery bypass grafting

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**Abstract:** This study evaluated the impact of viable myocardium amount before coronary artery bypass grafting (CABG) on left ventricular (LV) functional improvement and LV volume reduction after CABG in patients with coronary artery disease (CAD). Thirty-nine patients underwent gated <sup>99m</sup>Tc-MIBI SPECT and <sup>18</sup>F-FDG PET before CABG to assess the amount of viable myocardium. Left ventricular ejection fraction (LVEF), LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) were determined before and 3-6 months post-CABG. After CABG, 17 of 39 CAD patients exhibited LVEF improvement ( $\geq 5\%$ ) and 26 of 39 CAD patients appeared the reduction in LV end-diastolic volume (EDV) and end-systolic volume (ESV) ( $\geq 10\%$ ). Moreover, the amount of viable myocardium before CABG is an independent factor for predicting LVEF improvement (OR = 1.932,  $P < 0.05$ ) and LV volume reduction (OR = 1.623,  $P < 0.05$ ) after CABG by multiple logistic regression analysis. ROC curve analysis showed that the optimal cutoff levels of 4 and 3 viable myocardial segments before CABG can predict LVEF improvement and LV volume reduction after CABG, respectively. The amount of viable myocardium is an independent factor for predicting LVEF improvement and LV volume reduction in CAD patients after CABG. The amount of viable myocardium assessed by combining gated <sup>99m</sup>Tc-MIBI SPECT and <sup>18</sup>F-FDG PET before CABG can predict LVEF improvement and LV volume reduction after CABG.

**Keywords:** Viable myocardium, coronary artery disease, left ventricular ejection fraction, left ventricular volume, coronary artery bypass grafting

## Introduction

Myocardial infarction and extensive coronary artery disease (CAD) are the most common etiologies of heart failure [1], the prognosis of these patients is poor and proportionally decreases with the severity of LV dysfunction [2]. Coronary artery bypass grafting (CABG) is widely accepted as the preferred treatment for CAD especially for left main or multi-vessel coronary artery disease, it aims to recover the blood perfusion for ischemic myocardium, improve left ventricular function, reduce left ventricular volume, prevent further development of ventricular remodeling, allay heart failure symptoms and improve outcomes [2-4]. However, CABG is still an operation with relatively higher perioperative complications and

mortality. So it is important to identify the patients who can benefit from CABG.

Previous studies demonstrated that the assessment of viable myocardium prior to revascularization can predict functional recovery after revascularization and thus aid in decision making in the management of patients with CAD [3, 5]. Of the several techniques available for assessing viable myocardium, <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography (PET) combining with <sup>99m</sup>Tc-methoxy-isobutylisonitrile (MIBI) single photon emission computed tomography (SPECT) is confirmed as a sensitive method to predict functional recovery after revascularization [6]. However, the result of surgical treatment for ischemic heart failure (STICH) trial [7] questioned the necessity for

the assessment of viable myocardium before revascularization and indicated that the assessment of viable myocardium is not an effective biomarker for screening the beneficiaries after revascularization.

Therefore, there still are controversies about the necessity for viable myocardium assessment before CABG. Our study aimed to investigate whether the amount of viable myocardium assessed by  $^{18}\text{F}$ -FDG PET and  $^{99\text{m}}\text{Tc}$ -MIBI SPECT can predict the improvement of left ventricular function and reduction in left ventricular volume after CABG, which may verify the necessity of viable myocardium assessment before CABG in CAD patients.

### Materials and methods

#### *Patients*

Total 46 consecutive CAD patients were prospectively enrolled from the department of Cardiothoracic Surgery at our hospital between September 2012 and August 2014. Inclusion criteria were as follows: (1) severe CAD was diagnosed by coronary angiography with CABG indications [8]; (2) previous history of myocardial infarction (MI) >1 month or percutaneous coronary intervention (PCI); (3) obvious hypoperfusion area in some myocardial segments by rest myocardial perfusion imaging (rest MPI); (4) high quality images of  $^{18}\text{F}$ -FDG PET for reading and assessment. The patients who met all of the above criteria were enrolled in this study. All patients received gated  $^{99\text{m}}\text{Tc}$ -MIBI SPECT and  $^{18}\text{F}$ -FDG PET to assess myocardial viability and left ventricular function before CABG, and were re-examined by gated  $^{99\text{m}}\text{Tc}$ -MIBI SPECT at 3-6 months after CABG. Of 46 patients, 4 patients with normal rest MPI and 3 patients with poor images of  $^{18}\text{F}$ -FDG PET were excluded, 39 patients were finally enrolled in this study. All patients signed an informed consent and the study was approved by the Medical Ethics Committee of our hospital.

#### *$^{99\text{m}}\text{Tc}$ -MIBI SPECT and $^{18}\text{F}$ -FDG PET imaging*

MPI equipment was the SPECT/CT scanner (Symbia T16, Siemens, Germany) supplemented with a high resolution low-energy collimator. No attenuation correction was applied. Before procedure, the use of drugs that may affect heart rate or coronary vasodilation, such as  $\beta$ -receptor blocker and nitrates, was stopped.

The imaging agent was  $^{99\text{m}}\text{Tc}$ -MIBI (radiochemical purity >95%, injected dose of 555~740 MBq). Gated MPI was acquired using dual-head detector with the angle of 90° and 6° step 180° rotation (from the right anterior oblique of 45° to the left posterior oblique of 45°), with acquisition matrix of 128×128, magnification of 1.45, and 20% window centered on the 140keV peak energy. Detection was synchronized with the R wave of the ECG, and the cardiac cycle was segmented into 8 fractions.  $^{99\text{m}}\text{Tc}$ -MIBI SPECT after CABG was performed similarly.

One day after  $^{99\text{m}}\text{Tc}$ -MIBI SPECT Gated MPI,  $^{18}\text{F}$ -FDG PET imaging was performed by PET/CT scanner (Biography mCT-s (64), Siemens, German).  $^{18}\text{F}$ -FDG was used as a tracer for the assessment of myocardial viability. Patient preparation for  $^{18}\text{F}$ -FDG PET cardiac viability assessment referred to ASNC imaging guidelines [9]. 111-185 MBq of  $^{18}\text{F}$ -FDG was injected intravenously. While waiting for 60 minutes after  $^{18}\text{F}$ -FDG injection, a 10-min cardiac PET scan was performed.

#### *Image processing and analysis*

All imaging data were processed and analyzed by two experienced nuclear medicine physicians who were blinded to the clinical data and reached a consensus. Coronary stenosis was considered significant when it was greater than 70% in any of the 3 main coronary arteries (left anterior descending, left circumflex, and right coronary) or greater than 50% in the left main coronary artery [10].  $^{99\text{m}}\text{Tc}$ -MIBI SPECT Gated MPI data were reconstructed with Butterworth filter to obtain the images of short-axis, horizontal long-axis and vertical axis for left ventricle.  $^{18}\text{F}$ -FDG PET images were reconstructed using filtered back projection (FBP). All images from  $^{99\text{m}}\text{Tc}$ -MIBI SPECT and  $^{18}\text{F}$ -FDG PET were semi-quantitatively scored using a 17-segment model of the left ventricle and evaluated by a 5-point scale according to regional myocardial uptake of the tracer (0 = no defect; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; 4 = absent activity). The presence of perfusion/metabolism mismatch was defined by that the score of perfusion imaging is at least 2 points higher than that of metabolism imaging in the same myocardial segment, which reflects myocardial viability. In contrast, scar myocardium was defined by perfusion/

**Table 1.** Clinical characteristics of the patients

Clinical characteristics	Value
Age (years old)	63.7±8.9
Gender (male/female)	37/2
BMI (kg·m <sup>-2</sup> )	25.2±2.4
Hypertension, n (%)	34 (87.2%)
Diabetes mellitus, n (%)	15 (38.5%)
Hyperlipidemia, n (%)	6 (15.4%)
Serum creatinine (μmol/l)	94.1±18.2
Previous PCI, n (%)	2 (5.1%)
Previous MI, n (%)	20 (51.3%)
Angina (CCS class II~IV), n (%)	20 (51.3%)
Dyspnea (NYHA class II~IV), n (%)	31 (79.5%)
Coronary Angiography, n (%)	
Left main disease	8 (20.5%)
1-vessel disease	5 (12.8%)
2-vessel disease	14 (35.9%)
3-vessel disease	20 (51.3%)

BMI, Body mass index; PCI, percutaneous coronary intervention; MI, myocardial infarction; CCS, Canadian class classification of angina pectoris; NYHA, New York Heart Association classification of heart failure.

metabolism match, which exhibits defect in both perfusion and metabolism imaging in the same myocardial segment.

<sup>99m</sup>Tc-MIBI SPECT Gated MPI data were processed by Cedars-Sinai QGS software (Los Angeles, CA) to obtain of left ventricle global function parameters, including LV end-diastolic volume (EDV), LV end-systolic volume (ESV) and LVEF. By comparing the images of <sup>99m</sup>Tc-MIBI SPECT Gated MPI before and after CABG, the segments of myocardial perfusion improvement were recorded and calculated. The LVEF improvement of 5% or greater and LVEDV and LVESV reduction of 10% or greater after CABG were considered clinically significant, as described previously [11].

#### Statistical analysis

The data are presented at mean ± standard deviation (SD) and analyzed by SPSS 19.0 software (Chicago, IL). The independent-samples t test and  $\chi^2$  test were used to compare the clinical parameters, segments of viable myocardium and nonviable myocardium between with and without LVEF improvement groups or between reduced and non-reduced LV volume groups. Continuous variables that were not dis-

tributed normally were compared by the Mann-Whitney test. Multiple logistic regression analysis was used to examine the relationships between related factors and the changes in LVEF and LV volume. To obtain a cut-off value for predicting LVEF improvement and reduction of LV volume after CABG, receiver operating characteristic (ROC) curves were generated for significant factors from multiple logistic regression analysis. Cohen's kappa coefficient was used to assess the consistence between LVEF improvement and reduction of LV volume. Two-sided *P*-value <0.05 was considered statistically significance.

## Results

### Characteristics of studied subjects

The clinical characteristics of all patients are listed in **Table 1**.

### The improvement of myocardial perfusion and LVEF, the reduction of LV volume after CABG

There were 188 myocardial segments with abnormal perfusion in 39 patients before CABG, 60.1% (113/188) of myocardial segments with abnormal perfusion were improved after CABG. Before CABG, the segments of viable myocardium and scar myocardium were 147 and 41, respectively. After CABG, 74.8% (110/147) of viable myocardium segments were improved, which was significantly better than that in scar myocardium (3 of 41, 7.3%) ( $\chi^2 = 60.9$ ,  $P < 0.01$ ). Of total 39 CAD patients, there were 17 patients with improved LVEF and 26 patients with reduced LV volume after CABG. Moreover, of 26 patients with reduced LV volume, 10 patients appeared LVEF without improvement. And of 13 patients without reduced LV volume, one patient showed LVEF improvement. The changes in LV volume and LVEF after CABG were moderately consistent in 11 of 39 (28.2%) CAD patients (Kappa = 0.459).

### Factors that affect LVEF improvement and the reduction of LV volume in CAD patients after CABG

Compared with no LVEF improvement or no LV volume reduction group, the patients with improved LVEF or reduced LV volume showed significantly more segments of viable myocardium, but less segments of scar myocardium ( $P < 0.05$ , **Table 2**). However, the age, gender

## Amount of viable myocardium in CABG patients

**Table 2.** Characteristics of patients with and without improvement/reduction in LVEF/LV volume after CABG

Parameter	LVEF			LV Volume		
	Improvement (n = 17)	Without improvement (n = 22)	P value	Reduction (n = 26)	Without reduction (n = 13)	P value
Age	63.5±9.0	63.9±9.1	0.894	63.8±9.2	63.3±8.7	0.850
Gender (male/female)	16/1	21/1	1.000	25/1	12/1	1.000
BMI (kg·m <sup>-2</sup> )	25.5±2.6	24.9±2.2	0.469	24.9±2.3	25.7±2.5	0.297
Hypertension	14 (82.4%)	20 (90.9%)	0.636	23 (88.5%)	11 (84.6%)	1.000
Diabetes mellitus	8 (47.1%)	7 (31.8%)	0.332	11 (42.3%)	4 (30.8%)	0.485
Hyperlipidemia	4 (23.5%)	2 (9.1%)	0.374	6 (23.1%)	0 (0%)	0.081
Serum Creatinine (μmol/l)	92.5±20.2	95.3±16.8	0.641	92.8±17.9	96.7±19.2	0.533
Previous PCI	1 (5.9%)	1 (4.5%)	1.000	1 (3.8%)	1 (7.7%)	1.000
Previous MI	9 (52.9%)	11 (50.0%)	0.855	14 (53.8%)	6 (46.2%)	0.651
Angina (CCS class II~IV)	8 (47.1%)	12 (54.5%)	0.643	12 (46.2%)	8 (61.5%)	0.365
dyspnea (NYHA class II~IV)	13 (76.5%)	18 (81.8%)	0.709	20 (76.9%)	11 (84.6%)	0.575
EDV pre-CABG (ml)	114.2±44.3	113.6±53.8	0.966	112.4±38.8	116.8±67.4	0.797
ESV pre-CABG (ml)	59.9±38.2	58.9±48.8	0.943	56.4±33.5	65.4±60.9	0.552
LVEF pre-CABG (%)	51.4±12.0	53.1±13.9	0.691	52.9±11.3	51.2±16.2	0.699
EDV after-CABG (ml)	86.4±26.0	105.3±55.0	0.199	84.1±24.7	122.9±64.1	0.054
ESV after-CABG (ml)	36.8±19.9	59.3±50.3	0.091	37.4±20.5	73.7±59.4	0.051
LVEF after-CABG (%)	59.7±12.3	51.6±14.1	0.066	58.1±12.2	49.2±15.3	0.055
Number of viable segments	5.4±2.6	2.5±1.8	0.000*	4.5±2.8	2.4±1.5	0.005*
Number of scar segments	0.3±0.6	1.6±2.5	0.036*	0.5±1.0	2.1±3.0	0.093
Number of normal segments	11.3±2.7	12.9±3.2	0.113	12.5±3.6	12.0±2.8	0.611

BMI, Body mass index; PCI, percutaneous coronary intervention; MI, myocardial infarction; CCS, Canadian class classification of angina pectoris; NYHA, New York Heart Association classification of heart failure; EDV, end-diastolic volume; ESV, end-systolic volume. \*Significant difference.

**Table 3.** Multivariable logistic regression analysis for prediction of improvement of LVEF after CABG

Variables	Regression coefficient	OR	95% CI	P value
Number of viable segments	0.658	1.932	1.173~3.180	0.010*
Number of scar segments	-0.886	0.412	0.128~1.327	0.137

\*Significant difference.

**Table 4.** Multivariable logistic regression analysis for prediction of reduction of LV volume after CABG

Variables	Regression coefficient	OR	95% CI	P value
Number of viable segments	0.484	1.623	1.040~2.532	0.033*

\*Significant difference.

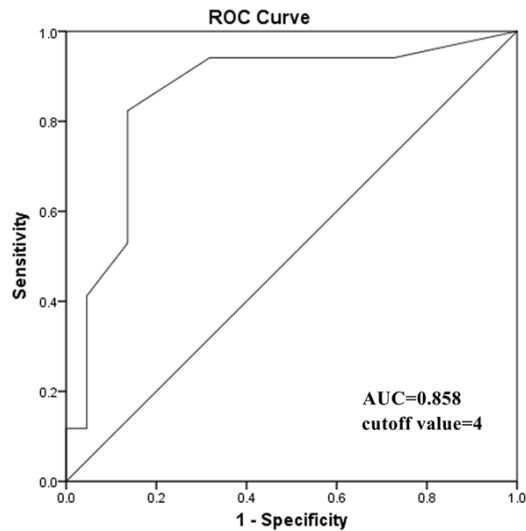
ratio, hypertension, diabetes mellitus, hyperlipidemia, serum creatinine, previous PCI, previous myocardial infarction, percentage of angina (CCS class II~IV), percentage of dyspnea (NYHA class II~IV), EDV pre-CABG, ESV pre-CABG, LVEF pre-CABG, EDV after-CABG, ESV after-CABG, LVEF after-CABG, the number of normal segments were not significant between two groups (Table 2).

Multiple logistic regression analysis was performed to screen the factors that affect LVEF improvement and the reduction of LV volume in CAD patients after CABG. The number of viable segments was found to be the only independent factor that affects the improvement of LVEF (OR = 1.932, P<0.05, Table 3) and the reduction of LV volume (OR = 1.623, P<0.05, Table 4) in CAD patients after CABG.

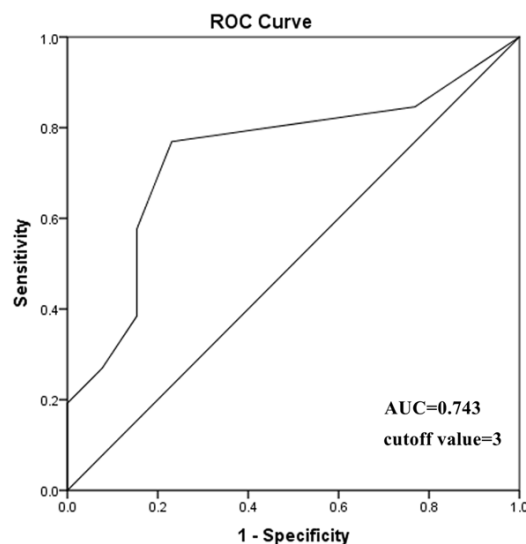
*ROC curve for the prediction of LVEF improvement and the reduction in LV volume after CABG according to the number of viable myocardium segments*

ROC curves for the prediction of LVEF improvement and the reduction in LV volume after CABG were generated by the amount of viable myocardium before CABG (Figures 1 and 2). Based on the segments of viable myocardium, the cutoff values for LVEF improvement and the

## Amount of viable myocardium in CABG patients



**Figure 1.** ROC curve for the prediction of LVEF improvement ( $\geq 5\%$ ) after CABG according to the number of viable myocardium segments (area under curve, AUC = 0.858). The optimal cutoff value was 4 or more for the number of viable myocardium segments.



**Figure 2.** ROC curve for the prediction of LV volume reduction after CABG (reduction of 10% or greater in EDV and ESV was considered clinically meaningful) by the number of viable myocardium segments (AUC = 0.743). The optimal cutoff value was 3 or more for the number viable myocardium segments.

reduction in LV volume were 4 segments and 3 segments after CABG, respectively, with 82.4% of sensitivity and 86.4% of specificity (AUC = 0.858, 95% CI = 0.729~0.988,  $P < 0.01$ ) for LVEF improvement (**Figure 1**), and with 76.9%

of sensitivity and 76.9% of specificity for LV volume reduction (AUC = 0.743, 95% CI = 0.578~0.907,  $P < 0.05$ ) (**Figure 2**). Of 17 patients with LVEF improvement, there were 14 patients in which the segment of viable myocardium was more than 4, but there were only 3 in 22 patients without LVEF improvement. Also, of 26 patients with LV volume reduction, there were 17 patients in which the segment of viable myocardium was more 3 segments, but only 3 in 13 patients without LV volume reduction (**Figure 3**).

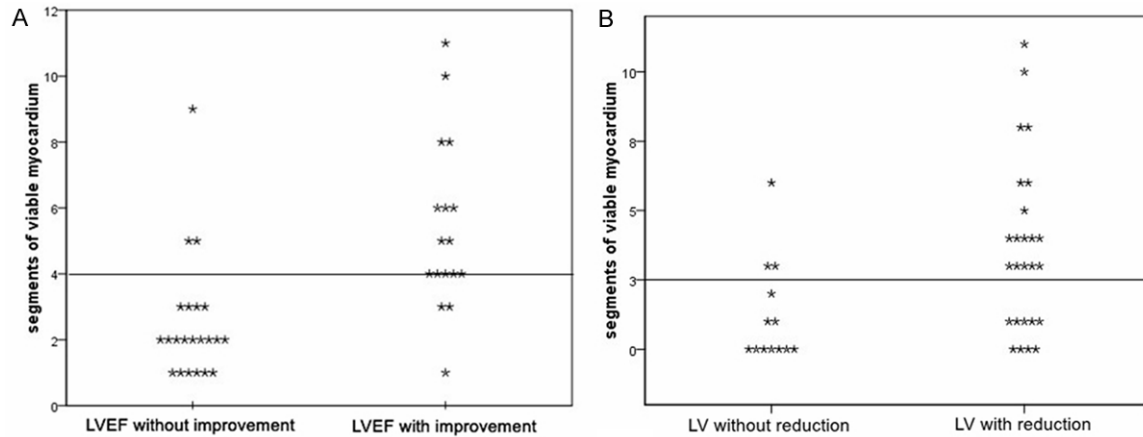
### Discussion

It is well established that CABG can recover myocardial blood flow for ischemic myocardium, improve heart function, reduce left ventricular volume, prevent or even reverse ventricular remodeling in CAD patients [2-4]. In our study, 60.1% (113 of 188) of myocardial segments with abnormal perfusion were improved after CABG, suggesting that CABG is an effective therapeutic method to rectify abnormal myocardial perfusion in CAD patients. Moreover, among the 147 viable myocardial segments, 110 myocardial segments were observed with improved perfusion (74.8%), while only 3 myocardial segments from total 41 scar myocardial segments (7.3%) were observed with improved perfusion. These data indicate that viable myocardium is the basis for improving abnormal myocardial perfusion after CABG. To better predict the perfusion improvement after CABG, it is necessary to evaluate viable myocardium before CABG in CAD patients.

Published studies have demonstrated that viable myocardium is closely related to the improvement of LV function after CABG [12-14]. Our study also observed that the patients with LVEF improvement after CABG exhibited significantly more segments of viable myocardium, but significantly less segments of scar myocardium before CABG, compared with group of LVEF without improvement. These results further support that the assessment of viable and scar myocardium before CABG in CAD patients is important for predicting LVEF improvement after CABG. Hibernating myocardium is a self-protective mechanism for myocardium under insufficient myocardial blood flow, which is featured with reduced contraction and energy consumption. In the viable myocardium, the contraction function will be completely or partially



## Amount of viable myocardium in CABG patients



**Figure 3.** LVEF improvement (A) and reduction of LV volume (B) based on the amount of viable myocardium. Of 17 patients with LVEF improvement, there were 14 patients that the segment of viable myocardium was more than 4, but there were only 3 in 22 patients without LVEF improvement. Also, of 26 patients LV volume reduction, there were 17 patients that the segment of viable myocardium was more 3 segments, but only 3 in 13 patients without LV volume reduction. A \*stand for a patient.

rescued after sufficient myocardial blood flow, but this function can't be rescued in scar myocardium because scar myocardium appears irreversible damages like degradation and fibrosis of myocardium [15]. A perspective study on PARR-1 [16] reported the ratio of viable and scar myocardium in the left ventricle is the important factor for predicting LVEF improvement after revascularization. Once viable score increased by 10%, LVEF might increase by 1.99% post revascularization, while the scar score increased by 10%, LVEF might decrease by 3.38% post revascularization.

Our multivariate logistic regression analysis showed that the number of viable segments before CABG is the independent factor for LVEF improvement after CABG, and more viable myocardium before CABG is associated with better LVEF improvement after CABG. ROC analysis reported that the cutoff value of 4 for the segment of viable myocardium before CABG exhibited the highest efficacy in predicting LVEF improvement after CABG, with 82.4% sensitivity and 86.4% specificity. However, 3 of 22 patients with >4 segments of viable myocardium didn't show LVEF improvement after CABG. Two patients didn't appear perfusion improvement after CABG, although there were more than 4 segments of viable myocardium before CABG, while another patient coexisted a large number of scar myocardia and enlarged left ventricle (EDV: 305 ml) before CABG. These

results support that improved myocardial perfusion after CABG is closely related to LVEF improvement, and the amount of scar myocardium and left ventricular remodeling before CABG are also important factors for affecting LVEF improvement after CABG. Previous studies reported that the CAD patients with enlarged left ventricle [17, 18] and large amount of myocardial scar [11, 16] appear poor LVEF improvement and prognosis after CABG. Myocardial scar may affect the wall motion of adjacent normal or viable myocardium, and thus limit the improvement of LV function after CABG. Bax *et al.* reported that LVEF improvement is very poor in CAD patients with extensive left ventricular remodeling, even in the presence of significant myocardial viability [18].

It has been demonstrated that the reduction in LV volume after CABG is closely associated with viable and nonviable myocardium [14, 19]. Compared to the patients without reduced LV volume after CABG, the patients with reduced LV volume after CABG appeared significantly more segments of viable myocardium and less segments of scar myocardium before CABG. These data indicate that segments of viable and scar myocardium before CABG are important factors for the change in LV volume after CABG. A study by Senior *et al.* [20] demonstrated that in the patients with chronic ischemic LV dysfunction, revascularization can improve not only the regional and global heart function, but

also LV geometry (shape and volume). The improvement in LV geometry contributes to better LV systolic function, and on long-term follow-up, the change in LVESV is the best predictor of survival after revascularization. Orn *et al.* [21] reported that large area of myocardial scar may result in obvious expansion and deformation of whole heart, ventricular remodeling, formation of ventricular aneurysm, weak, disappearance and reversal of wall motion of regional myocardium and reduced LVEF. They concluded that the size of myocardial scar, localization, transmuralities are independent predictors for LVEF and LV volume. However, here we observed the consistency between the improvement of LVEF and the reduction in LV volume after CABG was moderate ( $Kappa = 0.459$ ), suggesting that the reduction in LV volume after CABG is not associated with LVEF improvement after CABG. Clinical study showed some CAD patients whose LV function didn't improve after revascularization but they still gained good prognosis. Such situation may be explained by the reason that revascularization can reduce LV volume, especially ESV, which is the marker of severity of LV remodeling [22].

Multivariate logistic regression analysis found that the segment of viable myocardium before CABG is the independent factor for the reduction in LV volume after CABG, more viable myocardium before CABG is correlated with more significant reduction in LV volume after CABG. According to ROC analysis, when the segment of viable myocardium is  $\geq 3$ , their sensitivity and specificity for predicting the reduction in LV volume after CABG were both at 76.9%. Slart *et al.* [14] found that reverse LV remodeling could be predicted by use of FDG uptake of 50% or greater with the sensitivity and specificity of 89% and 65%, respectively, and by use of wall thickening of 10% or greater with the sensitivity and specificity of 78% and 70%, respectively. The efficacy of viable myocardium amount in predicting the reduction in LV volume is almost similar to our study, but the sensitivity and specificity are different, which may be caused by different methods for assessing viable myocardium and different criteria for patient enrollment.

However, there are a couple of limitations in our study: 1) the number of patients was not large and follow-up period was short; 2) The effects

of LVEF improvement and the reduction in LV volume on long-term prognosis in CAD patients after CABG were not clearly defined. Thus, the results in this study should be verified in a large number of patients and long follow-up period.

In summary, the amount of viable myocardium before CABG is the independent factor for the prediction of LVEF improvement and the reduction in LV volume in CAD patients after CABG. The  $\geq 4$  and  $\geq 3$  segments of viable myocardium before CABG can accurately predict LVEF improvement and the reduction in LV volume after CABG, respectively. The reduction in LV volume after CABG is not necessarily associated with LVEF improvement after CABG. Therefore, the combined evaluations for viable myocardium by  $^{99m}Tc$ -MIBI SPECT and  $^{18}F$ -FDG PET before CABG have important significance in predicting LVEF improvement and the reduction in LV volume after CABG in CAD patients.

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### Disclosure of conflict of interest

None.

### Authors' contribution

YT Wang and YX Qian conceived of the study, and participated in study design and coordination. XL Shao and YS Yang drafted the manuscript. XL Shao, YS Yang, JF Wang analysed the images and carried out the patient follow-up study. All authors read and approved the final manuscript.

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## Amount of viable myocardium in CABG patients

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