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Left atrial dysfunction can independently predict exercise capacity in patients with chronic heart failure who use beta-blockers

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Abstract

Background Beta-blockers are first-line clinical drugs for the treatment of chronic heart failure (CHF). In the guidelines for cardiac rehabilitation, patients with heart failure who do or do not receive beta-blocker therapy have different reference thresholds for maximal oxygen uptake (VO_{2max}). It has been reported that left atrial (LA) strain can be used to predict VO_{2max} in patients with heart failure, which can be used to assess exercise capacity. However, most existing studies included patients who did not receive beta-blocker therapy, which could have a heterogeneous influence on the conclusions. For the vast majority of CHF patients receiving beta-blockers, the exact relationship between LA strain parameters and exercise capacity is unclear.

Methods This cross-sectional study enrolled 73 patients with CHF who received beta-blockers. All patients underwent a thorough resting echocardiogram and a cardiopulmonary exercise test to obtain VO_{2max}, which was used to reflect exercise capacity.

Results LA reservoir strain, LA maximum volume index ($LAVI_{max}$), LA minimum volume index ($LAVI_{min}$) ($P < 0.0001$) and LA booster strain ($P < 0.01$) were all significantly correlated with VO_{2max}, and LA conduit strain was significantly correlated with VO_{2max} ($P < 0.05$) after adjusting for sex, age, and body mass index. LA reservoir strain, $LAVI_{max}$, $LAVI_{min}$ ($P < 0.001$), and LA booster strain ($P < 0.05$) were significantly correlated with VO_{2max} after adjusting for left ventricular ejection fraction, the ratio of transmitral E velocity to tissue Doppler mitral annulus e′ velocity (E/e′), and tricuspid annular plane systolic excursion. LA reservoir strain with a cutoff value of 24.9% had a sensitivity of 74% and specificity of 63% for the identification of patients with $VO_{2max} < 16$ mL/kg/min.

Conclusion Among CHF patients receiving beta-blocker therapy, resting LA strain is linearly correlated with exercise capacity. LA reservoir strain is a robust independent predictor of reduced exercise capacity among all resting echocardiography parameters.

Clinical Trial registration: This study is a part of the Baduanjin-Eight-Silken-Movement with Self-efficacy Building for Patients with Chronic Heart Failure (BESMILE-HF) trial NCT03180320 (ClinicalTrials.gov, registration date: 08/06/2017).

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Key points

- A significant linear correlation exists between resting LA strain and exercise capacity in CHF patients receiving beta-blocker therapy.
- LA reservoir strain is the strongest independent predictor of decreased exercise capacity among all LA strain parameters.
- LA booster strain is also an independent predictor of decreased exercise capacity.

Keywords Left atrial strain, Chronic heart failure, Exercise capacity, Maximal oxygen uptake, Beta-blockers

Introduction

Beta-blockers are first-line clinical drugs for the treatment of chronic heart failure (CHF). They can reduce exercise heart rate, increase exercise fatigue, and reduce maximum oxygen uptake (VO_{2max}) by approximately 7–15% [1, 2]. Therefore, in the guidelines for cardiac rehabilitation, patients with heart failure who do or do not receive beta-blocker therapy have different reference thresholds for VO_{2max} [3]. Previous studies have reported that left atrial (LA) reservoir strain, conduit strain and booster strain measured by speckle-tracking echocardiography can predict the VO_{2max} of patients with heart failure, which can be used to reflect exercise capacity [4, 5]. However, to the best of our knowledge, most existing studies have not limited the use of beta-blockers in the enrolled population. Therefore, the enrollment of a small number of patients with heart failure who did not use beta-blockers could lead to heterogeneity and influence study conclusions. In the real world, the majority of patients with heart failure use beta-blockers. No studies have reported the relationship between LA dysfunction and exercise capacity in patients with heart failure who do or do not receive beta-blocker therapy; thus, the results are unclear. Therefore, the main objectives of our study were to investigate the relationship between LA strain and exercise capacity in a CHF population who used beta-blockers.

Methods

Setting

This study involved patients from the Outpatient Clinic, Cardiac Rehabilitation Division, Ersha Branch, Guangdong Provincial Hospital of Chinese Medicine.

Study population

This was a cross-sectional study as well as a part of the Baduanjin-Eight-Silken-Movement with Self-efficacy Building for Patients with Chronic Heart Failure (BESMILE-HF) trial (NCT03180320, ClinicalTrials.gov, registration date: 08/06/2017) [6]. Patients with CHF were prospectively recruited between February 2019 and July 2022 if they fulfilled the following inclusion criteria: (1) $\geq$ 18 years of age; (2) met the diagnostic criteria for CHF [7]; (3) clinically stable, defined as symptoms/signs that remained generally unchanged for $\geq$ 1 month; (4) New York Heart Association class II or III; (5) used beta-blockers; and (6) provided informed consent [8].

The exclusion criteria were as follows: (1) patients with contraindications for exercise testing, namely, early phase after acute coronary syndrome (up to 6 weeks), life-threatening cardiac arrhythmias, acute heart failure (during the initial period of hemodynamic instability), uncontrolled hypertension (systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 110 mmHg), advanced atrioventricular block, acute myocarditis and pericarditis, moderate to severe aortic valve/mitral stenosis, severe aortic valve/mitral regurgitation, severe hypertrophic obstructive cardiomyopathy, acute systemic illness, or intracardiac thrombus; (2) patients with serious acute or chronic diseases affecting major organs or with mental disorders; (3) patients with a history of cardiac surgery, cardiac resynchronization therapy, intracardiac defibrillation, or implantation of a combined device within the previous 3 months; (4) patients with a history of cardiac arrest within 1 year; (5) patients with a history of peripartum cardiomyopathy, hyperthyroid heart disease, or primary pulmonary hypertension; and (6) patients unable to perform a recumbent bicycle stress test (Fig. 1) [6].

Eligible participants underwent clinical evaluation (including history of cardiac risk factors and medications), height and weight measurements, blood testing, and electrocardiography. They then underwent a cardiopulmonary exercise test (CPET) and transthoracic echocardiography assessment at rest on the same day (Fig. 2A, B). The BESMILE-HF study[6] was approved by the Ethics Committee of the Guangdong Provincial Hospital of Chinese Medicine (Approval No. B2016-202-01). All of the participants provided written informed consent.

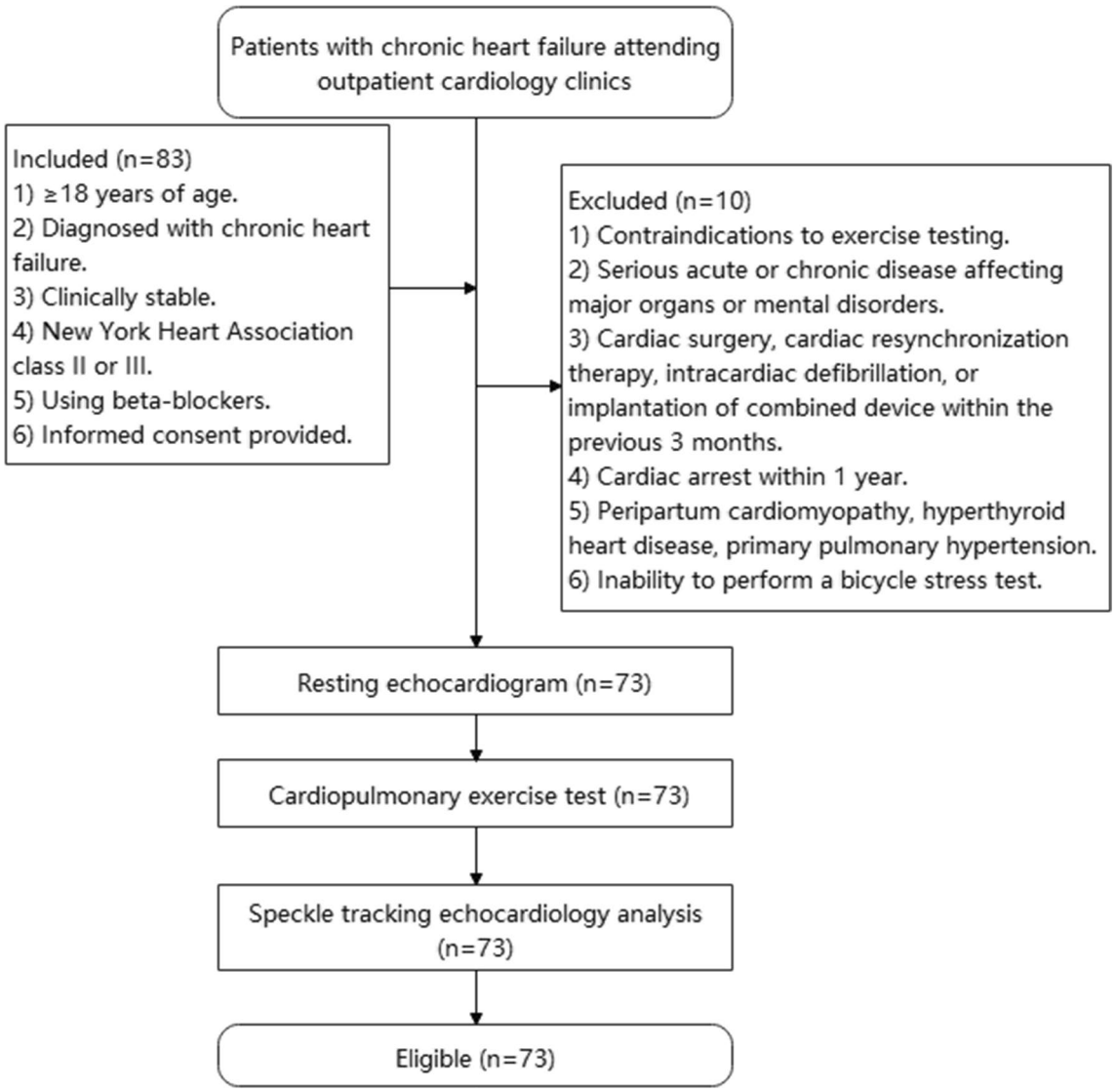

Fig. 1 Flow chart of this study

Cardiopulmonary exercise test

The CPET was performed using a standard ramp protocol (initial work rate of 0 W with an increase of 10% per minute of the predicted maximum work rate, which was calculated with a previously described formula[9]). The maximal exercise test was performed on an electronically calibrated recumbent bicycle (ERG 911S; Schiller, Baar, Switzerland). The patients started at 3 min of no-load cycling (0 W) and maintained pedaling with stepwise increases in the workload by 10% of the predicted VO_{2max} every minute until they reached the maximum perceived effort [10]. Finally, the patient was instructed to ride the recumbent bicycle for 3 min without any load. The peak VO_2 was averaged over 30 s as usually prescribed [3, 11]. Respiratory gas analysis was performed on a breath-by-breath basis with a metabolic cart (PowerCube, Ganshorn, Germany) and LF8 software (CARDIOVIT, CS-200 ergospirometer; Schiller AG, Switzerland). VO_{2max} and the maximum respiratory exchange ratio (RER_{max}) were measured during an adequately performed test (Fig. 2B, D).

Echocardiography

Transthoracic echocardiography was performed with the patients at rest on an EPIQ 7C ultrasound system (Philips Healthcare, Amsterdam, the Netherlands) according to the guidelines of the American Society of Echocardiography (2019) [12].

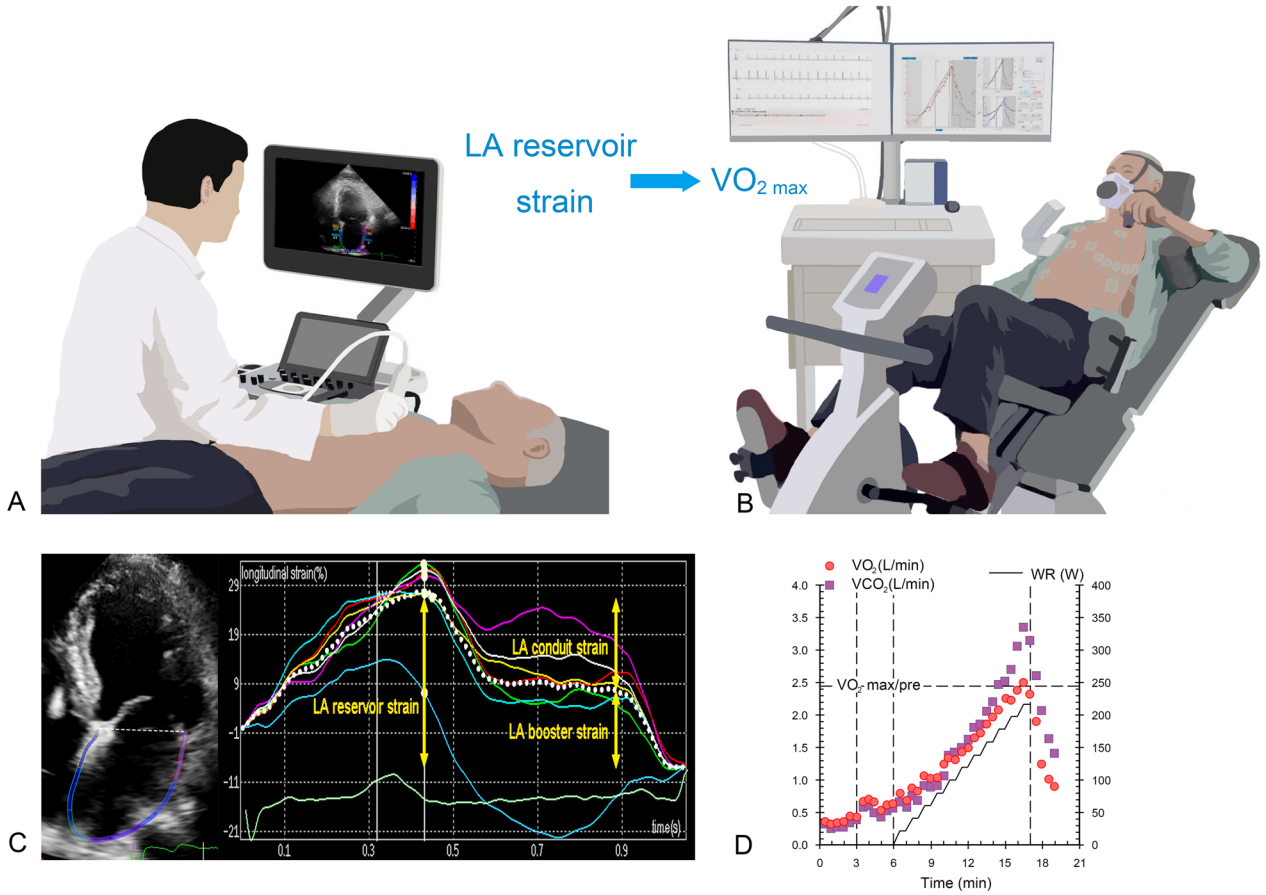

Fig. 2 Illustration of speckle-tracking echocardiography examination (**A**) and cardiopulmonary exercise testing (**B**). Strain analysis of the left atrium in the locally enlarged apical four-chamber view and the LA strain curve throughout the cardiac cycle (**C**). The curves of VO_2 and VCO_2 with time and work rate, respectively (**D**). LA, left atrial; VO_2, oxygen uptake; VCO_2, carbon dioxide uptake; $VO_{2max/pre}$, ratio of maximum to predicted oxygen uptake, WR, work rate

Additional optimized left ventricular (LV) and LA images were acquired at a frame rate > 50 frames/s. In apical 4-, 3-, and 2-chamber views of 3 continuous cardiac cycles at rest, the early diastolic peak flow velocity of the mitral valve on pulsed-wave Doppler (E), the early diastolic velocity of the septal and lateral wall annulus on tissue Doppler (e′) and the ratio of E to e′ (E/e′) were calculated. Three-dimensional full-volume images at rest were acquired to calculate the LV volume, stroke volume and ejection fraction. All images were stored digitally. The volume and strain analyses were performed offline using commercially available software (QLab 10.8.0; Philips Healthcare). The LA maximum and minimum volume index ($LAVI_{max}$ and $LAVI_{min}$, respectively) and the LA total empty fraction (LATEF) were evaluated from the apical 4- and 2-chamber views by the 2-dimensional quantitative speckle-tracking method [13].

Speckle-tracking echocardiography

All images were analyzed by a single investigator (S.C.) who was blinded to the participants' characteristics and exercise performance. For the LA strain, the LA endocardium was manually traced at the end systole stage of LV, and the software automatically tracked the myocardium throughout the cardiac cycle on electrocardiography using R-to-R gating. Figure 2C shows the LA strain curve throughout the cardiac cycle. The region of interest was adjusted to the smallest LA wall thickness for tracking. The LA strain is the average value measured in the 4- and 2-apical chamber views. In the reservoir phase, as the left atrium filled and stretched, there was a positive atrial strain that peaked in systole at the end of LA filling and before the opening of the mitral valve; this was the LA reservoir strain, which was defined as the difference between the nadir and the peak of the strain curve. Elevated LAVI was

defined as $LAVI_{max} \geq 34$ mL/m^2, while reduced LA reservoir strain was defined as LA reservoir strain < 23% [4, 14]. Subsequent passive LA emptying with the opening of the mitral valve was observed, with negative deflection of the strain curve until a plateau was reached; this was the LA conduit strain, which was defined as the difference between the peak of the strain curve and the onset of atrial contraction following the P wave. Then, a second negative deflection in the strain curve was observed corresponding to atrial systole, which represented LA active contraction. The LA booster strain was defined as the difference between the onset of atrial contraction and the nadir of the strain curve [13, 14] (Fig. 2C).

The LV endocardium was traced at end systole in the 4-, 3-, and 2- apical views; the region of interest was selected with software and was adjusted to accommodate the thickness of the LV myocardium. The LV global longitudinal strain (LVGLS) was measured as the average strain of 17 segments.

Statistical analysis

This was an observational cross-sectional study. The predictor variables were LA strains. Potential covariates or confounders were LA volume index, LV function, right ventricular function, age, sex, body mass index (BMI), biochemical index, etc. The outcome variable was VO_{2max}.

The independent sample t test was used to compare data with a normal distribution between groups. Data that did not conform to a normal distribution were compared using the rank sum test. Linear regression was performed using VO_{2max} as the dependent variable. Univariate regression was used to evaluate the independent contribution of LA strain and LA volume to VO_{2max}. Multivariate linear regression was used to combine clinical and LV function correction models.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the area under the curve (AUC) for LA strain to predict impaired VO_{2max}, which was defined as $VO_{2max} < 16$ mL/min/kg. This reference value of VO_{2max} was based on the Weber classification [15, 16]. DeLong's test was used to compare the AUC values.

Statistical analysis was performed using STATA 17.0 (STATA Corp, College Station, TX, USA) and MedCalc 20.1.0 (MedCalc Software Ltd., Ostend, Belgium). All tests were two-tailed, and $P < 0.05$ was considered statistically significant. Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers and percentages.

Results

Patient characteristics

Of the 83 CHF patients treated with beta-blockers included in the study, 10 were excluded due to medical histories or clinical conditions (Fig. 1). Therefore, the final sample included 73 patients (mean age of 61 ± 10 years; 78% men). In the overall population, 35 patients (48%) had a VO_{2max} of < 16 mL/kg/min, and 38 patients had a VO_{2max} (52%) of ≥ 16 mL/kg/min. In general, patients with a reduced VO_{2max} were older, were more likely to be female, had a higher NT-proBNP level, had a slightly lower hemoglobin level, and had worse renal function. There was no significant difference in comorbidities or combined medications between the two groups (Table 1).

Echocardiography parameters and VO_{2max}

Univariate linear regression showed that E/e′ ($P < 0.0001$), E, left ventricular end systolic volume index (LVESVI) (above $P < 0.01$), left ventricular end diastolic volume index (LVEDVI), and left ventricular ejection fraction (LVEF) (all $P < 0.05$) were significantly correlated with VO_{2max} (Table 2). The LV systolic function parameters LVGLS and left ventricular stroke volume index (LVSVI) and the right ventricular systolic function parameter tricuspid annular plane systolic excursion (TAPSE) were not significantly correlated with VO_{2max}.

LA function and VO_{2max}

This study explored LA function. In the overall population, 22 patients (30%) had an elevated LAVI (≥ 34 mL/m^2), and 36 patients (49%) showed a reduced LA reservoir strain (< 23%) [4, 14]. When VO_{2max} decreased, LAVI increased, and the absolute value of LA strain decreased (Fig. 3). An LA reservoir strain of < 24.9% predicted a VO_{2max} of < 16 mL/kg/min with high specificity and moderate sensitivity in this study (Table 3, Fig. 4).

Considering the results of univariate regression, clinical significance, and reducing collinearity of variables to avoid overfitting, the predictor variables of this study were LA reservoir strain, LA conduit strain, LA booster strain, $LAVI_{max}$ and $LAVI_{min}$. Potential covariates or confounders were LVEF, E/e', TAPSE, age, sex, BMI, NT-proBNP level and hemoglobin level, which were selected based on the positive results of the univariate regression and in combination with clinical physiology and pathology[4] (Tables 1, 2). The outcome variable was VO_{2max}. Therefore, we used three multivariate regression models to examine the independent effect of LA strain. The results showed that LA reservoir strain, $LAVI_{max}$, $LAVI_{min}$ ($P < 0.001$), and LA booster strain

Table 1 Baseline clinical characteristics of the patients with chronic heart failure who underwent cardiopulmonary exercise testing (n = 73)

Variables	Overall population (n = 73)	$VO_{2max} \geq 16$ mL/kg/min (n = 38)	$VO_{2max} < 16$ mL/kg/min (n = 35)	*P* value for comparison	*P* value for correlation with linear VO_{2max}
Demographics					
Age, years	61 ± 10	57 ± 10	65 ± 9	0.001**	< 0.0001***
Male	57 (78%)	34 (90%)	23 (66%)	0.014*	0.004**
Height, cm	166 ± 7	168 ± 7	164 ± 7	0.001**	0.022*
Weight, kg	68 ± 11	69 ± 12	67 ± 10	0.569	0.530
BMI, kg/m^2	25 ± 4	24 ± 3	25 ± 4	0.249	0.414
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	0.270	0.303
Comorbidities and etiology					
Coronary heart disease	43 (59%)	26 (68%)	17 (49%)	0.085	0.349
Myocardial infarction	20 (27%)	12 (32%)	8 (23%)	0.404	0.595
Dilated cardiomyopathy	19 (26%)	9 (24%)	10 (29%)	0.634	0.491
Hypertrophic cardiomyopathy	2 (3%)	1 (3%)	1 (3%)	0.953	0.485
NVM	2 (3%)	1 (3%)	1 (3%)	0.953	0.939
Moderate mitral regurgitation	16 (22%)	6 (16%)	10 (26%)	0.187	0.171
Diabetes	30 (41%)	16 (42%)	14 (40%)	0.860	0.999
Hypertension	32 (44%)	15 (39%)	17 (49%)	0.434	0.062
Hyperlipidemia	26 (36%)	13 (34%)	13 (37%)	0.794	0.752
Hyperuricemia	26 (36%)	11 (29%)	15 (43%)	0.215	0.036*
CKD (compensation stage)	7 (10%)	3 (8%)	4 (11%)	0.608	0.291
COPD	4 (5%)	3 (8%)	1 (3%)	0.360	0.670
Laboratory variables					
NT-proBNP, pg/mL	892 ± 1417	516 ± 664	1301 ± 1855	< 0.0001***	0.004**
Hemoglobin, g/L	145 ± 15	149 ± 12	139 ± 16	0.003**	0.003**
Creatinine, mg/dL	95 ± 23	98 ± 23	91 ± 24	0.695	0.371
Sodium, mEq/L	139 ± 6	139 ± 7	140 ± 3	0.636	0.055
GFR, mL/min/1.73 m^2	73 ± 17	76 ± 18	69 ± 16	0.082	0.044*
Glucose, mmol/L	7 ± 2	6 ± 2	7 ± 2	0.947	0.720
Triglycerides, mmol/L	1.5 ± 1.4	1.7 ± 1.8	1.4 ± 0.6	0.800	0.140
Cholesterol, mmol/L	4.2 ± 1.5	4.3 ± 1.8	4.1 ± 1.1	0.774	0.322
HDL, mmol/L	1.21 ± 0.28	1.21 ± 0.25	1.2 ± 0.3	0.995	0.682
nHDL, mmol/L	3.0 ± 1.5	3.1 ± 1.8	2.8 ± 1.1	0.770	0.265
LDL, mmol/L	2.4 ± 0.9	2.4 ± 0.8	2.4 ± 1.0	0.943	0.748
Oral drugs					
Inhibitors of RAS	48 (66%)	28 (74%)	20 (57%)	0.137	0.078
Spironolactone	47 (64%)	19 (50%)	28 (80%)	0.007**	0.003**
ARNI	15 (21%)	7 (18%)	8 (23%)	0.639	0.487
CCB	7 (10%)	2 (5%)	5 (14%)	0.204	0.411
P2Y12 receptor antagonist	29 (40%)	17 (45%)	12 (34%)	0.362	0.510
Statin	53 (73%)	26 (68%)	27 (77%)	0.404	0.390
Trimetazidine	7 (10%)	3 (8%)	4 (11%)	0.608	0.308
Aspirin	21 (29%)	10 (26%)	11 (31%)	0.630	0.878
Warfarin	10 (14%)	4 (11%)	6 (17%)	0.411	0.445

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Data are presented as the mean ± standard deviation or the n (%). BMI, body mass index; BSA, body surface area; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein. HR, heart rate; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; nHDL, nonhigh-density lipoprotein; NVM, noncompaction of ventricular myocardium; RAS renin-angiotensin system; ARNI, angiotensin receptor neprilysin inhibitor; CCB, calcium channel blocker

Table 2 Resting echocardiography parameters and cardiopulmonary exercise test parameters of the patients with chronic heart failure (n = 73)

Variables	Total (n = 73)	$VO_{2max} \geq 16$ mL/kg/min (n = 38)	$VO_{2max} < 16$ mL/kg/min (n = 35)	*P* value for comparison	*P* value for correlation with VO_{2max} in linear regression analysis
Left ventricular diastolic variables					
E, cm/s	82 ± 31	75 ± 25	90 ± 36	0.106	0.005**
e'_{ave}, cm/s	6.5 ± 2.2	6.8 ± 2.1	6.2 ± 2.4	0.174	0.277
E/e′	13.6 ± 6.0	11.6 ± 3.9	15.7 ± 7.1	0.006**	< 0.0001***
Left ventricular systolic variables					
LVEDVI, ml/m^2	80 ± 43	69 ± 20	93 ± 57	0.059	0.015*
LVESVI, ml/m^2	48 ± 35	38.30 ± 15	58 ± 47	0.079	0.008**
LVSVI, ml/m^2	32 ± 10	31 ± 7	34 ± 13	0.212	0.280
LVEF, %	44 ± 10	46 ± 8	42 ± 12	0.182	0.020*
LVEF ≥ 50%, n(%)	25 (34%)	15 (39%)	10 (29%)	0.143	–
LVEF = 41–49%, n (%)	21 (29%)	13 (34%)	8 (23%)		
LVEF ≤ 40%, n (%)	27 (37%)	10 (26%)	17 (49%)		
LVGLS, %	− 13.0 ± 3.5	− 13.3 ± 3.1	− 12.7 ± 4.0	0.431	0.191
TAPSE, cm	2.0 ± 0.4	2.0 ± 0.3	2.0 ± 0.5	0.760	0.300
Left atrial variables					
LA reservoir strain, %	24.3 ± 9.2	27.5 ± 9.7	20.9 ± 7.3	0.003**	< 0.0001***
LA conduit strain, %	− 12.9 ± 6.9	− 14.1 ± 7.2	− 11.6 ± 6.4	0.100	0.019*
LA booster strain, %	− 11.4 ± 6.5	− 13.5 ± 6.1	− 9.3 ± 6.3	0.005**	0.001**
$LAVI_{max}$, ml/m^2	31.1 ± 18.4	23.6 ± 9.7	39.3 ± 21.9	0.0002***	< 0.0001***
$LAVI_{min}$, ml/m^2	17.8 ± 14.8	11.8 ± 6.6	24.3 ± 18.2	0.0001***	< 0.0001***
LATEF, %	47 ± 14	51 ± 14	42 ± 12	0.004**	< 0.0001***
CPET variables					
RER_{max}	1.15 ± 0.08	1.17 ± 0.07	1.13 ± 0.08	0.032*	0.027*
$Load_{max}$, W	89 ± 32	110 ± 26	67 ± 20	< 0.0001***	< 0.0001***
VE/VCO_2 slope	32 ± 6	29 ± 4	36 ± 6	< 0.0001***	< 0.0001***
$VO_{2max/pre}$, %	63 ± 14	70 ± 11	55 ± 12	< 0.0001***	< 0.0001***
VO_{2max}, mL/kg/min	17 ± 4	20 ± 3	13 ± 2	< 0.0001***	–
O_2 $pulse_{max}$, mL/beat	9 ± 3	11 ± 2	8 ± 2	< 0.0001***	< 0.0001***
O_2 $pulse_{max/pre}$,%	78 ± 18	85 ± 14	70 ± 20	0.0006***	< 0.0001***
HR_{max}, bpm	126 ± 25	131 ± 19	121 ± 30	0.068	0.011*

*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Data are presented as the mean ± standard deviation. E, early diastolic peak flow velocity of the mitral valve; e'_{ave}, average early diastolic velocity of mitral annulus; E/e′, ratio of transmitral E velocity to tissue Doppler mitral annulus e′ velocity; LATEF, left atrial total empty fraction; LA, left atrial; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{min}$, minimum left atrial volume index; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume index; LVGLS, left ventricular global longitudinal strain; RER_{max}, maximum respiratory exchange ratio; $Load_{max}$, maximum load; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, minute ventilation to carbon dioxide production; VO_{2max}, maximum oxygen uptake; $VO_{2max/pre}$, ratio of maximum to predicted oxygen uptake; HR_{max}, maximum heart rate; O_2 $pulse_{max}$, maximum oxygen consumption per pulse; O_2 $pulse_{max/pre}$, ratio of maximum to predicted oxygen consumption per pulse

($P < 0.05$) were significantly correlated with VO_{2max} in the 3 models (Table 4).

In our study, the lower the LA reservoir strain was, the lower VO_{2max} was, and the larger $LAVI_{max}$ was (Fig. 5). The VO_{2max} of most patients with increased $LAVI_{max}$ and decreased LA reservoir strain was less than 16 mL/kg/min (Fig. 5, lower left quadrant); the VO_{2max} of most patients with normal $LAVI_{max}$ and normal LA reservoir strain was greater than 16 mL/kg/min (Fig. 5, upper right quadrant).

Discussion

Beta-blockers are first-line drugs for the treatment of heart failure, and they are administered to the majority of heart failure patients [7]. In cardiac rehabilitation guidelines, patients with heart failure who receive

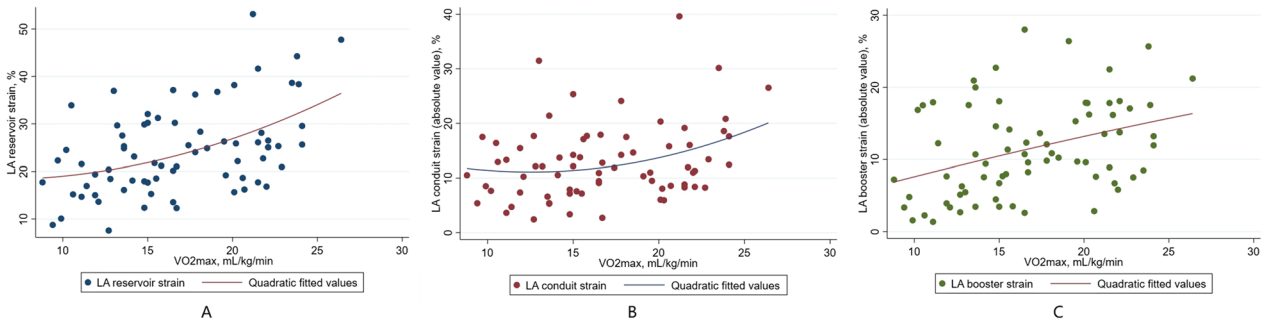

Fig. 3 Linear correlations between LA reservoir strain (**A**), conduit strain (**B**), booster strain (**C**) and VO_{2max} values in the overall study population. LA, left atrial; VO_{2max}, maximum oxygen uptake

Table 3 Receiver operating characteristic curve analysis of the parameters with the greatest area under the curve

Variable	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P*
LA reservoir strain	24.9%	74.29	63.16	0.70	0.59 to 0.81	< 0.001***
LA conduit strain	− 7.9%	40.00	92.11	0.61	0.49 to 0.72	0.097
LA booster strain	− 8.0%	60.00	84.21	0.69	0.57 to 0.80	0.003**
LVEF	38.9%	45.71	81.58	0.59	0.47 to 0.71	0.189
TAPSE	18 mm	51.52	74.19	0.56	0.43 to 0.69	0.396

** $P < 0.01$; *** $P < 0.001$

AUC, area under the curve; CI, confidence interval; LA, left atrial; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion

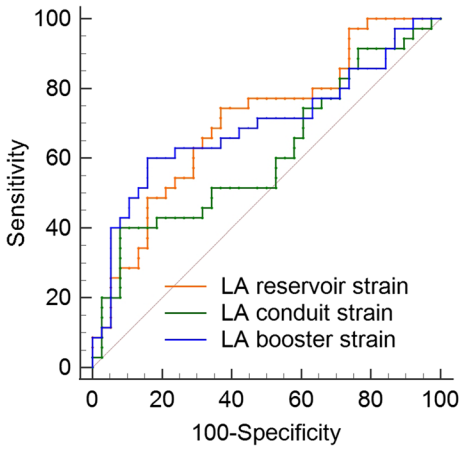

Fig. 4 Receiver operating characteristic curves of LA strain in the univariable regression model for predicting $VO_{2max} < 16$ mL/kg/min. LA, left atrial

beta-blockers and those who do not receive beta-blockers have different reference thresholds for VO_{2max} [3]. To avoid a heterogeneous effect of beta-blockers on assessing the association between LA dysfunction and reduced exercise capacity in patients with CHF, our study assessed only patients with CHF who received beta-blockers. To the best of our knowledge, our study is the first to confirm that in CHF patients receiving beta-blocker therapy (1) a linear correlation exists between resting LA strain and exercise capacity; (2) among all LA strain parameters, LA reservoir strain is the strongest independent predictor for detecting decreased exercise capacity and for identifying patients with $VO_{2max} < 16$ mL/kg/min; notably, LA reservoir strain has high sensitivity and moderate specificity, with a critical value of 24.9%; and 3) LA booster strain was also an independent predictor of decreased exercise capacity.

Effect of beta-blockers on maximal oxygen uptake

As widely used drugs for the treatment and management of patients with CHF [7], beta-blockers have a significant impact on the regulation of the heart and peripheral blood vessels and can reduce the mortality and hospitalization rate in CHF patients [17]. When the β-receptors of the heart are blocked, the exercise heart rate is 20–30% lower than that of patients not taking beta-blockers, but the stroke volume increases by 5–23% to maintain sufficient cardiac output [18]. Due to the increase in stroke volume, myocardial work efficiency increases, myocardial oxygen consumption increases, and VO_{2max} slightly decreases [1, 19]. In addition, β-receptor blockade causes peripheral vasodilation, pulmonary bronchoconstriction, and increased muscle and liver glycogenolysis; furthermore, this phenomenon affects the oxygen transport and

Table 4 Association between LA parameters, clinical or other echocardiographic variables, and VO_{2max} (mL/kg/min) in the univariate and multivariate linear regression analyses: ***P*** value, coefficient (95% confidence interval)

	LA reservoir strain	LA conduit strain	LA booster strain	$LAVI_{max}$	$LAVI_{min}$
Univariate	< 0.0001;0.23 (0.13 to 0.33)	0.019; 0.18 (0.03 to 0.32)	0.001; 0.25 (0.10 to 0.41)	< 0.0001; −0.13 (−0.17 to −0.08)	< 0.0001; −0.16 (−0.22 to −0.10)
Model 1	< 0.0001;0.19 (0.09 to 0.28)	0.004; 0.19 (0.06 to 0.32)	0.032; 0.16 (0.010 to 0.31)	< 0.0001; −0.10 (−0.15 to −0.05)	< 0.0001; −0.13 (−0.19 to −0.07)
Model 2	0.001; 0.19 (0.08 to 0.29)	0.140; −0.143 (−0.28 to −0.00)	0.015; −0.18 (−0.33 to −0.04)	< 0.0001; −0.10 (−0.16 to −0.05)	< 0.0001; −0.13 (−0.21 to −0.06)
Model 3	0.003; 0.18 (0.07 to 0.29)	0.114; −0.12 (−0.28 to 0.03)	0.021; −0.19 (−0.35 to −0.03)	0.002; −0.10 (−0.15 to −0.04)	0.003; −0.11 (−0.19 to −0.04)

Model 1: adjusted for age, sex, and BMI. Model 2: adjusted for NT-proBNP, hemoglobin and GFR. Model 3: adjusted for left ventricular ejection fraction, E/e' and TAPSE

LA, left atrial; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{min}$, minimum left atrial volume index; BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; GFR, glomerular filtration rate; E/e', ratio of transmitral E velocity to tissue Doppler mitral annulus e' velocity; TAPSE, tricuspid annular plane systolic excursion

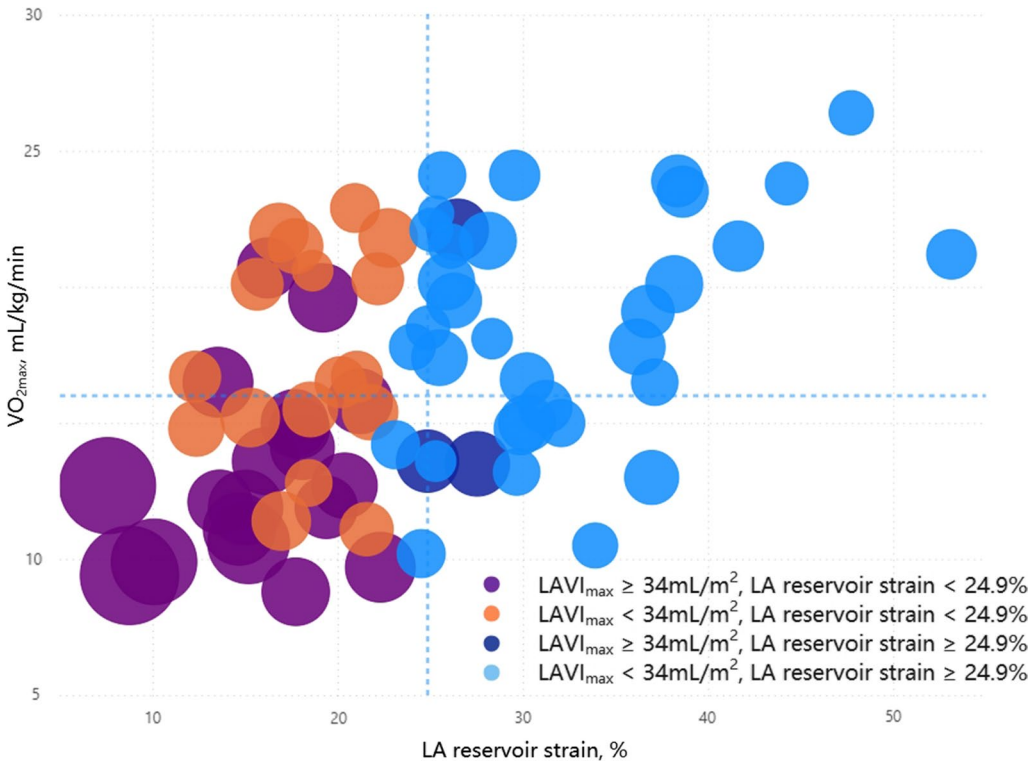

Fig. 5 Bubble chart of LA reservoir strain < or ≥ 24.9% and normal/dilated $LAVI_{max}$ in patients with chronic heart failure. The size of the bubble: $LAVI_{max}$. The x-axis of constant: LA reservoir strain = 24.9%. The y-axis of constant: VO_{2max} = 16 mL/kg/min. LA, left atrial; $LAVI_{max}$, maximum left atrial volume index; VO_{2max}, maximum oxygen uptake

work efficiency of skeletal muscles [20]. These conditions exist with both selective and nonselective beta-blockers.

Exercise capacity and maximal oxygen uptake in CHF patients

Cardiopulmonary dysfunction and skeletal muscle atrophy are the main causes of reduced exercise capacity in patients with heart failure [21]. With the progression of CHF, cardiac systolic and diastolic dysfunction leads to decreased exercise capacity, which is caused by impaired cardiac output, hemodynamic changes, and myocardial remodeling [22]. In addition, oxidative stress and proinflammatory conditions lead to muscle atrophy associated with a decrease in CHF physical function [23]. The exercise capacity of the included patients, represented by VO_{2max}, was generally reduced,

mainly due to heart-related cardiopulmonary function impairment.

LA dysfunction and reduced exercise capacity in CHF patients

Our study of patients with CHF who received beta-blockers showed that, compared with other echocardiographic parameters, LA reservoir strain was the strongest biomarker for predicting the exercise capacity of these patients. LA reservoir strain with a cutoff value of 24.9% had high sensitivity and moderate specificity in the detection of VO_{2max} < 16 mL/kg/min in all subjects. LA booster strain with a cutoff value of -8.0% had moderate sensitivity and high specificity in the detection of VO_{2max} < 16 mL/kg/min in all subjects. LA strain has been considered a useful echocardiographic marker in a series of patients with heart diseases and as an independent predictor of all-cause mortality [24, 25]. In terms of exercise capacity evaluation, previous heart failure studies that did not limit beta-blockers only found that LA reservoir strain was associated with VO_{2max} and VE/VCO_2slope [26]. LA reservoir strain can specifically reflect the pathophysiological mechanism of LA, such as LA myocardial remodeling and dysfunction [27], which can increase hemodynamic stress and pulmonary vascular resistance, resulting in a decrease in VO_{2max} [28].

A recent clinical study involving myocardial biopsy demonstrated that both LA reservoir strain and LA volume were predictors of LA fibrosis [29]. LAVI is a marker of LV systolic and diastolic dysfunction[30] and has been shown to be associated with exercise tolerance in HF patients [31]. However, an increased LA volume is unlikely to completely reflect the complex phenomenon of LA remodeling. Therefore, the introduction of LA strain can be used to more accurately evaluate the physiological and pathological LA changes in CHF patients; additionally, the predictive ability of LA reservoir strain is slightly better than that of LA volume [4, 29]. In our study, LA strain and exercise capacity were closely and independently correlated, and LA reservoir strain had the strongest predictive ability among the LA strain parameters in patients with CHF.

After adjusting for LVEF, E/e′, and TAPSE, LA reservoir strain still had a good ability to predict exercise capacity (P = 0.003). Considering that the interaction between atrial phasic function and ventricular mechanics regulates cardiovascular function, our findings are not surprising. Because the increase in preload led to more severe LA dysfunction [32], LA dysfunction in turn aggravated heart failure [33].

Advanced age, BMI and sex are important factors in exercise capacity [34]. In a healthy population, LA reservoir strain showed a decreasing trend with increasing age [35]. In our study, LA reservoir strain was linearly correlated with VO_{2max} after adjusting for age, sex, and BMI. These results suggest that the value of LA reservoir strain for predicting exercise capacity in patients with CHF is not affected by those clinical factors.

Our study showed that LA booster strain was also an independent predictor of VO_{2max}. In previous studies, it was unclear whether LA booster strain could independently predict VO_{2max} [4, 36, 37]. The previously reported contradictory findings may have been related to the limitation of LA booster strain measurement accuracy due to the inclusion of some patients with atrial fibrillation. In our study, only one patient had a history of paroxysmal atrial fibrillation. Due to the inhibitory effect of beta-blockers on atrial fibrillation, this patient did not develop atrial fibrillation during the study period. Relatively accurate LA conduit strain and LA booster strain values were obtained. LA booster strain represents the LA mechanical changes during the late LV diastole [13]. After active LA contraction, the pressure gradient from the left atrium to the left ventricle increases, and the left ventricle is further filled. Inoue's [36] study found that there was a strong correlation between LA booster strain and LA reservoir strain (r = 0.81, $P < 0.001$). The decrease in LA pressure after atrial contraction increases the pressure gradient from the pulmonary vein to the LA, thereby increasing LA filling [36]. Therefore, the active booster function of the left atrium is one of the determinants of LA reservoir strain. Unlu's [38] study proved that LA booster strain is the only LA strain parameter that can independently reflect the intrinsic LA function and is not affected by changes in blood volume because in the late LV diastolic phase (LA systolic phase), the participation of the left atrium in blood volume is relatively small, and it is almost unrelated to volume load. After the use of beta-blockers, the heart rate is reduced, which is manifested as prolonged diastolic time. As a result, the LA contraction time is relatively increased. Thus, LA booster strain in CHF patients using beta-blockers is more attributable to LA function.

Most LV filling is completed in the early LV diastole, and LA conduit strain is more susceptible to the effect of LV diastolic function than LA booster strain. Therefore, in our study, we corrected the representative parameter of diastolic function, which is also the early diastolic E/e′. Consequently, LA conduit strain was no longer an independent predictor of VO_{2max}.

Limitations

Our study had strict inclusion criteria; for example, only patients with stable New York Heart Association classification II or III CHF were included. The sample size was moderate but adequate because the VO_{2max} of nearly half

of the subjects was decreased. Second, the peak diastolic flow velocity of the mitral valve (A) or the average late-diastolic velocity of the mitral annulus (a'_{ave}) for patients with short-term or other cardiac diseases was not reached in 23 patients (32%) in this study. Therefore, A and a'_{ave} were not included in the univariate regression. Third, severe valvular regurgitation could be a manifestation or cause of CHF and affect LA function. To avoid these confounding factors, our study excluded patients with severe valvular regurgitation and only included patients with mild or moderate valvular regurgitation. Fourth, although there have been an increasing number of studies on LA strain, the current software package for measuring LA strain that was used to evaluate LV strain has inherent limitations. Fifth, the Jones formula we used to calculate the predicted VO_{2max} might overestimate the predicted VO_{2max} values. Finally, this study only included patients who took beta-blockers, and further studies are needed to compare patients who do and do not take beta-blockers.

Conclusion

This study demonstrated that in patients with CHF who received beta-blockers, LA reservoir strain is a robust independent predictor of reduced exercise capacity among resting echocardiographic parameters. LA booster strain is independently correlated with VO_{2max}. An LA reservoir strain of 24.9% can be used to identify patients with $VO_{2max} < 16$ mL/kg/min with high specificity and moderate sensitivity. LA strain is a potentially useful indicator for evaluating the efficacy of cardiac rehabilitation.

Abbreviations

BMI	Body mass index
CHF	Chronic heart failure
CI	Confidence interval
E	Early diastolic peak flow velocity of the mitral valve
e'_{ave}	Average early diastolic velocity of mitral annular
E/e′	Ratio of transmitral E velocity to tissue Doppler mitral annular e'_{ave} velocity
LA	Left atrial
LATEF	Left atrial total empty fraction
$LAVI_{max}$	Maximum left atrial volume index
$LAVI_{min}$	Minimum left atrial volume index
LV	Left ventricular
LVEDVI	Left ventricular end diastolic volume index
LVESVI	Left ventricular end systolic volume index
LVEF	Left ventricular ejection fraction
LVGLS	Left ventricular global longitudinal strain
RER_{max}	Maximum respiratory exchange rate
TAPSE	Tricuspid annular plane systolic excursion
VO_{2max}	Maximum oxygen uptake

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Author contributions

HC, PS, and WJ designed the research study. PS, SC and HZ performed the research. YL provided help with data curation. HC analyzed the data. HC and PS wrote the manuscript. XC and HL provided advice on revising the manuscript. WL and PS provided research funding. All authors contributed to editorial changes in the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Guangdong Provincial Hospital of Chinese Medicine (Approval No. B2016-202-01). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with those of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study. All procedures in this study were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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