Diastolic Intra−Left Ventricular Pressure Difference During Exercise: Strong Determinant and Predictor of Exercise Capacity in Patients With Heart Failure

SHINGO TSUJINAGA, MD,[1] HIROYUKI IWANO, MD, PhD,[1] MIWA SARASHINA, MD,[1] TAICHI HAYASHI, MD, PhD,[1] MICHITO MURAYAMA, MS,[2] AYAKO ICHIKAWA,[3] MASAHIRO NAKABACHI, MS,[3] HISAO NISHINO,[3] SHINOBU YOKOYAMA,[3] ARATA FUKUSHIMA, MD, PhD,[1] TAKASHI YOKOTA, MD, PhD,[1] KAZUNORI OKADA, PhD,[4] SANAE KAGA, PhD,[4] PAVLOS P. VLACHOS, PhD,[5] AND TOSHIHISA ANZAI, MD, PhD[1]

Sapporo, Japan; and West Lafayette, USA

ABSTRACT

Background: Although the enhancement of early-diastolic intra−left ventricular pressure difference (IVPD) during exercise is considered to maintain exercise capacity, little is known about their relationship in heart failure (HF).

Methods and Results: Cardiopulmonary exercise testing and exercise-stress echocardiography were performed in 50 HF patients (left ventricular [LV] ejection fraction 39 ± 15%). Echocardiographic images were obtained at rest and submaximal and peak exercise. Color M-mode Doppler images of LV inflow were used to determine IVPD. Thirty-five patients had preserved exercise capacity (peak oxygen consumption [VO_2] ≥14 $mL \cdot kg^{-1} \cdot min^{-1}$; group 1) and 15 patients had reduced exercise capacity (group 2). During exercise, IVPD increased only in group 1 (group 1: 1.9 ± 0.9 mm Hg at rest, 4.1 ± 2.0 mm Hg at submaximum, 4.7 ± 2.1 mm Hg at peak; group 2: 1.9 ± 0.8 mm Hg at rest, 2.1 ± 0.9 mm Hg at submaximum, 2.1 ± 0.9 mm Hg at peak). Submaximal IVPD ($r = 0.54$) and peak IVPD ($r = 0.69$) were significantly correlated with peak VO_2. Peak IVPD determined peak VO_2 independently of LV ejection fraction. Moreover, submaximal IVPD could well predict the reduced exercise capacity.

Conclusion: Early-diastolic IVPD during exercise was closely associated with exercise capacity in HF. In addition, submaximal IVPD could be a useful predictor of exercise capacity without peak exercise in HF patients. (*J Cardiac Fail 2019;25:268−277*)

Key Words: Heart failure, exercise capacity, exercise-stress echocardiography, intra−left ventricular pressure difference.

Limited exercise capacity is a major symptom and cause of disability in patients with chronic heart failure (HF). Moreover, exercise intolerance has been reported to be associated with poor prognosis in HF patients.[1,2] The exercise capacity is known to be maintained by the increase of cardiac output during exercise in HF regardless of left ventricular (LV) ejection fraction (EF).[3] In normal conditions, during exercise LV suction augments the pressure fall in the LV cavity in early diastole, and the generated early-diastolic intra−left ventricular pressure difference (IVPD) pulls blood from left atrium to the LV apex, which maintains or even increases diastolic filling despite the shortening of the filling time.[4] Therefore, early-diastolic IVPD during exercise has been considered to be associated with exercise capacity.

The IVPD can be estimated noninvasively by integrating the Euler equation from echocardiographic color M-mode Doppler (CMMD) data.[5] By applying this method to exercise-stress echocardiography, a previous study demonstrated that augmentation of early-diastolic IVPD by exercise was blunted and that its changes during exercise were strongly associated with exercise capacity in patients with HF with reduced EF.[6] However, the impact of the early-diastolic IVPD on exercise capacity in HF with preserved EF has not been elucidated. In addition, peak

From the [1]Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; [2]Diagnostic Center for Sonography, Hokkaido University Hospital, Sapporo, Japan; [3]Division of Clinical Laboratory and Transfusion Medicine, Hokkaido University Hospital, Sapporo, Japan; [4]Faculty of Health Sciences, Hokkaido University, Sapporo, Japan and [5]School of Mechanical Engineering, Purdue University, West Lafayette, Indiana, USA.

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Reprint requests: Hiroyuki Iwano, MD, PhD, Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo, 060-8638, Japan. Tel: +81-11-706-6974; Fax: +81-11-706-7874.
E-mail: h-iwano@med.hokudai.ac.jp

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exercise places excessive load on the patients with severe symptomatic HF, which is preferred to be avoided. Accordingly, the aim of the present study was to confirm that early-diastolic IVPD during exercise could be associated with exercise capacity in chronic HF patients with various LV EF, and moreover, that the IVPD at submaximal exercise could predict exercise capacity without excessive workload.

Methods

Study Population and Protocol

The screening process in this study is shown in Supplemental Fig. 1. The present study prospectively enrolled 160 consecutive HF patients who were admitted to our department for the management of HF and referred for clinically indicated cardiopulmonary exercise testing (CPX) from July 2016 to January 2018. All patients were diagnosed as stage B or C chronic HF according to the guidelines.[7] From the 160 patients, we excluded those with atrial fibrillation or flutter, inducible myocardial ischemia, significant left-sided valvular disease with the exception of secondary mitral regurgitation (MR) (moderate or severe aortic regurgitation, aortic stenosis, mitral stenosis, or primary MR assessed with the use of Doppler echocardiography according to guidelines),[8] prosthetic valve replacement, obstructive hypertrophic cardiomyopathy, peripheral artery disease, obvious anemia defined by hemoglobin <10 g/dL, congenital heart disease, respiratory disease, pericardial disease, or left ventricular assist device implantation. Accordingly, 55 patients with HF who denied the exclusion criteria were eligible for the present analysis. After the confirmation that HF was in stable condition, CPX and exercise-stress echocardiography were performed without discontinuing β-blockers if the patient was taking them. The study protocol was approved by the Institutional Review Board of the Hokkaido University Hospital, and written informed consents were obtained from all of the patients.

Cardiopulmonary Exercise Testing

A symptom-limited CPX was performed with the use of an upright electromechanical bicycle ergometer (Aerobike 75XLII; Combi Wellness, Tokyo, Japan) using a ramp protocol as previously described.[9] Peak oxygen consumption (VO_2), defined as the maximal VO_2 attained during exercise, was measured by means of simultaneous respiratory gas analysis with the use of a breathing apparatus (Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). The maximal work, peak respiratory exchange, and anaerobic threshold (AT) determined by means of the V-slope method[10] were also measured.

Exercise-Stress Echocardiography

Exercise-stress echocardiography with the use of a supine bicycle ergometer (Angio V2; Lode, Groningen, The Netherlands) and iE33 ultrasound system with S5-1 transducer (Philips Ultrasound, Bothell Washington) was performed within 7 days after CPX. To adjust the workload during the stress echocardiography among the patients, we determined the submaximal workload as the level of AT and peak workload as 80% of the CPX peak workload. The protocol of exercise stress was as follows: the workload was increased to the level of AT in 3 minutes and echocardiographic images at submaximal exercise were acquired within 5 minutes, and then the workload was further increased to 80% of the CPX peak workload in the following 3 minutes and the images at peak exercise were acquired within 5 minutes. Echocardiographic images including 2-dimensional, Doppler, and CMMD images were acquired at rest and submaximal and peak exercise. LV end-diastolic volume, end-systolic volume, and EF were measured by means of the method of disks. LV mass was calculated according to the Devereux formula. The Doppler image of LV outflow was recorded in the apical long-axis view, and time-velocity integral was measured for the estimation of stroke volume. Cardiac output was calculated as stroke volume × heart rate. Transmitral Doppler flow was recorded and peak early (E) and late diastolic velocity (A) measured. Septal and lateral peak systolic annular velocities (s′) as well as early-diastolic peak of mitral annular velocities (e′) were measured from the apical 4-chamber view with the use of pulsed-wave tissue Doppler imaging, and average of the septal and lateral velocities were used for the subsequent analysis. The ratio of E to e′ (E/e′) was calculated. CMMD images were recorded with the cursor parallel to LV inflow in the apical 4-chamber view.

Estimation of Arterial and End-Systolic Elastance

End-systolic pressure was estimated as $0.9 \times$ brachial systolic blood pressure,[11] and the arterial elastance (Ea) was derived as the ratio of end-systolic pressure to stroke volume as assessed by echocardiography.[12] The end-systolic elastance (Ees) was derived as the ratio of end-systolic pressure to LV end-systolic volume.[12]

Definition of Exercise Intolerance

Patients were divided into 2 groups according to peak VO_2: group 1 (preserved exercise capacity, defined by peak $VO_2 \geq 14$ mL·kg^{-1}·min^{-1}) and group 2 (reduced exercise capacity defined by peak $VO_2 < 14$ mL·kg^{-1}·min^{-1}).[13]

Analysis of the IVPD With the Use of CMMD Images

CMMD images were analyzed with the use of an automated analysis algorithm based in Matlab (The Mathworks, Natic, Massachusetts).[14] Briefly, the early-diastolic IVPD from the mitral annulus to the LV apex was determined with the use of CMMD data to integrate the Euler equation as previously described.[14] From the temporal profile of the IVPD, the early-diastolic peak IVPD from the mitral

annulus to the LV apex was calculated. This method has been validated by comparison with direct measurements with micromanometers.[5]

Reproducibility Analysis

The test-retest reproducibility of IVPD measurement was assessed in 15 of the study subjects. The same CMMD images at rest and peak exercise were analyzed on 2 separate days and compared. The absolute differences between repeated measurements of IVPD at rest and at peak exercise were 0.36 ± 0.33 mm Hg (20%) and 0.50 ± 0.40 mm Hg (13%), respectively.

Statistical Analysis

Quantitative variables were expressed as mean ± SD if normally distributed, and as median (interquartile range) if nonnormally distributed. Qualitative variables were reported as frequency and percentage. Parametric unpaired *t* test or nonparametric Wilcoxon test was used to compare quantitative variables. The chi-square test was used to compare qualitative variables. A mixed-effects measures analysis of variance was used in which one factor was a between-subjects variable and the other was a within-subjects variable, incorporating rest and submaximal and peak exercise responses. Tukey-Kramer test was used for post hoc analysis. Pearson correlation coefficient was used to examine the relationship between continuous variables. A linear regression analysis determined cofactors associated with peak VO_2, and a multiple linear regression analysis was performed establishing 4 models in which variables were selected based on significant cofactors in univariable analysis and determinants of peak VO_2 established in previous reports.[15–17] To test the correlations between IVPD and the parameters obtained during exercise-stress echocardiography, the datasets at rest and submaximal and peak exercise were used for the linear regression analyses. A linear regression analysis to clarify the factors associated with peak VO_2 and a receiver operating characteristic (ROC) analysis were performed to evaluate the utility of the IVPD at submaximal exercise for the prediction of reduced exercise capacity. The incremental value of the IVPD at submaximal exercise over clinical and echocardiographic characteristics to predict reduced exercise capacity was investigated by the significance of the increase in global chi-square. For all tests, a P value of <0.05 was considered to be statistically significant. Statistical analyses were performed with the use of JMP Pro 13.1.0 (SAS Institute, Cary, North Carolina).

Results

Patient Characteristics

Among the 55 eligible patients with HF, 5 were excluded owing to insufficient echocardiographic image quality obtained during exercise. Therefore, the final study population consisted of 50 patients. The baseline characteristics of the studied patients are presented in Table 1. Almost half of the patients had moderate HF symptom, and 18 (36%) had dilated cardiomyopathy. Prevalences of the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and of β-blockers were high, and loop diuretics were administered in roughly half of the patients. Plasma B-type natriuretic peptide (BNP) level was modestly increased, and the average LV EF was 39% overall. In addition, the study population included 22 patients (44%) with relatively preserved LV EF (≥40%).

Comparisons Between Patients With and Without Exercise Intolerance

Among the 50 patients with HF, 35 had preserved exercise capacity, defined by peak VO_2 ≥14 $mL \cdot kg^{-1} \cdot min^{-1}$ (group 1), and 15 had reduced exercise capacity (group 2; Table 1). There were some tendencies that dilated cardiomyopathy was more frequent and ischemic heart disease less frequent in group 1. Patients in group 2 were more likely to have diabetes mellitus and to be treated with loop diuretics, mineral corticoid receptor antagonist, and tolvaptan than those in group 1. However, β-blockers and ACE inhibitors or ARBs were administered similarly in both groups.

Hemoglobin was significantly higher and creatinine as well as plasma BNP level were lower in group 1 than in group 2. There were some tendencies that LV mass index, LV end-diastolic volume, and LV end-systolic volume were larger and LV EF lower in group 2. Respiratory exchange ratio was similar between the groups, with an average >1.15, suggesting that adequate stress could be achieved in both groups.

Responses to Exercise During Stress Echocardiography

The time from CPX to exercise-stress echocardiography was 3 ± 2 days. Changes in hemodynamic and echocardiographic parameters during the exercise-stress echocardiography are summarized in Table 2. Excise duration was similar between the groups. Although heart rate was increased in groups 1 and 2, it achieved higher values in group 1. Stroke volume did not change in both groups, although patients in group 1 had greater stroke volume at submaximal and peak exercise. As a result, cardiac output was significantly increased only in group 1. LV EF did not change in both groups, although the patients in group 1 showed a tendency to its increase and s′ significantly increased only in group 1. Increase in MR was more frequently observed in group 2 than in group 1. As shown in Fig. 1A, IVPD was significantly increased at submaximal and peak exercise overall. However, the increase was observed only in group 1, and in group 2 it remained at the same value as at rest during exercise (Fig. 1B). As a result, IVPD during exercise was significantly higher in group 1 than in group 2 (Fig. 2). The patients who showed increase in MR to more than moderate during exercise did not show an increase in IVPD during exercise (at rest 1.8 ± 0.8 mm

Table 1. Baseline Clinical Characteristics

Variable	Overall (n = 50)	Group 1 (n = 35)	Group 2 (n = 15)	*P* Value
Age, y	59 ± 16	57 ± 16	63 ± 13	.19
Male, n (%)	30 (60)	22 (63)	8 (53)	.53
Body surface area, m^2	1.65 ± 0.21	1.68 ± 0.22	1.59 ± 0.19	.16
Systolic BP, mm Hg	106 ± 18	109 ± 16	98 ± 22	.06
Diastolic BP, mm Hg	63 ± 11	66 ± 10	55 ± 12	<.01
Heart rate, beats/min	68 ± 11	67 ± 10	69 ± 15	.63
NYHA functional class				<.001
I	9 (18)	9 (26)	0 (0)	
II	18 (36)	17 (49)	1 (7)	
III	23 (46)	9 (26)	14 (93)	
Cardiac disease				.68
Dilated cardiomyopathy	18 (36)	14 (40)	4 (27)	
Ischemic heart disease	8 (16)	4 (11)	4 (27)	
Hypertensive heart disease	6 (12)	4 (11)	2 (13)	
Hypertrophic cardiomyopathy	5 (10)	4 (11)	1 (7)	
Other	13 (26)	9 (26)	4 (27)	
Comorbidity				
Hypertension	21 (42)	15 (43)	6 (40)	.85
Dyslipidemia	24 (48)	14 (40)	10 (67)	.08
Diabetes mellitus	10 (20)	3 (9)	7 (47)	<.01
Medication				
ACE inhibitors or ARBs	43 (86)	31 (89)	12 (80)	.42
β-Blockers	40 (80)	27 (77)	13 (87)	.70
Calcium antagonists	6 (12)	3 (9)	3 (20)	.35
Loop diuretics	28 (56)	15 (43)	13 (87)	<.01
Mineral corticoid receptor antagonists	22 (44)	11 (31)	11 (73)	<.01
Tolvaptan	12 (24)	5 (14)	7 (47)	.03
Statin	21 (42)	13 (37)	8 (53)	.29
Aspirin	10 (20)	5 (14)	5 (33)	.14
Laboratory data				
Hemoglobin, g/dL	13.4 ± 2.0	13.8 ± 1.9	12.3 ± 2.0	.02
Total protein, g/dL	6.9 ± 0.5	6.9 ± 0.5	7.0 ± 0.6	.42
Albumin, g/dL	4.1 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	.57
Total bilirubin, mg/dL	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	.99
Creatinine, mg/dL	0.9 ± 0.3	0.8 ± 0.2	1.2 ± 0.4	<.001
Triglyceride, mg/dL	110 (83−155)	107 (86−179)	114 (77−155)	.58
HDL cholesterol, mg/dL	54 ± 17	54 ± 15	55 ± 22	.92
LDL cholesterol, mg/dL	111 ± 33	113 ± 35	109 ± 29	.70
HbA_{1c}, %	6.0 ± 0.6	5.9 ± 0.4	6.2 ± 1.0	.29
BNP, pg/mL	138 (57−345)	119 (29−248)	364 (96−575)	.01
Echocardiographic data				
LV mass index, g/m^2	117 (90−151)	110 (89−146)	128 (99−154)	.35
LV EDV, mL	99 (80−186)	99 (77−181)	127 (80−199)	.46
LV ESV, mL	68 (42−129)	62 (38−123)	88 (44−161)	.22
LV EF, %	39 ± 15	42 ± 14	32 ± 13	.07
LV EF <40%	28 (56)	16 (46)	12 (80)	.03
LA volume index, mL/m^2	47 ± 21	42 ± 18	60 ± 21	<.01
Mitral regurgitation, n (%)				.04
None or trivial	24 (48)	20 (57)	4 (27)	
Mild	17 (34)	11 (31)	6 (40)	
Moderate	9 (18)	4 (11)	5 (33)	
Severe	0 (0)	0 (0)	0 (0)	
CPX data				
Peak VO_2, $mL \cdot kg^{-1} \cdot min^{-1}$	17.7 ± 5.2	20.2 ± 4.0	11.8 ± 1.6	<.001
AT, $mL \cdot kg^{-1} \cdot min^{-1}$	11.1 ± 3.4	11.9 ± 3.3	9.0 ± 2.6	<.01
Peak RER	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	.11

Data are expressed as mean ± SD if normally distributed, median (interquartile range) if nonnormally distributed, or n (%). *P* values are for the comparisons between patients with preserved exercise capacity (group 1) and those with reduced exercise capacity (group 2). BP, blood pressure; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA_{1c}, hemoglobin A_{1c}; BNP, B-type natriuretic peptide; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LA, left atrial; CPX, cardiopulmonary exercise testing; VO_2, oxygen consumption; AT, anaerobic threshold; RER, respiratory exchange ratio.

Hg, at submaximal exercise 2.2 ± 0.6 mm Hg, at peak exercise 2.3 ± 0.8 mm Hg; *P* = NS), which was the same finding in group 2 patients without increase in MR during exercise (at rest 2.0 ± 0.9 mm Hg, at submaximal exercise 2.1 ± 1.0 mm Hg, at peak exercise 2.3 ± 1.0 mm Hg; *P* = NS).

Determinants of Exercise Capacity

The results of the univariable and multivariable regression analyses to determine peak VO_2 are presented in Supplemental Table 1. Among the clinical parameters as well

Table 2. Exercise-Stress Echocardiographic Measurements Except IVPD

Variable	Overall	Group 1	Group 2	*P* Value
Exercise duration, min	12.1 ± 3.1	12.5 ± 3.1	11.3 ± 2.9	.23
Heart rate, beats/min				
Rest	67 ± 11	67 ± 10	67 ± 13	1.00
Submaximal exercise	94 ± 17*	97 ± 16*	86 ± 17*	.26
Peak exercise	104 ± 20*	111 ± 17*	88 ± 18*	<.001
Systolic BP, mm Hg				
Rest	110 ± 17	114 ± 16	101 ± 19	.51
Submaximal exercise	134 ± 25*	139 ± 22*	123 ± 28	.31
Peak exercise	155 ± 28*	162 ± 27*	138 ± 25*	.02
Stroke volume, mL				
Rest	58 ± 17	62 ± 16	48 ± 17	.18
Submaximal exercise	63 ± 21	69 ± 18	48 ± 21	<.01
Peak exercise	65 ± 21	72 ± 17	47 ± 22	<.001
Cardiac output, L/min				
Rest	3.8 ± 1.0	4.1 ± 1.0	3.1 ± 0.8	.53
Submaximal exercise	6.0 ± 2.4*	6.8 ± 2.2*	3.9 ± 1.2	<.001
Peak exercise	6.9 ± 2.9*	8.0 ± 2.4*	3.8 ± 1.4	<.001
LV EF, %				
Rest	39 ± 15	42 ± 14	32 ± 13	.07
Submaximal exercise	43 ± 17	47 ± 18	32 ± 12	.06
Peak exercise	45 ± 20	50 ± 20	34 ± 15	.04
s′, cm/s				
Rest	5.4 ± 1.6	5.6 ± 1.7	4.7 ± 0.9	.64
Submaximal exercise	6.4 ± 2.1*	7.0 ± 2.1*	4.8 ± 1.1	<.01
Peak exercise	6.9 ± 2.5*	7.6 ± 2.5*	5.2 ± 1.1	<.01
E-wave velocity, cm/s				
Rest	69 ± 20	65 ± 18	78 ± 21	.40
Submaximal exercise	100 ± 24*	98 ± 23*	106 ± 25*	.91
Peak exercise	108 ± 28*	105 ± 29*	115 ± 23*	.79
e′, cm/s				
Rest	5.4 ± 2.2	5.9 ± 2.3	4.5 ± 1.7	.62
Submaximal exercise	7.2 ± 3.0*	7.9 ± 3.0*	5.2 ± 2.0	.04
Peak exercise	7.6 ± 3.7*	8.6 ± 3.8*	5.1 ± 1.8	<.01
E/e′				
Rest	14.2 ± 5.9	12.4 ± 5.3	18.5 ± 5.1	<.001
Submaximal exercise	16.6 ± 7.8	14.4 ± 6.9	21.8 ± 7.4	<.001
Peak exercise	17.5 ± 10.4	14.7 ± 9.1	25.0 ± 10.0*	<.001
TR pressure gradient, mm Hg				
Rest	21 ± 9	19 ± 6	25 ± 13	<.01
Submaximal exercise	30 ± 8*	28 ± 7*	33 ± 10*	.04
Peak exercise	37 ± 14*	32 ± 12*	45 ± 14*	<.001
Increase in mitral regurgitation to more than moderate	7 (14)	1 (3)	6 (40)	<.001

Data are expressed as mean ± SD or n (%). *P* values are for the comparisons between patients with preserved exercise capacity and those with reduced exercise capacity. s′, average of the peak systolic myocardial velocity from septal and lateral sites of the mitral annulus; E, peak early-diastolic filling velocity; e′, average of the peak early-diastolic myocardial velocity from septal and lateral sites of the mitral annulus; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

*P<.05 versus rest within the groups.

as hemodynamic and echocardiographic parameters at peak exercise, age, plasma BNP level, heart rate, e′, E/e′, LV EF, stroke volume, and cardiac output were significantly correlated with peak VO_2. Although IVPD at rest did not correlate with peak VO_2, IVPD at peak exercise and its change during exercise were significantly correlated with peak VO_2 (Fig. 3), which was consistent with the previous report.[6] In addition, similar correlations were observed even in patients with preserved LV EF ($r = 0.64$; $P < .01$) as well as in those with reduced EF ($r = 0.65$; $P < .01$; Fig. 4). Multivariable analysis showed that IVPD at peak exercise was an independent determinant of peak VO_2 in all of the constructed models (Supplemental Table 1). Notably, IVPD remained a significant determinant independently from LV EF.

Determinants of IVPD

Overall, s′, e′, LV end-diastolic volume, LV end-systolic volume, and Ees were significantly correlated with IVPD, whereas Ea was not (Supplemental Table 2). When the correlations were tested in patients with reduced LV EF (<40%) and preserved LV EF (≥40%), only Ees significantly correlated with IVPD in patients with reduced LV EF. In contrast, in those with preserved LV EF, s′ and e′ in addition to Ees were significantly correlated with the IVPD.

IVPD at Submaximal Exercise as a Predictor of Reduced Exercise Capacity

The results of the regression analyses to clarify the factors associated with peak VO_2 and ROC analyses to predict

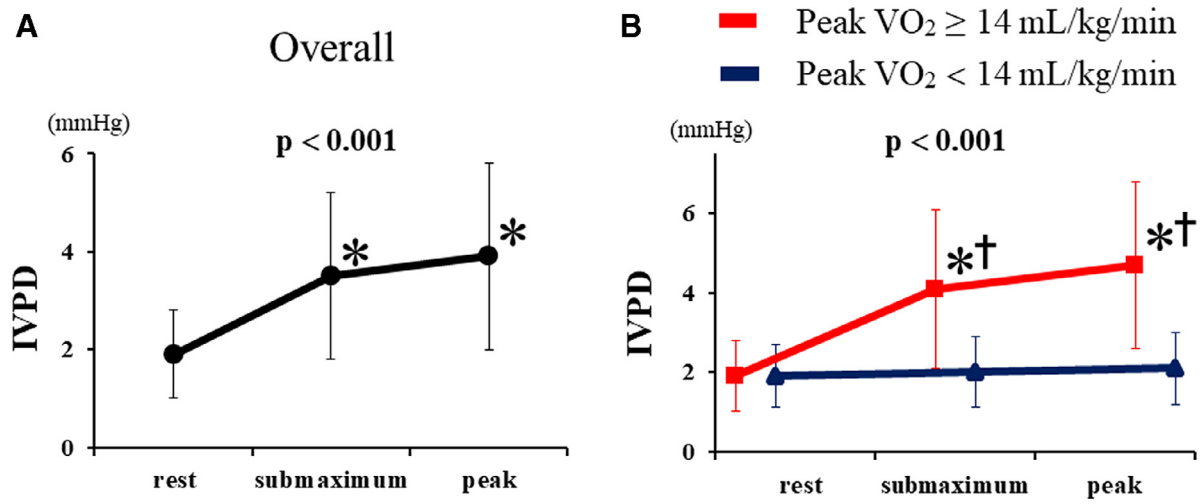


Fig. 1. (A) Changes in early-diastolic intra−left ventricular pressure difference (IVPD) during exercise in all patients. (B) Changes in early-diastolic IVPD during exercise in patients with preserved exercise capacity and reduced exercise capacity. VO_2, oxygen consumption; *P* values were derived from a mixed-effects analysis of variance. **P* < .05 versus rest within the groups; †*P* < .05 versus patients with reduced exercise capacity.

reduced exercise capacity with the use of the stress echocardiographic parameters at submaximal exercise are presented in Supplemental Table 3. Interestingly, although heart rate at submaximal exercise had modest predictive values, with an area under the ROC curve of 0.67 (95% confidence interval [CI] 0.47−0.82; *P* = .05), IVPD and cardiac output at the submaximal stage could well predict the reduced exercise capacity: the area under the ROC curve, sensitivity, and specificity were, respectively, 0.81 (95% CI 0.66−0.91; *P* < .001), 87%, and 71% for IVPD (cutoff value 3.0 mm Hg), and 0.87 (95% CI 0.73−0.94; *P* < .001), 92%, and 70% for cardiac output (cutoff value 5.5 L/min). Furthermore, an incremental value of the IVPD at submaximal exercise on clinical parameters, E/e′, and cardiac output at submaximal exercise for the prediction of reduced exercise capacity was observed (Fig. 5).

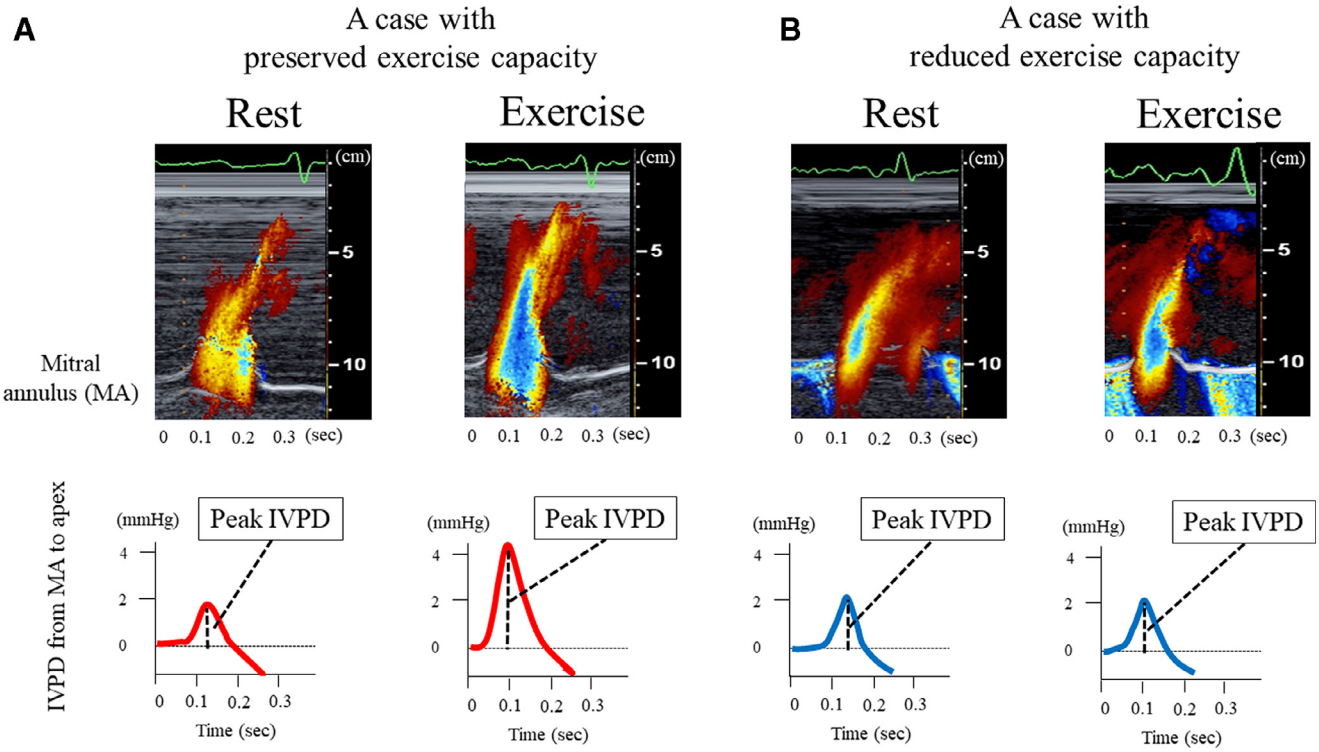


Fig. 2. Temporal profiles of intra−left ventricular pressure difference (IVPD) and corresponding color M-mode Doppler images obtained from (A) a patient with preserved exercise capacity and (B) a patient with reduced exercise capacity. It is noteworthy that IVPD was increased by exercise only in the patient with preserved exercise capacity.

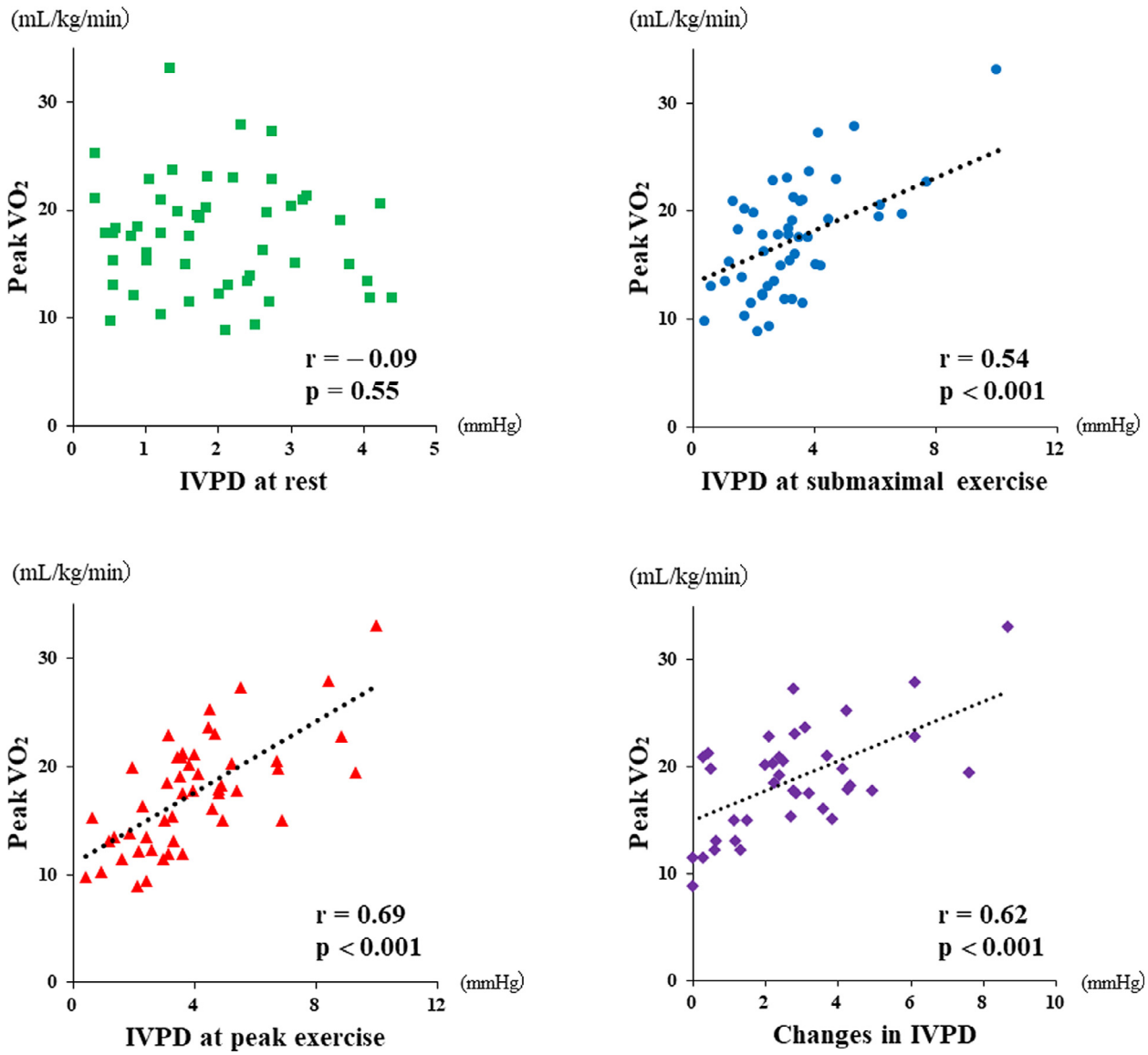


Fig. 3. Correlations between IVPD and peak VO_2 in overall patients. Abbreviations as in Fig. 1.

Discussion

In this study, we demonstrated that early-diastolic IVPD was a powerful determinant of exercise capacity in HF patients with various LV EF. Importantly, IVPD remained determinant even after adjustment for LV EF. Furthermore, IVPD at submaximal exercise could predict reduced exercise capacity with the cutoff value of 3.0 mm Hg having an incremental value on cardiac output, which directly determines VO_2 together with peripheral factors. This result can be interpreted that "gentle" exercise-stress echocardiographic IVPD could be a useful predictor of exercise capacity, reducing the physical burden associated with the stress test in HF patients.

Impact of the IVPD on Exercise Capacity in HF

To function as an effective pump, the LV needs to fill without an elevation of left atrial pressure. During exercise, in the normal situation, LV suction augments the early-diastolic IVPD, which contributes to the maintenance or even enhancement of LV filling and subsequent ejection without overt elevation of left atrial pressure despite the shortening of the filling time.[4] Given the formula "VO_2 = cardiac output × arteriovenous oxygen content difference," LV suction during exercise should be an important contributor for the exercise capacity through the increase in cardiac output resulting from the maintenance of stroke volume despite the increased heart rate.[4]

However, the impact of LV suction on exercise capacity has not been well investigated in HF patients despite the fact that exercise intolerance is a major symptom, and moreover a predictor of the outcome, in HF patients.[1,13] Only one previous study observed that augmentation of IVPD assessed by means of the same method as ours was diminished in HF patients. Rovner et al tested the CMMD-derived IVPD in HF patients with LV systolic dysfunction

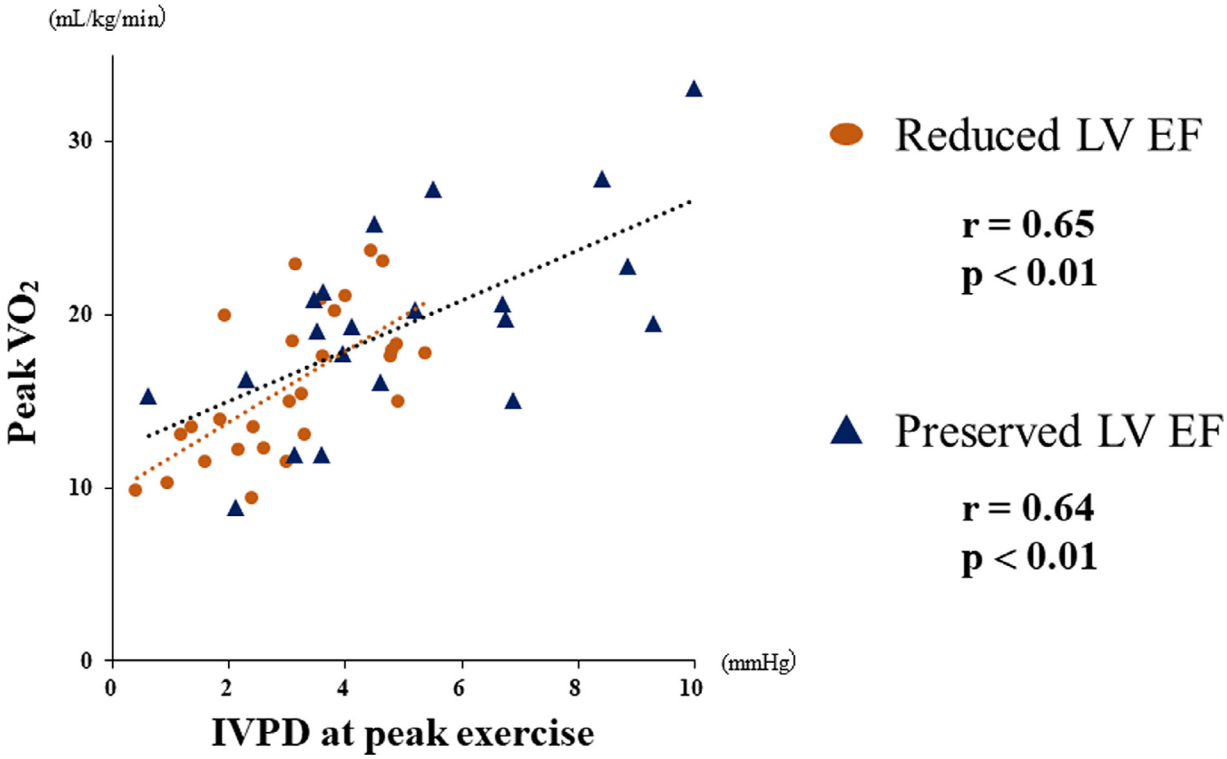
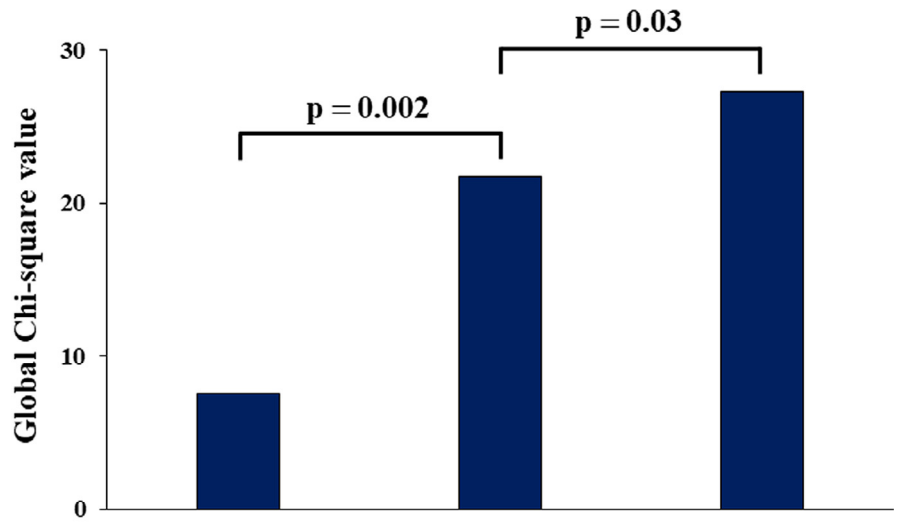


Fig. 4. Correlations between IVPD and peak VO_2 in patients with reduced left ventricular (LV) ejection fraction (EF) and those with preserved LV EF. Abbreviations as in Fig. 1.



	Model 1	Model 2	Model 3
Variables	Age BNP Submaximal E/e′	Age BNP Submaximal E/e′ Submaximal CO	Age BNP Submaximal E/e′ Submaximal CO Submaximal IVPD

Fig. 5. Incremental value of intra−left ventricular pressure difference (IVPD) at submaximal exercise over conventional parameters to predict reduced exercise capacity. The figure illustrates the global chi-square values of logistic regression models for the prediction of reduced exercise capacity defined by peak oxygen consumption <14 $mL \cdot kg^{-1} \cdot min^{-1}$, incorporating age, plasma B-type natriuretic peptide (BNP) level, submaximal E/e′, submaximal cardiac output (CO), and submaximal IVPD. Notably, the addition of submaximal IVPD as an explanatory variable to the other parameters significantly increased the global chi-square value.

(LV EF 25.9 ± 13.3%) and found that the augmentation of IVPD by exercise was reduced in HF patients compared with the normal control subjects and that this augmentation was positively associated with peak VO_2.[6] They therefore concluded that impaired myocardial relaxation was associated with reduced diastolic suction force during exercise in patients with HF with severe systolic dysfunction. Our study confirmed their observations and further extended the results for patients with preserved LV EF, which could be associated with reduced LV longitudinal function. This has not been previously demonstrated but could be expected because the relation of LV suction, ejection, and VO_2 is consistent regardless of LV EF. Although the mechanisms of the reduced LV suction might be different between HF with reduced LV EF and HF with preserved LV EF, as described in the next section, the present results provide a novel insight for the understanding of the mechanisms of exercise intolerance in HF patients with various LV EF.

Despite the usefulness of the early-diastolic IVPD, to understand the pathophysiology of exercise intolerance in HF, as of this moment, we need special software for its calculation. We hope that this method could become widely available in routine practice in the near future.

Determinants of the IVPD

Certain part of the LV suction is considered to be a result of elastic recoil of intramyocardial and extracellular components which were compressed and storing the energy of contraction during systole.[18] Therefore, the early-diastolic IVPD should be determined by the parameters of LV deformation during systole as well as early diastole, and in fact, previous studies have shown the relationships between IVPD and the parameters of LV systolic and diastolic function.[19] Intriguingly, when the determinants were tested in patients with reduced LV EF and with preserved LV EF in this study, we found differences in the results. Although Ees significantly correlated with IVPD in both groups, s′ and e′ correlated with IVPD only in patients with preserved LV EF. These results could be interpreted that LV contractility would determine the LV suction regardless of LV EF and that LV contractility would be mainly determined by longitudinal function in patients with preserved LV EF but not in those with reduced LV EF. These are consistent with the concept that decreased longitudinal LV function is a major contributor to the reduced LV diastolic function in HF with preserved LV EF.[20]

IVPD as a Predictor of Exercise Intolerance

Because reduced exercise capacity is an important prognostic factor of HF,[1,13] an objective assessment of exercise capacity is a critical issue in the management of HF. Peak VO_2 measured by means of CPX is an established marker of exercise capacity, and a predictor of peak VO_2 obtained without peak exercise might be preferred, especially in patients with advanced HF, to reduce the physical burden even though the safety of CPX in HF has been confirmed in many clinical studies.[21] Based on the strong relationship between IVPD at peak exercise and peak VO_2, we presumed that IVPD at submaximal exercise could predict exercise capacity. As expected, we could demonstrate that submaximal IVPD allowed a noninvasive evaluation of reduced exercise capacity (Supplemental Table 3). Importantly, the submaximal IVPD improved the predictive ability of the parameters consisting of clinical information and submaximal cardiac output (Fig. 5), suggesting that the additional measurement of IVPD during submaximal exercise-stress echocardiography could offer more accurate estimation of exercise capacity in HF patients without peak exercise. From the additive predictive value of IVPD on cardiac output despite the sequence of LV filling generated by IVPD and following ejection, IVPD might reflect intrinsic LV diastolic mechanics that can not be fully expressed by cardiac output. Further study is needed to elucidate the physiologic background of IVPD during exercise.

Study Limitations

First, as a single-center study, the present results suffer from the limitation of a small sample size, and further studies are needed to confirm our conclusions. Second, we excluded 105 out of 160 patients according to the exclusion criteria because of the diversity of HF in a clinical practice, which narrows the population to which we can apply our conclusions. On the other hand, this strict selection could exclude potential confounding factors that would affect the relationship between IVPD and exercise capacity in HF patients. Third, we did not consider peripheral determinants of exercise capacity, such as deconditioning, skeletal muscle atrophy, and oxygen metabolism. However, the relationship between IVPD during exercise and peak VO_2 is consistent regardless of the limiting factors of the exercise. Therefore, we think that the usefulness of IVPD for the prediction of exercise capacity could be solid regardless of the causal relationships between IVPD and peripheral factors. Fourth, we evaluated IVPD only along a single scan line from the mitral annulus to LV apex. Therefore, we could not evaluate IVPD outside of that scan line. Fifth, exercise stress was performed separately in CPX and stress echocardiography to adjust the workload with the use of the CPX data in stress echocardiography among the patients. Therefore, the difference in posture and the time between the tests would have weakened the relationship between peak VO_2 and IVPD during exercise.

Conclusion

Early-diastolic IVPD as a parameter of LV suction during exercise was closely associated with exercise capacity in chronic HF patients regardless of LV EF. In addition, IVPD at submaximal exercise could predict exercise capacity without peak exercise.

Disclosures

None.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.02.005.

References

1. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037–42.
2. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol 1987;59:634–8.
3. Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J Card Fail 2007;13:672–9.
4. Cheng CP, Igarashi Y, Little WC. Mechanism of augmented rate of left ventricular filling during exercise. Circ Res 1992;70:9–19.
5. Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. Am J Physiol Heart Circ Physiol 2001;280:H2507–15.
6. Rovner A, Greenberg NL, Thomas JD, Garcia MJ. Relationship of diastolic intraventricular pressure gradients and aerobic capacity in patients with diastolic heart failure. Am J Physiol Heart Circ Physiol 2005;289:H2081–8.
7. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240–327.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin 3rd JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.
9. Yokota T, Kinugawa S, Yamato M, Hirabayashi K, Suga T, Takada S, et al. Systemic oxidative stress is associated with lower aerobic capacity and impaired skeletal muscle energy metabolism in patients with metabolic syndrome. Diabetes Care 2013;36:1341–6.
10. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
11. Chen C-H, Fetics B, Nevo E, Rochitte CE, Chiou K-R, Ding P-A, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.
12. Antonini-Canterin F, Poli S, Vriz O, Pavan D, Bello VD, Nicolosi GL. The ventricular-arterial coupling: from basic pathophysiology to clinical application in the echocardiography laboratory. J Cardiovasc Echogr 2013;23:91–5.
13. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds Jr LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86.
14. Stewart KC, Kumar R, Charonko JJ, Ohara T, Vlachos PP, Little WC. Evaluation of LV diastolic function from color M-mode echocardiography. JACC Cardiovasc Imaging 2011;4:37–46.
15. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006;47:1891–900.
16. Podolec P, Rubis P, Tomkiewicz-Pajak L, Kopec G, Tracz W. Usefulness of the evaluation of left ventricular diastolic function changes during stress echocardiography in predicting exercise capacity in patients with ischemic heart failure. J Am Soc Echocardiogr 2008;21:834–40.
17. Borlaug BA, Reddy YN. Determinants and correlates of exercise capacity in heart failure. JACC Heart Fail 2015;3:815–7.
18. Bell SP, Nyland L, Tischler MD, McNabb M, Granzier H, LeWinter MM. Alterations in the determinants of diastolic suction during pacing tachycardia. Circ Res 2000;87:235–40.
19. Firstenberg MS, Greenberg NL, Garcia MJ, Thomas JD. Relationship between ventricular contractility and early-diastolic intraventricular pressure gradients: a diastolic link to systolic function. J Am Soc Echocardiogr 2008;21:501–6.
20. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283–9.
21. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. Circulation 2012;126:2465–72.