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ORIGINAL RESEARCH ARTICLE

Easy-to-use preload stress echocardiography by using combined dynamic postural stress can identify high-risk patients with heart failure with reduced ejection fraction

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Abstract

Aims Haemodynamic assessment during stress testing is not commonly performed in patients with heart failure with reduced ejection fraction (HFrEF) because of its invasiveness, lower feasibility, and safety concerns. This study aimed to assess the haemodynamic characteristics of patients with HFrEF in response to non-invasive preload stress during dynamic postural alterations achieved by combining both semi-sitting position and passive leg-lifting and to evaluate whether combined postural stress could be used for risk stratification in these patients.

Methods and results For this study, 101 patients with HFrEF and 35 age-matched and sex-matched healthy controls were prospectively recruited. After all standard echocardiographic measurements were obtained in the left decubitus position, all subjects underwent postural stress testing, which consisted of changing from semi-sitting position to passive leg-lifting. During a median follow-up period of 12.2 months, 21 (21%) patients developed adverse cardiovascular events. In patients without adverse cardiovascular events, the stroke volume index (SVi) significantly changed from 28 ± 8 to 35 ± 10 mL/m^2 ($P < 0.001$) during combined postural stress. By contrast, ΔSVi during combined dynamic postural stress was significantly smaller in patients with cardiovascular events than in those without events (ΔSVi 3.4 ± 4.0 vs. 6.4 ± 3.8 mL/m^2, $P = 0.002$), which indicated severely diseased heart operated on a relatively flat portion of the Frank–Starling curve. In a multivariate Cox proportional hazard analysis, ΔSVi (hazard ratio 0.81, $P = 0.02$) was an independent predictor of future adverse cardiovascular events.

Conclusions The combined assessment of dynamic postural stress is a non-invasive, simple, quick, and easy-to-use clinical tool for assessing preload reserve and risk stratification in HFrEF patients.

Keywords Heart failure with reduced ejection fraction; Stress echocardiography; Preload reserve; Passive leg-lifting; Semi-sitting position; Postural stress

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Introduction

Stress echocardiography is increasingly recognized for its utility in the evaluation of non-ischaemic heart diseases, including valvular heart disease, cardiomyopathy, pulmonary hypertension, and congenital heart diseases.[1] Owing to its diagnostic and prognostic value, stress echocardiography has recently been applied within the field of chronic heart failure.[1–4] However, in the daily clinical practice, haemodynamic assessment during stress testing is not commonly performed for patients with heart failure with reduced ejection fraction (HFrEF) because of its complexity, invasiveness, lower feasibility, and safety concerns.

As a simple alternative for exercise or pharmacological stress testing, a preload-increasing stress by using passive leg-lifting manoeuvre has been introduced[5–7]; however, the haemodynamic load imposed on the cardiovascular system through this method is unsatisfactory[6] and precludes the

accurate assessment of the preload reserve in patients with heart failure. By contrast, a postural change from the supine to an upright position leads to a decrease in the cardiac preload while minimizing the changes in contractility, afterload, and heart rate.[8–10] However, upright postural stress echocardiography has not been applied in clinical practice, and only a few reports have presented the utility of this manoeuvre in patients with heart failure.[9,10]

We hypothesized that combined postural stress when using both the preload-increasing (passive leg-lifting) and preload-decreasing (semi-sitting position) manoeuvres could introduce a more sufficient preload stress and could reliably assess the preload reserve in patients with HFrEF. The purpose of this study was to assess the haemodynamic responses during combined dynamic postural stress and to evaluate whether postural stress echocardiography could be used for risk stratification in patients with HFrEF.

Methods

Study population

A total of 101 patients with HFrEF and age-matched and sex-matched 35 healthy volunteers were prospectively recruited for this study. All subjects underwent transthoracic echocardiography for the regular evaluation of haemodynamic status between April 2019 and February 2020. HFrEF was defined as heart failure with left ventricular (LV) ejection fraction of less than 40% with having prior or current symptoms or signs of heart failure.[11] HFrEF with ischaemic origin was defined as cases with the angiographic evidence of the presence of $>$50% stenosis of one or more major epicardial coronary arteries and previous history of coronary revascularization or myocardial infarction. The exclusion criteria were as follows: (i) uncontrolled hypertension; (ii) current or prior severe disorders of other organs; (iii) heart failure with New York Heart Association (NYHA) Functional Class IV; (iv) pregnant women; (v) unstable angina; (vi) more than moderate valvular heart disease; and (vii) patients on regular haemodialysis. At the time of enrolment, all patients were in a clinically stable condition and undergoing standard guideline-directed and maximally tolerated heart failure therapy, if tolerated. This study was approved by the local ethics committee of our institution (protocol ID: 190018) and was compliant with the principles set by the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Echocardiographic examination

All echocardiographic studies were performed with commercially available ultrasound systems (Aplio Artida; Canon Medical Systems, Tochigi, Japan), equipped with a 3.0 MHz transducer. Digital routine grey-scale cine loops from three consecutive beats were obtained from LV parasternal and apical views. Echocardiographic measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging/American Society of Echocardiography.[12] LV volumes, LV ejection fraction (LVEF), and left atrial volumes were calculated using the modified biplane Simpson method. The transmitral early diastolic (E) and atrial wave (A) velocities were measured using pulsed-wave Doppler recordings from the apical four-chamber view. Early diastolic (e') mitral annular velocity was measured using spectral tissue Doppler imaging, and the E/e' ratio was calculated to estimate LV filling pressure.[13] Forward stroke volume (SV) was identified in terms of the velocity–time integral multiplied by the cross-sectional area of the LV outflow tract. In patients with atrial fibrillation, measurements were averaged from three non-consecutive beats with cycle lengths ranging from 10% to 20% of the average cycle length.[13]

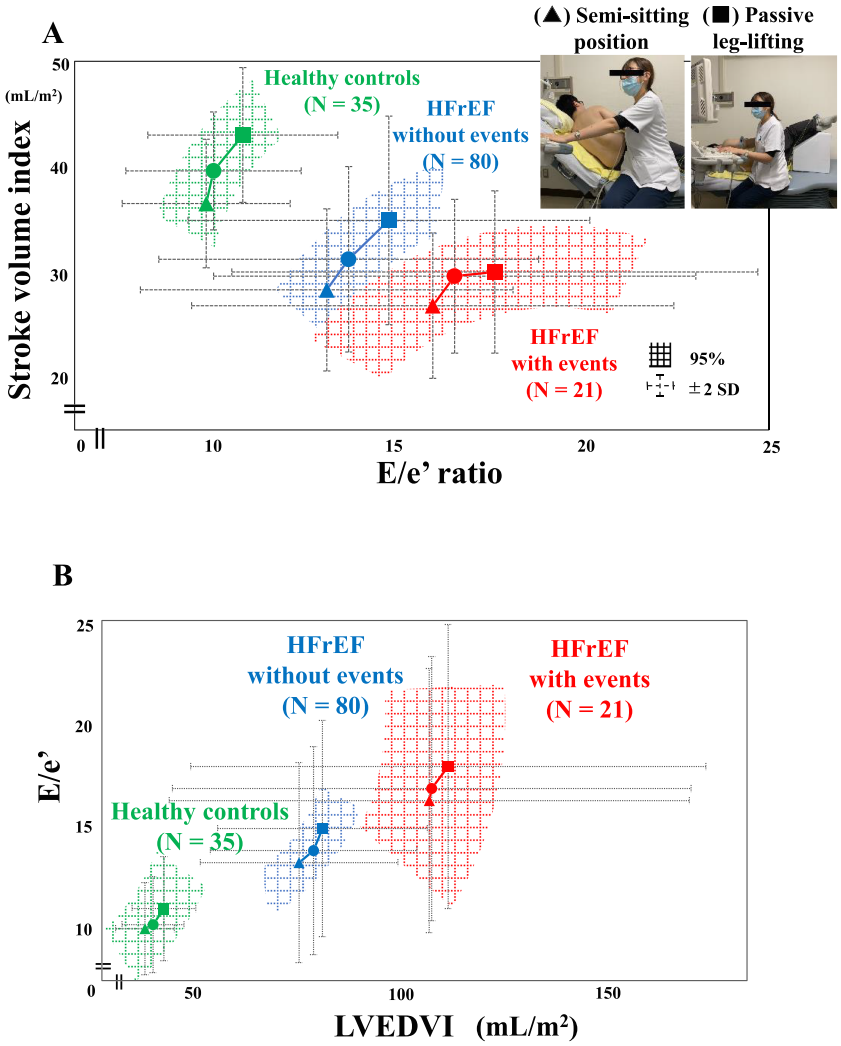
Postural stress echocardiography

After all standard echocardiographic measurements were obtained in the left decubitus position, all subjects underwent postural stress, which consisted of changing from semi-sitting position to passive leg-lifting. At each postural condition, subsequent to an equilibration period of 2 min, echocardiographic evaluation of cardiac structures and haemodynamic variables were measured. The left lateral decubitus position was used in all positions (i.e. baseline, semi-sitting position, and passive leg-lifting) to optimize acoustic windows. For semi-sitting position stress, the trunk was passively elevated at 45° using an electric echocardiography table (*Figure 1*, right upper panel). Subsequent to the semi-sitting position, both lower legs were passively lifted to 45° using a handmade carbon box for passive leg-lifting stress (*Figure 1*, right upper panel). Changes in the haemodynamic parameters were calculated as the net difference between the semi-sitting position and passive leg-lifting stress and were expressed as Δ. Electrocardiograms, blood pressure, and heart rate were monitored throughout the procedure.

Clinical endpoints and follow-up

Adverse cardiovascular events were pre-specified as the primary endpoint of death from or hospitalization for deteriorating heart failure, implantation of ventricular assist device for refractory heart failure, and sudden cardiac death. In this study, appropriate shock of implantable cardioverter defibrillator (ICD) was also pre-specified as a primary endpoint, because ICD shock is considered as a lethal cardiac event equivalent to sudden cardiac death.

Figure 1 Frank–Starling curves and passive length–tension relationships during dynamic postural stress in healthy controls and in heart failure with reduced ejection fraction (HFrEF) patients with and without cardiovascular events. Frank–Starling curves (A) and passive length–tension relationships (B) for healthy controls (green) and for HFrEF patients with (red) and without (blue) adverse cardiovascular events are shown. Solid dots, triangles, and squares indicate mean values obtained at baseline, during semi-sitting position, and with passive leg-lifting, respectively. Each bar and shading area indicate ±2 SDs and 95% confidence intervals. LVEDVI, left ventricular end-diastolic volume index.



Statistical analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data and as median and inter-quartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of subgroups were compared by using Student's *t*-test or Mann–Whitney *U* test as appropriate. To identify differences in haemodynamic and echocardiographic parameters between two time points, the paired *t*-test was used for comparisons of continuous variables. Proportional differences were evaluated using Fisher's exact test or the χ^2 test as appropriate. Event-free survival curves were constructed by using the Kaplan–Meier method and were compared using the log-rank test. The associations of clinical, haemodynamic, and echocardiographic parameters with cardiovascular events were identified using the Cox proportional hazards model for both univariate and multivariate analyses. In the selection of independent variables for entry into the multivariate model, Pearson's correlation analyses were performed in advance between independent variables to avoid multicollinearity. If more than two variables measured a pathophysiological parameter (e.g. LVEF and LV end-systolic volume as markers of LV ejection performance), a more clinically relevant parameter was entered into the model. Variables with a univariate value of $P < 0.10$ were incorporated into the multivariate analysis, while age and sex were forced into the model regardless of their association on the univariate analysis. Nested Cox proportional hazards models were then constructed to determine the incremental

prognostic value of preload reserve during the postural stress over clinical and standard echocardiographic variables. A statistically significant increase in the global log-likelihood χ^2 value of the model defined incremental prognostic value. All tests were two tailed with differences reported as significant if $P < 0.05$. In case of multiple comparisons, P values were adjusted with the use of Bonferroni's correction. All analyses were performed with MedCalc Version 19.0.5 (MedCalc Software; Ostend, Belgium).

Results

Baseline characteristics of patients with heart failure with reduced ejection fraction

The baseline clinical characteristics of all 101 patients with HFrEF are summarized in *Table 1*. The standard guideline-directed medical therapy was prescribed for most of the patients at a maximally tolerated dose, while spironolactone was prescribed for only 60% of the cohort owing to the presence of chronic kidney disease, hyperkalaemia, or symptomatic hypotension. Because angiotensin receptor–neprilysin inhibitor was not available during the study period, no one was on angiotensin receptor–neprilysin inhibitor in this cohort.

Table 2 shows changes in haemodynamic and echocardiographic parameters during each postural position in HFrEF patients and in age-matched (69 ± 12 years) and sex-matched (female sex, 29%) healthy controls. As expected, patients with HFrEF showed significantly lower blood pressure, smaller SV index (SVi), and significant global LV remodelling along with reduced LV contraction than healthy controls (*Table 2*). With respect to the baseline diastolic functional parameters, the E/e' ratio and left atrial volume index were significantly larger in patients with HFrEF (*Table 2*).

Table 1 Baseline clinical characteristics of patients with HFrEF

Variables	All HFrEF ($N = 101$)	HFrEF without events ($N = 80$)	HFrEF with events ($N = 21$)
Age (years)	69 ± 12	68 ± 13	71 ± 8
Female gender, *n* (%)	23 (23)	17 (21)	6 (29)
BMI	22.9 ± 4.0	23.1 ± 3.8	22.3 ± 4.6
Haemoglobin (g/dL)	13.2 ± 2.1	13.3 ± 2.0	12.6 ± 2.7
Creatinine (mg/dL)	1.3 ± 0.5	1.2 ± 0.5	1.5 ± 0.5[†]
BNP (pg/mL)	240 (107–454)	186 (87–409)	323 (203–668)[†]
Aetiology of heart failure			
Ischaemic, *n* (%)	44 (43)	33 (41)	11 (52)
Non-ischaemic, *n* (%)	57 (57)	47 (59)	10 (48)
Co-morbidity			
Hypertension, *n* (%)	33 (33)	24 (30)	9 (43)
Diabetes mellitus, *n* (%)	28 (28)	19 (24)	9 (43)
Dyslipidaemia, *n* (%)	49 (49)	40 (50)	9 (43)
Obesity, *n* (%)	27 (27)	19 (24)	8 (38)
Cardiac rhythm			
Sinus rhythm, *n* (%)	66 (65)	57 (71)	9 (43)[‡]
Atrial fibrillation, *n* (%)	11 (11)	8 (10)	3 (14)
Pacing rhythm, *n* (%)	24 (24)	15 (19)	9 (43)[‡]
NYHA functional class, *n* (%)			
II	77 (76)	66 (83)	11 (52)
III	24 (24)	14 (17)	10 (48)[†]
Medications, *n* (%)			
Loop diuretics	71 (70)	55 (69)	16 (76)
Beta-blockers	95 (94)	74 (93)	21 (100)
Spironolactone	61 (60)	50 (63)	11 (52)
ACE-I/ARB	79 (78)	63 (79)	16 (76)
Cardiac devices			
Pacemaker, *n* (%)	3 (3)	2 (3)	1 (5)
ICD, *n* (%)	10 (10)	8 (10)	2 (10)
CRT/CRT-D, *n* (%)	19 (19)	12 (15)	7 (33)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.
Data are presented as mean ± standard deviation, *n* (%), or median (inter-quartile range).
[*] $P < 0.001$ vs. HFrEF without events.
[†] $P < 0.01$ vs. HFrEF without events.
[‡] $P < 0.05$ vs. HFrEF without events.

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Table 2 Changes in haemodynamic and echocardiographic parameters during different postures for patients with HFrEF and healthy controls

	Healthy controls ($N = 35$)			All HFrEF ($N = 101$)			HFrEF without events ($N = 80$)			HFrEF with events ($N = 21$)		
	Baseline	Semi-sitting position	Passive leg-lifting	Baseline	Semi-sitting position	Passive leg-lifting	Baseline	Semi-sitting position	Passive leg-lifting	Baseline	Semi-sitting position	Passive leg-lifting
Haemodynamics												
Systolic BP (mmHg)	129 ± 18	123 ± 18†	121 ± 19†	111 ± 19§	105 ± 20*	107 ± 19	112 ± 18	106 ± 20*	109 ± 18	106 ± 24	99 ± 21‡	100 ± 22
Diastolic BP (mmHg)	74 ± 12	77 ± 12	70 ± 15†	66 ± 12§	66 ± 14	63 ± 15‡	67 ± 12	67 ± 14	64 ± 15	62 ± 14	62 ± 14	60 ± 15
HR (b.p.m.)	65 ± 10	65 ± 10	64 ± 9	69 ± 13	69 ± 14	68 ± 14	68 ± 13	69 ± 15	68 ± 14	69 ± 12	69 ± 12	69 ± 12
SVi (mL/m^2)	40 ± 6	37 ± 6*	43 ± 7*	31 ± 9§	28 ± 8*	34 ± 10*	31 ± 9	28 ± 8*	35 ± 10*	30 ± 7	27 ± 7†	30 ± 8
Echocardiographic indices												
LVEDVI (mL/m^2)	43 ± 8	41 ± 7†	45 ± 8†	88 ± 39§	86 ± 39*	91 ± 39*	82 ± 26	79 ± 25*	85 ± 26*	112 ± 66¶	111 ± 66	116 ± 65‡
LVEF (%)	65 ± 4	64 ± 4	65 ± 4	31 ± 7§	31 ± 7	32 ± 7*	32 ± 6	32 ± 6	33 ± 6*	27 ± 9¶	27 ± 9	28 ± 8
Transmitral E velocity (cm/s)	61 ± 19	56 ± 15*	71 ± 20*	66 ± 25	61 ± 24*	72 ± 26*	63 ± 21	58 ± 19*	70 ± 22*	77 ± 36	72 ± 34†	80 ± 38†
e′ velocity (cm/s)	6.4 ± 2.1	5.9 ± 1.6*	7.0 ± 2.0*	4.9 ± 1.6§	4.7 ± 1.5*	5.0 ± 1.7*	5.0 ± 1.7	4.8 ± 1.6*	5.2 ± 1.8†	4.6 ± 1.3	4.5 ± 1.3	4.6 ± 1.3
E/e′ ratio	9.8 ± 2.4	9.6 ± 2.3	10.6 ± 2.6*	14.1 ± 5.5§	13.7 ± 5.5*	15.2 ± 6.0*	13.5 ± 5.2	12.9 ± 5.1†	14.6 ± 5.5*	16.6 ± 6.7**	16.0 ± 6.7	17.7 ± 7.3*
LAVI (mL/m^2)	26 ± 6	23 ± 6*	27 ± 6	47 ± 14§	43 ± 14*	48 ± 15*	45 ± 14	41 ± 13*	45 ± 15	51 ± 14	49 ± 14	54 ± 14*
IVC diameter (mm)	11 ± 3	12 ± 4	12 ± 4‡	12 ± 5	13 ± 5*	13 ± 5*	11 ± 4	13 ± 5*	13 ± 4*	12 ± 6	13 ± 6	14 ± 7‡
TAPSE (mm)	18 ± 3	17 ± 3‡	19 ± 3	15 ± 4§	15 ± 4	16 ± 4*	15 ± 4	15 ± 4	16 ± 4‡	14 ± 5	14 ± 4	14 ± 5

BP, blood pressure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IVC, inferior vena cava; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.
Data are presented as mean ± standard deviation.
*$P < 0.001$ vs. baseline.
†$P < 0.01$ vs. baseline.
‡$P < 0.025$ vs. baseline.
§$P < 0.001$ healthy controls vs. all HFrEF.
||$P < 0.001$ vs. HFrEF without events.
¶$P < 0.01$ vs. HFrEF without events.
**$P < 0.05$ vs. HFrEF without events.

Dynamic postural stress testing for all patients with heart failure with reduced ejection fraction and healthy controls

Dynamic postural stress testing was well tolerated by all subjects without any complications. With this non-invasive easy-to-use protocol, the average duration of additional postural stress testing over standard echocardiographic examination was as short as 14.5 ± 2.3 min per patient, including both semi-sitting position and passive leg-lifting stress.

Overall, the haemodynamic responses to the dynamic postural stress were comparable between patients with HFrEF and healthy controls. That is, during the semi-sitting position, the LV end-diastolic volume, SVi, and transmitral E velocity significantly decreased in both controls and patients with HFrEF in response to the orthostatic gravitational change. Conversely, all these measurements significantly increased in both groups during passive leg-lifting stress as a result of the postural increase in venous return (*Table 2*).

Cardiovascular events during the follow-up period

Of all 101 patients with HFrEF, none were lost to follow-up. During the median follow-up period of 12.2 (inter-quartile range, 9.7–15.5) months, 21 patients (21%) developed adverse cardiovascular events, with nine dying of sudden cardiac death or receiving appropriate ICD shock. The remaining 12 were hospitalized because of worsening heart failure.

Heart failure with reduced ejection fraction patients with and without cardiovascular events

The clinical, haemodynamic, and echocardiographic characteristics of patients with and without cardiovascular events are presented in *Table 2*. No significant differences were observed between the two subgroups in terms of age and sex distribution. However, patients with cardiovascular events were more likely to have a higher brain natriuretic peptide (BNP) concentration and a higher serum creatinine concentration and were in a worse NYHA functional class. Patients with cardiovascular events were also more likely to have a larger LV volume index, lower LVEF, and a higher E/e' ratio, presumably reflecting more advanced heart failure at baseline.

Comparisons of haemodynamic response to postural stress between patients with and without cardiovascular events

Changes in haemodynamic parameters at each posture for patients with and without adverse cardiovascular events are shown in *Table 2*. For patients without adverse events, SVi significantly changed in response to preload fluctuations induced by postural stress, which indicated that the less-diseased heart operated on the left-hand portion (i.e. ascending limb) of the Frank–Starling curve (*Figure 1A*). By contrast, in patients with adverse cardiovascular events, responses in SVi were significantly blunted in both postures, indicating failure of the Frank–Starling mechanism (*Figure 1A*). In *Figure 1B*, passive length–tension relationships were defined by E/e' ratio and LV end-diastolic volume index from each group. A passive length–tension relationship of HFrEF patients with cardiovascular events was shifted to the right hand and upward, reflecting enlarged ventricles and higher LV end-diastolic pressure, indicating increased ventricular operative stiffness for these patients.

The net difference in SVi (ΔSVi) between each posture was significantly smaller in HFrEF patients with cardiovascular events than in those without events and in healthy controls (*Figure 2*).

Predictors of adverse cardiovascular events

Hazard ratios and 95% confidence intervals for each variable, determined with univariable and multivariable Cox proportional hazards analyses, are shown in *Table 3*. Multivariate Cox analysis revealed that ΔSVi during combined postural stress in the semi-sitting position and passive leg-lifting (hazard ratio 0.81, P = 0.02) was the only independent predictor of future cardiovascular events.

The incremental benefit of the postural stress test in the prediction of cardiovascular events is shown in *Figure 3*. In the nested Cox models, a model based on clinical variables (Model 1: age, sex, NYHA functional class, and serum BNP concentration) was not improved by adding resting echocardiographic parameters (Model 2: plus LVEF, LV end-diastolic volume index, and E/e' ratio, P = 0.15). However, Model 2 was improved by adding combined postural stress (Model 3: ΔSVi during combined postural stress, $P < 0.001$).

When patients were divided into three equal subgroups based on the ΔSVi during combined postural stress, patients with impaired preload reserve (third tertile; ΔSVi < 3.2 mL/m^2) showed significantly worse event-free survival than the other two subgroups (*Figure 4*; $P < 0.001$, respectively).

Discussion

To the best of our knowledge, this study is the first to demonstrate prognostic capability of the assessment of the preload reserve during dynamic postural stress combining semi-sitting position and passive leg-lifting in patients with HFrEF. In patients without cardiovascular events as well as healthy subjects, SVi significantly changed during combined

Figure 2 Comparisons of changes in stroke volume index during semi-sitting position and passive leg-lifting for healthy controls and for heart failure with reduced ejection fraction (HFrEF) patients with and without cardiovascular events. The net difference in stroke volume index (ΔSVi) during combined postural stress was comparable between healthy controls and HFrEF patients without cardiovascular events. However, ΔSVi was significantly smaller in patients with adverse events.

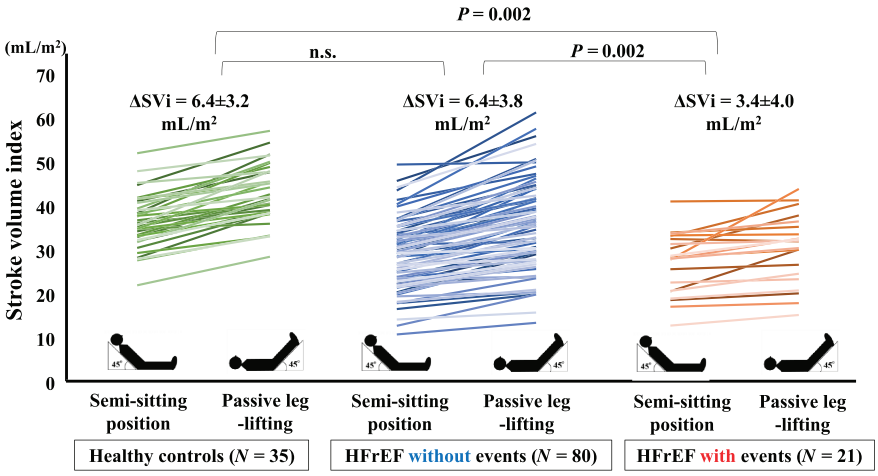


Table 3 Univariable and multivariable Cox proportional hazards analysis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Clinical variables						
Age (per 5 years)	1.10	0.90–1.34	0.35			
Gender (female)	0.71	0.27–1.82	0.47			
NYHA Functional Class III	3.60	1.52–8.52	<0.01	1.96	0.75–5.16	0.17
Log BNP	4.58	1.34–15.6	0.02	1.31	0.32–4.89	0.75
Baseline echocardiographic variables						
SVi (mL/m^2)	0.98	0.93–1.03	0.36			
LVEF (per 5%)	0.64	0.48–0.85	<0.01	0.77	0.55–1.07	0.12
E/e′ (per 5 units)	1.48	1.06–2.05	0.02	1.18	0.79–1.79	0.42
TAPSE (per 5 mm)	0.66	0.38–1.12	0.12	0.90	0.48–1.66	0.73
Variables between during postural stress						
ΔSVi (mL/m^2)	0.77	0.66–0.90	0.001	0.81	0.68–0.96	0.02
ΔE/e′ (per 5 unit increase)	1.00	0.28–3.64	0.99			
ΔTAPSE (per 5 mm increase)	1.61	0.55–4.86	0.37			

CI, confidence interval; HR, hazard ratio. All other abbreviations as in *Tables 1* and *2*.

postural stress. By contrast, in HFrEF patients with adverse cardiovascular events, changes in SVi during dynamic postural stress were blunted. The net difference in SVi during combined postural stress was an independent predictor of future adverse cardiovascular events and provided significant incremental prognostic value over clinical and resting haemodynamic parameters.

Haemodynamic response to postural stress

Healthy individuals are known to be able to increase cardiac output by as much as five times or more during strenuous exercise.[14] This extraordinary ability is attributed to the increase in ventricular contractility, chronotropic function, and peripheral arterial dilation, with instantaneous recruitment of the cardiac preload as the most important contributing factor.[15] The highly compliant splanchnic venous system reserves a large amount of blood volume as an 'unstressed volume', while a sympathetically stimulated reduction in venous capacitance would shift the blood volume of up to 800 mL out of the venous reservoir for a corresponding increase in the 'stressed volume' in response to the increased demand.[16] As shown in the previous studies, passive leg-lifting stress can shift the venous volume distributed in the lower limbs to the stressed volume by 150–200 mL of the blood volume,[17] which corresponds to an increase in SV by only 7–10%.[5–7] Although passive leg-lifting manoeuvre can be considered a model of volume central shift or endogenous volume challenge, the haemodynamic relevance of this

Figure 3 Comparisons of the prognostic value of different Cox models for predicting adverse cardiovascular events. This figure compares the prognostic value of different Cox models for predicting adverse cardiovascular events and illustrates the global χ^2 of nested Cox models, incorporating clinical, conventional echocardiographic, and combined postural stress parameters. BNP, brain natriuretic peptide; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ΔSVi, net difference in stroke volume index.

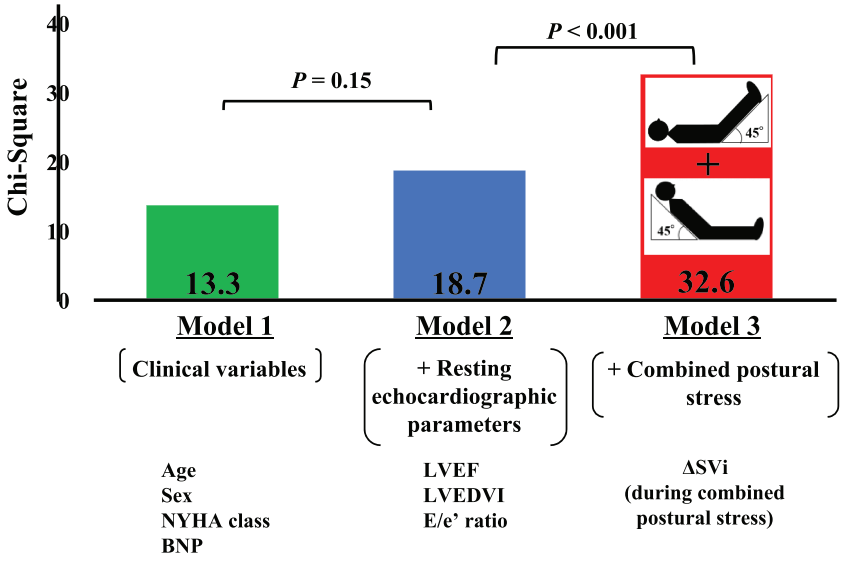
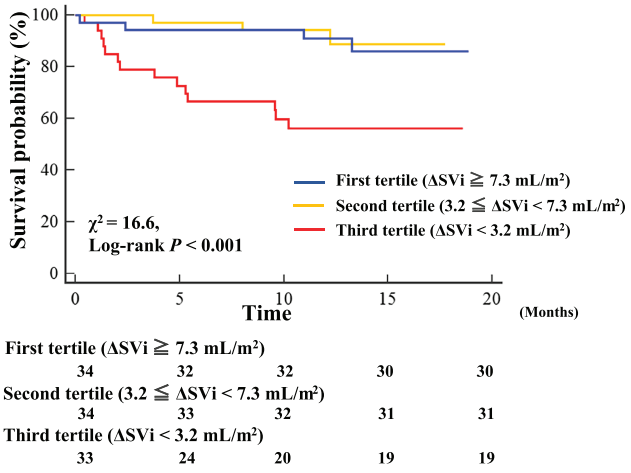


Figure 4 Comparison of event-free survival using Kaplan–Meier curve analysis stratified by the net difference in stoke volume index (ΔSVi) during combined postural stress. When patients were divided into three equal subgroups based on net difference in forward stroke volume index during combined postural stress (ΔSVi), patients with impaired preload reserve (third tertile, ΔSVi < 3.2 mL/m^2) showed significantly worse event-free survival compared with the other two subgroups.



manoeuvre has been questioned because of its minimal haemodynamic effect.[6]

By contrast, a head-up posture normally results in significant pooling of the blood volume within the capacitance vessels, resulting in a diminished gradient for venous return to the heart, a decrease in the filling pressure, ventricular end-diastolic volume, and ultimately forward SV.[8] However, as shown in the previous studies, a head-up posture was associated with relatively subtle decrease in SV by only 8–14%.[8–10] Although the head-up posture can be considered a model of preload reduction, the expected haemodynamic consequences are insufficient to adequately evaluate the preload-reducing effect on the cardiovascular system.

In this study, however, dynamic postural stress in the semi-sitting position and with passive leg-lifting was combined for the purpose of non-invasively producing a wide range of alterations in the venous return. As a result, changes in SVi during combined postural stress were as high as 21% for our patients with HFrEF, which was quite compatible to that observed during low-dose dobutamine stress of 20 μg/kg/min (ΔSVi of 19–22%).[3,4] The potential of a wide range of alterations in cardiac preload may be the reason why this combined postural stress could effectively evaluate the preload reserve as well as predict long-term outcome in patients with HFrEF.

Postural stress test for patients with heart failure

Only a few studies have reported on the clinical utility of the assessment of postural stress in patients with HFrEF. Bronzwaer *et al.*[9] studied 33 patients with HFrEF and evaluated the cardiovascular response to upright postural stress. They found that the magnitude of posture-induced reduction

in SV was blunted in patients with HFrEF. Furthermore, they reported that the upright posture-induced reduction in SV was inversely related to the severity of heart failure. With regard to preload-increasing interventions, Squara *et al*.[7] examined 50 patients with decompensated heart failure to show the relationship between treatment effects of heart failure and changes in preload reserve by using a non-invasively measured cardiac power index. They showed that the cardiac power index significantly increased during passive leg-lifting in patients with treatment responder. However, in patients who were treatment non-responders, the cardiac power index was unchanged or even decreased during passive leg-lifting.[7] As confirmed in our study, these findings suggest that the haemodynamic response to postural alterations was blunted in patients with advanced heart failure. As regards heart failure with preserved ejection fraction (HFpEF), Tossavainen *et al*.[18] recently investigated a total of 85 patients, consisting of 51 patients with elevated BNP concentration and 34 patients with normal BNP using right heart catheterization during passive leg-lifting and supine bicycle exercise. In HFpEF patients with elevated BNP, the mean pulmonary arterial pressure, pulmonary capillary arterial pressure (PCWP), and mean pulmonary arterial pressure/cardiac output significantly increased with exercise; however, cardiac output increased less in comparison with normal BNP counterparts. Of those with PCWP $>$ 25 mmHg during exercise, 91% had a PCWP $>$ 15 mmHg with passive leg-lifting. These findings were consistent with our findings, in which postural stress could be used for assessment of the preload reserve and for risk stratification even in patients with HFpEF. Because not only impaired contractile reserve[3,4] but also inability to increase ventricular compliance in response to acute myocardial stretching[19] would impair preload reserve in patients with heart failure, the cardiovascular system will be no longer able to maintain sufficient cardiac output. Unfortunately, the relationship between the response to the postural stress and the long-term outcome has not been evaluated in these previous reports. To the best of our knowledge, this is the first study to show that a change in SVi during combined postural stress may be a reliable marker for future adverse cardiovascular events in patients with HFrEF and provided significant incremental prognostic value over clinical and resting haemodynamic parameters.

Clinical implications

Recent studies have shown an additional value of preload stress testing for patients with various heart diseases, particularly for those with insufficient exercise capacity resulting from disease severity, orthopaedic problems, or senile frailty.[2,20,21] For these patients, cardiopulmonary exercise testing using treadmill and supine bicycle is not always feasible because of technical limitations. From a practical standpoint, the dynamic combined postural stress test could be an alternative assessment tool for patients with heart failure because it is safe, inexpensive, not time consuming, and quite easy to perform without any equipment. It is critically important to identify patients with heart failure with poor prognosis who are likely to experience clinical deterioration to improve the effectiveness of care, optimize patient outcomes, and effectively reduce overall cost by focusing resources on the high-risk patients.

Study limitations

This study has certain limitations. First, this pilot study was hypothesis generating in nature and thus covered a relatively small number of patients without sample size calculation based on the statistical power. Moreover, approximately 60% of cardiovascular events were hospitalization due to heart failure. Therefore, further multicentre studies with larger patient populations directed to hard endpoint will be needed to validate our findings. Second, this study did not include a simultaneous invasive haemodynamic study during postural stress test. Responses in SV with preload stress might be affected by baseline volume status and changes in cardiac afterload during postural alterations. However, the assessment of haemodynamics during the postural stress test was previously validated in comparison with invasive measurements.[22] Therefore, we believe that our overall results may not be significantly affected by these factors. Third, ongoing medication was not withheld before the intervention for safety reasons. Although background medications might have affected the results of this study, we believe that our findings are clinically relevant. Fourth, significant differences were observed in some baseline parameters between groups. Although this may partially reflect disease severity in patients with cardiovascular events, these variables were not selected as independent predictors of cardiovascular events in the multivariate Cox analysis. Nevertheless, concerns regarding insufficient statistical power should be considered. Not all established parameters that could potentially affect the prognosis were entered into the multivariate model, because of the lack of the statistical power and problem of overfitting. Therefore, we may be unable to draw a definitive conclusion regarding the clinical relevance of the postural stress echocardiography in patients with HFrEF. Fifth, because body position could not be blinded to a sonographer in principle, possible measurement bias could not be neglected. Moreover, the assessment of test–retest variability was not part of this study. Finally, a novel strain analysis was not included in this study. However, one of the major important aspects of this study is its simplicity without using any complicated techniques and equipment associated with stress testing.

Conclusions

The combined assessment of dynamic postural stress is a non-invasive, simple, quick, inexpensive, and easy-to-use clinical tool for assessing the preload reserve in patients with HFrEF. The combined postural stress may contribute to risk stratification and better management for these patients.

Conflict of interest

None declared.

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None.

Data availability statement

The data within this article may be shared after a reasonable request to the corresponding author.

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