Novel Echocardiographic Parameter Assessing Pulmonary Vascular Resistance in Patient with Acyanotic Congenital Heart Disease

Muhammad Raihan Ramadhan Natadikarta[1*], Charlotte Johanna Cool[1], Achmad Fitrah Khalid[1], Norman Sukmadi[1,] Januar Wibawa Martha[1]

[1]Departement of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

*Corresponding Author: Muhammad Raihan Ramadhan Natadikarta, Jalan Pasteur No 38, Pasteur, Bandung, Jawa Barat, Indonesia. Email: mraihanrn@gmail.com

Abstract

Background

Pulmonary vascular resistance (PVR) is an important variable in management of acyanotic congenital heart disease. Right heart catheterization (RHC) using impedance catheter remains gold standard for pulmonary vascular resistance (PVR) measurement. The ratio of peak tricuspid regurgitant velocity to the right ventricular outflow tract time-velocity integral (TRVmax/RVOTVTI) was presented as a reliable non-invasive method of estimating PVR. Recently, right ventricular 2-dimensional speckle tracking strain (RVGLS) was proven as a new promising parameter to evaluate PVR. This study performed to examine whether this new non-invasive variable ratio (TRVmax/RVGLS) provides clinically reliable method to determine pulmonary vascular resistance (PVR) obtained by echocardiography.

Methods

Cross-sectional observational study was performed in 56 patients with acyanotic congenital heart disease. All subject underwent cardiac catheterization and echocardiography data was obtain within 24 hours. The ratio of TRVmax/RVOTVTI and TRVmax/RVGLS analysis performed using receiver-operating characteristic curve analysis, a cutoff value for the ratio was generated to determine PVR more than 5 WU.

Results

A TRVmax/RVOTVTI cutoff value of 0.21 provided a sensitivity of 77.1% and a specificity of 81% (CI 81% to 97.5%) and TRVmax/RVGLS cutoff value of -23.16 provided sensitivity of 74.3% and a specificity of 90.5% to determine PVR > 5 WU (CI 79.6% to 98.2%).

Conclusions

The echocardiography parameter (TRVmax/RVGLS) could serve as a dependable noninvasive method to predict PVR greater than 5 WU in acyanotic congenital heart disease patients.

Keywords: Congenital heart disease, Echocardiography, Pulmonary hypertension, Pulmonary vascular resistance, Right ventricle global longitudinal strain

Introduction

Right heart catheterization (RHC) is the gold standard method for assessing the hemodynamic of individuals with pulmonary hypertension (PH), including determining pulmonary vascular resistance (PVR). Pulmonary vascular resistance is a hemodynamic variable that contributes to the management of patients with acyanotic congenital heart disease (CHD). It plays critical role in guiding decisions regarding defect closure and evaluating clinical response to pharmacological therapy. However, RHC considered as an invasive procedure and not always available in several hospital.[1–3]

Doppler echocardiography has significantly impacted clinical medicine by its ability to estimate intracardiac hemodynamics noninvasively. The estimation of pulmonary artery systolic pressure (PASP) using transtricuspid flow velocity (TTFV) is a fundamental aspect of echocardiographic assessment for suspected pulmonary hypertension (PH). However, pulmonary artery systolic pressure (PASP) does not provide a definition for pulmonary vascular resistance (PVR). Since flow and pressure variables can be estimated by echocardiography, we hypothesized that a measure of PVR might be accurately obtained by doppler-derived variables. Echocardiographic estimation of PVR using the ratio of peak tricuspid regurgitant velocity (TRV) to the right ventricular outflow tract time-velocity integral (RVOT VTI) was presented as a reliable and widely-known non-invasive method to determine PVR (Abbas Formula).[4–6] PVR is directly related to pressure difference (Δp) and inversely related to pulmonary flow (Qp). TRV can be used as surrogate of Δp, while TVI_{RVOT} correlates of pulmonary flow (Qp) which is influenced by RV function. However, doppler ultrasound beam alignment remains a crucial factor to acquire adequate measurement of TRV and RVOT VTI. Right ventricular 2-dimensional speckle tracking strain is a promising parameter, as it is angle-independent, less load-dependent, and highly reproducible to assess RV function. Recent study shows that RV global longitudinal strain (RVGLS) correlates strongly with mean pulmonary arterial pressure (mPAP) and PVR in pulmonary arterial hypertension (PAH) patients.[7–9] In acyanotic CHD, it is crucial to determine the timing of management especially for closure decision. From previous studies and guidelines, PVR with cut-off 5 WU is commonly used for closure decision.[1]

Based on recent advancement of echocardiography measurement of RV function and its relation to haemodynamic, we hypothesized that new echocardiography parameter can be proposed to predict PVR > 5 WU in acyanotic congenital heart disease patients.

Methods

This study is a cross-sectional observational study aimed in investigating echocardiography parameters and right heart catheterization results. The study protocol received approval from the Ethics Committee of Hasan Sadikin Hospital (DP.04.03/D.XIV.5.5/164/2024) and all the subjects gave informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki. We investigated all patients with CHD of different types, undergoing right heart catheterization (RHC). This study included patients visited our Grown Up Congenital Heart Disease Clinic who underwent RHC between August 2023 – August 2024. All subjects underwent echocardiographic examination with the maximum time interval of 24 hours before or after right heart catheterization. The inclusion criteria for this study was adults aged > 18 years with acyanotic CHD. Patients were excluded from the study if they had complex CHD, severe valvular heart disease, pregnancy, LVEF <50% by echocardiography, or poor echo window and right ventricular 2-dimensional speckle tracking strain cannot be performed. Potential source of bias were managed by performing the echocardiography by different cardiologist and blinded for cardiac catheterization results.

Echocardiographic Examination

Echocardiographic examination was conducted using a Phillips Epic CVx. The device was equipped with an adult 1.5 – 4.3 MHz phased array transducer. The parasternal long and short axis views, as well as the apical four-chamber image, were employed as standard imaging techniques. Flow velocities were acquired via pulsed and continuous wave Doppler techniques. The measurement of pulmonary artery flow was conducted by positioning the pulsed wave Doppler sample volume precisely at the midpoint of the transpulmonary valve jet, which was acquired from the short-axis view. Continuous wave Doppler was used to measure the peak tricuspid pressure drop by obtaining retrograde systolic transtricuspid flow from either the parasternal right ventricular input view or the apical four-chamber view. The Doppler recordings were conducted at a sweep speed of 50 - 100 mm/s, accompanied by an ECG (lead II) overlay. The study focused on assessing the strain of the right ventricular long-axis function using the speckle tracking echocardiography technique (STE). Pulmonary artery systolic pressure (PASP) calculated by 4 x $(TRVmax)^2$ + estimated RA pressure. Variable RA pressure of 3/8/15 mmHg is determined based on IVC diameter and collapsibility. Mean pulmonary

arterial pressure (mPAP) calculated by Aduen formula.[10] All measurement was obtained as recommended by the American Society of Echocardiography.[11]

Right Heart Catheterization

Cardiac interventionists who performed the invasive measurements were blinded to the echocardiographic findings. Venous access was achieved by putting an introducer sheath into the femoral vein. Subsequently, a catheterization was conducted using a MP-2 Catheter. The mean pulmonary arterial pressure (mPAp) was directly measured using a catheter placed in the pulmonary artery. Similarly, the mean left atrial pressure (mLAp) was recorded directly using a catheter implanted in the left atrium in patient with IAS defect (Atrial Septal Defect or Patent Foramen Ovale). Meanwhile, in patient without an IAS defect and no evidence of mitral stenosis, LVEDP measurement was performed with pigtail catheter. The measurements were automatically derived from the pressure graphics. Blood samples were collected from the superior and inferior cava veins, right atrium, pulmonary artery, four pulmonary vein, and left atrium to determine oxygen saturation. Pulmonary flow (Qp) measured by individual O2 consumption divided by delta of pulmonary vein oxygen saturation (PVO2) and pulmonary artery oxygen saturation (PAO2). The pulmonary vascular resistance (PVR) was calculated using Indirect Fick's method.[2,3]

Statistical Analysis

In the demographic data section, continuous variables were presented as mean ± standard deviation (SD) for normally distributed data, median-interquartile range (IQR) for nonnormally distributed data, categorical data are presented as percentages or frequencies. Normality was evaluated using the 1-sample Kolmogorov–Smirnov test. Difference between invasive PVR as the gold standard and echocardiography variables as independent variables were assessed by independent t-test for normally distributed data and Mann Whitney U test for nonnormally distributed data.

To assess the diagnostic value of the novel parameters, using PVR_{CATH} as the gold standard, receiver operating characteristic curves were plotted using a dichotomized function of PVR and a cut-off value of 5 woods unit (WU). Confidence interval of sensitivity and specificity were

assessed. All analyses were performed on software (SPSS 25.0, SPSS Inc, Chicago, IL) and $p<0.05$ was considered as statistically significant.

Results

There are 56 patients that remained in the final analysis. Baseline demography and standard echocardiographic parameters are presented in Table 1. The majority of patients were female, with most cases of ASD as aetiology of acyanotic congenital heart disease. There was no difference in LVEF, gender, RV basal diameter, RA Area and MPA diameter between both groups. A total of 35 patients had PVR_{CATH} > 5 WU, while 21 patients had PVR_{CATH} < 5 WU. Median PVR_{CATH} was 8.74 (0.82 – 69.16) WU measured by RHC with significant differences between two groups.

Table 1. Baseline Demographics

	Total (n=56)	**PVR > 5 WU (n=35)**	**PVR < 5 WU (n=21)**	***p***
Male/Female	13/43	6/26	7/14	0.165
Age (years)	31 (18-71)	30.00 (18 – 55)	39 (19 – 71)	**0.009**
Aetiology of CHD, n				
ASD	38	16	22	-
VSD	11	4	7	
PDA	6	0	6	
Other (ASD+VSD+PDA)	1	1	0	
NTproBNP	738 (35 – 25000)	961 (40-10729)	481 (35 – 25000)	0.178
Echocardiography				
LVEF (%)	62.45 ± 7.89	62.26 ± 8.42	62.76 ±7.10	0.819
RVOTVTI (cm)	17.6 (7-68)	14 (7-33)	23 (12-68)	**<0.001**
TRVmax (m/s)	3.8 (1.3 – 5.4)	4.3 (1.74 – 5.4)	3.4 (1.3 – 4.8)	**0.001**
TRmeanPG (mmHg)	40.60 ± 19.09	44.79 ± 20.65	33.62 ± 13.97	**0.033**
$PASP_{ECHO}$ (mmHg)	65.5 (9.76 – 127.36)	78.04 (15.11 – 127.36)	51.44 (9.76 – 95.16)	**<0.001**
$mPAP_{ECHO}$ (mmHg)	56.50 (21 – 97)	48 (10.30 – 99)	38 (8.6 – 61)	**0.028**
RVGLS (%)	-17.25 ± 7.03	-14.26 ± 5.84	-22.23 ± 6.99	**<0.001**
RV basal diameter (mm)	50.50 ± 8.13	49.62 ± 7.17	51.95 ± 9.53	0.305
RV FAC (%)	34.5 (12.8 – 54)	24 (12.8 – 45)	40 (27.2 – 54.0)	**<0.001**
RVS' (m/s)	11.7 (4 – 18)	11 (4 – 18)	12 (10 – 17)	**0.007**
TAPSE (mm)	19.48 ± 5.05	17.41 ± 4.38	22.95 ± 4.17	**<0.001**
RA area (mm^2)	20.15 (10 – 50)	19.45 (10 – 41)	23 (10 – 50)	0.089

MPA (mm)	36.16 ± 7.50	47.63 ± 8.04	33.71±5.90	0.058
TAPSE/PASP	0.27 (0.11 – 2.04)	0.20 (0.11 – 0.99)	0.47 (0.20 – 2.04)	**<0.001**
Right Heart Catheterization				
$PASP_{CATH}$ (mmHg)	91.46 ± 31.35	110.14 ± 20.27	60.33 ± 19.42	**<0.001**
$mPAP_{CATH}$ (mmHg)	56.48 ± 23.15	70.46 ± 16.52	33.19 ± 9.92	**<0.001**
PVR_{CATH} (WU)	8.74 (0.82 – 69.16)	16.18 (5.35 – 69.16)	2.37 (0.82 – 4.63)	**<0.001**
$PARI_{CATH}$ (WU/m^2)	10.84 (0.22 – 64.40)	20.18 (8.75 – 64.40)	3.17 (0.22 – 7.75)	**<0.001**

PVR: Pulmonary Vascular Resistance; CHF: Congenital Heart Disease; ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; PDA: Patent Ductus Arteriosus; LVEF: Left Ventricle Ejection Fraction; RVOTVTI: Right Ventricular Outflow Tract Velocity Time Integral; TRVmax: Tricuspid regurgitant peak velocity; TRmeanPG: Tricuspid regurgitation mean pressure gradient; PASP : Pulmonary artery systolic pressure; mPAP : mean pulmonary artery pressure; RVGLS: Right ventricle global longitudinal strain; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; RA area: Right atrial area; PARI

TRVmax, RVOT VTI, TRmeanPG, PASP, mPAP (Aduen Formula), RVGLS, FAC, RVS', TAPSE, TAPSE/PASP shows significant differences between groups. RVGLS was significantly more impaired in patients who had PVR > 5 WU. Based on previous study, TRVmax/RVOTVTI shows excellent correlation in predicting PVR. We perform analysis on several echocardiography parameters for predicting PVR > 5 WU. As the results, TRVmax/RVOTVTI, TRVmax/RVGLS, TRmeanPG/RVGLS, PASP/RVGLS, mPAP/RVGLS shows significant differences among both groups. (Table 2). Receiver operating characteristic (ROC) curves were calculated to evaluate the prediction of PVR > 5 WU by several echocardiographic parameters.

Table 2. Echocardiographic parameters ratio between two groups

Echocardiographic Parameters	**PVR > 5 (n=35)**	**PVR < 5 (n=21)**	***p***	**AUC**
TRVmax/RVOTVTI	0.24 (0.08 – 0.59)	0.12 (0.04-0.24)	**0.000**	**0.893**
TRVmax/RVGLS	-30.95 [-75 – (-10.81)]	-16.51 [-42 – (-5.67)]	**0.000**	**0.889**
TRmeanPG/RVGLS	-307.44 [-1043.48 - (55.53)]	-148.69 [-500 – (-20.67)]	**0.000**	0.822
$PASP_{ECHO}$/RVGLS	-574.59 [-1400 – (-93.85)]	-231.90 [-627.34 – (-48.53)]	**0.000**	0.884
$mPAP_{ECHO}$/RVGLS	-328.76 [-1076.09 – (74.16)]	-161.73 [-536.59 – (-30.67)]	**0.000**	0.833

RVOTVTI: Right Ventricular Outflow Tract Velocity Time Integral; TRVmax: Tricuspid regurgitant peak velocity; TRmeanPG: Tricuspid regurgitation mean pressure gradient; PASP : Pulmonary artery systolic pressure; mPAP : mean pulmonary artery pressure; RVGLS: Right ventricle global lingutudinal strain;

The area under the receiver-operating characteristic curve for TRVmax/RVOTVTI was calculated at 0.893. A TRVmax/RVOTVTI cutoff value of 0.13 provided a sensitivity of 91.4% and a specificity of 52.4% to determine PVR > 5 WU, meanwhile cutoff value of 0.21 provided a sensitivity of 77.1% and a specificity 81% (CI 81% to 97.5%). The area under the receiver-operating characteristics curve for TRVmax/RVGLS was calculated at 0.889. This result was comparable with previous formula in predicting PVR (TRVmax/RVOTVTI). A TRVmax/RVGLS cutoff value of -19.61 provided a sensitivity of 91.4% and a specificity of 76.2 % to determine PVR > 5 WU, meanwhile cutoff value -23.16 provided sensitivity of 74.3% and a specificity of 90.5% to determine PVR > 5 WU (CI 79.6% to 98.2%).

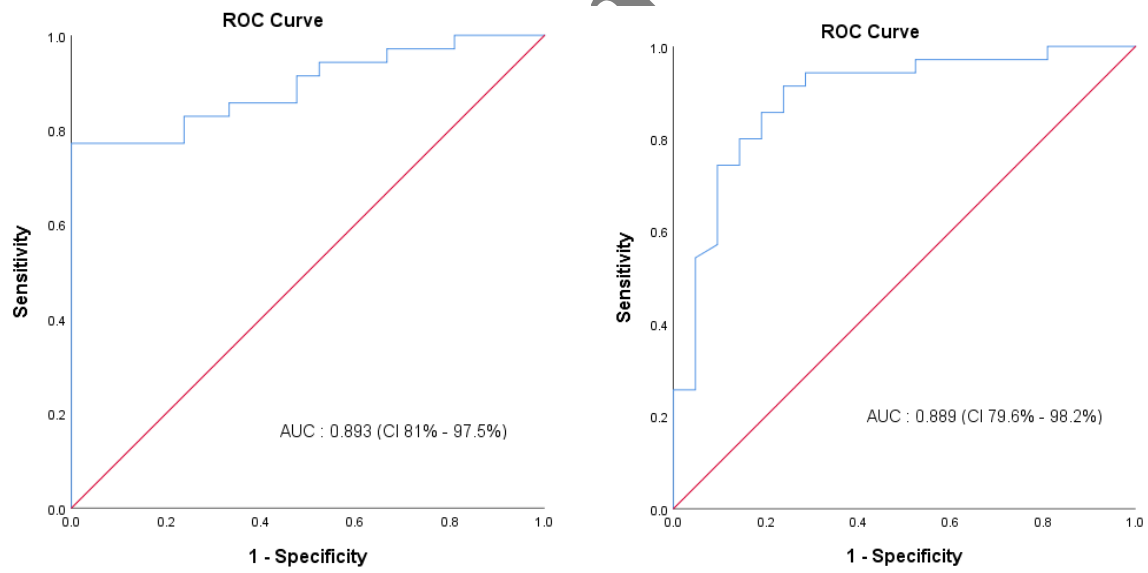

Figure 1. (a) receiver-operating characteristic curve for TRVmax/RVOTVTI with AUC 0.893 (CI 81% - 97.5%), (b) receiver-operating characteristic curve for TRVmax/RVGLS with AUC 0.889 (CI 79.6% - 98.2%)

Discussion

Previous studies have attempted to obtain a non-invasive measurement of PVR. The ratio of TRVmax to RVOT VTI was the most studied to predict PVR.[4–6,12–22] However, certain limitations was found to predict PVR in certain conditions such as unreliable formula in high PVR subjects. Recent advancement of RV function assessment shows RV GLS measurement can be performed to measure RV function and several studies shows excellent relationship to mPAP and PVR.[7–9,23,24] We present the process of developing novel echocardiography parameter to predict PVR. Our study shows, TRVmax/RVGLS have excellent performance in predicting PVR > 5 WU in patient with acyanotic congenital heart disease with cut-off point of -19.61 provided sensitivity 91.4% and specificity 76.2%.

Volume and/or pressure overload lead to alteration in RV physiology and function. Increase of RV pressure and wall stress results in RV dysfunction including RV dilatation, reduced RV wall motion, intraventricular, and interventricular RV dyssynchrony. Conventional RV functional parameters such as TAPSE, RV S' and RVFAC in early stages of PH can remain normal, consequently RV strain analysis is favourable for detecting subtle hemodynamic changes. Standard echocardiographic parameters (TAPSE, S', RVFAC, etc) are used for evaluation of RV function but they are affected by some factors such as image quality, angle dependent, heart motion or ventricular loading condition. RV strain has several advantages such as angle independency, less load dependency, accuracy in measurement of regional myocardial deformation, high availability, low cost, and high reproducibility. [9,11,25,26]

Right ventricular function has an important prognostic role in various condition, especially patient with pulmonary arterial hypertension (PAH). Changes in RVGLS value in congenital heart disease is not well defined in patient whom had chronic volume or pressure overload, but RVGLS has been shown to be a robust marker of RV function in patients with PAH and was proved to be strong predictor of mortality. However, there are several limitation or issues regarding the use of RVGLS such as no agreement about cut off normal values, demand high temporal resolution, visualization of RV endocardial border, and sometimes problem with window in term of poor visualization of RV free wall. [9,11,23–27]

Pulmonary hypertension in adult acyanotic congenital heart disease should be evaluated particularly and determination of PVR is mandatory. PVR was associated with outcome of closure intervention in congenital heart disease and patients with PVR > 5 are likely to have worse clinical outcome.[28–32] Previous study by Abbas et. al. shows TRVmax/RVOTVTI has

excellent performance in predicting PVR value.[4,6] In this study, TRVmax/RVOTVTI shows similar results with cutoff value of 0.13 provided a sensitivity of 91.4% and a specificity of 52.4% in predicting PVR > 5 WU. Abbas et. al. provided 0.175 as cutoff value for TRVmax/RVOTVTI with good sensitivity of 77% and specificity of 81% in predicting PVR > 2 WU.[4] Our result show similar area under the curve but with slightly differences in sensitivity and specificity cutoff value in predicting PVR (> 5 WU vs > 2 WU).

Prior researchers have documented the utilization of different doppler parameters for the assessment of pulmonary vascular resistance. The primary focus of these work has been on determining the timing of events such as the duration of right ventricular pre-ejection and ejection, the acceleration time of the right ventricular outflow tract velocity, and the velocities of flow propagation. Other studies show decent correlation between echocardiographic parameter estimation of PVR with PVR by RHC, but none of them using global longitudinal strain in their parameters.[4,6,19–22,33] Our study shows significant correlation between TRVmax/RVGLS and PVR_{CATH} and cut-off point of -19.61 provided sensitivity 91.4% and specificity 76.2% in terms of predicting PVR > 5 WU.

Our study has showed that our novel parameter TRVmax/RVGLS may have better performance in determining PVR in adult acyanotic congenital heart disease with pulmonary hypertension. We hope our models can be applied in centre that with no catheterization laboratory, in addition to start, evaluating medical therapy, and determine definite management in adult patients with acyanotic congenital heart disease and pulmonary hypertension. If the patient had estimated PVR > 5 WU, we can start medical therapy and refers to cardiac catheterization centre for invasive evaluation. Conversely, if the patient had estimated PVR < 5 WU, prompt referral to cardiac catheterization centre for closure management is a priority.

Limitation

Limitations inherent to the doppler technique are related to proper alignment of the ultrasound beam and have been reported elsewhere. Inability to obtain the tricuspid regurgitation jet is also a concern and has been addressed in the respective publications. Also, the peak TRV may vary with respiration, so using an average of multiple beats, rather than the maximum velocity obtained during sinus rhythm, may be a more appropriate representation of this parameter. RV GLS measurement have several weaknesses such as demand high temporal resolution, visualization of RV endocardial border, and sometimes have problem with window in term of poor visualization of RV free wall, leading to improper measurement of RV GLS.

All patient in this study had mPAP >20 mmHg thus this new method represents PH population in acyanotic congenital heart disease should be interpret cautiously.

Conclusion

The novel echocardiography parameters TRVmax/RVGLS, which are based on a non-invasive formula for predicting PVR, have a significant correlation with the gold standard measure and demonstrate high accuracy with excellent sensitivity and specificity in detecting individuals with elevated pulmonary vascular resistance (PVR >5 WU) for patient with acyanotic congenital heart disease. A cut-off point of -19.61 was proposed as a predictor of PVR > 5 WU.

Ethics approval and consent to participate

The research was performed in accordance with the Declaration of Helsinki and was approved by the Hasan Sadikin Hospital Ethics Committee.

Informed consent

Written informed consent was obtained from each participant.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interest

I have nothing to declare

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Author Contributions

All authors write and review the manuscript. MRRN and CJC took part on conceptualization. MRRN, CJC, and AFK took part on data curation. CJC and AFK took part on investigation. MRRN, JWM, and CJC took part on project administration. MRRN, CJC, and NS took part on data analysis. JWM, CJC, and AFK took part on supervision. MRRN, CJC, JWM, AFK, and NS took part on methodology.

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