Effect of Renal and Left Ventricular Function on Serial Pulmonary Arterial Pressure Changes After Device Closure of Atrial Septal Defect

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Research

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Abstract

Background: The age of candidates for device closure of atrial septal defect (ASD) has been increasing. Thus, concerns exist about dyspnea aggravation or atrial fibrillation development after device closure due to augmentation of left ventricular (LV) and left atrial (LA) preload. This study aimed to examine patterns and determinants of serial pulmonary arterial pressure and left ventricular filling pressure changes after device closure of ASD.

Methods: Among the 86 consecutive patients who underwent percutaneous device closure of ASD, those without pre- or post-procedural Doppler data and end-stage renal disease were excluded. The clinical, transesophageal, and transthoracic echocardiographic findings of 78 patients were collected at baseline, one day post-procedure, and one year follow-up.

Results: The mean age of study patients was 49.8 ± 15.0 years and the average maximal defect diameter and device size was 20.2 ± 6.0 mm and 23.8 ± 6.4 mm. Some patients (n = 21; 27%) exhibited paradoxically increased tricuspid regurgitant velocity (TRV) one-day post-procedure; they also were older with lower e', glomerular filtration rate, and LV ejection fraction and a higher LA volume index. However, even in these patients, TRV deceased below baseline levels one-year later. Both E/e' (9.0 ± 3.5 vs. 11.4 ± 4.3; $p < 0.001$) and LA volume index significantly increased immediately after device closure, but all decreased one-year later. Larger defect size and higher TRV were significantly correlated with immediate E/e' elevation.

Conclusion: In older, renal, diastolic and systolic dysfunctional patients with larger LA, scheduled for larger device implantation, peri-interventional preload reduction therapy would be beneficial.

Background

The age of candidates for device closure of atrial septal defect (ASD) has been increasing. Especially in older patients, concerns exist about dyspnea aggravation(1) or atrial fibrillation development after device closure due to the augmentation of left ventricular (LV) and left atrial (LA) preload.(2, 3) Although recent studies showed that the long-term outcome of device closure is quite good even in older patients, vulnerable patients must be identified to prepare them for peri-procedural preload reduction management. Thus, in this study, we sought to examine serial hemodynamic changes, including pulmonary arterial systolic pressure, LV filling pressure, stroke volume, and LA volume, after device closure of ASD. In addition, factors contributing to adverse hemodynamic changes from immediately after the procedure to one-year follow-up were determined.

Materials And Methods

Study population and clinical follow-up

The database of a single center of patients who underwent percutaneous device closure of ASD was analyzed. Patients underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) before the device closure procedure. Among the 86 consecutive patients who underwent percutaneous device closure of ASD, patients without pre- or immediate post-procedural Doppler and end-stage renal disease were excluded. In total, the clinical, transesophageal and transthoracic echocardiographic findings of 78 patients were collected at baseline, one day (immediately) after the procedure, and one-year follow-up. **(Figure 1)** All patients underwent blood chemistry and cell blood count analysis. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.(4) Clinical characteristics, medical history, laboratory findings, medications, and echocardiographic data were collected and used for analysis. The study protocol was approved by the institutional review board of Gangnam Severance hospital (3-2020-0026), and the need for written informed consent was waived due to the study's retrospective design.

Echocardiography at baseline and after device closure

Each patient underwent a complete standard TTE. TTE findings were collected at baseline, one day (immediately) post-closure, and one-year follow-up. LV dimensions and septal and posterior wall thickness were measured at end-diastole and end-systole in the two-dimensional (2D) parasternal long- or short-axis views. LV ejection fraction was calculated using the modified Quinones' method.(5) LV mass was measured by Devereux's methods as recommended by the American Society of Echocardiography. (5) LA volume was measured using the prolate ellipsoidal method at the point of LV end-systole at maximum LA size. From the apical window, a 1-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from 5–10 cardiac cycles were recorded. Peak early (E) and late (A) mitral inflow velocities were also measured. Mitral annular velocity was measured by tissue Doppler imaging using the pulsed-wave Doppler mode. The filter was set to exclude high-frequency signals, and the Nyquist limit was adjusted to a range of 15–20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. Systolic (S') and early (e') and late diastolic velocities of the mitral annulus were measured from the apical four-chamber view with a sample volume (2–5 mm) placed at the septal corner of the mitral annulus. Peak velocity of tricuspid regurgitation was measured. Pulmonary arterial systolic pressure (PASP) was calculated as follows: 4 × tricuspid regurgitant velocity $(TRV)^2$ + right atrial pressure, where right atrial pressure was estimated according to inferior vena cava diameter and its respiratory variations.(6) E/e' divided by stroke volume was defined as LV end-diastolic elastance index.(7) During TEE, multiplane 2D and zoomed 3D images were acquired, and both long- and short-axis diameters of the ASD were measured. Area was calculated as long-axis diameter multiplied by short-axis diameter and 3.14. In multiple defects, the sum of all diameters or areas was used. The margins to the aorta, posterior wall, superior vena cava, and inferior vena cava rims were also evaluated.

Device implantation and periprocedural imaging

Transcatheter ASD closure was performed, as described previously(8), using various types of septal occluders (Amplatzer/Cocoon/Figullar Flex II/Gore-Helix/Occlutech). Before the procedure, the pulmonary-to-systemic blood flow ratio and pulmonary artery pressure were evaluated using cardiac catheterization. During the procedure, 3D-TEE or intracardiac echocardiography (ICE) were performed to guide accurate device implantation and ensure successful device closure. After the procedure, all patients received 100 mg/day aspirin for at least 6 months and 75 mg clopidogrel for 3 months. Other medications, such as diuretics and antihypertensive medications, were continued.

Statistical analysis

Clinical characteristics and echocardiographic parameters are presented as the means ± standard deviation for continuous variables and the numbers (percentage) for categorical variables. Correlation analysis was performed between continuous variables using the Pearson correlation coefficient. Comparisons of echocardiographic findings between two groups were performed using the independent t-test. Serial changes of echocardiographic parameters were assessed using repeated ANOVA or the paired t-test. Variables with p values less than 0.05 in univariate analysis were included in the multivariable linear or logistic regression analysis. All the analyses were performed using SPSS (version 25.0, IBM, USA), and p values less than 0.05 were considered significant.

Results

Baseline characteristics, echocardiographic parameters, and hemodynamic findings

The mean age of enrolled patients was 49.8 ± 15.0 (range, 16–77) years, and 51 (65%) were female. The average body mass index was 22.5 ± 3.0 kg/m^2, and the average eGFR was 99.4 ± 20.0 mL/min. Mean LV ejection fraction and LV mass index was 66.1 ± 6.4 % and 63.3 ± 16.3 g/m^2, respectively. Among them 4 patients had more than one defects. Measured average defect maximal diameter was 20.2 ± 6.0 mm and defect area was 2.57±1.52 cm^2 on pre-procedural TEE. The calculated Qp/Qs ratio during right side catheterization before device implantation was 2.52 ± 0.85. Sixty-four patients underwent TEE, and 14 patients underwent ICE for periprocedural guidance. The average size of the septal occluder was 23.8 ± 6.4 mm. Baseline characteristics are described in Table 1.

Serial changes of LV filling pressure, LA volume, and stroke volume

At baseline, E/e' and LA volume index was 9.0 ± 3.5 and 30.5 ± 12.5 mL/m^2, respectively. One day after the procedure, these values significantly increased to 11.4 ± 4.0 and 32.5 ± 12.1 mL/m^2, respectively, due to increased LV filling from occlusion of a left-to-right shunt. LV stroke volume increased from 52.1 ± 11.2 mL to 61.5 ± 19.4 mL the day after the procedure. At one-year follow-up, E/e' and LA volume index decreased by 9.8 ± 3.0 and 27.8 ± 8.6 mL/m^2, which was accompanied by a further increase in LV stroke volume (Figure 2). Immediate E/e' changes after device closure (ΔE/e'-immediate) were significantly correlated with immediate LA volume index change ($r = 0.424$; $p < 0.001$). ASD defect area, maximal

defect diameter, and implanted device diameter were significantly correlated with ΔE/e'-immediate but not with age. Higher TRV and lower baseline E/e' were correlated with ΔE/e'-immediate (Table 2). In multivariate analysis, TRV and baseline E/e' were related to ΔE/e'-immediate.

Serial changes of pulmonary arterial pressure after device closure

Of the 78 patients enrolled in the study, in two patients pre- or post-TRV were not measurable and 39 underwent TTE at one-year follow-up. The average PASP decreased approximately -6.15 ± 11.6 mmHg immediately after closure, but some patients (n = 21; 28%) paradoxically exhibited increase in PASP. Patients with immediately increased PASP were older, with lower eGFR, LV ejection fraction, and e' and higher LA volume index (Table 3). In multivariate analysis for increased PASP-immediate, LV ejection fraction was significantly related to PASP increase immediate after closure. When serially followed, these patients also showed serially decreased PASP one year later below the baseline level, similar to patients with initially decreased PASP (Figure 3). In patients with immediately increased PASP, accompanying increase in LA size was significantly blunted compared to decreased PASP group (Figure 4).

Discussion

According to our study results, some patients who underwent device closure of ASD exhibited immediate PASP elevation even after transpulmonary arterial flow was reduced by blocking left-to-right shunt flow. This finding may be from immediately elevated pulmonary capillary wedge pressure due to increased LV filling flow to the noncompliant left ventricle or volume overload to the non-compliant left atrium (perhaps from not only the muscular part but also the device-covered noncompliant part).(9) This speculation was supported by our findings that impaired LV relaxation (as represented by lower e') and systolic function and higher LA volume index were found in the initial increased PASP group. This finding was more predominant in older patients with lower eGFR, suggesting that these patients need peri-interventional preload reducing medication, especially those with impaired diastolic function and larger LA size. When elevated LV filling pressure measured by E/e' was seen after device closure, larger defect size was more related to LV filling pressure elevation. Thus, especially in patients scheduled to close a larger defect, physicians should be cautious to avoid post-interventional pulmonary edema or exertional dyspnea aggravation. When considering the poor correlation between delta PASP elevation and delta E/e' elevation after device closure, increased PASP would be contributed by not only elevated LV filling pressure(10) but also LA noncompliance, which is also contributed by the device itself in the LA septum. An immediate increase in E/e' was significantly correlated with increase in LA volume index. However, at one-year follow-up, decreased LV filling pressure was accompanied by decreased LA volume index. When examining serial changes at one-year follow-up, we found that all patients showed decreased PASP below the baseline level regardless of the immediate PASP response, even in the paradoxically increased PASP group. Thus, despite the concern of device closure in older patients with renal dysfunction, these findings support that long-term hemodynamic response would be favorable in older patients. Therefore, with optimal preload reduction and volume control during and immediately after the procedure, device closure of ASD can be recommended even in vulnerable patients.(11)

This study has some limitations. Although we found a significant proportion of patients underwent paradoxically increase in PASP, especially in older patients, with renal dysfunction, impaired LV relaxation, and larger LA, the contribution of the device on the LA side could not be fully determined. We could only assume that with larger LA and marginal compliance, adding a prosthesis may worsen LA compliance. Although we could not find any difference in device type, future studies are warranted to determine how to reduce worsening LA compliance when selecting device size, device type, and deployment method.

Conclusions

In older patients with impaired LV relaxation, systolic dysfunction, renal dysfunction or larger LA size, PASP could paradoxically increase after device closure of ASD due to the immediate volume overload to a noncompliant left ventricle and left atrium. Therefore, peri-procedural preload manipulation, such as diuretics, are recommended in patients with these risk factors who are scheduled to close a larger defect. However, after the immediate peri-procedural period, TRV, LA volume index and E/e' continuously decreases, suggesting the favorable effects of ASD closure even in these high-risk patients.

Abbreviations

ASD: atrial septal defect; E: peak early diastolic mitral inflow velocity; e': peak early diastolic mitral annular velocity; eGFR: estimated glomerular filtration rate; ICE: intracardiac echocardiography; LA: left atrial; LV: left ventricular; LVOT: LV outflow tract; PASP: pulmonary arterial systolic pressure; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; TRV: tricuspid regurgitant velocity; 2D: two dimensional; 3D: three dimensional

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CS and EYC made the study design and wrote the manuscript. CS, EYC and SJR analyzed the echocardiography. ISK, YWY, JYK, BKL, PKM, BKH, and HMK analyzed cardiac catheterization data and provide critical comments to the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest. The authors had full access to the database and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review board of Gangnam Severance hospital (3-2020-0026)

Informed consent

Informed consent was waived due to the study's retrospective design.

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Tables

Table 1. Baseline clinical characteristics and echocardiographic measurements in patients with ASD

Variable (n = 78)	**Parameter**
Age, years	49.8 ± 15.0
Female, n (%)	51 (65)
Body mass index, kg/m^2	22.4 ± 3.0
Systolic blood pressure, mmHg	116.5 ± 15.7
Blood urea nitrogen, mg/dL	15.1 ± 4.4
Creatinine, mg/dL	0.75 ± 0.16
eGFR, mL/min/1.73 m²	99.8 ± 18.8
Atrial fibrillation, n (%)	6 (8)
LV mass index, g/m^2	63.3 ± 16.3
LA volume index, mL/m^2	30.5 ± 12.5
LV ejection fraction, %	66.1 ± 6.4
Stroke volume, mL	52.1 ± 11.2
TRV, m/sec	2.73 ± 0.48
PASP, mmHg	37.0 ± 12.3
PVR, Wood unit	1.47 ± 0.31
e', cm/s	9.3 ± 3.2
E/e'	9.0 ± 3.5
More than single defects, n (%)	4 (5)
ASD maximal defect diameter, mm	20.2 ± 6.0
ASD defect area, cm^2	2.57 ± 1.52
ASD device diameter, mm	23.8 ± 6.4
Qp/Qs ratio	2.52 ± 0.85
Procedure guidance by TEE/ICE	64/14
Amplatzer/Cocoon/Figullar Flex II/Gore-Helix/Occlutech	41/33/2/1/1

ASD, atrial septal defect; e', early diastolic septal mitral annular velocity; E/e', ratio of early mitral inflow velocity to e'; ICE, intracardiac echocardiography; LA, left atrial; LV, left ventricular; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; TEE, transesophageal echocardiography; TRV, tricuspid regurgitant velocity.

Table 2. Correlations of immediate E/e' changes after device closure of an ASD

Variable	Pearson's correlation coefficient (r value)	P value
Age, years	0.039	0.742
Male	-0.118	0.331
Body mass index, m^2	-0.168	0.123
Systolic blood pressure, mmHg	-0.042	0.738
Blood urea nitrogen, mg/dL	0.112	0.338
Creatinine, mg/dL	0.183	0.115
eGFR, mL/min/1.73 m^2	-0.110	0.349
ASD maximal defect diameter, mm	**0.248**	**0.032**
ASD defect area, cm^2	**0.309**	**0.008**
ASD Device diameter, mm	**0.248**	**0.033**
Qp/Qs ratio	0.217	0.103
LV mass index, g/m^2	0.080	0.519
LA volume index, mL/m^2	-0.078	0.509
LV ejection fraction, %	0.191	0.103
Stroke volume, mL	-0.137	0.251
TRV, m/sec	**0.332**	**0.004**
Pre-closure E/e'	-0.359	0.002
Pre-closure Ed	-0.227	0.055
ΔLA volume index-immediate	**0.424**	**<0.001**
Immediate LV Ed	0.480	<0.001

ASD, atrial septal defect; e', early diastolic septal mitral annular velocity; Ed, end-diastolic elastance; E/e', ratio of early mitral inflow velocity to e'; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; TRV, tricuspid regurgitant velocity.

Table 3. Comparison between patients with increased PASP and decreased PASP immediately after device closure of ASDs*.

Variable	PASP decrease (n = 55)	PASP increase (n = 21)	P value
Age, years	**47.7 ± 14.4**	**56.4 ± 15.2**	**0.022**
Female, n (%)	36 (66)	14 (67)	0.921
Body surface area, m^2	1.62 ± 0.14	1.57 ± 0.18	0.288
Body mass index, kg/m^2	22.3 ± 2.9	22.3 ± 3.1	0.986
Systolic blood pressure, mmHg	116.7 ± 13.7	115.1 ± 19.7	0.027
Atrial fibrillation, n (%)	4 (7)	2 (10)	0.745
Blood urea nitrogen, mg/dL	**14.4 ± 3.7**	**16.7 ± 5.8**	**0.046**
Creatinine, mg/dL	0.74 ± 0.15	0.80 ± 0.20	0.168
eGFR, mL/min/1.73 m^2	**102.6 ± 17.4**	**91.3 ± 20.3**	**0.018**
Maximal defect diameter, mm	20.1 ± 6.2	21.1 ± 5.7	0.522
Defect area, mm^2	253.0 ± 144.1	263.5 ± 156.4	0.794
Device diameter, mm	23.6 ± 6.5	25.0 ± 5.9	0.411
Qp/Qs ratio	2.46 ± 0.82	2.79 ± 0.95	0.214
LV mass index, g/m^2	62.6 ± 14.1	64.4 ± 21.3	0.673
LA volume index, mL/m^2	**29.0 ± 12.5**	**35.4 ± 11.7**	**0.046**
LV ejection fraction, %	**67.4 ± 5.9**	**63.4 ± 7.0**	**0.015**
Stroke volume, mL	52.4 ± 11.2	51.9 ± 11.7	0.869
TRV, m/sec	2.83 ± 0.46	2.48 ± 0.45	0.004
PASP, mmHg	39.2 ± 12.7	31.6 ± 9.6	0.016
PVR, Wood unit	1.49 ± 0.27	1.42 ± 0.42	0.425
e', cm/s	**9.8 ± 3.0**	**7.7 ± 3.4**	**0.013**
E/e'	8.65 ± 3.29	10.10 ± 3.94	0.120
Amplatzer/Cocoon/Figullar Flex II/Gore-Helix/Occlutech	29/23/0/2/1	10/10/1/0/0	0.412

*In two patients pre- or post-TRV were not measurable, ASD, atrial septal defect; e', early diastolic septal mitral annular velocity; E/e', ratio of early mitral inflow velocity to e'; eGFR, estimated glomerular filtration

rate; LA, left atrial; LV, left ventricular; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; TRV, tricuspid regurgitant velocity.

Figures

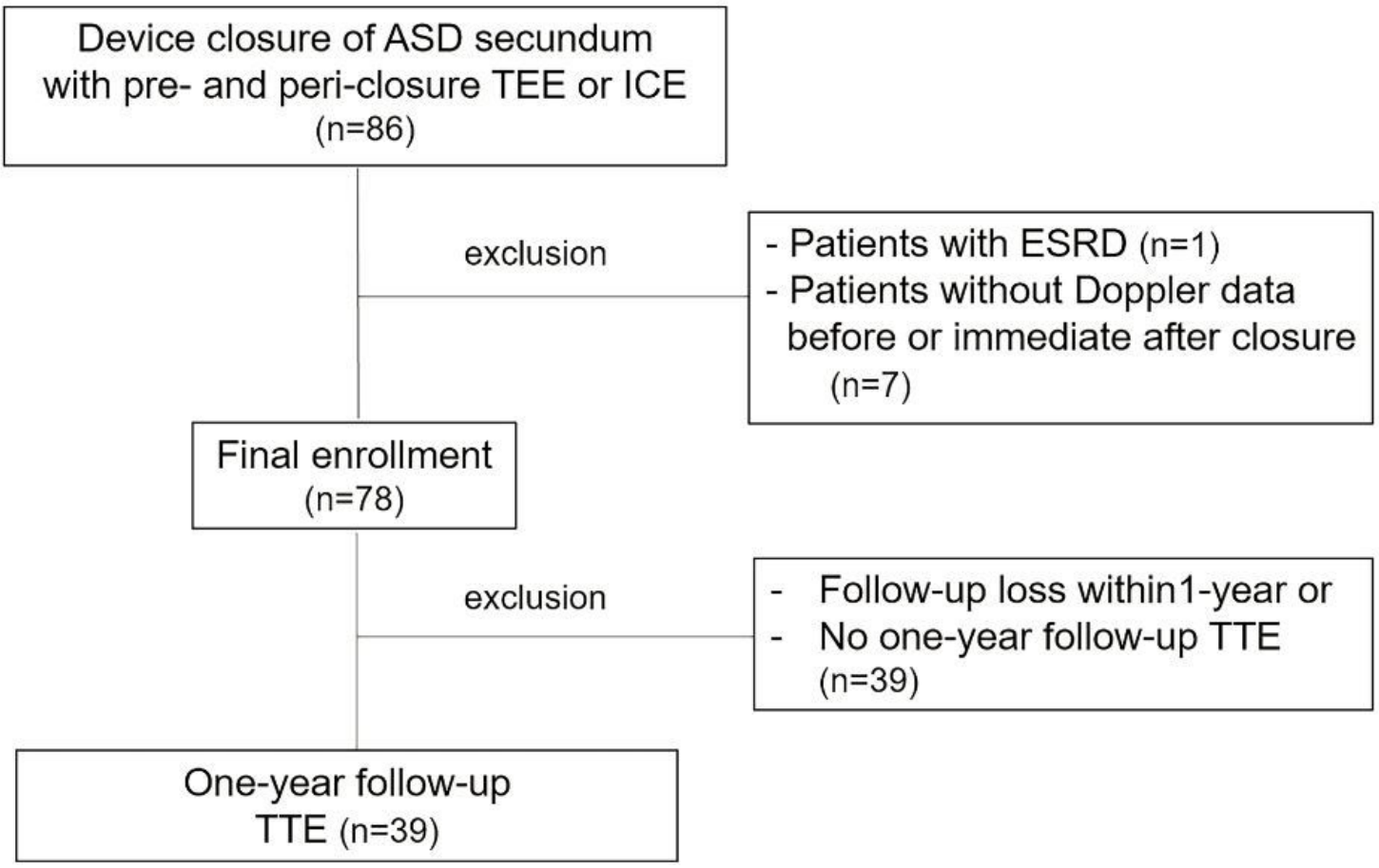

Figure 1

Schematic diagram of study patient selection process. ASD, atrial septal defect; ESRD, end-stage renal disease; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; ICE, intracardiac echocardiography.

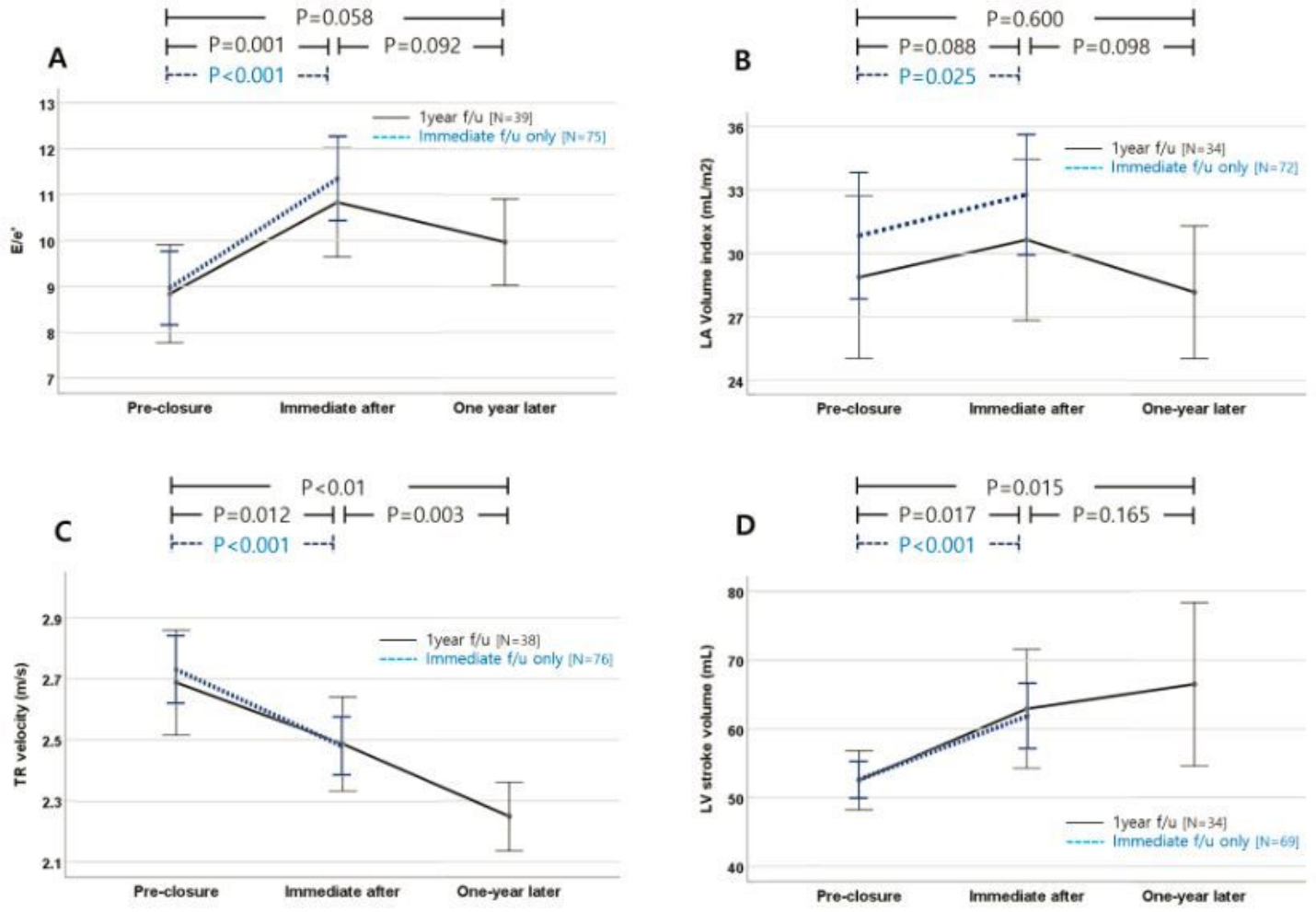

Figure 2

Serial changes of E/e' (A), left atrial (LA) volume index (B), tricuspid regurgitant (TR) velocity (C), and left ventricular (LV) stroke volume (D) from pre-closure to one-year follow-up (n=39). Blue dotted line represents comparisons between pre-closure state and immediate after (one-day after closure) follow-up only (n=78). Bars represent 95% confidence intervals.

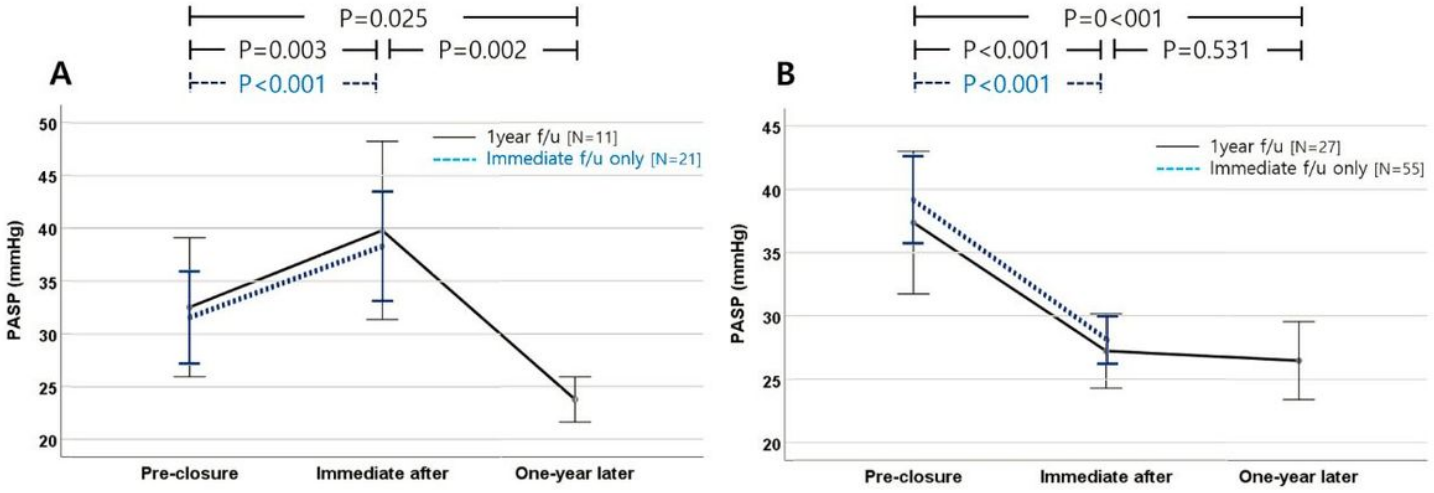

Figure 3

Serial changes of pulmonary arterial systolic pressure (PASP) from pre-closure stage to one-year follow-up by immediate PASP response group. (A) Immediate increased PASP group and (B) immediate decreased PASP group. Blue dotted line represents comparisons between pre-closure state and immediate after (one-day after closure) follow-up only. Bars represent 95% confidence intervals.

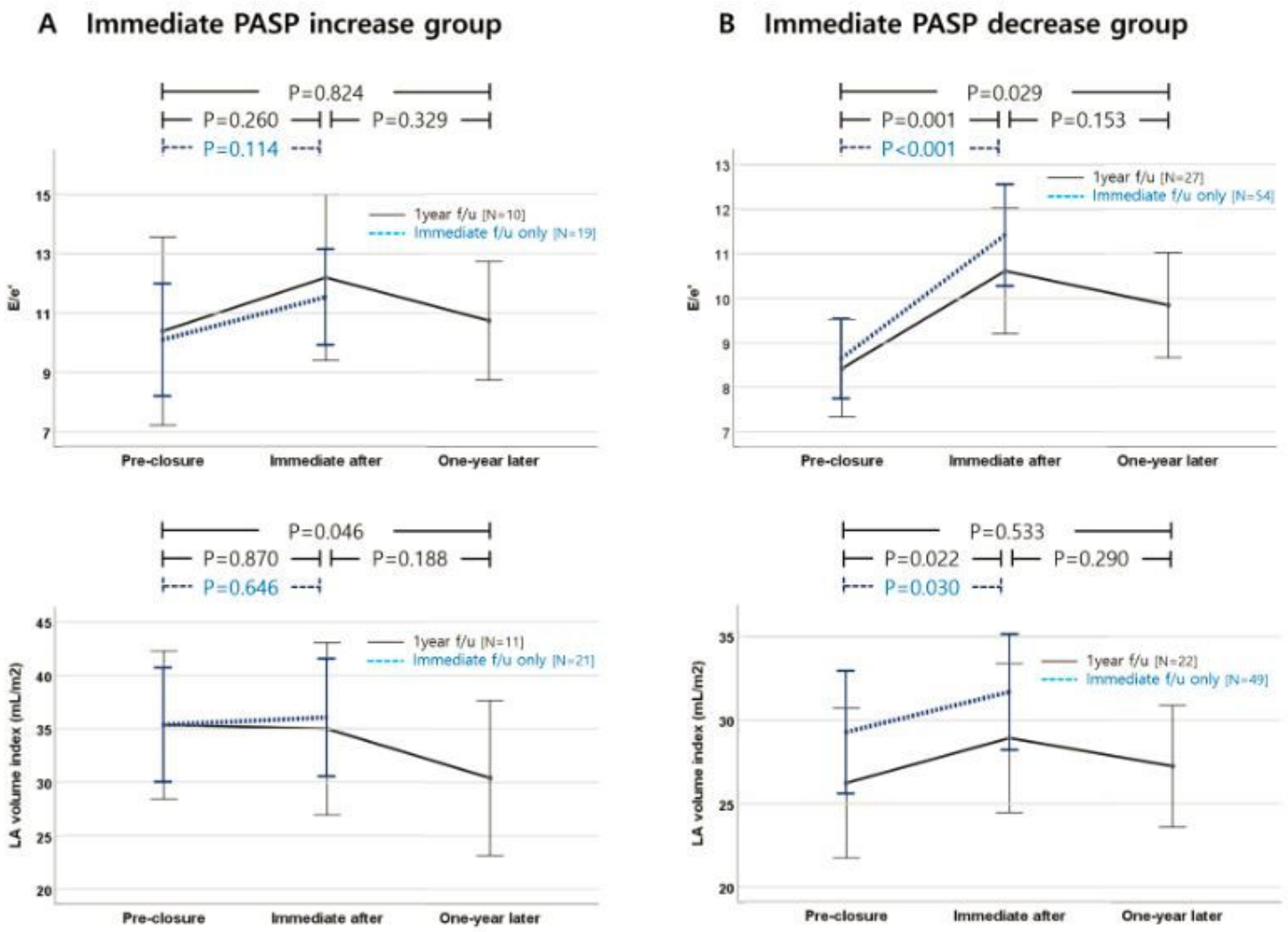

Figure 4

Serial changes of E/e', left atrial (LA) volume index, tricuspid regurgitant (TR) velocity, and left ventricular (LV) stroke volume from pre-closure stage to one-year follow-up in (A) immediate increased PASP group and (B) immediate decreased PASP group. Blue dotted line represents comparisons between pre-closure state and immediate after (one-day after closure) follow-up only. Bars represent 95% confidence intervals.