Predicting Postoperative Hypertension Among Patients With Ventricular Septal Defect in Infants

Junpei Kawamura

Kagoshima University Graduate School of Medical and Dental Sciences <https://orcid.org/0000-0001-9968-2248>

Kentaro Ueno (✉ ukenta@m3.kufm.kagoshima-u.ac.jp)

Kagoshima University Graduate School of Medical and Dental Sciences

Tsubasa Shimozone

Kagoshima University Graduate School of Medical and Dental Sciences

Yoshihiro Takahashi

Kagoshima University Graduate School of Medical and Dental Sciences

Koji Nakae

Kagoshima University Graduate School of Medical and Dental Sciences

Yasuhiro Okamoto

Kagoshima University Graduate School of Medical and Dental Sciences

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Abstract

Purpose: Patients with strong pulmonary vascular occlusive lesions are at risk of developing postoperative pulmonary hypertension (PH). We aimed to evaluate preoperative right ventricular (RV) function in patients with ventricular septal defect (VSD) who required cardiac surgery during infancy and consequently developed postoperative PH and to determine whether we could preliminarily evaluate postoperative PH in these patients.

Methods: We retrospectively analyzed 55 infants with VSD who underwent cardiac surgery between March 2014 and April 2020. We evaluated the measurements of preoperative atrial/ventricular general function and 2D atrial/ventricular strain between these two groups: a group with postoperative PH (post-PH) and a group without postoperative PH (post-NPH).

Results: Post-PH patients had a significantly lower tricuspid annular plane systolic excursion (TAPSE) (11.2 mm) and $TAPSE_{RA}$ (the proportion of TAPSE due to RA contraction alone) (6.6 mm) than the post-NPH patients (14.1 mm, 8.5 mm). Furthermore, the post-PH group had a significantly lower peak right atrial (RA) longitudinal strain (PRALS) (31.0%) than the post-NPH group (43.0%). Multivariate logistic regression analysis identified that PRALS and $TAPSE_{RA}$ were independent echocardiographic parameters for the presence of post-PH. The sensitivity and specificity of predicting post-PH for $\leq 38\%$ of the PRALS were 83.0% and 100.0%, respectively, with an area under the curve of 0.94 ($p < 0.01$).

Conclusion: Preoperative RA function and RV diastolic function decreased in the post-PH group. The RA strain and $TAPSE_{RA}$ could be useful factors for predicting postoperative PH.

Introduction

In patients with a congenital heart disease with an uncorrected left-to-right shunt, such as ventricular septal defects (VSDs), increased pulmonary pressure leads to vascular remodeling and dysfunction, resulting in a progressive increase in pulmonary vascular resistance and an increased pressure in the right chambers of the heart [1]. Therefore, patients with strong pulmonary vascular occlusive lesions are at risk for developing postoperative pulmonary hypertension (PH) [2]. Certain conditions such as Down syndrome (DS) are often associated with pulmonary vascular obstructive lesions and subsequently can cause postoperative PH [3]. Although home oxygen therapy and pulmonary vasodilators are effective treatments for prolonged postoperative PH after surgery for congenital heart defects [4, 5], PH still significantly impairs patients' exercise capacity and quality of life. Postoperative PH is often diagnosed based on the peak velocity of the pulse-Doppler in tricuspid regurgitation on echocardiography and pulmonary artery pressure on cardiac catheterization. However, it is difficult to predict postoperative PH after cardiac surgery in patients with VSD because their preoperative characteristics vary. In infants with large VSDs, preoperative RV stress findings are difficult to discern from symptoms due to shunting. In cases of severe idiopathic PH, RV function is impaired due to the high vascular resistance caused by pulmonary vascular occlusive lesions [6, 7]. Similarly, in infants and children with PH, such as that seen in

DS, RV contractility and diastolic capacity are impaired [8, 9]. We hypothesized that the right ventricle may be under pressure and the RV function may be impaired preoperatively in patients with a large VSD with strong pulmonary vascular occlusive lesions. In our study, we used echocardiography to evaluate the preoperative RV function in patients with VSD who required surgery during early infancy and determined whether we could preliminarily predict their development of postoperative PH.

Methods

The Kagoshima University Ethics Committee approved this study, which was performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, and the Declaration of Helsinki. All procedures involving human participants followed the ethical standards of the Institutional and/or National Research Committee (Kagoshima University Ethics Committee, 190055). The requirement for parental/patient informed consent was waived.

2.1 Subjects

Between March 2014 and April 2020, 61 patients with VSD underwent surgery within their first year of life at the Department of Cardiovascular Surgery, Kagoshima University Hospital. Among these patients, five were excluded in accordance with the study's exclusion criteria, leaving 55 patients included in the study. The exclusion criteria were as follows: patients with developmental lung disorder, air tract narrowing, other cardiac diseases such as atrial septal defect (ASD), patent ductus arteriosus, pulmonary artery stenosis, and chromosomal abnormalities other than DS. Indications for surgery were as follows: 1) a left ventricular (LV) volume overload of $>1.5\%$ of the estimated pulmonary to systemic blood flow ratio or 2) a preoperative PH of <30 mmHg in the LV–RV pressure gradient on echocardiography. We retrospectively analyzed the results based on medical and laboratory records. We examined the results by dividing the patients into two groups: the group with postoperative PH (post-PH) and the group without postoperative PH (post-NPH). Post-PH was defined as a patient with a tricuspid regurgitation pressure gradient (TRPG) >27 mmHg after surgery, with reference to three-quarters of 36 mmHg, which is the cutoff for TRPG in adult PH studies [10].

Preoperative measurements were taken in all patients within 3 months of VSD surgery.

Echocardiographic measurements of the left atrial/ventricular system included the following: left ventricular diastolic diameter per body surface area (LVDd/BSA, mm/m²), left ventricular fractional shortening (LVFS,%), left atrial volume index (cm³/m²), left atrial total ejection fraction (LA EF,%), and left atrial expansion index (LA expansion index,%) in the four-chamber view.

Echocardiographic measurements to assess the right atrial/ventricular system included the following: RV fractional area change (RV FAC,%), tricuspid annular plane systolic excursion (TAPSE, mm), right atrial area volume index (cm³/m²), right atrial ejection fraction (RAEF,%), and right atrial expansion index (RA expansion index,%) in the four-chamber view. TAPSE_{RA} (proportion of TAPSE due to RA contraction alone)

and $TAPSE_{RV}$ (RV displacement occurring without the influence of RA contraction) were compared between the two groups [11] (*Fig. 1*).

Postoperative measurements were taken 1–3 months after the VSD surgery in all patients. The VSD diameter (mm) of the aortic valve in the short-axis view and the trans-VSD pressure gradient (VSD PG, mmHg) were calculated using the simplified Bernoulli equation with the pulse-Doppler of the blood flow through the VSD, and the TRPG (mmHg) was also evaluated.

1.1 Speckle tracking

Objects were acquired using a 7-MHz probe on a GE Healthcare Japan E9 or E90 system. The analysis was performed using GE Healthcare Japan Echo PAC. The mean values were calculated [12-15]; further, the preoperative right ventricular free-wall longitudinal strain (RV free-wall longitudinal strain), peak RA longitudinal strain (PRALS), and peak left atrial peak longitudinal strain of the four-chamber views were compared by calculating the average of the strain values for each segment. Right atrial longitudinal strain was classified into right atrial reservoir strain (RA reservoir strain), right atrial conduit strain (RA conduit strain), and right atrial booster strain (RA booster strain) (*Fig. 2*).

1.2 Statistical analysis

The values for each group are presented as median (interquartile range). Analyses were performed using SPSS Statistics for Windows (version 27.0; SPSS Japan Inc., Tokyo, Japan). The Mann-Whitney U test and Fisher's exact test were used to compare the two groups. Multivariate logistic regression analysis was performed to identify independent echocardiographic parameters for the presence of post-PH. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of echocardiographic measurements for preoperative RV function estimating postoperative PH. Two-tailed p-values of <0.05 indicated statistical significance.

Results

2.1 Preoperative background characteristics between the two groups (Table 1)

The post-PH group included eight patients and the post-NPH group included 47 patients. There were no significant differences between the two groups in terms of patient background characteristics, but in terms of body weight, the post-PH group had a significantly lower body weight (4.4 kg) than the post-NPH group (5.3 kg). The proportion of patients with DS in the post-PH and post-NPH groups was 63.5% and 30.0%, respectively, with no significant differences between the two groups.

2.2 Comparison of preoperative echocardiographic measurements in two groups (Table 2,3,4)

There were no significant differences between the groups in terms of echocardiographic measurements of the left atrial and ventricular systems. Post-PH patients had a significantly lower TAPSE (11.2 mm) than post-NPH patients (14.1 mm). In terms of TAPSE content, post-PH patients had a significantly lower

TAPSE_{RA} (6.6 mm) than post-NPH patients (8.5 mm), while there were no significant differences in TAPSE_{RV}. Post-PH patients had significantly lower PRALS (31.0%) than post-NPH patients (43.0%). There were also no significant differences in the VSD dimension and VSD PG between the two groups. (*Table 2*)

Regarding RA longitudinal strain, post-PH patients had a significantly lower RA reservoir, conduit, and booster strains (31.0%, 11.0%, and 18.0%, respectively) than post-NPH patients (43.0%, 17.0%, and 29.0%, respectively). (*Table 3*) (*Fig. 3*)

Multivariate logistic regression analysis identified that PRALS and TAPSE_{RA} were independent risk factors for the presence of post-PH. (*Table 4*)

2.3 Accuracy of preoperative echocardiographic measurements in estimating postoperative PH (Fig. 4)

According to the ROC curve, the sensitivity and specificity of predicting postoperative when the RALS was $\leq 38\%$ were 83.0% and 100.0%, respectively, with an area under the curve (AUC) of 0.94 ($p < 0.01$, 95% confidence interval [CI]: 0.87-0.99). The sensitivity and specificity of predicting postoperative when the TAPSE_{RA} was ≤ 7.5 mm were 72.3% and 87.5%, respectively, with AUC of 0.82 ($p < 0.01$, 95% confidence interval [CI]: 0.68-0.95)

Discussion

Postoperative PH due to VSD is generally associated with delayed cardiac surgery and residual pulmonary vascular occlusive lesions [16]. In particular, among patients with DS, those with left-to-right shunt diseases, such as a VSD or an atrioventricular septal defect, are at an increased risk of postoperative PH [17]. In recent years, surgery has often been performed in early infancy. However, postoperative PH is often a complication of major VSDs that occur in these patients. Postoperative PH is associated with RV failure, elevated central venous pressure, and circulatory failure during the perioperative period, resulting in prolonged and life-threatening ventilator duration [18, 19]. Patients with severe postoperative PH are at risk of PH crisis. Individuals with high pulmonary artery resistance and low pulmonary vascular compliance are associated with postoperative PH [20]. However, it is difficult to preoperatively predict whether a patient with a large VSD will have a high pulmonary artery resistance, and consequently develop postoperative PH. We believe that it would be best to predict postoperative PH using a non-invasive method. Therefore, in this study, we examined the parameters of preoperative echocardiography for VSD.

Right ventricular afterload has a strong effect on the RV function [6]. Pulmonary vascular occlusive lesions are usually present in patients with DS and can cause a decrease in RV function [6, 21]. Our study showed that some parameters of preoperative RA/RV function, including RA longitudinal strain (all reservoir, conduit, and booster strain) and TAPSE (especially TAPSE_{RA}), were decreased in the post-PH group compared to those in the post-NPH group.

The mean value of the maximal atrial strain generally reflects ventricular end-diastolic pressure [22], and a significant inverse correlation with ventricular end-diastolic pressure has been shown in children and those with congenital heart disease [23, 24]. RA function is a useful index for evaluating RV diastolic function in pulmonary arterial hypertension [25, 26] and has been reported to have a significant negative correlation with pulmonary artery systolic pressure and pulmonary vascular resistance, indicating that the RA strain is directly related to the severity of PH [27, 28]. After an ASD is corrected using open-heart surgery, decreased RA strain is also associated with decreased RV diastolic stiffness [29]. Right atrial reservoir function decreases over time from mild RV maladaptation to severe RV maladaptation in PH [30] and is associated with RAP and mPAP in PH patients [31-33]. RA conduit and pump function were also related to the severity of PH and RV diastolic dysfunction [34]. In our study, we also found that all RA strains decreased in post-PH. Another recent study showed that RA reservoir strain is only correlated with mPAP, although RA conduit and booster strains are not [35]. Therefore, the RA reservoir function could change more than other RA strains in PH. Our study showed that RA reservoir strain of $\leq 38\%$ is the most useful parameter for detecting preoperative PH because of its high accuracy and AUC, and it may be the most sensitive parameter that reflects the possibility of post-PH compared to other RA strains preoperatively.

TAPSE has been regarded as an index of RV contractility [36], and its relationship with RV diastolic stiffness and RA function has been clarified [11, 37]. In the left ventricular system, mitral annular plane systolic excursion is also related to LV diastolic dysfunction [38]. In particular, TAPSER, which is TAPSE in the diastole phase, indicates the RA function of contractility [11]. Our study showed that TAPSER was decreased in post-PH patients, although TAPSERV was not different between the two groups. This indicated that RA contractility was impaired in post-PH patients postoperatively, while RV systolic function was not.

Therefore, we proved that RA function was impaired, and RV diastolic function decreased in VSD patients with post-PH. Although other parameters of RA function, such as RA EF and RA expansion index, are useful for evaluating RV diastolic function, they are sometimes less accurate than RA reservoir strain to evaluate the severity of PH [39]. Similarly, our study showed that RA EF and RA expansion index tended to be lower in the post-PH group, but did not have significant differences in both groups. Right ventricular diastolic stiffness increased in patients with idiopathic PH because of progressive pathologic RV hypertrophy and collagen deposition in the RV tissue [40-43]. Right ventricular diastolic dysfunction precedes RV systolic dysfunction in patients with PH, evaluating RV diastolic dysfunction by echocardiography can predict disease progression [44]. In the early stages of PH, contractility is preserved [45]. Our study showed that RV contractile capacity was preserved in post-PH in a similar condition in the early stages of pulmonary hypertension.

In our study, the body weight of post-PH patients was lower than that of post-NPH in the univariate analysis. Patients who need surgery during their early ages also tend to have strong preoperative PH and difficulty gaining weight, so many cases need to be performed before they gain weight. However, not all patients with low body weight will have post-PH, and the results of multivariate analysis show that other

factors are confounded, which may be an aspect of poor preoperative RV dysfunction, resulting in low body weight.

There was no significant difference in the ratio of patients with DS between the two groups. This may indicate that patients without DS have pulmonary vascular occlusive lesions with a greater or lesser degree. An adult PH study showed that RV dysfunction occurs when pulmonary artery pressure is mild (>27 mmHg) [46]. Therefore, preoperative RV dysfunction should be considered in patients with VSD, regardless of the DS status. Little is known about RV function in patients with postoperative PH complicated by VSD. Based on our study, preoperative RA strain and TAPSERA could be useful factors for predicting postoperative PH.

4.1 Limitations

The main limitations of this study include its cross-sectional retrospective design and the small number of enrolled patients. It is important to conduct a large prospective comparative study to more accurately evaluate RV function in the future. Second, other parameters of RV systolic and diastolic function, such as pulse-Doppler at the tricuspid valve E and A wave velocity, E', A, and S velocity of tissue Doppler, three-dimensional RV ejection fraction, and total ejection isovolume index, were neither measured nor examined in this study. Even though we were able to examine RV function at a minimum, a study using more parameters is necessary to verify preoperative RV function in detail. Third, we mainly used the TRPG-estimated pulmonary artery pressure on echocardiography for the diagnosis of PH, which may be less accurate than catheterization. However, since TRPG has been proven to be highly correlated with pulmonary artery systolic pressure [10], it is not expected to be a major problem in this study.

Conclusion

The RV diastolic function was already impaired prior to surgery in some patients with VSD during early infancy. During surgical management of these patients, attention should be given to the possible development of postoperative PH. We believe that our study may be useful because it may allow pediatric cardiologists to stratify the risk of VSD patients with high pulmonary vascular occlusive lesions by evaluating RA strain and TAPSERA to prevent postoperative PH crisis.

Declarations

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Conflicts of interest/competing interests: The authors declare that they have no conflict of interest.

Ethics approval: This study protocol was approved by the ethical standards of the institutional and/or national research committee (Kagoshima University Ethics Committee, 190055).

Consent: Informed consent was obtained from all participants. The authors affirm that human research participants provided informed consent for the publication of the study.

Data and/or Code availability: Not applicable

Authors' contributions: Conceptualization: *Junpei Kawamura*, Methodology: *Junpei Kawamura, Kentaro Ueno*, Formal analysis and investigation: *Junpei Kawamura, Kentaro Ueno, Tsubasa Shimozone, Yoshihiro Takahashi, Koji Nakae*, Writing - original draft preparation: *Junpei Kawamura*, Writing - review and editing: *Kentaro Ueno, Yoshihiro Takahashi, Koji Nakae, Yasuhiro Okamoto*, Supervision: *Yasuhiro Okamoto*.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Figure 1

M-mode tracking of the tricuspid annulus in a patient. TAPSE RA accounts for the proportion of TAPSE owed to RA function alone; TAPSE RV accounts for RV shortening without the influence of RA contraction. TAPSE = Tricuspid Annular Plane Systolic Excursion; RA = Right Atrium; RV = Right Ventricle

Figure 2

Speckle tracking analysis of atrial and ventricular strain. An apical 4-chamber view of the RV (upper left), LA (upper right) and RA (lower) longitudinal strains were obtained for each patient. Dotted white curve indicates mean of all segments. The maximum excursion of the average strain curve symbolizes the Peak LA longitudinal strain (PLALS). The maximum excursion of the average strain curve symbolizes the Peak RA longitudinal strain and reservoir function (PRALS, RA reservoir strain). RA conduit function was calculated from the difference between the peak RA strain and the end of the conduit phase in early diastole (RA conduit strain) and RA booster function was derived from the difference between the endpoint of conduit phase and the peak RA contraction (RA booster strain). RV=Right Ventricle; LA=Left Atrium; RA=Right Atrium

Figure 3

Comparison each values of RA longitudinal strain between post-PH patients and post-NPH patients at reservoir, conduit and contraction phase. RA = Right Atrium; PH = Pulmonary Hypertension; NPH = No Pulmonary Hypertension

Figure 4

Receiver operating characteristic curve of the RA longitudinal strain (PRALS and TAPSE_{RA}) for post-operative pulmonary hypertension. RA = Right Atrium; PRALS = Peak RA longitudinal strain; TAPSE = Tricuspid Annular Plane Systolic Excursion

Supplementary Files

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