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Preoperative coupling between right ventricle and pulmonary vasculature is an important determinant of residual symptoms after the closure of atrial septal defect

Running head: RV-PA coupling in patients with ASD

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Abstract

Purposes: The closure of atrial septal defect (ASD) is associated with a significant reduction in right ventricular (RV) overload and an improvement in functional capacity in most adults with ASD. However, a subset of patients remains symptomatic even after closure due to therapeutic delay. To date, no clinically robust preoperative predictor of postoperative residual symptoms has been clearly identified.

Methods: In this study, 120 adult patients with ASD and 39 controls were investigated.

As an index of RV myocardial deformation, RV global longitudinal strain (RV-GLS) was evaluated. The degree of coupling between RV and pulmonary artery (PA) was quantified by the tricuspid annular plane systolic excursion (TAPSE) divided by the PA systolic pressure (PASP).

Results: Compared to controls, baseline RV-GLS was significantly greater (-27 ± 7 vs. $-23\pm 5\%$, $P=0.02$) and **TAPSE/PASP ratio** was severely impaired (0.8 ± 0.3 vs. 2.1 ± 1.6 mm/mmHg, $P<0.01$) in ASD patients. At 6 months after closure, 15 patients (12.5%) remained symptomatic. In patients without residual symptoms, **TAPSE/PASP ratio** significantly improved from 0.9 ± 0.3 to 1.0 ± 0.6 mm/mmHg ($P=0.02$), and RV-GLS normalized (from -28 ± 11 to $-24\pm 7\%$, $P<0.01$) after closure. However, RV-GLS and **TAPSE/PASP ratio showed no significant change** in ASD patients with residual

symptoms. On multivariate analysis, preoperative **TAPSE/PASP ratio** (odds ratio [OR] 0.034, 95% confidence interval [CI] 0.000-0.604, $P=0.03$) and **pulmonary vascular resistance index** ([PVRI], OR 1.011, 95% CI 1.000-1.021, $P<0.05$) were associated with the postoperative symptomatic status.

Conclusion: In terms of integrated assessment of the RV-PA unit, preoperative **TAPSE/PASP ratio** and **PVRI** were important determinants of residual symptoms after ASD closure.

Key words: Atrial septal defect, heart failure, ventriculo-arterial coupling, right ventricle, myocardial deformation, residual symptom.

1 **Introduction**

2 Atrial **septal** defect (ASD) accounts for approximately 7% of congenital heart
3 diseases.¹ Although the hemodynamic consequence of ASD is chronic volume overload
4 of the right heart and pulmonary vasculature, pulmonary overcirculation is generally
5 compensated for by the right ventricular (RV) and pulmonary arterial (PA) reserve.²⁻⁴ If
6 left untreated, however, a longstanding left-to-right shunt results in RV myocardial cell
7 hypertrophy and myocardial fibrosis, eventually leading to irreversible myocardial
8 damage and consequent right-sided heart failure.^{5, 6} On the other hand, the pulmonary
9 vascular bed progressively remodels with intimal proliferation,⁷ medial hypertrophy,^{7, 8}
10 and increased collagen synthesis leading to obstructive pulmonary vasculopathy,^{7, 9}
11 ultimately resulting in irreversible pulmonary arterial hypertension (PAH).^{7, 8, 10}

12 Both transcatheter and surgical repair have low mortality and good long-term
13 outcomes with significant improvement in exercise capacity when performed in the
14 early stage of the disease process.^{11, 12} However, in a subset of patients, prolonged
15 overcirculation of the right heart induces insidious RV myocardial impairment and
16 pulmonary vasculopathy,^{3, 6-8, 13} resulting in postoperative residual symptoms even after
17 successful ASD closure,¹⁴ which is a major concern because it is closely associated with
18 poor outcomes and impaired quality of life.¹¹ However, to date, no clinically robust

preoperative predictor of postoperative residual symptoms has been clearly identified.

Therefore, this study sought to assess the hemodynamic characteristics of patients with ASD in terms of mechano-energetic parameters and to identify the predictors of residual symptoms in these patients.

Methods

Study population

Initially, 140 consecutive patients with ASD who underwent percutaneous or surgical closure between May 2011 and February 2020 at our institution were retrospectively recruited. For the preoperative evaluation of their hemodynamic status, **transthoracic echocardiography was performed by two experienced echocardiographers, who were well trained in adult congenital heart diseases.** Eleven of these subjects (7.9%) were excluded from all subsequent analyses because of suboptimal quality of images and nine (6%) were lost to follow-up. Thirty-nine age- and sex-matched healthy participants served as the control group. **Controls were healthy volunteers recruited from the community and were screened and excluded if they had any chronic medical illness, current medical complaints, or an abnormal physical examination finding.** Thus,

the final study cohort consisted of 159 participants: 120 with ASD and 39 normal controls.

Indications for ASD closure were a significant left-to-right shunt, evidence of RV volume overload, or clinical symptoms of heart failure or paradoxical embolism.¹⁵ Exclusion criteria included severe PAH with pulmonary vascular resistance >8 Wood units¹⁵ and other concomitant congenital heart diseases.

All of the participants provided written informed consent for the procedure. The study protocol was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN ID: 000038542) and conformed to the ethical principles outlined in the Declaration of Helsinki. This study was approved by the local ethics committee of our institution (protocol ID: B200022).

Comprehensive echocardiographic examination

All baseline echocardiographic studies were performed within a week before ASD closure using a commercially available echocardiographic system. Digital routine cine loops were obtained from standard parasternal and apical views, and echocardiographic measurements were obtained in accordance with the guidelines of the American Society of Echocardiography/The European Association of Cardiovascular Imaging.^{16, 17} Left ventricular (LV) volumes, LV ejection fraction (EF), and left atrial

(LA) volumes were calculated using the modified biplane Simpson method. The transmitral early diastolic (E) and atrial wave velocities were measured using pulsed-wave Doppler recordings from the apical four-chamber view. Early diastolic (e') mitral annular velocity was measured using spectral tissue Doppler imaging, and the E/e' ratio was calculated to estimate LV filling pressure.¹⁸ LV and RV stroke volumes (SV) were calculated using the pulsed-wave Doppler method, as the product of the velocity-time integral at the LV and RV outflow tract and their respective cross sectional areas. RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), RV fractional area change (RVFAC), and right atrial (RA) area were measured from the RV-focused apical four-chamber view.¹⁹ Tricuspid annular plane systolic excursion (TAPSE) was measured as an index of RV longitudinal systolic function.¹⁹

As previously described, the simplified RV contraction pressure index (sRVCPI) was calculated as an index of RV external work by multiplying the TAPSE by the pressure gradient between the RV and RA.²⁰ As an index of RV-PA coupling, TAPSE/PA systolic pressure (PASP) ratio was calculated, wherein TAPSE represented the longitudinal RV contractile function, and PASP the developed pressure.²¹ LV stroke work index (LVSWI) was approximated as the product of SV index and mean systemic blood pressure.

1 **Speckle-tracking strain analysis**

2 Speckle-tracking analyses were performed with dedicated software
3 (AutoSTRAIN, TOMTEC-ARENA; TOMTEC Imaging Systems GmbH,
4 Unterschleißheim, Germany), as described previously.²² Briefly, the average values of
5 18 regional LV longitudinal strain from three apical views were calculated to obtain the
6 LV global longitudinal strain (LV-GLS). GLS from the RV (RV-GLS) was calculated by
7 averaging the regional strain values from the RV free-wall on the RV-focused apical
8 four-chamber view (Figure 1).²²

9 **Hemodynamic assessment and clinical follow-up**

10 Before ASD closure, all patients underwent invasive cardiac catheter
11 examination to assess hemodynamic status, including intracardiac pressures, pulmonary
12 vascular resistance index (PVRI), and pulmonary-to-systemic blood flow (Qp/Qs) ratio
13 preoperatively. Postoperative clinical assessments were scheduled at 1, 3, 6, and 12
14 months after the procedure and annually thereafter. At each visit, plasma B-type
15 natriuretic peptide (BNP) levels were evaluated and hemodynamic status was non-
16 invasively assessed using transthoracic echocardiography. Preoperative symptomatic
17 status was assessed according to the Framingham criteria²³ by two independent
18 cardiologists who specialized in adult congenital heart diseases, and residual

symptomatic status was evaluated likewise at the scheduled visit to the outpatient clinic at 6 months after ASD closure.

Catheter intervention

Transcatheter ASD closure was performed using the Amplatzer Septal Occluder (St. Jude Medical, St. Paul, MN, USA) or Figulla Flex II ASD occluder (Occlutech GmbH, Jena, Germany). All procedures were performed under general anesthesia with endotracheal intubation and guided by transesophageal echocardiography and fluoroscopy. After hemodynamic assessment, all patients underwent balloon sizing of the defect. An atrial septal occluder 2-4 mm larger than the stretched diameter was chosen.

Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two groups were compared by using the Student's t test or Mann-Whitney U test as appropriate. Differences in baseline echocardiographic and hemodynamic parameters among the three subgroups were tested by one-way analysis of variance (ANOVA) followed by post hoc comparisons by the Tukey test. To identify

differences in hemodynamic and echocardiographic parameters between the two time points, the paired *t*-test was used for comparisons of continuous variables. Proportional differences were evaluated using the Fisher's exact test or the χ^2 test, as appropriate.

Differences in clinical, hemodynamic, and echocardiographic changes between groups were tested by 2-way repeated measures ANOVA, with case status as grouping factor (i.e., three sub-groups) and time point (i.e., baseline and 6 months after ASD closure) as the repeated factor. For symptomatic patients before ASD closure, an initial univariate logistic regression analysis to identify univariate predictors of residual symptoms after ASD closure was followed by a multivariate model using stepwise selection, with the *P* value for entry into the model set at < 0.10 . Age and sex were forced into the multivariate analysis regardless of their association on univariate analysis. Receiver operating characteristic (ROC) curves analysis was performed for symptomatic patients before ASD closure to determine optimal cutoff points for postoperative symptomatic status. The association between the variables were assessed by using Pearson's correlation coefficient or Spearman's correlation coefficient, as appropriate. For all steps, *P* values < 0.05 were considered statistically significant. All analyses were performed using MedCalc version 18.11.6 (MedCalc Software; Ostend, Belgium).

1 **Results**

2 **Baseline Characteristics**

3 The baseline clinical, hemodynamic, and echocardiographic characteristics of
4 120 patients with ASD and 39 healthy controls are summarized in Table 1. As expected,
5 patients with ASD showed significant structural remodeling of the right heart, as
6 evidenced by larger RVEDA, RVESA, and RA area compared to normal controls. As a
7 result of chronic volume overload in the RV, sRVCPI (728 ± 293 vs. 349 ± 186
8 mmHg·mm, $P < 0.01$) and RV-GLS (-27 ± 7 vs. $-23 \pm 5\%$, $P = 0.02$) were significantly
9 greater in patients with ASD than those in controls, indicating RV “overwork”.
10 Moreover, coupling of the RV and the pulmonary vasculature was significantly impaired
11 (**TAPSE/PASP ratio**; 0.8 ± 0.3 vs. 2.1 ± 1.6 mm/mm Hg, $P < 0.01$) in patients with
12 ASD. With respect to the left heart, LV volumes were more likely to be smaller and
13 LVSWI was significantly reduced (3400 ± 1000 vs. 3900 ± 900 mmHg·mL/m², $P <$
14 0.01), which suggests LV unloading in patients with ASD.

15 **Changes in cardiac structure and hemodynamics at 6 months after ASD closure**

16 Only one patient underwent surgical ASD closure because of insufficient
17 surrounding rim, while the remaining 119 patients successfully underwent transcatheter
18 closure without any complications.

Table 2 shows the changes in the cardiac structure and hemodynamics of the patients 6 months after the ASD closure. On the whole, a reverse remodeling of the right heart was observed, as evidenced by the significant reduction in RVEDA and RA area. As a result of disappearance of chronic volume overload, RV functional parameters including TAPSE, RV-SV, and RV-GLS decreased (i.e., “normalized”) after the shunt closure. Moreover, RV “overwork” was significantly alleviated (sRVCPI; from 728 ± 293 to 473 ± 238 mmHg·mm, $P < 0.01$) and **TAPSE/PASP ratio** was significantly improved (0.8 ± 0.3 vs. 1.0 ± 0.6 mm/mmHg, $P < 0.01$) at 6 months after the closure.

Conversely, as a result of appropriate volume loading, LV volumes and E/e' ratio significantly increased and both cardiac index (from 2.6 ± 0.6 to 3.0 ± 0.7 L/min/m², $P < 0.01$) and LVSWI (from 3400 ± 1000 to 4100 ± 1000 mmHg·mL/m², $P < 0.01$) normalized at 6 months after the closure.

Subgroup analysis of ASD patients with or without residual symptoms after the closure

Of the 120 ASD patients, 59 (49%) were asymptomatic from baseline (group A). Of the 61 patients who were symptomatic at baseline, the NYHA functional class improved in 46 (Group B), while the remaining 15 (Group C) patients remained symptomatic 6 months after ASD closure. None of the patients had deteriorated in their

1 NYHA functional class at 6 months after closure.

2 As shown in Table 3, patients with residual symptoms (Group C) were more
3 likely to be older, showed higher BNP concentrations, and had higher PVRI compared
4 to the other two subgroups, indicating a more advanced disease status at baseline.

5 Although parameters of LV structure and function were quite comparable among the
6 three subgroups of ASD, with regard to the baseline RV functional parameters, RV
7 “overwork” (sRVCPI; 660 ± 277 vs. 783 ± 27 vs. 831 ± 346 mmHg·mm, ANOVA $P <$
8 0.05), “uncoupling” between RV and PA vasculature (TAPSE/PASP ratio; 0.9 ± 0.4 vs.
9 0.8 ± 0.2 vs. 0.5 ± 0.2 mm/mmHg, ANOVA $P < 0.01$), and RV myocardial dysfunction
10 (RV-GLS; -27 ± 6 vs. -29 ± 8 vs. $-20 \pm 7\%$, ANOVA $P < 0.01$) were progressively
11 pronounced in the order of groups A, B, and C, respectively.

12 At 6 months after closure, RV functional parameters including TAPSE,
13 RVFAC, and RV-GLS, all normalized in the two subgroups of ASD patients without
14 symptoms after closure (groups A and B), while the changes in these parameters were
15 significantly blunted in patients with residual symptoms (group C). Of note, although
16 significant reverse remodeling of the right heart was accomplished in all three
17 subgroups, not only RV “overwork” (sRVCPI; from 831 ± 346 to 589 ± 234 , n.s), but
18 also RV-PA “uncoupling” (TAPSE/PASP ratio; from 0.5 ± 0.2 to 0.6 ± 0.3 mm/mmHg,

n.s) failed to improve in patients with residual symptoms (Group C, Table 3).

Determinants of residual symptoms after ASD closure

Table 4 shows the odds ratio (OR) and 95% confidence intervals (CI) of each of the baseline variables of univariate and multivariate logistic regression analysis for determinants of residual symptoms after ASD closure. Among the univariate variables, age at operation, sex, BNP concentration, PVRI, TAPSE, TR-PG, RV-GLS, and TAPSE/PASP ratio were entered into the final multivariate model, using stepwise selection. However, only baseline TAPSE/PASP ratio and PVRI were found to be the independent determinants of residual symptoms on multivariate analysis.

The results of the ROC curve analyses are presented in Figure 2 and table 5. These results can be translated to the fact that the patients with a TAPSE/PASP ratio < 0.66 mm/mmHg had a 7.5-fold higher risk (HR 7.5, 95% CI 1.8- 30.5, $P < 0.01$) of residual symptoms than those with a ratio ≥ 0.66 mm/mmHg. Similarly, the patients with an PVRI > 158 dyne·sec·cm⁻⁵ had a 7.7-fold higher risk (HR 7.7, 95% CI 1.6 to 38, $P < 0.01$) of residual symptoms than those with a value ≤ 158 dyne·sec·cm⁻⁵. The area under the curve (AUC) of TAPSE/PASP ratio was slightly larger than that of PVRI but the difference was not statistically significant (difference between areas = 0.067, $P = 0.52$).

PVRI showed a weak relationship with age ($r = 0.36$, $P < 0.05$), while TAPSE/PASP ratio did not correlate significantly ($r = -0.17$, $P = 0.18$). On the other hand, PVRI ($r = 0.30$, $P < 0.01$) and TAPSE/PASP ratio ($r = -0.36$, $P < 0.001$) showed a weak positive and negative correlation between the incidence of atrial fibrillation, respectively.

There were 16 patients with preserved TAPSE/PASP ratio (≥ 0.66 mm/mmHg) and PVRI (< 158 dyne·sec·cm⁻⁵) at baseline, and this pattern was associated with the lowest risk of postoperative symptomatic status (0%), among the three subgroups (Figure 3). In contrast, 13 patients with both impaired baseline TAPSE/PASP ratio (< 0.66 mm/mmHg) and PVRI (> 158 dyne·sec·cm⁻⁵) constituted a subgroup with the worst symptomatic status (77%). In addition, there were 20 patients with either impaired TAPSE/PASP ratio or elevated PVRI at baseline. These patients were associated with an intermediate risk of residual symptoms (20%).

Figure 4 shows the representative cases of ASD patients with and without residual symptoms.

Discussion

The major findings of this study are as follows: In terms of mechano-energetic

function, “overwork” of the RV, “uncoupling” of the RV-PA unit, and unloading of the LV were significantly pronounced in patients with ASD. On the whole, RV “overwork”, RV-PA “uncoupling”, and LV unloading were alleviated at 6 months after ASD closure, however, these favorable changes were blunted in patients with residual symptoms. Moreover, preoperative **TAPSE/PASP ratio** and **PVRI** were important determinants of residual symptoms after ASD closure.

Hemodynamic adaptation in patients with ASD

From a pathophysiological point of view, hemodynamic adaptation in patients with ASD can be summarized as the following two aspects: compensatory “overwork” of the RV⁴ and pulmonary vasodilation^{3, 8} via recruitment of the preload reserve and pulmonary vascular reserve. As observed in this study, all baseline parameters of RV contraction were significantly greater in patients with ASD, which can be translated to compensatory “overwork” of the RV myocardium. The pulmonary vascular bed is a low-resistance system that can accommodate large amounts of blood flow without a significant elevation in PA pressure.⁸ Moreover, further decrease in PVR can be achieved during exercise.³ Thus, most patients with ASD tend to be asymptomatic until their third or fourth decade^{11, 24} due to the large amount of preload reserve of the RV and pulmonary vascular reserve.

Hemodynamic mal-adaptation in ASD patients

The longstanding compensatory mechanisms, including RV dilation and myocardial hypercontraction, eventually reach their limit. In this scenario, chronic RV overwork and myocardial overstretch ultimately lead to irreversible myocardial damage. Although pulmonary vasculature is initially able to receive a large amount of cardiac output by diminishing PVR,³ the persistent pulmonary overcirculation causes shear stress on the pulmonary arterial endothelium, inducing progressive pulmonary vasculopathy.^{7, 10}

As observed in our patients with residual symptoms after ASD closure, RV “unloading” could not be accomplished due to persistent elevation in PA pressure even after ASD closure, which indicates that these patients had already reached the stage of exhaustion of the hemodynamic reserve,³ and therefore, passed the “point of no return”.

Determinants of residual symptoms after ASD closure

In this study, baseline **TAPSE/PASP ratio and PVRI were** found to be the independent determinants of residual symptomatic status after the ASD closure.

Engelfriet et al.²⁵ previously reported, by analyzing 882 patients with ASD who were registered with the Euro Heart Survey for adult congenital heart disease, that the best independent predictors of functional limitations were the presence of PAH and RV

1 volume overload. Consequently, the probability of RV dysfunction increased with the
2 level of pulmonary pressure. More recently, Cossio-Aranda et al.²⁶ revealed that systolic
3 PA pressure best determined the RV contractile dysfunction, as evidenced by the
4 impairment of TAPSE and RVFAC in a retrospective echocardiographic cohort
5 consisting of 92 adults with ASD. Our results are consistent with these previous reports
6 in that the baseline PVRI, which is a major determinant of PA pressure, was an
7 independent determinant of postoperative residual symptomatic status in our study.
8 Unfortunately, however, these previous investigators neglect the fact that there is a
9 significant interplay between volume overload imposed on the RV, PAH due to
10 pulmonary vasculopathy, and RV myocardial dysfunction when assessing ASD-specific
11 hemodynamics. In fact, the hemodynamic derangements in ASD patients can be
12 considered as a combination of RV myocardial damage and pulmonary vasculopathy;
13 thus, from a pathophysiological point of view, it is more logical to evaluate the
14 comprehensive pulmonary circulation in patients with ASD in terms of the integrated
15 assessment of the RV-PA unit as a whole. Because the TAPSE/PASP ratio could be
16 considered as a useful clinical index of longitudinal RV contractile function to the
17 developed pressure,²¹ the TAPSE/PASP ratio might potentially be more robust in
18 detecting the disease process than each of the two variables separately. Therefore, in this

study, preoperative TAPSE/PASP ratio could successfully detect impairment of the homeostasis of the pulmonary circulation unit and may be a reliable determinant of postoperative residual symptoms.

In this study, RV-GLS normalized in the subgroups of ASD patients without residual symptoms after ASD closure, while the postoperative change in RV-GLS was significantly blunted in patients with residual symptoms. Strictly speaking, myocardial strain is not a marker that purely reflects cardiac contractility. Rather, it is actually a dependent variable highly affected by cardiac preload,²⁷ afterload,²⁸ and myocardial contractility.²² Thus, RV-GLS can reflect the entire hemodynamic burden imposed on the RV-PA unit, including excessive preload brought on by the chronic left-to-right shunt, pulmonary vasculopathy resulting from pulmonary overcirculation, afterload mismatch between RV and pulmonary vasculature, and intrinsic RV myocardial contractility. Therefore, from a pathophysiological point of view, it is not surprising that RV-GLS significantly reduced after ASD closure according to the Frank-Starling's principle in patients without residual symptoms. However, when the Frank-Starling curve shifts downward due to irreversible RV myocardial impairment, "normalization" of the excessive RV preload would no longer lead to the change in RV-GLS as a result of a relatively flat Frank-Starling curve, as observed in our patients with residual

1 symptoms. Therefore, one can speculate that the blunted response in RV-GLS after the
2 shunt closure may be considered as an important marker of the RV myocardial
3 irreversibility, which may result in residual symptoms even after ASD closure.

4 **Clinical implications**

5 Although evidence of RV volume overload, the presence of PAH, and patients'
6 symptomatic status have been widely used in the planning of therapeutic strategies for
7 patients with ASD,¹⁵ the clinical significance of **TAPSE/PASP ratio** and **PVRI** has not
8 been well investigated. The present study showed that the preoperative **TAPSE/PASP**
9 **ratio** (< 0.66 mm/mmHg) and **PVRI** (> 158 dyne·sec·cm⁻⁵) were related to postoperative
10 impaired quality of life. Our results may support the concept that the hemodynamic
11 burden imposed on the RV myocardium should be evaluated from the standpoint of a
12 crosstalk between the RV myocardium (i.e., supplier) and pulmonary vasculature (i.e.,
13 receiver). This will open up newer perspectives in the management of ASD patients,
14 according to which the shunt should be closed earlier, before the development of RV-PA
15 uncoupling, even if the patients do not fulfill the current criteria. **In terms of integrated**
16 **assessment of the RV-PA unit, preoperative TAPSE/PASP ratio and PVRI may be**
17 **important determinants of residual symptoms after ASD closure.**

18 **Study limitations**

1 There are certain limitations to this study. First, as with most studies of
2 congenital heart diseases, this retrospective study included a small number of patients
3 from a single center. Moreover, the number of the patients with residual symptoms are
4 also small; thus, concerns regarding insufficient statistical power should be considered.
5 Furthermore, not all parameters that could potentially affect the residual symptoms after
6 ASD closure were entered into the multivariate model. Therefore, we were not be able
7 to draw a definitive conclusion regarding the clinical importance of the measurements
8 of preoperative TAPSE/PASP ratio and PVRI in patients with ASD. Therefore, future
9 prospective studies with larger patient populations are needed to validate our findings.
10 Second, the clinical effects of preoperative TAPSE/PASP ratio and PVRI on hard
11 endpoints were not evaluated in this study. Therefore, future studies should address the
12 impact of these measures on cardiovascular outcomes. However, the therapeutic goals
13 are not only to reduce the mortality, but also to improve patients' quality of life and
14 restore well-being. Therefore, we believe that the results of our study are meaningful for
15 the appropriate management of ASD patients. Third, the assessment of functional
16 capacity in this study was based on the judgement by two independent cardiologists
17 who specialized in adult congenital heart diseases, at relatively short-term follow-up.
18 Therefore, quantitative assessment of exercise capacity, including cardiopulmonary

exercise testing or the 6-minute walk test in a longer-term follow-up would be more desirable to confirm our findings. Finally, RV-PA coupling was calculated as TAPSE divided by PASP in this study, based on the concept that TAPSE could be regarded as the surrogate of RV contractility and PASP as the afterload to the RV. Although the essential concept is that contractility is an intrinsic property of ventricular contraction, completely independent of loading condition, however, TAPSE is infact a dependent variable affected by cardiac preload, afterload, and myocardial contractility. Moreover, ventriculo-arterial coupling should be primarily obtained as the ratio of arterial to ventricular elastance. Although TAPSE/PASP ratio has been used as a non-invasively obtainable surrogate of RV-PA coupling, its experimental validation to the invasively obtained RV-PA coupling is required.

Conclusions

In terms of integrated assessment of the RV-PA unit, preoperative TAPSE/PASP ratio and PVRI were important determinants of residual symptoms after ASD closure.

Disclosures: None.

1

2 **Conflicts of interest:** The authors have no conflicts of interest to declare.

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Figure legends

Figure 1: Right ventricular (RV) longitudinal speckle tracking strain (RV-GLS) was calculated by using the RV-focused four-chamber view for averaging the 3 regional peak systolic strains (basal, middle, and apical lateral) from the right ventricular free wall.

RV = right ventricle, GLS = global longitudinal strain.

Figure 2: Receiver operating characteristic curve analyses for the prediction of residual symptoms after closure of atrial septal defect.

TAPSE/PASP ratio and PVRI showed high accuracy in predicting residual symptoms after closure of the atrial septal defect.

TAPSE = tricuspid annular plane systolic excursion, PASP = pulmonary arterial systolic pressure, PVRI = pulmonary vascular resistance index.

Figure 3: Bar graphs showing the relationship between postoperative residual symptoms and combined assessment of PVRI and TAPSE/PASP ratio.

The patients with intact RV-pulmonary arterial coupling (TAPSE/PASP ratio ≥ 0.66 mm/mmHg) and preserved pulmonary vascular resistance index (PVRI < 158

dyne·sec·cm⁻⁵) showed 0% symptomatic status at 6 months after ASD closure. Conversely, patients with impaired RV-PA coupling (TAPSE/PASP ratio <0.66 mm/mmHg) and reduced PVRI (PVRI >158 dyne·sec·cm⁻⁵) had the worst symptomatic status of 77%. Patients with either impaired TAPSE/PASP ratio or elevated PVRI showed an intermediate risk of postoperative symptomatic status. RV = right ventricular, TAPSE = tricuspid annular plane systolic excursion, PASP = pulmonary arterial systolic pressure, PVRI = pulmonary vascular resistance index, ASD = atrial septal defect.

Figure 4: Representative cases of atrial septal defect with and without residual symptoms after the closure.

(A) In a patient without residual symptoms after atrial septal defect (ASD) closure, the right ventricle (RV) and right atrium significantly reverse remodeled along with a reduction in the RV global longitudinal strain (GLS) and improvement of TAPSE/PASP ratio. (B) Both reduction of the RV overload and improvement of TAPSE/PASP ratio were not observed despite closure of the ASD in patient with residual symptoms at 6 months after the closure.

ASD = atrial septal defect, RV = right ventricle, GLS = global longitudinal strain,

- 1 TAPSE = tricuspid annular plane systolic excursion, PASP = pulmonary arterial systolic
- 2 pressure, TR = tricuspid regurgitation, PG = pressure gradient.

Figure 1

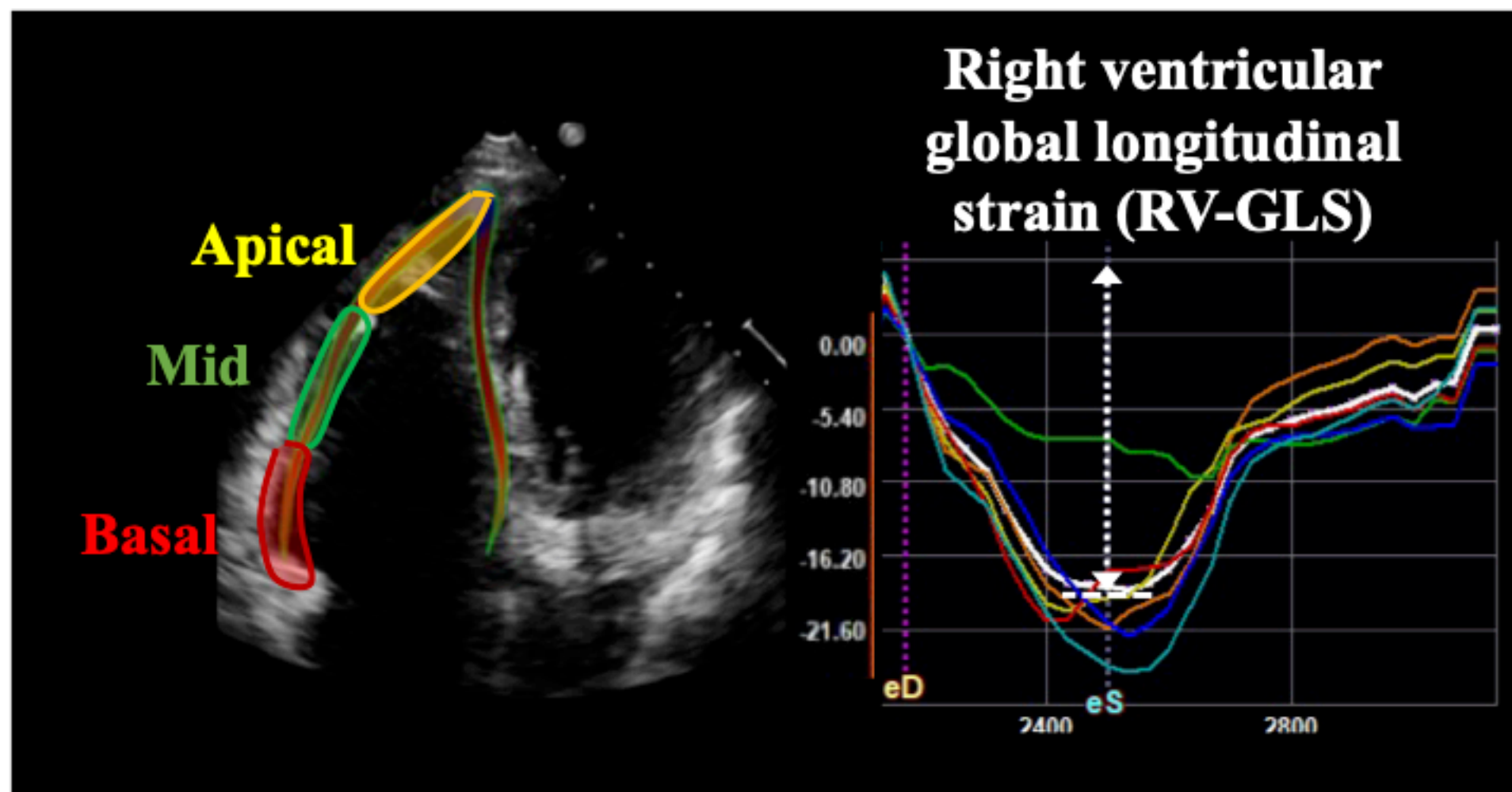


Figure 2

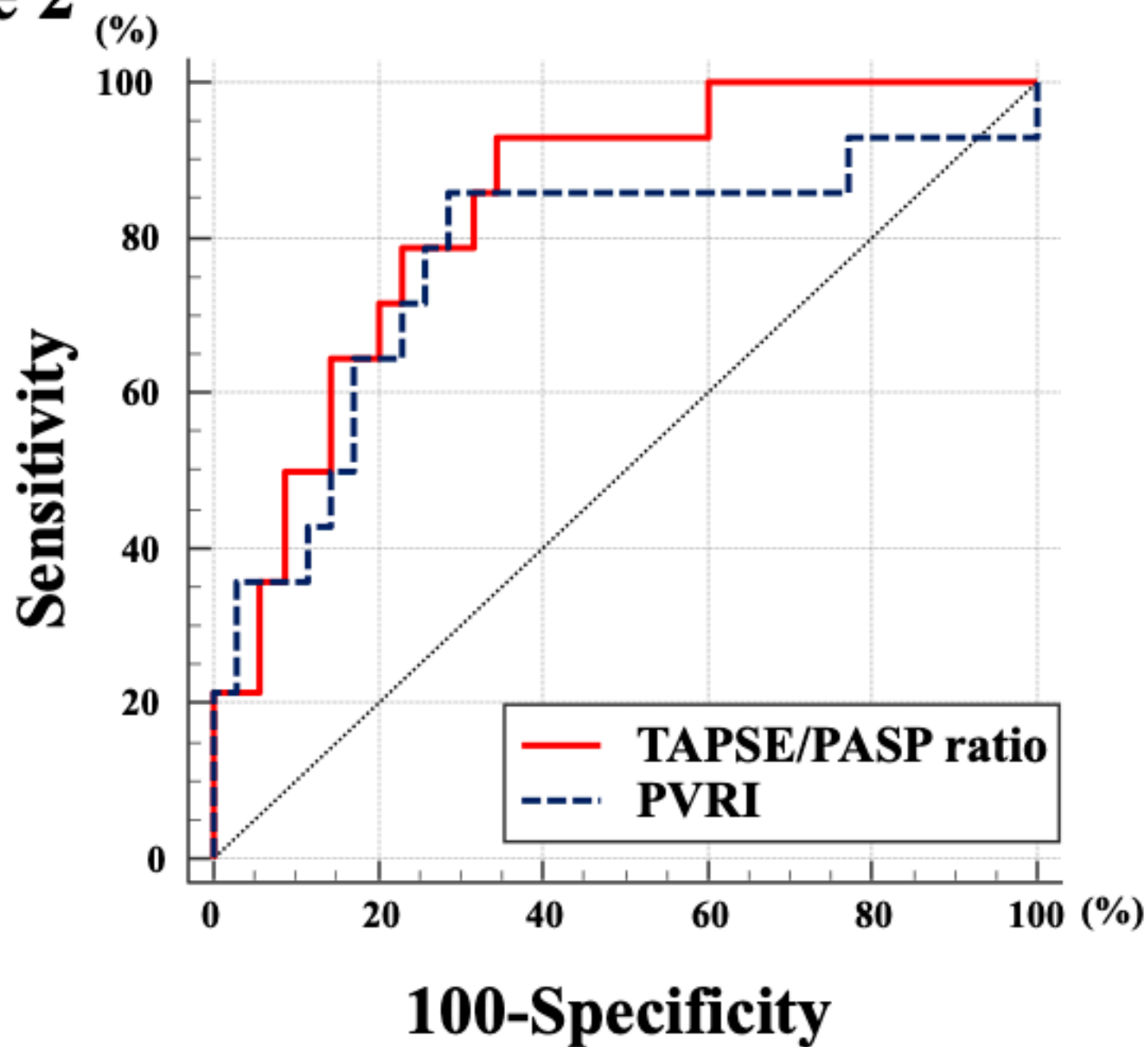


Figure 3

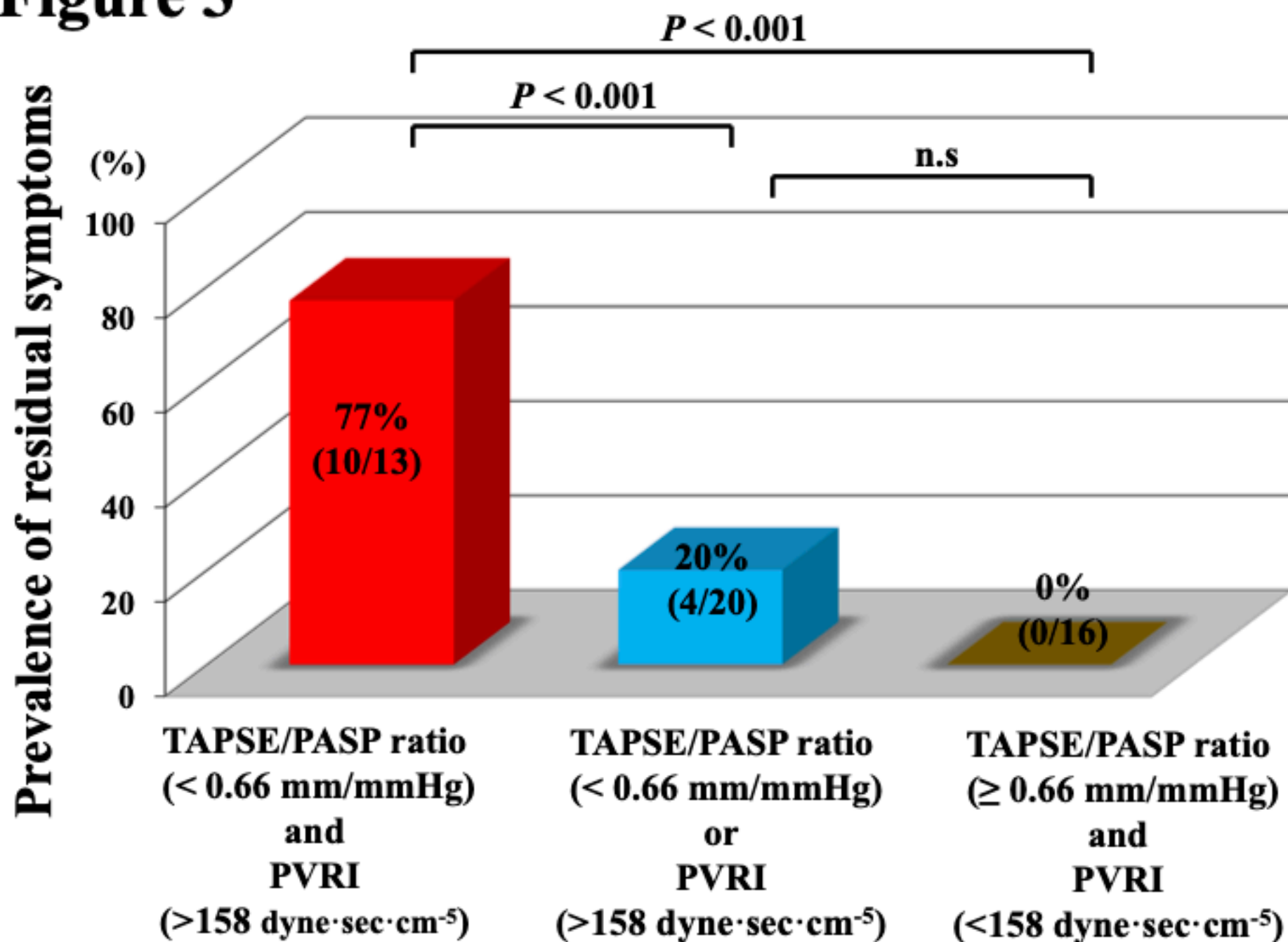
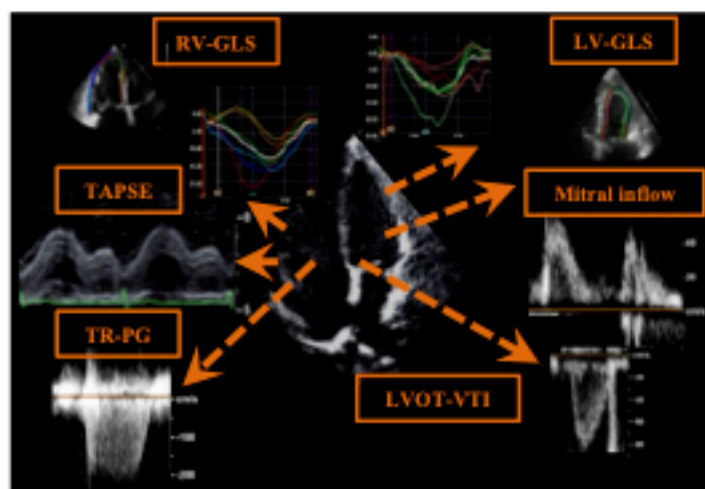


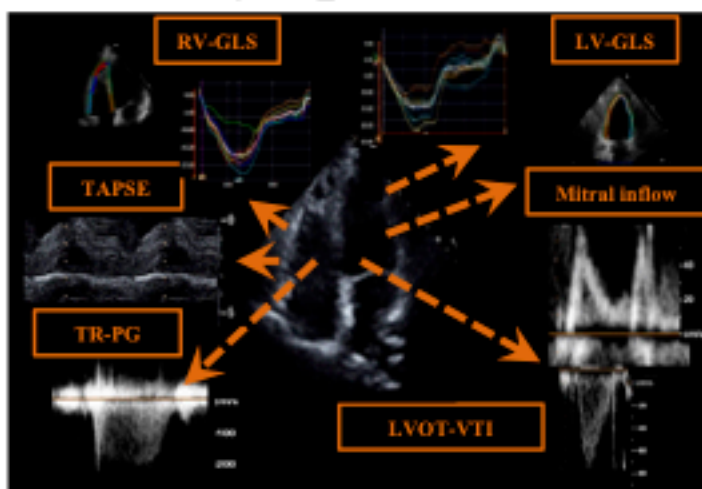
Figure 4

(A) Patients WITHOUT residual symptoms



Baseline

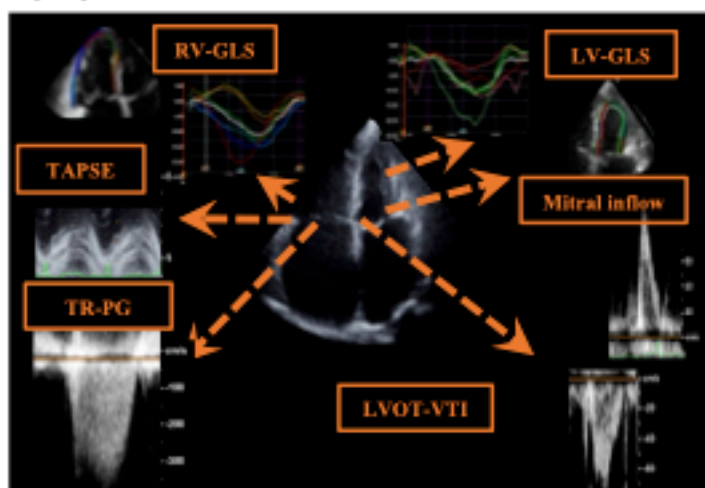
RVCPI: 521 mmHg·mm
 TAPSE/PASP ratio: 0.68 mm/mmHg
 RV-GLS: 26%
 LVSWI: 3290 mL·mmHg/m²



6 months after ASD closure

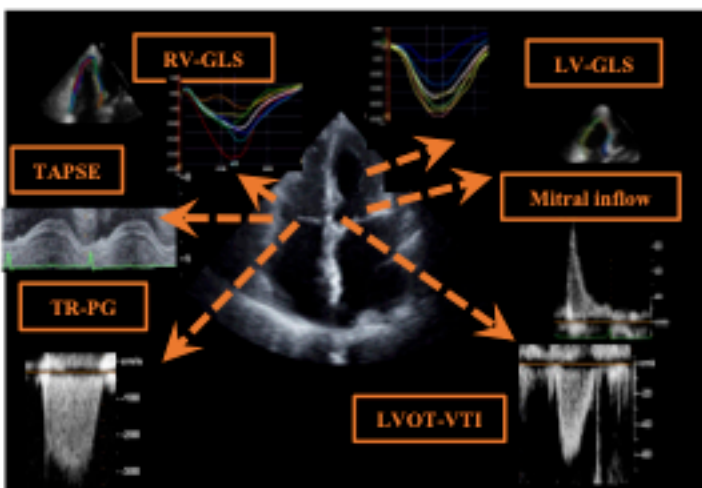
RVCPI: 347 mmHg·mm
 TAPSE/PASP ratio: 0.84 mmHg/mm
 RV-GLS: 19%
 LVSWI: 4300 mL·mmHg/m²

(B) Patients WITH residual



Baseline

RVCPI: 496 mmHg·mm
 TAPSE/PASP ratio: 0.40 mm/mmHg
 RV-GLS: 16 %
 LVSWI: 1860 mL·mmHg/m²



6 months after ASD closure

RVCPI: 413 mmHg·mm
 TAPSE/PASP ratio: 0.50 mmHg/mm
 RV-GLS: 16 %
 LVSWI: 2670 mL·mmHg/m²

Table.1 Baseline clinical, hemodynamic and echocardiographic characteristics of patients with atrial septal defect and normal controls

Variables	Normal control (N=39)	Patients with ASD (N=120)	<i>P</i> value
Clinical characteristics			
Age, y	61 ± 18	58 ± 17	0.41
Female, n (%)	19 (49)	64 (53)	0.62
NYHA class ≥ II, n (%)	0 (0)	61 (51)	<0.01
BNP, pg/dL	-	33.9 (2 - 628.1)	
Hemodynamic and echocardiographic characteristics			
Systolic BP, mmHg	125 ± 17	125 ± 21	0.93
Diastolic BP, mmHg	73 ± 12	71 ± 14	0.75
HR, bpm	64 ± 11	70 ± 11	0.01
LV-SVi, mL/m ²	54 ± 10	38 ± 8	<0.01
LVSWi, mmHg·mL/m ²	3900 ± 900	3400 ± 1000	<0.01
CI, L/min/m ²	2.7 ± 0.8	2.6 ± 0.6	0.30
Qp/Qs ratio	1.0 ± 0.1	2.2 ± 0.7	<0.01
LVEDV, mL	70 ± 16	65 ± 20	0.09
LVESV, mL	25 ± 8	22 ± 11	0.20
LVEF, %	64 ± 4	67 ± 8	0.09
LV-GLS, %	-18 ± 3	-18 ± 4	0.87
E/A ratio	1.1 ± 0.6	1.2 ± 0.5	0.13
LA volume index, mL/m ²	25 ± 7	42 ± 17	<0.01
e', cm/sec	7.0 ± 2.6	7.4 ± 3.0	0.38
E/e' ratio	9 ± 2	11 ± 4	0.05
RVEDA, cm ²	14 ± 4	26 ± 7	<0.01
RVFAC, %	44 ± 5	45 ± 9	0.59
RV-SVi, mL	51 ± 12	79 ± 20	<0.01
TAPSE, mm	20 ± 4	26 ± 6	<0.01
RV-GLS, %	-23 ± 5	-27 ± 7	0.02
sRVCPI, mmHg·mm	349 ± 186	728 ± 293	<0.01
RA area, cm ²	13 ± 3	22 ± 7	<0.01
TR-PG, mmHg	18 ± 10	28 ± 10	<0.01
TAPSE/PASP ratio , mm/mmHg	2.1 ± 1.6	0.8 ± 0.3	<0.01

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

ASD, atrial septal defect; NYHA, New York Heart Association; BNP, brain natriuretic

peptide; BP, blood pressure; HR, heart rate; SVi, stroke volume index; LV, left ventricular; SWI, stroke work index; CI, cardiac index; Qp/Qs, pulmonary-to-systemic blood flow ratio; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; RV, right ventricular; EDA, end-diastolic area; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; sRVCPI, simplified right ventricular contraction pressure index; TR, tricuspid regurgitation; PG, pressure gradient; **PASP, pulmonary arterial systolic pressure.**

Table. 2 Changes in hemodynamic and echocardiographic parameters 6 months after ASD closure

	Patients with ASD (N=120)				
	Baseline	6 months after the closure	<i>P</i> value	Mean difference	95% CI of the mean difference
Hemodynamic characteristics					
Systolic BP, mmHg	125 ± 21	131 ± 18	0.04	4	0.19 to 7.97
Diastolic BP, mmHg	72 ± 14	73 ± 13	0.95	0	-2.88 to 3.07
HR, bpm	70 ± 11	66 ± 15	<0.01	-4	-7.01 to 1.28
LV-SVi, mL/m ²	38 ± 8	45 ± 10	<0.01	7	5.91 to 8.87
LVSWI, mL·mmHg/m ²	3400 ± 1000	4100 ± 1000	<0.01	710	527 to 884
Echocardiographic characteristics					
LVEDV, mL	65 ± 21	76 ± 21	<0.01	10	7.45 to 13.5
LVESV, mL	23 ± 12	26 ± 10	<0.01	3	1.53 to 5.12
LVEF, %	67 ± 8	66 ± 6	0.13	-1	-2.31 to 0.29
LV-GLS, %	-18 ± 4	-17 ± 4	<0.01	1	-2.25 to 0.02
E/e' ratio	11 ± 4	13 ± 5	<0.01	2	1.02 to 3.10
RVEDA, cm ²	26 ± 7	19 ± 5	<0.01	-7	-8.33 to 6.04
RV-SVi, mL/m ²	79 ± 20	46 ± 12	<0.01	-34	-37.8 to -29.7
TAPSE, mm	26 ± 6	23 ± 5	<0.01	-3	5.91 to 8.87
RV-GLS, %	-27 ± 7	-24 ± 8	<0.01	3	-4.78 to 0.68
sRVCPI, mmHg·mm	728 ± 293	473 ± 238	<0.01	-247	-303 to 191
RA area, cm ²	22 ± 7	16 ± 6	<0.01	-6	-7.62 to 5.23
TR-PG, mmHg	27 ± 10	21 ± 10	<0.01	-6	-8.12 to 4.58
TAPSE/PASP ratio, mm/mmHg	0.8 ± 0.3	1.0 ± 0.6	<0.01	0.1	-0.07 to 0.23

Data are presented as mean ± standard deviation or median (interquartile range).

CI, confidence interval. All other abbreviations as in Table 1.

Table. 3 Comparisons of clinical, hemodynamic, and echocardiographic characteristics among the three subgroups of ASD

Variables	(A) Asymptomatic patients		Symptomatic patients before ASD closure				<i>P</i> values for Interaction
			(B) Asymptomatic after the closure		(C) Residual symptoms		
	(N=59)		(N=46)		(N=15)		
	Baseline	6 months	Baseline	6 months	Baseline	6 months	
Systolic BP, mmHg	121 ± 17	128 ± 18*	131 ± 22	132 ± 18	126 ± 22	139 ± 16*	0.12
Diastolic BP, mmHg	71 ± 13	73 ± 13	74 ± 15	74 ± 14	72 ± 15	74 ± 10	0.86
HR, bpm	69 ± 10	67 ± 13	69 ± 12	63 ± 16‡	74 ± 10	75 ± 10	0.31
LV-SVi, mL/m²	38 ± 8	44 ± 10*	38 ± 8	46 ± 9*	34 ± 9	42 ± 10*	0.50
LVSWI, g·m/m²	3300 ± 900	4000 ± 1100*	3500 ± 1000	4300 ± 1000*	3100 ± 1300	4100 ± 1000†	0.61
BNP, pg/dL	28 (5-469)	46 (11-178)	28 (2-316)§	46 (7-208)	125 (24-233)§,	147 (34-228)	0.14
LVEDV, mL	69 ± 19	79 ± 21*	63 ± 21	74 ± 20*	56 ± 23§	66 ± 25‡	0.84
LVESV, mL	26 ± 13	28 ± 9	21 ± 9	25 ± 9*	18± 9§	22 ± 11‡	0.95
LVEF, %	66 ± 9	65 ± 6	66 ± 7	65 ± 5	68 ± 6	68 ± 5	0.69
LV-GLS, %	-17 ± 5	-17 ± 4	-19 ± 4	-17 ± 4†	-18 ± 3	-15 ± 6	0.76
E/e' ratio	10 ± 3	11 ± 4†	12 ± 4§	14 ± 6‡	12 ± 4	15 ± 5†	0.49
RVEDA, cm²	26 ± 7	20 ± 5*	26 ± 7	18 ± 5*	28 ± 6	19 ± 5*	0.32
RV-SVi, mL/m²	76 ± 19	46 ± 11*	83 ± 21	47 ± 12*	80 ± 17	43 ± 17*	0.26
TAPSE, mm	27 ± 5	23 ± 4*	27 ± 6	23 ± 5*	23 ± 6§,	22 ± 6	0.18
RV-GLS, %	-27 ± 6	-24 ± 8‡	-29 ± 8	-24 ± 7†	-20 ± 7§,	-21 ± 8	0.005
sRVCPI, mmHg·mm	660 ± 277	433 ± 271*	783 ± 27§	492 ± 182*	831 ± 346	589 ± 234	0.59
RA area, cm²	22 ± 7	15 ± 5*	22 ± 6	16 ± 4*	27 ± 8§,	21 ± 7†	0.68
TR-PG, mmHg	24 ± 9	19 ± 10*	28 ± 9§	21 ± 7*	36 ± 10§,	31 ± 11	0.62
TAPSE/PASP ratio, mm/mmHg	0.9 ± 0.4	1.1 ± 0.7	0.8 ± 0.2§	0.9 ± 0.6	0.5 ± 0.2§,	0.6 ± 0.3	0.89
Clinical characteristics							<i>P</i> values for one-way ANOVA

Age, years	51 ± 18	62 ± 14 [§]	72 ± 10 ^{§,}	<0.001
Female, n (%)	23 (39)	29 (63) [§]	12 (80) [§]	0.06
Hemodynamic characteristics				
mean RAP, mmHg	5.1 ± 3.5	4.9 ± 2.7	5.4 ± 5.2	0.87
mean PAP, mmHg	17 ± 5	17 ± 5	23 ± 8 ^{§,}	<0.001
mean PCWP, mmHg	7.9 ± 3.7	7.8 ± 3.2	7.7 ± 4.6	0.96
PVRI, dyne·sec·cm ⁻⁵	146 ± 90	152 ± 68	252 ± 124 ^{§,}	0.001
Qp/Qs ratio	2.1 ± 0.6	2.3 ± 0.8	2.5 ± 0.7	0.05

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index.

All other abbreviations as in Table 1.

* $P < 0.001$ vs. baseline, † $P < 0.01$ vs. baseline, ‡ $P < 0.05$ vs. baseline.

§ $P < 0.05$ vs. group A, || $P < 0.05$ vs. group B.

Table. 4 Univariate and multivariate logistic regression analysis for prediction of residual symptoms after the closure

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age, years	1.069	1.006-1.137	0.03			
Sex (Female)	1.172	0.343-4.008	0.80			
BNP, pg/dL	1.011	1.003-1.020	<0.01			
Qp/Qs ratio	1.537	0.708-3.337	0.28			
PVRI, dyne·sec·cm ⁻⁵	1.008	1.004-1.021	<0.01	1.011	1.000-1.021	<0.05
LV-GLS, %	0.886	0.743-1.056	0.18			
LVSWI, mL·mmHg/m ²	1.000	0.999-1.000	0.19			
E/e' ratio	0.976	0.847-1.126	0.74			
RVEDA, cm ²	1.052	0.959-1.153	0.28			
TAPSE, mm	0.867	0.766-0.981	0.02			
TR-PG, mmHg	1.114	1.026-1.208	0.01			
RV-GLS, %	0.830	0.736-0.937	<0.01			
sRVCPI, mmHg·mm	1.001	0.999-1.003	0.64			
TAPSE/PASP ratio, per 0.1 mmHg/mm increase	0.120	0.000-0.850	<0.01	0.034	0.000-0.604	<0.05

OR, odds ratio; CI, confidence interval.

All other abbreviations as in Table 1 and 3.

Table 5. Comparisons of parameters for predicting residual symptoms after ASD closure

	Cut-off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	<i>P</i> value
Qp/Qs ratio	1.84	0.62 (0.48 to 0.74)	86.7	40.0	32.5	90.0	0.16
PVRI, dyne·sec·cm ⁻⁵	158	0.77 (0.63 to 0.88)	85.7	71.4	54.5	92.6	<0.01
TAPSE, mm	23.8	0.72 (0.59 to 0.83)	80.0	67.4	44.4	91.2	0.02
RV-GLS, %	-22.9	0.82 (0.69 to 0.91)	73.3	82.1	61.1	88.9	<0.01
TAPSE/PASP ratio, mmHg/mm	0.66	0.81 (0.69 to 0.90)	86.7	65.2	44.8	93.7	<0.01
Systolic PA pressure, mmHg	39	0.73 (0.60 to 0.84)	66.7	69.6	41.7	86.5	<0.01

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

All other abbreviations as in Table 1.