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Author(s)	Okada, Kazunori; Kaga, Sanae; Abiko, Rika; Murayama, Michito; Hioka, Takuma; Nakabachi, Masahiro; Yokoyama, Shinobu; Nishino, Hisao; Ichikawa, Ayako; Abe, Ayumu; Nishida, Mutsumi; Asakawa, Naoya; Tsujinaga, Shingo; Hayashi, Taichi; Iwano, Hiroyuki; Yamada, Satoshi; Masauzi, Nobuo; Mikami, Taisei
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**Novel Echocardiographic Method to Assess Left Ventricular Chamber Stiffness and Elevated End-Diastolic Pressure Based on Time-Velocity Integral Measurements of Pulmonary Venous and Transmitral Flows**

Kazunori Okada<sup>1\*</sup>, Sanae Kaga<sup>1</sup>, Rika Abiko<sup>2</sup>, Michito Murayama<sup>3</sup>, Takuma Hioka<sup>3</sup>, Masahiro Nakabachi<sup>3</sup>, Shinobu Yokoyama<sup>3</sup>, Hisao Nishino<sup>3</sup>, Ayako Ichikawa<sup>3</sup>, Ayumu Abe<sup>3</sup>, Mutsumi Nishida<sup>3</sup>, Naoya Asakawa<sup>4</sup>, Shingo Tsujinaga<sup>4</sup>, Taichi Hayashi<sup>4</sup>, Hiroyuki Iwano<sup>4</sup>, Satoshi Yamada<sup>4</sup>, Nobuo Masauzi<sup>1</sup>, and Taisei Mikami<sup>1</sup>

<sup>1</sup>Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo 060-0812, Japan

<sup>2</sup>Department of Health Sciences, School of Medicine, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo 060-0812, Japan

<sup>3</sup>Diagnostic Center for Sonography, Hokkaido University Hospital, Kita-14, Nishi-5, Kita-ku, Sapporo 060-8648, Japan

<sup>4</sup>Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

**\*Corresponding author:** Kazunori Okada, PhD

Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo 060-0812, Japan; Tel: +81-11-706-3730; Email: [ichinori@hs.hokudai.ac.jp](mailto:ichinori@hs.hokudai.ac.jp)

**Running title:** Echocardiographic assessment of LV stiffness

**Conflict of interest:** None to declare

**ABSTRACT**

**Aims:** The detection of increased left ventricular (LV) chamber stiffness may play an important role in assessing cardiac patients with potential but not overt heart failure. A noninvasive method to estimate it is not established. We investigated whether the echocardiographic backward/forward flow volume ratio from the left atrium (LA) during atrial contraction reflects the LV chamber stiffness.

**Methods:** We studied 62 patients who underwent cardiac catheterization and measured their LV end-diastolic pressure (LVEDP) and pressure increase during atrial contraction ( $\Delta Pa$ ) from the LV pressure waveform. Using the echocardiographic biplane method of disks, we measured the LV volume change during atrial contraction indexed to the body surface area ( $\Delta Va$ ), and  $\Delta Pa/\Delta Va$  was calculated as a standard for the LV operating chamber stiffness. Using pulsed Doppler echocardiography, we measured the time-velocity integral (TVI) of the backward pulmonary venous (PV) flow during atrial contraction ( $I_{PVA}$ ) and the ratio of  $I_{PVA}$  to the PV flow TVI throughout a cardiac cycle ( $F_{PVA}$ ). We also measured the TVI of the atrial systolic forward transmitral flow ( $I_A$ ) and the ratio of the  $I_A$  to the transmitral TVI during a cardiac cycle ( $F_A$ ) and calculated  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$ .

**Results:**  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$  were well correlated with  $\Delta Pa/\Delta Va$  ( $r=0.79$  and  $r=0.81$ ) and LVEDP ( $r=0.73$  and  $r=0.77$ ). The areas under the ROC curve to discriminate LVEDP  $>18$  mmHg were 0.90 for  $I_{PVA}/I_A$  and 0.93 for  $F_{PVA}/F_A$ .

**Conclusion:** The  $F_{PVA}/F_A$ , the backward/forward flow volume ratio from the LA during atrial contraction, is useful for noninvasive assessments of LV chamber stiffness and elevated LVEDP.

**Key words:** left ventricular chamber stiffness, left ventricular end-diastolic pressure, pulmonary venous flow, heart failure

## INTRODUCTION

It is well known that the left ventricular (LV) diastolic pressure rises more steeply as the LV volume increases in a curvilinear relation and becomes the highest during atrial contraction up to end-diastole. A pathological increase in chamber stiffness, usually associated with a prominent "A"-wave and elevated LV end-diastolic pressure, may precede an elevation of mean left atrial (LA) pressure and resultant pulmonary congestion [1,2]. Thus, even in patients without apparent symptoms of heart failure, the detection of increased chamber stiffness and elevated LV end-diastolic pressure may play a key role in managing patients with potential heart failure in order to prevent the development of overt heart failure [1–5].

At present, the measurement of LV operating chamber stiffness requires both an invasive pressure recording and the volume measurement using conductance catheter volumetry, sonomicrometry or echocardiography [3,4,6,7], but cardiac catheterization is invasive and not entirely free from complications. A completely noninvasive method to precisely assess LV chamber stiffness could thus be extremely valuable in clinical practice, but such a method has not yet been established.

An increase in LV chamber stiffness results in a decrease in forward transmitral flow and an increase in the pulmonary venous (PV) backward flow during atrial contraction. Based on this phenomenon, it was reported that the velocity of the atrial systolic backward PV flow [8] and the difference between the PV and transmitral flow durations during atrial contraction [5,9] reflect the LV pressure increase during atrial contraction and LV end-diastolic pressure. However, there are some questions regarding the diagnostic power of these parameters [10–12]. We speculate that the backward/forward flow volume ratio from the LA during atrial contraction would reflect the LV chamber stiffness more accurately than the conventional indices.

The aim of this study was to determine the clinical usefulness of a novel noninvasive index reflecting the backward/forward flow volume ratio from the LA during atrial

contraction, which was derived from time-velocity integral measurements of the PV and transmitral flows, for estimating LV operating chamber stiffness and identifying patients with elevated LV end-diastolic pressure.

## **METHODS**

### **Subjects**

We retrospectively examined consecutive patients who were admitted to Hokkaido University Hospital from January 2013 to December 2015 and underwent echocardiographic examination and left heart catheterization under stable clinical condition within 1 week. In regard to the study enrollment, we carefully excluded patients with changes in clinical condition such as symptoms and signs of heart failure, body weight and plasma BNP level or in cardiovascular medications between echocardiography and catheterization. Patients with atrial fibrillation, frequent premature beats, advanced atrioventricular block, congenital heart disease, any degree of mitral stenosis, or severe mitral regurgitation were also excluded. Among the remaining 71 patients, an adequate Doppler flow velocity waveform of PV flow could not be obtained in five patients, and transmitral flow Doppler flow velocity measurements could not be made in other four patients due to the summation of the early-diastolic and atrial systolic waves caused by tachycardia. Thus, the measurements of both PV flow and transmitral flow waveforms were successful in 62 of the 71 patients (87%).

This study was approved as a retrospective observational study by both the Research Ethics Committee of Hokkaido University Hospital and the Ethics Committee of the Faculty of Health Sciences at Hokkaido University. Instead of obtaining informed consent, the program of the present study was opened to the public both through the home page and on the bulletin board of Hokkaido University Hospital.

### **Echocardiographic Measurements**

Echocardiography was performed using an Artida system equipped with a 3.0 MHz probe (Toshiba Medical Systems, Otawara, Japan), a Vivid E9 system with an M4S probe (GE Healthcare, Buckinghamshire, UK), or an iE33 system with an S4 probe (Philips Medical Systems, Eindhoven, The Netherlands). In accord with the guidelines of the American Society of Echocardiography (ASE) [13], the LV end-diastolic dimension and the thicknesses of the interventricular septum and the LV posterior wall were measured in the end-diastolic parasternal long- and short-axis images at the chordal level, and the LV mass index was calculated.

The LA volume index was measured from apical two-chamber and four-chamber images using the biplane disk-summation method. The LV end-diastolic volume, end-systolic volume and pre-atrial systolic volume were also measured using the biplane disk-summation method, and the LV ejection fraction and the volume change during atrial contraction were calculated. The latter was corrected for each patient's body surface area ( $\Delta V_a$ ).

With standard transthoracic pulsed-Doppler echocardiography using the apical approach, we measured the peak early-diastolic and atrial systolic transmitral flow velocities (E and A, respectively), the deceleration time of the E wave (DT), the peak systolic and diastolic forward PV flows (S and D), and the backward PV flow during atrial contraction ( $V_{PVA}$ ), and we calculated the E/A and S/D. In addition, we measured the duration and time-velocity integral of the atrial systolic forward transmitral flow ( $D_A$  and  $I_A$ , respectively) and the ratio of the  $I_A$  to the transmitral flow time-velocity integral throughout a cardiac cycle ( $F_A$ ). We also measured the duration and time-velocity integral of the backward PV flow during atrial contraction ( $D_{PVA}$  and  $I_{PVA}$ , respectively) and the ratio of the  $I_{PVA}$  to the PV flow time-velocity integral during a cardiac cycle ( $F_{PVA}$ ), and then we calculated  $D_{PVA}-D_A$ ,  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$  (**Fig. 1**). Tissue Doppler imaging of the mitral annulus was performed in the apical four-chamber view. The peak systolic and early-diastolic annular velocity ( $s'$  and  $e'$ , respectively) was measured at the septal and lateral sides of the annulus. They were averaged,

and  $E/e'$  was calculated.

### **Measurements of LV End-Diastolic Pressure and LV Operating Chamber Stiffness**

Left ventricular catheterization was performed using a fluid-filled catheter. From the LV pressure records, we measured the LV pre-atrial contraction pressure, the LV pressure increase during the atrial contraction ( $\Delta Pa$ ), and the LV end-diastolic pressure (**Fig. 2**). Averaged values of five consecutive beats during end-expiratory breath-holding were used for the analysis. Then, using the catheterization  $\Delta Pa$  and echocardiographic  $\Delta Va$ , we calculated the  $\Delta Pa/\Delta Va$  ratio as an index for LV operating chamber stiffness during late-diastole [1].

### **Statistical Analysis**

The statistical analysis was performed with standard statistical software (SPSS ver. 22 for Windows, SPSS, Chicago, IL, USA). All numerical data are presented as the mean  $\pm$  SD. Relationships between pairs of parameters were assessed by the linear correlation and regression analysis. A stepwise multiple regression analysis was performed to find independent determinants of the  $\Delta Pa/\Delta Va$  ratio and LV end-diastolic pressure among multiple parameters. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability to predict the elevation of the catheterization LV end-diastolic pressure ( $>18$  mmHg). The areas under the ROC curves were compared using the Z test. Inter- and intra-observer reproducibilities for the  $V_{PVA}$ ,  $D_{PVA}-D_A$ ,  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$  were studied in 25 randomly selected patients. For all statistical tests, a p-value  $<0.05$  was considered significant.

## **RESULTS**

### **Patient Characteristics**

The clinical, echocardiographic and hemodynamic parameters of the study patients are

summarized in **Table 1**. Among the 62 patients, LV hypertrophy (LV mass index  $>115 \text{ g/m}^2$  for males,  $>95 \text{ g/m}^2$  for females) was present in 33 (53%) patients; reduced LV pump function (LV ejection fraction  $<50\%$ ) was present in 24 (39%) patients; LA dilatation (LA volume index  $>34 \text{ ml/m}^2$ ) was identified in 37 (60%) patients, and elevated LV end-diastolic pressure was present in 12 (19%) patients.

### **Relationships between Doppler Parameters for Estimating Left Ventricular Chamber Stiffness and Hemodynamic Data**

The correlations between the Doppler parameters for estimating LV chamber stiffness and the  $\Delta\text{Pa}/\Delta\text{Va}$  are shown in **Fig. 3**. The  $V_{\text{PVA}}$  and  $D_{\text{PVA}}-D_{\text{A}}$  were significantly correlated with the  $\Delta\text{Pa}/\Delta\text{Va}$  ( $r=0.38$  and  $r=0.56$ , respectively), but the correlations were relatively weak. The  $I_{\text{PVA}}/I_{\text{A}}$  and  $F_{\text{PVA}}/F_{\text{A}}$  were significantly and well correlated with the  $\Delta\text{Pa}/\Delta\text{Va}$  ( $r=0.79$  and  $r=0.81$ , respectively). Similarly, correlations between the Doppler parameters and LV end-diastolic pressure are shown in **Fig. 4**. The  $V_{\text{PVA}}$  did not significantly correlate with the LV end-diastolic pressure and the  $D_{\text{PVA}}-D_{\text{A}}$  significantly but relatively weakly correlated with the LV end-diastolic pressure ( $r=0.52$ ). The  $I_{\text{PVA}}/I_{\text{A}}$  and  $F_{\text{PVA}}/F_{\text{A}}$  were significantly and well correlated with the LV end-diastolic pressure ( $r=0.73$  and  $r=0.77$ , respectively). The DT was significantly but only weakly correlated with the  $\Delta\text{Pa}/\Delta\text{Va}$  ( $r=-0.28$ ,  $p=0.028$ ) and LV end-diastolic pressure ( $r=-0.37$ ,  $p=0.003$ ). The  $s'$  and  $e'$  did not significantly correlate with  $\Delta\text{Pa}/\Delta\text{Va}$  ( $r=-0.20$  and  $r=-0.05$ , respectively) and LV end-diastolic pressure ( $r=-0.18$  and  $r=-0.16$ , respectively). The  $E/e'$  significantly correlated with LV end-diastolic pressure ( $r=0.53$ ,  $p<0.01$ ), but did not significantly correlate with  $\Delta\text{Pa}/\Delta\text{Va}$  ( $r=0.25$ ).

The stepwise multivariate analysis to find determinants of  $\Delta\text{Pa}/\Delta\text{Va}$  and LV end-diastolic pressure among systolic blood pressure, heart rate, LV mass index, LV ejection fraction, degree of mitral regurgitation, and  $F_{\text{PVA}}/F_{\text{A}}$  revealed that the  $F_{\text{PVA}}/F_{\text{A}}$  was identified as the single independent determinant of  $\Delta\text{Pa}/\Delta\text{Va}$  ( $\beta=0.82$ ,  $p<0.001$ ) and LV end-diastolic

pressure ( $\beta=0.78$ ,  $p<0.001$ ).

### Utility for Discriminating Patients with Elevated LV End-Diastolic Pressure

The utility of the Doppler parameters for discriminating patients with LV end-diastolic pressure  $>18$  mmHg from those without is summarized in **Table 2**. The area under the ROC curve (AUC) values were 0.93 for the  $F_{PVA}/F_A$  and 0.90 for the  $I_{PVA}/I_A$ , and these values were tended to be greater than the AUC of 0.86 for the  $D_{PVA}-D_A$  ( $p=0.42$  and  $p=0.63$ , respectively) and significantly greater than that of 0.49 for the  $V_{PVA}$  (both  $p<0.001$ ) (**Fig. 5**). The  $I_{PVA}/I_A >0.51$  showed 83% sensitivity and 80% specificity, and  $F_{PVA}/F_A >0.47$  showed 83% sensitivity and 82% specificity, and these values were greater than the corresponding values of the  $D_{PVA}-D_A >1$  ms. In addition, after adjusting for the systolic blood pressure, heart rate, LV mass index, LV ejection fraction and degree of mitral regurgitation, the AUC was 0.93 for the  $F_{PVA}/F_A$  and 0.91 for the  $I_{PVA}/I_A$ , which were tended to be greater than the AUC of 0.84 for the  $D_{PVA}-D_A$  ( $p=0.37$  and  $p=0.52$ , respectively) and significantly greater than that of 0.68 for the  $V_{PVA}$  (both  $p<0.05$ ).

### Reproducibility of Measurements

The inter- and intra-observer reproducibilities are summarized in the **Table 3**. The intraclass correlation coefficients for the inter- and intra-observer comparisons were good or excellent for  $V_{PVA}$  (0.91 and 0.97, respectively),  $I_{PVA}$  (0.89 and 0.92, respectively),  $F_{PVA}$  (0.83 and 0.94),  $I_A$  (0.92 and 0.96),  $F_A$  (0.96 and 0.96),  $I_{PVA}/I_A$  (0.92 and 0.94) and  $F_{PVA}/F_A$  (0.88 and 0.96), whereas they were inadequate for  $D_{PVA}-D_A$  (0.50 and 0.53).

## DISCUSSION

Our present findings demonstrated that our new echocardiographic parameters for LV

chamber stiffness using the time-velocity integral of the backward PV and forward transmitral flows during atrial contraction, i.e.,  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$ , can more accurately reflect late-diastolic LV chamber stiffness and could be more useful to detect an elevation of LV end-diastolic pressure compared to conventional noninvasive parameters such as  $V_{PVA}$  and  $D_{PVA}-D_A$  in patients with different cardiac diseases.

### **Comparison with Previous Investigations of Doppler Parameters for Estimating Left Ventricular Chamber Stiffness**

Several investigators have reported the utility of the DT of the transmitral flow for estimating LV chamber stiffness. Little et al. demonstrated that the DT was significantly inversely correlated with an invasive parameter of LV operating chamber stiffness during the total filling period ( $K_{LV}$ ) in an experiment using eight conscious dogs [14]. Subsequently, Garcia et al. showed that the DT was significantly and inversely correlated with  $K_{LV}$  and also LV end-diastolic pressure in 18 adult patients with cardiac diseases undergoing open-heart surgery [15]. On the other hand, Yamamoto et al. reported that the DT was correlated with LV end-diastolic pressure in patients with reduced ejection fraction, but not in patients with preserved ejection fraction [16]. The DT is an early- to mid-diastolic parameter, and can be greatly influenced also by an elevated mean LA pressure. In the present study, the DT did not correlate well with the  $\Delta Pa/\Delta Va$ . Although  $e'$  and  $E/e'$  are also important diastolic parameters, their correlations with invasive LV chamber stiffness parameters were weak. We considered that  $e'$  and  $E/e'$  reflect LV relaxation and mean left atrial pressure, respectively, rather than the LV chamber stiffness.

Nakatani et al. reported a good correlation between the  $V_{PVA}$  and the LV end-diastolic pressure in 34 patients with various cardiac diseases [8]. In their study, patients with LA dilatation (LA diameter >35 mm) were excluded because  $V_{PVA}$  can be strongly influenced by LA contractility. However, LA dilatation is frequently present in patients with left heart

disease because almost all of such patients have LV diastolic dysfunction. The  $V_{PVA}$  did not significantly correlate with LV end-diastolic pressure in our patient population, more than half of whom had LA dilatation. Moreover, the  $V_{PVA}$  may be greatly affected by LA preload (i.e., the LA volume before atrial contraction) and the Doppler incident angle.

The usefulness of the parameter  $D_{PVA}-D_A$  was reported by several investigators and cited as a parameter reflecting the LV end-diastolic pressure by the ASE/EACVI guidelines [1,2,5,9,16]. However, this parameter requires delicate timing measurements and does not use the velocity information. In the present study, the relationships of the  $D_{PVA}-D_A$  with LV chamber stiffness and LV end-diastolic pressure were modest, and the inter- and intra-observer reliability was not adequate.

The  $I_{PVA}/I_A$ , one of our novel parameters, which uses both the velocity and duration information, was well correlated with the LV chamber stiffness and LV end-diastolic pressure, much better than the  $V_{PVA}$  and  $D_{PVA}-D_A$  were. However, the  $I_{PVA}/I_A$  is not a backward/forward flow volume ratio because it is simply a time-velocity integral ratio and depends on the difference in the Doppler incident angle among patients. In contrast, the  $F_{PVA}/F_A$  is considered to represent a backward/forward flow volume ratio during LA contraction because the  $F_{PVA}$  theoretically represents a backward flow fraction and the  $F_A$  does a forward flow fraction during LA contraction, respectively. Thus, the  $F_{PVA}/F_A$ , which may be free from angle dependency, was actually best correlated with the LV chamber stiffness and LV end-diastolic pressure among the Doppler parameters in this study.

### **Clinical Importance of Assessing Left Ventricular Chamber Stiffness**

In patients with increased chamber stiffness but without apparent left heart failure, the LV end-diastolic pressure and mean LA pressure may be dissociated because the LV end-diastolic pressure can distinctly exceed the mean LA pressure due to the prominent pressure rise during atrial contraction (**Fig. 6**) [2,17]. Although parameters reflecting the mean LA pressure,

such as  $E/A$  and  $E/e'$ , are widely used to evaluate patients with heart failure, the estimation of LV stiffness may have a role independent from them in the assessment of cardiac patients and may be useful to predict overt heart failure before its onset [1,2].

For example, in patients with abnormally increased LV stiffness but without a mean LA pressure rise, greater venous return to the heart induced by exercise or excessive circulatory volume load may cause a further increase in LV stiffness and LV end-diastolic pressure. A further increase in preload or myocardial damage may lead to an elevation of the mean LA pressure and pulmonary congestion. Our new index  $F_{PVA}/F_A$  may be useful in such a situation for making decisions regarding the therapeutic strategy.

Several investigators have reported that the detection of increased chamber stiffness [18] and elevated LV end-diastolic pressure [19–22], evaluated using cardiac catheterization, were useful to predict poor prognosis or future cardiac events in patients with coronary artery disease [19,20], non-coronary artery disease [18], and various heart diseases [21]. Among them, Watanabe et al. reported that increased LV chamber stiffness was the strongest prognostic marker for cardiac death or admission for decompensation in patients with chronic heart failure [18]. Using Doppler echocardiography, Dini et al. reported that the  $D_{PVA}-D_A$  had a prognostic value independent of the mean LA pressure in patients with LV systolic dysfunction [22].

### **Clinical Implications**

Our present findings demonstrated that our parameters  $F_{PVA}/F_A$  and  $I_{PVA}/I_A$  were more accurate indices for chamber stiffness and LV end-diastolic pressure than the  $D_{PVA}-D_A$ . Thus, the noninvasive estimation of LV stiffness by using our parameters, especially  $F_{PVA}/F_A$ , may have utility for stratifying cardiac patients for the risk of heart failure before their mean LA pressure distinctly rise.

**Limitations**

There are several limitations in this study. First, left heart catheterization and echocardiography were not performed simultaneously. Although we carefully excluded patients with unstable hemodynamics and/or loading conditions between cardiac catheterization and echocardiography, the possibility of hemodynamic alteration might not be completely excluded. Second, the Doppler parameters for estimating LV chamber stiffness could not be obtained in 13% of the initial candidates. This percentage, however, is smaller than that reported in past studies (13%–38%) [8,9,11,16,22] and seems to be acceptable for clinical practice. Further advancement of ultrasound technology may increase the detection rate of PV Doppler waveform. Third, patients with elevated LV end-diastolic pressure are relatively few. This can limit the findings of this study. Fourth, our method cannot be applied to patients without synchronized atrial activity due to arrhythmias such as atrial fibrillation, atrial flutter and complete atrioventricular block.

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1295-302.

**Table 1.** Patient characteristics

	Mean $\pm$ SD (n=62)	Range
<b>Clinical characteristics</b>		
Age (years)	63.6 $\pm$ 14.8	21–87
Male/female	38/24	
Body surface area (cm <sup>2</sup> )	1.62 $\pm$ 0.23	1.18–2.12
Systolic blood pressure (mmHg)	122 $\pm$ 21	83–190
Diastolic blood pressure (mmHg)	68 $\pm$ 14	36–106
Heart rate (bpm)	68.5 $\pm$ 11.9	51–100
Underlying heart disease, n (%)		
Ischemic heart disease	23 (37%)	
Cardiomyopathy	13 (21%)	
Valvular heart disease	11 (18%)	
Hypertensive heart disease	5 (8%)	
Pericardial disease	2 (3%)	
Others	8 (13%)	
<b>Two-dimensional echocardiographic parameters</b>		
LV end-diastolic dimension (mm)	50.9 $\pm$ 9.0	33–79
LV ejection fraction (%)	53.0 $\pm$ 15.9	17–82
LV mass index (g/m <sup>2</sup> )	112 $\pm$ 35	45–216
Left atrial volume index (mL/m <sup>2</sup> )	40.7 $\pm$ 15.0	12–76
<b>Transmitral and pulmonary venous flow parameters</b>		
E (cm/s)	71.3 $\pm$ 22.4	30.7–155.0
A (cm/s)	74.4 $\pm$ 22.5	18.2–127.8
E/A	1.10 $\pm$ 0.71	0.36–5.07
DT (ms)	205 $\pm$ 51	127–364
S (cm/s)	58.8 $\pm$ 17.8	32.9–121.0
D (cm/s)	48.1 $\pm$ 16.5	17.1–102.8
S/D	1.34 $\pm$ 0.52	0.36–2.78
V <sub>PVA</sub> (cm/s)	35.1 $\pm$ 15.4	17.9–115.0
D <sub>PVA</sub> –D <sub>A</sub> (ms)	–6.7 $\pm$ 24.8	–52–66

$I_{PVA}/I_A$	$0.51 \pm 0.31$	0.21–1.83
$F_{PVA}/F_A$	$0.44 \pm 0.24$	0.13–1.28
<b>Hemodynamic parameters</b>		
LV pre-A pressure (mmHg)	$10.1 \pm 4.7$	2.5–28.7
$\Delta Pa$ (mmHg)	$5.7 \pm 3.3$	0.9–14.7
$\Delta Pa/\Delta Va$ (mmHg·m <sup>2</sup> /ml)	$0.49 \pm 0.41$	0.07–1.89
LV end-diastolic pressure (mmHg)	$15.2 \pm 5.7$	6.6–35.0

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A, peak atrial systolic transmitral flow velocity; D, peak diastolic PV flow velocity;  $D_A$ , duration of the A wave;  $D_{PVA}$ , duration of the atrial systolic PV flow; DT, deceleration time of the E wave; E, peak early-diastolic transmitral flow velocity;  $F_A$ , ratio of the  $I_A$  to transmitral time-velocity integral during a cardiac cycle;  $F_{PVA}$ , ratio of the  $I_{PVA}$  to PV flow time-velocity integral during a cardiac cycle;  $I_A$ , time-velocity integral of the A wave;  $I_{PVA}$ , time-velocity integral of the backward PV flow; LV, left ventricle; PV, pulmonary venous; S, peak systolic PV flow velocity;  $V_{PVA}$ , peak atrial systolic PV backward flow velocity;  $\Delta Pa$ , left ventricular pressure increase during atrial contraction;  $\Delta Va$ , volume change during atrial contraction corrected for each patient's body surface area.

**Table 2.** Performance of pulmonary venous and transmitral flow Doppler parameters for discriminating elevated left ventricular end-diastolic pressure

	<b>AUC</b>	<b>p-value</b>	<b>Optimal Cut-off value</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Accuracy</b>
$V_{PVA}$ (cm/s)	0.49	0.28				
$D_{PVA}-D_A$ (ms)	0.86	<0.001	1 ms	76%	75%	76%
$I_{PVA}/I_A$	0.90	<0.001	0.51	83%	80%	81%
$F_{PVA}/F_A$	0.93	<0.001	0.47	83%	82%	82%

Abbreviations are the same in Table 1.

**Table 3.** Inter- and intra-observer reproducibility

	Inter-observer			Intra-observer		
	ICC	95% CI	p	ICC	95% CI	p
$V_{PVA}$ (cm/s)	0.91	0.77–0.96	<0.001	0.97	0.92–0.98	<0.001
$D_{PVA-D_A}$ (ms)	0.50	0.14–0.75	0.002	0.53	0.17–0.77	0.003
$I_{PVA}/I_A$	0.92	0.83–0.97	<0.001	0.94	0.86–0.97	<0.001
$F_{PVA}/F_A$	0.88	0.75–0.95	<0.001	0.96	0.92–0.98	<0.001

ICC, intraclass correlation coefficient. Other abbreviations are the same in Table 2.

## FIGURE LEGENDS

### **Fig. 1. Measurements of the pulmonary venous flow and transmitral flow parameters.**

From the pulmonary venous (PV) flow waveform (*left upper panel*), the velocity, duration and time-velocity integral of the backward flow during atrial contraction ( $V_{PVA}$ ,  $D_{PVA}$  and  $I_{PVA}$ , respectively) were measured, and the ratio of  $I_{PVA}$  to the time-velocity integral of PV flow through a cardiac cycle ( $F_{PVA}$ ) was calculated (*right upper panel*). From the transmitral flow waveform (*left lower panel*), the duration and time-velocity integral of the forward flow during atrial contraction ( $D_A$  and  $I_A$ , respectively), and the ratio of the  $I_A$  to the transmitral time-velocity integral during a cardiac cycle ( $F_A$ ) were calculated (*right lower panel*). The  $D_{PVA}-D_A$ ,  $I_{PVA}/I_A$  and  $F_{PVA}/F_A$  values were then calculated.

### **Fig. 2. Measurements of left ventricular pressure increase during atrial contraction ( $\Delta Pa$ ) and end-diastolic pressure (LVEDP).**

### **Fig. 3. Correlation of Doppler parameters of pulmonary venous and transmitral flows with the left ventricular stiffness during atrial contraction.**

$\Delta Va$ , left ventricular volume change during atrial contraction corrected for the body surface area. Other abbreviations are explained in the Table 2 footnote.

### **Fig. 4. Correlation of Doppler parameters of pulmonary venous and transmitral flows with the left ventricular end-diastolic pressure (LVEDP).**

Abbreviations are explained in the Table 2 footnote.

### **Fig. 5. ROC curve analyses of various Doppler parameters.**

ROC curves of  $V_{PVA}$ ,  $D_{PVA}-D_A$ ,  $I_{PVA}/I_A$ ,  $F_{PVA}/F_A$  have been plotted for the differentiation of

patients with left ventricular end-diastolic pressure  $>18$  mmHg from those without.

Abbreviations are explained in the Table 2 footnote.

**Fig. 6. Pulmonary venous and transmitral Doppler recordings in a patient with increased LV chamber stiffness**

This figure shows pulmonary venous (*upper panels*) and transmitral (*lower panels*) flow velocity waveforms in a 47-years-old male patient with hypertensive heart disease and with increased LV chamber stiffness (LV end-diastolic pressure of 24 mmHg,  $\Delta Pa/\Delta Va$  of 1.89 mmHg·m<sup>2</sup>/ml, and  $F_{PVA}/F_A$  of 1.16) but without any increase in mean pulmonary artery wedge pressure (8 mmHg).

Abbreviations are explained in the footnotes of Table 1 and 2.

Figure 1

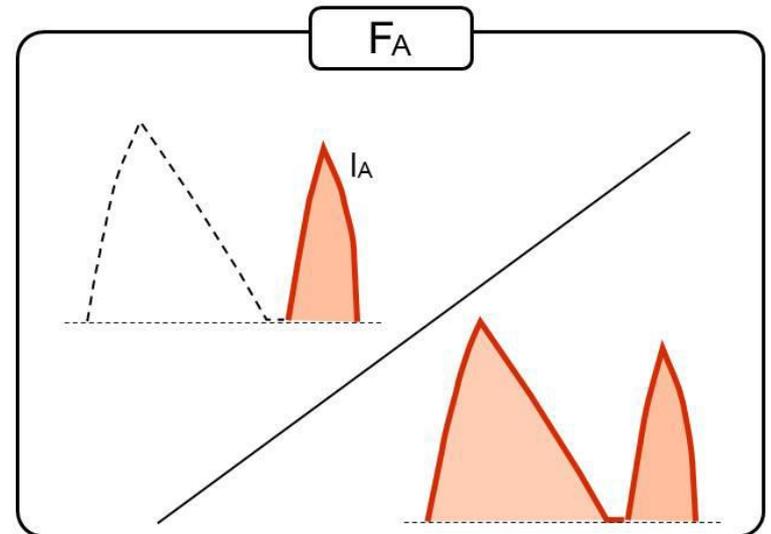
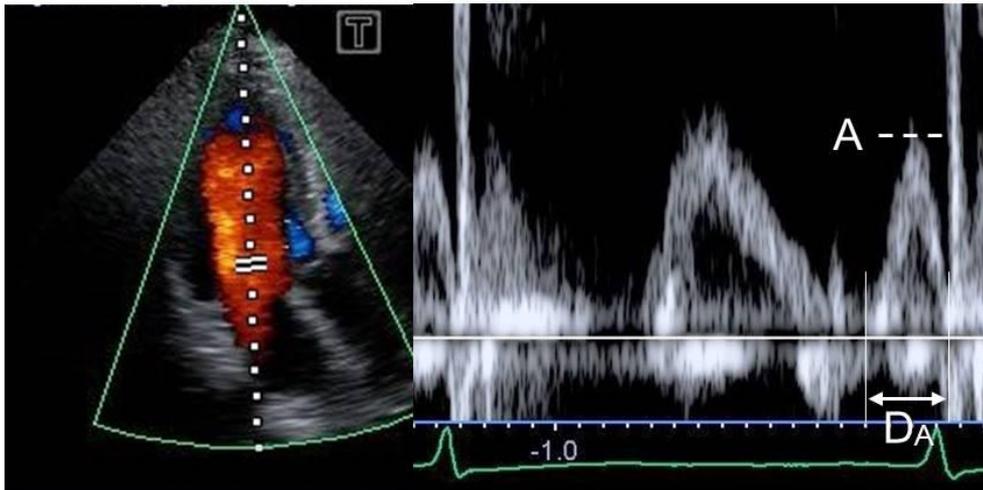
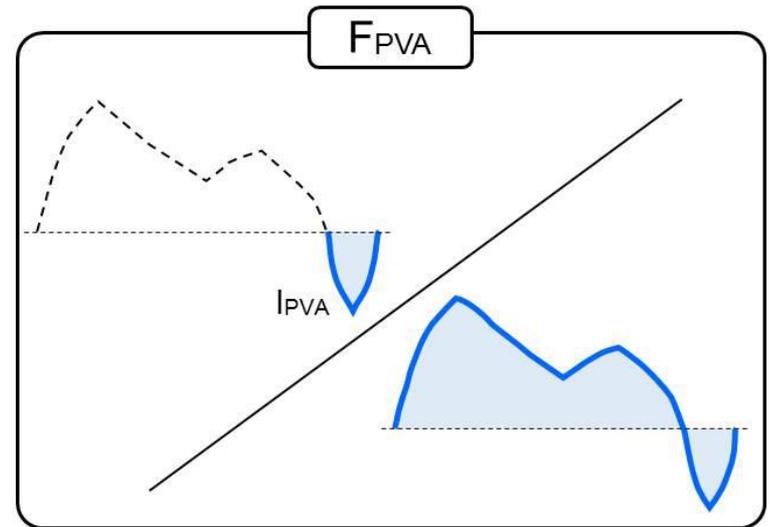
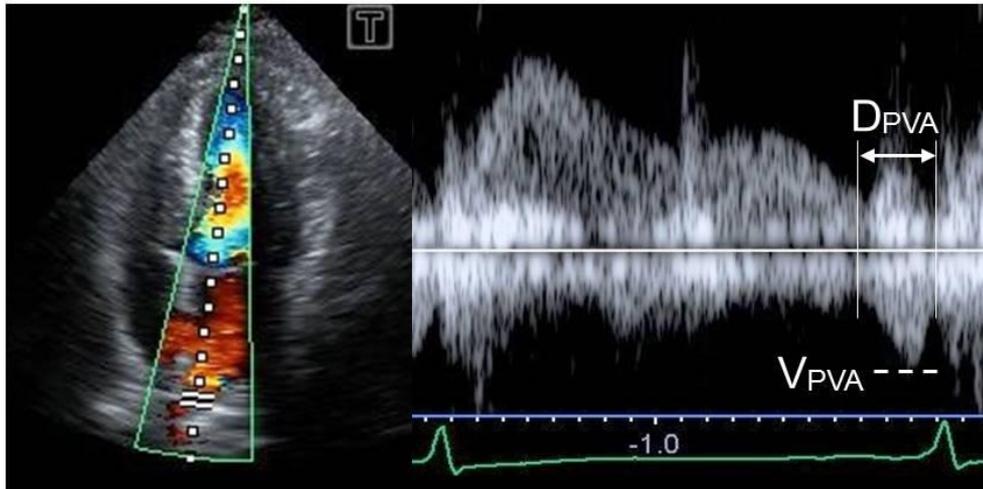
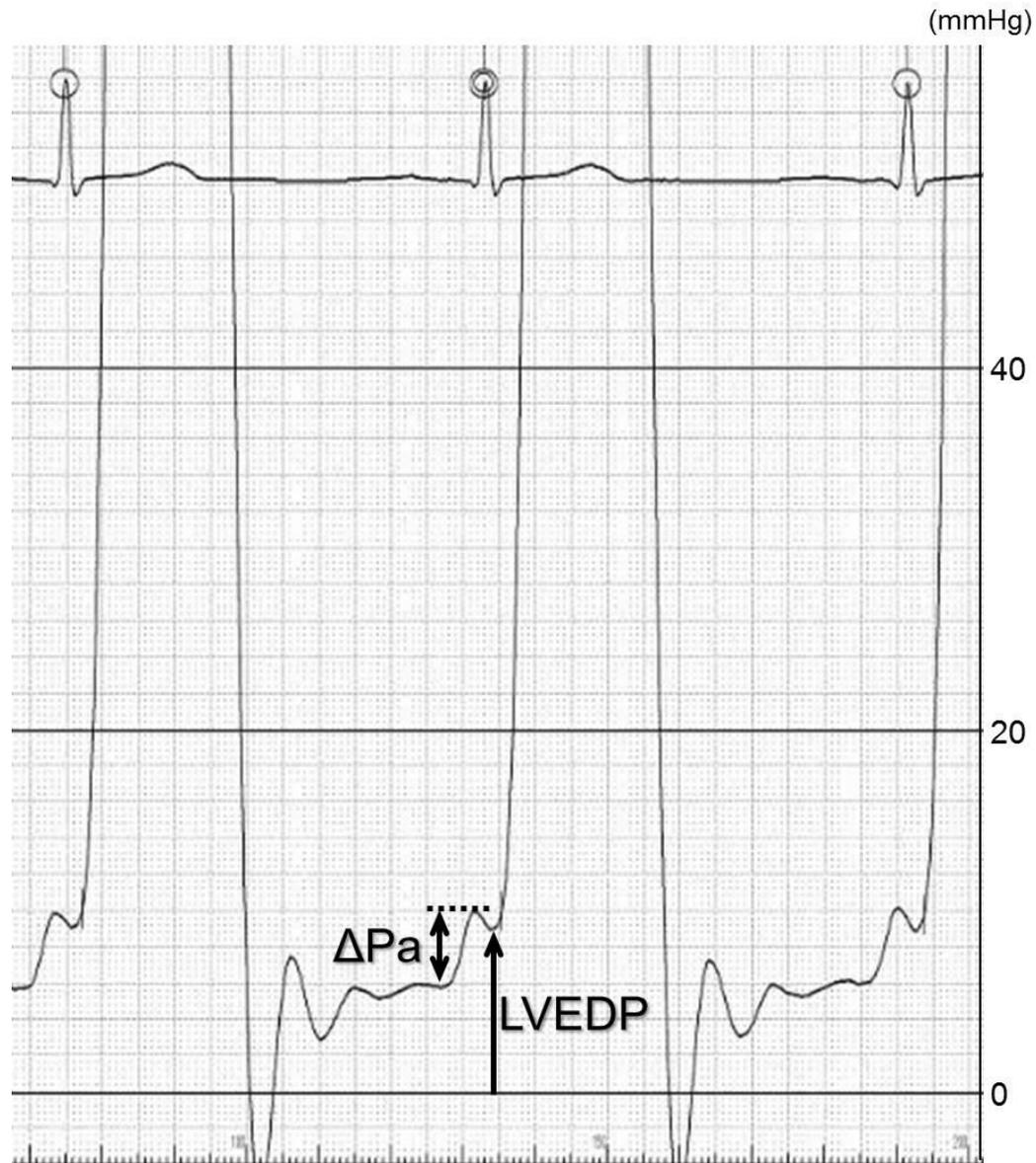
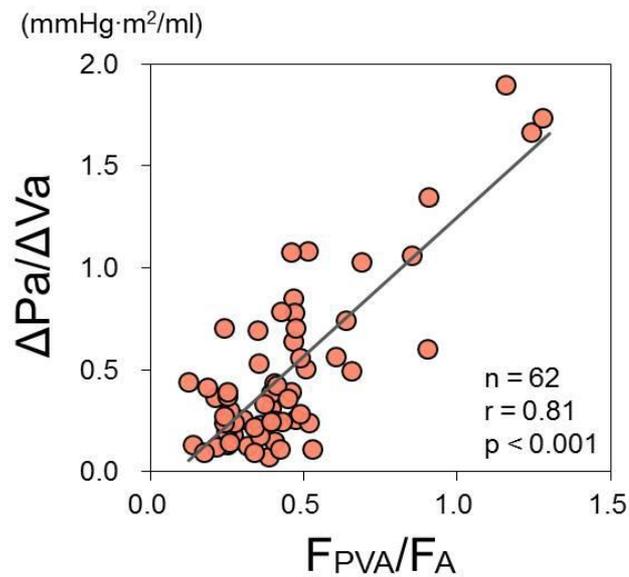
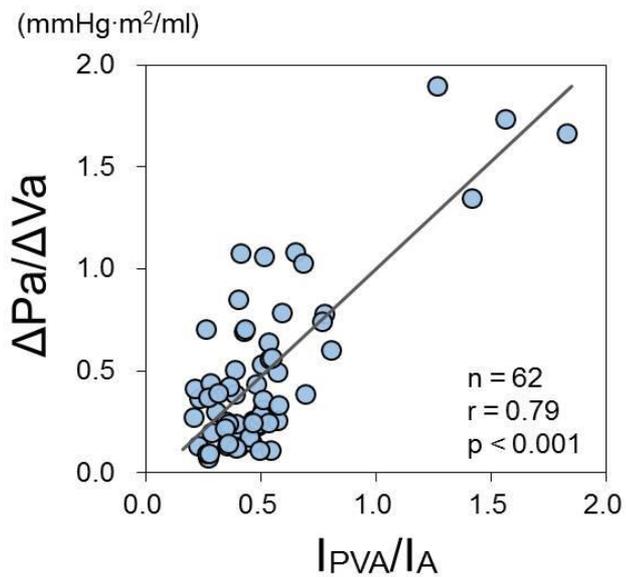
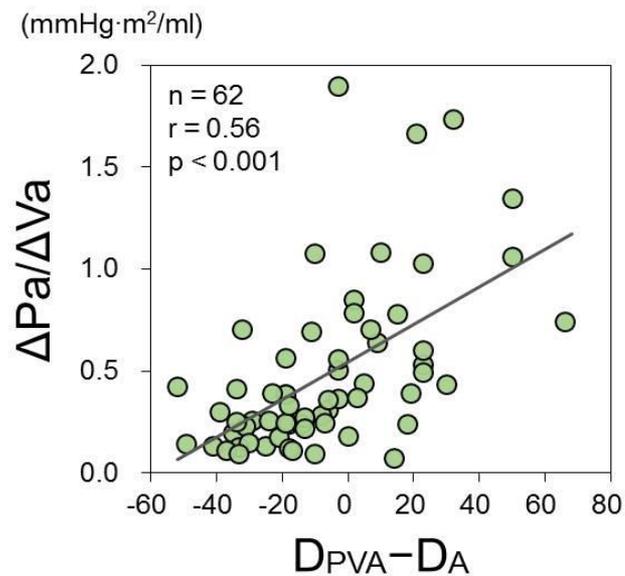
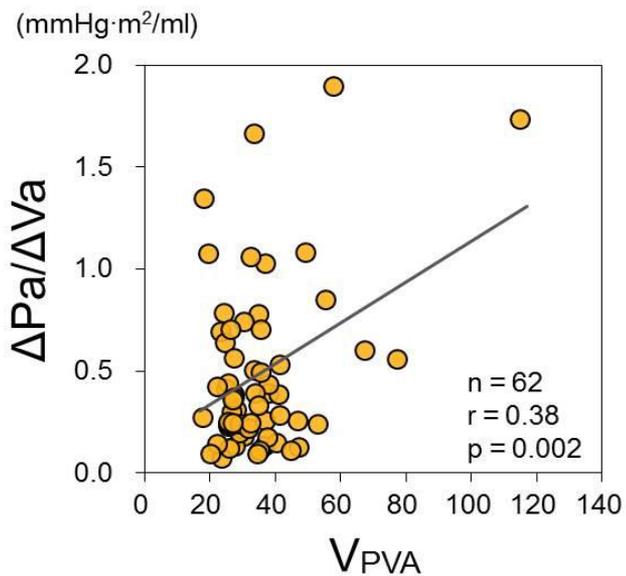


Figure 2



# Figure 3



# Figure 4

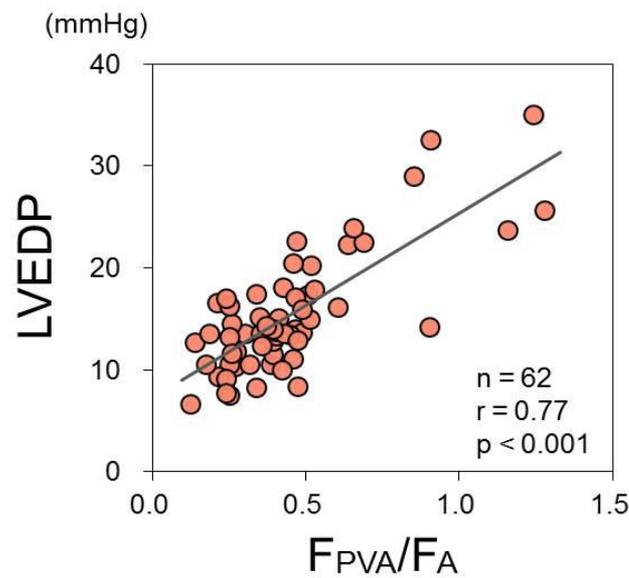
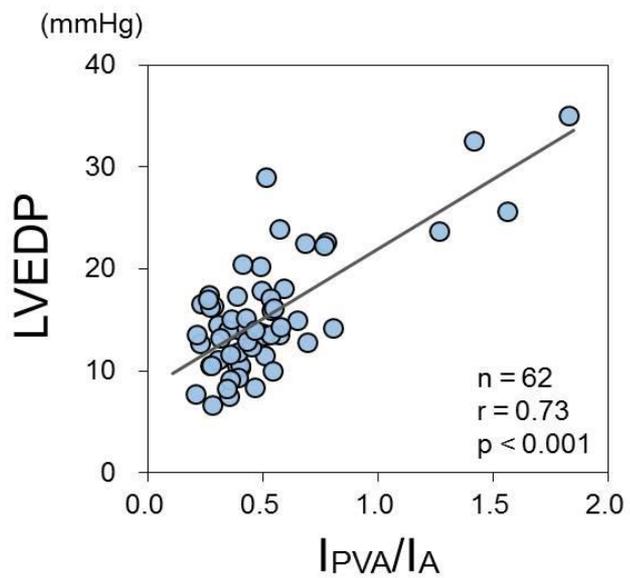
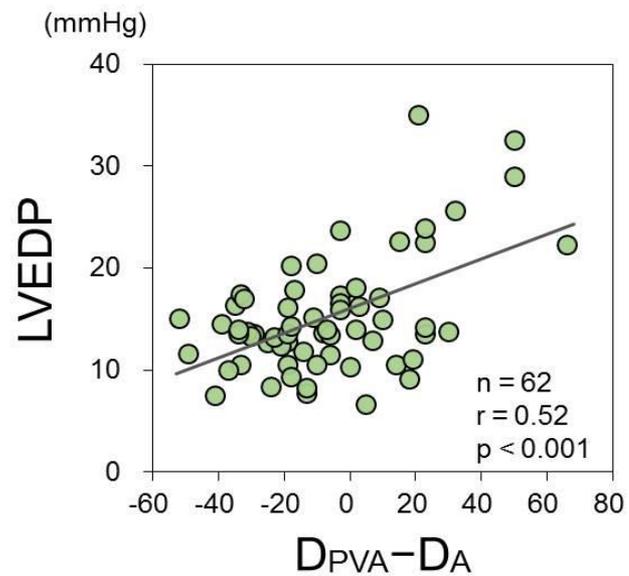
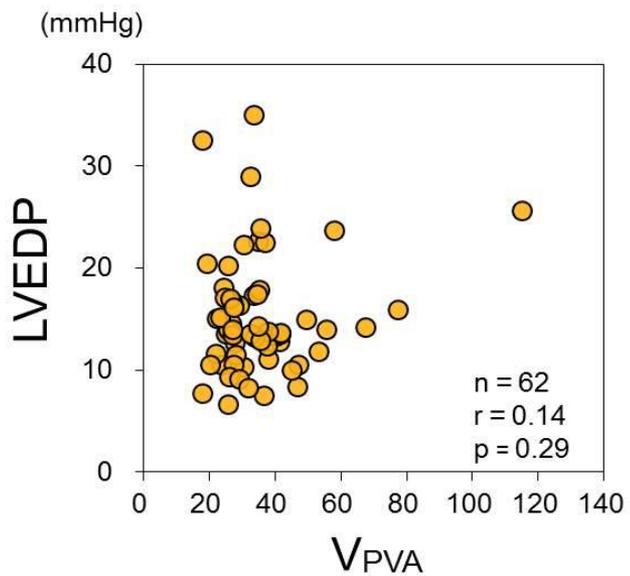


Figure 5

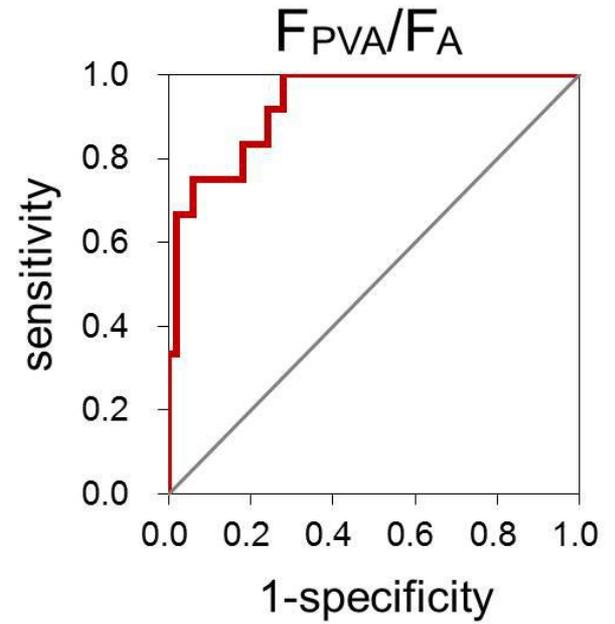
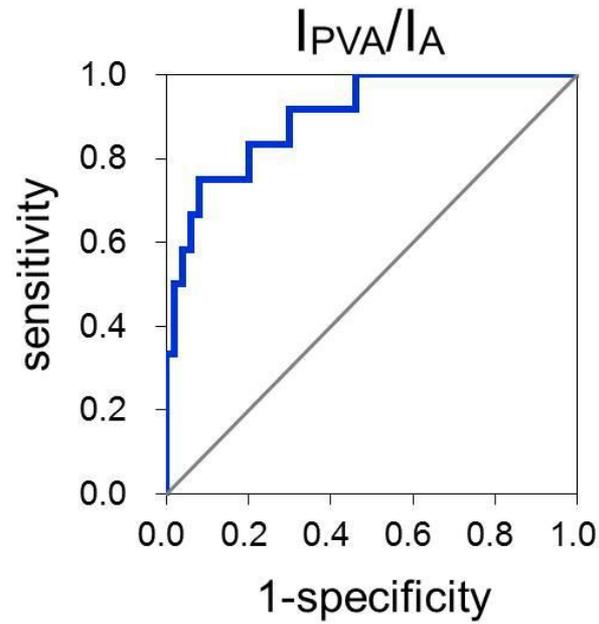
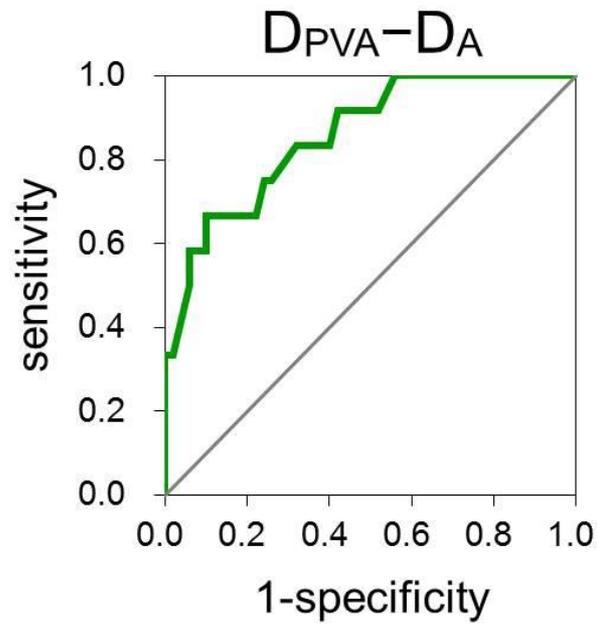


Figure 6

