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Myocardial contrast echocardiography evaluation of coronary microvascular dysfunction to Predict MACEs in patients with heart failure with preserved ejection fraction follow-up

Fuhua Chen[1], Wenchao Weng[1], Daoling Yang[1], Xiaomin Wang[2] and Yibo Zhou[1*]

Abstract

Background CMD refers to the abnormalities of the tiny arteries and capillaries within the coronary artery system, which result in restricted or abnormal blood flow. CMD is an important mechanism involved in ischemic heart disease and secondary heart failure. CMD can explain left ventricular dysfunction and poor prognosis.The European Association of Cardiovascular Imaging recommends the use of MCE for the assessment of myocardial perfusion. Myocardial contrast echocardiography (MCE) is used to evaluate the accuracy of Coronary microvascular dysfunction (CMD) for predicting major adverse cardiac events (MACEs) in patients with heart failure with preserved ejection fraction (HFpEF) at follow-up.

Methods The clinical data of 142 patients diagnosed with HFpEF in our hospital from January 2020 to January 2022 were retrospectively summarized and stratified into 77 cases (> 1) in the CMD group and 65 cases (= 1) in the non-CMD group based on the perfusion score index (PSI) of the 17 segments of the left ventricle examined by the admission MCE, and the perfusion parameters were measured at the same time, including the peak plateau intensity (A value), the curve slope of the curve rise (βvalue) and A × β values. At a median follow-up of 27 months till October 2023, MACEs were recorded mainly including heart failure exacerbation, revascularization, cardiac death, etc.

Results Increasing age, hypertension, diabetes, and coronary artery disease in the CMD group resulted in decreased left ventricular ejection fraction (LVEF), increased plasma NT-B-type natriuretic peptide (BNP) and left ventricular global longitudinal strain (LVGLS), decreased A-values and A × β-values, and an increased incidence of MACEs ($P < 0.05$). Univariate and multivariate Cox regression analyses showed that LVGLS (HR = 1.714, 95% CI = 1.289–2.279, $P < 0.001$) and A × β values (HR = 0.636, 95% CI = 0.417 to 0.969, $P = 0.035$) were independent predictors of MACEs in patients with HFpEF. The receiver operating characteristic curve (ROC) showed that the area under the curve (AUC) of LVGLS combined with A × β value for diagnosis of MACEs was 0.861 (95% CI = 0.761 ~ 0.961, $P < 0.001$), which was

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significantly higher than that of LVGLS or A × β value ($P < 0.05$). The Kaplan-Meier survival curves showed that the cumulative survival rate in CMD group was significantly lower than non-CMD group (logrank $\chi^2 = 6.626$, $P = 0.010$), with the most significant difference at 20 months of follow-up.

Conclusion MCE can evaluate CMD semi-quantitatively and quantitatively, LVGLS combined with A × β value has good performance in predicting the risk of developing MACEs in patients with HFpEF at 3 years of follow-up, and CMD can be used as an important non-invasive indicator for assessing clinical prognosis.

Keywords Myocardial contrast echocardiography, Coronary microvascular dysfunction, Heart failure with preserved ejection fraction, Major adverse cardiac events, Perfusion score index, Left ventricular global longitudinal strain

Background

Coronary atherosclerosis and lumen stenosis are the main causes of types of ischemic heart disease [1]. However, with further research, coronary microcirculation dysfunction (CMD) is more prevalent and is an important mechanism involved in ischemic heart disease and secondary heart failure [2]. CMD refers to the abnormalities of the tiny arteries and capillaries within the coronary artery system, which result in restricted or abnormal blood flow. CMD can be stratified as primary or secondary. Despite the restoration of smooth epicardial coronary circulation, a large portion of patients with ST segment elevation myocardial infarction (STEMI) has insufficient coronary microcirculation perfusion after percutaneous coronary intervention (PCI), which is an important adverse factor leading to ventricular remodeling and reduced cardiac function [3]. In addition to atherosclerotic stenosis of epicardial coronary arteries, myocardial ischemia may also be caused by CMD. Absence of reflow after PCI is considered a key factor in the decline of left ventricular ejection fraction (LVEF), which may increase the long-term mortality in young STEMI patients [4]. Therefore, CMD can explain left ventricular dysfunction and poor prognosis.

Cardiovascular magnetic resonance is a non-invasive tool for detecting CMDs, although CMR in patients with STEMI has some limitations [5]. Myocardial contrast echocardiography (MCE) is a well-established technique for assessing myocardial perfusion. The contrast agent is red blood cell-sized microbubbles (<7 μm), and the intensity of the myocardial signal emitted by the contrast agent reflects the concentration of microbubbles within the myocardium, which is fully saturated when the myocardium is infused with microbubbles in a continuous infusion process, the signal intensity reflects the relative capillary blood volume and a decrease in myocardial blood flow prolongs the filling time of the contrast agent in proportion to the decrease in myocardial blood flow [6]. The European Association of Cardiovascular Imaging recommends the use of MCE for the assessment of myocardial perfusion [7]. MCE has the advantages of being non-invasive, low cost, easy to perform, good reproducibility, sensitivity, and safety, and is more acceptable to patients.

The research focuses on the accuracy of MCE to evaluate CMD for predicting major adverse cardiac events (MACEs) in patients with heart failure preserved ejection fraction (HFpEF) at follow-up to provide a reference to guide clinical practice.

Methods

Subject

The clinical data of 142 patients diagnosed with HFpEF in our hospital from January 2020 to January 2022 were retrospectively summarized, 82 males and 60 females, aged from 50 to 76 with an average of (62.7±5.5) years old. inclusion criteria: ① Over 18 years old; ② Meet the diagnostic criteria of HFpEF, LVEF≥50% [8]; ③ Patients should sign for research, complete MCE examination, and the images are clear to preserve;④Treat and rehabilitate under the guideline recommendations, with ethical approval and complete clinical and follow-up data. Exclusion criteria: ①congenital heart disease, severe myocarditis, heart failure caused by chemotherapeutic drugs, pulmonary hypertension, severe cirrhosis, etc.; ② history of previous myocardial infarction or PCI treatment, malignant tumor, severe lung, liver, kidney, and other dysfunctions; ③ intolerance to contrast or risk of contrast nephropathy; ④ concurrently participating in other researches or loss of follow up.

Research methodology

Group methodology

The 142 patients were divided into 77 cases (>1) in the CMD group and 65 cases (=1) in the non-CMD group according to the perfusion score index (PSI) of the 17 segments of the left ventricle examined by MCE. Myocardial perfusion was scored using the semiquantitative method [9], with 1 point for uniform enhancement, 2 points for reduced or uneven enhancement, and 3 points for absence of enhancement, and the PSI was calculated by summing the scores of the 17 segments and dividing by 17 to reach the PSI value.

MCE inspection

Philips EPIQ CVX colour Doppler ultrasound machine with an S5-1 probe at 1.0–5.0 MHz, reaching MCE condition and QLAB15.5 offline analysis software. The mechanical index of the MCE mode was 0.18, and the flash frame rate was 15 frames/s. βblockers and calcium antagonists were stopped for at least 24 hs before the examination.

With the patient lying on the left side, we connected electrocardiogram and adjusted the images to optimize routine transthoracic two-dimensional echocardiography and cardiac strain testing to obtain left ventricular end diastolic diameter (LVEDd) and left ventricular end diastolic volume (LVEDV), left ventricular end systolic diameter (LVESd) and left ventricular end systolic volume (LVESV), through biplane Simpson to calculate LVEF. Three consecutive cardiac cycle images of apical four-chamber, three-chamber, and two-chamber views were acquired and stored, imported into the QLAB15.5 workstation, selected apical four-chamber, three-chamber, and two-chamber views, and clicked on Auto Strain LV to obtain left ventricular global longitudinal strain (LVGLS).

We use the ultrasound contrast agent Sono Vue (specification 59 mg of SF6 gas and 25 mg of lyophilized powder) from Bracco. First, we add 5 mL of 0.9% sodium chloride injection and fully shook to obtain a milky white suspension, then withdraw 2 mL of the milky white suspension with a 10 mL syringe. Then, switch to MCE mode, push 1 mL of enhancer into the left median elbow vein, inject it into the vein at a slow and uniform speed (about 1 ml/min), and use 5 ml of saline to flush the tube after the injection. After a stable myocardium, collect the apical 4-chamber, 2-chamber, 3-chamber, and papillary muscle horizontal short-axis section consecutively in the first 5 and last 15 cardiac cycles of the "flash", with at least 20 cardiac cycles stored in each section. We save images and analyze offline to obtain the time-intensity curve [10], and the measure perfusion parameters, which include the peak intensity of the plateau (A value), the upward slope of the curve (βvalue), and the A×β value, where the A value represents the blood volume of the local myocardium, theβvalue represents the local myocardial blood flow rate, and the A×βvalue represents the local myocardial perfusion blood flow (see Fig. 1). LVGLS measurement by 2D-tissue strain imaging(see Fig. 2) The entire process of ultrasound examination and post-processing was performed independently by ultrasound specialists with at least 10 years of experience, and all parameters were repeated three times to take the average value.

Clinical information and Follow-Up

Clinical data including gender, age, body mass index (BMI), hypertension, diabetes mellitus and coronary artery disease, and plasma N-terminal b-type natriuretic peptide (BNP) were recorded, with coronary artery disease determined based on at least 50% stenosis of the lumen diameter of coronary arteries as shown by enhanced coronary arterial CT or digital angiography. Coronary artery disease was determined based on coronary artery CT-enhanced imaging or digital angiography showing at least 50% narrowing of the lumen diameter.

All patients underwent a combination of medications, PCI, and rehabilitation instructions according to guideline recommendations, and were routinely followed up after discharge until October 2023, with a follow-up time of 10 to 45 months and a median time of 27 months. MACEs and time of occurrence were recorded, mainly including heart failure exacerbation, revascularization, and cardiac death.

Statistical methods

We used SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA) for data processing, and the measurements that conformed to normal distribution and chi-square were expressed as mean±standard deviation, and the comparison between two groups was performed by independent samples t-test, and the measurements that did not conform to normal distribution were expressed as median and quartiles, and the comparison was performed by Mann -Whitney U test, and count data comparison [cases (%)] were tested by χ2; univariate and multivariate Cox risk proportional models were used to screen the predictors along with the stepwise regression method; The area under curves (AUC), sensitivity and specificity were calculated by receiver operating characteristic curves (ROC) to obtain the optimal critical value, and the Z test was used in AUC comparison; the cumulative survival rate was plotted from the Kaplan-Meier survival curve, and the comparison was by the log-rank χ^2 test. $P<0.05$ was considered statistically significant.

Results

Comparison of clinical data and ultrasound parameters between the two groups

In the CMD group, patients with increasing age, hypertension, diabetes mellitus, and coronary artery disease had decreased LVEF, increased BNP levels and LVGLS, decreased A-value and A×βvalue, and an increased incidence of MACEs, which was under statistically significant differences ($P<0.05$),as shown in Table 1.

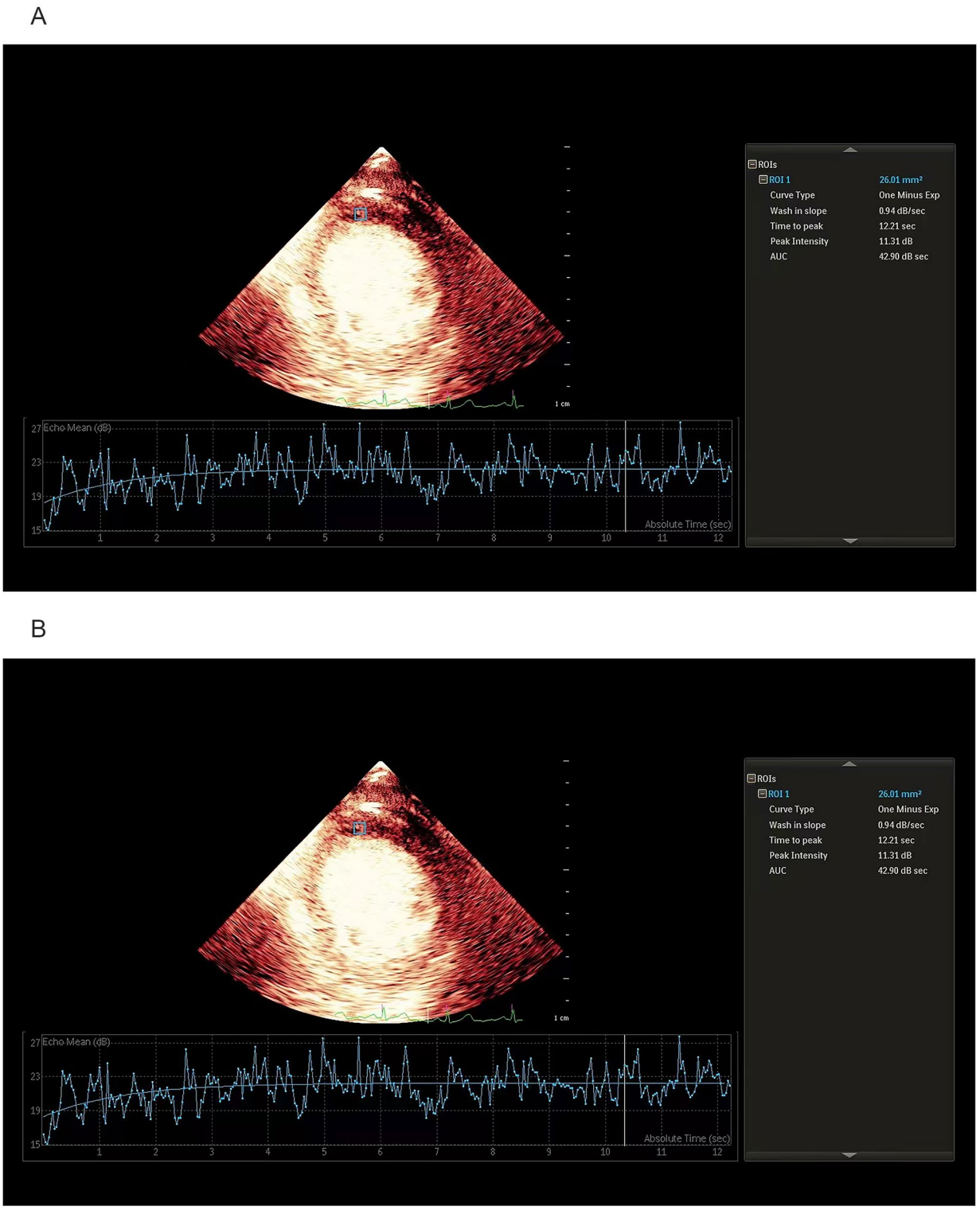

Fig. 1 Time-intensity plot of A and β values measured by MCE
A: Time-intensity curves without MACEs in non-CMD group
B: Time-intensity curve for the occurrence of MACEs in CMD group

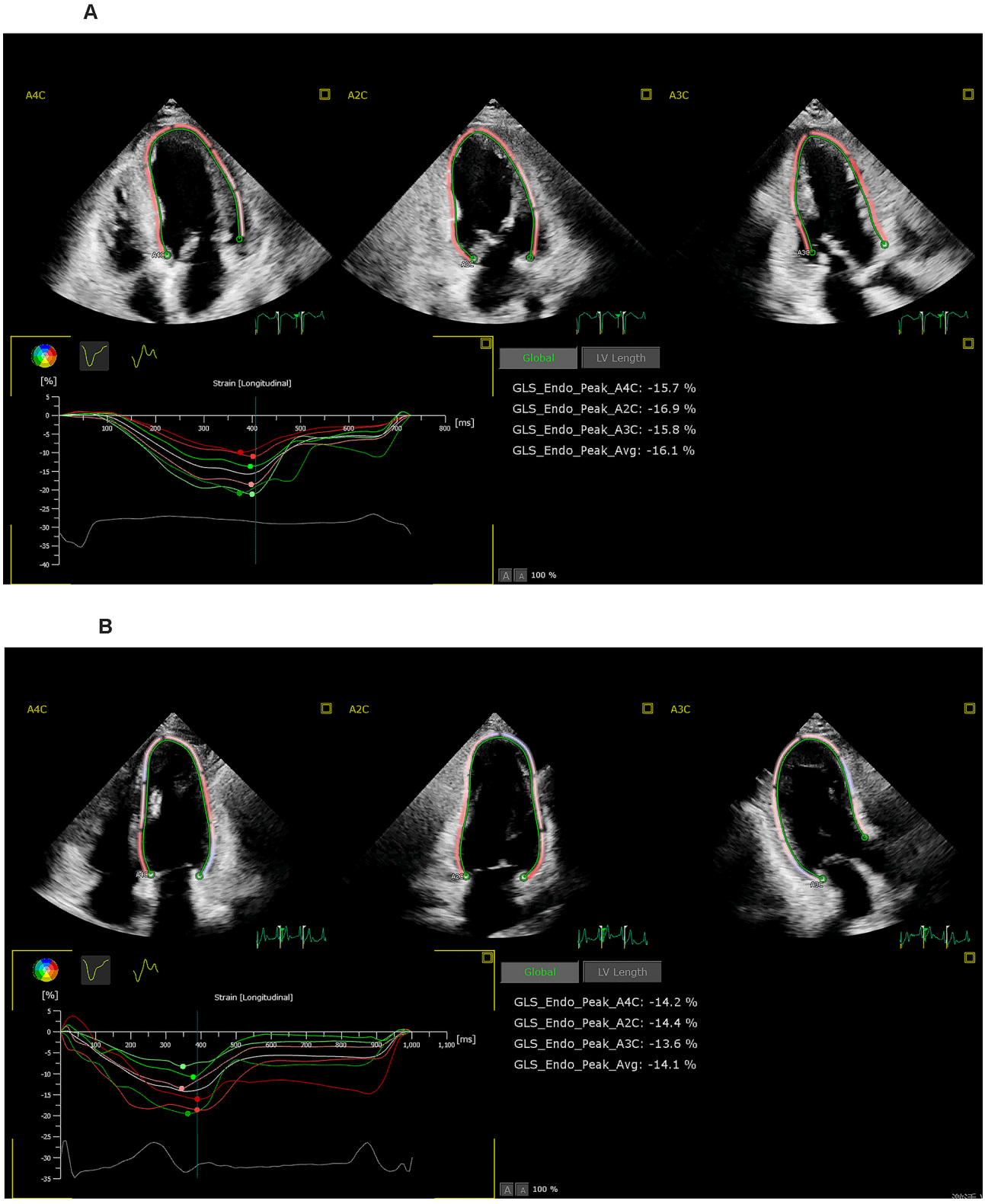

Fig. 2 LVGLS measurement by 2D-tissue strain imaging
A: non-MACE group
B: MACE group

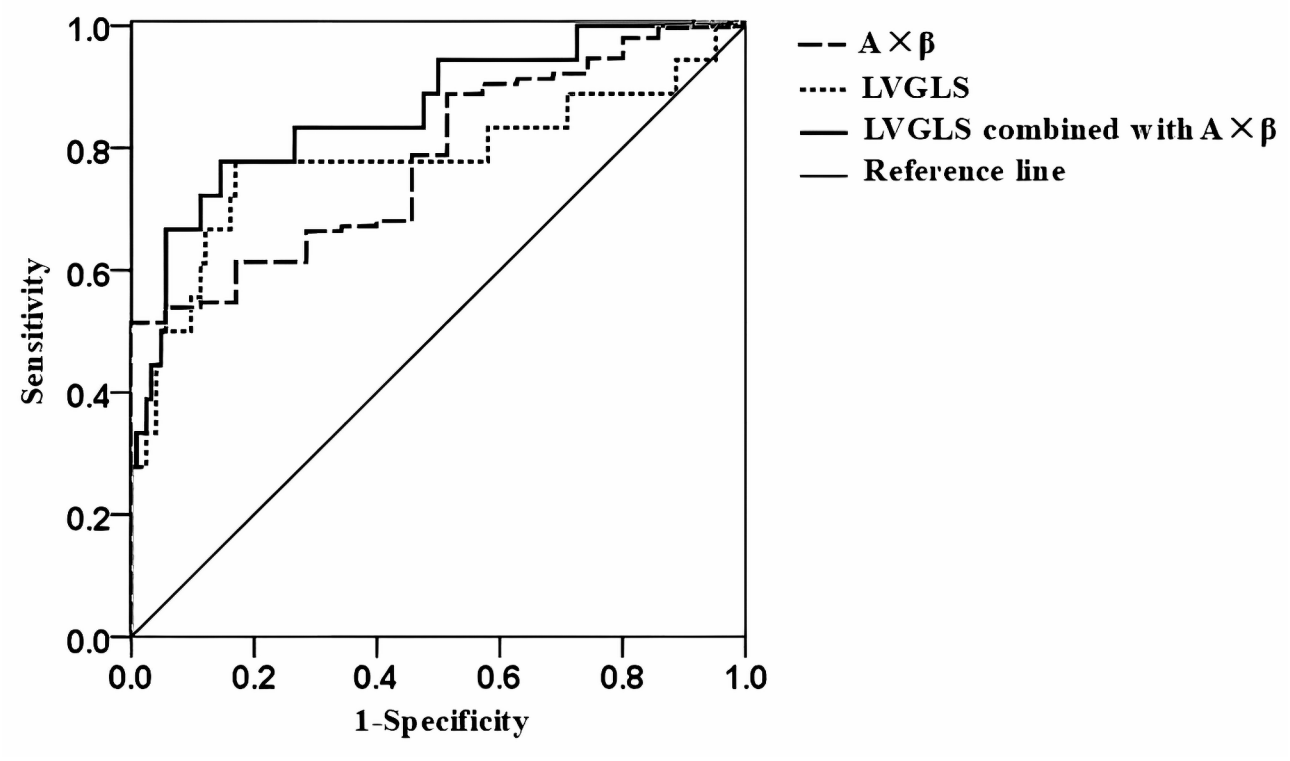

Fig. 3 ROC curves of LVGLS and A × β values for diagnosis of MACEs

Table 1 Comparison of clinical data and ultrasound parameters between the two groups

Variables:	Non-CMD group (*n* = 65)	CMD group (*n* = 77)	Z/t/χ^2 value	*P* value
M/F	37/28	45/32	0.033	0.855
Age, (years)	60.5 ± 5.4	64.5 ± 5.0	-4.539	<0.001
BMI, (kg/m^2)	23.1 ± 1.2	22.9 ± 1.3	0.950	0.344
Hypertension, n (%)	15 (23.1)	33 (42.9)	6.163	0.013
Diabetes, n (%)	10 (15.4)	25 (32.5)	5.538	0.019
Coronary artery disease, n (%)	38 (58.5)	60 (77.9)	6.242	0.012
LVEDd, (mm)	45.5 ± 3.4	45.8 ± 3.1	-0.647	0.519
LVESd, (mm)	31.9 ± 2.4	31.7 ± 2.6	0.575	0.566
LVEDV, (mL)	143.9 ± 14.4	146.2 ± 15.2	-0.904	0.368
LVESV, (mL)	67.3 ± 7.0	69.0 ± 6.9	-1.495	0.137
LVEF, (%)	53.3 ± 1.5	52.7 ± 1.5	2.038	0.043
BNP, (pg/mL)	528.3 ± 61.5	552.0 ± 72.4	-2.078	0.040
LVGLS, (%)	-16.2 ± 2.6	-14.3 ± 2.4	-4.611	<0.001
A-value	12.6 ± 2.1	11.3 ± 1.6	4.474	<0.001
β-value	3.56 (2.55,5.32)	2.96 (2.39,4.09)	-1.845	0.065
A x β-value,	43.1 (28.29,64.20)	33.2 (24.44,45.89)	-2.823	0.005
MACEs, n (%)	4 (6.2)	14 (18.2)	4.607	0.032

Note: CMD: coronary microcirculation dysfunction; BMI: body mass index; LVEDd: left ventricular end diastolic diameter; LVESd: left ventricular end systolic diameter; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; BNP: b-type natriuretic peptide; LVGLS: left ventricular global longitudinal strain; MACEs: major adverse cardiac events

Table 2 The comparison results of clinical datas and ultrasound parameters between MACEs subgroup patients

Variables:	Non-MACEs group (*n* = 124)	MACEs group (*n* = 18)	Z/t/χ^2 value	*P* value
CMD	63(50.8)	14(77.8)	4.607	0.032
M/F	72/52	10/8	0.041	0.840
Age, (years)	62.7 ± 5.5	62.4 ± 5.6	0.241	0.810
BMI, (kg/m^2)	23.0 ± 1.3	22.8 ± 0.8	0.542	0.589
Hypertension, n (%)	43 (34.7)	5 (27.8)	0.334	0.563
Diabetes, n (%)	31(25.0)	4(22.2)	0.065	0.798
Coronary artery disease, n (%)	86(69.4)	12(66.7)	0.053	0.818
LVEDd, (mm)	45.5 ± 3.2	46.5 ± 3.5	-1.204	0.231
LVESd, (mm)	31.7 ± 2.5	32.0 ± 2.3	-0.357	0.722
LVEDV, (mL)	145.4 ± 14.9	143.2 ± 14.8	0.605	0.546
LVESV, (mL)	68.3 ± 7.0	67.6 ± 7.3	0.407	0.684
LVEF, (%)	53.0 ± 1.5	52.8 ± 1.3	0.558	0.578
BNP, (pg/mL)	540.1 ± 67.6	548.5 ± 75.7	-0.491	0.625
LVGLS, (%)	-15.5 ± 2.4	-12.7 ± 3.1	-4.483	<0.001
A-value	12.0 ± 1.9	10.8 ± 1.9	2.583	0.011
β-value	3.37(2.58,4.81)	2.53(1.69,3.29)	-2.900	0.004
A x β-value,	40.88(27.12,57.47)	24.38(19.30,35.74)	-3.771	<0.001

Table 3 Factor analysis of the occurrence of MACEs in patients with HFpEF

factor	univariate				multivariate			
	β	Wald	*P*-value	OR (95% CI)	β	Wald	*P*-value	OR (95% CI)
CMD	1.362	5.708	0.017	3.904 (1.277 ~ 11.933)				
age	-0.005	0.012	0.912	0.995 (0.918 ~ 1.079)				
BMI	-0.107	0.313	0.576	0.898 (0.616 ~ 1.309)				
sexes	-0.116	0.060	0.806	0.890 (0.351 ~ 2.258)				
hypertensive	-0.302	0.328	0.567	0.739 (0.262 ~ 2.082)				
diabetes	-0.135	0.056	0.813	0.874 (0.287 ~ 2.664)				
coronary artery disease	0.075	0.022	0.882	1.077 (0.402 ~ 2.888)				
LVEDd	0.113	2.207	0.137	1.119 (0.965 ~ 1.299)				
LVESd	0.038	0.177	0.674	1.039 (0.869 ~ 1.242)				
LVEDV	-0.008	0.245	0.621	0.992 (0.960 ~ 1.024)				
LVESV	-0.009	0.072	0.789	0.991 (0.925 ~ 1.061)				
LVEF	-0.105	0.419	0.517	0.901 (0.656 ~ 1.237)				
BNP	0.001	0.132	0.716	1.001 (0.995 ~ 1.008)				
LVGLS	0.448	18.534	<0.001	1.566 (1.277 ~ 1.920)	0.539	13.706	<0.001	1.714(1.289 ~ 2.279)
A-value	-0.381	7.833	0.005	0.683 (0.523 ~ 0.892)				
β value	-0.566	7.393	0.007	0.568 (0.377 ~ 0.854)				
A × βvalue	-0.065	9.784	0.002	0.938 (0.900 ~ 0.976)	-0.453	4.427	0.035	0.636(0.417 ~ 0.969)

The comparison results of clinical datas and ultrasound parameters between MACEs subgroup patients

The CMD and LVGLS of patients in the MACEs group increased compared to those without MACEs, while the A value, β value, and A×β value decreased, with statistically significant differences ($P<0.05$). See Table 2.

Factor analysis of the occurrence of MACEs in patients with HFpEF

Univariate and multivariate Cox regression analyses showed that LVGLS (HR = 1.714, 95% CI = 1.289 to 2.279, $P<0.001$) and A×β values (HR = 0.636, 95% CI = 0.417 to 0.969, $P=0.035$) were independent predictors of MACEs in HFpEF patients, as shown in Table 3.

Performance analysis of LVGLS and a × β values for diagnosing MACEs

The ROC showed that the AUC of LVGLS with A×β values for the diagnosis of MACEs was 0.861 (95% CI = 0.761 to 0.961, $P<0.001$), which was significantly higher than the AUC of LVGLS or A×β values (Z value = 3.562 and 3.958, $P<0.05$), as shown in Table 4; Fig. 2.

Table 4 ROC analysis of LVGLS and a × β values for diagnosis of MACEs

norm	AUC	95% CI	*P*-value	Sensitivity (%)	Specificity (%)	Critical value
A × βvalue	0.776	0.682 ~ 0.869	<0.001	79.2	57.5	37.4
LVGLS	0.781	0.634 ~ 0.928	<0.001	78.6	80.9	-15.0%
LVGLS with A × βvalue	0.861	0.761 ~ 0.961	<0.001	82.6	74.3	-

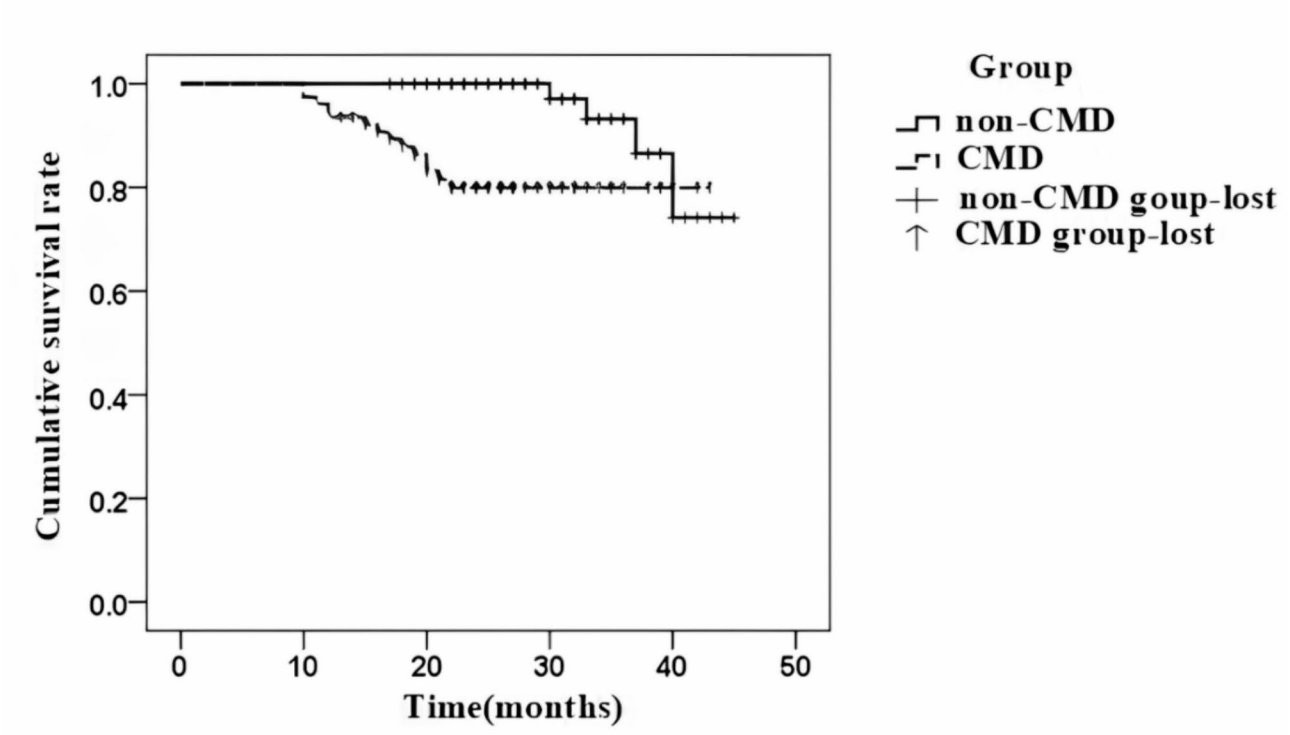

Fig. 4 Kaplan-Meier survival curves for follow-up prognosis of patients with CMD and HFpEF

Relationship between CMD and the prognosis of HFpEF patients at follow-up

Kaplan-Meier survival curves showed that cumulative survival was significantly lower in the CMD group than in the non-CMD group (logrank $\chi^2=6.626$, $P=0.010$), with the most significant difference at 20 months of follow-up, as shown in Fig. 4.

Discussion

Primary CMD refers to the presence of CMD even after exclusion of obvious abnormalities such as atherosclerosis and coronary artery myocardial bridges, which may be related to endothelial dysfunction, coronary artery abnormalities themselves, and myocardial metabolic abnormalities [11]. Secondary CMD, on the other hand, is caused by organic diseases such as coronary artery stenosis and hypertension, often because of other cardiovascular pathologies. The etiology and pathogenesis of CMD are complex and varied and may be related to a variety of factors such as endothelial factors, metabolic modulation, inflammatory factors, neurological factors, and so on [12, 13]. Endothelial dysfunction can lead to abnormal vasodilation and contraction, metabolic dysregulation can lead to abnormal cardiomyocyte metabolism, inflammation can cause abnormal vascular wall function, and neurological factors can also lead to dysregulation of the cardiovascular system. Various factors interact with each other to lead to the development of CMD.

The research shows the detection rate of CMD in patients with HFpEF is 54.2% (77/142). There is still a lack of objective and accurate epidemiological findings on the actual incidence of CMD, but more and more studies have begun to pay attention to the relationship between CMD and the occurrence and progression of various cardiovascular diseases [14]. The lack of typical clinical symptoms in the early stage of patients with HFpEF, and the lack of clear organic even though coronary artery disease is the main cause of heart failure, a significant proportion of patients present with no significant coronary artery stenosis, and the possibility of CMD needs to be considered [15]. In this research, the detection rate of coronary artery disease in HFpEF patients was 69.0% (98/142), suggesting that patients with HFpEF

may have both coronary artery disease and CMD, and that the two may interact with each other and participate in the development and progression of the disease [16]. Increasing age, hypertension, diabetes mellitus, and coronary artery disease in the CMD group suggest that age, hypertension, diabetes mellitus, and coronary artery disease may increase the risk of CMD. disease may increase the risk of CMD.

The research shows that LVEF decreases and BNP and LVGLS increase in the CMD group, suggesting that the presence of CMD may reduce cardiac function and myocardial strain, thus affecting ventricular remodeling and cardiac pumping function. A values and A×β values decrease in the CMD group, suggesting that the presence of CMD is consistent with the alteration of the MCE parameters. CMD mainly affects blood perfusion to the microvessels of distal coronary arteries, which are also the end and key segments of myocardial. The end and key segments of blood supply directly leads to insufficient myocardial perfusion, which contributes to the continuous aggravation of myocardial ischemia, the progression of ventricular remodeling, the decline of cardiac function and the increase of the incidence of MACEs [17, 18]. Decrease in A value and A×βvalue on the MCE map can visually and accurately reflect the decline of myocardial perfusion. we use univariate and multivariate Cox regression analyses to show that LVGLS (HR=1.714, 95% CI=1.289 ~ 2.279, $P<0.001$) and A×β values (HR=0.636, 95% CI=0.417 ~ 0.969, $P=0.035$) are independent predictors of MACEs in patients with HFpEF. The risk of MACEs increases 0.714-fold for each 1 standard deviation increase, and the risk of MACEs in patients with a 1 standard deviation decrease in A×β values was 0.636-fold higher than in those without a decrease. It is further shown that the AUC of LVGLS combined with A×β values for the diagnosis of MACEs is 0.861 (95% CI=0.761–0.961, $P<0.001$), which is significantly higher than the AUC of LVGLS or A×β values ($P<0.05$). It is suggested that the two-dimensional strain parameter LVGLS combined with the MCE parameter A×β value has a better predictive performance for the occurrence of MACEs in HFpEF patients at follow-up.

Finally, the research shows that cumulative survival is significantly lower in the CMD group than in the non-CMD group, with the most significant difference at 20 months of follow-up. Wang L et al. [19]. used MCE to test 105 patients with PCI-treated STEMI to show that CMD is detected in 62.9% of patients, that CMD is an independent predictor of total MACEs at 13 months of follow-up (corrected OR=2.457, 95% CI=1.042 to 5.790, $P=0.040$) and patients with CMD have a higher risk of hospitalization for heart failure (corrected OR=5.184, 95% CI=1.044 to 25.747, $P=0.044$) and repeat myocardial infarction (corrected OR=2.896, 95% CI=1.109 to 7.565, $P=0.030$). Yang N et al. [20]. showed a β value of ≤1.6 (OR=29.96, 95% CI=3.5 ~ 241.27, $P=0.002$) in 227 patients with nonobstructive coronary artery disease (CAD) who underwent MCE with adenosine triphosphate disodium (ATP) loading with a median follow up of 5.3 years, coronary flow reserve (CFR)≤2.0 (OR=25.21, 95% CI=3.01 ~ 182.32, $P=0.003$) and diabetes mellitus (OR=33.11, 95% CI=3.65 ~ 300.02, $P=0.002$) significantly increased the non-obstructive CAD patients' risk of MACEs occurrence. Quantitative MCE of ATP load is a feasible and validated method for evaluating CMD and can be used for clinical analysis, risk stratification, and guiding clinical treatment in early CAD.

This study also had some limitations: firstly, the sample size was limited, observation time was short, and there were fewer MACEs positive events, which may affect the stability of results; next step is to validate through multicenter, larger sample size, and prospective case-control trial. Secondly, MCE has not been widely popularized in clinical practice, the safety of examination needs to be comprehensively considered. However, the results of this study provided objective evidences for promoting the use of MCE in screening CMD during coronary artery ischemic disease and heart failure.

Conclusions

In conclusion, MCE can evaluate CMD semi-quantitatively and quantitatively, LVGLS combined with A×β values have good performance in predicting the risk of developing MACEs in patients with HFpEF at 3 years of follow-up, and CMD can be used as an important non-invasive indicator for assessing clinical prognosis. Next, we will explore whether MCE has equally important value in distinguishing primary and secondary CMD, and provide a practical diagnostic tool for studying the mechanisms related to coronary artery ischemic disease and heart failure in the development of CMD.

Abbreviations

MCE	myocardial contrast echocardiography
CMD	coronary microcirculation dysfunction
HFpEF	heart failure preserved ejection fraction
MACEs	major adverse cardiac events
LVEF	left ventricular ejection fraction
PCI	percutaneous coronary intervention
STEMI	ST segment elevation myocardial infarction
LVEDd	left ventricular end diastolic diameter
LVEDV	left ventricular end diastolic volume
LVESd	left ventricular end systolic diameter
LVESV	left ventricular end systolic volume
LVGLS	left ventricular global longitudinal strain
BMI	body mass index
BNP	b-type natriuretic peptide
ROC	receiver operating characteristic
AUC	area under curve

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Author contributions
Yb and Fh designed this study. Fh was responsible for collating the data and writing the manuscript. Wc was responsible for the statistical analysis of the data. Dl and Xm were responsible for the patient's follow-up. All authors have participated in this article and approved the submission of the version.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of JinHua Municipal Central Hospital(2023 Lun Shen No. 211) and conformed to the principles outlined in the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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