*Original article*

**Usefulness of the Pulmonary Venous Flow Waveform for Assessing Left Atrial Stiffness**

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**ABSTRACT**

**Purpose**: This study investigated the novel non-invasive left atrial (LA) stiffness parameter using pulmonary venous (PV) flow measurements and the clinical usefulness of the novel LA stiffness parameter.

**Methods:** We retrospectively analyzed 237 patients who underwent right heart catheterization and echocardiography less than one week apart. From the pulmonary artery wedge pressure waveform, the difference between x-descent and v-wave ($\Delta P$) was measured. Using the echocardiographic biplane method of disks, the difference between LA maximum volume and that just before atrial contraction ($\Delta V_{MOD}$) was calculated, and the $\Delta P/\Delta V_{MOD}$ was calculated as a standard LA stiffness index. From the PV flow waveform, the peak systolic velocity (S), peak diastolic velocity (D), and minimum velocity between them (R) were measured, and S/D, S/R, and D/R were calculated. From the speckle tracking echocardiography-derived time–LA volume curve, the difference between LA maximum volume and that just before atrial contraction ($\Delta V_{STE}$) was measured. Each patient's prognosis was investigated until three years after echocardiography.

**Results:** Among the PV flow parameters, D/R was significantly correlated with $\Delta P$ ($r=0.62$), and the correlation coefficient exceeded that between S/D and $\Delta P$ ($r=-0.39$) or S/R and $\Delta P$ ($r=0.14$). The $[D/R]/\Delta V_{STE}$ was significantly correlated with $\Delta P/\Delta V_{MOD}$ ($r=0.61$). During the follow-up, 37 (17%) composite endpoints occurred. Kaplan-Meier analysis showed that patients with $[D/R]/\Delta V_{STE}$ greater than 0.13 /mL were at higher risk of cardiac events.

**Conclusion:** The $[D/R]/\Delta V_{STE}$ was useful for assessing LA stiffness non-invasively and might be

valuable in the prognostic evaluation of patients with cardiac diseases.

**Keywords**: echocardiography, pulmonary venous flow, left atrial stiffness, speckle tracking echocardiography, left atrial v-wave

## INTRODUCTION

Left atrial (LA) function is now recognized as an important indicator for risk stratification in patients with cardiovascular diseases who suffer from heart failure or atrial fibrillation [1,2]. Two-dimensional speckle tracking echocardiography (2DSTE) is a well-known technique to assess LA myocardial function. Using 2DSTE, several phasic parameters can be obtained, such as atrial systolic strain (which reflects active booster pump function), conduit or passive reservoir strain (which reflects passive distensibility), and total reservoir or global strain (which reflects total LA function) [3].

LA stiffness is defined as the ratio of LA pressure change to volume change during the passive filling (late-reservoir) phase of the LA [1,4]. The increase in LA stiffness is considered to precede the decrease in LA strain parameters, and thus the assessment of increased LA stiffness may allow for more sensitive detection of pathophysiological changes in the LA. Several investigators recently revealed that the evaluation of LA stiffness was more useful in predicting recurrence after catheter ablation for atrial fibrillation [4-6] and in predicting prognosis in patients with chronic heart failure [7] compared to the LA strain parameters. Thus, the assessment of LA stiffness has been attracting attention.

The pulmonary venous (PV) flow waveform is determined by the pressure gradient between the PV and LA, and is known to be similar to the shape of the inverted waveform of the LA pressure [8,9]. The systolic wave of the PV flow corresponds to the x-descent of the LA pressure, the diastolic wave of the PV flow to the y-descent of the LA pressure, and the minimal velocity between the systolic and diastolic waves to the v-wave of the LA pressure. We hypothesize that, by measuring a novel PV flow parameter assessing the minimal velocity between the systolic and diastolic waves, it may be possible to estimate the increase in LA pressure during the late-reservoir phase and detect any abnormal increase in the LA v-wave. This study aimed to investigate the novel non-invasive LA stiffness parameter using PV flow measurements, which reflect the LA pressure change during the late-reservoir phase and v-wave, as well as to investigate its usefulness to predict patient outcome.

## METHODS

### Patient population

We retrospectively enrolled 476 patients who were admitted to Hokkaido University Hospital from January 2013 to December 2018 and performed right-heart catheterization and echocardiography within one week under stable conditions in those in whom good pulmonary artery wedge pressure recordings were obtained. We excluded patients with an implanted left ventricular (LV) assist device, post-heart transplantation, or intra-aortic balloon pumping; those under hemodialysis; those with arrhythmias such as atrial fibrillation, atrial flutter, or bigeminy during the examination; and those with post mitral valve replacement or mitral annuloplasty and congenital heart disease. The remaining 273 patients were investigated (**Figure 1**).

### Right-heart catheterization

Right-heart catheterizations were performed by trained physicians using a 7F fluid-filled balloon-tipped catheter and the waveform of the pulmonary artery wedge pressure was recorded at end-expiration. From the waveform, we measured the nadir of the x-descent, peak v-wave, nadir of the y-descent, and mean pulmonary artery wedge pressure (PAWP) (**Figure 2**). The difference between the x-descent and peak v-wave ($\Delta P$) was calculated as a pressure increase of the late-reservoir phase. All measurements were obtained from 3 to 5 consecutive beats and the averaged values were used for analysis. We defined the elevated v-wave as greater than 21 mmHg [10].

**Echocardiographic measurements**

Comprehensive echocardiography was performed for each patient in accordance with the guidelines of the American Society of Echocardiography [11]. Using the biplane method of disks in apical two- and four-chamber views, the maximum LA volume and the LA volume just before atrial contraction were measured, and the difference between them ($\Delta V_{MOD}$) was calculated as the LA volume change. The ratio of invasive $\Delta P$ to $\Delta V_{MOD}$ ($\Delta P/\Delta V_{MOD}$) was calculated as a standard index of the LA stiffness in this study.

From the PV flow velocity waveform, the peak systolic velocity (S), the peak diastolic velocity (D), and the minimum velocity between them (R) were measured, and the S/D, S/R, and D/R were calculated (**Figure 3**). Using Doppler echocardiography with an apical approach, the peak early-diastolic transmitral flow velocity (E) was measured. The peak early-diastolic mitral annular velocity (e′) was measured at the septal and lateral sides of the annulus and averaged, and the E/e′ was calculated.

**Two-dimensional speckle tracking echocardiography**

Analysis of 2DSTE was performed offline using TomTec ImageArena (version 2.40, TomTec, Munich, Germany). For the analysis, the highest-quality digital image was selected. The endocardial border of the LA in the apical four-chamber view was manually traced, and then the time–LA volume curve and time–LA global strain curve with P-P gating were obtained (**Figure 4**). From the time–LA volume curve, LA maximum volume and LA volume just before atrial contraction were measured and the difference between them ($\Delta V_{STE}$) was calculated. From the time–LA global longitudinal strain curve, the LA passive reservoir strain ($LA\text{-}LS_{PR}$) and the LA global longitudinal strain (LA-GLS) were measured.

**Follow-up and endpoint**

We retrospectively reviewed each patient's electronic medical records until three years after the echocardiographic examination, and we carefully investigated the occurrence of all-cause mortality, LV assist device implantation, rehospitalization due to worsening heart failure, and new onset of atrial fibrillation or atrial flutter. We defined the occurrence of these composite endpoints as the primary endpoint.

**Statistical analyses**

All statistical analyses were performed using a standard statistical software package (IBM SPSS ver. 25 for Windows; IBM, Chicago, IL). All continuous data are expressed as the mean±SD or median (interquartile range) as appropriate, and all categorical data are expressed as counts and percentages. The correlation between the two variables was assessed using Pearson's correlation analysis. To test the difference between the two correlation coefficients, a test for the difference in the maternal correlation coefficient was used. A receiver operating characteristic (ROC) analysis was used to evaluate the ability of echocardiographic parameters to estimate elevated v-wave (>21 mmHg). The area under the curve (AUC) of each parameter, the optimal cut-off value, and the sensitivity and specificity were calculated, and a test for difference in the AUC was performed if necessary. The prognostic value of the LA stiffness parameters was evaluated by Cox regression analysis and Kaplan-Meier analysis with the log-rank test. A significant difference was defined as a p-value <0.05. In the study, to explore the best parameter reflecting $\Delta P$ and $\Delta V_{MOD}$, we investigate the correlation of multiple parameters to the standard parameter, thus, Bonferroni correction was applied to avoid the increased risk of a type 1 error, and a p-value less than 0.05/n was considered statistically significant for the correlation analysis.

## RESULTS

**Patient characteristics and comparison of the parameters by standard LA stiffness**

Among the 273 patients, an adequate PV flow velocity waveform was not available in 44 patients, and LA tracking was inadequate due to poor echocardiographic quality in 7 patients. After excluding these patients, the remaining 222 patients were analyzed. The clinical, hemodynamic, and echocardiographic parameters are summarized in **Table 1**. Among the 222 patients, LA dilation (LA volume index >34 mL/m$^2$) was observed in 158 (71%), increased PAWP (>15 mmHg) was seen in 55 (25%), and increased v-wave (>21 mmHg) was found in 41 patients (18%). The median value of the $\Delta P/\Delta V_{MOD}$ was 0.25 mmHg/mL, and patients with higher $\Delta P/\Delta V_{MOD}$ (>0.25 mmHg/mL) had significantly greater D/R, E/e′, PAWP, v-wave, and ΔP values. The S/R, $\Delta V_{MOD}$, and LA-GLS were significantly lower in patients with higher $\Delta P/\Delta V_{MOD}$ than those without.

**Relationships between echocardiographic parameters and catheter-derived ΔP and v-wave**

The relationships of PV flow parameters with ΔP and v-wave were summarized in **Table 2**. Among the PV flow parameters, D/R was significantly correlated with ΔP and v-wave (r=0.62 and r=0.63) (**Figure 5**). The S/D was also significantly correlated with ΔP and v-wave (r=−0.39 and r=−0.51). The S/R was not significantly correlated with ΔP (r=0.14) or v-wave (r=−0.04). The E/e′ was also significantly correlated with ΔP and v-wave (r=0.22, p=0.001 and r=0.36, p<0.001), and the correlation coefficients were significantly smaller than those between D/R and either ΔP or v-wave (p<0.001 for both).

The results of ROC analysis to evaluate the ability of D/R and E/e' to detect elevated v-wave are shown in **Figure 6**. The AUC of D/R was 0.87, with a sensitivity of 85% and specificity of 74% at the optimal cutoff value of 2.7, and that of E/e' was 0.71, with a sensitivity of 51% and specificity of 82% at the optimal cutoff value of 15.1. The AUC of D/R was significantly greater than that of E/e′ ($p<0.001$).

**Correlation between 2DSTE-derived parameters and $\Delta V_{MOD}$**

The $\Delta V_{STE}$ was strongly and significantly correlated with $\Delta V_{MOD}$ ($r=0.81$, $p<0.001$). LA-$LS_{PR}$ was also significantly correlated with $\Delta V_{MOD}$, but the correlation was weak ($r=0.31$, $p<0.001$). LA-GLS was not significantly correlated with $\Delta V_{MOD}$ ($r=0.11$, n.s.).

**Non-invasive parameter of LA stiffness**

As described above, the D/R and $\Delta V_{STE}$ were the best parameters to reflect $\Delta P$ and $\Delta V_{MOD}$, respectively. Thus, we next investigated the validity of the $[D/R]/\Delta V_{STE}$ as a noninvasive parameter of LA stiffness. The results showed that the $[D/R]/\Delta V_{STE}$ was well correlated with $\Delta P/\Delta V_{MOD}$ ($r=0.61$, $p<0.001$). [E/e′]/LA-GLS was also significantly correlated with $\Delta P/\Delta V_{MOD}$ ($r=0.47$, $p<0.001$), but the correlation coefficient was significantly smaller than that for the $[D/R]/\Delta V_{STE}$ and $\Delta P/\Delta V_{MOD}$ ($p=0.039$) (**Figure 7**).

**Prognostic value of non-invasive LA stiffness parameters**

During the follow-up period of three years, 37 (17%) primary composite endpoints occurred (9 deaths, 5 LV assist device implantations, 18 rehospitalizations for worsening heart failure, and 5 developments of new atrial fibrillation or atrial flutter). The results of the univariable and multivariable Cox regression analyses are summarized in **Tables 3** and **4**. In the univariable analysis, LV ejection fraction, LA volume index, E/e', D/R, LA-GLS, LA-$LS_{PR}$, PAWP, v-wave, $\Delta P$, $\Delta P/\Delta V_{MOD}$, $[D/R]/\Delta V_{STE}$, and [E/e']/LA-GLS were significantly associated with the primary endpoint. In the multivariable analysis adjusted for age, LV ejection fraction, and LA volume index, each of the following were independent prognostic factors for the development of cardiac events: $\Delta P/\Delta V_{MOD}$, [E/e']/LA-GLS, and $[D/R]/\Delta V_{STE}$.

The results of the Kaplan-Meier analysis are shown in **Figure 8**. The patients with $\Delta P/\Delta V_{MOD}$ >0.25 mmHg/mL (the median value) had a significantly higher risk of cardiac events than the group with $\Delta P/\Delta V_{MOD}$ ≤0.25 mmHg/mL (p=0.002). Similarly, the group with $[D/R]/\Delta V_{STE}$ >0.13 /mL (the median value) had a significantly lower event-avoidance rate than the group with $[D/R]/\Delta V_{STE}$ ≤0.13 /mL (p<0.001).

**Reproducibility**

The reproducibility of parameters related to the LA stiffness is shown in **Supplemental Table**. Excellent inter- and intra-observer agreement were observed for $\Delta P/\Delta V_{MOD}$ (ICC=0.81, p<0.001 and ICC=0.91, p<0.001, respectively) and $[D/R]/\Delta V_{STE}$ (ICC=0.87, p<0.001 and ICC=0.94, p<0.001 respectively).

## DISCUSSION

The principal findings of the present study were as follows. (a) The D/R ratio of the PV flow, i.e., the ratio of the diastolic wave to the minimal velocity between systolic and diastolic waves, was useful to estimate LA pressure increase during the late-reservoir phase and to detect abnormal increases in the LA v-wave, and the performance of this ratio in both capacities was better than that of the E/e′. (b). The ratio of D/R to $\Delta V_{STE}$ was well correlated with the invasive LA stiffness parameter, $\Delta P/\Delta V_{MOD}$. (c) The $[D/R]/\Delta V_{STE}$ was as useful as the $\Delta P/\Delta V_{MOD}$ for predicting the occurrence of cardiac events in patients with cardiac diseases.

To our knowledge, this is the first study focusing on the minimal velocity between the systolic and diastolic waves of the PV flow. We demonstrated the usefulness of the D/R of the PV flow for detecting abnormal increases in LA pressure during the late-reservoir phase and resultant prominent v-wave, and showed that the $[D/R]/\Delta V_{STE}$ might be applied as an alternative indicator to LA stiffness. We also demonstrate the usefulness of the $[D/R]/\Delta V_{STE}$ for the risk stratification of patients.

**Relationships between echocardiographic parameters and invasive LA pressure during the late-reservoir period**

It has long been known that the R of the PV flow, i.e., the minimal velocity between the S and D waves, corresponds to the v-wave of the LA pressure waveform [8]. As LA v-wave increases, the R of the PV flow decreases. At the beginning of this study, we expected that the S/R ratio would correlate with $\Delta P$, but we found that in fact the S/R was not correlated with either $\Delta P$ or the v-wave. This result may be attributable to several previously reported phenomena. Namely, when the LA v-wave increases prominently, the LA pressure rises rapidly from the mid-systolic phase, which decreases the pressure gradient between the PV and LA, and then the x-descent becomes obscure. As a result, the S wave is expected to decrease or disappear [8,9]. On the other hand, we found that the D wave of the PV flow, which corresponds to the y-descent, was not affected by the mid-systolic pressure difference between PV and LA. In general, the difference between the x-descent and the v-wave is almost the same as the difference between the v-wave and y-descent, and thus the D/R might be well correlated with ΔP and LA v-wave.

In the present study, the E/e′ was significantly correlated with both ΔP and the v-wave, the relationships of E/e′ with ΔP and v-wave were relatively rough, and the area under the ROC of the E/e′ for detecting an increased v-wave was significantly smaller than that of the D/R ratio. The E/e′ is one of the most widely used echocardiographic parameters in clinical routine practice and has been known to reflect the mean LA pressure [12]. Although the mean LA pressure is largely determined by the pressure increase during the late-reservoir phase and v-wave, they do not always coincide. Thus, the appropriateness of using E/e′ as a component of the LA stiffness index is still a matter of debate. In addition, several conditions are known to reduce the accuracy of LA pressure estimation by E/e′ [12]. These factors may have been the cause of the inadequate relationships between E/e′ and ΔP and v-wave in the present study.

**Relationships between 2DSTE parameters and volume change in LA**

In the present study, 2DSTE-derived LA-GLS was not significantly correlated with LA volume change during the late-reservoir phase. The LA strain parameters represent the change rate of the LA myocardium relative to its initial circumference, and therefore do not necessarily reflect the change in LA volume. Thus, it seems inappropriate to use the LA strain parameters as a surrogate for the LA volume change. In the present study, the 2DSTE-derived volume change parameter, $\Delta V_{STE}$, was well correlated with the

$\Delta V_{MOD}$. While the $\Delta V_{MOD}$ requires four separate manual tracings of the LA endocardial surface, the $\Delta V_{STE}$ can be obtained simultaneously when measuring LA-GLS. This is a great advantage of the $\Delta V_{STE}$ compared with the $\Delta V_{MOD}$.

Several investigators have reported the usefulness of the 2DSTE-derived LA-GLS for predicting the prognosis of patients with valvular heart diseases [13,14], ischemic heart diseases [15], and heart failure [16,17]. We consider that LA-GLS has the potential to become a routine echocardiographic parameter in the coming years. As noted above, the $\Delta V_{STE}$ can be obtained simultaneously with LA-GLS. Thus, we believe that measuring 2DSTE-derived $\Delta V_{STE}$ as one of the components of LA stiffness in routine examinations might be reasonable.

**Clinical implications of noninvasive LA stiffness assessment**

Ideally, it would be valuable to be able to perform a routine stiffness assessment based on the P-V loop of the LA. However, its highly invasive aspect makes this impractical. Therefore, the establishment of a noninvasive LA stiffness index is desirable. Although 2DSTE-derived LA strain parameters are well-known to reflect the corresponding LA functions, they only represent the degree of wall expansion or contraction, and do not directly correspond to the LA stiffness based on the pressure–volume relationship. Myocardial fibrosis in the LA occurs due to aging [18], hypertension [19], accumulation of burden from chronic LV diastolic dysfunction [20], mitral valve disease [13,21], and cardiomyopathy [22]. Increased fibrosis in the LA, which is thought as the main cause of the increased LA stiffness, has been reported to be related to the development of atrial fibrillation [23]. The LA stiffness index was reported to be superior to the LA strain parameters in detecting an increase in LA myocardial fibrosis [24]. Regardless of whether the LV ejection fraction is reduced or preserved, the LA burden increases as LV diastolic dysfunction progresses. Accumulation of this increased burden is thought to result in increased LA stiffness [20]. Thus, a more precise method for evaluating LA stiffness is desired.

Kurt et al. were the first to report that the scatter plot between pulmonary artery systolic pressure and the ratio of PAWP to LA-GLS was analogous to that between pulmonary artery systolic pressure and the [E/e']/LA-GLS, and based on this finding, they argued for the validity of using [E/e']/LA-GLS as an LA stiffness index [25]. Since the publication of their paper, several studies have used the [E/e']/LA-GLS as a non-invasive method of estimating LA stiffness [7,24,26], but to our knowledge, there has been no report directly investigating the relationship between the [E/e']/LA-GLS and an invasively obtained LA stiffness parameter, and an echocardiographic method to estimate the LA stiffness has not been well established. In the present study, we established a novel LA stiffness parameter based on the measurement from PV flow and the 2DSTE-derived time–LA volume curve, $[D/R]/\Delta V_{STE}$, and also demonstrated that the $[D/R]/\Delta V_{STE}$ and $\Delta P/V_{MOD}$ are equally valuable for assessing the prognosis of patients with heart diseases.

**Limitations**

There are several limitations to this study. First, because this study was performed retrospectively, the right heart catheterization and echocardiography were not performed simultaneously; there was a time difference of 2.1±3.2 days [0–7 days]. We carefully checked each patient’s medical record and excluded patients in which there was a change in medications or weight between echocardiography and RHC. However, the possibility of hemodynamic alteration might not be completely excluded and this remains still one of the main limitations of this study. Second, in patients who cannot record a sharp PV flow waveform, the novel LA stiffness index, $[D/R]/\Delta V_{STE}$, cannot be calculated. In addition, even if PV flow can be obtained, the D/R ratio cannot be calculated when the S wave becomes reversed due to severe mitral regurgitation [27]. In the present study, 6 of the initial study subjects had the reversal S-wave, and all of them were excluded as an inadequate PV flow waveform. Third, while $\Delta V_{STE}$ was well correlated with $\Delta V_{MOD}$, the former tended to overestimate the latter ($p < 0.001$ for paired t-test). The main reason for the overestimation of the ΔVSTE may come from the suboptimal two-chamber view [28]. In addition, there is a possibility of a difference between manually traced endocardial borders and automatically generated endocardial borders by 2DSTE at pre-atrial contraction. Fourth, because of the small number of patients who experienced the primary endpoint, it was difficult to examine the superiority or inferiority of $[D/R]/\Delta V_{STE}$ to other indices of LA function, such as LA-GLS. In addition, we simply used the median value of our 222 patients for a cutoff value. Further studies are needed to establish the prognostic value of $[D/R]/\Delta V_{STE}$ and investigate a better cutoff value.

## CONCLUSION

The D/R ratio of the PV flow successfully estimated the LA pressure change during the late-reservoir phase and v-wave, and $[D/R]/\Delta V_{STE}$, which was calculated by dividing the D/R ratio by the 2DSTEderived LA volume change, was a useful method for non-invasive evaluation of LA stiffness. In addition, this novel index for LA stiffness might be valuable in the prognostic evaluation of patients with cardiac diseases.

## Statements and Declarations

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**Ethics approval**: This study was approved by the Research Ethics Committee of Hokkaido University Hospital (No. 020-0436).

**Consent to participate**: As all examinations were performed within the scope of medical care, to obtain informed consent was waived. The objectives and methods of this study were shared with the public both through our institution's website and on a physical bulletin board; patients who did not wish to participate could request that their data be removed from the study.

**Consent to publish**: Not applicable

**Data Availability Statements**: The data underlying this article will be shared on reasonable request to the corresponding author.

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**Table 1. Patient characteristics**

| | **All patients (n=222)** | **$\Delta P/\Delta V_{MOD}$ ≤0.25 (n=111)** | **$\Delta P/\Delta V_{MOD}$ >0.25 (n=111)** | **p-value** |
|---|---|---|---|---|
| Age, yrs | 61.7±15.9 | 61.5±15.5 | 62.0±16.3 | 0.82 |
| Female, n (%) | 89 (40%) | 43 (39%) | 47 (42%) | 0.50 |
| Body surface area, $m^2$ | 1.63±0.20 | 1.65±0.21 | 1.60±0.18 | 0.09 |
| Systolic blood pressure, mmHg | 117±21 | 118±18 | 117±23 | 0.93 |
| Heart rate, bpm | 66±12 | 66±12 | 67±12 | 0.39 |
| **Medications, n (%)** | | | | |
| ACE inhibitor or ARB | 122 (55%) | 63 (57%) | 59 (53%) | 0.59 |
| Beta-blocker | 102 (46%) | 54 (49%) | 48 (43%) | 0.42 |
| Diuretics | 98 (44%) | 45 (41%) | 53 (48%) | 0.28 |
| Mineralocorticoid antagonist | 61 (27%) | 30 (27%) | 31 (28%) | 0.88 |
| **Laboratories** | | | | |
| Hemoglobin, g/dL | 12.7±2.0 | 12.9±2.0 | 12.6±2.2 | 0.32 |
| Albumin, g/dL | 3.9±0.5 | 4.0±0.5 | 3.9±0.6 | 0.49 |
| Cholinesterase, g/dL | 270 (222-327) | 282 (235-328) | 263 (208-315) | 0.07 |
| Creatinine, mg/L | 0.84 (0.70-1.06) | 0.84 (0.71-1.01) | 0 .85 (0.70-1.16) | 0.60 |
| BNP, pg/mL | 122 (43-328) | 88 (42-243) | 160 (43-441) | 0.013 |
| **Echocardiographic parameters** | | | | |
| LV diastolic dimension, mm | 54±11 | 54±10 | 54±11 | 0.995 |
| LV mass index, g/$m^2$ | 118±38 | 119±36 | 118±41 | 0.91 |
| LV ejection fraction, % | 49±17 | 49±17 | 47±17 | 0.33 |
| LA volume index, mL/$m^2$ | 47±20 | 45±20 | 48±20 | 0.29 |
| $\Delta V_{MOD}$, mL | 17.0±8.8 | 18.9±8.6 | 15.1±8.6 | 0.001 |
| MR ≥moderate, n (%) | 44 (20%) | 27 (24%) | 17 (15%) | 0.09 |
| E/e′ | 12.4±5.7 | 11.3±4.4 | 13.5±6.7 | 0.006 |
| S, cm/s | 53.1±19.3 | 53.9±18.4 | 52.3±20.2 | 0.56 |
| D, cm/s | 50.9±18.0 | 46.8±14.5 | 55.0±20.2 | 0.001 |
| R, cm/s | 21.7±8.9 | 23.5±8.8 | 19.9±8.6 | 0.002 |
| S/D | 1.2±0.5 | 1.2±0.5 | 1.1±0.6 | 0.11 |
| S/R | 2.7±1.3 | 2.5±1.0 | 2.9±1.5 | 0.013 |
| D/R | 2.8±1.8 | 2.2±1.1 | 3.4±2.1 | <0.001 |
| LA-GLS, % | 18.8±7.9 | 19.9±7.4 | 17.8±8.2 | 0.042 |
| LA-$LS_{PR}$, % | 10.1±5.4 | 10.4±5.2 | 9.8±5.7 | 0.40 |
| $\Delta V_{STE}$, mL | 20.5±10.6 | 21.6±10.5 | 19.4±10.8 | 0.14 |
| [E/e′]/LA-GLS, /% | 0.87±0.82 | 0.67±0.42 | 1.08±1.06 | <0.001 |

| | | | | |
|---|---|---|---|---|
| **Hemodynamic parameters** | | | | |
| PAWP, mmHg | 11.9±6.8 | 9.2±4.4 | 14.6±7.6 | <0.001 |
| x-descent, mmHg | 9.6±6.4 | 7.9±4.3 | 11.8±7.5 | <0.001 |
| v-wave, mmHg | 14.6±9.6 | 10.3±4.9 | 18.9±11.2 | <0.001 |
| y-descent, mmHg | 9.9±5.6 | 7.8±4.3 | 11.9±6.0 | <0.001 |
| ΔP, mmHg | 4.8±4.4 | 2.4±1.3 | 7.2±5.1 | <0.001 |
| **LA stiffness parameters** | | | | |
| $\Delta P/\Delta V_{MOD}$, mmHg/mL | 0.33±0.29 | 0.14±0.06 | 0.52±0.30 | <0.001 |

BNP, brain natriuretic peptide; LV, left ventricular; LA, left atrial; $\Delta V_{MOD}$, LA volume change during late-reservoir phase by biplane method of disks; MR, mitral regurgitation; E/e′, ratio of the early-diastolic transmitral flow velocity to early-diastolic mitral annular velocity; S, peak systolic pulmonary venous flow velocity; D, peak diastolic pulmonary venous flow; R, minimum velocity between the systolic and diastolic pulmonary venous flow. LA-GLS, LA global longitudinal strain; LA- $LS_{PR}$, LA longitudinal strain during the passive reservoir period; $\Delta V_{STE}$, LA volume change during late reservoir phase by two-dimensional speckle tracking, PAWP: mean pulmonary artery wedge pressure; ΔP, pressure change between x-descent and v-wave.

**Table 2. The relationships of PV flow parameters with ΔP and v-wave**

| | vs ΔP | | vs v-wave | |
|---|---|---|---|---|
| **parameter** | **r** | **p** | **r** | **p** |
| **S/D** | −0.31 | <0.001 | −0.47 | <0.001 |
| **S/R** | 0.14 | 0.032 | −0.04 | 0.60 |
| **D/R** | 0.62 | <0.001 | 0.63 | <0.001 |

After applying Bonferroni correction, $p<0.017$ was considered significant.

**Table 3. Univariate Cox regression analysis results**

| Variables | $\chi^2$ | Hazard ratio (95%CI) | p-value |
|---|---|---|---|
| Age, per 1 year | 0.98 | 1.01 (0.99-1.03) | 0.32 |
| Female | 0.76 | 0.77 (0.43-1.39) | 0.38 |
| Body surface area, per 1 year | 0.16 | 1.34 (0.33-5.50) | 0.69 |
| Systolic blood pressure, per 1 mmHg | 3.30 | 0.99 (0.97-1.00) | 0.07 |
| Heart rate, per 1 bpm | 0.47 | 0.99 (0.97-1.02) | 0.49 |
| LV diastolic dimension, per 1 mm | 1.74 | 1.02 (0.99-1.04) | 0.19 |
| LV mass index, per 1 g/m$^2$ | 0.15 | 1.00 (0.99-1.01) | 0.70 |
| LV ejection fraction, per 1% | 6.37 | 0.98 (0.96-1.00) | 0.012 |
| LA volume index, per 1 mL/m$^2$ | 25.5 | 1.03 (1.02-1.04) | <0.001 |
| E/e′, per unit | 21.4 | 1.10 (1.06-1.15) | <0.001 |
| S/D, per unit | 18.3 | 0.23 (0.12-0.46) | <0.001 |
| S/R, per unit | 0.57 | 0.91 (0.72-1.16) | 0.45 |
| D/R, per unit | 22.9 | 1.38 (1.21-1.57) | <0.001 |
| MR ≥moderate | 5.32 | 2.08 (1.12-3.89) | 0.021 |
| LA-GLS, per 1% | 28.0 | 0.87 (0.82-0.91) | <0.001 |
| LA-$LS_{PR}$, per 1% | 8.01 | 0.90 (0.84-0.97) | 0.005 |
| $\Delta V_{MOD}$, per 1 mL | 0.36 | 1.01 (0.98-1.05) | 0.55 |
| $\Delta V_{STE}$, per 1 mL | 1.32 | 1.02 (0.99-1.04) | 0.25 |
| PAWP, per 1 mmHg | 36.3 | 1.11 (1.07-1.15) | <0.001 |
| v-wave, per 1 mmHg | 42.4 | 1.07 (1.05-1.10) | <0.001 |
| $\Delta P$, per 1 mmHg | 33.4 | 1.12 (1.09-1.18) | <0.001 |
| $\Delta P/\Delta V_{MOD}$, per 1 mmHg/mL | 19.9 | 3.80 (2.11-6.83) | <0.001 |
| [E/e′]/LA-GLS, per 1 /% | 52.7 | 2.40 (1.90-3.05) | <0.001 |
| [D/R]/$\Delta V_{STE}$, per 1 /mL | 8.21 | 8.20 (1.95-34.6) | 0.004 |

CI, confidence interval. Other abbreviations are the same as in **Table 1**.

**Table 4. Multivariate Cox regression analysis results**

| Variables | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\chi^2$ | Hazard ratio (95%CI) | p-value | $\chi^2$ | Hazard ratio (95%CI) | p-value | $\chi^2$ | Hazard ratio (95%CI) | p-value |
| Age, per 1 year | 2.09 | 1.02 (1.00-1.04) | 0.15 | 0.04 | 1.00 (0.98-1.02) | 0.84 | 1.53 | 1.01 (0.99-1.03) | 0.22 |
| LA volume index, per 1 mL/m$^2$ | 18.3 | 1.03 (1.02-1.04) | <0.001 | 8.43 | 1.02 (1.01-1.04) | 0.004 | 21.7 | 1.03 (1.02-1.05) | <0.001 |
| LV ejection fraction, per 1% | 1.98 | 0.99 (0.97-1.01) | 0.16 | 0.02 | 1.00 (0.98-1.02) | 0.89 | 1.14 | 0.99 (0.97-1.01) | 0.29 |
| $\Delta P/\Delta V_{MOD}$, per 1 mmHg/mL | 17.1 | 3.55 (1.95-6.48) | <0.001 | | | | | | |
| [E/e′]/LA-GLS, per 1/% | | | | 26.6 | 2.15 (1.61-2.88) | <0.001 | | | |
| [D/R]/$\Delta V_{STE}$, per 1/mL | | | | | | | 9.19 | 9.83 (2.25-43.0) | 0.002 |

CI, confidence interval. Other abbreviations are the same as in **Table 1**.

**Figure legends**

**Figure 1. Inclusion and exclusion criteria for the study subjects**

**Figure 2. Measurements of left atrial pressure change during reservoir phase**

From the waveform of the pulmonary artery wedge pressure, the nadir of the x-descent and the peak v-wave were measured and the difference between them ($\Delta P$) was calculated.

**Figure 3. Measurements of pulmonary venous (PV) flow**

From the PV flow waveform, the peak systolic velocity (S), the peak diastolic velocity (D), and the minimum velocity between them (R) were measured, and the S/D, S/R, and D/R were calculated.

**Figure 4. Two-dimensional speckle tracking echocardiography**

From the time–LA global longitudinal strain curve, the LA passive reservoir strain (LA-$LS_{PR}$) and LA global longitudinal strain (LA-GLS) were measured. From the time–LA volume curve, the difference between the LA maximum volume and LA volume just before atrial contraction ($\Delta V_{STE}$) was calculated.

**Figure 5. Relationships between echocardiographic parameters and $\Delta P$**

**Figure 6. Receiver operating characteristic curve for detecting increased v-wave**

**Figure 7. Relationships between non-invasive LA stiffness parameters and $\Delta P/\Delta V_{MOD}$**

**Figure 8. Kaplan-Meier curve for the cardiac event-free probability in patients stratified by $\Delta P/\Delta V_{MOD}$ (A) and $[D/R]/\Delta V_{STE}$ (B)**

# Figure 1

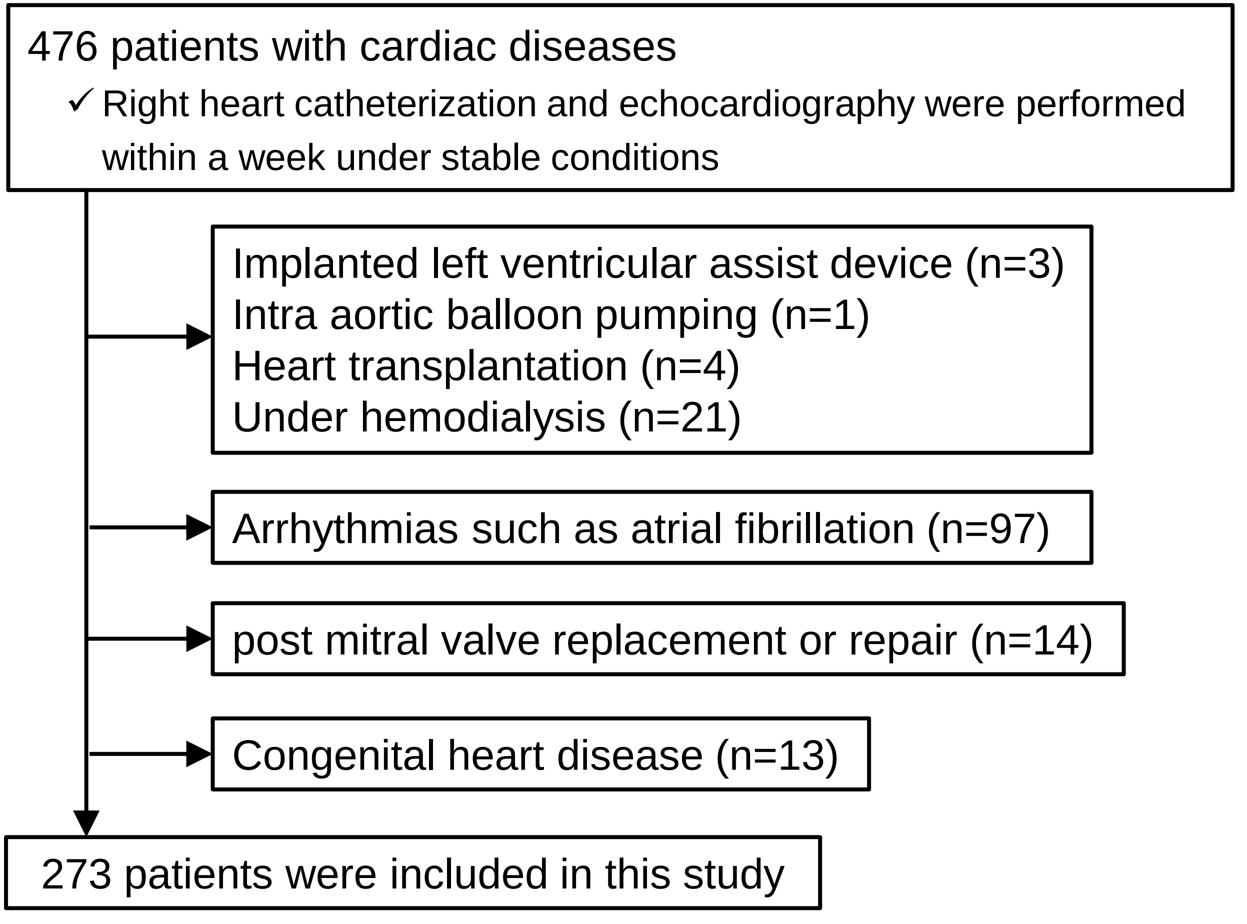

476 patients with cardiac diseases
✓ Right heart catheterization and echocardiography were performed within a week under stable conditions
Implanted left ventricular assist device (n=3)
Intra aortic balloon pumping (n=1)
Heart transplantation (n=4)
Under hemodialysis (n=21)
Arrhythmias such as atrial fibrillation (n=97)
post mitral valve replacement or repair (n=14)
Congenital heart disease (n=13)
273 patients were included in this study

Figure 2

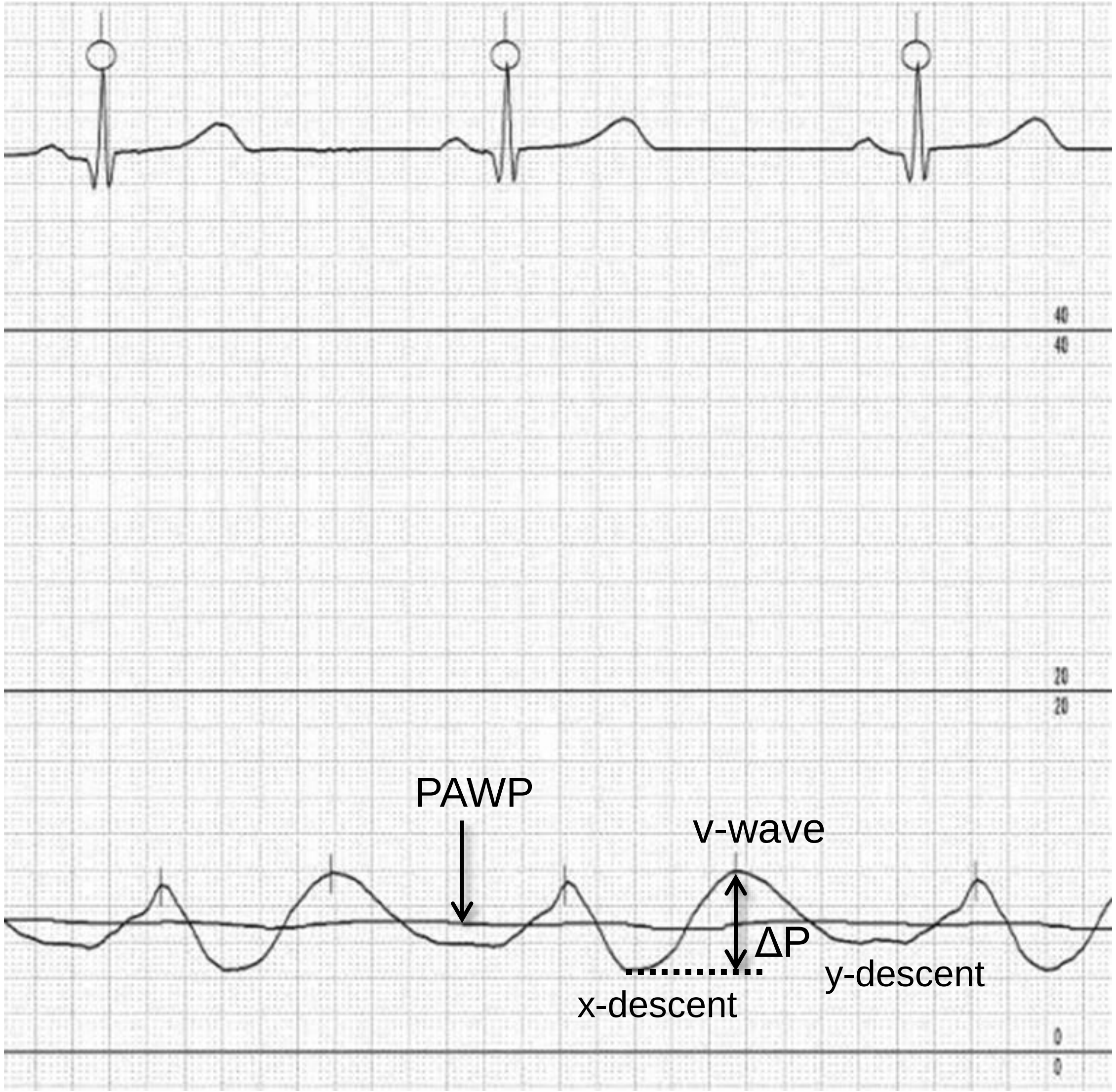
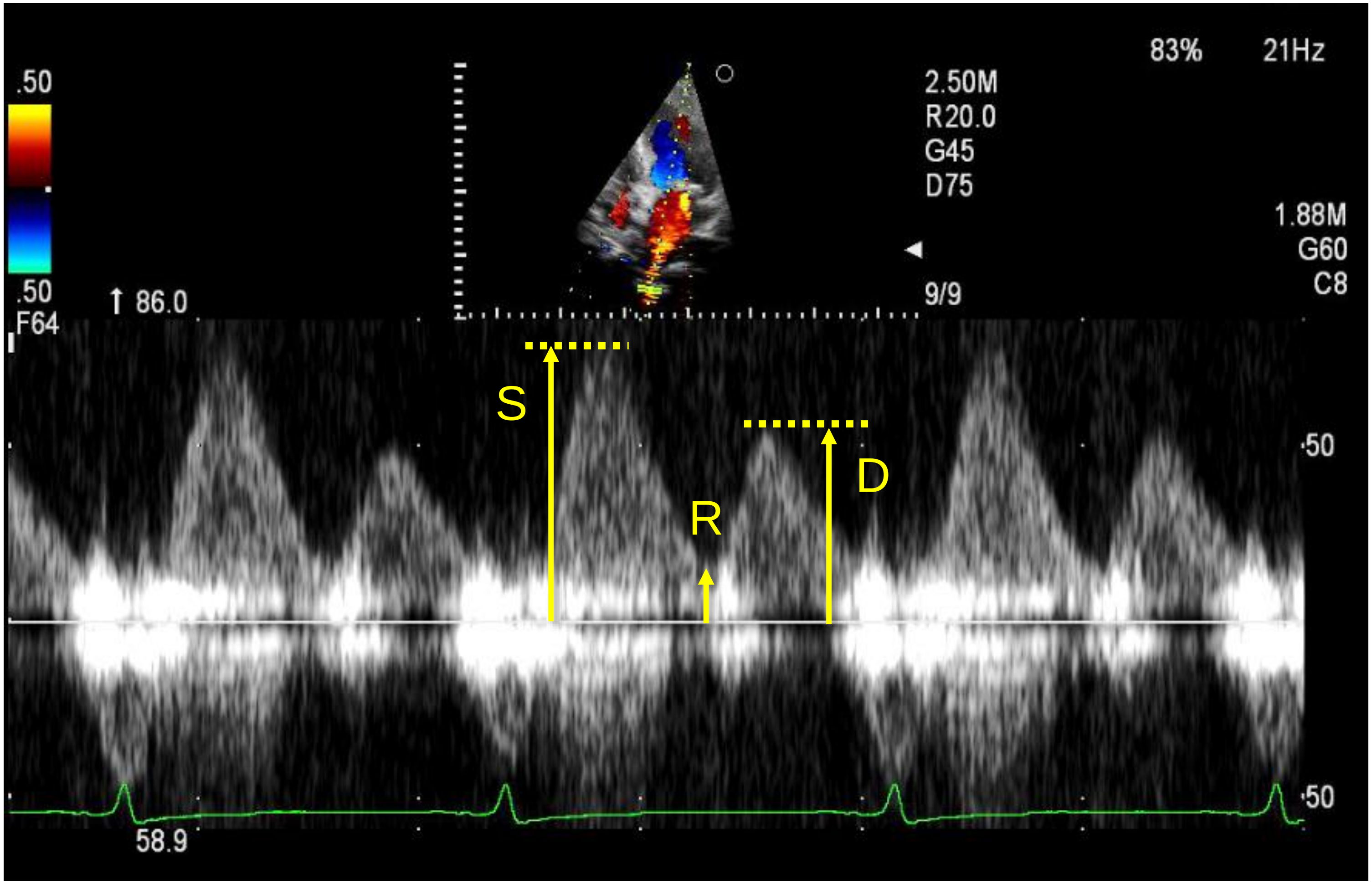
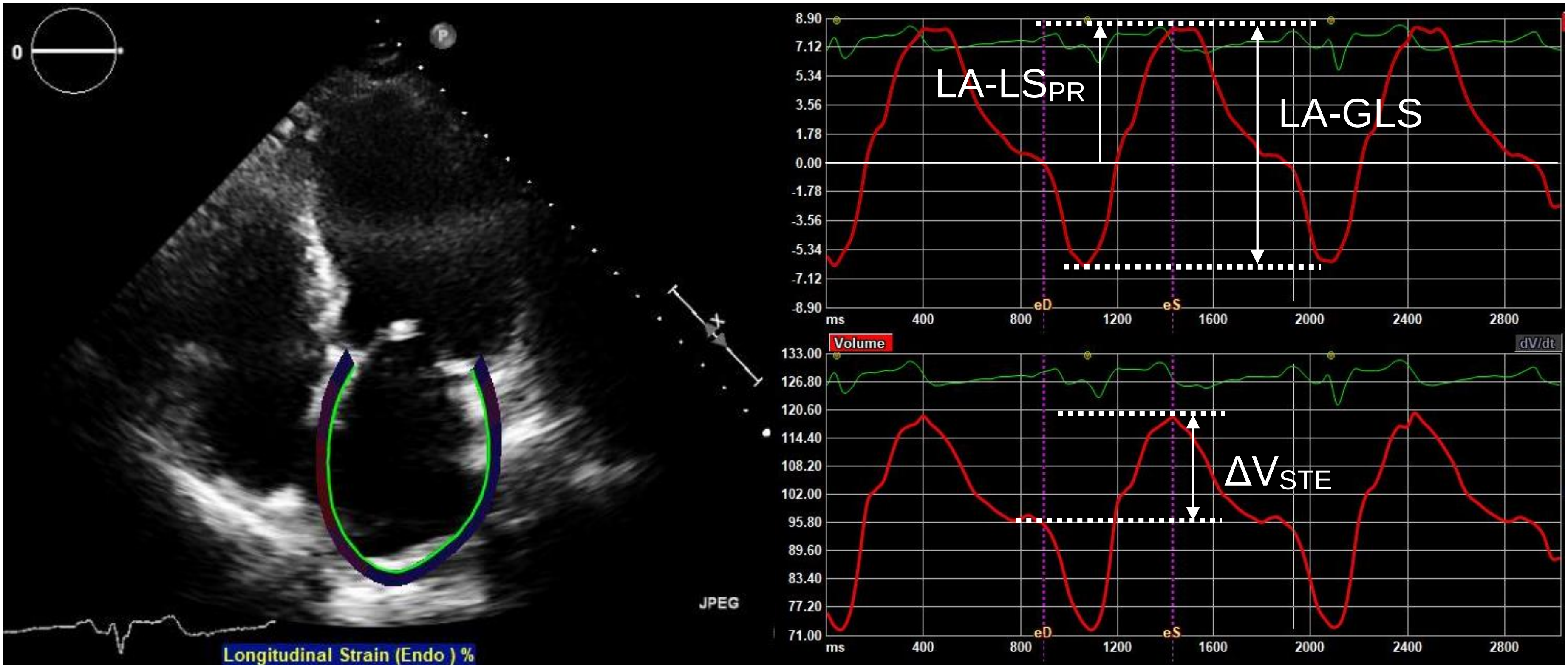


Figure 3



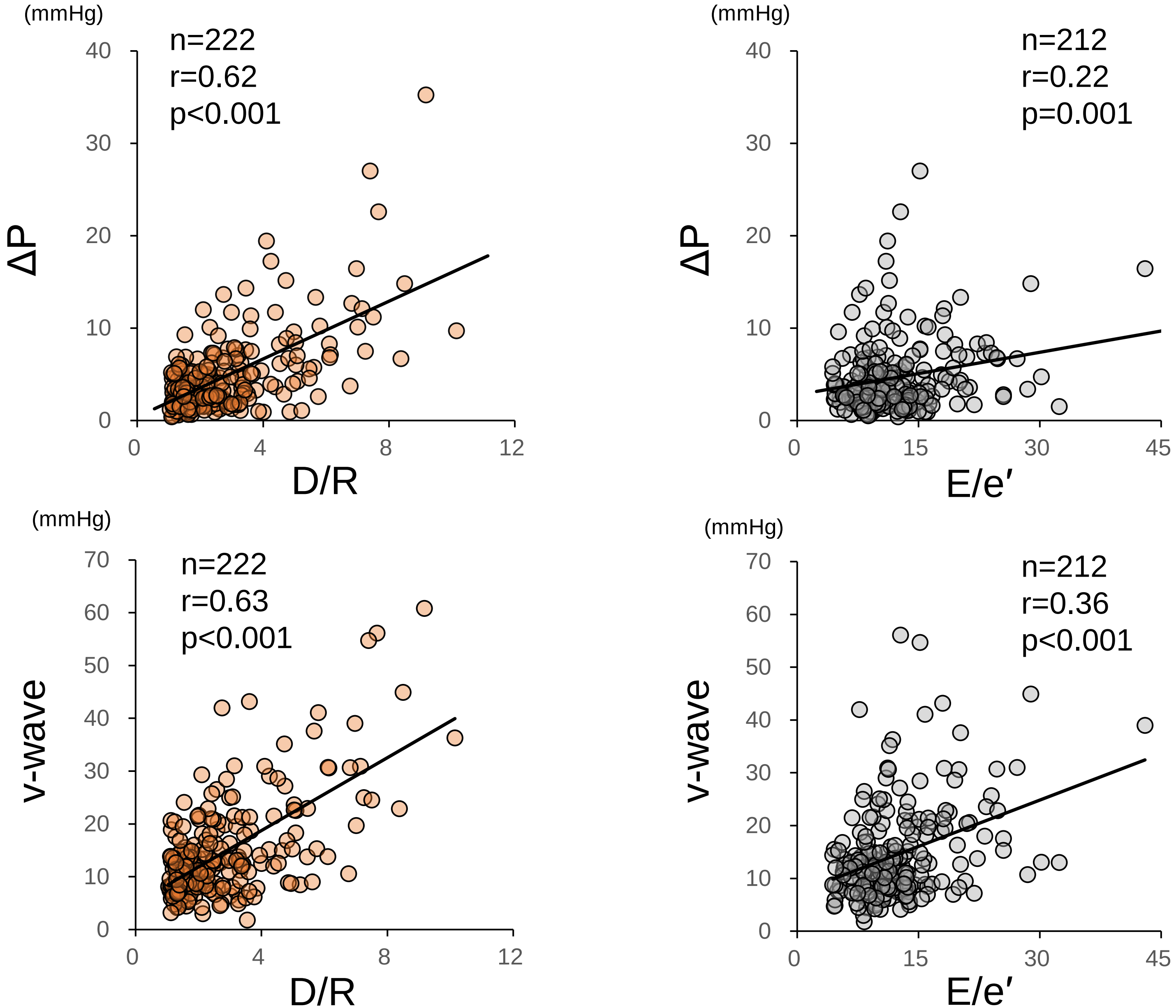
.50
.50
F64
86.0
2.50M
R20.0
G45
D75
9/9
83%
21Hz
1.88M
G60
C8
50
50
58.9
S
R
D

Figure 4



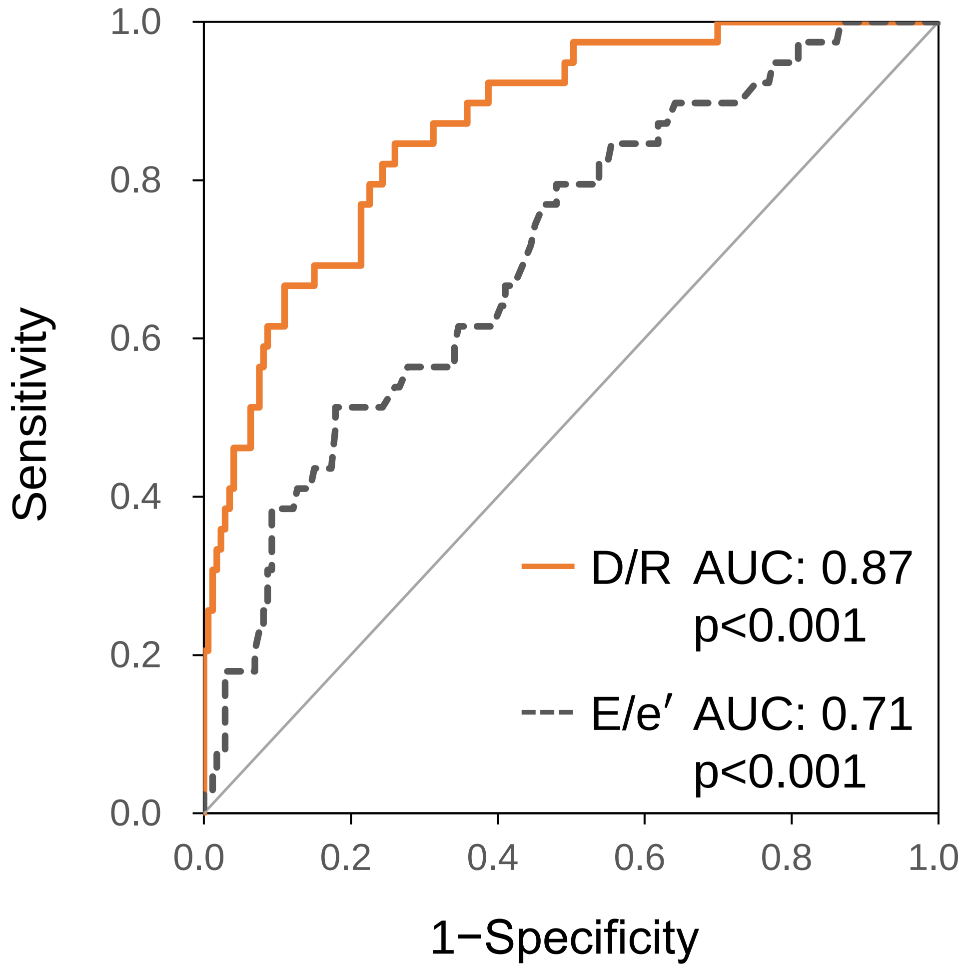
LA-LSPR
LA-GLS
ΔVSTE
Longitudinal Strain (Endo ) %
JPEG
Volume
dV/dt
eD
eS
ms

Figure 5



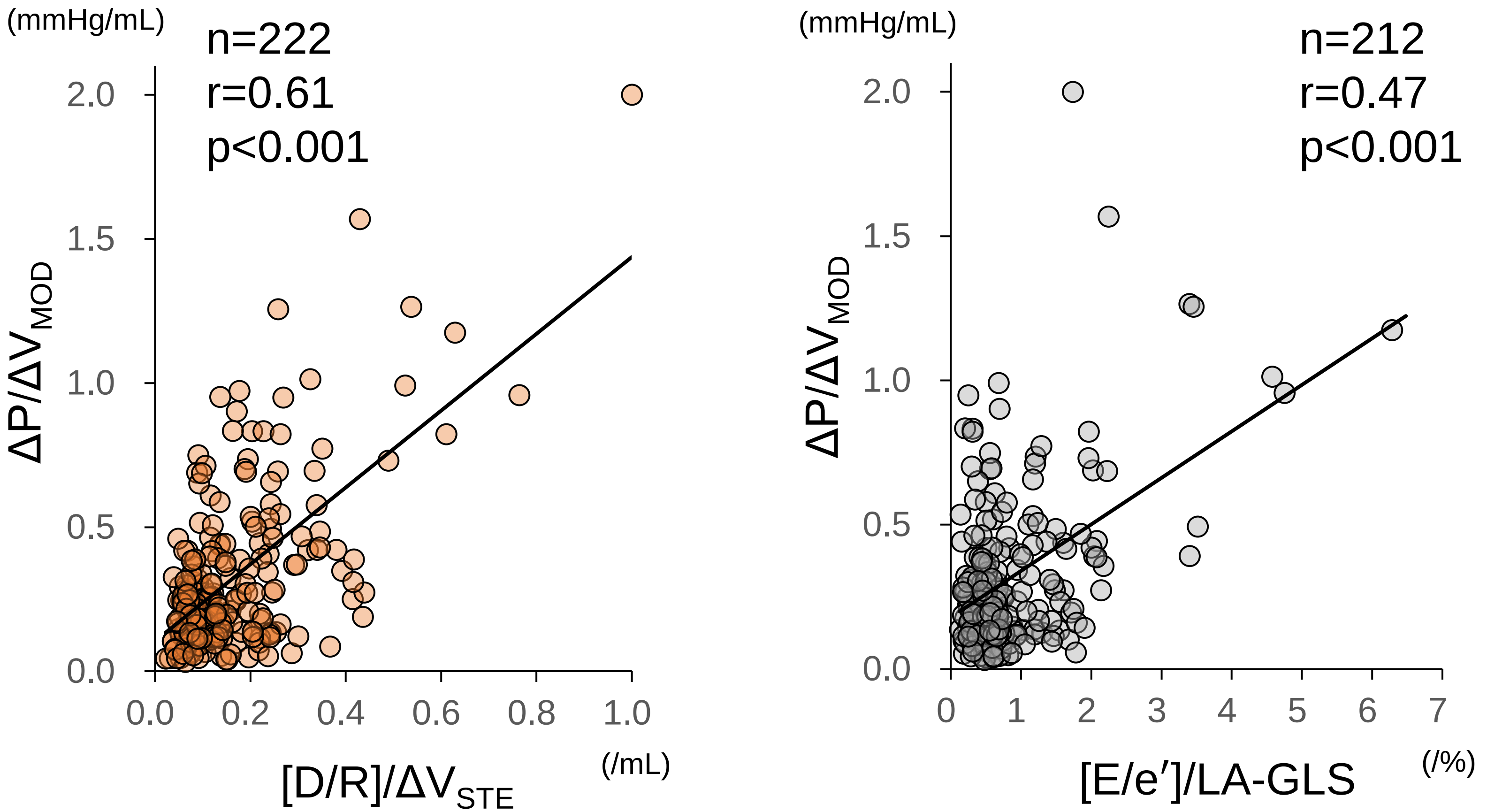
(mmHg)
n=222
r=0.62
p<0.001
ΔP
D/R
(mmHg)
n=212
r=0.22
p=0.001
ΔP
E/e′
(mmHg)
n=222
r=0.63
p<0.001
v-wave
D/R
(mmHg)
n=212
r=0.36
p<0.001
v-wave
E/e′

Figure 6

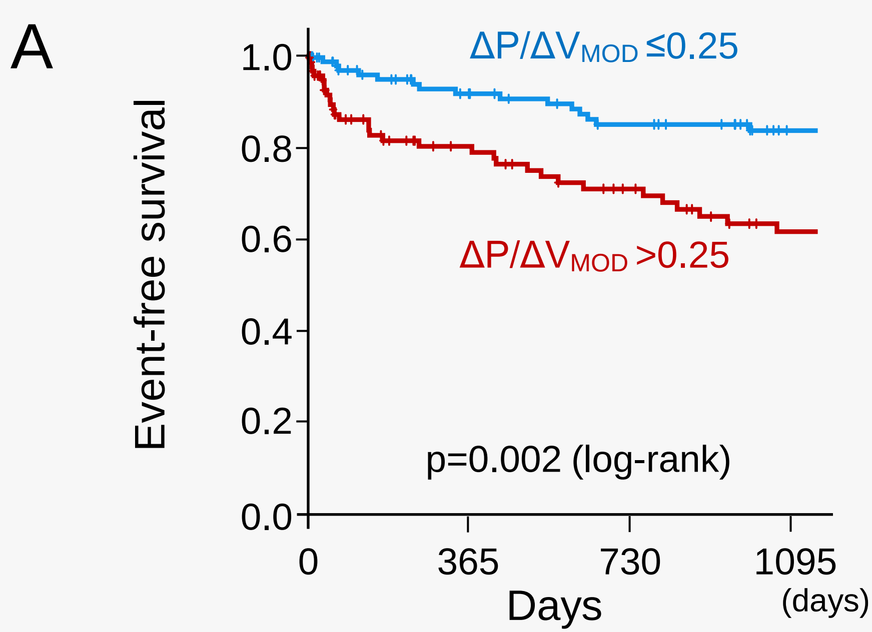


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1−Specificity
D/R AUC: 0.87
p<0.001
E/e′ AUC: 0.71
p<0.001

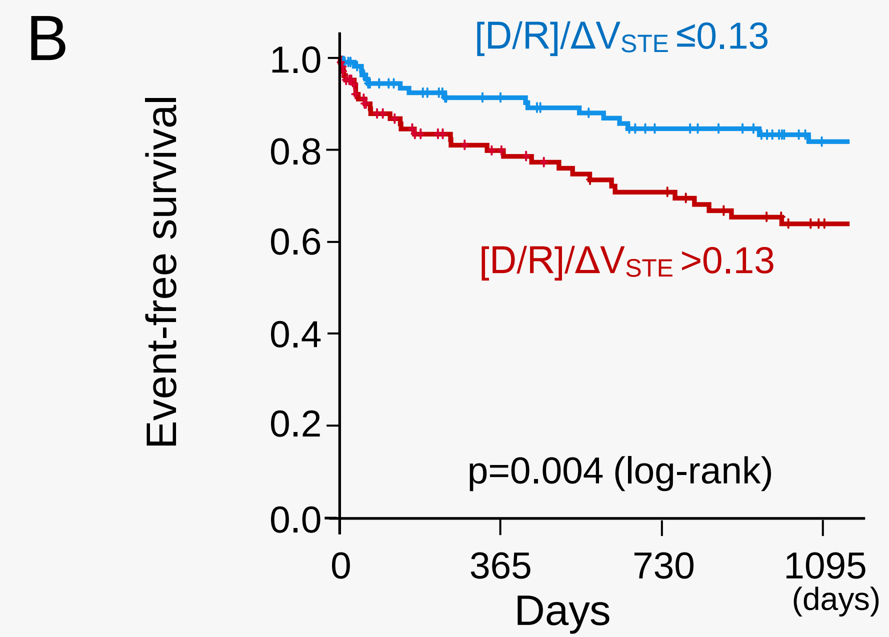
# Figure 7


(mmHg/mL)
n=222
r=0.61
p<0.001
2.0
1.5
1.0
0.5
0.0
ΔP/ΔV_MOD
0.0
0.2
0.4
0.6
0.8
1.0
(/mL)
[D/R]/ΔV_STE
(mmHg/mL)
n=212
r=0.47
p<0.001
2.0
1.5
1.0
0.5
0.0
ΔP/ΔV_MOD
0
1
2
3
4
5
6
7
(/%)
[E/e′]/LA-GLS

# Figure 8




| Number at risk | | | | |
|---|---|---|---|---|
| $\Delta P/\Delta V_{MOD}$ ≤0.25 | 111 | 84 | 73 | 56 |
| $\Delta P/\Delta V_{MOD}$ >0.25 | 111 | 65 | 51 | 38 |




| Number at risk | | | | |
|---|---|---|---|---|
| $[D/R]/\Delta V_{STE}$ ≤0.13 | 111 | 82 | 68 | 53 |
| $[D/R]/\Delta V_{STE}$ >0.13 | 111 | 67 | 56 | 41 |