ORIGINAL RESEARCH ARTICLE

Impact of right ventricular contractile reserve during low-load exercise on exercise intolerance in heart failure

Masaki Kinoshita, Katsuji Inoue*, Haruhiko Higashi, Yusuke Akazawa, Yasuhiro Sasaki, Akira Fujii, Teruyoshi Uetani, Shinji Inaba, Jun Aono, Takayuki Nagai, Kazuhisa Nishimura, Shuntaro Ikeda and Osamu Yamaguchi

Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan

Abstract

Aims   Traditional criteria for heart transplantation by cardiopulmonary exercise testing (CPX) include peak oxygen uptake (VO$_2$) $<$ 14 mL/kg/min. Reaching a sufficient exercise load is challenging for patients with refractory heart failure (HF) because of their exercise intolerance. Recently, a substantial impact of right ventricular (RV) dysfunction was highlighted on urgent heart transplantation and mortality. This study aims to investigate the impact of RV contractile reserve, assessed by low-load exercise stress echocardiography (ESE), on exercise intolerance defined as peak VO$_2$ $<$ 14 mL/kg/min, in patients with HF.

Methods and results   We prospectively examined 67 consecutive patients hospitalized for HF who underwent ESE and CPX under a stabilized HF condition. Although low-load ESE was defined as 25 W load exercise, an increment in RV systolic (s') velocity was regarded as the preservation of RV contractile reserve. All patients completed low-load ESE. During low-load ESE, the variation in RV s' velocity significantly correlated with peak VO$_2$ (r = 0.787, P $<$ 0.001). The change in RV s' velocity during low-load ESE accurately identified patients with peak VO$_2$ $<$ 14 mL/kg/min (area under the curve, 0.95; sensitivity, 92%; specificity, 85%). The intraclass correlation coefficient for intra-observer and inter-observer agreement for the change in RV s' velocity was 0.96 (95% confidence interval, 0.88–0.99, P $<$ 0.001) and 0.86 (95% confidence interval, 0.64–0.95, P $<$ 0.001), respectively. The RV-to-pulmonary circulation (PC) coupling, which was assessed by the slope of the relationship between RV s' velocity and pulmonary artery systolic pressure at rest and low-load exercise, was worse in the low-peak VO$_2$ group ($<$14 mL/kg/min) than the preserved-peak VO$_2$ group ($\geq$14 mL/kg/min).

Conclusions   The change in RV s' velocity during low-load ESE could estimate the exercise capacity in HF patients. The assessments of RV contractile reserve and RV-to-PC coupling could be clinically beneficial to distinguish high-risk HF patients.

Keywords   exercise stress echocardiography; cardiopulmonary exercise testing; right ventricular contractile reserve; heart failure; low-load exercise; right ventricular-to-pulmonary circulation coupling

Introduction

In a clinical setting, cardiopulmonary exercise testing (CPX) is used to evaluate the exercise capacity of patients with heart failure (HF).[1] Peak oxygen uptake (VO$_2$) is the most objective indicator of exercise capacity during maximum exercise as well as a crucial prognostic parameter in patients with HF.[2]

Essentially, peak VO$_2$ $<$ 14 mL/kg/min is a critical value when estimating high-risk patients who require advanced HF interventions such as heart transplantation and ventricular assist devices.[3] Thus, the threshold of peak VO$_2$ $<$ 14 mL/kg/min is one of the most extensively used criteria for heart transplantation.[4] Nevertheless, peak VO$_2$ cannot be precisely measured in some cases because of an insufficient exercise

load. Hence, it is clinically beneficial to identify another parameter that can estimate peak VO_2 in patients with advanced HF, even those with exercise intolerance.

Recently, a study demonstrated a considerable impact of right ventricular (RV) dysfunction on urgent heart transplantation and mortality.[5] Motoki et al. demonstrated that RV echocardiographic parameters, such as RV systolic (s') velocity and RV strain, were lower in patients with cardiac events, including all-cause mortality, cardiac transplantation, and HF hospitalization.[6] Guazzi et al. also reported that the ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) was a potent surrogate of RV contractility and RV-to-pulmonary circulation (PC) coupling. [7]

As an alternative to CPX, exercise stress echocardiography (ESE) can be used to determine the exercise capacity by assessing the cardiac function.[8] However, reaching the maximum exercise load is challenging for patients with refractory HF because of their exercise intolerance. Thus, this study hypothesizes that low-load ESE could be used to estimate the exercise capacity in patients with HF. To the best of our knowledge, the potential of low-load ESE to estimate peak VO_2 remains unclear to date.

Hence, this study aims to examine the impact of RV contractile reserve, measured by low-load ESE, on exercise intolerance, which is defined as peak $VO_2 < 14$ mL/kg/min, in patients with HF.

Methods

Study design

This prospective, single-centre, cross-sectional study was conducted at Ehime University Hospital (Toon, Japan). All procedures listed in this study were performed in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines. This study protocol was approved by the Ethics Committee of Ehime University Hospital. Furthermore, all patients provided written informed consent before any study procedures were initiated.

Study population

We enrolled 76 consecutive hospitalized patients with HF who underwent ESE and CPX from May 2018 to January 2020 at Ehime University Hospital. The HF diagnosis was based on the criteria of the European Society of Cardiology guidelines.[9] The types of HF hospitalization were new-onset HF (n = 25) and acute exacerbation of chronic HF (n = 51). After stabilizing the HF condition, we performed ESE and CPX, within 48 h of each other. The exclusion criteria were as follows: (i) acute myocardial infarction; (ii) congenital heart disease; (iii) history of tricuspid valve surgery; and (iv) pulmonary arterial hypertension.

Cardiopulmonary exercise testing

All patients underwent incremental symptom-limited exercise testing using an upright cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co. Ltd., Tokyo, Japan). In addition, CPX was performed using a ramp protocol, including a 2 min recovery after peak effort.[2] All patients started with 2 min rest and 3 min warm-up at 10 W, followed by a 10 W ramp. Then, we evaluated breath-by-breath VO_2, carbon dioxide production, and minute ventilation using the gas analysis system (Cpex-1; Inter-Reha Co. Ltd., Tokyo, Japan). Of note, peak VO_2 was defined as the highest VO_2 observed during CPX.

Exercise stress echocardiography

An experienced echocardiographer performed two-dimensional echocardiography using the Vivid E9 ultrasound system (GE Healthcare, Milwaukee, WI). Standard two-dimensional greyscale still and moving images were recorded while three cardiac cycles in sinus rhythm and five cardiac cycles in atrial fibrillation, respectively. All echocardiographic data were transmitted on EchoPAC software (EchoPAC ver. BT13; GE Healthcare) for subsequent offline analyses. In addition, ESE was performed using an ergometer in the semi-supine and left lateral decubitus position (Ergoline 1200 EL; Inter-Reha Co. Ltd.). The workload was usually started at 25 W and increased by 25 W every 3 min, and echocardiographic images were recorded at rest and at each exercise stage.[10] Of note, we defined a 25 W load exercise for 3 min as low-load exercise.

We acquired conventional echocardiographic parameters based on the American Society of Echocardiography guidelines.[11] We evaluated the left ventricular (LV) ejection fraction and left atrial (LA) volume using the biplane disk summation method. The LA volume was indexed to the body surface area. The LV mass index was evaluated according to the area–length method. We obtained early diastolic transmitral flow velocity (E-wave) in the apical long-axis view using pulsed-wave Doppler and placed the sample volume at the level of the mitral valve tips. Then, early diastolic mitral annular motion (e') was assessed at the septal mitral annular sites in the apical four-chamber view, and E/e' was calculated. We evaluated stroke volume by multiplying the cross-sectional area of the LV outflow tract by the velocity–time integral in the LV outflow tract measured using pulsed-wave Doppler. Next, PASP was evaluated by the sum of the peak tricuspid pressure gradient and right atrial pressure estimated from the inferior vena cava diameter and collapsibility. We assessed the RV area and RV fractional

area change by manually tracing the RV endocardial border. In addition, TAPSE was measured by M-mode echocardiography from the RV focused apical four-chamber view. Furthermore, RV s' velocity was evaluated as the peak systolic velocity at the tricuspid annulus by pulsed-wave tissue Doppler from the RV focused apical four-chamber view.

Standard two-dimensional greyscale images were recorded in the apical four-chamber, two-chamber, and long-axis views as well as the RV focused apical four-chamber view. Using speckle tracking echocardiography, we measured LV global longitudinal strain (GLS), RV strain, and LA reservoir strain with high frame rates (>60 frames/s); these strain values were analysed using EchoPAC software (EchoPAC ver. BT13; GE Healthcare, Milwaukee, WI).[12] Then, GLS was evaluated by the average peak strain from three apical views. RV strain was evaluated as the average peak strain in the RV free wall, and LA reservoir strain was evaluated as the global positive peak LA longitudinal strain in the apical four-chamber view. On the basis of the recent recommendation of atrial deformation imaging, ventricular end-diastole was set as the zero baseline for the atrial strain curve.[13] All references to changes in GLS and RV strain indicated an increase or decrease in the absolute value of strain. When deemed necessary to correct the automatically tracked region of interest by the software, each strain analysis was manually corrected.

In this study, we defined increments in RV s' velocity, TAPSE, and RV strain during low-load exercise as a marker of RV contractile reserve. In addition, RV-to-PC coupling was assessed by the slopes of the relationship between RV s' velocity or TAPSE and PASP at rest and low-load exercise. Furthermore, TAPSE/PASP was applied as a non-invasive surrogate of RV-to-PC coupling.[14]

Right heart catheterization

Using the Swan–Ganz catheter, we performed right heart catheterization as adjudged by each physician to assess the haemodynamic condition. We evaluated RV $dP/dt/P$ max, which was RV dP/dt divided by the instantaneously developed isovolumetric pressure, as an index of RV contractility.[15,16] Of note, the invasive data were only analysed for patients in whom the duration between ESE and right heart catheterization was within 1 week; on the date of the invasive study, these patients were treated with oral medical treatment without intravenous inotropes.

Statistical analyses

If normal distribution was indicated by the Kolmogorov–Smirnov test, continuous variables were expressed as mean ± standard deviation (SD); else, median values (25th and 75th percentiles) were used. Conversely, categorical variables were presented as numbers with percentages. Patients were categorized into the low-peak VO_2 group (peak $VO_2 < 14$ mL/kg/min) and the preserved-peak VO_2 group (peak $VO_2 \geq 14$ mL/kg/min). Both groups were compared using the Student *t*-test or the Mann–Whitney *U*-test, as deemed suitable. We used univariate linear regression analysis with Pearson's correlation or Spearman's correlation coefficient. In addition, the intra-observer and inter-observer reproducibilities were evaluated using the intraclass correlation coefficient, and they were assessed in 15 randomly selected patients at a different time point (>1 month). Two experienced observers repeatedly assessed the parameters of RV contractile reserve. We defined statistical significance as $P < 0.05$. All statistical analyses were performed using the Social Science software version 20.0 (SPSS Inc., Chicago, IL) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17]

Results

Patients' characteristics

Table 1 presents the baseline characteristics of the study population. After the exclusion of patients (acute myocardial infarction, *n* = 2; congenital heart disease, *n* = 5; history of tricuspid valve surgery, *n* = 1; pulmonary arterial hypertension, *n* = 1), we analysed 67 patients with HF.

Cardiopulmonary exercise test and exercise stress echocardiographic parameters

Table 2 and Appendix S1 present the results of the CPX and ESE parameters. The median load of achieved exercise was 50 W (interquartile range: 25–75 W), and all patients completed low-load ESE without any adverse events. Among the echocardiographic parameters at rest, TAPSE and RV strain were lower in the low-peak VO_2 group than in the preserved-peak VO_2 group. Among the echocardiographic parameters at low-load exercise, TAPSE, RV s' velocity, RV strain, and TAPSE/PASP were lower in the low-peak VO_2 group than in the preserved-peak VO_2 group.

Echocardiographic correlates of exercise capacity

Table 3 shows the correlations between echocardiographic parameters and peak VO_2. The change in RV s' velocity during low-load exercise markedly correlated with peak VO_2 (*Figure* 1A), although the change in RV strain during low-load exercise exhibited a weak correlation with peak VO_2 (*Figure* 1B). Appendix S2 presents the correlations between the

Table 1 Baseline characteristics of the study population

Variables	All patients ($n = 67$)	Low-peak VO_2 group ($n = 26$)	Preserved-peak VO_2 group ($n = 41$)	P
Age, years	65 ± 12	71 ± 10	62 ± 13	0.004
Male	50 (74.6)	19 (73.1)	31 (75.6)	1.000
Body surface area, m^2	1.69 ± 0.20	1.67 ± 0.19	1.70 ± 0.21	0.492
NYHA functional class				0.001
NYHA I	3 (4.5)	0 (0)	3 (7.3)	
NYHA II	44 (65.7)	12 (46.2)	32 (78.0)	
NYHA III	20 (29.9)	14 (53.8)	6 (14.6)	
Aetiology of heart failure				
Ischaemic heart disease	13 (19.4)	8 (30.8)	5 (12.2)	0.110
Non-ischaemic heart disease	54 (80.6)	18 (69.2)	36 (87.8)	0.110
Hypertension	28 (41.8)	14 (53.8)	14 (34.1)	0.133
Diabetes mellitus	19 (28.4)	10 (38.5)	9 (22.0)	0.172
Dyslipidaemia	32 (47.8)	14 (53.8)	18 (43.9)	0.462
Chronic kidney disease	38 (56.7)	20 (76.9)	18 (43.9)	0.011
Atrial fibrillation	17 (25.4)	10 (38.5)	7 (17.1)	0.082
Laboratory data				
Brain natriuretic peptide, pg/mL	207 (80–361)	338 (226–546)	96 (67–233)	<0.001
Haemoglobin, g/dL	13.3 ± 2.1	12.5 ± 1.9	13.9 ± 2.1	0.011
Albumin, g/dL	3.9 ± 0.5	3.7 ± 0.5	4.0 ± 0.5	0.011
Creatinine, mg/dL	1.03 (0.83–1.33)	1.24 (0.96–1.70)	0.91 (0.80–1.22)	0.004
eGFR, mL/min/1.73 m^2	51.7 ± 17.9	42.8 ± 15.3	57.3 ± 17.4	0.001
Therapy				
ACE-I or ARB	58 (86.6)	25 (96.2)	33 (80.5)	0.138
Beta-blocker	59 (88.1)	25 (96.2)	34 (82.9)	0.138
Loop diuretic	51 (76.1)	22 (84.6)	29 (70.7)	0.247
Aldosterone blocker	44 (65.7)	18 (69.2)	26 (63.4)	0.793
Inotropic support	21 (31.3)	11 (42.3)	10 (24.4)	0.177
Device (PM, ICD, CRT)	19 (28.4)	12 (46.2)	7 (17.1)	0.014
Open heart surgery	11 (16.4)	4 (15.4)	7 (17.1)	1.000

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; eGFR, estimatedglomerular filtration rate; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; PM, pacemaker.
Data are expressed as mean ± SD, median (25th and 75th percentiles), or number (%).

change in RV s′ velocity during low-load and other CPX parameters.

Figure 2 shows two representative cases of low-peak and preserved-peak VO_2. *Table* 4 shows that the reproducibility for the change in RV s′ velocity during low-load exercise was superior to that of TAPSE and RV strain.

Receiver-operating characteristic curve analyses showed that the change in RV s′ velocity during low-load exercise had more predictive value for low-peak VO_2 than that of RV strain (*Figure* 3). In addition, the cut-off value of 0.68 cm/s for the change in RV s′ velocity during low-load exercise exhibited good sensitivity (92.3%), specificity (85.4%), and accuracy (89.6%) to identify patients with low-peak VO_2. Logistic regression analysis showed that the change in RV s′ velocity during low-load exercise was an independent predictor of low-peak VO_2 (*Table* 5). *Figure* 4 illustrates the slope between the relationship of RV s′ velocity or TAPSE and PASP at rest and low-load exercise. Notably, the slopes were steeper in the low-peak VO_2 group than in the preserved-peak VO_2 group, suggesting higher RV-to-PC uncoupling in the low-peak VO_2 group. Appendix S3 shows the relationship between RV s′ velocity and cardiac output at rest and low-load exercise. In the low-peak VO_2 group, the increase of cardiac output was limited with the blunted increase of RV s′ velocity during low-load exercise.

Correlation between change in right ventricular s′ velocity and right ventricular d*P*/d*t*/*P* max

We analysed invasive parameters in 26 patients during right heart catheterization. The change in RV s′ velocity during low-load exercise markedly correlated with RV d*P*/d*t*/*P* max (*Figure* 5). TAPSE/PASP at low-load exercise also had a significant correlation to RV d*P*/d*t*/*P* max ($r = 0.588$, $P < 0.001$).

Discussion

The major findings of this study are as follows: (i) low-load ESE was safely completed in all participants with HF; (ii) the blunted increase in RV s′ velocity during low-load exercise correlated with low-peak VO_2 and RV-to-PC uncoupling was observed in the low-peak VO_2 group; (iii) the diagnostic accuracy of increments in RV s′ velocity and TAPSE during low-load exercise to predict low-peak VO_2 was superior to that of RV strain; and (iv) the reproducibility of the change in RV s′ velocity was better than that of TAPSE and RV strain.

Assessing the RV function is challenging because of complex RV geometry; however, the RV longitudinal function

Table 2 Characteristics during cardiopulmonary exercise testing and exercise stress echocardiography

Variables	All patients ($n = 67$)	Low-peak VO_2 group ($n = 26$)	Preserved-peak VO_2 group ($n = 41$)	P
Cardiopulmonary exercise test				
Peak workload, W	71.8 ± 25.4	55.4 ± 21.5	82.4 ± 22.1	<0.001
Exercise duration, min	8.8 ± 3.7	7.1 ± 3.3	9.6 ± 3.6	0.059
Peak VO_2, mL/kg/min	15.1 ± 5.2	9.9 ± 2.4	18.4 ± 3.4	<0.001
Peak VO_2, % predicted	63.3 ± 19.6	45.3 ± 11.6	74.8 ± 14.4	<0.001
VE/VCO_2 slope	28.7 (26.0–34.0)	36.7 (32.1–39.6)	27.6 (24.6–30.2)	<0.001
Minimum VE/VCO_2	33.3 ± 8.0	39.3 ± 8.6	29.7 ± 4.9	<0.001
RER	1.10 ± 0.11	1.09 ± 0.13	1.10 ± 0.10	0.554
O_2 pulse max, mL/beat	86.8 ± 40.2	67.0 ± 17.5	99.2 ± 45.4	0.004
$ETCO_2$, %	5.0 ± 0.7	4.6 ± 0.6	5.3 ± 0.7	<0.001
Echocardiography at rest				
LVEF, %	35.9 ± 17.7	32.9 ± 13.1	37.8 ± 19.4	0.269
LVEF < 40%	44 (65.7)	19 (73.1)	25 (61.0)	0.429
LVEF ≥ 50%	13 (19.4)	3 (11.5)	10 (24.4)	0.225
Stroke volume, mL/beat	49.6 ± 18.5	45.0 ± 19.5	52.4 ± 17.5	0.112
LVGLS, %	−8.4 ± 4.6	−6.9 ± 4.5	−9.4 ± 4.5	0.036
E/e' ratio	15.2 (10.7–21.4)	18.4 (15.5–25.8)	13.3 (11.1–18.7)	0.001
PASP, mmHg	26.0 ± 14.9	33.4 ± 18.5	21.3 ± 9.9	0.001
RV FAC, %	39.4 ± 11.8	35.1 ± 10.8	42.1 ± 11.7	0.016
TAPSE, mm	15.9 ± 3.8	14.7 ± 3.5	16.7 ± 3.9	0.032
RV s' velocity, cm/s	8.6 ± 2.4	8.2 ± 2.3	8.8 ± 2.4	0.333
RV strain, %	−15.8 ± 5.6	−13.6 ± 5.0	−17.1 ± 5.5	0.009
TAPSE/PASP, mm/mmHg	0.72 (0.43–1.02)	0.42 (0.33–0.82)	0.81 (0.62–1.06)	0.002
RV s' velocity/PASP, cm/s/mmHg	0.36 (0.27–0.54)	0.28 (0.17–0.38)	0.42 (0.33–0.66)	0.008
Echocardiography at low-load				
LVEF, %	39.2 ± 17.6	34.5 ± 14.3	42.1 ± 18.9	0.084
Stroke volume, mL/beat	55.4 ± 19.7	45.2 ± 18.9	61.8 ± 17.6	0.001
LVGLS, %	−9.9 ± 4.9	−8.3 ± 4.7	−11.0 ± 4.7	0.025
E/e' ratio	16.0 (12.6–22.1)	19.1 (15.5–25.1)	13.5 (10.2–18.0)	0.001
PASP, mmHg	38.9 ± 17.5	47.5 ± 20.2	33.3 ± 12.9	0.001
RV FAC, %	39.0 ± 12.5	31.0 ± 11.8	44.1 ± 10.2	<0.001
TAPSE, mm	17.5 ± 4.7	14.3 ± 3.9	19.6 ± 3.9	<0.001
RV s' velocity, cm/s	10.1 ± 3.0	8.1 ± 2.2	11.4 ± 2.7	<0.001
RV strain, %	−17.6 ± 6.1	−13.9 ± 4.8	−20.0 ± 5.6	<0.001
TAPSE/PASP, mm/mmHg	0.46 (0.33–0.71)	0.27 (0.22–0.45)	0.60 (0.44–0.81)	<0.001
RV s' velocity/PASP, cm/s/mmHg	0.29 (0.18–0.40)	0.17 (0.13–0.27)	0.32 (0.27–0.54)	<0.001
Peak workload, W	50 (25.0–75.0)	25.0 (25.0–50.0)	50.0 (50.0–75.0)	<0.001

E/e' ratio, early diastolic transmitral flow velocity and early diastolic mitral annular motion ratio; $ETCO_2$, end-tidal carbon dioxide; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; O_2 pulse, oxygen consumption per cardiac cycle; PASP, pulmonary artery systolic pressure; RER, respiratory exchange ratio; RV FAC, right ventricular fractional area change; RV strain, right ventricular strain; RV s' velocity, right ventricular systolic velocity; RV s' velocity/PASP, right ventricular systolic velocity and pulmonary artery systolic pressure ratio; TAPSE, tricuspid annular plane systolic excursion; TAPSE/PASP, tricuspid annular plane systolic excursion and pulmonary artery systolic pressure ratio; VE/VCO_2, ventilatory equivalent for carbon dioxide; VO_2, oxygen uptake.
Data are expressed as mean ± SD, median (25th and 75th percentiles), or number (%).

can be assessed using RV s' velocity and TAPSE, although it is assumed that the velocity and displacement of the basal segment in the RV focused apical four-chamber view reflect the function of the entire RV.[18] A recent study reported the utility of RV strain, which could provide a more global function of the RV.[19] However, it remains challenging to obtain optimal curves of RV strain, especially during exercise, because of requirements in its acquisition with adequate image quality. The guideline related to RV function assessment states that RV s' velocity and TAPSE should be incorporated into routine clinical use, whereas RV strain remains a research tool in experienced laboratories.[20] In a porcine model, RV s' velocity detected early impairments in RV systolic function.[21] In addition, an observational study reported that RV s' velocity and RV strain independently correlated with exercise capacity measured by CPX performed in

patients with severe LV systolic dysfunction.[22] Besides, Sharma *et al.* established a correlation between increased RV s' velocity and exercise capacity.[23] D'Alto *et al.* suggested that RV s' velocity was more sensitive to changes in RV longitudinal function than TAPSE.[24] Our study was consistent to their finding that the rate of change in RV s' velocity increased at low-load ESE more than that of TAPSE. In this study, the change in RV s' velocity during low-load exercise exhibited more predictive and reproducible values for low-peak VO_2 (<14 mL/kg/min) compared with the changes in TAPSE and RV strain. Furthermore, results of RV s' velocity were obtained immediately after ESE without requiring any additional software.

As judged by the respiratory exchange ratio (RER) > 1.0, evaluation on CPX should start with an assessment of the maximum volitional effort.[25] In a previous study, 42% of

Table 3 Correlations between peak VO$_2$ and exercise stress echocardiographic parameters

Variables	Rest (r value)	P	Low load (r value)	P
LVEF, %	0.053	0.668	0.193	0.118
LVEDV, mL	0.087	0.486	0.064	0.607
LVESV, mL	0.075	0.547	−0.009	0.943
Stroke volume, mL/beat	0.025	0.843	0.304	0.012
LVGLS, %	−0.190	0.124	−0.207	0.093
LA volume index, mL/m^2	−0.334	0.006	−0.318	0.009
LA reservoir strain, %	0.264	0.031	0.399	<0.001
E/e' ratio	−0.387	0.001	−0.384	0.001
PASP, mmHg	−0.495	<0.001	−0.512	<0.001
TAPSE, mm	0.305	0.012	0.653	<0.001
RV s' velocity, cm/s	0.088	0.478	0.553	<0.001
RV strain, %	−0.343	0.005	−0.501	<0.001
TAPSE/PASP, mm/mmHg	0.503	<0.001	0.634	<0.001
RV s' velocity/PASP, cm/s/mmHg	0.445	<0.001	0.608	<0.001

E/e' ratio, early diastolic transmitral flow velocity and early diastolic mitral annular motion ratio; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; PASP, pulmonary artery systolic pressure; RV strain, right ventricular strain; RV s' velocity, right ventricular systolic velocity; RV s' velocity/PASP, right ventricular systolic velocity and pulmonary artery systolic pressure ratio; TAPSE, tricuspid annular plane systolic excursion; TAPSE/PASP, tricuspid annular plane systolic excursion and pulmonary artery systolic pressure ratio.

patients with HF could not attain peak RER > 1.0 during CPX.[26] In another study, some patients could not attain 50 W load exercise among patients with peak VO$_2$ < 14 mL/kg/min.[27] This study secured the safety of low-load ESE because all patients with HF completed the tests without any adverse events.

According to Frank Starling's law, cardiac output gradually increases by enhancing the venous return during exercise. An increase in the cardiac output causes an increment in VO$_2$. In a failing heart, a preload recruitment during exercise could elevate the LV filling pressure, which, in turn, increases the RV

afterload. As the RV is highly sensitive to afterload than the LV, a lack of RV contractile reserve directly induces exercise intolerance in the presence of left-sided heart disease.[28] Of note, ESE enables the investigation of RV function when both preload and afterload are increased during exercise; consequently, there could be a clinical potential to evaluate RV contractile reserve during low-load exercise in patients with reduced exercise capacity. In invasive studies, RV dP/dt is extensively used as one of the haemodynamic indices of RV contractility; however, it has a limitation of preload dependence. Conversely, RV dP/dt/P max is regarded as less independent on both preload and afterload.[15] Kanzaki *et al.* reported using Doppler echocardiography that there was a significant correlation between RV dP/dt/P max and peak VO$_2$.[16] In this study, the change in RV s' velocity during low-load ESE significantly correlated with the invasively measured RV dP/dt/P max, suggesting that the change in RV s' velocity could be a non-invasive marker of RV contractility.

Left-sided HF causes pulmonary hypertension by elevated pulmonary venous pressure besides pulmonary vascular remodelling. The impact of pulmonary hypertension on adverse outcomes in patients with HF is primarily related to the coexistence of RV systolic dysfunction.[29] In our study, higher E/e', lower LA reservoir strain and higher grade of mitral regurgitation during low-load exercise were associated with low-peak VO$_2$. Usually, the RV adapts to increased afterload by enhancing RV contractility; however, the RV dilates to preserve the cardiac output in patients with RV dysfunction and is progressively maladapted to pulmonary hypertension, resulting in a decrease of cardiac output. This study showed that the increment in RV s' velocity during low-load exercise was associated with the increase of cardiac output, which is known as a key determinant of peak VO$_2$ as previously reported.[30]

Recently, a study reported the concept of RV-to-PC coupling as the significance of RV function when considering

Figure 1 Correlation between peak VO$_2$ and RV function during low-load exercise. (A) Correlation between the change in RV s' velocity and peak VO$_2$ during low-load exercise (r = 0.787; P < 0.001). (B) Correlation between the change in RV strain and peak VO$_2$ during low-load exercise (r = 0.244; P < 0.001). RV s' velocity, right ventricular systolic velocity; RV strain, right ventricular strain; VO$_2$, oxygen uptake.
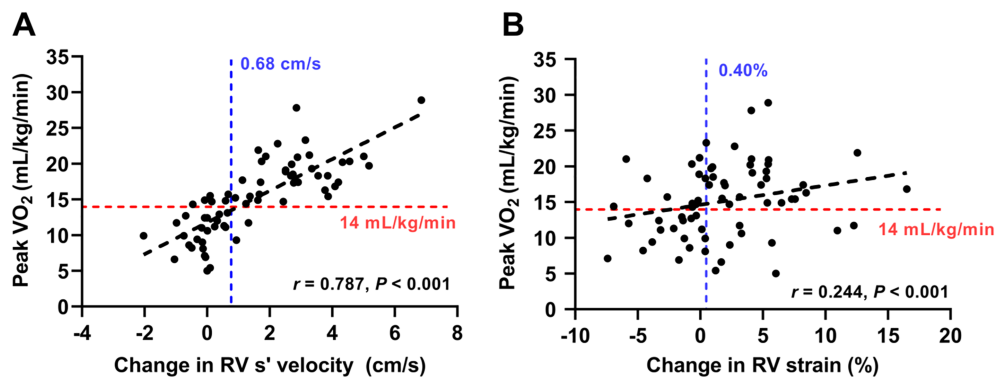
Figure 2 Representative cases of a patient in the low-peak VO₂ group and a patient in the preserved-peak VO₂ group. (A) Representative case in a low-peak VO₂ group (peak VO₂, 12.9 mL/kg/min). (B) Representative case in a preserved-peak VO₂ group (peak VO₂, 21.0 mL/kg/min). RV s′ velocity did not increase in a patient with low-peak VO₂ compared with a patient with preserved-peak VO₂. PASP was higher in a patient with low-peak VO₂ than a patient with preserved-peak VO₂. PASP, pulmonary artery systolic pressure; RV s′ velocity, right ventricular systolic velocity; VO₂, oxygen uptake.
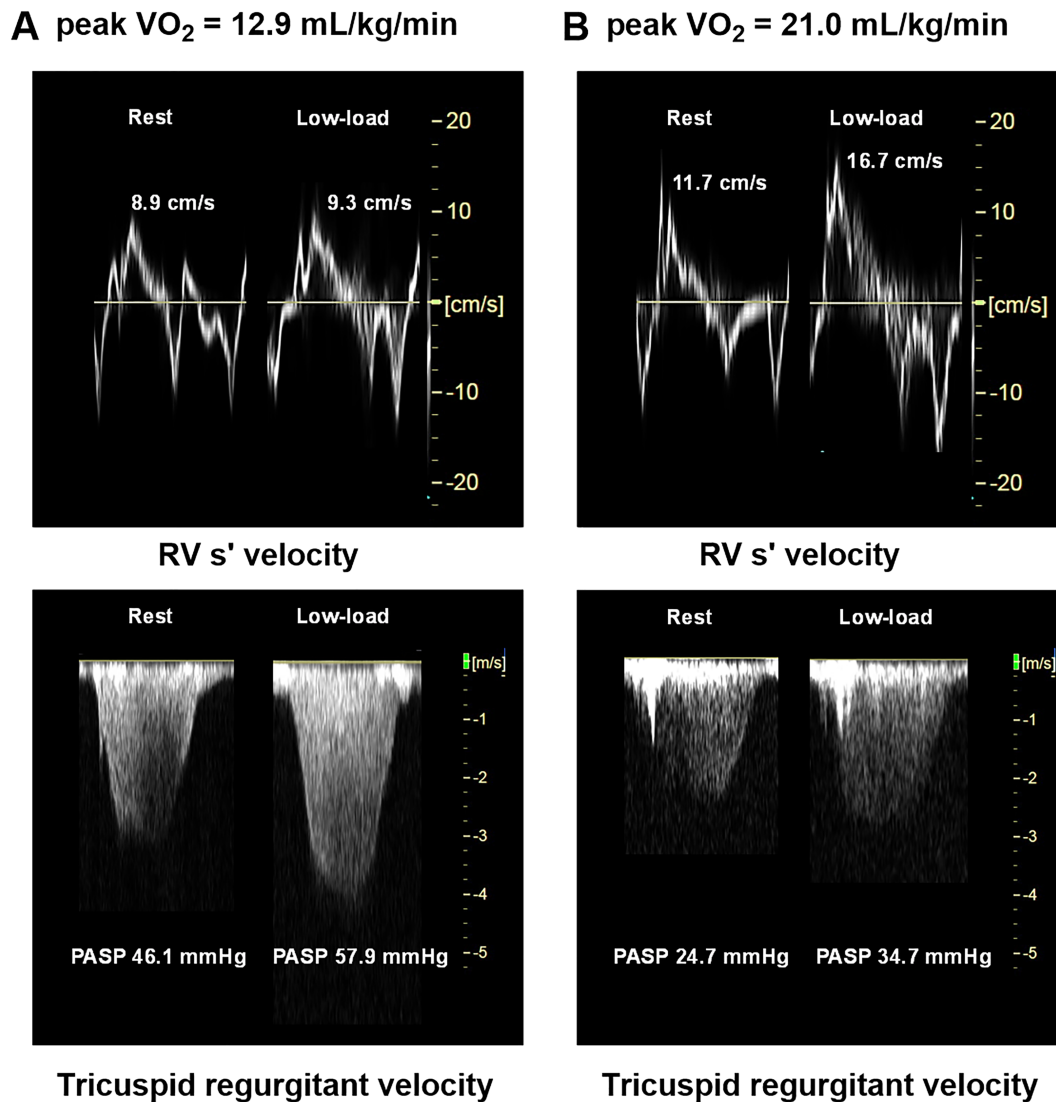

A peak VO$_2$ = 12.9 mL/kg/min

B peak VO$_2$ = 21.0 mL/kg/min

Table 4 Reproducibility for the change in right ventricular function during low-load exercise

Variables	ICC	95% CI	*P*
Intra-observer			
Change in RV s′ velocity, cm/s	0.96	0.88–0.99	<0.001
Change in TAPSE, mm	0.59	0.14–0.84	0.007
Change in RV strain, %	0.70	0.32–0.84	0.001
Inter-observer			
Change in RV s′ velocity, cm/s	0.86	0.64–0.95	<0.001
Change in TAPSE, mm	0.41	0.11–0.75	0.057
Change in RV strain, %	0.63	0.19–0.86	0.005

CI, confidence interval; ICC, intraclass correlation coefficient; RV strain, right ventricular strain; RV s′ velocity, right ventricular systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

the afterload in patients with HF.[31] Singh *et al.* reported that RV-to-PC uncoupling impaired the response of stroke volume during exercise and correlated with reduced exercise capacity.[32] The RV-to-PC coupling can be assessed by the combined assessments of RV systolic function and PASP.[33] TAPSE/PASP is a clinically relevant and valid surrogate of invasively measured end-systolic/arterial elastance ratio to assess RV-to-PC coupling. As shown in previous studies, TAPSE/PASP _x0003C; 0.31 mm/mmHg predicted RV-to-PC uncoupling, which was associated with poor prognosis in patients with HF.[14,33] In this study, TAPSE/PASP was markedly decreased (0.27 mm/mmHg) at low-load exercise in the

Figure 3 Receiver-operating characteristic curve analysis of echocardiographic parameters during low-load exercise to predict low-peak VO$_2$. The change in RV s' velocity during low-load exercise had higher AUC (0.95; $P < 0.001$) than the change in RV strain. AUC, area under the curve; RV s' velocity, right ventricular systolic velocity; RV strain, right ventricular strain; TAPSE, tricuspid annular plane systolic excursion; VO$_2$, oxygen uptake.
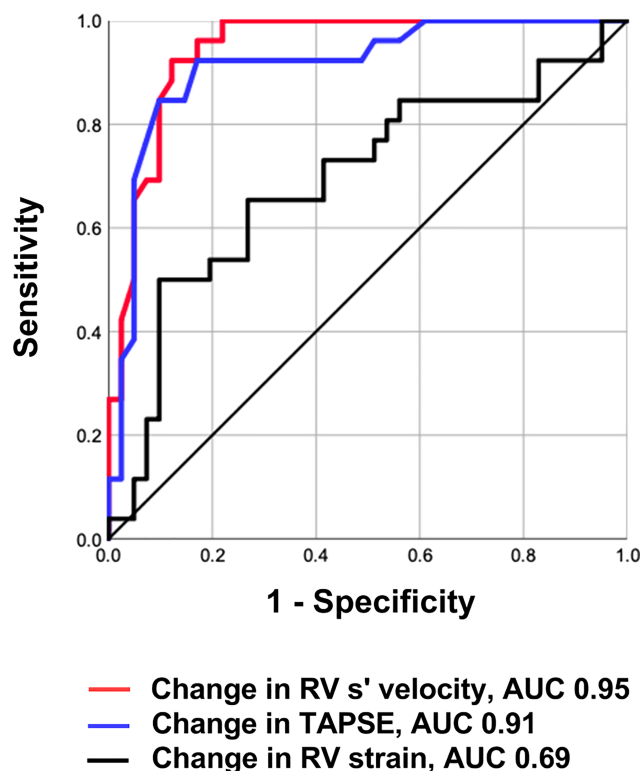
low-peak VO$_2$ group, suggesting RV-to-PC uncoupling was provoked during submaximal exercise in patients with exercise intolerance.

Study limitations

This was a single-centre, cross-sectional study performed using a relatively small sample size, and the study population included relatively high-risk patients. We did not assess clinical outcomes. Thus, it is essential to establish that RV contractile reserve assessed by low-load ESE has a predictive value to identify high-risk patients with HF. Our protocols in CPX and ESE were different in terms of patient position and loading method. Because Frank Starling's law depends on gravity and venous return, haemodynamic changes may be different in each exercise protocol. Finally, RV s' velocity is angle dependent and not entirely representative of the RV

Table 5 Logistic regression analysis for association with low-peak VO$_2$

Variables	Univariable odds ratio (95% CI)	P	Multivariable odds ratio (95% CI)	P
Age, year	1.07 (1.02–1.12)	0.007	1.11 (1.00–1.23)	0.054
Atrial fibrillation	3.04 (0.98–9.40)	0.055		
Change in LVEF, %	0.95 (0.88–1.02)	0.136		
E/e' ratio at low load, per 1	1.06 (1.01–1.11)	0.025	0.95 (0.86–1.04)	0.268
LA volume index at low load, mL/m^2	1.02 (1.00–1.04)	0.108		
LA reservoir strain at low load, %	0.89 (0.83–0.97)	0.006	0.91 (0.81–1.02)	0.116
Mitral regurgitation grade at low load (≥moderate)	3.81 (1.11–13.10)	0.034	0.67 (0.51–8.67)	0.757
Change in RV s' velocity, cm/s	0.10 (0.03–0.33)	<0.001	0.08 (0.01–0.45)	0.004
Change in RV strain, %	0.88 (0.77–0.99)	0.040	0.94 (0.71–1.25)	0.678
TAPSE/PASP at low load, mm/mmHg	0.01 (0.00–0.15)	0.002	2.42 (0.38–152.00)	0.677

E/e' ratio, early diastolic transmitral flow velocity and early diastolic mitral annular motion ratio; LA, left atrial; LVEF, left ventricular ejection fraction; RV strain, right ventricular strain; RV s' velocity, right ventricular systolic velocity; TAPSE/PASP, tricuspid annular plane systolic excursion and pulmonary artery systolic pressure ratio; VO$_2$, oxygen uptake.

Figure 4 Relationship between right ventricular systolic function and pulmonary artery systolic pressure during low-load exercise. (A) Relationship between RV s′ velocity and PASP at rest and low-load exercise. (B) Relationship between TAPSE and PASP at rest and low-load exercise. Red symbols, low-peak VO_2 group; blue symbols, preserved-peak VO_2 group. The slopes in the low-peak VO_2 group were steeper than that in the preserved-peak VO_2 group. PASP, pulmonary artery systolic pressure; RV s′ velocity, right ventricular systolic velocity; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen uptake.
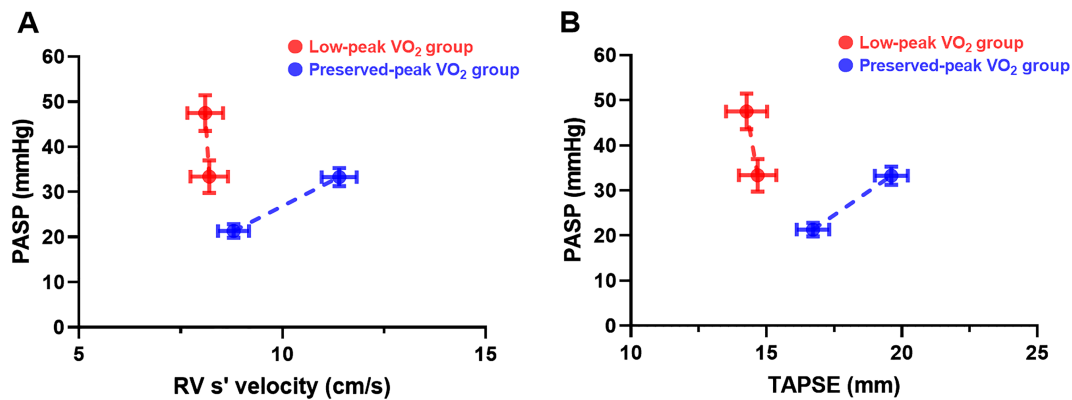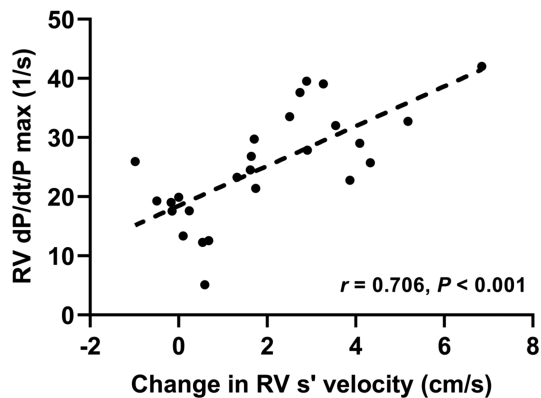

Figure 5 Correlation between RV dP/dt/P max and change in RV s′ velocity during low-load exercise. The change in RV s′ velocity during low-load exercise significantly correlated with RV dP/dt/P max (r = 0.706; $P < 0.001$). RV s′ velocity, right ventricular systolic velocity; RV, right ventricular.

global function. Despite the limitation, it is clinically crucial that RV s′ velocity is a simple and reproducible measure with good discriminatory ability to determine exercise intolerance in patients with HF.

Conclusions

The change in RV s′ velocity during low-load ESE correlates with peak VO_2 and is a robust predictor to determine exercise intolerance in patients with HF. It could be clinically beneficial to assess RV contractile reserve against afterload increase during exercise to identify high-risk patients with HF.

Nevertheless, further studies are warranted to validate whether RV contractile reserve and RV-to-PC coupling during low-load ESE have a predictive value of prognosis in patients with HF.

Conflict of interest

None declared.

Permission

The authors confirm that all material is original to this submission.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Characteristics during cardiopulmonary exercise testing and exercise stress echocardiography

Appendix S2. Correlations between the change in RV s′ velocity during low-load and CPX parameters

Appendix S3. Relationship between RV s′ velocity and cardiac output during low-load exercise. The increase of cardiac output was limited

with the blunted increase of RV s′ velocity during low-load exercise in the low-peak VO$_2$ group (Red symbols) compared with the preserved-peak VO$_2$ group (Blue symbols). RV s′ velocity, right ventricular systolic velocity; VO$_2$, oxygen uptake.

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