


# Clinical course and decision-making in heart failure by preload stress echocardiography: a preliminary study

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## Abstract

**Aims** Abnormal left ventricular diastolic response to preload stress can be an early marker of heart failure (HF). The aim of this study was to assess clinical course in patients with HF with preserved ejection fraction (HFpEF) who underwent preload stress echocardiography. In the subgroup analysis, we assessed the prognosis of patients with unstable signs during preload stress classified by treatment strategies.

**Methods and results** We prospectively conducted preload stress echocardiographic studies between January 2006 and December 2013 in 211 patients with HFpEF. Fifty-eight patients had abnormal diastolic reserve during preload stress (unstable impaired relaxation: unstable IR). Of 58 patients with unstable IR, 19 patients were assigned to additional therapy by increased or additional therapy and 39 patients were assigned to standard therapy. Composite outcomes were prespecified as the primary endpoint of death and hospitalization for deteriorating HF. During a median period of 6.9 years, 19 patients (33%) reached the composite outcome. Unstable group with standard therapy had significantly shorter event-free survival than stable group. Patients with uptitration of therapy had longer event-free survival than those with standard therapy group after adjustment of laboratory data (hazard ratio, 0.20, 95% confidence interval, 0.05–0.90;  $P = 0.036$ ); the 10 year event-free survival in patients with and without uptitration of therapy was 93% and 51%, respectively ( $P = 0.023$ ).

**Conclusions** Patients with unstable sign had significantly shorter event-free survival than patients with stable sign. After additional therapy, the prognosis of patients with unstable signs improved. This technique may impact decision-making for improving their prognosis.

**Keywords** Echocardiography; Diastolic dysfunction; Heart failure

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## Introduction

Identification of individuals at risk for heart failure (HF) brings preventive strategies and maximizes the benefit of interventions.<sup>1–3</sup> HF with preserved ejection fraction (HFpEF) currently represents around 50% of HF cases and is well known as a leading cause of morbidity and mortality. Due to the increasing prevalence of HFpEF and lack of evidence for medications, we need an effective assessment of HFpEF.<sup>4</sup> There is no room for doubt that echocardiographic examinations can be useful to clarify the aetiologies of HF and predict outcomes. Because HF often occurs even when the ejection fraction (EF) is normal, left ventricular (LV)

diastolic dysfunction plays a principal role in the management of this phenotype of HF.<sup>5</sup>

The mitral inflow pattern has been used to assess LV diastolic function. However, the mitral inflow pattern dynamically varies with a change in loading conditions. Several investigators showed that the responses of mitral inflow to nitroprusside or leg lifting identified subgroups of patients who have markedly different prognoses despite similar baseline mitral inflow patterns.<sup>6,7</sup> In our previous papers, we used leg-positive pressure (LPP) as an alternative technique for non-invasive preload augmentation, and we estimated the LV diastolic reserve by the change in mitral inflow pattern.<sup>8–11</sup> Impaired responses to an increment

during preload stress provided additional prognostic information to conventional echocardiographic parameters in HF.<sup>12,13</sup> Thus, abnormal LV diastolic response to preload stress can be an occult sign of HF. On the other hand, the effective treatment in HFpEF patients with unstable signs during preload stress is unclear, and a therapeutic option should be tested in further studies. There are few standards of care for HFpEF with LV diastolic dysfunction in the clinical setting. The renin-angiotensin-aldosterone system (RAAS) affects both blood pressure (BP) and volume by regulating vascular tone and sodium reabsorption, respectively.<sup>14,15</sup> Theoretically, the administration of RAAS inhibitors (RAASi) can inhibit HF progression. We hypothesized that additional RAASi might prevent future clinical worsening in HFpEF patients with unstable signs.

The aim of this study was to assess clinical course in patients with HFpEF who underwent preload stress echocardiography. In the subgroup analysis, we assessed the prognosis of patients with unstable signs during preload stress classified by treatment strategies.

## Methods

### Study population

We designed a prospective, single-centre, open-label, non-randomized trial of unstable impaired relaxation (IR) with uptitration of RAASi [angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB)]. We prospectively conducted preload stress echocardiographic studies between January 2006 and December 2013 in 211 patients with HFpEF for evaluation of their haemodynamic status. Patients with HFpEF were defined as having a clear history of HF with typical symptoms that were accompa-

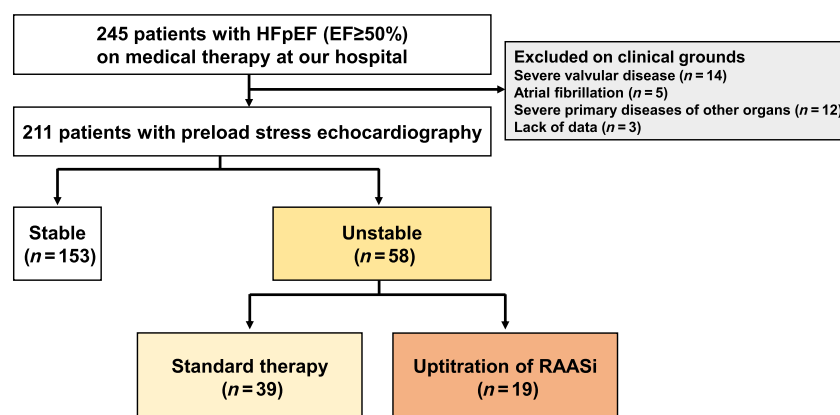
nied by signs, including pulmonary congestion by chest radiography and BNP elevation ( $\geq 35$  pg/mL), and an EF  $\geq 50\%$ .<sup>2,16–18</sup> Exclusion criteria were (i) moderate/severe aortic or mitral regurgitation or mitral stenosis; (ii) atrial fibrillation; (iii) severe primary diseases of other organs; and (iv) technically inadequate two-dimensional and Doppler echocardiograms. Seventy-seven patients had abnormal diastolic reserve during preload stress (unstable IR). Of 58 patients with unstable IR, 19 patients were assigned to additional therapy by increased or additional RAASi and 39 patients were assigned to standard therapy (Figure 1).

All patients with unstable IR were followed in our hospital according to the research protocol (follow-up visits at least every 3 months). Medications were selected after a discussion with the patients evaluating the BP (systolic BP: over 125 mmHg) for uptitrating RAASi (enalapril up to 10 mg/day or candesartan up to 8 mg/day) and benefits of treatment for unstable IR. In the additional therapy group, patients agreed to initiate or uptitrate RAASi to have a therapeutic option for preventing future cardiovascular (CV) events related to an abnormal response to preload stress. The medication dosage was maintained for patients with uptitration or additional therapy throughout the study period. The protocol was registered with the University Hospital Medical Information Network Clinical Trial Registry as UMIN000015915. This study was approved by the local ethics committee and Institutional Review Board of the University of Tokushima, and written informed consent was obtained from all subjects (protocol: 2550-2).

### Echocardiographic assessment

Transthoracic echocardiography was performed by experienced sonographers/doctors using a commercially available ultrasound machine. Measurements and recordings

**Figure 1** Patient selection. HFpEF, heart failure with preserved ejection fraction; IR, impaired relaxation; RAASi, renin-angiotensin-aldosterone system inhibitors.



were obtained according to the American Society of Echocardiography recommendations.<sup>19</sup> Mitral inflow was recorded from the apical long-axis or four-chamber view. The peak early diastolic (E) and peak atrial systolic (A) velocities were measured. The mitral annular motion velocity was recorded from the apical four-chamber view with a sample volume placed at the lateral and septal side of the mitral annulus using pulsed tissue Doppler echocardiography. Early diastolic peak velocity ( $e'$ ) was measured, and the ratio of E to averaged  $e'$  was calculated. All Doppler recordings were performed during an end-expiratory breath hold. The mean values of three consecutive cardiac cycles were used in the analysis.

### Preload stress echocardiography

Preload stress echocardiography is easily used to assess several CV diseases in the clinical setting.<sup>9,20–22</sup> We customized a commercially available leg-massage machine (Leg Compression System, Corona Industries LTD, Tokushima, Japan) and used a setting of 90 mmHg based on findings from our studies.<sup>8,11</sup> Doppler echocardiographic variables were obtained at baseline and during LPP. All patients tolerated 90 mmHg LPP without any complications. The LV diastolic dysfunction was divided into two categories according to changes in the mitral inflow and mitral annular velocity during LPP: Stable IR was defined as normal left atrial pressure (LAP) at rest and during LPP, and unstable IR was defined as normal LAP at rest and elevated LAP during LPP. LAP was defined on the basis of E/A (cut-off: 0.8 and 2), E wave velocity (cut-off: 50 cm/s), and averaged E/ $e'$  (cut-off: 14) using the recommendations (Figure 2).<sup>23</sup>

In our previous study, we have examined the haemodynamic study using 6 F high-fidelity manometer-tipped catheters. In patients with unstable IR, LV end-diastolic pressure increased from  $15.8 \pm 4.7$  to  $20.5 \pm 5.0$  mmHg and the E/A significantly increased from  $0.69 \pm 0.10$  to  $1.29 \pm 0.28$  during LPP (all  $P$  values  $< 0.05$ ).<sup>8</sup> Thus, the LPP can increase preload appropriately and the increased preload leads to changes of Doppler parameters in the clinical setting.

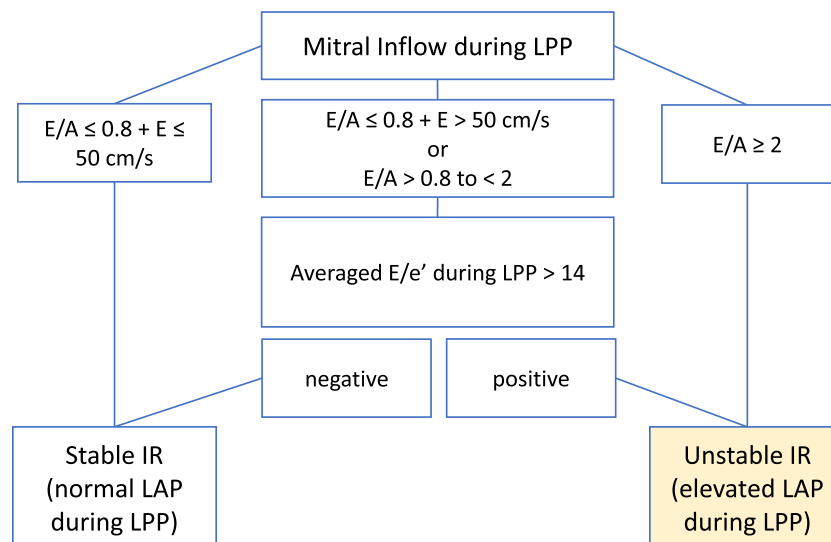
### Clinical outcomes

All patients were followed up at Tokushima University Hospital. They underwent follow-up visits at least every 3 months. The duration of follow-up was begun at the initial preload stress echocardiography and ended in May 2021. In cases where hospital visits were interrupted, patients' events were determined by telephone interview. The primary endpoint was a composite of hospitalization for deteriorating HF or CV death. Preload stress echocardiographic data were blinded to the attending physicians after initiation of this study.

### Statistical analysis

Data are presented as mean  $\pm$  standard deviation (SD). Data were tested for normality using the Kolmogorov–Smirnov test. Continuous variables were compared using an unpaired Student's  $t$ -test or Mann–Whitney  $U$  test as appropriate, whereas categorical variables were compared using the  $\chi^2$  test or Fisher's exact test, as appropriate. The association of clinical variables with the outcome was identified by Cox

**Figure 2** Flow chart to identify the stable and unstable impaired relaxation (IR). LAP, left atrial pressure; LPP, leg-positive pressure.



proportional-hazards models in univariate and multivariate analyses. A hazard ratio (HR) with a 95% confidence interval (CI) was calculated for each variable. The scaled Schoenfeld residuals for each independent variable were plotted against time to assess the assumption of proportional hazards; these correlations were found to be non-significant. Statistical analysis was performed using standard statistical software packages (SPSS Software 21.0, SPSS Inc, Chicago, IL, USA; MedCalc Software 17, Mariakerke, Belgium; R 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined by  $P < 0.05$ .

## Results

### Patient characteristics

Baseline characteristics of the study group were presented in *Table 1*. The study population consisted of 58 patients with unstable IR. In this cohort, 19 of 77 patients had been treated with an increased dose of RAASi ( $n = 11$ ) or the initiation of RAASi ( $n = 8$ ) at the next visit (within 1 month of the initial

echocardiographic study). Clinical background, echocardiographic variables, and haemodynamic parameters did not differ between patients with and without uptitration of RAASi except for E wave and E/A ratio. In patients with uptitration of RAASi, systolic BP was slightly decreased from  $131 \pm 16$  to  $125 \pm 16$  mmHg at follow-up. There was no difference in systolic BP between patients with and without uptitration of RAASi ( $130 \pm 25$  vs.  $125 \pm 14$  mmHg) at follow-up. We examined the follow-up preload stress echocardiography in 9 of 19 patients with uptitration of RAASi. At follow-up of preload stress echocardiography (median period:  $10 \pm 3$  months), eight of nine patients improved the response from unstable IR to stable IR, and one patient did not change response during preload stress.

### Changes of Doppler parameters during leg-positive pressure

Doppler parameters at rest and during LPP were shown in *Table 2*. The E wave, E/A, and E/e' ratios were significantly increased (all  $P < 0.05$ ) during LPP. BPs were also increased

**Table 1** Clinical characteristics

	All	Standard therapy	Uptitration of RAASi	P value
<i>N</i>	58	39	19	
Age (years)	67 ± 12	69 ± 11	63 ± 15	0.10
Male, <i>n</i> (%)	26 (45)	19 (49)	7 (37)	0.40
BSA (m <sup>2</sup> )	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	0.47
Heart rate (b.p.m.)	67 ± 16	69 ± 17	62 ± 11	0.24
Systolic BP (mmHg)	134 ± 23	133 ± 24	136 ± 20	0.76
<b>Clinical history</b>				
Hypertension, <i>n</i> (%)	41 (71%)	29 (74%)	12 (63%)	0.41
Hyperlipidaemia, <i>n</i> (%)	27 (47%)	18 (46%)	9 (47%)	0.93
ICM, <i>n</i> (%)	17 (29%)	11 (28%)	6 (32%)	0.80
<b>Medications</b>				
RAASi, <i>n</i> (%)	28 (48%)	18 (46%)	10 (53%)	0.65
Beta-blocker, <i>n</i> (%)	22 (38%)	14 (36%)	8 (42%)	0.66
Diuretics, <i>n</i> (%)	13 (22%)	10 (26%)	3 (16%)	0.38
Aldosterone antagonist, <i>n</i> (%)	3 (5%)	3 (8%)	0 (0%)	0.08
<b>Laboratory data</b>				
eGFR (mL/min/1.73 m <sup>2</sup> )	62 ± 22	59 ± 20	69 ± 24	0.13
BNP (pg/mL)	155 (76, 319)	115 (77, 242)	230 (56, 456)	0.13
<b>Echocardiographic parameters</b>				
LVEF (%)	63 ± 8	61 ± 8	65 ± 8	0.14
LVEDVi (mL/m <sup>2</sup> )	52 ± 16	54 ± 16	48 ± 16	0.16
LVESVi (mL/m <sup>2</sup> )	20 ± 9	21 ± 10	16 ± 7	0.06
LVMi (g/m <sup>2</sup> )	155 ± 51	148 ± 48	170 ± 55	0.16
LAVi (mL/m <sup>2</sup> )	33 ± 13	34 ± 14	33 ± 11	0.73
E (cm/s)	63 ± 15	65 ± 16	58 ± 12	0.07
A (cm/s)	88 ± 25	76 ± 14	88 ± 31	0.10
E/A	0.74 ± 0.14	0.76 ± 0.14	0.70 ± 0.13	0.10
e' (cm/s)	5.6 ± 1.9	5.7 ± 1.7	5.5 ± 2.4	0.79
E/e' ratio	12.8 ± 5.0	12.6 ± 4.1	13.4 ± 6.6	0.67
TR-V (m/s)	2.4 ± 0.3	2.4 ± 0.3	2.5 ± 0.3	0.19

*Note:* Data are presented as number of patients (percentage), mean ± standard deviation (SD), or median (interquartile range). Abbreviations: A, late diastolic transmitral flow velocity; BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular motion; eGFR, estimated glomerular filtration rate; ICM, ischaemic cardiomyopathy; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; RAASi, renin-angiotensin aldosterone system inhibitors; TR-V, tricuspid regurgitant velocity.

during LPP, and heart rates were not changed. L-wave (mid-diastolic forward flow velocity of mitral inflow) occurred in 11 patients with unstable IR during LPP.

### Unstable impaired relaxation on treatment

During a median period of 6.9 years, 19 patients (33%) reached the composite outcome. In the uptitration of RAASi group, two patients (11%) reached the composite outcome with one CV death and one HF admission. In the standard therapy group, 17 patients (44%) reached the composite outcome with 2 CV deaths and 15 HF admissions.

HRs of the relevant parameters were shown in *Table 3*. In univariate analysis, age (HR, 1.05;  $P = 0.05$ ), estimated glomerular filtration rate (eGFR) (HR, 0.98;  $P = 0.04$ ), and uptitration of RAASi (HR, 0.21;  $P = 0.03$ ) were associated with event-free survival. In multivariate Cox proportional-hazards models, uptitration of RAASi was independently associated with event-free survival (*Table 4*). The robustness on uptitration of RAASi was tested using two models, and

**Table 2** Changes of echocardiographic parameters during leg-positive pressure (LPP)

	Rest	LPP
E (cm/s)	63 ± 15	91 ± 17*
A (cm/s)	88 ± 25	94 ± 23
E/A	0.74 ± 0.14	1.00 ± 0.25*
e' (cm/s)	5.6 ± 1.9	5.4 ± 0.9
E/e'	12.8 ± 5.0	16.8 ± 3.2*
Systolic BP (mmHg)	134 ± 23	136 ± 24*
Heart rate (b.p.m.)	67 ± 16	67 ± 16

Abbreviations: See *Table 1*.

\* $P < 0.05$ , vs. rest.

**Table 3** Univariate associations of event

	Univariate model		
	HR	95% CI	$P$ value
Age	1.05	1.00–1.11	0.05
Male, %	0.84	0.32–2.18	0.72
Hypertension, $n$ (%)	1.13	0.40–3.17	0.82
Hyperlipidaemia, $n$ (%)	0.98	0.39–2.48	0.97
ICM, $n$ (%)	1.87	0.72–4.84	0.20
eGFR (mL/min/1.73 m <sup>2</sup> )	0.98	0.95–0.99	0.04
Log BNP	1.53	0.52–4.51	0.44
LVEF (%)	0.98	0.92–1.04	0.55
LVEDVi (mL/m <sup>2</sup> )	1.01	0.98–1.04	0.64
LVESVi (mL/m <sup>2</sup> )	1.03	0.98–1.08	0.34
LVMi (g/m <sup>2</sup> )	1.00	0.99–1.01	0.66
LAVi (mL/m <sup>2</sup> )	1.01	0.97–1.05	0.57
E (cm/s)	1.03	0.99–1.06	0.08
A (cm/s)	1.01	0.99–1.03	0.29
E/A	4.83	0.19–122.5	0.34
e' (cm/s)	0.89	0.69–1.16	0.39
E/e' ratio	1.05	0.95–1.16	0.37
TR-V (m/s)	2.70	0.78–9.39	0.12
Uptitration vs. standard therapy	0.21	0.05–0.92	0.03

Abbreviations: See *Table 1*. CI, confidence interval; HR, hazard ratio.

uptitration of RAASi had a consistently significant association with event-free survival in every model, and HRs were similar.

*Figure 3* shows the time to event of patients stratified according to stable group and unstable group with standard therapy. Unstable group with standard therapy had significantly shorter event-free survival than stable group; the 10 year event-free survival in stable group and unstable group with standard therapy was 86% and 51%, respectively ( $P < 0.001$ ).

*Figure 4* shows the time to event of patients stratified according to standard or uptitration of RAASi groups. Patients with uptitration of RAASi had longer event-free survival than those with standard therapy group after adjustment of eGFR (HR, 0.20, 95% CI, 0.05–0.90;  $P = 0.036$ ); the 10 year event-free survival in patients with and without uptitration of RAASi was 93% and 51%, respectively ( $P = 0.023$ ). *Table 5* shows the BPs at baseline and follow-up with or without outcomes. There is no difference of systolic BP at baseline and follow-up between patients with outcome and without outcome. Three patients did not reach the target dose of RAASi due to hypotension (BP < 100 mmHg,  $n = 1$ ), dizziness ( $n = 1$ ), and fatigue ( $n = 1$ ).

## Discussion

We demonstrated that 58 of 211 HFpEF patients with Grade I diastolic dysfunction had impaired LV diastolic reserve (unstable) by preload stress echocardiography. Patients with unstable IR had significantly shorter event-free survival than patients with stable IR. In addition, patients with unstable IR who had additional treatment had longer event-free survival than those with standard therapy. To our knowledge, this is the first study to suggest a clinical potential of early intervention in patients with unstable IR based on preload stress echocardiography to improve their outcomes.

### Impaired left ventricular diastolic reserve

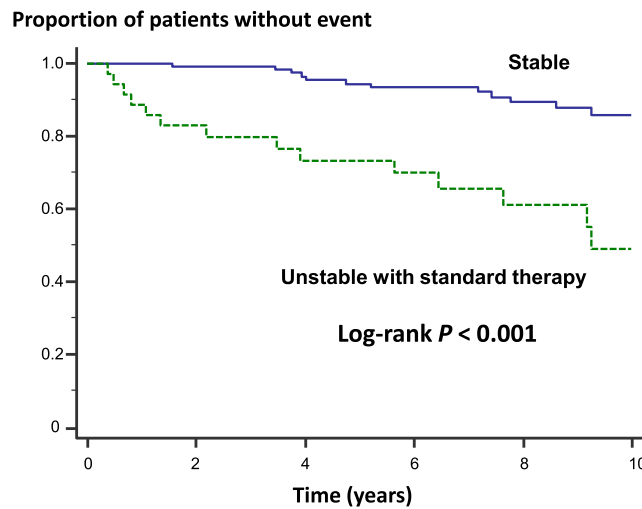
The management of the HF remains a matter of debate. The large capacity of haemodynamic circulation indicates that HF is usually diagnosed late in its course, and an asymptomatic stage precedes the onset. Patients with HF at an early stage may present with almost normal resting haemodynamics but show an abnormal response to stress by an increase in blood flow.<sup>24,25</sup> From the perspective of haemodynamics during preload stress, the clinical utility of mitral inflow assessment has previously been described in several studies.<sup>6,7</sup> LV diastolic reserve assessed by mitral inflow was associated with clinical outcomes compared with resting echocardiographic parameters. In the previous study, we showed that patients with unstable IR based on mitral inflow assessment during preload stress had significantly shorter event-free sur-

**Table 4** Multivariate associations of event

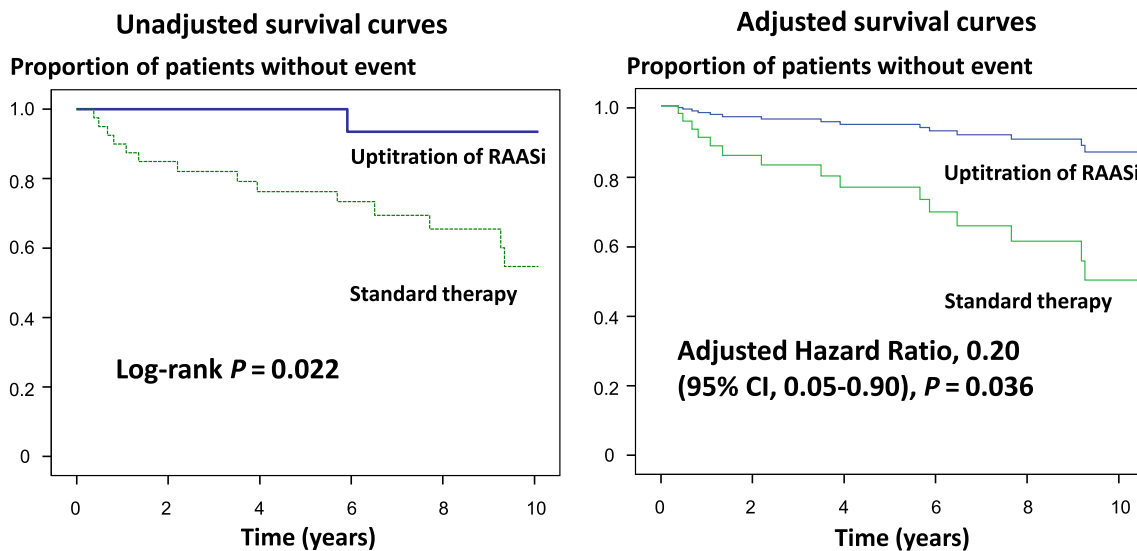
	Model 1 ( $\chi^2$ : 7.6)			Model 2 ( $\chi^2$ : 7.3)		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.05	0.99–1.11	0.08	0.98	0.95–1.01	0.15
eGFR (mL/min/1.73 m <sup>2</sup> )						
Uptitration vs. standard therapy	0.24	0.04–0.99	0.048	0.20	0.05–0.90	0.036

Abbreviations: See Tables 1 and 3.

**Figure 3** Survival curves in unstable group with standard therapy and stable group.



**Figure 4** Unadjusted and adjusted survival curves in patients with and without uptitration of RAASi (renin-angiotensin-aldosterone system inhibitors). CI, confidence interval.



**Table 5** Blood pressures at baseline and follow-up with or without outcomes

	Standard therapy (n = 39)	Uptitration of RAASi (n = 19)	P value
At baseline			
Systolic BP (mmHg)	132 ± 23	131 ± 16	0.82
Systolic BP in patients with outcomes (mmHg)	136 ± 25	129 ± 14	0.14
Systolic BP in patients without outcomes (mmHg)	130 ± 20	132 ± 16	0.75
At follow-up			
Systolic BP (mmHg)	130 ± 25	125 ± 14	0.31
Systolic BP in patients with outcomes (mmHg)	134 ± 27	122 ± 18	0.13
Systolic BP in patients without outcomes (mmHg)	129 ± 24	126 ± 15	0.70
Dose level at follow-up, no. (%)			
50% (5 mg enalapril or 4 mg candesartan)	—	3 (16)	
100% (10 mg enalapril or 8 mg candesartan)	—	16 (84)	

Note: Maximal dose indicates for Japanese population. Abbreviations: See Table 1.

vival than with stable IR.<sup>8</sup> Most resting echocardiographic measures were similar between the stable IR and unstable IR groups. This emphasizes the importance of stress echocardiography to identify unstable IR. The mechanism of mitral inflow changes by preload stress has been well explained.<sup>26</sup> Preload stress can augment venous return and lead to a rightward shift of LV filling volume on an end-diastolic pressure–volume relationship (EDPVR). Patients with low operant stiffness did not show marked changes in Doppler profile after preload intervention (low operant stiffness, stable IR). Patients with low operant stiffness occurred on the flat portion of the EDPVR. Patients with high operating stiffness had a changed mitral inflow profile showing PN (unstable IR; high operant stiffness). The non-invasive assessment of EDPVR should be examined to assess operant stiffness in further studies.

### Treatment for left ventricular diastolic reserve

HF guidelines recommend that we distinguish between HF with reduced ejection fraction (HFrEF) and HFpEF because the two groups have different treatment options.<sup>3</sup> Although ACEi/ARB agents are effective in HFrEF, clear evidence was not observed in HFpEF.<sup>27</sup> Thus, the target of RAASi should be reconsidered especially in HFpEF practice. Generally, it has been shown that lowering BP can reduce the risk of HF hospitalizations.<sup>28</sup> In our cohort, additional RAASi have improved the prognosis of HFpEF with unstable condition during preload stress. LV diastolic reserve has been implicated as a potential contributor to the development of cardiac dysfunction in patients with early phase HF. In our cohort, based upon attending physician decision, many of our patients were treated with an increased dose of RAASi. The increased dose of RAASi can lead to decreased BP. Thus, one possible explanation of the mechanism was that the lower BP can mainly influence our results. In our data, the systolic BP was significantly decreased after the initiation of additional therapies. At follow-up of preload stress echocardiography, 82% of patients improved the response from unstable IR to stable IR

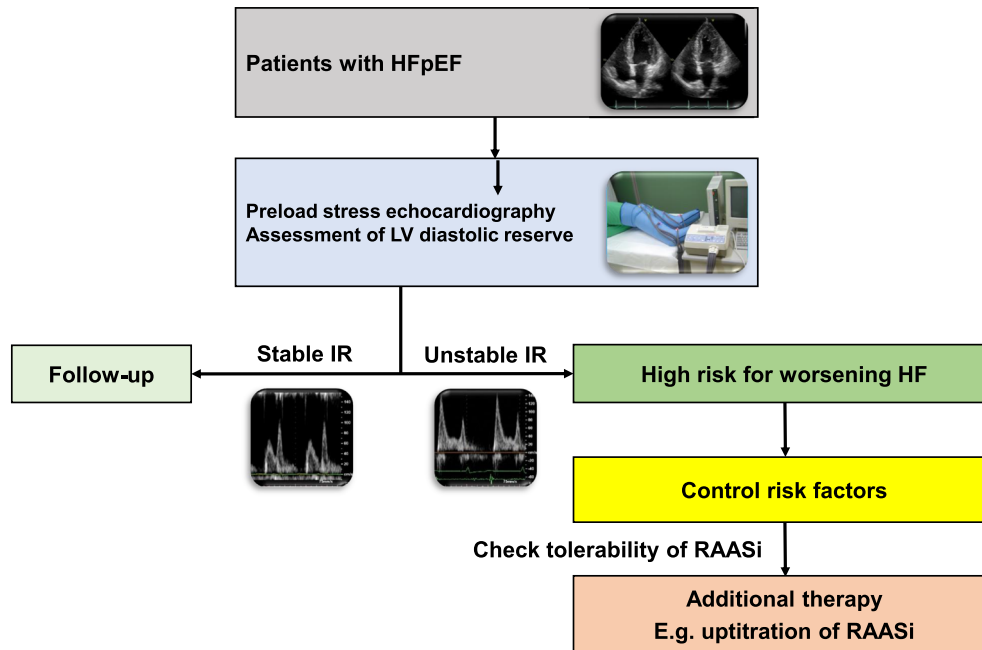
in the additional therapy group. Thus, the data support the hypothesis. Unfortunately, our population is too small to compare types of RAASi. A future randomized controlled study comparing the prognosis differences in patients with impaired cardiac reserve is warranted. Another explanation of the mechanism was that the presence of coronary artery disease (CAD) (around 40% of patients) could have explained the beneficial effect of RAAS administration because of augmented wall tension with LPP and subsequently subendocardial ischemia.

Overactivation of the RAAS associated with myocardial fibrosis is thought to be one of the pathogenic mechanisms of diastolic HF.<sup>29</sup> Angiotensin II and aldosterone also increase inflammatory cytokines causing endothelial myocardium injury.<sup>30</sup> In this study, although there was no difference in BP between patients with and without uptitration of RAASi, patients with uptitration of RAASi had a more favourable prognosis. Uptitration of RAASi to patients with unstable signs may balance the RAAS and decrease inflammatory cytokines, independent of a decrease in BP.

### Clinical implications

In our study, unstable condition during preload augmentation was related to the CV events, and we can use this condition as an early marker of subclinical LV diastolic dysfunction. From our subgroup analysis, the patients with uptitration of RAASi were associated with better outcomes than those without uptitration of RAASi. Figure 5 shows a potential approach using preload stress echocardiography in HFpEF. Preload stress echocardiography can be considered to assess LV cardiac reserve. In our results, not only stress echocardiography but also clinical backgrounds were the important factors for the primary endpoint. Therefore, we should assess and control risk factors before considering therapeutic intervention. When we consider the additional therapy, we should also check the tolerability or RAASi by BP and kidney function.

**Figure 5** Potential approach to abnormal response by preload stress in HFpEF. Although findings of this study support the selection for treatment based on the findings of imaging surveillance, definitive multicentre prospective evaluation is required. HFpEF, heart failure with preserved ejection fraction; IR, impaired relaxation; LV, left ventricular; RAASi, renin-angiotensin-aldosterone system inhibitors.



## Limitations

This is a non-randomized study and has potential flaws relating to selection bias, unmeasured covariates, and non-random allocation to treatment. We did not use the tricuspid valve regurgitant velocity during preload stress for the classification, because data were limited, and it would be more clinically useful to make a simple classification. In the further study, the tricuspid valve regurgitant velocities during preload stress will be assessed for the clinical setting. Because follow-up stress echocardiography was not prespecified in the protocol, the lack of follow-up stress echocardiographic data in all patients is another limitation. We prospectively conducted preload stress echocardiographic studies between January 2006 and December 2013. Because evidences of prognostic values were not established during this period, only 32% of patients with unstable IR pattern agree to the treatment changed. Although there is no difference of physicians' type between standard therapy and uptitration of RAASi, the physicians' experience may affect the results. In our country, where most of the population is Asian, the upper limit of RAASi is set lower than the Western standard. Even if recent sodium-glucose cotransporter (SGLT)-2 inhibitors can improve the prognosis in HFpEF, there was no patient with SGLT-2 inhibitors in this cohort due to the inclusion period of this study (between January 2008 and December 2013). Although the treatment will be, in principle and if possible, unchanged during the interval, the other

medications might affect on outcomes in this study. Unfraternally, we did not gather the detail of medication modifications during the study period. According to these limitations, especially the treatment part of this study should be considered as hypothesis-generating. We believe that larger prospective multicentre studies are warranted.

## Conclusions

Patients with unstable IR had significantly shorter event-free survival than patients with stable IR. This technique is potentially more practical than other stress echocardiography methods and may impact decision-making for medications in HFpEF.

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## Conflict of interest

None declared.



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## References

- Bozkurt B, Hershberger RE, Butler J, Grady KL, Heidenreich PA, Isler ML, Kirklin JK, Weintraub WS. 2021 ACC/AHA key data elements and definitions for heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). *J Am Coll Cardiol*. 2021; **77**: 2053–2150. PubMed PMID: 33250265. Epub 2020/12/01.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; **37**: 2129–2200. PubMed PMID: 27206819. Epub 2016/05/22.
- Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, Kitakaze M, Kinugawa K, Kihara Y, Goto Y, Komuro I, Saiki Y, Saito Y, Sakata Y, Sato N, Sawa Y, Shiose A, Shimizu W, Shimokawa H, Seino Y, Node K, Higo T, Hirayama A, Makaya M, Masuyama T, Murohara T, Momomura SI, Yano M, Yamazaki K, Yamamoto K, Yoshikawa T, Yoshimura M, Akiyama M, Anzai T, Ishihara S, Inomata T, Imamura T, Iwasaki YK, Ohtani T, Onishi K, Kasai T, Kato M, Kawai M, Kinugasa Y, Kinugawa S, Kuratani T, Kobayashi S, Sakata Y, Tanaka A, Toda K, Noda T, Nochioka K, Hatano M, Hidaka T, Fujino T, Makita S, Yamaguchi O, Ikeda U, Kimura T, Kohsaka S, Kosuge M, Yamagishi M, Yamashina A, Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure—digest version. *Circ J*. 2019; **83**: 2084–2184. PubMed PMID: 31511439. Epub 2019/09/13.
- Othman F, Abushahba G, Salustri A. Adherence to the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations for the evaluation of left ventricular diastolic function by echocardiography: a quality improvement project. *J Am Soc Echocardiogr*. 2019; **32**: 1619–1621. PubMed PMID: 31668767. Epub 2019/11/02.
- Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014; **11**: 507–515. PubMed PMID: 24958077. Epub 2014/06/25.
- Pozzoli M, Traversi E, Cioffi G, Stenner R, Sanarico M, Tavazzi L. Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. *Circulation*. 1997; **95**: 1222–1230. PubMed PMID: 9054853. Epub 1997/03/04.
- Ishizu T, Seo Y, Kawano S, Watanabe S, Ishimitsu T, Aonuma K. Stratification of impaired relaxation filling patterns by passive leg lifting in patients with preserved left ventricular ejection fraction. *Eur J Heart Fail*. 2008; **10**: 1094–1101. PubMed PMID: 18755627. Epub 2008/08/30.
- Yamada H, Kusunose K, Nishio S, Bando M, Hotchi J, Hayashi S, Ise T, Yagi S, Yamaguchi K, Iwase T, Soeki T, Wakatsuki T, Sata M. Pre-load stress echocardiography for predicting the prognosis in mild heart failure. *JACC Cardiovasc Imaging*. 2014; **7**: 641–649. PubMed PMID: 24954460. Epub 2014/06/24.
- Kusunose K, Yamada H, Nishio S, Torii Y, Hirata Y, Seno H, Saijo Y, Ise T, Yamaguchi K, Yagi S, Soeki T, Wakatsuki T, Sata M. Preload stress echocardiography predicts outcomes in patients with preserved ejection fraction and low-gradient aortic stenosis. *Circ Cardiovasc Imaging*. 2017; **10**: e006690. PubMed PMID: 29021259. Epub 2017/10/13.
- Saijo Y, Yamada H, Kusunose K, Bando M, Nishio S, Torii Y, Hirata Y, Seno H, Matsuura T, Ise T, Tobiume T, Yamaguchi K, Yagi S, Soeki T, Wakatsuki T, Sata M. A clinical application of pre-load stress echocardiography for predicting future hemodynamic worsening in patients with early-stage heart failure. *Echocardiography*. 2018; **35**: 1587–1595. PubMed PMID: 30005132. Epub 2018/07/14.
- Kusunose K, Yamada H, Nishio S, Tamai R, Niki T, Yamaguchi K, Taketani Y, Iwase T, Soeki T, Wakatsuki T, Sata M. Interval from the onset of transmitral flow to annular velocity is a marker of LV filling pressure. *JACC Cardiovasc Imaging*. 2013; **6**: 528–530.
- Matsumoto K, Onishi A, Yamada H, Kusunose K, Suto M, Hatani Y, Matsuzoe H, Tatsumi K, Tanaka H, Hirata KI. Non-invasive assessment of preload reserve enhances risk stratification of patients with heart failure with reduced ejection fraction. *Circ Cardiovasc Imaging*. 2018; **11**: e007160. PubMed PMID: 29748312. Epub 2018/05/12.
- Kusunose K, Yamada H, Saijo Y, Nishio S, Hirata Y, Ise T, Yamaguchi K, Fukuda D, Yagi S, Soeki T, Wakatsuki T, Sata M. Preload stress echocardiography for the assessment of heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging*. 2021; **15**: 375–378.
- Ruiz-Hurtado G, Ruilope LM. Cardiorenal protection during chronic renin-angiotensin-aldosterone system suppression: evidences and caveats. *Eur Heart J Cardiovasc Pharmacother*. 2015; **1**: 126–131. PubMed PMID: 27533982. Epub 2015/04/01.
- Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med*. 2019; **33**: 363–382. PubMed PMID: 30806496. Pubmed Central PMCID: PMC6430926. Epub 2019/02/27.
- Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen D, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019; **381**: 1609–1620. PubMed PMID: 31475794. Epub 2019/09/03.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinnlay SM. Spironolactone for heart failure with

- preserved ejection fraction. *N Engl J Med*. 2014; **370**: 1383–1392. PubMed PMID: 24716680. Epub 2014/04/11.
18. Zile MR, Jhund PS, Baicu CF, Claggett BL, Pieske B, Voors AA, Prescott MF, Shi V, Lefkowitz M, McMurray J, Solomon SD, Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) Investigators. Plasma biomarkers reflecting profibrotic processes in heart failure with a preserved ejection fraction: data from the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Study. *Circ Heart Fail*. 2016; **9**: e002551. PubMed PMID: 26754625. Pubmed Central PMCID: PMC5485256. Epub 2016/01/13.
  19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015; **28**: 1–39.e14. PubMed PMID: 25559473. Epub 2015/01/07. eng.
  20. Kusunose K, Yamada H, Nishio S, Ishii A, Hirata Y, Seno H, Saijo Y, Ise T, Yamaguchi K, Yagi S, Soeki T, Wakatsuki T, Sata M. RV myocardial strain during pre-load augmentation is associated with exercise capacity in patients with chronic HF. *JACC: Cardiovascular Imaging*. 2017; **10**: 1240–1249.
  21. Kusunose K. Clinical application of stress echocardiography in management of heart failure. *Heart Fail Clin*. 2020; **16**: 347–355.
  22. Kusunose K, Seno H, Yamada H, Nishio S, Torii Y, Hirata Y, Saijo Y, Ise T, Yamaguchi K, Fukuda D, Yagi S, Soeki T, Wakatsuki T, Sata M. Right ventricular function and beneficial effects of cardiac rehabilitation in patients with systolic chronic heart failure. *Can J Cardiol*. 2018; **34**: 1307–1315.
  23. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *European Heart Journal-Cardiovascular Imaging*. 2016; **17**: 1191–1229.
  24. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010; **3**: 588–595. PubMed PMID: 20543134. Pubmed Central PMCID: PMC3048586. Epub 2010/06/15.
  25. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018; **6**: 665–675. PubMed PMID: 29803552. Pubmed Central PMCID: PMC6076329. Epub 2018/05/29.
  26. Böhm M, Reil J-C. Stiff by stress: operant LV diastolic stiffness assessed with pre-load stress echocardiography. American College of Cardiology Foundation, Washington, DC; 2014, Stiff by Stress.
  27. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld JA, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021; **77**: 772–810. PubMed PMID: 33446410. Epub 2021/01/16.
  28. Oh GC, Cho HJ. Blood pressure and heart failure. *Clin Hypertens*. 2020; **26**: 1 PubMed PMID: 31908841. Pubmed Central PMCID: PMC6939331. Epub 2020/01/08.
  29. Gerdes AM. Cardiac myocyte remodeling in hypertrophy and progression to failure. *J Card Fail*. 2002; **8**: S264–S268.
  30. Luther JM, Gainer JV, Murphey LJ, Yu C, Vaughan DE, Morrow JD, Brown NJ. Angiotensin II induces interleukin-6 in humans through a mineralocorticoid receptor-dependent mechanism. *Hypertension*. 2006; **48**: 1050–1057.