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Pulmonary Doppler Notch Pattern in Relation with Pulmonary Vascular Resistance Index in Patients with Atrial Septal Defect

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Abstract

Background: Atrial septal defect (ASD) potentially causes pulmonary hypertension (PH) and increased pulmonary vascular resistance (PVR). In previous studies, pulmonary Doppler notch was evident in patients with high PVR. There was a distinct notch pattern in different types of PH. This study aims to examine whether echocardiographic notch pattern could estimate PVR in secundum ASD patients.

Methods: Cross sectional study was conducted in secundum ASD patients ≥18 years old who underwent clinically indicated right heart catheterization. Association of notch presence and PVR index (PVRi) and correlation of notch ratio (NR), a parameter of notch location, and PVRi were analyzed. The best cut off of NR value was obtained using the receiver operating characteristics curve.

Results: Among 60 patients, the notch was present in 50 patients (83%) and significantly associated with PVRi ≥6 WU m^2 ($p<0.0001$). Notch ratio and PVRi had a moderate negative correlation ($r=-0.410$, $p=0.003$). Receiver operating characteristics curve with area under the curve 0.709 showed that cutoff NR value of 1.635 was an acceptable discriminator for PVRi ≥6 WU m^2, with 70% sensitivity, 70% specificity, 56.8% positive predictive value, and 14.9% negative predictive value. Patients were then classified into three groups of notch pattern based on its presence and location, which was significantly associated with PVRi ($p<0.0001$).

Conclusion: Pulmonary Doppler notch pattern is associated with PVRi in secundum ASD patients. This may be used clinically to estimate PVR to aid patient selection for further invasive investigation

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Keywords: atrial septal defect, Doppler echocardiography, notch, notch ratio, pulmonary vascular resistance

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Introdution

Atrial septal defect (ASD) is one of the most common congenital disorders, contribute to 8-10% of all congenital heart disease (CHD).[1,2] Atrial septal defect causes an increase in pulmonary blood flow, which results in flow-related pulmonary hypertension (PH). This may eventually lead to medial hypertrophy and arterioles muscularization causing pulmonary vascular disease (PVD), marked by increased pulmonary arterial pressure and pulmonary vascular resistance (PVR).[1] The gold standard diagnostic tool to measure PVR is invasive right heart catheterization (RHC). However, noninvasive echocardiographic parameters have been studied widely to predict PVR with varied accuracy.[3,4]

Pulmonary hypertension patients showed echocardiographic sign of pulmonary Doppler notch which represents partial closure of pulmonary valve in systolic phase.[5-7] It has also been found that only 53% of PH patients had this notch, indicating the role of factors other than pulmonary arterial pressure in the presence of this notch, one of the well-known factor being the PVR. There is also a distinct pattern of notch location in different types of PH. One of the parameters to assess this pattern is notch ratio (NR). The presence and location of this notch may give the estimated hemodynamic profile information in a specific type of PH.[5,7,8]

There is no study yet examining the relationship between the pattern of presence and location of pulmonary Doppler notch with PVR index (PVRi), specifically in patients with secundum ASD. We expect that this study may provide information about how this echocardiographic notch pattern could estimate PVR in this population.

Methods

Subjects

Consecutive sampling was conducted in this cross-sectional study in secundum ASD patients age ≥ 18 years old who underwent clinically indicated RHC. Patients with coexisting other CHD, coexisting moderate to severe valve disease (except tricuspid regurgitation), and not willing to participate in this study were excluded. Baseline characteristic data, including clinical, echocardiography, and RHC, were collected from patients meeting inclusion criteria. Echocardiography study was done before or after RHC, with a time interval between two examinations not exceeded 24 hours. We intend to analyze the relation of echocardiographic notch pattern with invasive PVRi. Notch pattern would be classified into three groups based on the presence and location of notch; no notch, early notch, and late notch. Early and late notch will be based on the cut off NR value obtained from receiver operating characteristics curve. Invasive PVRi would be classified into two groups of low PVRi <6 WU m^2 and high PVRi ≥6 WU m^2.

Echocardiography

Trans-thoracic echocardiography study was done by an experienced operator using Vivid E9 cardiac ultrasound machine with a 1.5 - 2 MHz transducer. Standard echocardiographic right heart study was performed based on the guideline for the echocardiographic assessment of the right heart in adults.[9] Pulsed-wave Doppler was done by locating sample volume 1 cm proximal to the pulmonary valve in basal short axis view while holding the breath in the respiratory expiration phase, with sweep speed of 100 mm/s. The presence or absence of pulmonary Doppler notch was noted, and the location of the notch was evaluated using the NR parameter. Notch ratio was obtained from the ratio of the time interval between onset of pulmonary Doppler spectral curve to notch (t1) and notch to the end of the curve (t2), which were measured three times in sinus rhythm and six times in atrial fibrillation for mean values. These were measured twice by two observers, and measurement done by the first observer was done twice at different times.

Right Heart Catheterization

Right heart catheterization was done, and results were calculated by the interventionist, who was not aware of echocardiography examination results. Multipurpose and pigtail catheters were inserted to the right femoral vein and artery to measure right and left heart pressure and oxygen saturation, respectively. Pulmonary vascular resistance was measured from the pressure gradient between mean left atrial (mLAP) and pulmonary artery (mPAP) divided by the pulmonary flow (Qp). Measurement of pulmonary flow was done using the Fick method by dividing oxygen consumption with pulmonary artery (O_2 sat PA) - venous oxygen content (O_2 sat PV) difference.[3] In this study, PVR was expressed by PVRi in Woods Unit.meter^2 (WU m^2). If oxygen vasoreactivity test was indicated, pre-test hemodynamic data were used. The value of PVRi was calculated using the formula; PVRi = [(mPAP – mLAP) / Qp] x body surface area. While, Qp = O_2 consumption / (1.36 x 10 x hemoglobin x [O2 sat PV – O_2 sat PA])

Statistical Analysis

Data analysis was done using SPSS program for Mac (25.0 version, IBM, New York). Numerical data were expressed in mean with standard deviation or median with minimum-maximum value, while categorical data were expressed in percentage. Kolmogorov-Smirnov or Shapiro Wilk normality test was done to determine numerical data distribution. Chi-square or Fisher test was used to compare proportions between groups, or Mann-Whitney test if one variable was ordinal. Correlation of numerical variables was analyzed using Pearson for normal data distribution or Spearman if not normal. Receiver operating characteristics (ROC) curve was used to determine the best cut off value for numerical data. Sensitivity, specificity, positive predictive value, and negative predictive value were also obtained. Inter- and intra-observer variability were analyzed using intra-class correlation (ICC) and 95 % confidence interval (CI) for numerical data and Kappa value for categorical data. A p value of < 0.05 was considered statistically significant.

Results

From a total of sixty five secundum ASD patients age ≥ 18 years old, five patients were excluded due to the coexistence of moderate to severe mitral regurgitation. A total of 60 patients were included in the analysis.

Patient Characteristics

The baseline characteristics of patients are presented in Table 1. The majority was in the third decade of life, female, and underweight (body mass index < 18.5 kg/m^2).

Table 1. Patient characteristics

Parameter	All Patients (n = 60)	Notch (-) (n=10)	Notch (+) (n=50)
Clinical			
Age (year)	36 (19-69)	40.7 ± 11.5	36 (19-69)
Female gender, n (%)	50 (83)	6 (60)	44 (88)
Body mass index (kg/m2)	17.7 (12.3-32.9)	21.4 ± 5	17.6 (12.3-32.9)
Systolic blood pressure (mmHg)	112 (88-194)	123.3 ± 18.4	111 (88-194)
Diastolic blood pressure (mmHg)	69 ± 10.5	67.5 ± 9.9	70 (47-98)
Heart rate (beats per minute)	84.2 ± 14.8	82.7 ± 11.2	81 ± 13.8
Echocardiography			
LVEF (%)	76.6 ± 11.2	75.1 ± 8.2	77 ± 11.7
TAPSE (mm)	20.4 ± 6.7	25.7 ± 5.7	19.4 ± 6.3
RV GLS (%)	-13.9 (-29.6 – (-5))	-22.6 ± 5.7	-13.4 (-28.5 – (-5))
RVOT VTI (cm)	17.7 ± 7.4	24 ± 8.7	15.3 (7.2 – 35.7)
PVAT (ms)	81 (46-161)	115 ± 34.3	77.5 (46-151)
TR Vmax (m/s)	4.0 ± 1.1	2.8 ± 0.5	4.4 (1.9-5.8)
MPA diameter (mm)	35.4 ± 4.8	28 (25-41)	36.5 (30-50)
Basal RV EDD (mm)	52 (39-79)	56.4 ± 12	51 (40-65)
Right heart catheterization			
mPAP (mmHg)	47 ± 18.6	23.4 ± 7.3	51.4 ± 16.5
mLAP (mmHg)	7 (2-24)	8.2 ± 2.5	6 (2-24)
PVRi (WU.m^2)	10.2 (0.5-54)	3.7 ± 6.1	12.4 (1-54)
Qp:Qs	1.6 (0.4-25.9)	3.3 ± 2.4	1.5 (0.4-26)

Definition of abbreviations: LVEF = left ventricular ejection fraction, MPA = main pulmonary artery, mLAP = mean left atrial pressure, mPAP = mean pulmonary artery pressure, PVRi = pulmonary vascular resistance index, PVAT = pulmonary velocity acceleration time, Qp = pulmonary flow, Qs = systemic flow, RV EDD = right ventricular end diastolic diameter, RV GLS = right ventricular global longitudinal strain, RVOT VTI = right ventricular outflow tract velocity time integral, SV = stroke volume, TAPSE = tricuspid annular plane systolic excursion, TR Vmax = maximal tricuspid velocity. Kolmogorov-Smirnov normality test was done to determine numerical data distribution. Normal and non-normal distributed numerical data were expressed in mean ± standard deviation and median (minimum-maximum value), respectively. Categorical data were expressed in nominal (percentage).

Presence of Notch and PVRi

Notch was present in 50 patients (83%) and significantly associated with PVRi ≥ 6 WU m² ($p < 0.0001$), as presented in table 2.

Table 2. Presence of notch based on PVRi

Parameter	PVRi < 6 n (%)	PVRi ≥ 6 n (%)	P value
Notch (-)	9 (90)	1 (10)	< 0.0001
Notch (+)	12 (24)	38 (76)	
Total	21	39	

Definition of abbreviation: PVRi = pulmonary vascular resistance index (WU m²).
Fisher test was used to compare proportions between groups. A p value of < 0.05 was considered statistically significant.

Fagan's Nomogram showed that the positive likelihood ratio was 1.71 and negative likelihood ratio was 0.06, as illustrated in figure 1

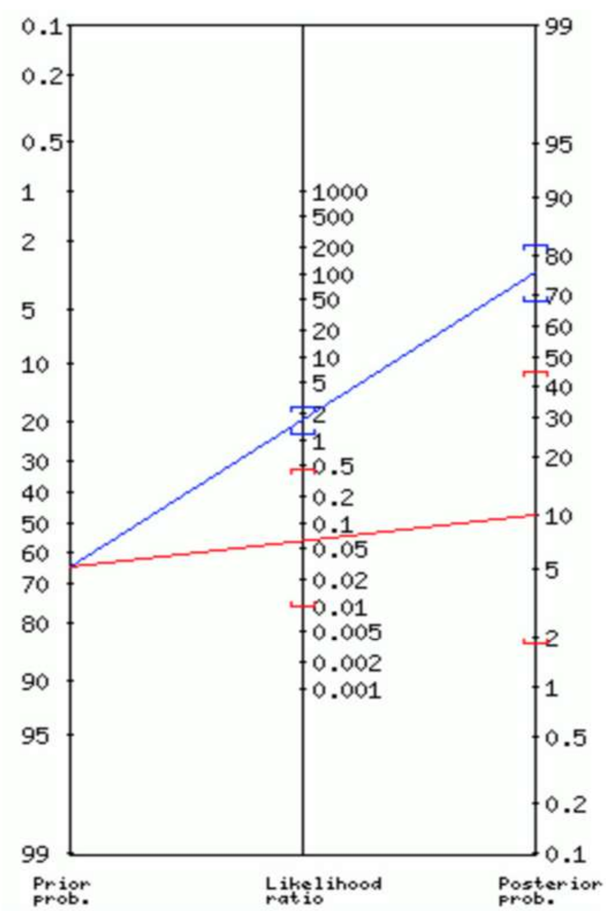

Figure 1. Fagan's Nomogram for Presence of Notch and PVRi

Location of Notch and PVRi

The location of the notch was examined by the NR parameter. Notch ratio and PVRi had a significant moderate negative correlation ($r = -0.410$, $p = 0.003$) as illustrated in figure 2.

Receiver operating characteristics (ROC) curve analysis with the area under the curve (AUC) of 0.709 (CI 95% 0.541-0.877) showed that a cutoff NR value of 1.635 was an acceptable discriminator for PVRi ≥ 6 WU m², with 70% sensitivity, 70% specificity, 56.8% positive predictive value, and 14.9% negative predictive value, as presented in figure 3.

Patients were then classified into three groups of notch patterns based on their presence and location. The location of the notch was distinguished based on the cut off value obtained from ROC curve analysis; late notch if ≥1.635 and early notch if <1.635. Notch pattern was significantly associated with PVRi, as illustrated in table3.

Table 3. Notch pattern based on PVRi

Parameter	PVRi < 6 n (%)	PVRi ≥ 6 n (%)	P value
No Notch	9 (90)	1 (10)	< 0.0001*
Late Notch	9 (43)	12 (57)	
Early Notch	3 (10)	26 (90)	
Total	21	39	

Definition of abbreviations: PVRi = pulmonary vascular resistance index (WU.m²).
Chi square, Fisher test, and Mann-Whitney test were used to compare proportions between groups. A p value of < 0.05 was considered statistically significant.
* P < 0.0001 (Mann-Whitney test), p = 0.02 for No Notch versus Late Notch (Fisher test), p = 0.02 for Late Notch versus Early Notch (Chi square test), p < 0.0001 for No Notch versus Early Notch (Fisher test).

Fagan's Nomogram for early notch showed that the positive likelihood ratio was 3.85 and negative likelihood ratio was 0.05, while in late notch the positive likelihood ratio was 1.85 and negative likelihood ratio was 0.15, as illustrated in figure 4.

The ROC curve to predict PVRi ≥ 6 for early notch versus no notch showed that the AUC was 0.856 (CI 95% 0.702-1) which was better compared to late notch versus no notch with AUC 0.712 (CI 95% 0.529-0.895), as depicted in figure 5. Early notch has a sensitivity and specificity of 96.3% and 75%, respectively meanwhile late notch 92.3% and 50%, respectively.

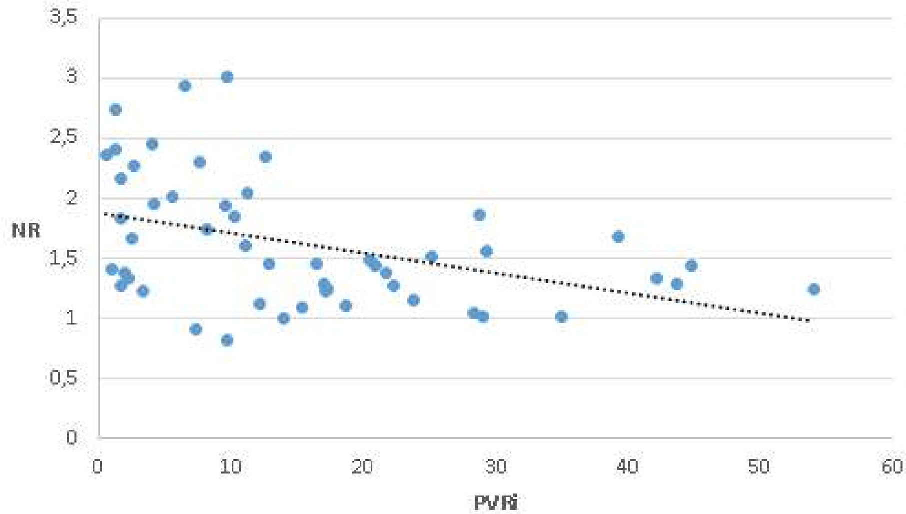

Figure 2. Negative moderate correlation of NR and PVRi
Definition of abbreviations: NR = notch ratio, PVRi = pulmonary vascular resistance index.
The correlation was analyzed using Spearman analysis. A p value of < 0.05 was considered statistically significant.

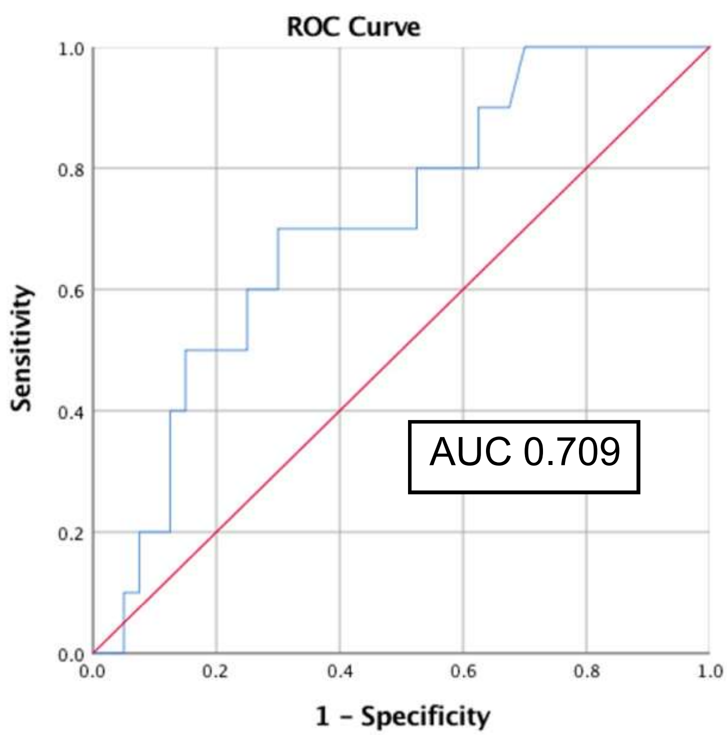

Figure 3. The ROC curve for a cutoff of NR value
Definition of abbreviations: AUC = area under the curve, NR = notch ratio, ROC = receiver operating characteristics.
Receiver operating characteristics curve was used to determine the best cut off value. Sensitivity, specificity, positive predictive value, and negative predictive value were also obtained.

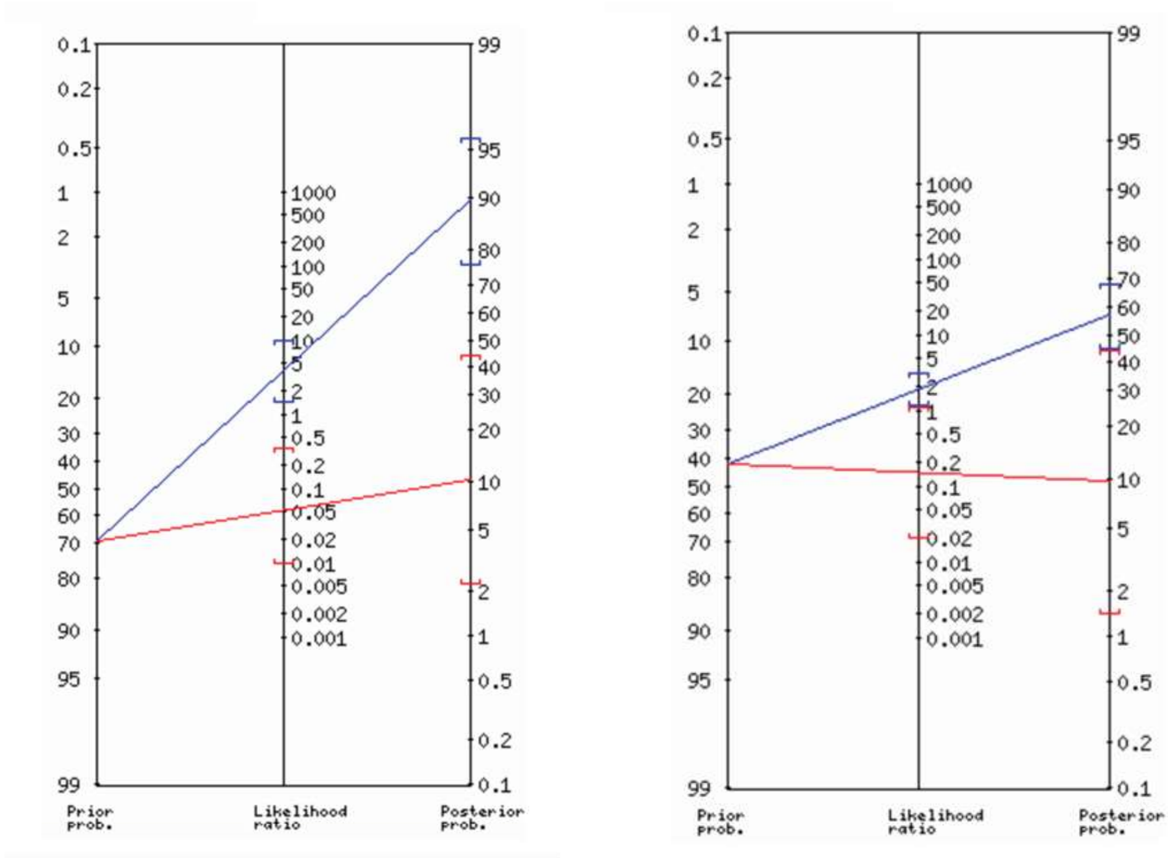

Figure 4. Fagan's Nomorgram for Early Notch (Left) and Late Notch (Right) and PVRi

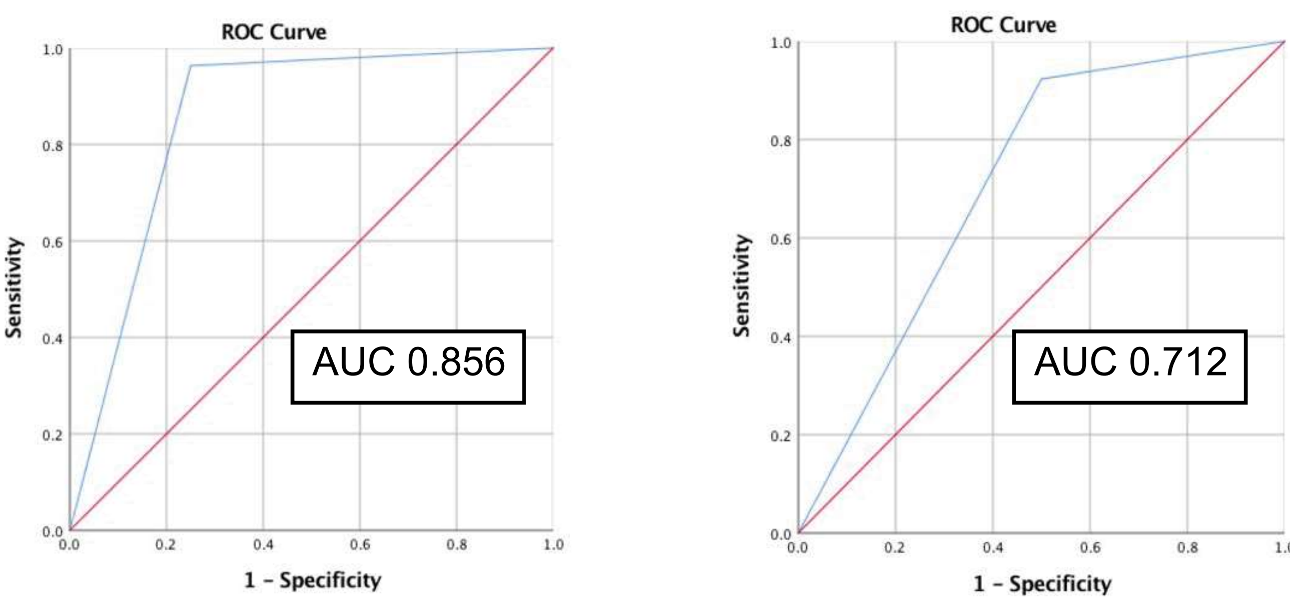

Figure 5. The ROC curve for Early Notch versus No Notch (Left) and Late Notch versus No Notch (Right) to predict PVRi ≥6

Discussion

Increased pulmonary blood flow in ASD may result in PH, which occurs in 8-10% of patients in previous studies. Pulmonary hypertension eventually leads to PVD, marked by high PVR. While the gold standard diagnostic measurement of PVR is done by invasive RHC, non-invasive echocardiography estimation of PVR has also been studied widely to select patients who need further invasive investigation. Pulmonary Doppler notch has been known to be associated with PH, specifically in patients with high PVR.

Clinical Characteristics

The majority of patients in this study were in the third decade of life, older than subjects in the study done by Ostovan et al[10]. These late presenters may be caused by the lack of knowledge and access to health insurance in Indonesia, which is a developing country. The majority was female which is similar with previous studies stating that ASD is predominated by a female by 2:1.[10,11] Most patients are underweight which may be caused by hypermetabolic state, malnutrition due to loss of appetite and/or malabsorption, and activation of growth hormone/insulin growth factor - I axis.[12].

Hemodynamic Characteristics

Our patients show signs of PH, marked by high TR V max and dilated right ventricle and pulmonary artery, and decreased intrinsic right ventricular function. In the previous study by Ozturk et al[13], adult ASD patients had smaller basal right ventricular end diastolic diameter and better right ventricular function. These differences may be understood by the fact that higher volume load in our patients, as demonstrated by dilated right ventricle, is associated with worse RV function. This function may reverse months after defect closure.[14, 15] Invasive data in our study show more severe PH with high mPAP and PVR, indicating the condition of PVD. While patients in the study done by Song et al[16] and Dalvi et al[17] had milder PH with lower mPAP and PVR and higher flow ratio (Qp:Qs). These results consistent with the direct correlation of mPAP and PVR, based on the equation to calculate PVR. High PVR also associated with decreased left to right shunt, as evidenced by reduced Qp:Qs.[17]

Pulmonary Doppler Notch Pattern

Pulmonary hypertension patients with high PVR have been showing echocardiographic signs of pulmonary Doppler notch. This notch represents partial pulmonary valve closure in the systolic phase, associated with the pathological reflection wave, which propagated from pulmonary vasculature to the valve. However, the presence of notch only occurred in 53% of PH patients, indicating that other factors also contribute to the notch formation other than increased pulmonary arterial pressure.[5-8]

In our study, the presence of notch was observed in 50 patients (83%). This high prevalence was due to the fact that our study population consisted of secundum ASD patients who were suspected for PVD, expected to have high PVR. While in previous studies, the prevalence of notch was examined in all PH patients with or without suspicion of increased PVR. Our data show that the presence of notch was significantly associated with PVRi ≥6 WU m^2 ($p < 0.0001$).

Besides the presence of a notch, we also examined the location of the notch with the measurement of the NR parameter. Notch ratio and PVRi have a significant moderate negative correlation ($r = -0.410$, $p = 0.003$). This result indicates that the lower NR value, which means the earlier notch location, the higher PVRi. In contrast to the study done by Hardziyenka et al[5] in chronic thromboembolic pulmonary hypertension (CTEPH) population, in which higher NR value (NR > 1), which means later notch location, was associated with higher PVR. However, our result is similar with the study done by Arkles et al[8] in type I, II, III, and V PH population which showed that the earlier notch location in mid systolic notch (MSN) group was associated with higher PVR compare to late systolic notch (LSN) group and no notch (NN) group.

The differences of our study results with CTEPH population, or type IV PH, is thought to be based on the different pathophysiology basis of notch formation. In CTEPH patients, notch formation is related to thromboembolic obstruction location. The more proximal the obstruction, the earlier pathologic wave reflection propagated, and partial closure of the pulmonary valve occurred, which was represented by the notch formation. This more proximal obstruction is situated in larger arteries in which medial hypertrophy and muscularization remodeling occur later, hence lower PVR in patients with earlier notch location. Our patients showed that lower NR correlates with higher PVR. This finding matched the population of type I, II, III, and V PH as reported in previous study.[8] Earlier notch in these populations is theoretically related to higher PVR, lower pulmonary artery compliance, and right ventricular dysfunction. The compatibility of these results is thought to be due to the fact that PH in secundum ASD is included in type I PH thus have the same pathophysiological basis in notch formation, although Arkles et al[8] only examined 2% CHD patients from all PH study population, and the exact CHD diagnosis was not described.

We then classify our patients into three groups of notch patterns based on their presence or absence and location. The location of the notch was distinguished based on the cut off value obtained from ROC curve analysis. The receiver operating characteristics curve with AUC of 0.709 showed that a cutoff NR value of 1.635 was an acceptable discriminator for PVRi ≥ 6 WU m^2, with 70 % sensitivity, 70 % specificity, 56.8% positive predictive value, and 14.9% negative predictive value. Patients were then classified into three groups of notch pattern; 1) no notch, 2) late notch if NR ≥ 1.635, and 3) early notch if NR < 1.635. Notch pattern was associated with PVRi, with a trend from lower PVRi < 6 to higher PVRi ≥ 6 significantly associated with no notch, late notch, and early notch, respectively ($p < 0.0001$). Early notch may predict PVRi ≥6 better than late notch with AUC 0.856 vs 0.712, respectively, when compared to patients without notch. Practically, these results indicate that the pulmonary Doppler notch pattern may provide an estimation of PVR in patients with secundum ASD, specifically those suspected of PVD requiring further examination.

Study Limitations

Limitations of our study include the non-simultaneous examination of echocardiography and RHC, which may cause hemodynamic profile differences. However, we tried to minimize this possibility by restricting the time interval between two examinations to be done within 24 hours. Intra-observer and inter-observer variability of the NR parameter and notch pattern in our study showed good results. However, external validation needs to be tested in different samples to evaluate the consistency of these measurements, since our study population is limited only to secundum ASD patients with PH who were clinically indicated for RHC. Patients' medications were not recorded in this study which may affect hemodynamic condition of the patients.

Conclusion

Pulmonary Doppler notch pattern is associated with PVRi in secundum ASD patients. This pattern may be used clinically to estimate PVR in this population to aid patient selection for further invasive investigation.

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Informed consent

A written informed consent was obtained from each patients prior to enrollment.

Publication approval

All authors read and approved the final manuscript.

Conflict of Interest

None.

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Ethical Clearance

Approval from The Committee on Institutional Review Board/ Health Reseach Ethics of National Cardiovascular Center Harapan Kita was granted prior to patients' enrollment.

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List of abbreviations:

ASD: atrial septal defect
AUC: area under the curve
CHD: congenital heart disease
CI: confidence interval
CTEPH: chronic thromboembolic pulmonary hypertension
ICC: intra-class correlation
LSN: late systolic notch
LVEF: left ventricular ejection fraction
mLAP: mean left atrial pressure
MPA: main pulmonary artery
mPAP: mean pulmonary artery pressure
MSN: mid systolic notch
NN: no notch
NR: notch ratio
PH: pulmonary hypertension
PVAT: pulmonary velocity acceleration time
PVD: pulmonary vascular disease
PVR: pulmonary vascular resistance
PVRi: PVR index
Qp: pulmonary flow
Qs: systemic flow
RHC: right heart catheterization
ROC: Receiver operating characteristics
RV EDD: right ventricular end diastolic diameter
RV GLS: right ventricular global longitudinal strain
RVOT VTI: right ventricular outflow tract velocity time integral
SV: stroke volume
TAPSE: tricuspid annular plane systolic excursion
TR Vmax: maximal tricuspid velocity
WU m^2: Woods Unit.meter2

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