Pressure-flow Responses to Exercise in Heart Failure Treated with Angiotensin Receptor Neprilysin Inhibitor

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Background: The role of the angiotensin receptor neprilysin inhibitor (ARNI) in cardiac function, particularly its impact on pulmonary circulation, remains underexplored. Recent studies have described abnormal mean pulmonary artery pressure (mPAP)-cardiac output (CO) responses as having the potential to assess the disease state. The aim of this study was to assess the effects of ARNI on pulmonary circulation in heart failure. We measured echocardiographic parameters post 6-minute walk (6MW) and compared the changes with baseline and follow-up. Our hypothesis was that pulmonary pressure-flow relationship of the pulmonary circulation obtained by 6MW stress echocardiography would be improved with treatment.

Methods: We prospectively enrolled 39 heart failure patients and conducted the 6MW test indoors. Post-6MW echocardiography measured echocardiographic variables, and CO was derived from electric cardiometry. Individualized ARNI doses were optimized, with follow-up echocardiographic evaluations after 1 year.

Results: Left ventricular (LV) volume were significantly reduced (160.7±49.6ml vs 136.0±54.3ml, P<0.001), and LV ejection fraction was significantly improved (37.6±11.3% vs 44.9±11.5%, P<0.001). Among the 31 patients who underwent 6MW stress echocardiographic study at baseline and 1 year later, 6MW distance increased after treatment (380m vs 430m, P=0.002). The ΔmPAP/ΔCO by 6MW stress decreased with treatment (6.9mmHg/L/min vs 2.8mmHg/L/min, P=0.002). The left atrial volume index was associated with the response group receiving ARNI treatment for pulmonary circulation.

Conclusions: Initiation of ARNI was associated with improvement of left ventricular size and LVEF. Additionally, the 6MW distance increased and the ΔmPAP/ΔCO was improved to within normal range with treatment.

Introduction

Heart failure (HF) constitutes a critical issue in global health, affecting an estimated 26 million individuals globally and contributing to substantial morbidity, mortality, and healthcare expenditures.[1] In Japan, this condition is particularly alarming due to its impact on about 1.5 million individuals and the aging population, which intensifies its prevalence.[2] While clinical trials have substantiated that treatments for heart failure with reduced ejection fraction (HFrEF) improve clinical outcomes, the specific role of angiotensin receptor neprilysin inhibitor (ARNI) in cardiac function is not fully elucidated.[3] Several pieces of evidence suggest ARNI's pivotal role in rectifying imbalances in the renin angiotensin aldosterone system (RAAS) and neprilysin (NP) systems, demonstrating efficacy in left HF.[4, 5] Furthermore, basic research also denotes ARNI capability as a guanylyl cyclase activator that enhances natriuretic peptides, signaling through cyclic guanosine monophosphate (cGMP) and exerting substantial antimitogenic and vasodilatory effects.[6-8] Experimental findings, such as its potential role in reducing pulmonary vascular remodeling in pulmonary hypertension rat models, underscore its promise on pulmonary circulation.[9] These preliminary findings accentuate the need for robust human studies to authenticate these observations.

Recent studies have shown that exercise echocardiography can provide detailed examination of cardio-pulmonary function even when resting filling pressures appear

normal.[10-12] Various stress-testing methods have gained traction in clinical settings; among these, the 6-minute walk (6MW) test stands out as uncomplicated, cost-effective, and broadly implemented. [13, 14] Previous research has indicated that the pressure-volume relationship during exercise—measured via the change in mean pulmonary artery pressure (mPAP) divided by the change in cardiac output (CO) using 6MW stress echocardiography correlates with cardiovascular events in LV dysfunction and systemic sclerosis.[15-19] This link between pulmonary circulation and such events positions this metric as a reliable gauge of hemodynamic responses in heart failure. Despite these advancements, a noticeable gap persists in understanding the hemodynamic influence of ARNI on pulmonary circulation within the context of HF. This investigation aims to assess the effects of maximum tolerated dose of ARNI on pulmonary circulation measured using a stress echocardiography in chronic heart failure patients.

Materials and Methods

Study population. We designed a prospective, single-center, open-label trial of stress echocardiography with ARNI (**Figure 1**). All patients have a history of hospitalization for heart failure. In this study, all patients were titrated up to the maximum dose of ARNI during the study. To ensure a safe introduction of the treatment, ARNI was initiated when the condition of HF was controlled (NYHA II or III) with the other medications before starting the therapy. The attending physician made every effort to avoid changes to medications other

than ARNI during the study period. The study population consisted of patients with HF without well preserved ejection fraction (<60%) undergoing 6MW stress echocardiography for evaluation of their hemodynamic status between September 2020 and December 2021. Exclusion criteria were: (1) 18 years of age and younger; (2) symptomatic hypotension; (3) severe primary diseases of other organs; (4) unacceptable side effects when receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; and (5) technically inadequate 2-dimensional and Doppler echocardiograms. 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: 3828-1).

Echocardiographic assessment. We planned that transthoracic echocardiography was performed before the start of ARNI and one year after the start of maximum tolerated dose by experienced sonographers/doctors using a commercially available ultrasound machine (Vivid E9, GE Vingmed, Horten, Norway). The measurements and recordings were obtained according to the recommendations of the American Society of Echocardiography.[20] Systolic PAP was measured from the maximal continuous-wave Doppler velocity of the tricuspid regurgitant jet using the systolic trans-tricuspid pressure gradient calculated by the modified Bernoulli equation. Right atrial pressure was estimated from the inferior vena cava diameter and collapsibility.[21] Mean PAP was calculated as 0.6×systolic PAP+2.[22] Peak systolic longitudinal strain measurements were obtained from gray-scale images recorded in

the apical four-chamber, two-chamber, and long-axis views. The frame rate was maintained at >40 frame/s. All the measurements of strain were analyzed offline using speckle tracking vendor-independent software (EchoPAC PC software, GE Vingmed, Horten, Norway). Global longitudinal strain (GLS) was calculated by averaging all the segmental strain values from the apical four-chamber, two-chamber, and long-axis views.

Six-minute walk stress echocardiography. **Online supplemental clip** shows the Six-minute walk (6MW) stress echocardiography. The 6MW tests were performed according to the American Thoracic Society guidelines.[23] Transcutaneous arterial oxygen saturation was determined by pulse oximetry. The peak tricuspid regurgitation jet observed by echocardiography was obtained immediately after the 6MW test in the supine position (i.e., within 10 seconds). CO was also determined at the same time using electric cardiometry (Aesculon Electrical Velocimetry, Osypka Medical GmbH, Berlin, Germany). We calculated the PAP - CO relationship as mPAP divided by CO (mPAP/CO), and calculated the slope of mPAP/CO in individual patients (ΔmPAP/ΔCO). The reproducibility of ΔmPAP/ΔCO obtained by echocardiography, expressed as the coefficient of variation, has been reported by our group as 5.6±3.8% and 7.2±5.1% for intra-observer and inter-observer variation, respectively.[15]

Definition of study endpoint. The primary endpoint was defined as a comparison of exercise echocardiographic parameters at baseline and one year after initiation of the maximum tolerated dose of ARNI for each group.

Laboratory data. All patients were measured plasma N-terminal pro brain natriuretic peptide (NT-pro BNP) level before treatment, but 18 patients were only plasma brain natriuretic peptide (BNP) level measured one year later, so their plasma NT-pro BNP levels were converted by using the following formula: log BNP=0.8*log NT-pro BNP－0.018.[24]

Statistical analysis. The continuous variables were expressed as mean ± SD of the normal distribution, while the non-normal continuous variables were expressed as median (interquartile range). Wilcoxon W test or Kruskal Wallis test was used to assess the differences among groups. Categorical data were expressed as percentages (%), and chi-squared test was used for comparison between the groups. Logistic regression was employed to calculate odds ratios and 95% CIs, adjusting for selected confounders. In univariate analysis, these confounders were chosen based on factors that demonstrated a significance level of $p < 0.2$ when comparing the baseline backgrounds of responders and non-responders. They were then incorporated into a multivariate model using a stepwise selection method. The statistical analyses were performed using standard statistical software packages (SPSS software 21.0; SPSS Inc, Chicago, IL, USA and MedCalc Software 17; Mariakerke, Belgium). Statistical significance was defined as a *p* value <0.05.

Results

Patient characteristics. A total of 43 patients were enrolled between September 2020 and December 2021 for this study. Out of these, three patients were unavailable for follow-up echocardiography, and one underwent cardiac surgery during the study period. Consequently, a final cohort of 39 patients was subjected to analysis (**Figure 1**). **Table 1** showed a summary of the baseline characteristics, revealing a mean age of 66±12 years. Males constituted 77% of the study population. The majority (62%) of the patients exhibited dilated cardiomyopathy, whereas 18% had ischemic cardiomyopathy. Nearly 80% of the patients fell under NYHA class II, and the remaining 20% were categorized under NYHA class III. The predominant comorbidities included hypertension (44%), diabetes mellitus (31%), and dyslipidemia (56%). Medication utilization rates among the patients were as follows: ACE inhibitors/ARBs were used by 37 patients (95%), β-blockers by 38 (97%), mineralocorticoid receptor antagonists by 20 (51%), sodium-glucose co-transporter 2 inhibitors by 12 (31%), diuretics by 25 (64%), and Ivabradine by 6 (15%). At the time of patient enrollment, the insurance coverage and guidelines for heart failure treatment in Japan were still adapting to incorporate the use of SGLT2i. This period of transition and the evolving clinical guidelines significantly influenced our decision-making process. As a result, there was a lower prevalence of SGLT2i usage among our study cohort.

Rest echocardiographic parameters following initiation of ARNI. Prior to the initiation of ARNI therapy, significant left ventricular dilation and volume enlargement were observed, coupled with an LVEF of 37.6±11.3%, indicating LV systolic dysfunction. Post-ARNI initiation, significant reductions were noted in left ventricular diameter and volume (**Figure 2A**). Additionally, LVEF demonstrated considerable improvement. Tissue Doppler e' was found to be elevated, while E/e' values decreased. However, no significant changes were noted in LAVi and TR-V (**Table 2**). Notably, tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio (TAPSE/sPSP) was improved from 0.52±0.15 mm/mmHg to 0.63±0.16 mm/mmHg (p=0.045). The treatment corresponded with a decrease in NT-proBNP levels.

Stress echocardiographic parameters following initiation of ARNI. Within the cohort of 39 patients, 31 (79%) underwent 6MW tests both before and one year after the initiation of ARNI therapy. Resting levels of blood pressure, heart rate, and SpO_2 remained largely unchanged after ARNI therapy. Notably, the 6MW distance exhibited an increase post-treatment (**Figure 2B**). This was accompanied by a decline in the ΔmPAP/ΔCO ratio during 6MW stress, bringing it within the normal range (**Figure 3**). In patients on ARNI therapy alone, the ΔmPAP/ΔCO improved from 7.1±5.7 mmHg/L/min to 3.3±2.1 mmHg/L/min (P=0.004), while in those on combined ARNI and SGLT2i therapy, the improvement was from 5.1±4.0 mmHg/L/min to 1.8±1.3 mmHg/L/min (P=0.04). **Figure 4**

showed the representative cases. Baseline and follow-up echocardiographic parameters are displayed side-by-side for comparison. At baseline, 6MW distance was 290m and Borg score was 3. E/e' was elevated and mild pulmonary hypertension was induced by 6MW. At follow up study, the 6MW distance increased to 300m, and Borg score was 2. E/e' was low both at rest and after walking, and pulmonary hypertension was not induced. ΔmPAP/ΔCO slope was improved 6.9 to 2.0.

Comparing Responders to Non-Responders in Treatment Outcomes.

Patients were divided into 2 groups according to whether ΔmPAP/ΔCO improved to within normal range at follow-up study.[25] Patients with ΔmPAP/ΔCO less than 3 were considered as responders and there were 19 patients. The characteristics of the 2 groups were shown in **Table 3**. There were no significant differences in comorbidities, medications, ARNI dose and resting blood pressure between the 2 groups, however responders tended to be younger. Most of echocardiographic parameters were not significantly different, but the baseline LAVi was significantly smaller in responders (p=0.029). After treatment, log NT-proBNP was significantly lower in responders. To identify the predictors of non-responders, we conducted both univariate and multivariate analyses. In the univariate model, non-responders were correlated with LAVi. In the multivariate logistic regression model, after adjusting for LVEF, non-responders were still correlated with LAVi (odds ratio: 1.15, 95% confidence interval: 1.02 to 1.29; p=0.018) (**Table 4**).

Discussion

In this study, we assessed the effects of Sacubitril/Valsartan (ARNI) on cardiac function in patients with HF using the 6MW stress echocardiography test. We found that ARNI treatment was associated with improvements in LV size and LVEF. Additionally, the 6MW distance increased, and the ΔmPAP/ΔCO slope, representing pulmonary vascular functional reserve, returned to the normal range after treatment. These results suggest that ARNI might improve cardiac reactivity to exercise in HF patients. A unique aspect of this study was the use of 6MW stress echocardiography to assess the impact of ARNI on pulmonary pressure-flow response during exercise stress. This method is a simple, non-invasive, and cost-effective method for assessing cardiac function in the clinical setting. A major strength of this study is the prospective enrollment of patients, enhancing the reliability and accuracy of the collected data.

Effect of ARNI. Many studies have investigated the effects of ARNI on LV function and outcomes in HF patients.[4, 5] Our results are consistent with previous research that has demonstrated the beneficial effects of ARNI therapy on LV function. For instance, the PARADIGM-HF trial found that ARNI reduced the risk of death from cardiovascular causes by 20% compared to enalapril in patients with heart failure with reduced ejection fraction.[26] The PROVE-HF trial also showed that ARNI improved left ventricular remodeling compared to enalapril in patients with HF with reduced ejection fraction.[27]

In contrast, fewer studies have investigated the effects of ARNI therapy on pulmonary hemodynamics and exercise capacity in HF patients. The findings of our study suggest that ARNI therapy might enhance the pulmonary pressure-flow relationship of the pulmonary circulation as measured by the 6MW stress echocardiography. However, it's crucial to highlight that research on the effects of ARNI therapy on pulmonary hemodynamics and exercise capacity remains sparse. Sharifi et al. postulated that the ARNI might protect against the development of detrimental RV structural and functional alterations in a pressure overload model in rats through banding of the primary pulmonary artery.[9] This study provides mechanistic insights, suggesting that ARNI may have a protective role in preventing maladaptive pulmonary circulation changes. Furthermore, there have been case series illustrated the innovative use of ARNI therapy in treating advanced HFrEF patients with severe PH, indicating a potential expanded role of ARNI in this patient population.[28] A comprehensive review points out that pulmonary hypertension due to left heart disease affects a significant portion of PH patients and exacerbates the prognosis of those with left HF.[8] Given the limited therapeutic efficacy of specific drugs for pulmonary arterial hypertension in these patients, the possible applications of ARNI, considering its vasodilatory and natriuretic drainage roles, in treating PH-LHD are gaining attention. Although ARNI has demonstrated benefits for LV function, its therapeutic potential for patients with concomitant PH and HF remains a significant area of interest. The findings of our study concur with these

observations, suggesting that ARNI therapy might improve the pulmonary pressure-flow relationship of the pulmonary circulation. However, the specific mechanisms by which ARNI enhances pulmonary hemodynamics are not yet fully understood and warrant more detailed investigation in future studies.

In our study, categorizing patients based on improvements in ΔmPAP/ΔCO to within normal limits revealed notable findings. Those deemed as responders, with a ΔmPAP/ΔCO less than 3, demonstrated distinctive characteristics. Although there were no significant differences in coexisting conditions, medication use, ARNI dosage, and some echocardiographic measures between the groups, the baseline LAVi emerged as a significant parameter. Responders exhibited a lower baseline LAVi, suggesting a potential link between LAVi and responsiveness to therapy. A small LAVi could indicate minimal atrial remodeling or stress, possibly making these individuals more receptive to therapeutic benefits.[29] In addition, post-treatment data showed a marked decrease in log NT-proBNP levels among the responders. As NT-proBNP is a recognized indicator of HF severity and prognosis, the improved ΔmPAP/ΔCO might correlate with an enhanced neurohormonal state. Our results emphasize the potential relationship between LA function and biochemical markers in forecasting therapeutic outcomes, underscoring the need for a comprehensive approach in evaluating and managing HF patients.

The improvement in ΔmPAP/ΔCO indicates a rise in pulmonary artery pressure during exercise and an increase in cardiac output during activity. However, it is challenging in this cohort to discern whether the improvement is solely due to improved pulmonary circulation or if it is also a result of reduced left atrial pressure from improved left ventricular function. In our study, a significant proportion (85%) of the cases had an EF below 50%. The effect of ARNI on HFrEF is likely majorly attributed to its role in enhancing left ventricular function. This makes it difficult to infer a direct impact of ARNI on pulmonary circulation especially in HFrEF. Future studies focusing on cohorts with HFpEF where EF is maintained above 60% are crucial. Researching whether ARNI administration in such groups results in pulmonary circulation improvement will be vital. Our study serves as a catalyst for future investigations.

Clinical implications. The improvements in LV size, LVEF, 6MW distance, and the ΔmPAP/ΔCO slope observed in this study suggest that ARNI might be beneficial in enhancing cardiac function and responsiveness to exercise for HF patients. Additionally, the 6MW stress echocardiography appears to be a valuable method to assess the influence of ARNI on cardiac function in a clinical environment. Given these results, clinicians might view ARNI treatment as a viable option for HF patients experiencing exercise intolerance.

Limitations. Our study presents several limitations that warrant consideration. First our sample size was relatively modest, potentially restricting the broader applicability of our

results. Second, since the study was localized to a single center and focused only on HF patients, the results might not be universally applicable. Third, with a follow-up duration of merely one year, the long-term consequences of ARNI treatment were not thoroughly assessed. Forth, the absence of a control group in our study hampers our capacity to ascertain definitive outcomes associated with ARNI treatment. Fifth, while the protocol aimed to minimize the addition of other medications, 9 out of the 39 patients had the addition of SGLT2 inhibitors due to clinical necessity. Nevertheless, no significant impact was observed on the improvement of left ventricular function attributed to ARNI, regardless of the administration of these other medications. Future research, encompassing more extensive participant groups, elongated monitoring durations, and the inclusion of control groups, will be crucial to validate and build upon our observations.

Conclusion

This study underscores the association between ARNI treatment and marked improvements in parameters like LV size, LVEF, 6MW distance, and the ΔmPAP/ΔCO slope among HF patients. These results point towards ARNI's potential in improvement of pulmonary pressure-flow responsiveness in these patients. It's imperative to conduct additional research to corroborate these observations and delve into ARNI's long-term implications and mechanisms for HF patients.

Disclosures: None

Contributors: KK conceived the idea for this study. NY conducted the data analyses. The initial draft of the manuscript was produced by KK and NY. All the authors were involved in interpreting the results and writing the manuscript. All authors read and approved the final manuscript.

Sources of Funding: This work was partially supported by JSPS Kakenhi Grants (23K07509 to K. Kusunose), AMED grant (JP22uk1024007 to K. Kusunose), and the Vehicle Racing Commemorative Foundation (M. Sata). The funding source had no role in the design and conduction of the study, the collection, management, analysis, or interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Data availability statement: Data are available on reasonable request.

Patient consent for publication: Not applicable.

Ethics approval: The study was approved by the local ethics committee and Institutional Review Board of the University of Tokushima (protocol: 3828-1).

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Figure legends:

Figure 1: Patient Selection.

Patients who underwent echocardiographic study were recruited consecutively between September 2020 and December 2021.

Figure 2: Clinical and echocardiographic parameters pre and post treatment.

A: LVEF was significantly improved with treatment (37.6±11.3% vs 44.9±11.5%, P<0.001)

B: The 6MW distance was increased after treatment (380m vs 430m, P=0.003).

Figure 3: Individual multipoint mPAP and cardiac output plot pre and post treatment.

The ΔmPAP/ΔCO by 6MW stress decreased with treatment (6.9mmHg/L/min vs 2.8mmHg/L/min, P=0.002). The ΔmPAP/ΔCO was improved to within normal range with treatment.

Figure 4: Representative cases.

Baseline and follow-up echocardiographic parameters are displayed side-by-side for comparison.

The 6MW distance increased and hemodynamics improved after treatment. ΔmPAP/ΔCO also improved to within normal range with treatment.

Table 1: Baseline characteristics of patients

Demographics	
Age, years	66±12
Male	30 (77%)
Etiology	
Dilated cardiomyopathy	24 (62%)
Ischemic cardiomyopathy	7 (18%)
Others	8 (20%)
Physical features	
Systolic BP, mmHg	113.8±21.3
Body surface area, m^2	1.72±0.20
HR, bpm	65.8±9.6
Comorbidities	
Hypertension	17 (44%)
Diabetes mellitus	12 (31%)
Dyslipidemia	22 (56%)
Blood examination	
Hb, g/dL	13.5 (12.2-1[illegible]5)
CRP, mg/dL	0.15 (0.07-0.27)
eGFR, mL/min/1.73 ㎡	52 (3[illegible]-68)
NT-proBNP, pg/mL	956 ([illegible]24-2235)
NYHA class	
Class I	0 (0%)
Class II	31 (79%)
Class III	8 (21%)
Class IV	0 (0%)
Medications	
ACE inhibitors/ARBs	37 (95%)
β-blockers	38 (97%)
MRAs	20 (51%)
SGLT2 inhibitors	12 (31%)
Diuretics	25 (64%)
Ivabradine	6 (15%)

Data are expressed as the number of patients (percentage) and mean ± SD or median (interquartile range).

Abbreviations: BP, blood pressure; HR, heart rate; Hb, hemoglobin; CRP, C-reactive protein; eGFR, estimated Glomerular Filtration Rate; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors.

Table 2: Comparison of echocardiographic parameters at rest between baseline and 1 year after the administration of ARNI

	Baseline	Follow up	P value
Rest variables			
HR, bpm	65.8±9.6	67.9±11.2	0.172
Systolic BP, mmHg	113.8±21.3	110.7±21.1	0.360
LVEDV, mL	160.7±49.6	136.0±54.3	<0.001
LVESV, mL	104.2±47.2	79.2±48.9	<0.001
LVEF, %	37.6±11.3	44.9±11.5	<0.001
GLS, %	-10.7±4.2	-11.5±6.3	0.440
LAVi, ml/㎡	41.4±17.1	40.6±16.8	0.746
TR-V, m/s	2.32±0.28	2.30±0.31	0.698
E/e'	15.5±8.7	12.1±6.7	0.008
TAPSE/sPSP, mm/mmHg	0.52±0.15	0.63±0.16	0.045
IVC max, mm	9.9±3.8	10.4±4.0	0.363
log NT-proBNP	6.86 (5.75-7.74)	5.69 (4.35-7.06)	<0.001
Exercise hemodynamics			
6MW distance, meter	380 (330-468)	430 (370-485)	0.003
HR (during exercise), bpm	79.7±12.4	80.8±10.5	0.659
Systolic BP (during exercise), mmHg	119.0±21.4	116.0±19.2	0.626
SpO_2 (at rest), %	96.4±1.4	96.8±1.4	0.161
SpO_2 (during exercise), %	95.3±2.6	95.5±2.5	0.693
E/e' (during exercise)	17.6±9.6	13.9±6.3	0.015
Mean PAP (at rest), mmHg	15.2 ± 3.0	14.3 ± 2.2	0.122
CO (at rest), L/min	3.31±0.82	3.54±1.04	0.225
Exercise mean PAP, mmHg	23.6 ± 6.3	19.8 ± 4.6	<0.001
Exercise CO, L/min	4.98±1.13	5.69±1.48	0.014
ΔmPAP/ΔCO, mm Hg/L/min	6.91 ± 6.9	2.76 ± 1.96	0.002

Data are expressed as the number of patients (percentage) and mean ± SD or median (interquartile range).

Abbreviations: LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; GLS, Global longitudinal

strain; LAVi, left atrial volume index; TR-V, tricuspid regurgitant velocity; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular motion; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; IVC, inferior vena cava; SpO_2, percutaneous oxygen saturation; CO, cardiac output; 6MW, Six-minute walk.

Table 3: Comparison of Baseline Background between Responders and Non-Responders.

	All (n=31)	Responders (n=19)	Non-Responders (n=12)	P value
Age, years	66±13	62±13	72±11	0.057
Comorbidities				
Hypertension	15 (48%)	7 (37%)	8 (67%)	0.111
Diabetes mellitus	9 (29%)	7 (37%)	2 (17%)	0.236
Dyslipidemia	17 (55%)	11 (58%)	6 (50%)	0.672
Physical features				
Systolic BP, mmHg	114.9±19.1	111.9±17.6	119.8±21.2	0.273
SpO_2, %	96.4 ± 1.4	96.5 ± 1.3	96.3 ± 1.6	0.679
Medications				
ACE inhibitors/ARBs	30 (97%)	19 (100%)	11 (92%)	0.208
β-blockers	30 (97%)	18 (95%)	12 (100%)	0.427
MRAs	17 (55%)	12 (63%)	5 (42%)	0.249
SGLT2 inhibitors	11 (35%)	9 (47%)	2 (17%)	0.087
Diuretics	19 (61%)	12 (63%)	7 (58%)	0.792
Ivabradine	6 (19%)	5 (26%)	1 (8%)	0.225
Dose of ARNI				
100 mg/day	5 (16%)	4 (80%)	1 (20%)	
200 mg/day	8 (26%)	5 (63%)	3 (37%)	0.609
400 mg/day	18 (58%)	10 (57%)	8 (43%)	
Baseline				
LVEDV, ml	160.4±46.7	156.2±47.9	167.1±45.9	0.537
LVESV, ml	101.5±44.9	103.1±48.4	98.8±40.8	0.801
LVEF, %	39.1±11.6	36.8±12.4	42.7±9.6	0.176
LAVi, ml/㎡	40.6±18.3	34.9±14.6	49.5±20.6	0.029
TR-V, m/s	2.33±0.27	2.26±0.25	2.44±0.27	0.072
e', cm/s	4.55±2.30	4.95±2.49	3.91±1.88	0.226
E/e'	15.2±8.4	14.3 ± 8.5	16.6±8.5	0.459
IVC max, mm	9.8±3.2	9.5±3.4	10.3±3.0	0.525

log NT-proBNP	6.65 (5.50-7.59)	6.47 (5.11-7.42)	7.27 (5.78-7.63)	0.351
GLS, %	-11.3±4.1	-10.7±4.4	-12.3±3.6	0.272
Follow-up				
LVEDV, ml	131.3±45.6	119.5±31.2	150.0±58.8	0.069
LVESV, ml	72.6±39.3	65.4±29.5	83.9±50.6	0.207
LVEF, %	47.0±10.9	46.8±11.4	47.3±10.9	0.922
LAVi, ml/㎡	39.5±20.6	33.0±14.1	49.9±25.2	0.023
TR-V, m/s	2.25±0.20	2.22±0.16	2.31±0.25	0.231
e', cm/s	5.16±2.14	5.42±2.29	4.76±1.91	0.410
E/e'	10.9±4.5	10.6±4.7	11.3±4.3	0.700
IVC max, mm	10.0±3.4	10.0±3.6	9.9±3.1	0.945
GLS, %	-12.4±6.6	-14.0±3.2	-9.8±9.5	0.186
log NT-proBNP	5.42 (4.12-6.78)	4.64 (3.33-6.14)	6.89 (5.40-7.41)	0.005

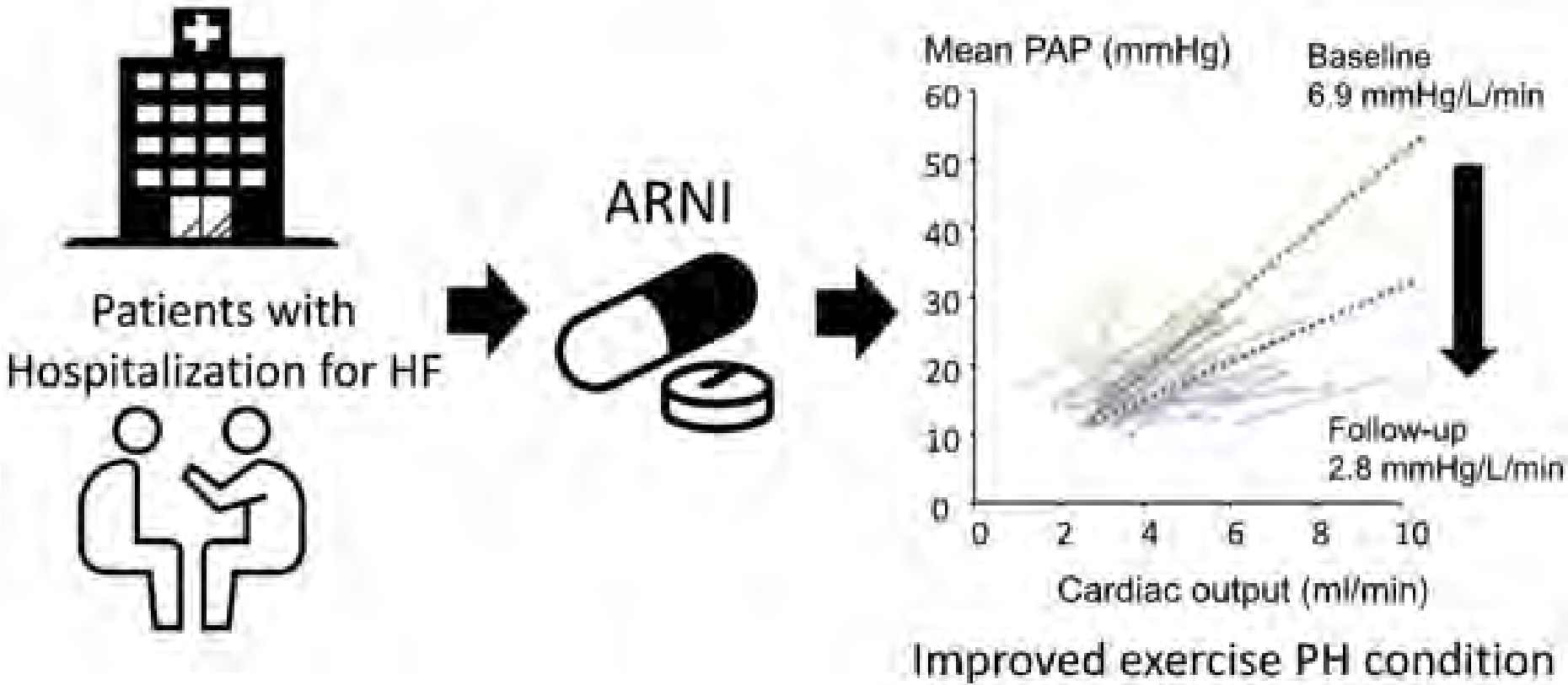
Data are expressed as the number of patients (percentage) and mean ± SD or median (interquartile range). Abbreviations: see Table1 and Table2.

Table 4: Associations of Patients Classified as Non-Responders.

Variables	Univariate		Multivariate	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Age, per 1year	1.07 (0.99-1.15)	0.071		
Hypertension	3.43 (0.75-15.67)	0.112		
SGLT2 inhibitors	0.22 (0.04-1.30)	0.095		
LVEF, per 1%	1.05 (0.98-1.12)	0.176	1.19 (1.03-1.37)	0.021
LAVi, per 1ml/m^2	1.05 (1.00-1.10)	0.046	1.15 (1.02-1.29)	0.018
TR-V, per 1m/s	14.83 (0.73-302.42)	0.080		

Highlights

- The initiation of ARNI treatment was associated with a reduction in left ventricular volume and a improvement in left ventricular ejection fraction.
- The HF patients who underwent the 6MW stress echocardiography at both baseline and 1 year later, there was an increase in the 6MW distance post-treatment.
- The ΔmPAP/ΔCO ratio, assessed by the 6MW stress echocardiography, decreased with treatment, indicating an improvement in the pressure-flow relationship of the pulmonary circulation.



Graphics Abstract

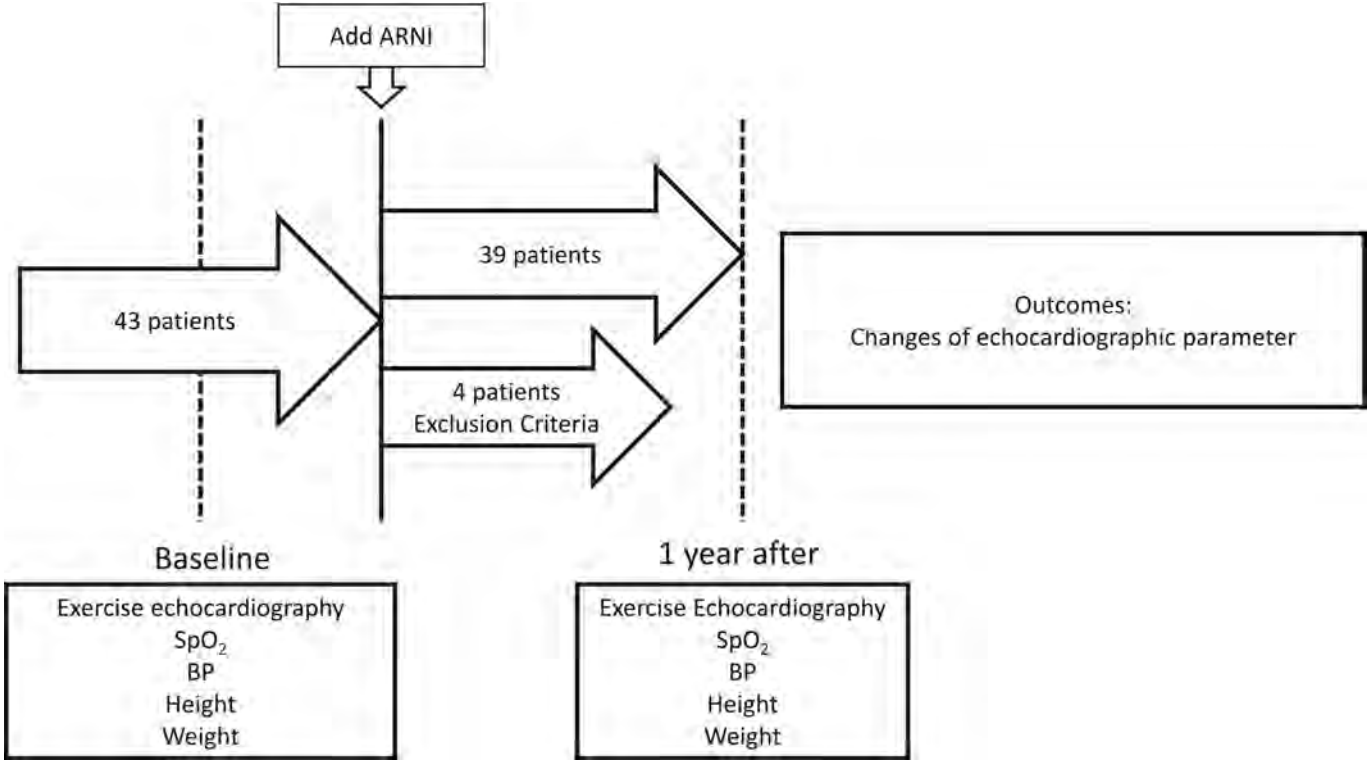

Add ARNI
43 patients
39 patients
4 patients
Exclusion Criteria
Outcomes:
Changes of echocardiographic parameter
Baseline
1 year after
Exercise echocardiography
SpO2
BP
Height
Weight
Exercise Echocardiography
SpO2
BP
Height
Weight

Figure 1

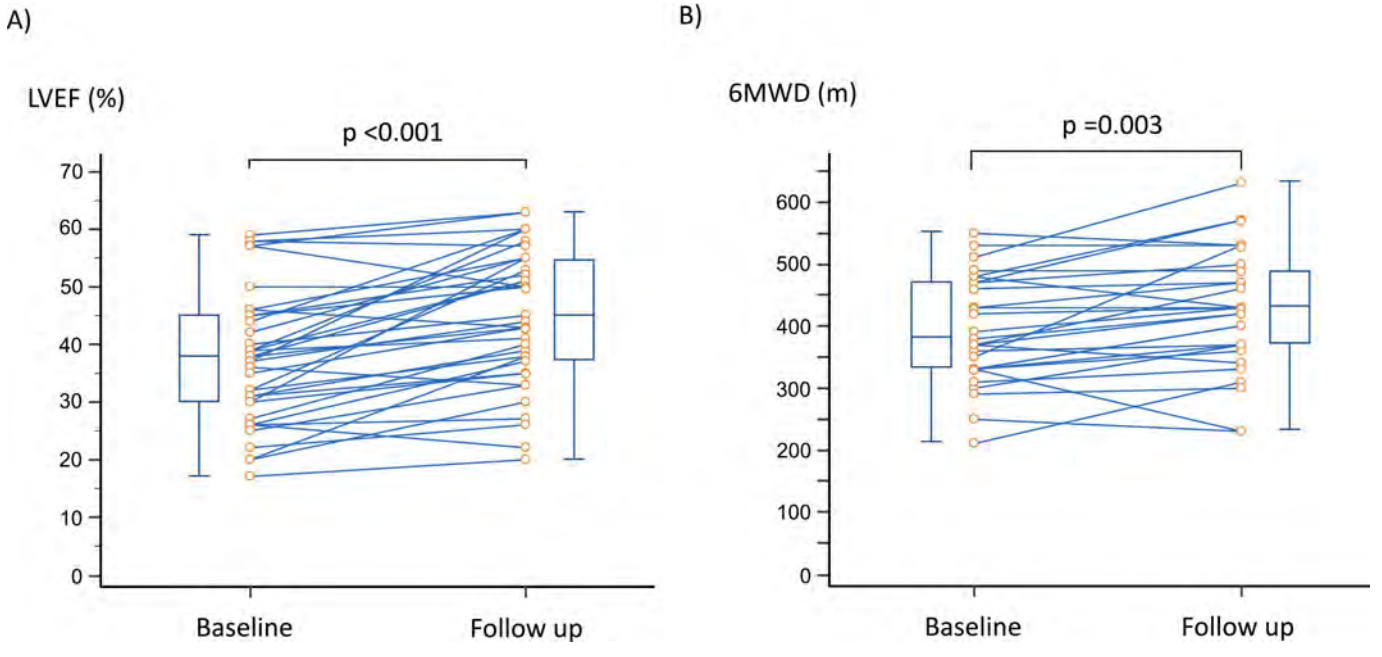

A)
LVEF (%)
p <0.001
70
60
50
40
30
20
10
0
Baseline
Follow up
B)
6MWD (m)
p =0.003
600
500
400
300
200
100
0
Baseline
Follow up

Figure 2

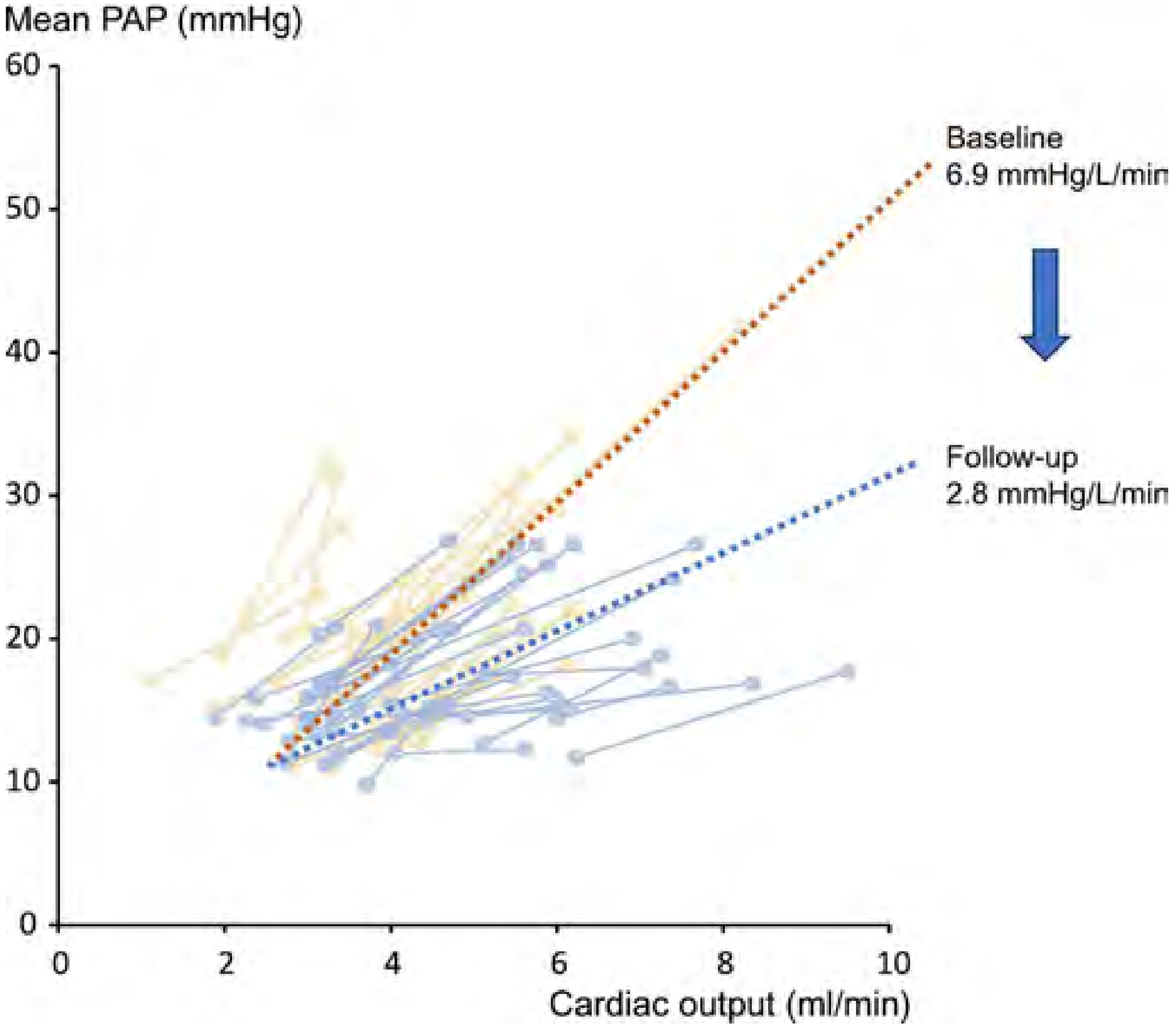

Mean PAP (mmHg)
60
50
40
30
20
10
0
0
2
4
6
8
10
Cardiac output (ml/min)
Baseline
6.9 mmHg/L/min
Follow-up
2.8 mmHg/L/min

Figure 3

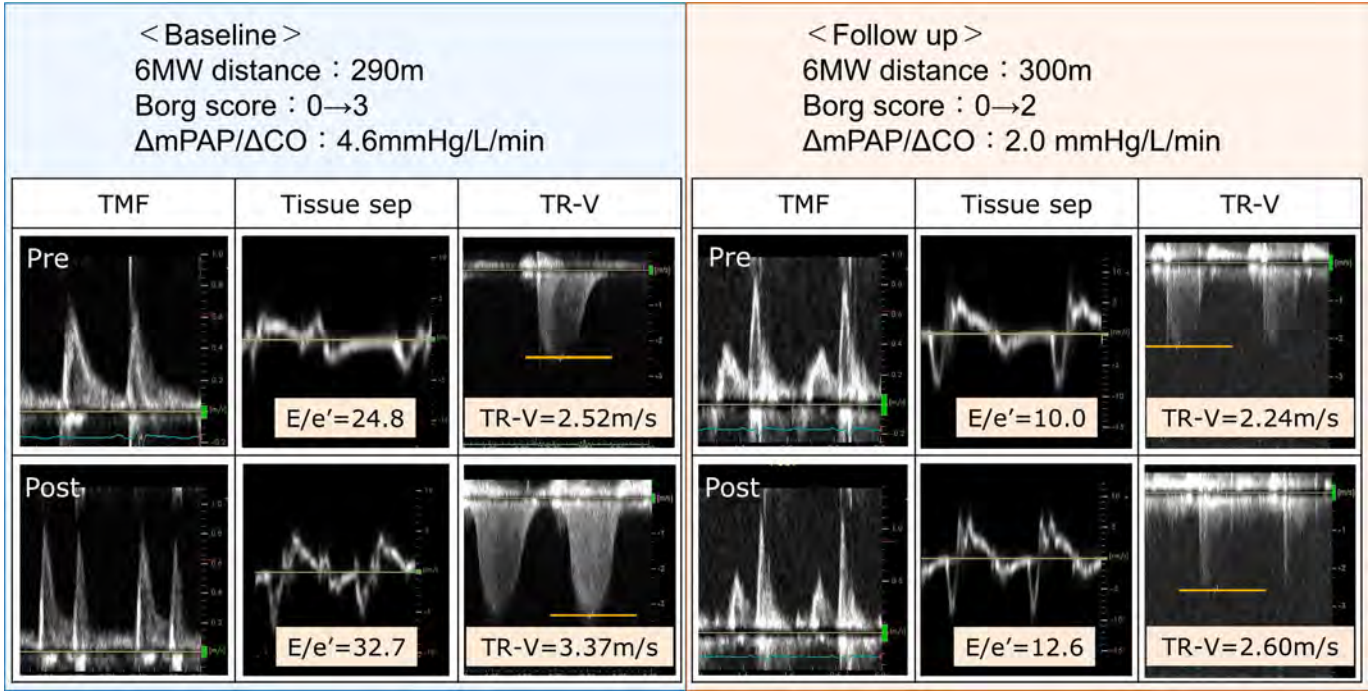

＜Baseline＞
6MW distance：290m
Borg score：0→3
ΔmPAP/ΔCO：4.6mmHg/L/min
＜Follow up＞
6MW distance：300m
Borg score：0→2
ΔmPAP/ΔCO：2.0 mmHg/L/min
TMF
Tissue sep
TR-V
Pre
E/e'=24.8
TR-V=2.52m/s
Post
E/e'=32.7
TR-V=3.37m/s
TMF
Tissue sep
TR-V
Pre
E/e'=10.0
TR-V=2.24m/s
Post
E/e'=12.6
TR-V=2.60m/s

Figure 4