JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 7, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.04.009

ORIGINAL RESEARCH

Pre-Load Stress Echocardiography for Predicting the Prognosis in Mild Heart Failure

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ABSTRACT

OBJECTIVES This study sought to introduce and confirm the efficacy of pre-load stress echocardiography with leg-positive pressure (LPP) for improving risk stratification of patients with mild stable heart failure.

BACKGROUND Heart failure patients with mild symptoms and a poor prognosis should be identified and treated aggressively to improve clinical outcome.

METHODS We performed transthoracic echocardiography with LPP in 202 patients with chronic cardiac disease. Twenty-two of these patients also underwent cardiac catheterization, and left ventricular pressure was measured during LPP along with simultaneous Doppler recordings. Patients were classified into 3 groups on the basis of their left ventricular (LV) diastolic dysfunction as assessed by transmitral flow velocity: restrictive or pseudonormal (PN) at rest, impaired relaxation (IR) at rest and during LPP (stable IR), and IR at rest and PN during LPP (unstable IR). Clinical outcome was compared among these groups.

RESULTS The LPP increased LV end-diastolic pressure from 15.8 ± 4.7 mm Hg to 20.5 ± 5.0 mm Hg in the unstable IR group and from 10.5 ± 2.6 mm Hg to 14.7 ± 3.8 mm Hg in the stable IR group (both $p < 0.001$). During an average follow-up of 548 ± 407 days, 5 patients had cardiac death, 37 had acute heart failure, 4 had an acute myocardial infarction, and 7 had a stroke. The all-cause cardiac event rate in unstable IR was higher than in stable IR ($p < 0.001$), and was similar in the PN group ($p = 0.81$). Event-free survival was significantly lower in unstable IR than in stable IR ($p = 0.003$). In a Cox proportional hazards model, unstable IR was an independent predictor of all-cause cardiac events (hazard ratio: 8.0; $p < 0.001$).

CONCLUSIONS The left LV end-diastolic pressure-volume relationship can be estimated by changes in transmitral flow velocity during LPP. Thus, pre-load stress echocardiography using LPP provides additional prognostic information in mild heart failure beyond that provided by conventional Doppler echocardiography at rest. (J Am Coll Cardiol Img 2014;7:641–9) © 2014 by the American College of Cardiology Foundation.

The assessment of left ventricular (LV) diastolic dysfunction using the transmitral flow (TMF) velocity pattern obtained by Doppler echocardiography has been widely used in the management of various cardiac diseases, especially in patients with heart failure (1). Its prognostic value in a variety of cardiac conditions has been demonstrated by several investigators (2–4). Most previous

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Manuscript received January 5, 2014; revised manuscript received March 4, 2014, accepted April 10, 2014.

ABBREVIATIONS AND ACRONYMS

A = peak atrial systolic transmitral flow velocity

a′ = peak atrial systolic mitral annular velocity

BNP = B-type natriuretic peptide

DT = deceleration time of early diastolic transmitral flow velocity wave

E = peak early diastolic transmitral flow velocity

e′ = peak early diastolic mitral annular velocity

IR = impaired relaxation

IVRT = isovolumic relaxation time

LPP = leg-positive pressure

LV = left ventricular

LVEDP = left ventricular end-diastolic pressure

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

PN = pseudonormal

TMF = transmitral flow

studies found a poor survival prognosis in patients with a restrictive or pseudonormal (PN) filling pattern, and patients with an impaired relaxation (IR) pattern seemed to have a better prognosis.

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It has been shown that the TMF velocity pattern varies dramatically with a change in loading conditions (5). This may limit the prognostic value of a single baseline Doppler evaluation; however, the change in the TMF velocity pattern to an altered load may provide an estimate of cardiovascular reserve and improve risk assessment. Pozzoli et al. (6) demonstrated that the responses to nitroprusside and leg lifting identified subgroups of patients who have markedly different prognoses despite similar baseline TMF velocity patterns. Moreover, Ishizu et al. (7) showed that passive leg lifting was useful to identify patients at high risk of the development of diastolic heart failure. Leg lifting is an easy noninvasive maneuver to increase pre-load, although it is sometimes difficult to perform, especially in obese or elderly patients. In this study, we used leg-positive pressure (LPP) as an alternative technique for noninvasive pre-load augmentation.

Consequently, the first purpose of this study was to evaluate the effect of LPP on LV hemodynamics by performing this maneuver during LV catheterization. Second, we aimed to assess whether changes in TMF in response to LPP could provide additional information on the prognosis of mild heart failure patients with intermediate diastolic dysfunction, in which there was an IR pattern of TMF velocity.

METHODS

PATIENT POPULATION. The study population consisted of 202 consecutive patients with various chronic cardiac diseases (134 men and 68 women) with a mean age of 67 ± 11 years (range 36 to 92 years) undergoing transthoracic echocardiography for the evaluation of their hemodynamic status between January 2006 and December 2007. All patients fulfilled the following inclusion criteria: 1) sinus rhythm; 2) stable clinical condition at the time of echocardiography defined by no signs of peripheral or pulmonary congestion and stable body weight with optimal medical treatment; 3) absence of severe primary diseases of other organs such as malignancy or pulmonary disorders; 4) absence of unstable angina; and 5) technically adequate 2-dimensional and Doppler echocardiograms. There were 175 patients taking an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, 67 taking a beta-blocker, 52 taking a nitrate, 48 taking a diuretic, and 20 taking digitalis. The patient population consisted of 104 patients with hypertension with left ventricular hypertrophy (52%), 60 with ischemic cardiomyopathy (30%), and 42 with nonischemic cardiomyopathy (21%). Patients with reduced LV ejection fraction (LVEF) (<50%), significant coronary artery stenosis (>50%) in >1 epicardial coronary vessel on angiography, revascularization, and/or a history of myocardial infarction were classified as having ischemic cardiomyopathy. Patients with reduced LVEF were classified as having nonischemic cardiomyopathy if they had none of these ischemic features. This study, which was performed in accordance with the Declaration of Helsinki, was approved by the Institutional Review Board of the University of Tokushima, and each subject gave written informed consent.

ECHOCARDIOGRAPHY. Two-dimensional, M-mode, pulsed Doppler, color Doppler, and tissue Doppler echocardiography were performed using a commercially available ultrasound machine (SSA-770, Toshiba Medical Systems, Tokyo, Japan or EUB-8500, Hitachi Medico, Kashiwa, Japan) with patients in the left lateral decubitus position. Left ventricular end-diastolic volume (LVEDV), LV end-systolic volume, and LVEF were measured and calculated from the apical 2- and 4-chamber view using the modified Simpson rule (8). LV mass was calculated as reported previously (9). Sex-specific values of LV hypertrophy were defined: LV mass index >95 g/m^2 (female) and >115 g/m^2 (male). TMF velocity was recorded from the apical long-axis or 4-chamber view. The peak early diastolic (E) and the peak atrial systolic (A) velocities, isovolumic relaxation time (IVRT), and deceleration time of early diastolic TMF velocity wave (DT) were measured. Similarly, pulmonary venous flow velocity signals were recorded from the apical 4-chamber view and systolic and diastolic pulmonary venous flow peak velocity as well as atrial reversal pulmonary venous flow velocity, and the duration was calculated. Stroke volume was calculated as the product of the cross-sectional area of the LV outflow tract and the time-velocity integral in the LV outflow tract flow velocity wave. The mitral annular motion velocity pattern was recorded from the apical 4-chamber view with a sample volume placed at the lateral side of the mitral annulus using pulsed tissue Doppler echocardiography. Early diastolic (e′) and atrial systolic (a′)

peak velocities were measured and the ratio of E to e′ was calculated. All Doppler recordings were performed during an end-expiratory breath hold. The mean values of 5 consecutive cardiac cycles were used in the analysis.

LEG-POSITIVE PRESSURE. We customized a commercially available leg massage machine (Dr. Medomer DM-5000EX, Medo Industries Co., Ltd., Tokyo, Japan) because it could maintain a constant loading pressure around the legs for 5 min. Although the loading pressure could be varied, we used a setting of 90 mm Hg because this pressure did not significantly increase either heart rate or systolic blood pressure, based on findings from our preliminary study (10).

CLASSIFICATION OF LV DIASTOLIC FUNCTION. The LV diastolic dysfunction was divided into 3 categories according to the TMF pattern: restrictive or PN at rest, IR at rest and during LPP (stable IR), and IR at rest and PN during LPP (unstable IR). IR was defined as an E/A ratio <1 or DT >240 ms in patients younger than 55 years of age with an E/A ratio <0.8 and DT >240 ms in patients 55 years of age or older. PN was defined as an E/A ratio of 1.0 to 1.5 and 160 < DT < 200 ms. TMF velocity pattern was confirmed by the pulmonary venous flow velocity pattern and IVRT (1). The LPP maneuver was performed in patients with IR during echocardiographic recording, and the patients were divided into 2 subgroups according to the change in transmitral flow pattern during LPP. In stable IR, both E and A were increased by LPP, whereas E increased, but A decreased in unstable IR.

HEMODYNAMIC RECORDINGS. The effect of LPP at 90 mm Hg was examined by performing this maneuver during LV catheterization. Simultaneous recordings of LV pressure and Doppler echocardiograms were achieved in 22 patients in our study. A 6-F high-fidelity manometer-tipped catheter (MIKRO-TIP Angiographic Catheter Model SPC-464D, Millar Instruments, Houston, Texas) was inserted from the right brachial artery into the left ventricle. The LV pressure curves, transmitral flow, and mitral annular velocity were recorded before and during LPP. LV end-diastolic pressure (LVEDP) and the pressure before atrial contraction (pre-A) were measured. The LV relaxation time constant (tau) was determined by the nonlinear least-squares, parameter-estimate technique using the following exponential equation: $P = P0e^{-t/tau} + b$, where P is the instantaneous LV pressure, P0 is LV pressure at minimal dP/dt, and b is the theoretical asymptote. To exclude respiratory variation, pressures were measured at end expiration during a breath hold. The mean values of the 5 consecutive cardiac cycles were used in the analysis. Blood samples were taken within 1 week of echocardiographic examination. A 2-ml blood sample was drawn from an antecubital vein after 10 min of supine rest, placed in a tube containing ethylenediamine tetraacetic acid, and analyzed within 2 h. Plasma concentrations of B-type natriuretic peptide (BNP) were measured by chemiluminescence enzyme immunoassay. The physicians who measured the invasive hemodynamic parameters were blinded to the Doppler echocardiographic findings.

CLINICAL OUTCOME. Cardiac death, hospitalization due to acute heart failure, acute myocardial infarction, and stroke were considered major cardiac events. If a patient died during follow-up, the cause of death was identified by medical record review or telephone contact. Cardiac death was defined as either a death directly related to cardiac disease, mainly congestive heart failure, stroke, or sudden death. Similarly, hospitalization due to various cardiac events during follow-up was identified by medical record review.

STATISTICAL ANALYSIS. Data are presented as mean ± SD. Data were tested for normality using the Kolmogorov-Smirnov test. Continuous variables were compared using an unpaired Student *t* or Mann-Whitney *U* test as appropriate, whereas categorical variables were compared using the chi-square or Fisher exact test, as appropriate. Changes in continuous variables from baseline to during LPP were analyzed using repeated-measures analysis of variance. One-way analysis of variance for repeated measures was used to compare echocardiographic parameters between groups. The Bonferroni correction was used for post-hoc analysis of significant results. A Cox proportional hazards model was used to determine the predictors of survival in the groups defined here. Sequential Cox models were performed to determine the incremental prognostic benefit of pre-load stress echocardiographic parameters over clinical data, with the incremental prognostic value being defined by a significant increase in global chi-square value. Survival was estimated by the product-limit Kaplan-Meier method, and the comparison between groups was carried out by the log-rank test. A p value <0.05 was considered significant. All statistical analyses were carried out with Medcalc Software version 12.7.5.0 (Medcalc, Ghent, Belgium) and SPSS software version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

FEASIBILITY AND SAFETY OF LPP. All patients tolerated 90-mm Hg LPP during the echocardiographic examination. No major complications were

observed during and after the LPP maneuver; however, 1 patient with hypertrophic cardiomyopathy had slight dyspnea, and 1 patient with previous myocardial infarction reported leg pain. Both minor complications were relieved immediately by terminating LPP.

HEMODYNAMIC ASSESSMENT. Hemodynamic and echocardiographic data at baseline and during LPP are shown in Table 1. The BNP level did not differ between the stable IR and unstable IR groups ($p = 0.35$). LPP resulted in significant increases in LVEDP and pre-A pressure as well as increments of peak E velocity and E/e′ (all p values <0.05). Tau and e′ were not significantly changed by LPP. Individual changes in LVEDP in response to LPP are shown in Figure 1. Baseline LVEDP ($p = 0.013$) and pre-A pressure ($p = 0.005$) in unstable IR were greater than the respective values in the stable IR group. The right panel in Figure 1 demonstrates simultaneous Doppler and pressure recordings in representative cases from the stable and unstable IR groups. During LPP, the LVEDP increased from 15.8 ± 4.7 mm Hg to 20.5 ± 5.0 mm Hg in the unstable IR group and from 10.5 ± 2.6 mm Hg to 14.7 ± 3.8 mm Hg in the stable IR group ($p < 0.001$ in both). The tau in the unstable IR group tended to be prolonged in the unstable IR group compared with the stable IR group (41.0 ± 6.5 vs. 46.9 ± 10.3, $p = 0.06$). There was no difference in e′ and IVRT between the stable and unstable IR groups. In addition, the LPP caused significant increases in the LVEDV and stroke volume in the stable IR group ($p < 0.05$), but no significant change in the unstable IR group ($p = 0.41$ for the LVEDV and $p = 0.35$ for the stroke volume).

DOPPLER AND HEMODYNAMIC CHARACTERISTICS AT BASELINE AND IN RESPONSE TO LPP. At baseline, TMF in 175 patients exhibited an IR pattern (E < A) and 27 patients exhibited a PN pattern (E > A). According to the change in TMF pattern caused by LPP, IR patients were divided into stable IR (n = 121) and unstable IR (n = 54) groups. Table 2 shows the clinical, 2-dimensional and Doppler echocardiographic indexes in all 3 groups. There were no significant differences in age, diagnosis, blood pressure, and sex between the stable and unstable IR groups.

TABLE 1 Effect of Leg-Positive Pressure on Hemodynamic and Echocardiographic Parameters

	All (n = 22)		Stable IR (n = 16)		Unstable IR (n = 6)	
	Baseline	During LPP	Baseline	During LPP	Baseline	During LPP
HR, beats/min	64 ± 9	66 ± 8	61 ± 14	62 ± 12	66 ± 6	67 ± 6
Systolic BP, mm Hg	133 ± 20	132 ± 22	135 ± 21	133 ± 25	126 ± 20	130 ± 15
Diastolic BP, mm Hg	72 ± 11	71 ± 8	72 ± 12	72 ± 9	72 ± 7	70 ± 4
BNP, pg/ml	171 ± 124	–	156 ± 112	–	213 ± 158	–
Echocardiography						
LVEDV, ml	93 ± 38	99 ± 41*	96 ± 41	104 ± 43*	84 ± 33	83 ± 32
LVESV, ml	41 ± 29	42 ± 30	40 ± 30	40 ± 29	45 ± 28	47 ± 32
Stroke volume, ml	52 ± 18	57 ± 25*	56 ± 18	65 ± 26*	39 ± 5	37 ± 4
LAVi, ml/m^2	27 ± 7	31 ± 8*	26 ± 8	31 ± 8*	27 ± 2	31 ± 2*
LVEF, %	58 ± 14	60 ± 17	61 ± 14	64 ± 14	50 ± 14	49 ± 19
LVMi, g/m^2	140 ± 26	–	141 ± 25	–	138 ± 31	–
IVC, cm	1.0 ± 0.5	–	0.9 ± 0.3	–	1.1 ± 0.4	–
E, cm/s	64 ± 8	82 ± 10*	65 ± 10	79 ± 10*	63 ± 6	90 ± 6*
A, cm/s	95 ± 11	93 ± 18	95 ± 10	100 ± 12	94 ± 12	73 ± 17*
E/A	0.68 ± 0.08	0.92 ± 0.28*	0.68 ± 0.08	0.78 ± 0.09*	0.69 ± 0.10	1.29 ± 0.28*
e′, cm/s	7.2 ± 2.9	7.9 ± 3.4	7.0 ± 1.1	8.0 ± 2.3	7.3 ± 3.4	7.7 ± 3.7
IVRT, ms	82 ± 24	79 ± 23	82 ± 28	79 ± 24	82 ± 9	82 ± 19
E/e′	9.2 ± 4.0	11.6 ± 7.0*	9.0 ± 2.0	10.7 ± 3.2	9.6 ± 4.6	13.4 ± 7.9*
Cardiac catheterization						
LVEDP, mm Hg	11.6 ± 4.1	16.3 ± 5.8*	10.5 ± 2.6	14.7 ± 3.8*	15.8 ± 4.7	20.5 ± 5.0*
Pre-A pressure, mm Hg	7.1 ± 2.8	9.6 ± 4.2*	6.4 ± 2.4	9.3 ± 2.9*	9.6 ± 4.0	11.8 ± 6.1*
Tau, ms	42.6 ± 7.9	44.1 ± 9.3	41.0 ± 6.5	41.3 ± 8.4	46.9 ± 10.3	48.2 ± 7.4

Values are mean ± SD. *$p < 0.05$, baseline versus during LPP.

A = atrial systolic transmitral flow velocity; BNP = B-type natriuretic peptide; BP = blood pressure; E = early diastolic transmitral flow velocity; e′ = early diastolic mitral annular velocity; HR = heart rate; IR = impaired relaxation; IVC = inferior vena cava; IVRT = isovolumic relaxation time; LAVi = left atrial volume index; LPP = leg-positive pressure; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVMi = left ventricular mass index.

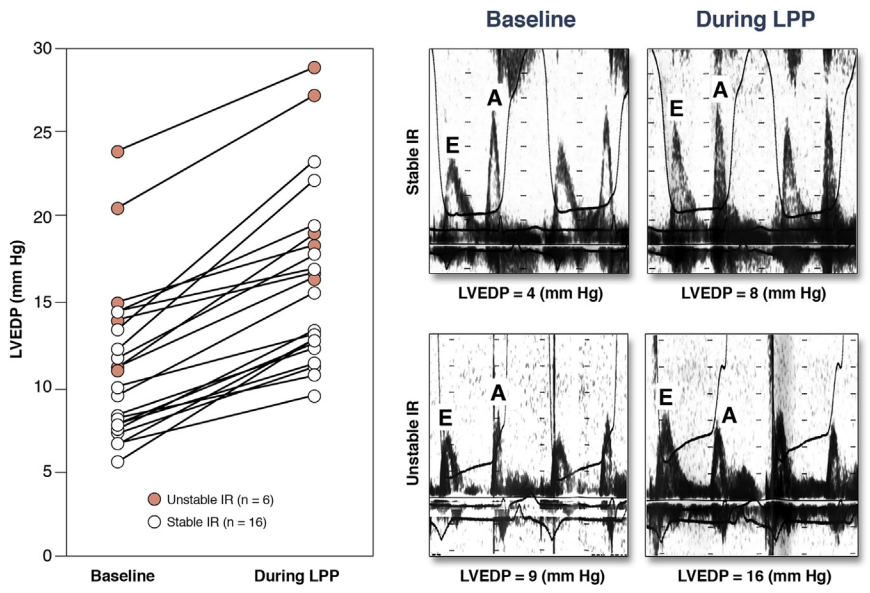

FIGURE 1 Invasive Hemodynamic Observation at Baseline and During Leg-Positive Pressure

Left ventricular end-diastolic pressure (LVEDP) was elevated by leg-positive pressure (LPP) in each patient with stable and unstable impaired relaxation groups **(left)**. Representative simultaneous recordings of left ventricular pressure and Doppler transmitral flow velocity patterns in the stable **(top right)** and the unstable **(bottom right)** impaired relaxation groups at baseline and during LPP are shown. **Solid line in the right panels** indicates left ventricular pressure recorded by a Millar catheter. A = atrial systolic transmitral flow velocity; E = early diastolic transmitral flow velocity; IR = impaired relaxation pattern.

Compared with the stable IR group, the unstable IR group had a larger left atrial size, higher E/e′ ratio, and lower a′ (all p values <0.05). LV size, LV mass, E, E/A ratio, and e′ did not differ between these 2 groups.

SURVIVAL ANALYSIS. During an average follow-up period of 548 ± 407 days, there were 5 cardiac deaths (2.4%) and 4 noncardiac deaths (2.0%). Table 2 shows the baseline clinical and echocardiographic characteristics of each group. Table 3 summarizes the clinical event rates in the 3 groups. The number of all-cause cardiac events was significantly higher in the PN group than in the combination group of stable and unstable IR groups ($p = 0.013$) and was also significantly higher in the PN group than in the stable IR group ($p < 0.001$). On the other hand, the rate of all-cause cardiac events during the follow-up period did not differ significantly between the unstable IR and PN groups ($p = 0.81$). In addition, all-cause mortality did not differ significantly between the groups (PN group vs. stable and unstable IR, $p = 0.34$; PN group vs. stable IR, $p = 0.30$). Kaplan-Meier analysis of both cardiac events and acute heart failure (Fig. 2) showed that the survival rate during follow-up was significantly higher in the unstable IR group than in the stable IR group (log-rank, $p = 0.003$ for survival free from acute heart failure and $p = 0.002$ for survival free from cardiac events). A Cox proportional hazards analysis showed that unstable IR and E/e′ >15 cm/s were both independent predictors of cardiac events in patients presenting the IR pattern, although the change in the TMF velocity pattern during LPP was the most powerful predictor of cardiac events (Table 4). We could not detect a significant difference in cardiac or all-cause event-free survival between the E/e′ <15 and the E/e′ ≥15 groups by Kaplan-Meier analysis (Fig. 2). The addition of pre-load stress echocardiographic parameters significantly improved the prognostic power of a model containing clinical variables (model 1: age, sex, and LVEF, chi-square = 11.6; model 2: plus stable IR or unstable IR, chi-square = 26.7, $p < 0.001$).

DISCUSSION

Our data suggest that pre-load stress echocardiography using LPP has important prognostic information beyond that provided by resting Doppler echocardiography in patients with mild heart failure. Patients

TABLE 2 Baseline Clinical and Echocardiographic Characteristics

	Stable IR (n = 121)	Unstable IR (n = 54)	PN (n = 27)
Diagnosis			
Hypertension	67 (55)	31 (58)	6 (22)
Ischemic cardiomyopathy	30 (25)	21 (39)	9 (33)
Nonischemic cardiomyopathy	25 (21)	11 (20)	6 (22)
Diabetes mellitus	23 (19)	9 (17)	7 (26)
History of stroke	4 (3)	2 (4)	1 (4)
Age, yrs	67 ± 13	66 ± 11	61 ± 14*†
Male/female	74/47	38/16	22/5
Male	61.2	70.3	81.5
HR, beats/min	62 ± 14	66 ± 13	63 ± 16
Systolic blood pressure, mm Hg	138.0 ± 20.7	133.0 ± 20.3	105.0 ± 9.2*†
Diastolic blood pressure, mm Hg	73.8 ± 13.9	73.2 ± 8.4	56.5 ± 4.1*†
Echocardiographic parameters			
LV end-diastolic dimension, mm	48.0 ± 7.2	51.1 ± 5.6	52.1 ± 11.1
LV end-systolic dimension, mm	31.4 ± 7.7	34.3 ± 9.4	35.3 ± 7.9
Interventricular septal thickness, mm	12.1 ± 5.0	11.9 ± 5.2	12.1 ± 5.2
LV posterior wall thickness, mm	10.6 ± 1.8	9.9 ± 1.7	10.6 ± 1.10
LVMi, g/m^2	116.4 ± 22.6	121.8 ± 24.7	126.9 ± 21.8
LAVi, ml/m^2	28.6 ± 9.8	32.8 ± 10.6*	31.4 ± 8.1*
IVC diameter, mm	12.2 ± 9.4	11.0 ± 8.4	18.8 ± 14.4
LVEDV, ml	84.4 ± 34.3	90.4 ± 33.6	107.4 ± 40.6*
LVESV, ml	37.7 ± 24.6	41.2 ± 28.9	48.6 ± 37.1
LVEF, %	60.6 ± 11.5	58.9 ± 16.9	51.6 ± 17.1
E, cm/s	51.6 ± 12.4	55.7 ± 12.8	78.3 ± 24.5*†
A, cm/s	81.7 ± 16.7	78.7 ± 18.5	54.5 ± 13.8*†
DT, ms	248 ± 78	230 ± 50	182 ± 72*†
E/A	0.77 ± 0.19	0.80 ± 0.20	1.37 ± 0.27*†
e′, cm/s	6.6 ± 2.5	6.4 ± 2.0	6.9 ± 4.1
a′, cm/s	10.4 ± 2.6	8.4 ± 2.7*	6.9 ± 3.8*†
E/e′	8.8 ± 2.6	9.6 ± 2.9*	11.2 ± 5.6*†
PVS, cm/s	54.3 ± 13.3	48.9 ± 14.8	43.9 ± 16.7*
PVD, cm/s	35.3 ± 13.3	35.3 ± 13.0	52.2 ± 14.6*†
PVA, cm/s	26.9 ± 6.2	31.2 ± 3.4	26.9 ± 6.4

Values are n (%), mean ± SD, or %. *p < 0.05 versus stable IR. †p < 0.05 versus unstable IR.

a′ = peak atrial systolic mitral annular velocity; DT = deceleration time of early diastolic transmitral flow velocity; LV = left ventricular; PN = pseudonormal; PVA = atrial reversal pulmonary venous flow velocity; PVD = diastolic pulmonary venous flow velocity; PVS = systolic pulmonary venous flow velocity; other abbreviations as in Table 1.

TABLE 3 Clinical Events During Follow-up

	Stable IR (n = 121)	Unstable IR (n = 54)	PN (n = 27)
All-cause cardiac events	14 (11.6)	22 (40.7)	12 (44.4)
Cardiac death	2 (1.7)	1 (1.8)	2 (7.4)
Acute heart failure	10 (8.3)	18 (33.3)	9 (33.3)
Acute myocardial infarction	1 (0.8)	2 (3.7)	1 (3.7)
Stroke	3 (3.3)	2 (3.7)	2 (7.4)
All-cause death	4 (3.3)	3 (5.6)	2 (7.4)
Cardiac death	2 (1.7)	1 (1.8)	2 (7.4)
Noncardiac death	2 (1.7)	2 (3.7)	0 (0.0)

Values are n (%).

Abbreviations as in Tables 1 and 2.

with an IR pattern have been thought to have a better prognosis than patients with a PN pattern. However, our results clearly demonstrated that the change in the TMF velocity pattern during LPP can identify a patient subgroup that has a poor prognosis, and this prognosis is similar to that of the PN group despite similar baseline IR patterns.

PROGNOSTIC VALUE OF DOPPLER ECHOCARDIOGRAPHY IN PATIENTS WITH HEART FAILURE. Previous studies have shown that a PN or restrictive diastolic filling pattern or short deceleration time is a poor prognostic indicator in patients with and without systolic dysfunction (2–4). More recent studies reported that E/e′ is a strong predictor of mortality (11–13). The PN or restrictive TMF velocity pattern may indicate significant elevation of LVEDP; however, it may not be useful in patients with slightly increased LVEDP, such as the IR patients in our study. E/e′ also has a wide gray zone in which the parameter has no discriminatory valuable. In our subjects with only mild heart failure, E/e′ ≥15 cm/s was an independent predictor of cardiac events, whereas this parameter was not useful for the prediction of survival free from cardiac events by Kaplan-Meier analysis.

In most previous studies, the TMF velocity pattern was assessed only once at rest, and this represents an important limitation. A single measurement at rest may not provide sufficient information because the pattern may be easily changed by respiration, loading conditions, medications, or postural changes (14). It has been reported that patients able to respond favorably to hemodynamic manipulation appear to have a better prognosis because they likely represent those with less severe disease (15). The response of the TMF velocity pattern to the Valsalva maneuver (2), administration of nitroprusside, and leg lifting (6,7) have been used to identify patients who have a worse prognosis. Leg lifting is a procedure similar to our LPP for increasing pre-load. Passive leg lifting is sometimes difficult to perform, especially in obese and/or elderly patients in whom we can conduct the LPP. Another advantage of the LPP is that it does not require an additional examiner to lift the patient's leg and the patient can be left in the decubitus position during the maneuver, which enables us to obtain clear Doppler recordings.

LPP ALTERS VENTRICULAR PRE-LOAD. The TMF velocity pattern is known to be affected by loading conditions (16). Therefore, it is possible to evaluate the difference in LV and left atrial functional reserve by assessing changes in flow velocities during

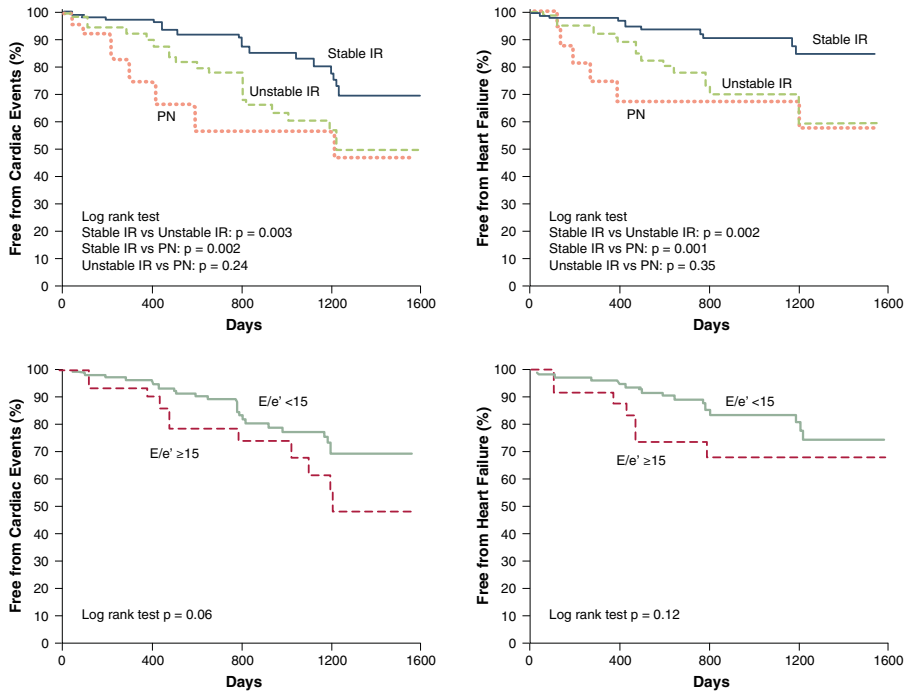

FIGURE 2 Kaplan-Meier Plots of Survival Free From Cardiac Events and Heart Failure

Kaplan-Meier plots of survival free from cardiac events or survival free from heart failure are shown **(top)** on the basis of the response of the mitral flow velocity pattern to LPP. **(Bottom)** Kaplan-Meier plots of survival free from cardiac events and survival free from heart failure in patients stratified on the basis of E/e′ (E/e′ <15 and E/e′ ≥15). e′ = peak early diastolic mitral annular velocity; PN = pseudonormal or restrictive pattern; other abbreviations as in Figure 1.

increases in pre-load (5). To increase venous return noninvasively, previous investigators used leg lifting (17), lower body positive pressure with a wooden box or a steel container sealed at the level of the iliac crest (5,18,19), or an anti-G garment (20–22). The lower body positive pressure elicited an increase in cardiac output in some studies (1,18,19), whereas others reported that cardiac output tended to decrease (23). This discrepancy was due to the magnitude of the lower body pressure, the patient's posture, and interactions between the sympatho-inhibitory effect of the cardiopulmonary baroreflex and the sympathoexcitatory effect of the intramuscular pressure-sensitive mechanoreflex (23). Instead of these methods, we used LPP in which air bags were inflated around both lower limbs. The 90 mm Hg of LPP that we used did not increase arterial blood pressure, heart rate, or LVEF, but did increase LVEDP and pre-A pressure. This could be accounted for by increased venous return with minimal change in sympathetic tone. There were no major short- or long-term complications of LPP. We found that LPP was a safe, noninvasive maneuver to induce a significant increase in LVEDP. Advantages of LPP are that it is easy to perform, does not require muscle contraction or a change in the patient's posture, and the pressure load can be precisely controlled at any desired level. Furthermore, the effect of LPP can be immediately terminated by

TABLE 4 Cox Proportional Hazards Analysis in Patients With IR (All-Cause Cardiac Events)

	p Value	Risk Ratio	95% Confidence Limits	
			Lower	Upper
Unstable IR	<0.001	8.0	2.8	22.8
E/e′ >15, cm/s	0.022	4.1	1.2	3.7
a′ <5, cm/s	0.051	2.8	0.99	7.9
LAVi >32, ml/m^2	0.327	1.6	0.6	4.2
LVEF <50%	0.912	0.9	0.4	2.3
e′ <5, cm/s	0.112	3.7	0.9	8.4
Male	0.551	1.3	0.5	3.1

Abbreviations as in Tables 1 and 2.

deflating the air bags, which also allowed confirmation of the effect of LPP.

DIFFERENCE BETWEEN STABLE AND UNSTABLE IR. The LPP caused a significant increase in LVEDV and stroke volume but no significant increase in LVEDP in the stable IR group; on the other hand, it led to a marked increase in LVEDP but caused no significant changes in LVEDV in the unstable IR group. Thus, it is thought that the end-diastolic pressure-volume relationship is steeper in these patients than in stable IR patients (i.e., the LV compliance is more reduced in unstable IR patients than in the stable IR group). Furthermore, the LA volume index was greater and the a′ was smaller in the unstable IR group compared with the stable IR group. This indicates that left atrial dysfunction may have progressed in the unstable IR group. Left atrial function has been reported to play a role in the LV filling and cardiac output responses to preload augmentation (24). The peak systolic pulmonary venous flow velocity tended to decrease more in the unstable IR group than in the stable IR group in our study, which suggests that left atrial reservoir function was more impaired in the unstable IR group. It is our hypothesis that pre-load reserve in the unstable IR patients was reduced because of impaired LV compliance and/or left atrial reservoir function.

STUDY LIMITATIONS. The number of patients in our study was small, especially in the invasive hemodynamic study. During long-term follow-up, the number of clinical outcome events was limited and the difference in cardiac death rates was not significant between the 2 groups. A study with a larger number of patients and longer duration of follow-up is needed to confirm these findings. The other limitation is the lack of a validation cohort. The present study should be considered as hypothesis generating, and we believe that larger multicenter studies are warranted. It also needs to be assessed in the future whether medical interventions improve the worse prognosis of unstable IR patients. Finally, we were unable to assess the biomarkers (e.g., BNP) in this cohort, whereas there was no significant difference in BNP level between the stable and unstable IR groups in the invasive study.

CONCLUSIONS

The LV diastolic pressure-volume relationship could be estimated by the change in TMF velocity pattern during LPP. The LPP maneuver is useful for pre-load stress echocardiography because it allows noninvasive pre-load augmentation during an echocardiographic examination. A change in the TMF velocity pattern in response to an increment in pre-load provides additional prognostic information beyond that provided by conventional Doppler echocardiographic parameters obtained at rest in mild heart failure patients with an IR pattern.

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KEY WORDS **Doppler echocardiography, heart failure, leg-positive pressure, stress echocardiography, survival**