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Original Research

Changes and predictors of secondary mild mitral regurgitation after coronary artery bypass grafting

Han Wang[1], Bing Zhang[1], Wei-Chun Wu[1], Zhen-Hui Zhu[1], Hao Wang[1,*]

[1]Department of Echocardiography, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037 Beijing, China
*Correspondence: hal6112@163.com (Hao Wang)
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Abstract

Background: Secondary mitral regurgitation (SMR) has been related to left ventricular (LV) remodeling and geometric deformation of the mitral apparatus after myocardial infarction (MI), and proved to be associated with adverse cardiac events. We assessed the proportion of mild SMR before and after isolated coronary artery bypass grafting (CABG) surgery, and further study to evaluate dynamic changes of MR and the determinants of such process on 1 year follow-up. **Methods**: From 2019 to 2021, cohort study of 171 consecutive hospitalized patients who underwent selective isolated CABG surgery were included and divided into the control group and mild MR group according to whether mild MR occurred at baseline. Univariate analysis and multivariate logistic regression analysis were used to test the associations of changes in MR after CABG, and $p < 0.05$ was considered significant. **Results**: The mean age of the cohort was 61.31 $\pm$ 8.71 years and 78.95% were male at baseline, divided into the control group (74.85%) and mild MR group (25.15%), respectively. The LV volumetric and size parameters were higher in the mild MR group, with decline in LV and left atrial (LA) strain measurements. About half participants with mild MR at baseline persisted in that category and the rest reverted to none MR on follow-up, while preoperative left main coronary artery occlusion may impede the improvement ($p < 0.05$). The control group at baseline tended to maintain none MR and one-eighth progressed to mild MR on follow-up, moreover older age and lower LVEF emerged as key correlation of this development. LA volume index (LAVi) was associated with an increased risk of developing mild MR ($p < 0.05$). **Conclusions**: Patients with secondary mild MR had LA dysfunction and CABG surgery promoted regression of MR. LAV has an incremental role for early detection of change in MR over time after surgery.

Keywords: CABG; echocardiography; mitral regurgitation; left atrium

1. Introduction

Secondary mitral regurgitation (SMR) is often induced by coronary artery disease, especially myocardial infarction (MI), and a powerful predictor of adverse prognosis with increased risk for death and heart failure [1,2]. SMR is associated with a higher prevalence of comorbidities and adverse cardiovascular outcomes in subjects with previous cardiovascular events [3,4] and progression of MR after MI promotes an increased likelihood of cardiovascular morbidity [5–7]. Moreover, left ventricular (LV) remodeling causes left atrial (LA) enlargement which is common in chronic moderate to severe MR [8,9], and LA remodeling and dysfunction can be considered as indicators of underlying LA myopathy and might also contribute to low-grade functional MR [10,11].

In order to reduce the risk of sudden cardiac death and improve myocardial function, coronary artery bypass grafting (CABG) is an effective revascularization treatment [12], and concomitant mitral valve surgery at the time of CABG is recommended patients with symptoms of severe MR and promotes to eliminate moderate MR [13,14]. However mild MR is often neglected in clinical practice, which has been shown to be associated with mortality in a diabetic population even in the presence of normal ejection fraction [15]. The present study design excluded moderate or severe MR to evaluate percentage of patients with mild MR before CABG, and observe dynamic changes in MR and explored clinical related risk factors and echocardiographic derived parameters as a potential predictor of dynamic changes in MR on 1-year follow-up.

2. Methods

2.1 Study population

This study was conducted in Fuwai Hospital, National Center for Cardiovascular Diseases (Beijing, China) from January 2019 to January 2021 and the medical records of consecutive patients who underwent selective isolated CABG were screened. The protocol was consistent with the principles of the Declaration of Helsinki and approved by the institutional ethics committee of Fuwai hospital and all participants provided written informed consent.

Preoperative echocardiography was performed within 1 week before surgery to determine the etiology and severity of MR and patients with trivial to mild MR were enrolled. Exclusion criteria were absence of sinus rhythm, moderate or severe valve stenosis or insufficiency, mitral

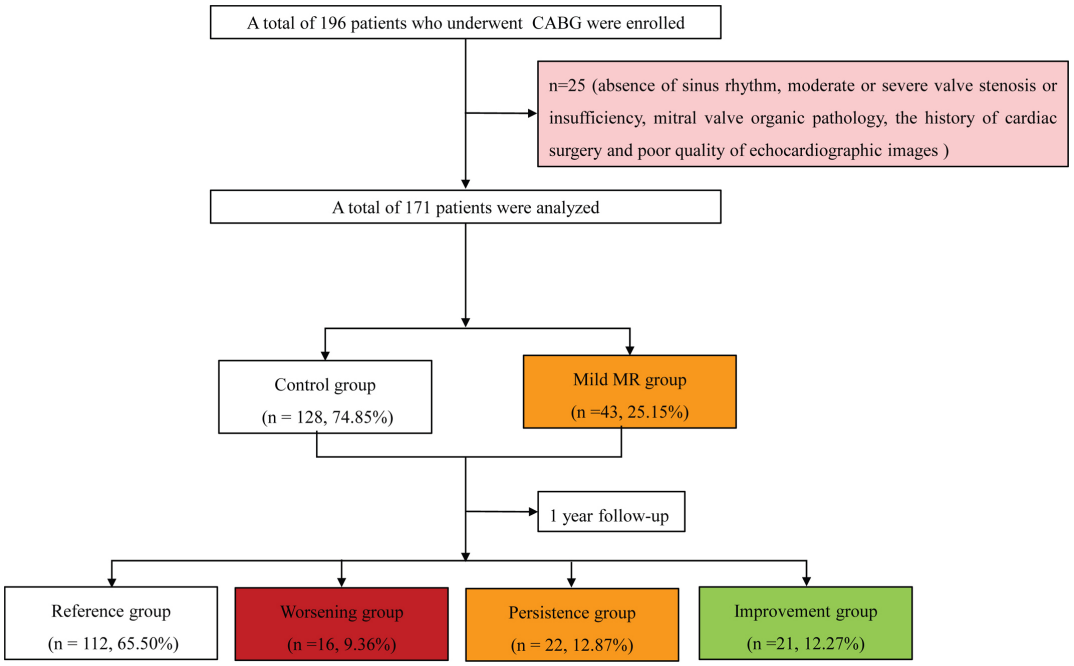

Fig. 1. Flow chart of study inclusion. Flow chart of study enrollment to illustrate the inclusion and exclusion criteria. CABG, coronary artery bypass graft.

valve organic pathology (prolapse, rheumatic, endocarditis, leaflet perforation, annular or leaflet calcification), valve prosthesis, the history of CABG or other cardiac surgery, unstable clinical conditions and poor quality of echocardiographic images (Fig. 1).

2.2 Transthoracic echocardiography

Echocardiography was performed by an experienced sonographer in accordance with American Society Echocardiography guidelines [16], preoperative (1 week before surgery), postoperative (1 week after surgery) period and 1 year follow-up. Comprehensive 2-dimensional (2D) echocardiography studies were performed with commercial equipment (EPIQ7 and iE33, Philips, Andover, MA), 3.5-MHz transducer and stored in DICOM format and transferred to TOMTEC image system (TOMTEC IMAGE SYSTEMS GMBH).

MR was assessed using a multiparametric approach in accordance with ASE and European Society of Cardiology valvular regurgitation guidelines, and defined as no or trace, mild (central jet area $<$20% LA and vena contracta $<$0.3 cm), moderate (effective regurgitant orifice area (EROA) $<$0.20 cm^2, regurgitant volume (RV) $<$30 mL, and regurgitant fraction (RF) $<$50%), or severe (EROA $>$0.20 cm^2, RV $>$30 mL, and RF $>$50%). All of the included patients were divided into two groups: the control group (no or trace MR) and the mild MR group.

LV ejection fraction (LVEF) was obtained by the Simpson's biplane method. LV end-diastolic dimension (LVEDd), end-systolic dimension (LVESd), wall thickness (LVPW), LA dimension and right ventricular dimension (RVD) were obtained in 2-dimensional or M-mode images, and relative wall thickness (RWT = 2 * LVPW/LVEDd) derived. LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) and LA volume (LAV) measured from the apical 2-chamber and 4-chamber views, calculated stroke volume (SV = LVEDV – LVESV). The LV mass (LVM) was calculated from formula. Parameters were normalized to body surface area (BSA). Peak velocities of early (E) and late (A) diastolic filling were obtained from Doppler recordings of mitral inflow, and peak early (e') velocities were measured by tissue Doppler imaging recordings of mitral valve movement. The mitral E/A and E/e' ratios were also calculated. In addition, mitral annulus (MA) diameter was measured in parasternal long-axis view and the interpapillary muscle distance (IPMD) was measured at parasternal short-axis view.

2.3 Strain analysis

Speckle-tracking echocardiography (STE) was performed on the apical 4-chamber, 3-chamber and 2-chamber views, and calculated LV global longitudinal strain (LVGLS) by averaging the peak value of 3 apical views. LA function showed by three strain components on the same apical 4-chamber, respectively LA reservoir function (LASr), LA pump function (LASct) and LA conduit function (LAScd). The right ventricular global longitudinal strain (RVGLS) was measured similarly with LVGLS, and RV free wall strain (RVFWS) was the mean value recorded for basal, mid, and apical segments, both performed on the apical focused RV-4-chamber. All Strain measurements were analyzed by the TOMTEC image system (TOMTEC

IMAGE SYSTEMS GMBH). The myocardium border detection was automated to ensure optimal tracking throughout cardiac cycle by the software, and the operator confirmed that the true boundaries were traced.

Reproducibility in measurement of strain was evaluated in 30 randomly selected patients using the interclass correlation coefficient. The results of intra- and interobserver variabilities for strain measurements were showed in Appendix Table 6.

2.4 Statistical analysis

2.4.1 Change in MR grade on 1 year follow-up

The study analyzed MR at baseline and 1 year follow-up, to assess the proportion of individuals who remained in the same category or changed on follow-up.

(1) Reference group: individuals without MR or less than mild MR at baseline, who remained in the same pattern;

(2) Persistence group: individuals with mild MR at baseline who persisted;

(3) Improvement group: individuals who reverted to none or less than mild MR from mild MR at baseline;

(4) Worsening group: individuals who developed to mild MR from none or less than mild MR at baseline.

2.4.2 Statistical methods

Statistical calculations were performed using IBM SPSS Statistics version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). Continuous variables were performed by Kolmogorov-Smirnov tests to check for a normal distribution and are expressed as mean $\pm$ SD or median and interquartile range. Categorical data are reported as counts and percentages. Comparisons between two groups used *t*-tests for continuous variables, and the chi-square test for categorical data. Variables associated with changes in MR in the univariate analysis ($p < 0.1$) are included in the multivariate analysis, after adjusting for age and gender. Bland-Altman method was used for assessing the agreement of inter-observer difference. Two-sided $p < 0.05$ was considered indicative of statistical significance.

3. Results

3.1 Patient characteristics

The clinical characteristics of 171 patients are summarized in Table 1, the mean age of the total study population was 61.31 $\pm$ 8.71 years and 78.95% were male, included none or trivial MR in 74.85% (n = 128) and mild MR in 25.15% (n = 43). There was no significant difference between age, gender, BSA, diastolic blood pressure, systolic blood pressure and preoperative medications. Compared with the control group, mild MR group had higher heart rate, New York Heart Association (NYHA) classification and preoperative N-terminal pro-brain natriuretic peptide (NT-proBNP) but lower hypertension ($p < 0.05$). The cohort patients underwent similar types of surgery, and the technique of using cardiopulmonary bypass (CPB) and number of grafts were similar in both groups. In terms of medications at discharge, there was no significant difference between the two groups, but the proportion of antiplatelet drugs increased compared to preoperative use ($p < 0.05$).

3.2 Echocardiographic parameters and strain measurements before surgery

The mean LVEF was 58.38 $\pm$ 9.72%, and significant lower in the mild MR group ($p < 0.01$), shown in the Table 2. The volumetric parameters (iLVEDV, iLVESV, LAVi) and size parameters (iLVEDd, iLVESd, LA dimension) were higher in the mild MR group ($p < 0.05$). The mild MR group had lower IVSd and RWT but greater LVMI ($p < 0.01$). The aortic structure including aortic valve ring, ascending, and sinus were no significant difference. Tricuspid regurgitation (TR) occurred more in the mild MR group ($p < 0.01$). The MA diameter and IPMD increased significantly in patients with mild MR ($p < 0.01$).

LVGLS, LASr, LAScd and LASct were lower in the mild MR group ($p < 0.05$), shown in Table 2. The levels of RVGLS and RVFWS were similar in both group ($p > 0.05$).

3.3 Transition rates of MR after 1-year follow-up

Of the 128 patients in the control group, MR had progressed in 16 patients (12.50%) at one year after surgery. Of the 43 patients, MR had regressed in 21 patients (48.84%) and persisted in 22 patients (51.16%).

3.4 Predictive value of change in MR

In this study, there were 37 individuals describing the change in MR after 1-year follow-up (Tables 3,4). 112 individuals (white form) remained without MR (reference group), 16 participants (red form) progressed to mild MR from the control group (worsening group), and 21 individuals (green form) who regressed from mild MR (improvement group). Furthermore, 22 individuals (yellow form) who remained in the mild MR (persistence group).

Table 5 reported the results from the univariate and multivariate logistic regression analysis. In multivariate analysis, LVEF (OR = 0.91 [95% CI: 0.84–1.00]; $p = 0.042$) and LAVi (OR = 1.17 [95% CI: 1.00–1.37]; $p = 0.045$) were associated with an increased risk of developing MR (worsening group) ($p < 0.05$), while not emerged as key correlates of the contrary process (improvement group) ($p > 0.05$). In terms of mitral apparatus, larger =MA diameter (OR = 1.55 [95% CI: 1.01–2.38]; $p = 0.043$) and IPMD (OR = 2.06 [95% CI: 1.32–3.21]; $p = 0.001$) had associations with development of MR, while not with regression of MR. Moreover, preoperative left main coronary artery occlusion impeded the regression of MR following CABG surgery ($p < 0.05$).

Table 1. Baseline characteristics and operative data.

Variable	Total (n = 171)	Control group (n = 128)	Mild MR group (n = 43)	*p*
Age, yrs	61.31 ± 8.71	60.80 ± 8.85	62.81 ± 8.19	0.191
Female	36 (21.05%)	26 (20.31%)	10 (23.26%)	0.682
Body surface area, m^2	1.78 ± 0.16	1.78 ± 0.15	1.76 ± 0.18	0.557
Systolic blood pressure, mmHg	124.43 ± 19.74	125.55 ± 21.34	121.07 ± 13.57	0.198
Diastolic blood pressure, mmHg	73.18 ± 10.56	73.16 ± 11.02	73.23 ± 9.17	0.967
Basic heart rate, beats/min	68.70 ± 10.60	67.43 ± 9.57	72.47 ± 12.60	0.007
NYHA functional classification	2.26 ± 0.62	2.20 ± 0.62	2.42 ± 0.59	0.047
Smoking	94 (54.97%)	69 (53.91%)	25 (58.14%)	0.629
Underlying disease				
Hypertension	112 (65.50%)	90 (70.31%)	22 (51.16%)	0.022
Diabetes mellitus	61 (35.67%)	46 (35.94%)	15 (34.88%)	0.901
Stroke	29 (16.96%)	21 (16.41%)	8 (18.60%)	0.740
Peripheral artery disease	27 (15.79%)	21 (16.41%)	6 (13.95%)	0.703
Chronic kidney disease	21 (12.28%)	12 (9.38%)	9 (20.93%)	0.046
Old myocardial infarction	59 (34.50%)	42 (32.81%)	17 (39.53%)	0.422
Percutaneous intervention	26 (15.20%)	17 (13.28%)	9 (20.93%)	0.227
Preoperative angina pectoris	154 (90.06%)	113 (88.28%)	41 (95.35%)	0.180
Medications at baseline				
Beta-blockers	99 (57.89%)	75 (58.59%)	24 (55.81%)	0.749
ACEI/ARB	44 (25.73%)	30 (23.44%)	14 (32.56%)	0.237
Antiplatelets	94 (54.97%)	71 (55.47%)	23 (53.49%)	0.821
Diuretics	15 (8.77%)	9 (7.03%)	6 (13.95%)	0.165
Laboratory exam				
White blood cell count, 10^9/L	6.61 ± 1.86	6.70 ± 2.03	6.34 ± 1.18	0.270
Hemoglobin, g/dL	138.12 ± 18.30	139.59 ± 19.12	133.72 ± 14.98	0.069
Platelet count, 10^9/L	216.00 (175.00–257.00)	219.50 (174.75–261.25)	205.00 (175.00–246.00)	0.139
Creatinine, μmol/L	86.29 ± 16.84	86.18 ± 17.52	86.62 ± 14.85	0.883
Glucose, mmol/L	5.46 (3.59–13.24)	5.46 (3.59–13.24)	5.41 (4.04–8.20)	0.205
Glycated hemoglobin	6.61 ± 1.20	6.65 ± 1.21	6.50 ± 1.17	0.510
High-density lipoprotein, mmol/L	1.10 ± 0.28	1.09 ± 0.26	1.11 ± 0.29	0.897
Low-density lipoprotein, mmol/L	2.13 (0.93–5.71)	2.20 (0.93–5.71)	1.96 (1.12–4.36)	0.261
Total cholesterol, mmol/L	3.95 ± 1.12	4.01 ± 1.18	3.76 ± 0.91	0.204
NT-proBNP, pg/mL	153.90 (58.40–543.95)	118.50 (49.63–329.47)	578.95 (211.55–1233.40)	<0.001
Angiographic findings				
LM	59 (34.50%)	44 (34.38%)	15 (34.88%)	0.952
LAD	135 (78.95%)	100 (78.12%)	35 (81.40%)	0.649
LCX	147 (85.96%)	107 (83.59%)	40 (93.02%)	0.124
RCA	153 (89.47%)	113 (88.28%)	40 (93.02%)	0.381
Intraoperative off-pump	74 (43.27%)	56 (43.75%)	18 (41.86%)	0.829
Number of grafts, n	3.19 ± 0.90	3.16 ± 0.87	3.28 ± 1.01	0.472
POAF	29 (16.96%)	20 (15.62%)	9 (20.93%)	0.423
In-hospital day, n	16.08 ± 6.45	15.60 ± 6.24	17.49 ± 6.94	0.097
Medication at discharge				
Beta-blockers	114 (66.67%)	85 (66.41%)	29 (67.44%)	0.901
ACEI/ARB	50 (29.24%)	37 (28.91%)	13 (30.23%)	0.869
Antiplatelets	168 (98.25%)	126 (98.44%)	42 (97.67%)	0.742
Diuretics	57 (33.33%)	39 (30.47%)	18 (41.86%)	0.170

NYHA, New York Heart Association; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; LM, left main coronary artery; LAD, left anterior descending branch; LCX, left circumflex branch; RCA, right coronary artery; POAF, postoperative atrial fibrillation.

Table 2. Echocardiographic parameters and strain measurements at baseline.

Variable	Total (n = 171)	Control group (n = 128)	Mild MR group (n = 43)	*p*
LVEF, %	58.38 ± 9.72	61.21 ± 6.47	49.96 ± 12.61	<0.001
LVGLS, %	–11.82 ± 4.92	–12.58 ± 4.60	–9.49 ± 5.21	0.005
iLVEDd, mm/m^2	28.47 ± 3.84	27.59 ± 3.05	31.10 ± 4.70	<0.001
iLVESd, mm/m^2	20.54 ± 4.66	19.00 ± 3.19	24.08 ± 5.61	<0.001
iLVEDV, mL/m^2	69.32 ± 22.36	64.55 ± 17.19	88.15 ± 29.98	<0.001
iLVESV, mL/m^2	30.62 ± 18.62	25.60 ± 11.03	50.44 ± 27.75	<0.001
iSV, mL/m^2	38.69 ± 8.65	38.94 ± 9.01	37.70 ± 7.12	0.570
IVSd, mm	9.89 ± 1.61	10.04 ± 1.58	9.44 ± 1.65	0.035
LVPW, mm	9.17 ± 1.26	9.22 ± 1.24	9.02 ± 1.31	0.354
RWT	0.37 ± 0.07	0.38 ± 0.06	0.34 ± 0.07	<0.001
LVMI, g/m^2	98.96 ± 28.18	95.48 ± 25.70	109.32 ± 32.73	0.005
E/A	1.19 ± 0.63	1.28 ± 0.59	1.17 ± 0.64	0.401
E/e’	10.89 ± 3.99	10.54 ± 4.11	10.91 ± 4.09	0.932
Mitral apparatus				
MA diameter, mm	19.32 ± 1.79	19.04 ± 1.65	20.18 ± 1.92	<0.001
IPMD, mm	22.38 ± 1.67	22.10 ± 1.55	23.21 ± 1.76	0.001
Aortic values				
Ao Ann, mm	22.13 ± 2.70	22.14 ± 2.81	22.12 ± 2.38	0.973
Ao Asc, mm	32.99 ± 4.88	32.65 ± 5.13	34.00 ± 3.93	0.118
Ao SV, mm	32.78 ± 3.96	32.71 ± 3.96	32.98 ± 4.02	0.711
AR				0.072
<mild	155 (90.64%)	119 (92.97%)	36 (83.72%)	
mild	16 (9.36%)	9 (7.03%)	7 (16.28%)	
Left atrial values				
LA dimension, mm	36.82 ± 4.48	36.06 ± 4.24	39.07 ± 4.46	<0.001
LAVi, mL/m^2	31.34 ± 9.41	29.73 ± 8.51	37.49 ± 10.52	0.013
LASr, %	22.70 ± 14.88	24.44 ± 14.82	17.45 ± 13.96	0.008
LAScd, %	–14.32 ± 8.67	–15.16 ± 8.69	–11.76 ± 8.16	0.027
LASct, %	–9.23 (–15.75 to –0.79)	–9.50 (–16.56 to –1.09)	–6.06 (–13.23 to –0.75)	0.049
Right ventricular values				
RVD, mm	22.97 ± 2.77	23.05 ± 2.91	22.74 ± 2.34	0.537
MPA, mm	23.24 ± 2.47	23.20 ± 2.55	23.37 ± 2.27	0.707
RVGLS, %	–12.43 ± 7.06	–12.78 ± 6.99	–11.37 ± 7.24	0.264
RVFWS, %	–15.47 ± 9.22	–15.80 ± 9.15	–14.45 ± 9.49	0.410
TR				<0.001
<mild	149 (87.13%)	120 (93.75%)	29 (67.44%)	
mild	22 (12.87%)	8 (6.25%)	14 (32.56%)	

LVEF, left ventricular ejection fraction; LVGLS, LV global longitudinal strain; iLVEDd, indexed LV end-diastolic dimension; iLVESd, indexed LV end-systolic dimension; iLVEDV, indexed LV end-diastolic volume; iLVESV, indexed LV end-systolic volume; iSV, indexed stroke volume; LVMI, indexed LV mass; RWT, relative wall thickness; IVSd, interventricular septum thickness; LVPW, LV posterior wall thickness; MA, mitral annular; IPMD, interpapillary muscle distance; LA, left atrial; LAVi, LA volume index; LASr, LA reservoir strain; LAScd, LA conduit strain; LASct, LA contraction strain; RVD, right ventricular dimension; MPA, main pulmonary artery; RVGLS, RV global longitudinal strain; RVFWS, RV free wall strain; TR, tricuspid regurgitation.

Table 3. Transition rates of MR 1-year after CABG (n = number of observations).

Preoperative MR	MR 1-year after surgery	
	None	Mild
None (n = 128)	87.50% (n = 112)	12.50% (n = 16)
Mild (n = 43)	48.84% (n = 21)	51.16% (n = 22)

White form: individuals without MR or less than mild MR at baseline, who remained in the same pattern (reference group);
Yellow form: individuals with mild MR at baseline who persisted (persistence group);
Green form: individuals who reverted to no MR or less than mild MR from mild MR at baseline (improvement group);
Red form: individuals who developed to mild MR from no MR or less than mild MR at baseline (worsening group).

4. Discussion

This study showed that regurgitation disappeared in the 48.84% patients with mild MR, while 12.50% progressed to mild MR from no or trace regurgitation one year after surgery. Consistent with previous studies, MA diameter and IPMD were associated with development of mild MR. Furthermore, LAVi has the potential for predicting the change of MR on follow-up, meanwhile preoperative left main coronary artery occlusion may impede the improvement from mild MR.

The post MI remodeling in LV composition, geometry and function is accompanied with inflammatory changes within the MI region and followed by myocardial hypertrophy, progressive cavity dilation and contractile dysfunction [17,18]. The extent of ventricular dilation is directly related to the magnitude of the initial myocardial damage, but subsequent changes in ventricular geometry may also be associated with the effect of the tissue healing process, leading to further hemodynamic consequences, including more ischemic MR [19]. A mild degree of ischemic MR is often concerned for its progression to heart failure and increases short- or long-term mortality [20]. The study observed more than a quarter individual with mild MR at baseline, with significant lower LVEF and LVGLS. Previous studies have shown that baseline MR is associated with worse LV function, greater LV enlargement and chamber distortion after high-risk MI [21]. Otsuji *et al.* [22] found that global contractile dysfunction leads to functional MR especially in presence of a dilated left ventricle. Kim *et al.* [23] reported IPMD were increased significantly in patients with FMR than in those without FMR, and was the major determinant of mitral tenting volume and FMR severity. Consistent with previous studies, we observed significant increases in LV end-systolic and end-diastolic volumes and more TR occurred, with greater MA diameter and IPMD in patients with mild MR.

LV and LA function are tightly interdependence, and LV remodeling affects LA structure and function, which plays a key role in maintaining optimal cardiac performance [24,25]. Previous studies showed that subtle LV remodeling and dysfunction lead to progression of regurgitation and LA remodeling, meanwhile MR is a cause of progressive LA impairment and eventually LV dysfunction [26,27]. Consistent with these studies, we observed increased LA dimension and volume, and impaired LA reservoir, conduit and pump function in the mild MR group. Cameli *et al.* [28] reported a compensatory increase of LA strain was observed for patients with mild MR and a progressive impairment in those with moderate or severe MR. This controversial result may be caused by different aetiology of MR since the previous study included only organic MR, which was excluded in this study. As well-known, the association between MR and LA remodeling was common in moderate to severe MR, while the study suggested a substantial LA maladaptive process also in the early stage of functional MR.

CABG surgery is an effective common revascularization treatment for severe coronary artery disease to reduce the risk of sudden cardiac death and improve myocardial function [12]. Functional MR is commonly observed after MI and an independent predictor of mortality and cardiovascular morbidity [13]. CABG companied with mitral valve surgery may improve left ventricular performance, reverse left ventricular remodeling and then provide a more durable correction of moderate IMR [14]. However, mild MR is often overlooked and the dynamic changes of MR are relatively scarce in patients undergoing CABG surgery over time. In this study, patients with mild MR at baseline showed different trends on follow-up, about half regressed from mild MR and the rest remained in mild MR. LV remodeling increases annular tethering force and LV dysfunction decreases closing force, together leading to incomplete closure of the mitral valve [29]. MR regression indicates that effective revascularization promotes reverse remodeling, suggesting reversible ischemia rather than nonviable scar formation in MI region, while preoperative left main coronary artery occlusion may impede the process. We also found that one in eight individuals without MR at baseline progressed to mild MR on follow-up. Older age and lower LVEF were associated with this development. Further observations in our present analysis, LA volume could predict alterations in MR and larger LAVi was associated with progression to mild MR. Generally, LA is believed to play a role as cushion between the mitral valve or left ventricle and the pulmonary circulation and LV remodeling after MI directly impacts LA function and structure [26]. Maria *et al.* [30] reported patients with mild or moderate MR displayed greater LA myopathy, evidenced by worse LA remodeling and dysfunction, which tended to be associated with adverse outcomes. Tourneau *et al.* [10] found that greater LAVi incur excess mortality and frequent cardiac events, which is a strong and independent predictor of mitral valve

Table 4. Echocardiographic parameters and strain measurements according to change of MR on 1-year follow-up.

Variables	Reference group (n = 112)	Worsening group (n = 16)	Persistence group (n = 22)	Improvement group (n = 21)	*p*
LVEF, %	60.78 ± 6.40	55.88 ± 10.75	54.33 ± 10.22	56.10 ± 8.78	0.001
LVGLS, %	–13.88 ± 4.08	–9.35 ± 4.62	–11.64 ± 3.28	–11.61 ± 3.99	0.013
iLVEDd, mm/m^2	27.07 ± 2.60	28.22 ± 3.83	30.85 ± 3.91	27.36 ± 4.74	<0.001
iLVESd, mm/m^2	18.04 ± 2.96	19.43 ± 5.75	22.16 ± 2.90	17.45 ± 2.46	0.027
iLVEDV, mL/m^2	61.65 ± 13.50	72.36 ± 21.54	76.85 ± 19.36	72.64 ± 25.18	0.014
iLVESV, mL/m^2	24.93 ± 9.80	32.74 ± 16.26	36.27 ± 18.13	34.72 ± 13.02	0.018
iSV, mL/m^2	37.04 ± 6.35	39.62 ± 5.45	42.13 ± 8.49	39.37 ± 8.36	0.008
IVSd, mm	9.94 ± 1.51	9.21 ± 1.72	9.85 ± 1.51	10.25 ± 1.84	0.239
LVPW, mm	9.15 ± 1.02	8.65 ± 1.70	8.83 ± 1.23	9.29 ± 1.55	0.282
RWT	0.38 ± 0.06	0.36 ± 0.07	0.34 ± 0.07	0.38 ± 0.10	0.120
LVMI, g/m^2	90.95 ± 16.93	99.57 ± 23.27	105.76 ± 22.26	97.27 ± 24.61	0.021
E/A	1.21 ± 0.60	1.47 ± 0.59	1.44 ± 0.47	1.33 ± 0.51	0.322
E/e’	9.36 ±3.11	12.42 ±2.71	12.18 ± 2.28	11.89 ± 2.31	0.597
Mitral apparatus					
MA diameter, mm	18.91 ± 1.61	19.82 ± 1.73	20.53 ± 1.88	19.67 ± 1.93	<0.001
IPMD, mm	21.87 ± 1.34	23.16 ± 1.99	23.38 ± 2.05	22.84 ± 0.74	<0.001
Aortic values					
Ao Ann, mm	21.68 ± 1.77	20.76 ± 1.79	21.48 ± 1.91	21.69 ± 2.15	0.311
Ao Asc, mm	33.00 ± 3.55	33.18 ± 3.41	32.05 ± 4.24	34.06 ± 3.05	0.396
Ao SV, mm	32.76 ± 3.34	30.81 ± 3.83	32.05 ± 3.84	33.69 ± 5.04	0.138
AR					0.008
<mild	106 (94.64%)	13 (81.25%)	16 (72.73%)	21 (100.00%)	
mild	6 (5.36%)	3 (18.75%)	6 (27.27%)	-	
Left atrial values					
LA dimension, mm	37.92 ± 4.20	41.76 ± 6.44	40.94 ± 6.15	39.86 ± 4.44	0.005
LAVi, mL/m^2	28.58 ± 7.63	36.19 ± 10.81	41.10 ± 9.40	31.18 ± 10.44	0.020
LASr, %	23.89 ± 13.09	15.81 ± 10.84	18.51 ± 9.73	20.38 ± 11.32	0.033
LAScd, %	–14.22 ± 7.94	–11.58 ± 9.96	–11.56 ± 6.35	–12.21 ± 5.54	0.280
LASct, %	–9.81 (–15.60 to –4.29)	–5.20 (–8.68 to –2.54)	–8.74 (–13.38 to –2.01)	–10.54 (–13.70 to –0.03)	0.187
Right ventricular values					
RVD, mm	22.31 ± 2.73	22.66 ± 3.71	21.02 ± 3.36	22.53 ± 2.83	0.254
MPA, mm	22.54 ± 2.47	22.59 ± 2.21	22.37 ± 1.64	23.28 ± 2.87	0.645
RVGLS, %	–10.05 ± 6.72	–10.03 ± 7.40	–11.29 ± 6.52	–10.37 ± 6.62	0.892
RVFWS, %	–9.90 ± 5.27	–9.11 ± 5.81	–9.76 ± 4.96	–9.28 ± 5.44	0.921
TR					<0.001
<mild	105 (93.75%)	6 (37.50%)	10 (45.45%)	19 (90.48%)	
mild	7 (6.25%)	10 (62.50%)	12 (54.55%)	2 (9.52%)	

surgery results of patients with chronic organic MR. Our results are in line with previous study, showing significant remodeling and impaired contractile function in patients with progressed MR after isolated CABG. This is the first time to provide new insights by evaluating the relationship between LA remodeling and dysfunction and functional MR following isolated CABG and the current data indicate that greater LA volume is associated with the presence of mild MR on 1-year follow-up. Thus, larger proportion of individuals and longer period of follow-up are required to observe such a transition and subsequent dynamic changes in MR.

5. Study limitations

Several limitations should be mentioned. First, it was performed with a relatively small sample size and restricted duration of follow-up time. Second, the study was a single-center study, which may influence the generalizability of its results. Third, this study excluded patients with poor quality images, which might cause selection bias. Thus, a multicenter study, in larger sample size and longer follow-up period, will be needed.

Table 5. Univariate and multivariate analysis for changes in MR.

Variable	Worsening group (n = 16)				Improvement group (n = 21)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, yrs	1.13 (1.04, 1.22)	0.003			0.99 (0.91, 1.06)	0.693		
Female	2.76 (0.90, 8.47)	0.076			0.75 (0.17, 3.31)	0.707		
NYHA functional class	1.71 (0.70, 4.13)	0.237			0.75 (0.27, 2.15)	0.598		
LM occlusion	2.11 (0.73, 6.08)	0.166			0.26 (0.06, 1.03)	0.056	0.03 (0.00, 0.55)	0.018
LVEF, %	0.94 (0.87, 1.00)	0.064	0.91 (0.84, 1.00)	0.042	1.02 (0.97, 1.07)	0.474		
iLVEDD, mm/m^2	1.03 (0.87, 1.22)	0.716			0.89 (0.77, 1.02)	0.094	0.87 (0.70, 1.08)	0.214
LAVi, mL/m^2	1.16 (1.01, 1.32)	0.030	1.17 (1.00, 1.37)	0.045	0.89 (0.74, 1.05)	0.170		
RVD, mm	0.75 (0.60, 0.94)	0.013	0.83 (0.65, 1.07)	0.153	1.03 (0.80, 1.34)	0.813	0.84 (0.56, 1.28)	0.428
MA diameter, mm	1.43 (1.01, 2.02)	0.043	1.55 (1.01, 2.38)	0.043	0.90 (0.67, 1.22)	0.512	0.54 (0.25, 1.19)	0.128
IPMD, mm	1.78 (1.19, 2.64)	0.005	2.06 (1.32, 3.21)	0.001	0.79 (0.53, 1.17)	0.238	0.71 (0.31, 1.60)	0.404

6. Conclusions

Patients with mild SMR after MI had LV and LA dysfunction, and about half regressed on follow-up following isolated CABG, while preoperative left main coronary artery occlusion may impede the improvement. One in eight individuals without MR at baseline progressed to mild MR on follow-up and LA volume has the potential for predicting this process.

Author contributions

HanW, HaoW—Conceptualization; HanW, BZ, HaoW—Methodology; HanW, ZHZ—Data acquisition, analysis, and interpretation; HanW—Writing original draft preparation; HanW, WCW—Writing, review and editing; HanW, HaoW—Supervision.

Ethics approval and consent to participate

All participants provided their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Fuwai hospital (2021-HG06).

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Conflict of interest

The authors declare no conflict of interest.

Appendix

See Table 6.

Table 6. Interclass correlation coefficients for strain measurements.

Variable	Interobserver		Intraobserver	
	ICC	*p*	ICC	*p*
LVGLS	0.952	<0.001	0.982	<0.001
LASr	0.946	<0.001	0.973	<0.001
LAScd	0.931	<0.001	0.961	<0.001
LASct	0.933	<0.001	0.934	<0.001
RVGLS	0.899	<0.001	0.921	<0.001
RVFWS	0.896	<0.001	0.908	<0.001

ICC, intraclass correlation coefficient; LVGLS, left ventricular global longitudinal strain; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contraction strain; RVGLS, right ventricular global longitudinal strain; RVFWS, right ventricular free wall strain.

References

[1] Lehmann KG. Mitral Regurgitation in Early Myocardial Infarction. Annals of Internal Medicine. 1992; 117: 10.

[2] Alam M, Thorstrand C, Rosenhamer G. Mitral regurgitation following first-time acute myocardial infarction–early and late findings by Doppler echocardiography. Clinical Cardiology. 1993; 16: 30–34.

[3] Lamas GA, Mitchell GF, Flaker GC, Smith SC, Gersh BJ, Basta L, *et al*. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. Circulation. 1997; 96: 827–833.

[4] Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation. 2001; 103: 1759–1764.

[5] Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, *et al*. Heart failure and death after myocar-

dial infarction in the community: the emerging role of mitral regurgitation. Circulation. 2005; 111: 295–301.

[6] Grigioni F, Detaint D, Avierinos J, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. Journal of the American College of Cardiology. 2005; 45: 260–267.

[7] Amigoni M, Meris A, Thune JJ, Mangalat D, Skali H, Bourgoun M, *et al*. Mitral regurgitation in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: prognostic significance and relation to ventricular size and function. European Heart Journal. 2007; 28: 326–333.

[8] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, *et al*. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2016; 29: 277–314.

[9] Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. The Lancet. 2009; 373: 1382–1394.

[10] Le Tourneau T, Richardson M, Juthier F, Modine T, Fayad G, Polge A, *et al*. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. Heart. 2010; 96: 1311–1317.

[11] Rossi A, Dini FL, Agricola E, Faggiano P, Benfari G, Temporelli PL, *et al*. Left atrial dilatation in systolic heart failure: a marker of poor prognosis, not just a buffer between the left ventricle and pulmonary circulation. Journal of Echocardiography. 2018; 16: 155–161.

[12] Spadaccio C, Benedetto U. Coronary artery bypass grafting (CABG) vs. percutaneous coronary intervention (PCI) in the treatment of multivessel coronary disease: quo vadis? -a review of the evidences on coronary artery disease. Annals of Cardiothoracic Surgery. 2018; 7: 506–515.

[13] Shen J, Xia L, Song K, Wang Y, Yang Y, Ding W, *et al*. Moderate Chronic Ischemic Mitral Regurgitation. International Heart Journal. 2019; 60: 796–804.

[14] Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, *et al*. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. The New England Journal of Medicine. 2016; 374: 1932–1941.

[15] Rossi A, Zoppini G, Benfari G, Geremia G, Bonapace S, Bonora E, *et al*. Mitral Regurgitation and Increased Risk of all-Cause and Cardiovascular Mortality in Patients with Type 2 Diabetes. The American Journal of Medicine. 2017; 130: 70–76.e1.

[16] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal Cardiovascular Imaging. 2015; 16: 233–270.

[17] Kostuk WJ, Kazamias TM, Gander MP, Simon AL, Ross J. Left ventricular size after acute myocardial infarction. Serial changes and their prognostic significance. Circulation. 1973; 47: 1174–1179.

[18] Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, *et al*. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults with ST-Elevation and Non-ST-Elevation Myocardial Infarction: a Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circulation: Cardiovascular Quality and Outcomes. 2017; 10: e000032.

[19] Erlebacher JA, Weiss JL, Weisfeldt ML, Bulkley BH. Early dilation of the infarcted segment in acute transmural myocardial infarction: role of infarct expansion in acute left ventricular enlargement. Journal of the American College of Cardiology. 1984; 4: 201–208.

[20] Aronson D, Goldsher N, Zukermann R, Kapeliovich M, Lessick J, Mutlak D, *et al*. Ischemic mitral regurgitation and risk of heart failure after myocardial infarction. Archives of Internal Medicine. 2006; 166: 2362–2368.

[21] Meris A, Amigoni M, Verma A, Thune JJ, Køber L, Velazquez E, *et al*. Mechanisms and predictors of mitral regurgitation after high-risk myocardial infarction. Journal of the American Society of Echocardiography. 2012; 25: 535–542.

[22] Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song J, Guerrero JL, *et al*. Insights from Three-Dimensional Echocardiography into the Mechanism of Functional Mitral Regurgitation. Circulation. 1997; 96: 1999–2008.

[23] Kim K, Kaji S, An Y, Nishino T, Tani T, Kitai T, *et al*. Interpapillary muscle distance independently affects severity of functional mitral regurgitation in patients with systolic left ventricular dysfunction. The Journal of Thoracic and Cardiovascular Surgery. 2014; 148: 434–40.e1.

[24] Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction. Journal of the American College of Cardiology. 2019; 73: 1961–1977.

[25] Deferm S, Martens P, Verbrugge FH, Bertrand PB, Dauw J, Verhaert D, *et al*. LA Mechanics in Decompensated Heart Failure: Insights From Strain Echocardiography With Invasive Hemodynamics. JACC. Cardiovascular Imaging. 2020; 13: 1107–1115.

[26] Melenovsky V, Hwang S, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circulation. Heart Failure. 2015; 8: 295–303.

[27] Dziadzko V, Dziadzko M, Medina-Inojosa JR, Benfari G, Michelena HI, Crestanello JA, *et al*. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. European Heart Journal. 2019; 40: 2194–2202.

[28] Cameli M, Lisi M, Giacomin E, Caputo M, Navarri R, Malandrino A, *et al*. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography. Echocardiography. 2011; 28: 327–334.

[29] Chaput M, Handschumacher MD, Tournoux F, Hua L, Guerrero JL, Vlahakes GJ, *et al*. Mitral leaflet adaptation to ventricular remodeling: occurrence and adequacy in patients with functional mitral regurgitation. Circulation. 2008; 118: 845–852.

[30] Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, *et al*. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. European Journal of Heart Failure. 2020; 22: 489–498.