Left Atrial Reservoir Longitudinal Strain is a Resting Marker of Exercise Capacity in Chronic Heart Failure: A Cross-sectional Study

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**Left atrial reservoir longitudinal strain is a resting marker
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sectional study**

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Abstract

Background: Left atrial (LA) function is an important parameter for assessing left ventricular performance. This study investigated the relationship between LA function as determined by strain analysis and exercise capacity in patients with chronic heart failure (CHF).

Methods: A total of 51 patients with CHF were prospectively recruited from the Baduanjin-eight-silken-movement With Self-efficacy Building for Patients With Chronic Heart Failure study. Resting echocardiographic parameters including the ratio of transmitral E velocity to tissue Doppler mitral annulus e' velocity (E/e'), minimum left atrial volume index (LAVI_{min}), maximum left atrial volume index (LAVI_{max}), and left atrial empty fraction (LAEF) as well as global phasic longitudinal strain (reservoir strain [LALSr], conduit strain [LALScd], and contractile strain [LALSct]) were measured and compared with maximum oxygen uptake (VO_{2max}) in terms of performance in predicting reduced exercise capacity.

Results: Mean age of study patients was 60.18 ± 10.41 years, mean left ventricular ejection fraction was $32.8 \pm 14.2\%$, and mean VO_{2max} was 17.02 ± 4.64 mL/kg/min. Eleven (21.57%) patients were women, and 32 (62.75%) had coronary heart disease. Univariate linear regression analysis identified age and N-terminal pro-hormone of brain natriuretic peptide level as independent clinical parameters associated with VO_{2max} (both $P < 0.05$); independent resting echocardiographic parameters included LALSr ($P < 0.001$); average late diastolic velocity of septal and lateral wall annulus, LAVI_{max}, LAVI_{min}, LALSr, LALSct, and LAEF (all $P < 0.01$); and E and E/e' (both $P < 0.05$). The multivariate linear regression analysis revealed 4 independent clinical predictors of VO_{2max} including ($\beta = 0.351$; $P = 0.007$), age ($\beta = -0.271$; $P = 0.027$), body mass index ($\beta = -0.260$; $P = 0.032$) and N-terminal pro-hormone of brain natriuretic peptide ($\beta = -0.257$; $P = 0.041$).

Conclusions: LALSr is a marker of decreased LA compliance and an independent correlate of VO_{2max} with high diagnostic value in patients with CHF. Thus, LALSr can be used for risk stratification of CHF patients with reduced exercise capacity and poor cardiovascular outcome.

Trial registration: NCT03180320 (ClinicalTrials.gov). Registered 8 June 2017, <https://clinicaltrials.gov/ct2/show/NCT03180320?term=Baduanjin-eight-silken-movement&draw=2&rank=1>.

Keywords: left atrial strain, left atrium, chronic heart failure, exercise capacity, echocardiography.

Introduction

Chronic heart failure (CHF) is caused by myocardial infarction, cardiomyopathy, hemodynamic overload, inflammation, and myocardial damage, resulting in ventricular pumping or filling dysfunction that reduces exercise capacity. According to the research, the age-standardized prevalence and years lived with disability rates of HF were 831.0 and 128.2 per 100 000 people in globe [1].

Reduced exercise capacity is correlated with high cardiovascular risk in patients with CHF [2, 3]. Exercise capacity is an established prognostic determinant of adverse cardiovascular outcomes and mortality, with an incremental benefit over established cardiovascular risk factors [4]. Maximum oxygen uptake (VO_{2max}) measured by the cardiopulmonary exercise test (CPET) is the gold standard measure of exercise capacity and an important predictor of the incidence of major cardiovascular events in patients with CHF [5-7]. However, CPET has certain contraindications such as acute myocardial infarction and disability that limit its clinical application [5, 6]. Additionally, CPET is time-consuming to measure and is thus inconvenient for disease screening and follow-up. Therefore, a marker of cardiac functional capacity that can be evaluated at rest is more practical and would aid risk stratification in patients [5].

The left atrium plays an important role in modulating left ventricular (LV) performance, accounting for up to one-third of cardiac output [8]. Given its dynamic relationship with the LV chamber, left atrial (LA) function is thought to predominantly reflect changes in LV systolic and diastolic functions. Conventionally, LA function is assessed by volumetric measures [9]; LA volume has emerged as an important biomarker for adverse cardiac events in a variety of cardiovascular conditions [10]. However, evaluating LA phasic function by strain analysis was recently shown to be feasible and reproducible, with alterations in LA strain preceding changes in LA volume. There is evidence that LA reservoir strain combined with the ratio of transmitral E velocity to tissue Doppler mitral annulus e' velocity (E/e') is a useful single measure for predicting elevated LV filling pressure reflecting LV function in patients with coronary artery disease [11]. Although various LA parameters have been proposed, there is no single parameter that best defines LA function in CHF patients with reduced exercise capacity.

Based on these considerations, the present study investigated the relationship between LA function—as assessed by resting echocardiographic strain analysis—and exercise capacity in patients with CHF, with the aim of identifying resting echocardiographic parameters that most accurately reflect reduced exercise capacity.

Methods

Study population

This cross-sectional study was part of the Baduanjin-eight-silken-movement With Self-efficacy Building for Patients with Chronic Heart Failure (BESMILE-HF) study [12]. Patients with CHF were prospectively recruited between January 2019 and May 2021 if they fulfilled the following inclusion criteria: 1) ≥ 18 years of age, 2) meeting the diagnostic criteria for CHF, 3) clinically stable, defined as symptoms/signs that have remained generally unchanged for ≥ 1 month, 4) New York Heart Association class II or III, 5) Informed consent provided[12, 13].(Fig. 1)

The excluded criteria are as follows. 1) Patients who have contraindications to exercise testing: 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/mitral stenosis; severe aortic/mitral regurgitation; severe hypertrophic obstructive cardiomyopathy; acute systemic illness; or intracardiac thrombus. 2) Patients who have serious acute or chronic disease affecting major organs, or mental disorders. 3) History of cardiac surgery, cardiac resynchronization therapy, intracardiac defibrillation, or implantation of combined device within the previous 3 months. 4) History of cardiac arrest within 1 year. 5) History of peripartum cardiomyopathy, hyperthyroid heart disease, primary pulmonary hypertension. 6) Inability to perform a bicycle stress test[12]. (Fig. 1)

Study protocol

Eligible participants underwent clinical evaluation (including history of cardiac risk factors and medications), height and weight measurement, blood testing, and electrocardiography. They then underwent CPET and transthoracic echocardiography at rest and under stress. The BESMILE-HF study[12] was approved by the Ethic Committee of the Guangdong Provincial Hospital of Chinese Medicine (approval no. B2016-202-01). All participants provided written informed consent.

Cardiopulmonary exercise test

CPET was performed using standard Ramp protocol (initial work rate of 0 W with an increase of 10% of the predicted maximum work rate per minute). The maximal exercise test was performed on an electronically calibrated upright bicycle (ERG 911S; Schiller, Baar, Switzerland). Patients were encouraged to exercise at maximal effort. Medications likely to suppress heart rate (HR) response during exercise were withheld for 24 h before stress testing. The patients started at 0 W and maintained pedaling at 60 rotations per min with stepwise increases in workload by 10% of the predicted maximum work rate every minute until they reached maximum perceived effort. 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). VO_{2max} and maximum respiratory exchange ratio

(RER_{max}) were measured during an adequately performed test. A test with an $RER \geq 1.05$ was considered sufficient. (Fig. 2B, D)

Echocardiography

Transthoracic echocardiography at rest was performed on an EPIQ 7C ultrasound system (Philip Healthcare, Amsterdam, The Netherlands) in accordance with the recommendations of the American Society of Echocardiography 2017[14].

Additional images with optimized left ventricle and left atrium were acquired at a high frame rate (>70 frames/s). In apical 4-, 3-, and 2-chamber views of 3 continuous cardiac cycles at rest, E, early diastolic peak flow velocity of the mitral valve on pulsed-wave Doppler, e' , and late diastolic velocity of septal and lateral wall annulus on tissue Doppler were measured and the ratio of E to e' (E/e') was 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, volume and strain analyses were performed offline using a commercially available software (QLab 10.8.0; Philip Healthcare). The LA maximum and minimum volume indices ($LAVI_{max}$ and $LAVI_{min}$, respectively) and LA empty fraction (LAEF) were evaluated from the apical 4- and 2-chamber views by the 2-dimensional quantitative speckle-tracking method[11, 15, 16]. All images were analyzed by 2 investigators who were blinded to participants' characteristics and exercise performance. (Fig. 2A)

Speckle - tracking echocardiography

The LV endocardium was traced at end systole in the 3 apical views; a region of interest (ROI) was selected with the software that was adjusted when required to accommodate the thickness of the LV myocardium. An 18-segment LV model (6 segments in each apical view) was obtained; global longitudinal strain was measured as the average of 18 segments.

For LA strain, the LA endocardium was manually traced in end systole and the software automatically tracked the myocardium throughout the cardiac cycle on electrocardiography using R-to-R gating. Fig. 2C shows the LA strain curve throughout the cardiac cycle. The ROI was adjusted to the smallest LA wall thickness for tracking. The LA wall was divided into 6 segments (basal, mid, and apical) in the apical 4- and 2-chamber views. In the reservoir phase, as the left atrium filled and stretched, there was a positive atrial strain that reached a peak at end-systole time. Subsequent passive LA empty with opening of the mitral valve reduced atrial strain, with negative deflection of the strain curve until a plateau was reached. A second negative deflection that reach a nadir in the strain curve was observed corresponding to atrial systole. The LA reservoir longitudinal strain (LALSr) was measure as the difference between nadir of strain curve and peak of systolic strain curve, meaning the difference between end-diastole and onset of LV filling. The LA conduit longitudinal strain (LALScd) was measure as difference between onset of LV filling and onset of

atrial contraction. LA contractile longitudinal strain (LALSct) was measure as difference between onset of atrial contraction and end-diastole.[16] (**Fig. 2C**)

LALSr was measured at the end of the reservoir phase as the average of the peak systolic strain from 12 segments; LALSct was measured as the peak positive strain following the P wave (atrial contraction); and LALScd was measured as the difference between peak reservoir and contractile strain. We defined impaired LALSr as a value $\leq 27.6\%$ based on a previously reported lower limit reference value according to a recent meta-analysis[17].

Statistical analysis

Statistical analyses were performed using STATA v15.0 (Stata Corp, College Station, TX, USA). All tests were 2-tailed with a P value <0.05 considered statistically significant. Continuous variables are presented as mean $\pm$ standard deviation and categorical variables as number and percentage.

Univariate linear regressions were performed with VO_{2max} as dependent variable. Multivariable linear regression analysis was used to evaluate the independent contributions of clinical and resting echocardiographic variables to VO_{2max} . Variables exhibiting a statistically significant or near significant in the univariate linear regression (P value < 0.10) were considered as candidate variables for the multivariable regression analysis.

Finally, a comparison of the VO_{2max} was proposed between patients with abnormal LALSr $< 27.6\%$ and those with normal LALSr $\geq 27.6\%$ [17].

Results

Patient characteristics

The final sample consisted of 51 patients (mean age, 60.18 ± 10.41 years; 79% male). Eleven patients excluded because of the medical history or clinical conditions and four because of unclear images (**Fig. 1**). **Table 1** shows the baseline clinical characteristics, comorbidities, and laboratory values of the study population, and **Table 2** shows the echocardiographic data and parameters associated with LA mechanical function and volume and LV function and in the CPET.

Individual LA parameters and VO_{2max}

Univariate linear regressions were done between resting echocardiography parameters and VO_{2max} (**Table 3**). Results showed that LALSr, LALSrR, LALSrct, $LAVI_{max}$, $LAVI_{min}$, LAEF, E, E/e' were correlated with VO_{2max} ($P < 0.05$, Table 3);

while LALScd, LALSct and LALSr have no significant correlation with VO_{2max} ($P > 0.05$, **Table 3**).

Univariate linear regressions showed that the clinical parameters associated with VO_{2max} included age and N-terminal pro brain natriuretic peptide (NTpro-BNP) ($P < 0.05$); while the resting echocardiographic parameters included LALSr ($P < 0.0001$), LALSr, LALSrct, LAVImax, LAVImin, and LAEF ($P < 0.01$ for all above).

Relationship between LALSr and VO_{2max}

A multivariate linear regression model was performed for LA strain, LA volume, Doppler echocardiography and clinical variables. To avoid leaving important variables behind, variables with $P < 0.2$ in the univariate regressions were selected as the independent variables in the multivariate regression, including LALSr, LALScd, LALSct, LAVImax, LAVImin, LAEF, E, E/e'. In addition, clinically significant variables - age, body mass index and NTpro-BNP were also selected. The model was using forward-stepwise entry, adding variables with P value less than 0.1. Four independent clinical predictors of VO_{2max} , including LALSr ($\beta = 0.351$; $P = 0.007$), age ($\beta = -0.271$; $P = 0.027$), body mass index ($\beta = -0.260$; $P = 0.032$) and NT-proBNP ($\beta = -0.257$; $P = 0.041$). (**Table 4**)

In our study, 66.67% of patients had a reduced LALSr ($< 27.6\%$). Patients with normal LALSr ($\geq 27.6\%$) had significantly higher VO_{2max} value than those with abnormal LALSr (19.58 ± 4.88 vs 15.74 ± 4.00 ml/kg/min; $P = 0.004$).

Discussion

In this study, we demonstrated a linear association between resting LA strain and exercise capacity in patients with CHF. LALSr was the strongest resting echocardiographic parameter for detecting reduced exercise capacity. A multivariate model combining LALSr and clinical correlates of exercise (age, BMI and NTproBNP) showed a robust capacity to predict VO_{2max} during exercise in patients with CHF.

Exercise capacity in CHF

A reduction in physical function and exercise capacity is common in patients with CHF. The underlying pathophysiologic processes are multifactorial and broadly related to cardiac systolic and diastolic dysfunction (eg, myocardial infarction, microvascular dysfunction, and myocardial remodeling), irregularities in oxygen delivery (eg, vascular dysfunction), and extraction mechanisms (eg, skeletal muscle) [18]. With progressive CHF, altered hemodynamics and myocardial remodeling attributable to systolic and diastolic dysfunction impair cardiac output in response to increased stress during exercise [18, 19]. Moreover, oxidative stress and a

proinflammatory state—both of which are associated with HF with preserved ejection fraction—contribute to muscle wasting and were shown to be correlated with physical fitness [6, 20, 21].

Mechanism for LA Function and Exercise Capacity

There is increasing evidence that LA dysfunction contributes to cardiorespiratory symptoms and exercise capacity [22, 23]. A strong association between reduced LALSr and impaired exercise capacity was observed in patients with HF with preserved or mid-range ejection fraction [24]. Impaired LALSr and LALSct have also been linked to abnormal exercise dynamics and elevated pulmonary pressure in these patients [11, 25]. Moreover, LALSr has been approved as an independent correlate of exercise capacity in patients with stage 3 and 4 chronic kidney diseases [26]. These findings are unsurprising given that the interplay between atrial phasic function and ventricular mechanics modulates cardiovascular performance. Impaired LA function can increase hemodynamic stress on lung vasculature and is correlated with increased pulmonary vascular resistance and peak oxygen volume to a greater extent than traditional markers of diastolic function including E/e' and LA volume [27]. Additionally, chronic pulmonary venous congestion in the context of abnormal LA mechanics results in altered pulmonary artery compliance, which hinders oxygen delivery and gas exchange [28]. Our findings demonstrate that impaired LALSr preceding changes in left ventricular ejection fraction and left ventricular global longitudinal strain is strongly associated with reduced exercise capacity. Thus, LALSr may specifically reflect LA pathophysiologic mechanisms such as LA myocardial remodeling and dysfunction.

Innovation and Clinical Relevance

To the best of our knowledge, our study first demonstrated that LALSr is the strongest resting echocardiographic parameters association with VO_{2max} in patients with CHF.

Although the utility of LA strain is largely confined to the research arena at present, a growing body of literature supports its clinical use particularly in the evaluation of populations with diastolic dysfunction, in which it was shown to be an independent predictor of all-cause mortality[27].

As exercise capacity is a known prognostic marker for adverse cardiovascular outcomes[2], our findings have potential application. In patients who are unable to exercise because of limiting comorbidities or frailty, resting LALSr can be used as an alternative to VO_{2max} . Identifying patients with CHF with impaired LALSr may also improve cardiovascular risk stratification and intensification of risk factor management in this patient group at risk of developing adverse cardiovascular events.

Limitations

Our study had stringent eligibility criteria and included only stable CHF patients with New York Heart Association class II or III. Despite the modest sample size, more than half of the cohort had reduced LALSr. Further, 17 patients (33%) in this study did not have diastolic peak flow velocity of the mitral valve (A); average late diastolic velocity of mitral annulus (a'_{ave}) - for the short cardiac cycle or other cardiac condition, A and a'_{ave} were not included in the univariate regression. Moreover, the LALSr cut off point 27.6% was according to a meta-analysis that included studies not using QLAB software. Therefore, this study may slightly underestimate or overestimate the cutoff points measured using QLAB software. Finally, while LA longitudinal strain is increasingly being used, it is currently measured using a software package developed for the evaluation of LV longitudinal strain, which has inherent limitations.

Conclusion

In patients with CHF, LALSr showed the strongest association with reduced exercise capacity among resting echocardiographic parameters and may be a useful marker for evaluating the efficacy of cardiac rehabilitation.

Abbreviations

A: mitral inflow peak late diastolic velocity; CHF: Chronic heart failure; CPET: Cardiopulmonary exercise testing; E: mitral inflow peak early diastolic velocity; LA: left atrial; LALScd: left atrial longitudinal strain at conduit phase; LALSct: left atrial longitudinal strain at contractile phase; LALSr: left atrial longitudinal strain at reservoir phase; LAVImax: maximum left atrial volume index; LAVImin: left atrial volume index; LV: left ventricular; NTpro-BNP: N-terminal pro brain natriuretic peptide; VO_{2max} : maximum oxygen uptake

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Pengtao Sun: Conceptualization, writing - review & editing, data curation. Huan Cen: Formal analysis and writing - original draft. Sinan Chen: Software and data curation. Xiankun Chen: methodology and writing - review & editing. Wei Jiang: Project administration. Huiying Zhu: Data curation. Yuexia Liu: Validation. Hongmei Liu: Supervision, Weihui Lv: Funding acquisition. All authors contributed important intellectual content to the critical revision of the manuscript. All authors read and approved the final manuscript.

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451 **Table 1.** Baseline clinical characteristics of patients with chronic heart failure who
452 underwent cardiopulmonary exercise testing (n=51)

Demographic variables	
Age, years	60.18 ± 10.41
Male	40 (80%)
Height, cm	165.76 ± 7.37
Weight, kg	68.69 ± 11.37
BMI, kg/m ²	24.95 ± 3.55
BSA, m ²	1.59 ± 0.30
HR at rest, bpm	99.88 ± 22.99
Comorbidities and etiology	
Chronic heart disease	31 (60.78%)
Myocardial infarction	14 (27.45%)
Dilated cardiomyopathy	8 (15.69%)
Hypertrophic cardiomyopathy	0 (0.00%)
NVM	1 (2.04%)
Rheumatic heart disease	1 (1.96%)
Valvular disease	11 (21.57%)
Diabetes	21 (41.18%)
Hypertension	26 (50.98%)
Hyperlipidemia	21 (41.18%)
Hyperuricemia	16 (31.37%)
CKD	4 (7.84%)
COPD	2 (3.92%)
Laboratory variables	
NT-proBNP, pg/ml	846.32 ± 1487.63
Hemoglobin, g/l	143.10 ± 15.81
Creatinine, mg/dl	98.39 ± 21.33
Sodium, mEq/l	139.28 ± 6.31
GFR, ml/min/1.73 m ²	71.71 ± 18.21
Glucose, mg/dl	6.77 ± 2.21
Triglycerides, mmol/l	1.62 ± 1.62
Cholesterol, mmol/l	4.15 ± 1.52
HDL, mmol/l	1.16 ± 0.28
nHDL, mmol/l	2.99 ± 1.54
LDL, mmol/l	2.34 ± 0.73
Oral drugs	
ACEI	17 (33.33%)
ARB	9 (17.65%)
ARNI	14 (28.00%)
β-blocker	43 (84.31%)
Spironolactone	35 (68.63%)
CCB	8 (16.00%)

Statin	38 (76.00%)
Trimetazidine	7 (13.73%)
P2Y12 receptor antagonist	18 (36.00%)
Aspirin	18 (36.00%)
Warfarin	10 (20.41%)

453 Data are presented as mean±standard deviation or n (%).BMI, body mass index; BSA,
454 body surface area; CKD, chronic kidney disease; COPD, chronic obstructive
455 pulmonary disease; GFR, glomerular filtration rate; HDL, high density lipoprotein;
456 HR, heart rate; LDL, low density lipoprotein; NT-proBNP, N-terminal pro brain
457 natriuretic peptide; nHDL, nonhigh density lipoprotein; NVM, noncompaction of
458 ventricular myocardium; ACEI, angiotensin converting enzyme inhibitor; ARB,
459 angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CCB,
460 calcium channel blockers.

Table 2. Resting echocardiography parameters and cardiopulmonary exercise test parameters of patients with chronic heart failure (n=51)

Variable	Mean $\pm$ SD
E, cm/s	82.53 $\pm$ 30.05
A, cm/s	48.57 $\pm$ 40.96
e'ave, cm/s	6.61 $\pm$ 2.28
a'ave, cm/s	4.76 $\pm$ 3.65
E/e'	13.39 $\pm$ 5.51
Left ventricular parameters	
LVEDVI, ml/m ²	87.85 $\pm$ 45.62
LVESVI, ml/m ²	47.60 $\pm$ 35.18
SVI, ml/m ²	40.25 $\pm$ 19.84
LVEF, %	50.71 $\pm$ 23.19
LVGLS, %	-12.54 $\pm$ 3.57
Left atrial parameters	
LALSr	25.15 $\pm$ 9.98
LALScd	12.26 $\pm$ 7.33
LALSct	12.94 $\pm$ 7.92
LAVI _{max} , ml/m ²	36.10 $\pm$ 23.68
LAVI _{min} , ml/m ²	20.52 $\pm$ 18.72
LAEF, %	47.68 $\pm$ 12.88
CPET parameters	
RER _{max}	1.17 $\pm$ 0.07
Load _{max} , W	92.33 $\pm$ 30.41
VO _{2max} , ml/kg/min	17.02 $\pm$ 4.64
VO _{2max/pre} , %	63.27 $\pm$ 14.89
O ₂ pulse _{max} , ml	9.36 $\pm$ 2.80
O ₂ pulse _{max/pre} , %	74.78 $\pm$ 17.72
HR _{max} , bpm	127.45 $\pm$ 27.76

A, late diastolic peak flow velocity of the mitral valve; a'ave, average late diastolic velocity of mitral annulus; 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; HR_{max}, maximum heart rate; LAEF, left atrial empty fraction; LALSr, left atrial longitudinal strain at reservoir phase; LALScd, left atrial longitudinal strain at conduit phase; LALSct, left atrial longitudinal strain at contractile phase; LAVI_{max}, maximum left atrial volume index; LAVI_{min}, left atrial volume index; Load_{max}, maximum load; 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; O₂ pulse_{max}, maximum oxygen consumption per pulse; O₂ pulse_{max/pre}, ratio of maximum to predicted oxygen consumption per pulse; RER_{max}, maximum respiratory exchange ratio; VO_{2max}, maximum oxygen uptake; VO_{2max/pre}, ratio of maximum to predicted oxygen uptake.

477 **Table 3.** Clinical and echocardiographic factors associated with VO_{2max} (ml/kg/min) in the univariate
478 linear regression analysis

Variable	coefficient	SE	95% CI		β	P
			lower	upper		
E (cm/s)	-0.048	0.021	-0.090	-0.006	-0.312	0.026*
e' _{ave} (cm/s)	0.128	0.290	-0.456	0.711	0.063	0.662
E/e'	-0.288	0.113	-0.515	-0.061	-0.342	0.014*
LVEDVI (ml/m ²)	-0.009	0.014	-0.038	0.021	-0.084	0.556
LVESVI (ml/m ²)	-0.008	0.019	-0.046	0.029	-0.064	0.656
SVI(ml/m ²)	-0.019	0.033	-0.086	0.048	-0.080	0.575
LVEF (%)	-0.020	0.028	-0.078	0.037	-0.102	0.477
LVGLS (%)	-0.160	0.185	-0.531	0.210	-0.123	0.389
LALSr	0.223	0.058	0.106	0.341	0.480	0.000***
LALScd	0.140	0.088	-0.038	0.317	0.220	0.120
LALSct	0.235	0.077	0.081	0.389	0.401	0.004**
LAVI _{max} (ml/m ²)	-0.071	0.026	-0.124	-0.019	-0.363	0.009**
LAVI _{min} (ml/m ²)	-0.094	0.033	-0.160	-0.028	-0.380	0.006**
LAEF (%)	0.142	0.047	0.046	0.237	0.393	0.004**
Age	-0.142	0.06	-0.263	-0.02	-0.318	0.023*
Gender	-1.681	1.636	-4.969	1.606	-0.145	0.309
BMI	0.229	0.184	-0.599	0.14	-0.175	0.219
NT-proBNP	-0.001	0.000	-0.002	0.000	-0.357	0.010*

479 **P* < 0.05, ***P* < 0.01, ****P* < 0.0001.

480 β , beta regression coefficients; BMI, body mass index; CI, confidence interval; E, early diastolic peak
481 flow velocity of the mitral valve; NT-proBNP, N-terminal pro brain natriuretic peptide; E/e', ratio of
482 transmitral E velocity to tissue Doppler mitral annulus e' velocity; LAEF, left atrial empty fraction;
483 LALSr, left atrial longitudinal strain at reservoir phase; LALScd, left atrial longitudinal strain at
484 conduit phase; LALSct, left atrial longitudinal strain at contractile phase; LAVI_{max}, maximum left
485 atrial volume index; LAVI_{min}, left atrial volume index; LVEF, left ventricular ejection fraction;
486 LVGLS, left ventricular global longitudinal strain; SE, standard error; VO_{2max}, maximum oxygen
487 uptake.

488

489 **Table 4.** Clinical and echocardiographic factors associated with $VO_{2\max}$ (ml/kg/min) in the
490 multivariate linear regression analysis

Variable	Coefficient	SE	95% CI		β	<i>P</i>
			Lower	Upper		
LALSr	0.163	0.058	0.048	0.279	0.351	0.007**
Age	-0.121	0.053	-0.227	-0.014	-0.271	0.027*
BMI	-0.340	0.153	-0.649	-0.031	-0.260	0.032*
NT-proBNP	-0.001	0.000	-0.002	0.000	-0.257	0.041*

491 * $P < 0.05$, ** $P < 0.01$.

492 β , beta regression coefficients; BMI, body mass index; CI, confidence interval; LALSr, left atrial
493 longitudinal strain at reservoir phase; NT-proBNP, N-terminal pro brain natriuretic peptide; SE,
494 standard error; $VO_{2\max}$, maximum oxygen uptake.

495 **Fig. 1.** Flow chart of this study.
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Fig. 2. Illustrative photo of speckle tracking echocardiography examination (A) and cardiopulmonary exercise test (B). Strain analysis of the left atrial (C₁). The left atrial strain curve throughout the cardiac cycle (C₂). The curves of VO₂ and VCO₂ with time and work rate respectively (D).

LALSr, left atrial longitudinal strain at reservoir phase; LALScd, left atrial longitudinal strain at conduit phase; LALSct, left atrial longitudinal strain at contractile phase; VO₂max, maximum oxygen uptake; VCO₂max, maximum carbon dioxide uptake; VO₂max/pre, ratio of maximum to predicted oxygen uptake, WR, work rate.