A clinical application of preload stress echocardiography for predicting future hemodynamic worsening in patients with early-stage heart failure

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Aim: To improve the prognosis of patients with heart failure, risk stratification in their early stage is important. We assessed whether the change in transmitral flow (TMF) velocity pattern during preload augmentation can predict future hemodynamic worsening in early-stage heart failure patients with impaired relaxation TMF pattern.

Methods: We designed a prospective cohort study that included 155 consecutive patients with impaired relaxation (IR) pattern at rest. Preload stress echocardiography was achieved using leg positive pressure (LPP), and changes of TMF pattern during the LPP was observed during baseline echocardiographic examination. The patients whose TMF pattern developed to pseudonormal (PN) pattern throughout the study period were classified into the change to PN group, and patients whose TMF pattern stayed in IR pattern were classified into the stay in IR group.

Results: The median follow-up period was 17 months. The average age was 68 ± 11 years old, and 97 patients (63%) were male. Among 155 patients, 27 were classified into the change to PN group. A Cox proportional hazard analysis confirmed that the change in the peak atrial systolic TMF velocity during the LPP (ΔA, hazard ratio = 0.58 per 1SD; 95% CI = 0.39 - 0.88, P = 0.010) was the powerful independent predictor of change into PN pattern. Kaplan-Meier analysis revealed that the patients with ΔA ≤ -7 cm/s had more likely to develop into PN pattern than patients with ΔA > -7 cm/s (P = 0.001).

Conclusions: Evaluation of a response in TMF during the LPP might provide an incremental diagnostic value to detect future overt heart failure in patients with early-stage heart failure.

KEYWORDS

Doppler echocardiography, heart failure, stress echocardiography, diastolic function.

1 INTRODUCTION

Aging of the population and life prolongation in patients with cardiac diseases by various therapeutic innovations have led to an increased prevalence of heart failure.[1-3] Despite advances in modern therapy, the mortality rate and the rehospitalization rate of patients with heart failure remain unacceptably high. It has been reported that repeated hospitalization accelerates poor prognosis of heart failure.[4, 5] Therefore, the urgent task for us is to find patients who can benefit from preventive treatment before the onset of overt heart failure which may need hospitalization.

In patients with symptoms and signs of heart failure, echocardiography is one of the easy-to-use clinical tools to prove heart failure. Echocardiography can also determine the underlying background pathophysiology and severity of heart failure, and it also helps clinicians to estimate prognosis and judge therapeutic effects. In the evaluation of heart failure by contemporary echocardiographic examination, comprehensive measurements and evaluations of various indices are performed, and classification of severity of left ventricular (LV) diastolic dysfunction is an important part in a series of diagnostic processes.[6-8] In daily practice, classical method of classification of transmitral flow (TMF) pattern is still frequently used for the assessment of LV diastolic dysfunction, and patients with “pseudonormal (PN)” or “restrictive” pattern are thought to have elevated left atrial (LA) pressure with poor prognosis.[9-12] On the other hand, patients with impaired relaxation (IR) pattern have been thought to be in early-stage heart failure with normal LA pressure and have a better prognosis than patients with the PN or restrictive pattern. When the TMF pattern changes from IR to PN in the clinical course, however, the prognosis becomes unfavorable.[13, 14]

We had previously reported that patients whose TMF pattern changed from IR to PN by preload stress echocardiography had a poor prognosis, which was similar to the prognosis of patients with PN and restrictive pattern at rest.[15] We think that it is important to detect the change

of the peak atrial systolic of TMF (A) velocity during preload stress because this change reflects the change of transmitral pressure gradient, which is generated by LA contractility and affected by LV end-diastolic pressure (LVEDP). Consequently, we hypothesized that our preload stress echocardiography can be used for detecting the subgroup of IR patients whose TMF pattern developed to PN pattern in the future. Thus, the purposes of this study were to assess the change in TMF patterns during leg positive pressure (LPP) in patients with early-stage heart failure with IR pattern and to clarify its association with the future development to PN pattern.

2 METHODS

2.1 Study population

We designed a prospective cohort study to assess the change in TMF pattern during LPP in patients with IR pattern and its association with their future TMF pattern at rest. The study population consisted of 155 consecutive patients with various cardiac diseases (97 men and 58 women) with a mean age of 68 ±11 years undergoing transthoracic echocardiography for the evaluation of hemodynamic status between January 2011 and December 2014. All patients fulfilled the following inclusion criteria: 1) had sinus rhythm; 2) had the suspicion of heart failure according to clinical symptoms or elevated serum B-type natriuretic peptide level (serum BNP level >100 pg/ml); 3) had IR pattern in TMF pattern; 4) underwent LPP echocardiography at baseline and follow-up echocardiography during study period at least once; and 5) underwent technically adequate two-dimensional and Doppler echocardiograms. Exclusion criteria were the following: 1) presence of moderate and severe valve diseases or mitral annular calcification; 2) presence of deep vein thrombus and leg pain at baseline; and 3) absence of consent. The institutional medical ethics committee of Tokushima University Hospital approved, and each subject gave written informed consent.

2.2 Echocardiography

An experienced sonographers and doctors performed standard echocardiographic examination according to the guideline from the American Society of Echocardiography [16] using commercially available ultrasound examination machines (Vivid E9, GE Healthcare, Milwaukee, WI, USA; iE33, Philips Healthcare, Best, the Netherlands; Aplio500, Toshiba Medical Systems, Tochigi, Japan; α10 or Preirus, Hitachi-Aloka Medical, Ltd., Tokyo, Japan). Both LV and LA volumes were calculated using method of disks and subsequently indexed by body surface area.[17] TMF pattern was obtained from the apical long-axis view with a sample volume positioned adjacent to the tip of the mitral leaflets in diastole. The peak early diastolic (E) and A velocities and deceleration time (DT) of E wave were measured. Similarly, pulmonary venous flow was measured by placing the sample volume into the right superior pulmonary vein from the four-chamber view, and systolic (PVS) and diastolic (PVD) pulmonary venous flow peak velocities were measured. The peak early diastolic (e') and the peak atrial systolic (a') mitral annular tissue motion velocities were measured with sample volume placed at the lateral and septal side of mitral annulus, and we calculated their average values. We calculated the E/A and E/e' ratio by using average e'. The IR pattern was characterized by an E/A ratio <1 or DT ≥240 ms in patients younger than 55 years of age and an E/A ratio <0.8 with DT >240 ms in patients 55 years of age or older. The PN pattern was defined as an E/A ratio ≥1 with 160 <DT <200 ms. Diastolic dysfunction grade was assessed according to the current guidelines of American Society of Echocardiography.[18]

2.3 Preload stress echocardiography

We used LPP to increase preload during echocardiographic examination using a customized leg massage machine (Dr. Medomer DM 5000-EX. Medo Industries Co., Ltd., Tokyo, Japan), in which air bags were inflated around both lower limbs. This could maintain a constant loading pressure around the legs for 5 minutes, and the pressure was set to 90 mm Hg to increase venous return. This

procedure does not significantly increase either heart rate or systolic blood pressure in the previous invasive study. Thus, we can provide pure preload augmentation using this technique.[15, 19] When hemodynamic conditions had stabilized, echocardiographic data were acquired. We measured the E velocity, A velocity, and DT during LPP and calculated the E/A ratio. Subsequently, changes of those parameters from baseline to during LPP (ΔE, ΔA, ΔDT and ΔE/A ratio) were calculated.

2.4 Study endpoint and follow-up

Follow-up echocardiography was performed every 12 months. Echocardiographic examination was also performed when patient complained symptoms of heart failure or when signs of heart failure appeared. The endpoint was defined so that the TMF pattern became PN pattern at the follow-up echocardiography, because we thought that it is crucial to detect worsening of heart failure before patients need hospital admission. Patient who reached the endpoint within 12 months, follow-up echocardiography did not schedule. If the TMF pattern stayed IR pattern at the follow-up study, we planned the next follow-up echocardiography and repeated it up to 36 months. The follow-up information was obtained from medical records. The patients whose TMF pattern developed to PN pattern were classified into the change to PN group, and patients with sustained IR pattern throughout the study period were classified into the stay in IR group.

2.5 Statistical analysis

Descriptive data are expressed as a mean value ± standard deviation (SD). Comparisons between groups of continuous variables were tested by unpaired t-test or Mann-Whitney U test, if appropriate. The Chi-square test was used to compare categorical variables. The association of baseline variables with event was identified by the Cox Proportional Hazard method. Initially, to understand the association between clinically relevant variables, univariable analysis was performed. Subsequently, forward stepwise multivariable survival analysis was performed using relevant variables (associated with event) after adjustment for age, incorporating a P value

threshold < 0.05 as entry cutoff. A hazard ratio (HR) with a 95% confidence interval (CI) was calculated for each variable. Since serum BNP level was not normally distributed, we divided the subject into 2 groups by the median value and carried out these analyses. Sequential Cox models were performed to determine the incremental prognostic benefit of preload stress echocardiographic parameters over other significant univariable predictors of change to PN, with an incremental prognostic value being defined by a significant increase in global chi-index. The diagnostic ability of the predictor to distinguish the change to PN group from the stay in IR group was determined using a receiver-operating characteristic curve. The optimal cutoff was taken when the sum of sensitivity and specificity was the highest. Additionally, to assess the prognostic value, cumulative survival curves for the Kaplan-Meier analysis were constructed and compared using the log-rank test. A value of $P < 0.05$ was considered significant. All statistics were calculated by the MedCalc version 16.8.4 for Windows (MedCalc Software, Mariakerke, Belgium) and IBM SPSS Statistics version 21.0 (IBM, Armonk, New York, USA).

3 RESULTS

3.1 Comparison of baseline clinical characteristics and echocardiographic measurements at rest

The subjects consisted of 73 patients with coronary artery disease, 23 patients with hypertrophic cardiomyopathy, 20 patients with dilated cardiomyopathy, and 39 patients with other conditions. Among 155 patients, 128 patients were classified into the stay in IR group and 27 patients into the change to PN group. Median follow-up period was 17 months (1 - 36 months). No additional heart failure therapeutic drugs were administered during the study period.

Table 1 shows the comparison of clinical background between the two groups. There was no significant difference in baseline New York Heart Association (NYHA) functional class between

the two groups (P = 0.056). The change to PN group had significantly higher serum BNP level at baseline than the stay in IR group (114 ± 162 vs. 354 ± 389 pg/ml, P < 0.001). There was no significant difference in the other clinical characteristics and background diseases between the two groups, respectively. During the observation period, NYHA functional class was significantly increased in the change to PN group (1.6 ± 0.6 to 2.2 ± 1.0, P = 0.001), and the serum BNP level in the change to PN group also tended to be increased (354 ± 389 to 615 ± 831 pg/ml, P = 0.220).

Table 2 shows the comparisons of two-dimensional echocardiographic variables at baseline between the two groups. The patients in the change to PN group showed significantly higher LV end-diastolic volume index (P = 0.037), LV end-systolic volume index (P = 0.019), and LV mass index (LVMi, P = 0.011) compared with the stay in IR group. Patients in the change to PN group had significantly shorter DT (P = 0.045) and lower a' (P = 0.022) and PVS (P = 0.006) than those in the stay in IR group. There are no significantly difference in numbers of LVEF <50% between two groups (P=0.19). The diastolic dysfunction grades at baseline were significantly higher in the change to PN group than that in the stay in IR group (P = 0.043).

3.2 Effect of LPP on the echocardiographic parameters

Table 3 shows the comparisons of TMF variables during LPP between the two groups. In all the subjects, the E velocity and E/A ratio were significantly greater, and DT was significantly shorter (P <0.001) during LPP than these at rest. In the change to PN group, the A velocity during LPP was likely to decrease. On the other hand, in the stay in IR group, the A velocity during LPP was likely to increase. Consequently, ΔA (P <0.001) was smaller, and the ΔE/A ratio (P = 0.016) was greater in the change to PN group than these in the stay in IR group.

3.3 Relationship between clinical and echocardiographic parameters at baseline and development of PN

Table 4 shows the univariable and multivariable analysis for the association of change to PN.

Univariable analysis revealed that clinical variables such as LVMi (P = 0.036), a' (P = 0.011), E/e' ratio (P = 0.006), PVS (P = 0.026), diastolic dysfunction grade (P = 0.014), ΔA (P = 0.002), and ΔE/A ratio (P = 0.01) were associated with change to PN, which were independent of age. Multivariable analysis-adjusted age confirmed thatΔA (HR = 0.58 per 1SD; 95% CI = 0.39 - 0.88, P = 0.01) and a' (HR = 0.60 per 1 SD; 95% CI = 0.39 - 0.92, P = 0.02) were independent predictors of change to PN in patients with IR pattern at rest. The incremental benefit of the LPP echocardiographic parameter in the prediction of change to PN is shown in Figure 1. The addition of the ΔA to the conventional echocardiographic predictors (a', E/e', and diastolic dysfunction grade) improved the global chi-square results from 12.2 to 19.8 (P = 0.005), 13.5 to 19.2 (P = 0.016), and 11.7 to 18.9 (P = 0.004), respectively.

Receiver-operating characteristic curve analysis yielded a cutoff value of -7 cm/s for ΔA to distinguish between the change to PN and the stay in IR groups. The ΔA ≤ -7 cm/s could identify the patients in the change to PN group from patients in the stay in IR group with sensitivity of 48% and specificity of 83% (area under the curve: 0.68). Figure 2 illustrates the survival curves according to ΔA. Patients with ΔA ≤ -7 cm/s had significantly were more likely develop the PN pattern than patients with ΔA > -7 cm/s (P = 0.001).

4 DISCUSSION

We found that the ΔA, change of the TMF A velocity during the LPP, in patients with IR pattern was associated with the future development of PN pattern, which in turn represented worsening of heart failure. Patients with ΔA ≤ -7 cm/s more frequently developed to PN pattern than patients with ΔA >-7 cm/s. The progress in heart failure could not be predicted by any conventional resting echocardiographic parameters; thus, our preload stress echocardiography has the advantage in detecting only subtle pathologic changes in patients with early-stage heart failure. The effect of

preload stress echocardiography on the LV diastolic function had been evaluated by visual pattern change of TMF profile. This is the first study to show clinical usefulness of quantitative assessment of TMF pattern changed by the LPP.

4.1 Noninvasive evaluation of LV compliance

Assessment of LV diastolic dysfunction has been an integral part of Doppler echocardiographic examination, particularly for the diagnosis of heart failure. LV diastolic dysfunction leads to elevated LA pressure (i.e., left heart failure) due to the impairment of both active LV relaxation and passive LV compliance. The current gold standard of the LV relaxation is time constant of LV pressure decay (tau) and that of LV compliance is end-diastolic pressure-volume relationship obtained by conductance catheter with volume alteration. Because pressure-volume analysis by conductance catheter is too complicated for daily clinical routine practice, the assessment of LV diastolic compliance remains challenging. To address this problem, we had developed preload stress echocardiography using LPP (+90 mm Hg).[15] Using our technique, we could separate patients with preserved LV compliance and those with impaired LV compliance. There was a significant difference in diastolic dysfunction grade between both groups at baseline. However, because the difference is subtle, the grading was not useful for predicting future development of PN in patients with IR pattern.

4.2 Method for preload augmentation

Leg lifting and dextran infusion have been used for preload increment during echocardiography.[20-22] Dextran infusion stress was irreversible, and some complications occurred. Leg lifting is an easy noninvasive maneuver to increase preload stress. However, it is sometimes difficult to perform echocardiography with the patient in the supine position, especially in obese or elderly patients. Conversely, LPP can be performed on the left decubitus position and does not require an additional examiner to lift the legs. The LPP constantly provides a stable pressure to both lower limbs and

augment a stable preload stress. The preload stress is removed immediately when the switch is turned off. In our study, we could perform the LPP during echocardiography in all the subjects. It is a safe, reversible, and reproducible maneuver for increasing preload stress without increasing systemic blood pressure and heart rate.[15, 19)]

4.3 Hemodynamics in atrial-systole

The A velocity is determined by the pressure gradient between LV and LA during atrial systolic phase. Thus, the velocity is affected by both LVEDP and LA systolic function.[11, 23, 24)] In patients with impaired LV compliance, LVEDP was markedly elevated by the preload augmentation, which resulted in the reduction of the A velocity. Impairment of LA contraction also reduces the A velocity. In our study, the a' at baseline was smaller in the change to PN group than in the stay in IR group, and a' was a significant predictor of change to PN in the multivariable analysis. A previous study showed the E/A ratio was increased and LA reservoir and booster pump function were deteriorated during leg lifting in the patients with heart failure with preserved EF.[25-27)] The underlying LA dysfunction may also play some role in the response of TMF pattern to preload augmentation. The LA systolic function may be modulated by the increment of preload in part; however, we think the impact was much less than that of elevated LVEDP in early-stage heart failure patients.

4.4 Novelty of this study

Our subjects whose TMF pattern showed IR pattern were classified into less than diastolic dysfunction grade 2 (with normal LA pressure). In such patients, response of TMF pattern during LPP was the beneficial parameter for predicting their prognosis.[15)] In the preceding study, primary endpoints were death and/or hospitalization for heart failure, and we visually evaluated the change of pattern in TMF profile during LPP. The present study had two advanced points from our previous report. First, we set worsening of the resting TMF pattern (developing PN pattern) as the

surrogate endpoint of our observation. Because, we may be able to avoid adverse outcomes such as rehospitalization by additional medical intervention in such patients. Second, we tried to find a quantitative cutoff value for determining LPP's effect on the TMF pattern with the different subjects from our preceding study. We found that the ΔA< -7 cm group were more likely to develop the pre-specified event of change into PN pattern.

4.5 Clinical implication

The ΔA obtained by LPP echocardiography added incremental information to conventional echocardiographic findings for predicting future development of PN pattern in patients with early-stage heart failure with normal LA pressure. This information could affect the strategy of treatment in these patients and thus may improve the prognosis by early intervention and careful follow-up. We will perform the additional study to examine whether the therapeutic intervention can improve the prognosis for the IR patients whose A velocity was decreased ≥ -7 cm/s during LPP. Patients with heart failure with diastolic dysfunction grade 2 or less are not usually considered to be treated, and patients with NYHA Ⅲ or less described symptoms only with exertion and frequently no symptoms at resting state. Only stress echocardiography can reveal this early hemodynamic abnormality, which cannot be detected by resting echocardiography. Our LPP can be applied to overcome this issue instead of exercise echocardiography, which takes time and cost more than our LPP stress echocardiography.

4.6 Limitations

This was a single-center study, and the sample size was small, with relatively few events, which poses a potential risk of model over-fit. Although the ΔA ≤ -7 cm/s distinguished the patients in the change to PN group from those in the stay in IR group, the sensitivity was insufficient.

The second limitation is that the LPP echocardiography needs a special machine. The third limitation was that the patients with heterogeneous group of cardiac myopathies, including heart

failure with preserved and reduced EF, were recruited. However, it becomes advantage that our method can be applied regardless of differences in systolic function and morphology of the LV as well as regardless of heart failure with preserved and reduced ejection fraction. For example, it is known that the E/e' is influenced by the LV function and morphology and unable to estimate LV filling pressure in patients with normal ejection fraction or hypertrophy.28) The forth limitation is the lack of a validation cohort. The present study should be considered as hypothesis-generating, and we believe that larger multicenter studies, preferably divided into those with heart failure with reduced or preserved ejection fraction, are warranted to confirm our promising results.

5 CONCLUSIONS

The change in the A velocity by LPP (ΔA) could predict the future development of PN pattern in patients with early-stage heart failure whose TMF pattern showed IR pattern. The preload stress echocardiography, which can assess the changes in TMF pattern by the LPP, provides additional prognostic information beyond resting echocardiography in patients with early-stage heart failure.

DISCOLURE

None.

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FIGURE LEGENDS

FIGURE 1 Incremental prognostic value of preload stress echocardiographic parameters.

The addition of ΔA to the conventional echocardiographic predictors improve the global chi-square results.

ΔA , the change of peak atrial systolic transmitral flow velocity during leg positive pressure.

FIGURE 2 Kaplan-Meier analysis according to change in atrial systolic transmitral flow velocity by leg positive pressure (ΔA)

Orange line: $\Delta A \leq$-7 cm/s (13/35 [37%]); **blue line:** $\Delta A >$-7 cm/s (14/120 [12%]).

TABLE 1 Comparisons of baseline patients' characteristics between no-event and event groups

	All (n = 155)	**Stay in IR group (n = 128)**	**Change to PN group (n = 27)**	***P* value**
Age, yrs	68 ± 11	69 ± 10	63 ± 12	0.01
Male, n (%)	97 (63)	82 (64)	15 (56)	0.41
Body surface area, m^2	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.84
Heart rate, bpm	68 ± 13	67 ± 13	69 ± 14	0.50
Systolic blood pressure, mm Hg	130 ± 22	131 ± 22	128 ± 22	0.17
Diastolic blood pressure, mm Hg	71 ± 14	71 ± 14	70 ± 13	0.67
NYHA functional class	1.4 ± 0.6	1.4 ± 0.6	1.6 ± 0.6	0.056
B-type natriuretic peptide, pg/ml	193 ± 243	114 ± 162	354 ± 389	<0.001
Background diseases				
Coronary artery disease, n (%)	73 (47)	61 (48)	12 (44)	0.76
Hypertrophic cardiomyopathy, n (%)	23 (15)	18 (14)	5 (19)	0.56
Dilated cardiomyopathy, n (%)	20 (13)	17 (14)	3 (9)	0.76
Others, n (%)	39 (25)	32 (25)	7 (26)	0.92
Medications				
Diuretics, n (%)	48 (31)	37 (29)	11 (41)	0.23
Aldosterone antagonist, n (%)	28 (18)	21 (16)	7 (26)	0.24
ACE-I/ARB, n (%)	95 (61)	75 (57)	20 (74)	0.13
β-blocker, n (%)	86 (56)	67 (52)	19 (70)	0.089
Ca-antagonist, n (%)	57 (37)	50 (39)	7 (26)	0.20
History of PCI/CABG, n (%)	73 (47)	65 (51)	8 (30)	0.05
History of HF hospitalization, n (%)	37 (24)	29 (23)	8 (30)	0.43
Statin, n (%)	88 (57)	72 (56)	16 (59)	0.77
Anti-arrhythmic, n (%)	24 (15)	20 (16)	4 (15)	0.92
Aspirin, n (%)	75 (48)	64 (50)	11 (41)	0.38
Digitalis, n (%)	8 (5)	5 (4)	3 (11)	0.13

Values are n (%) or mean ± standard deviation. P <0.05, stay in IR group vs. change to PN group.

IR, impaired relaxation pattern; PN, pseudonormal pattern, NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft.

TABLE 2 Comparisons of baseline echocardiographic parameters between no-event and event groups.

	All (n = 155)	**Stay in IR group (n = 128)**	**Change to PN group (n = 27)**	***P* value**
LVEDVi, ml/m^2	66 ± 34	64 ± 27	79 ± 57	0.037
LVESVi, ml/m^2	34 ± 32	31 ± 24	47 ± 54	0.019
LVEF, %	54 ± 16	55 ± 15	50 ± 17	0.15
LVEF <50%, n (%)	52 (34)	40 (31)	12 (44)	0.19
LAVi, ml/m^2	38 ± 21	37 ± 23	38 ± 12	0.82
LVMi, g/m^2	142 ± 54	137 ± 49	166 ± 56	0.011
E, cm/sec	60 ± 16	59 ± 16	62 ± 15	0.39
DT, msec	236 ± 72	241 ± 75	210 ± 56	0.045
A, cm/sec	87 ± 22	87 ± 21	84 ± 22	0.55
E/A ratio	0.71 ± 0.15	0.75 ± 0.13	0.70 ± 0.16	0.12
e', cm/sec	5.8 ± 1.8	5.9 ± 1.8	5.5 ± 1.9	0.37
a', cm/sec	9.4 ± 2.0	9.5 ± 1.9	8.6 ± 2.2	0.022
E/e' ratio	11.1 ± 4.4	10.8 ± 4.2	12.6 ± 5.1	0.063
PVS, cm/sec	59 ± 15	60 ± 15	51 ± 16	0.006
PVD, cm/sec	37 ± 11	37 ± 11	37 ± 11	0.89
TRV, m/s	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.4	0.59
TAPSE, mm	19 ± 5	19 ± 4	21 ± 6	0.20
LV diastolic dysfunction grade Ⅰ / Ⅱ / Ⅲ	125/30/0	107/21/0	18/9/0	

Values are mean ± standard deviation. *P* <0.05, no-event group vs. event group.

LVEDVi, left ventricular end diastolic volume index; LVESVi, left ventricular end systolic volume index; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; E, peak early diastolic wave velocity; DT, deceleration time of early diastolic wave; A, peak atrial diastolic wave velocity; e', peak early diastolic mitral annular velocity; a', peak atrial systolic mitral annular velocity; PVS, systolic pulmonary venous flow velocity; PVD, diastolic pulmonary venous flow velocity; TR-PG, tricuspid regurgitation- pressure gradient; TAPSE, tricuspid annular plane systolic excursion.

TABLE 3 Effect of LPP on TMF variables

	All (n = 155)			Stay in IR group (n = 128)			Change to PN group (n = 27)			*P* value (Stay in RF vs. Change to PN group)
	rest	**LPP**	***P* value***	**rest**	**LPP**	***P* value***	**rest**	**LPP**	***P* value***	
E, cm/sec	60 ± 16	78 ± 21	< 0.001	59 ± 16	78 ± 21	< 0.001	62 ± 15	80 ± 20	< 0.001	
DT, msec	236 ± 72	202 ± 51	< 0.001	241 ± 75	206 ± 54	< 0.001	210 ± 56	189 ± 39	0.21	
A, cm/sec	87 ± 22	87 ± 23	0.74	87 ± 21	89 ± 23	0.41	84 ± 22	79 ± 22	0.36	
E/A ratio	0.71 ± 0.15	0.93 ± 0.26	< 0.001	0.75 ± 0.13	0.90 ± 0.26	< 0.001	0.70 ± 0.16	1.05 ± 0.25	< 0.001	
ΔE, cm/sec		18 ± 13			18 ± 13			17 ± 12		0.70
ΔDT, msec		-21 ± 58			-19 ± 61			-29 ± 42		0.54
ΔA, cm/sec		1 ± 11			2 ± 11			-6 ± 10		<0.001
ΔE/A ratio		0.22 ± 0.19			0.20 ± 0.19			0.30 ± 0.20		0.016

Values are mean ± standard deviation. The *P* values* were for comparisons between parameters at rest and them during the LPP.

ΔE, change of E velocity by the LPP; ΔDT, change of DT by the LPP; ΔA, change of A velocity by the LPP; ΔE/A ratio, change of E/A ratio by the LPP; other abbreviations as in Table 1, 2.

TABLE 4 Univariable and multivariable analysis for association of development of PN

Adjustment for Age	Univariable		Multivariable	
	Hazard Ratio (CI 95%)	***P* value**	**Hazard Ratio (CI 95%)**	***P* value**
Body surface area (per 1 SD)	0.81 (0.55-1.21)	0.31		
Heart rate (per 1 SD)	1.08 (0.75-1.55)	0.69		
Systolic blood pressure (per 1 SD)	0.75 (0.50-1.14)	0.18		
High B-type natriuretic peptide*	2.35 (0.93-5.96)	0.072		
LVEDVi (per 1 SD)	1.25 (0.98-1.61)	0.078		
LVESVi (per 1 SD)	1.26 (0.99-1.60)	0.055		
LVEF (per 1 SD)	0.80 (0.56-1.13)	0.21		
LAVi (per 1 SD)	1.39 (0.96-2.01)	0.083		
LVMi (per 1 SD)	1.35 (1.02-1.80)	0.036		
TMF-E (per 1 SD)	1.36 (0.91-2.03)	0.14		
TMF-DT (per 1 SD)	0.67 (0.42-1.05)	0.081		
TMF-A (per 1 SD)	1.02 (0.70-1.50)	0.92		
E/A ratio (per 1 SD)	1.27 (0.87-1.90)	0.23		
e' (per 1 SD)	0.74 (0.50- 1.10)	0.14		
a' (per 1 SD)	0.58 (0.38-0.89)	0.011	0.60 (0.39-0.92)	0.02
E/e' ratio (per 1 SD)	1.66 (1.16-2.37)	0.006		
PVS (per 1 SD)	0.59 (0.37-0.94)	0.026		
PVD (per 1 SD)	1.06 (0.72-1.56)	0.77		
TR-PG (per 1 SD)	1.31 (0.87-1.96)	0.20		
Diastolic dysfunction grade	2.80 (1.23-6.36)	0.014		
ΔE (per 1 SD)	1.04 (0.71-1.53)	0.85		
ΔDT (per 1 SD)	0.91 (0.56-1.46)	0.68		
ΔA (per 1 SD)	0.53 (0.35-0.79)	0.002	0.58 (0.39-0.88)	0.01
ΔE/A ratio (per 1 SD)	1.55 (1.11-2.16)	0.01		

* High B-type natriuretic peptide; over the median values of serum B-type natriuretic peptide level (the median values of serum B-type natriuretic peptide level: 109 pg/dl).

CI, confidence limits; other abbreviations as in Table 1, 2, 3.

Figure 1

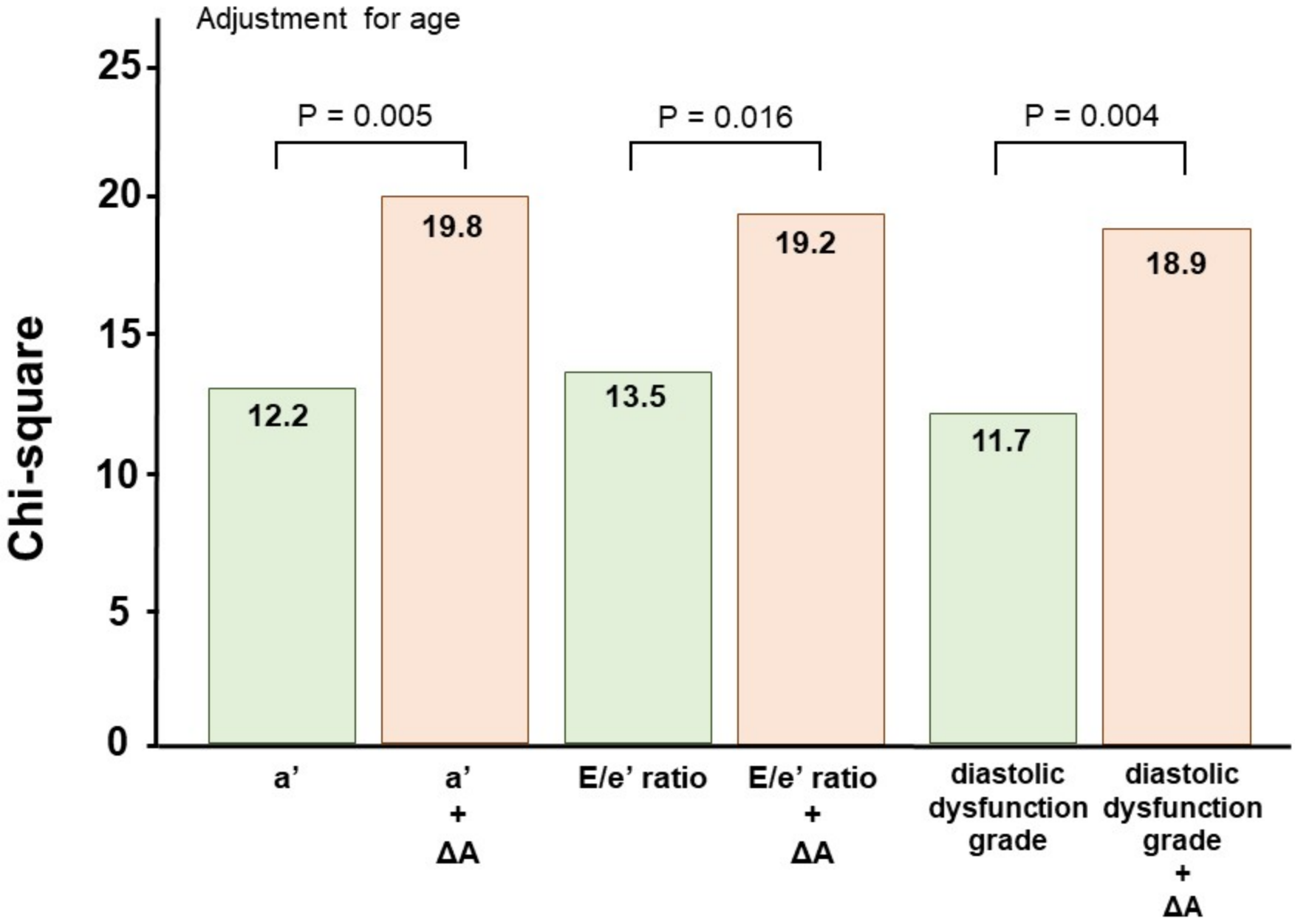
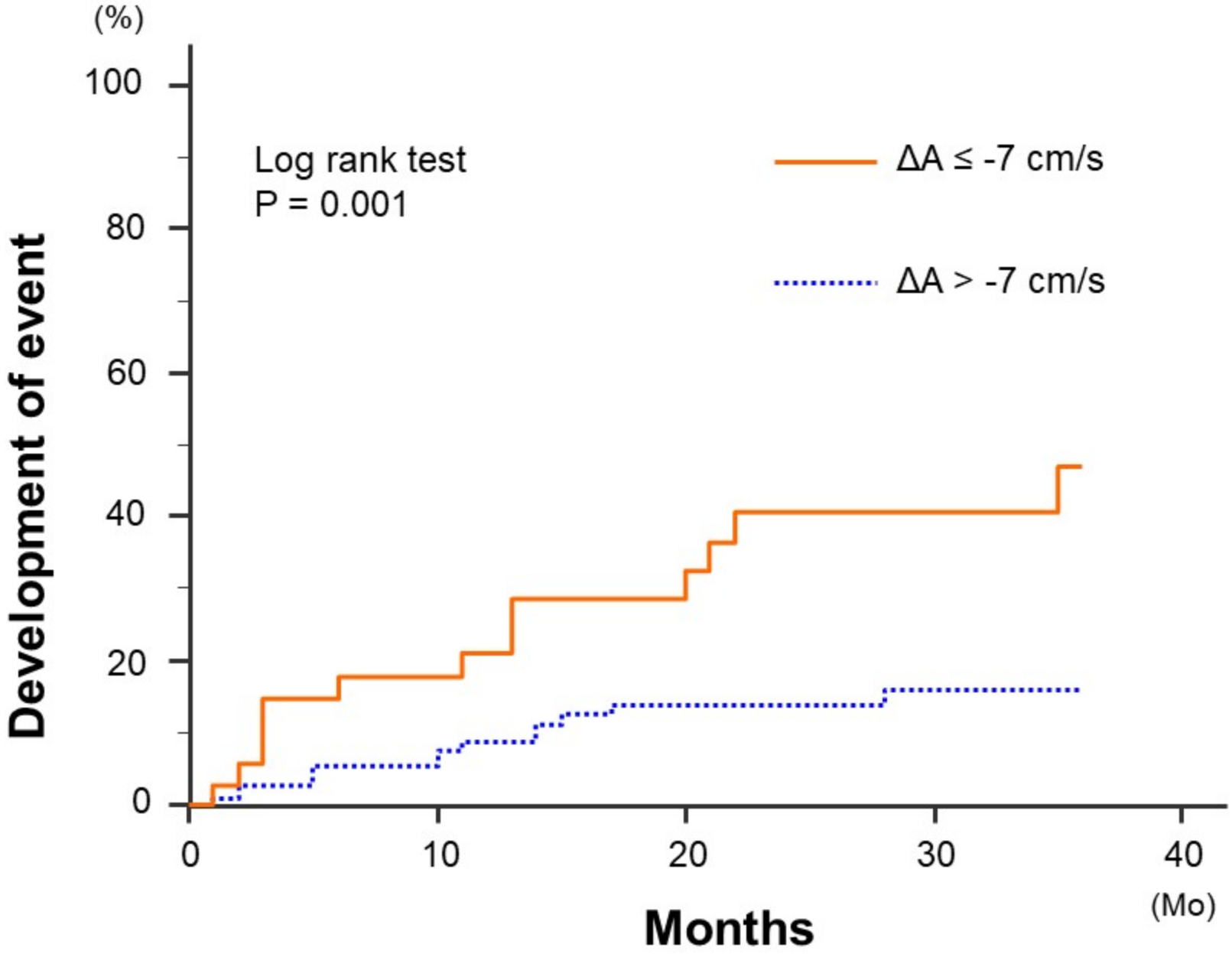

Adjustment for age
Chi-square
25
20
15
10
5
0
P = 0.005
P = 0.016
P = 0.004
12.2
19.8
13.5
19.2
11.7
18.9
a'
a' + ΔA
E/e' ratio
E/e' ratio + ΔA
diastolic dysfunction grade
diastolic dysfunction grade + ΔA

Figure 2


(%)
100
80
60
40
20
0
Development of event
Log rank test
P = 0.001
ΔA ≤ -7 cm/s
ΔA > -7 cm/s
0
10
20
30
40
(Mo)
Months