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Original Article

Correlation of pulmonary venous flow Doppler with pulmonary vascular resistance index in children with ventricular septal defects and pulmonary hypertension

Amitesh Nagarwal*, Sumod Kurien**
**Assistant Professor, Department of Cardiology NIMS Medical College, Jaipur*
***Professor, Department of Cardiology 1st Floor, Academic block GIPMER, New Delhi*

Abstract

Background : Currently measurement of pulmonary vascular resistance (PVR) is done through cardiac catheterization technique which is invasive in nature and has associated procedural risk factors. The aim of the current investigation was to assess the relationship between pulmonary vein flow Doppler measurements and pulmonary vascular resistance index in children with ventricular septal defects.

Methods : It is a cross-sectional observational study conducted at a tertiary care set-up, GIPMER based at New Delhi. Total 22 patients with moderate or large isolated ventricular septal defect were enrolled in the study. Pulmonary vein flow Doppler indices and catheterization parameters were measured in all the patients. The measure pulmonary vein flow Doppler indices were correlated using Pearson's correlation test with pulmonary vascular resistance index (PVRI), pulmonary blood flow (QP) and pulmonary to systemic blood flow ratio (QP/QS) obtained by cardiac catheterization.

Results : Mean value of PVRI at base line was 5.577 Woods/m^2 which reduced to 4.277 Woods/m^2 after oxygenation. Mean value of pulmonary venous blood flow velocity time integral (VTIpv) at base line was 28.36 cm which increased to 34.86 cm after oxygenation for 24 hours. The observed correlation coefficient between VTIpv and PVRI was -0.560 and between Δ%VTIpv and Δ%PVRI was 0.669.

Conclusions : VTIpvhad moderate positive correlation with pulmonary vascular resistance index thus pulmonary vein VTI can be useful non-invasive markers of PVRI and its response to oxygen inhalation and pulmonary vein flow Doppler study along with echo parameters can be an efficient substitute to invasive method for determining PVRI.

Keywords: Pulmonary hypertension, VSD, Cardiac catheterization, PVRI, Pulmonary vein flow Doppler (Indian J Cardiol 2022;25 (1-2):17-24)

Introduction

VSD is the most common cardiac malformation with a prevalence rate of 25-30%[1]. Worldwide prevalence of VSD in premature infants is reported to be at a rate of 5 to 7 of 1000 infants[2]. If the VSD is of small or medium size, it is refereed as restrictive VSD. In restrictive VSD the blood flow is usually from left to right; magnitude and direction of shunt in blood flow depends on size of VSD and pressure

Address for Correspondence :
Dr Amitesh Nagarwal, Assistant Professor, Department of Cardiology NIMS Medical College, Jaipur
E mail - amitesh.nagarwal2007@gmail.com

gradient. Whereas if the VSD is of larger size, it is referred as non restrictive VSD and the magnitude and direction of shunt in blood flow depends on systemic and pulmonary resistance; no pressure gradient exist in such cases[3, 4].

Large shunt in blood flow from left to right direction due to VSD may result in significant increase in pulmonary blood flow leading to pulmonary injury and irreversible pulmonary hypertension[3,5]. Administration of pulmonary vasodilator drugs or oxygen inhalation reduces pulmonary vascular resistance (PVR) which is due to arterial vasoconstriction[6]. This in turn would further increase pulmonary blood and if significant variation in PVR is observed in patients in response to pulmonary vasodilator drugs; closure of VSD is recommended to reverse pulmonary hypertension which may further progress to irreversible pulmonary vascular occlusive disease (PVOD)[6].

Occurrence of PVOD can be prevented by early diagnosis or detection of pulmonary hypertension. Currently right heart catheterization is the widely used diagnostic method and is considered to be the gold standard to measure PVR in patients with pulmonary hypertension that is secondary to CHD[7]. In patients with pulmonary hypertension secondary to CHD, specifically in small children a suitable non-invasive technique is highly desirable to measure PVR. Non-invasive technique to determine PVR such as echocardiography would add benefits of regular turn up of patients for follow-up leading to constant monitoring of PVR that may lead to efficiently determining the suitable time phase for invasively measuring PVR prior to repair of VSD[7,8]. Non-invasive technique to determine PVR would also make it possible to assess the response of the given medical treatment on regular basis. Current study was carried out with the aim of determining the efficacy of non-invasive Doppler investigation in predicting pulmonary hypertension by correlating pulmonary venous flow Doppler investigation with pulmonary vascular resistance index (PVRI). The study investigation was based on the hypothesis that variation in pulmonary vascular resistance and pulmonary blood flow can be indirectly estimated by pulmonary venous Doppler study.

Objectives

Current investigation was conducted with the objective of assessing the correlation between the pulmonary venous blood flow, measured by transthoracic echocardiography and PVRI estimated by cardiac catheterization in patients with VSD. In current study the correlation between the pulmonary venous blood flow variation measured by transthoracic echocardiography and PVRI variation estimated by cardiac catheterization in patients with VSD tested along with oxygen administration was also assessed.

Methods

Study design, location, duration and sample size

Current study is a cross-sectional observational study conducted at GobindBallabh Pant institute of post-graduate medical education and research (GIPMER); a tertiary care set-up facility based at New Delhi. The study was conducted from January 2016 to December 2017 on twenty two subjects after getting an ethical committee clearance from Maulana Azad Medical College (MAMC) and associated hospitals.

Inclusion and exclusion criteria

Children aged between 2 to 12 years;diagnosed with isolated moderate or large VSD's and undergoing cardiac catheterization were included in the study. Patients with associated cardiac defects like ventricular dysfunction, associated respiratory disease, syndromic associations such as Down's syndrome and with baseline fixed PVR or SPO2< 92% were excluded from the current study.

Procedure

Informed consent was obtained from all patients according to the guidelines of ethical committee prior to initiation of investigation. Comprehensive history of patients was taken and documented. All the participating patients were examined for electrocardiography, chest X-ray followed by detailed 2D echocardiography and for other required clinical examinations.

Pulmonary venous flow Doppler

The pulmonary vein flow velocity pattern was determined by recording the pulsed-wave Doppler. The sample was placed at 1 to 2 cm into the orifice of the right superior pulmonary vein in apical four chamber view (Figure 1). Normal primary ventricular fibrillation (PVF) usually depicts a tri or quadriphasic

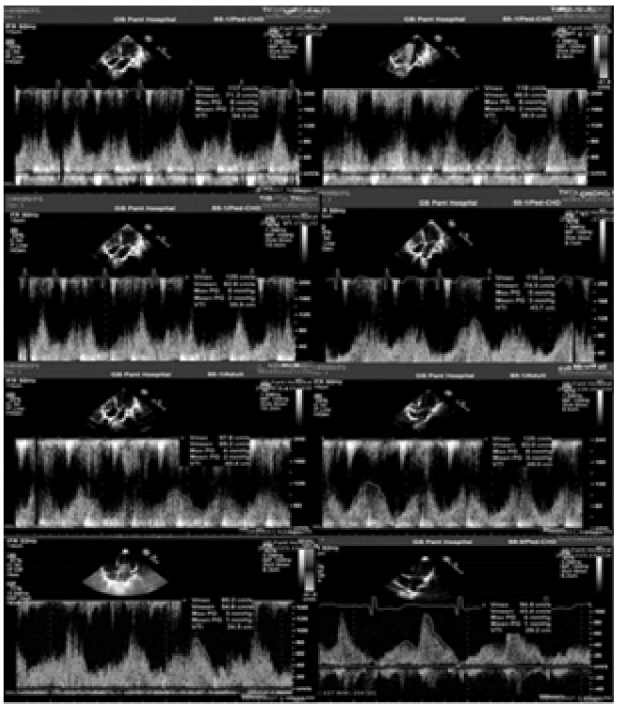

Fig. 1 : Pulmonary vein VTI of four patients before (left) and after (right) oxygenation.

pattern consisting of a pulmonary venous first systolic wave (S1), pulmonary venous second systolic wave (S2), pulmonary venous early diastolic wave (D), and pulmonary venous atrial reversed flow wave (AR). The pulmonary venous blood flow velocity time integral (VTIpv) was calculated from the end of first wave A to the beginning of the second wave A (excluding the atrial contraction wave)[7-9]. Oxygen test: after the baseline measurements while breathing air, the patient was given 100% oxygen at a flow rate of 10 l/min with adequate sized mask for 24 hours in the pediatric ICU. All measurements obtained by echocardiography were repeated 24 hours later.

Cardiac catheterization

The patients were subjected to catheterization for pressure measurements and blood sample collections for oximetric determinations after sedation with ketamine. The catheters were introduced to femoral vein and artery through percutaneous punctures. The pressure values were obtained using isotonic saline-filled catheters connected to a pressure transducer. The hemodynamic variables analyzed were PVR expressed in Wood units (mmHg/l/min) and Qp:Qs ratio. The PVR was calculated using the below mentioned equation:

$$PVR = (MPAP - MPVP)/Qp,$$

Where MPAP was taken as mean pulmonary artery pressure and MPVP was taken as mean pulmonary venous pressure obtained during the study. The Qp(pulmonary blood flow) and Qs (systemic blood flow) were determined through Fick's method using estimated oxygen consumption (VO2)and oxygen content derived from oxygen saturation[10]. Oxygen test: after the baseline measurements while breathing air, the patient was given 100% oxygen at a flow rate of 10 l/min with adequate sized mask for 15 minutes in the catheterization lab. The venous and arterial catheters were maintained in the pulmonary artery and aorta respectively, to obtain a simultaneous recording of oxygen pressure and saturation in both vessels. All measurements obtained by catheterization were repeated 15 minutes later.

Statistical analysis

Data were expressed as mean ±SD. The Wilcoxon range test was used to compare VTIpv, PVRI, QP and QP/QS ratio before and after oxygen inhalation. For correlation between VTIpv, PVRI, QP and QP/QS ratio Pearson correlation coefficient test was used. To compare the variation of each variable before (pre) and after (post) oxygen administration, the percentage difference defined as delta percentage variation was calculated using equation;

$$\Delta\% = \{[(post - pre)/pre] \times 100\}.$$

The Pearson's correlation test was used to find correlation between Δ% of VTIpv, PVRI, QP and Qp : Qs ratio. Correlations were considered significant at $p \leq 0.05$. ROC analysis was one to determine the correlation between parameters VTIpv and PVRI.

Results

In the current study, 22 patients in the age group between 2-12 years with moderate or large VSD; who were diagnosed with pulmonary hypertension and were undergoing cardiac catheterization for evaluation were included. Gender based distribution of participating patients revealed that 12 (55%) patients were males and 10 (45%) patients were females. Out of 22 participating patients, 13 (59.09%) patients had peri-membranous VSD, 6 (27.27%) patients had sub-aortic VSD, 1 (4.54%) patient had sub-pulmonic VSD, 1 (4.54%) patient had mid muscular and 1 (4.54%) patient had inlet VSD. Common complaints of all the patients were dyspnea on exertion and failure to thrive. Basic echocardiographic parameters are depicted in (Table 1).

Table 1 : Basic echocardiographic parameters

Parameters	Mean ± SD	Range
Size of the VSD (cm)	1.4± 0.4	0.7-2.6
Gradient (mmHg)	30 ± 17.2	15-40
LA (cm)	3.1± 0.7	1.5-4.2
Left ventricular internal dimension (LVID) (cm)	4.2± 0.9	3.0-5.4
Right ventricular internal dimension (RVID) (cm)	2.9± 0.5	2.3-4.4
Aorta (cm)	1.8± 0.3	1.2-2.6
Right ventricular outflow tract diameter (RVOT) (cm)	2.2± 0.3	1.6-2.5

During the current investigational study; PVRI and pulmonary blood flow were measured in all the patients at baseline and after oxygenation (Table 2). Mean values of PVRI and Qp at baseline were observed

Table 2 : Observed parameters at baseline and post oxygenation

Patient	Baseline					Post oxygenation				
	VTIpv* (cm)	QP/ QS*	QP*	PVRI* (Woods/m2)	PVR/ SVR*	VTIpv (cm)	QP/ QS	QP	PVRI (Woods/m2)	PVR/ SVR
1	27.1	1.9	8.2	6.2	0.3	31.8	2.1	10.1	5.2	0.3
2	40.4	2.7	11.4	4	0.2	49.1	3.1	14.6	2.9	0.2
3	30.5	2.9	8.2	8	0.3	37.5	3.2	10.7	5.4	0.3
4	21.8	3.3	7.7	9.3	0.2	28.5	3.9	10.5	7.1	0.2
5	20.6	2.7	6.5	9	0.3	25.1	2.9	8.5	7.3	0.3
6	25.6	2.7	10.1	5.8	0.3	32.2	3	13	4.9	0.2
7	37.2	2.3	14.1	3	0.2	45.8	2.6	16.9	2.1	0.2
8	33.1	3.1	14.3	5.2	0.2	40.3	4	20	3.6	0.2
9	35.1	4	10.1	5.4	0.2	41.3	5.3	13.5	4.7	0.2
10	29.8	3	13.8	2.6	0.2	36.2	4	18.4	2.2	0.1
11	31.4	2.9	12.4	3.8	0.3	39.1	3.2	19.3	2.5	0.2
12	24.4	2.3	15	5.9	0.3	33.1	3.8	25	2.4	0.2
13	18.8	1.4	2.1	20	0.4	20.2	1.4	2.2	18.3	0.4
14	25.8	3.7	12.4	4.8	0.2	31.7	4	14.9	3.6	0.2
15	23.4	3.2	7.8	4.1	0.1	28.9	4.1	11.6	2.7	0.1
16	22.6	2.6	11.8	5.7	0.3	27.1	3.2	15.7	4.6	0.2
17	34.8	4	16.4	2.9	0.1	43.8	4.6	19.3	2.4	0.1
18	22.9	2.4	10.7	4	0.2	26.2	2.8	11.9	3.2	0.1
19	33.9	4.4	10.9	4.3	0.1	40.7	5.8	17.5	2.9	0.1
20	31.5	2.8	8.3	1.5	0.1	39.3	4.2	14.7	1.3	0.1
21	28.3	3.3	12	2.3	0.1	33.2	3.7	15.4	2	0.1
22	24.8	2.5	11.6	5.9	0.3	31.9	3.1	16.8	3.8	0.2
Mean	28.36	2.91	10.71	5.57	0.22	34.68	3.54	14.56	4.27	0.19

*Pulmonary vascular resistance index (PVRI), pulmonary blood flow (QP) and pulmonary to systemic blood flow ratio (QP/QS), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR)

to be 5.57 Woods/m2 and 10.71 respectively. After oxygenation 26.12% reduction in mean PVRI value was observed (4.27 Woods/m^2), whereas; mean Qpvalue increased by 35.13% to 14.56. Mean Qp/Qs ratio value at baseline was observed to be 2.91 which increased by 21.12% after oxygenation to a mean ratio value of 3.54. Mean VTIpv value observed at baseline was 28.36 cm, which significantly increased by 22.21% to 34.68 cm after 24 hours of oxygenation (Figure 2).

Results of correlation test for significance indicated that a significant (p=0.007) and moderate strong inverse correlation exist between VTIpv and PVRI (Figure 3), the value of correlation coefficient between the above mentioned parameters was observed to be -0.560. Results also indicated that a significantly positive correlation (p=0.013) existedbetween VTIpv and Qp with a correlation coefficient value of 0.523. Similarly correlation coefficient value of 0.414 between VTIpv and QP/

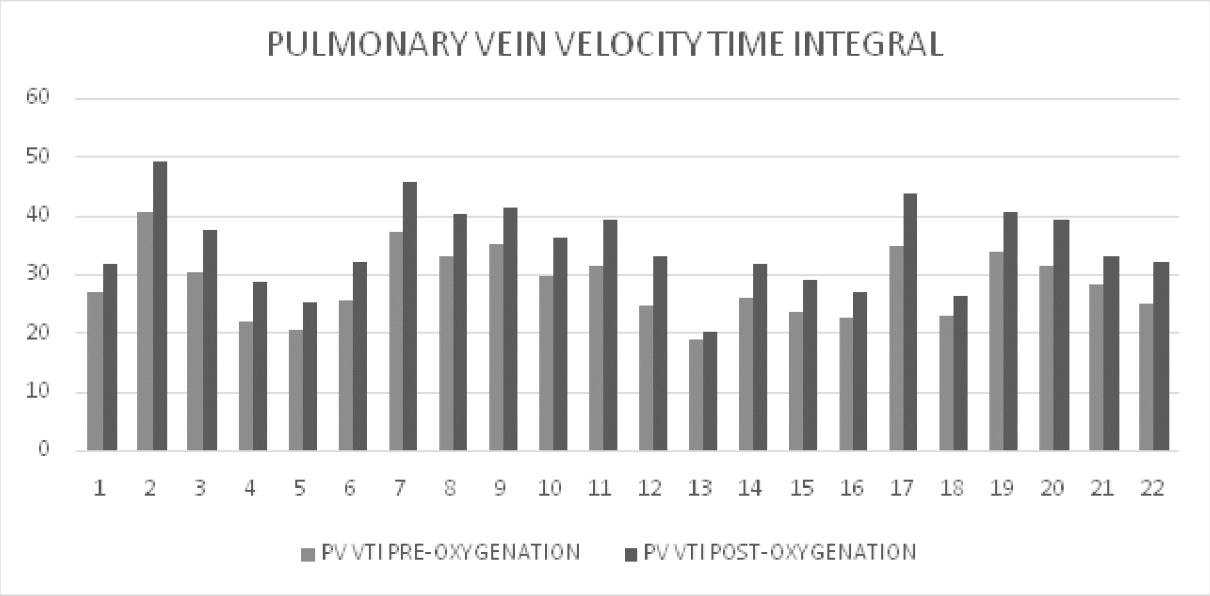

Fig. 2 : Pulmonary vein velocity time integral in twenty two patients

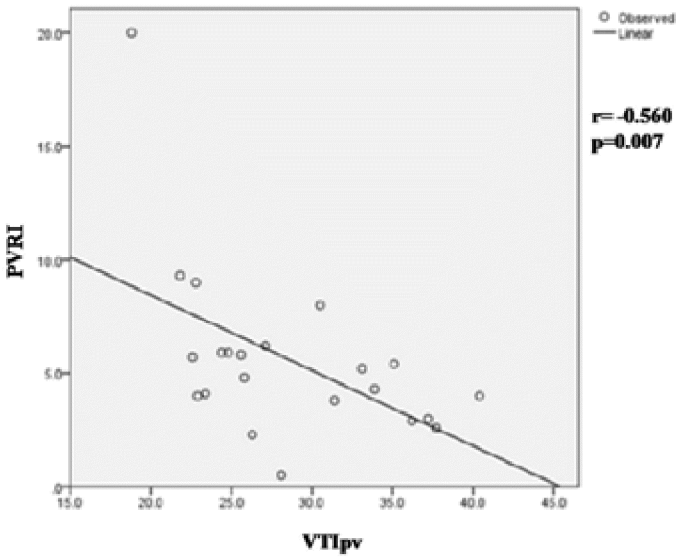

Fig. 3 : Linear regression analysis for correlation between VTIpv and PVRI

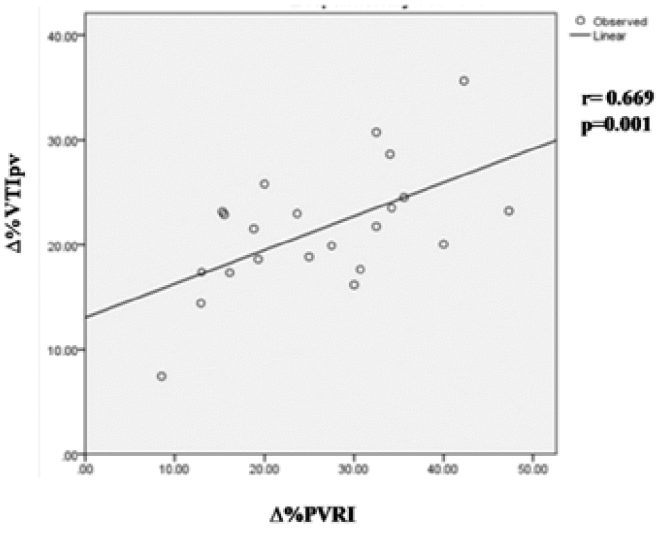

Fig. 3 : Linear regression analysis for correlation between Δ%VTIpv and Δ%PVRI

QS indicated a moderate positive and significant (p=0.055) correlation between the parameters. It was observed through current study findings that ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) exhibited significant (p=0.005) and inverse correlation with VTIpv with a correlation coefficient value of -0.447. Results correlation studies of percentage difference (Δ%) observed in various parameters post and prior to oxygenation revealed that significant and strong correlation existed between Δ%VTIpv and Δ%PVRI (coefficient=0.669, p=0.001), Δ%VTIpv and Δ%QP (coefficient=0.576, p=0.005), whereas correlation between Δ%VTIpv and Δ%QP/QS was observed to be moderate (coefficient=0.505, p=0.016). ROC curve analysis depicted that VTIpvcutoff value of >15.8% provided the highest balanced sensitivity (93%) and specificity (87%) to determine PVRI variation >20%. The area under this ROC curve was 0.821 (SE=0.990) and p=0.014.

Discussion

One of the most important and decisive parameter in early detection of pulmonary hypertension for preventing its progression in to more severe and irreversible PVOD is pulmonary vascular resistance (PVR)[11-13]. However; currently only invasive catheterization-derived measurements are used to calculate the ratio of the trans-pulmonary pressure gradient (Dp) to flow (Qp) which in turn aids in estimating PVR[5,6,14]. The currently employed catheterization technique, because of its invasive nature and requirement of general anaesthesia for sedation during the procedure exhibits several complications precluding it from being used as a routine procedure on patients specifically during their follow-up visits. Thus need of the hour is to investigate the effectiveness of non invasive methods in determining PVR for more frequent, routine and remote site monitoring of PVR during treatment of pulmonary hypertension.

In current study non invasive determination of VTIpv was investigated as a parameter to evaluate PVR. VTIpv was measured in right superior pulmonary vein in typical four chamber view. In present study it is was observed in participating patients that there was an almost continuous pattern of pulmonary vein flow with no clear return to baseline tracings and separation between systolic and diastolic waves was also not very well defined. Current study results of baseline pulmonary velocity time integral measurement revealed a higher value (28.36±5.84 cm) than that reported in the literature (18.8±4.2 cm) by (AbdurRahahman et al)[15]. Comparison of age with VTIpv in all the participating patients in current study revealed that there is a significant difference ($p \leq 0.05$), this finding was in accordance to prior reports published by Rivera et al, Pickoff et al and Harada et al[16-18]. Published reports by Rivera et al reveals a significantly higher VTIpv in children with CHD associated increased pulmonary blood flow. Harada et al in their study on 26 patients with VSD reported that abnormal pulmonary venous flow patterns in VSD might be associated with large left-to-right shunting. Pickoff et al also concluded that there was a higher pulmonary venous signal in left atrium when there was increased pulmonary blood flow. Similar to this previously published reports current study findings reinforce that VTIpvis higher in patients with increased pulmonary blood flow and there is a statistically significant strong correlation between VTIpvand pulmonary blood flow (r=0.523 p=0.013).

Pulmonary and systemic blood flow were estimated based on the calculations made through determination of oxygen consumption as per LaFarge and Miettinen with the assumption that pulmonary and systemic blood flow would not change while the patient was breathing oxygen[10,19]. However; a random change toward one direction decrease or increase in the calculated Qp or Qs-values cannot be ruled out. Earlier published reports by Barratt-Boyes and Woodrevealed no change in VO_2 in normal humans breathing air and oxygen, but Swan and Marshall et alreported an increase of 3% and 5% respectively in VO_2 in patients with atrial septal defect and VSD with varying severity of PVOD[19,20]. Previouspublished reports were in accordance in direction and magnitude to current study findings,where increase of 35% in the pulmonary blood flow and decrease of 26% in the pulmonary resistance was observed indicating that no change in oxygen consumption of significant degree had occurred.

Abnormal shear stress, circumferential wall stretch and endothelial dysfunction is observed in CHD patients with high pulmonary blood flow and high pressure in the pulmonary arteries. Above mentioned conditions together may contribute towards progressive increase in PVR, with concomitant decrease in pulmonary blood flow that returns through pulmonary veins[21-23]. Thus it can be assumed that

with increase in PVR, pulmonary venous return will decrease. Current study findings also revealed that there was strong inverse correlation between VTIpv and PVRI (r= -0.56, p=0.007). As evident from earlier published reports PVR is initially increased due to vasoconstriction in hypertrophied aretrioles; this can be reversed by administration of vasodilators. Before progression of PVR to end stage irreversible disease it can be characterized by neo-intimal lesions such as concentric plexiform lesions and laminar intimal fibrosis[21-24]. Several published literature reports the role of oxygen inhalation in diagnosing a reversible phase of PVOD[25,26]. Current study findings revealed that after oxygenation there was a significant increase in VTIpv, pulmonary blood flow area and Qpalong with significant reduction of PVRI in all except one patient who had irreversible pulmonary arterial hypertension and did not show significant changes after oxygenation.

Results of current investigation reveal a strong and significant correlation between Δ% VTIpv with Δ% PVRI and Δ%QP. Results also reveal a moderate correlation of Δ% VTIpvwith Δ% QP/QS. ROC curve analysis revealed that VTIpv analysis correlated with PVRI thus VTIpv can be efficiently used to track change in PVRI. Findings of current study were in accordance to the study report published by Rivera et alwith slightly lower values of correlation coefficients; the probable reason for the noticed variation would be the age of the 15 out of 18 patients included in Rivera et al study was less than 3 years while in current study all patients were>3 year of age.[8]This was hypothesized using the background of report published by Abdurrahman et alwhich stated children age and heart rate as the major determinants of pulmonary venous flow[15]. Some other probable reasons for justifying slight variations in current study findings in comparison to published reports were; in the study published by Rivera et al correlation of pulmonary vein VTI and PVRI wasreported by investigating patients of various CHDassociated increased pulmonary blood flow values; while current study included patients of VSD only. Also Rivera et al measured VTIpv in the left inferior pulmonary vein, while in current study VTIpv was measured in right superior pulmonary vein which can be easily identified and is easily accessible also since it was difficult to align transducer parallel to the vein flow in left inferior pulmonary vein[8]. It was observed while conducting the current study that in all VSD patients due to high pulmonary blood flow, it was easier to place sample volume inside the vein, alsosince the direction of venous flow was towards the transducer and exit of the atria it produced less turbulence than that produced due to opposite flow in the left inferior pulmonary vein. In addition it was also observed that highest signal of pulmonary venous return was directly from right superior pulmonary vein. Thus current study findings revealed that pulmonary vein flow area is a good marker of increased pulmonary venous return in cases of high pulmonary blood flow. In addition it was also observed through current study findings that increase of VTIpv was also strongly and significantly correlated with PVRI decrease and increase in pulmonary blood flow after oxygenation.

Results of the current investigation and correlation indices values determined through current study findings indicated that non invasive pulmonary vein flow Doppler study along with echo parameters to differentiate high pulmonary blood flow and fixed high pulmonary vascular resistance would be a promising and emerging technique that holds a potential of substituting invasive conventional approach to determine PVRI.

Limitations

Small sample size was the major limitation of the current study but the promising results of current study pave the path in future for exploring the effectiveness of noninvasive techniques in PVRI determination with a larger sample size. Another limitation of current study is the possibility of errors in the measurement of cardiac output using Fick's method because of the use of assumed oxygen consumption. Intra- and inter-observer variability is important since Doppler indices can vary in different users, whether or not the presence of significant intra or inter-observer variability among any of these Doppler indices will limit their use in clinical practice remains a possibility that needs to be examined in future studies.

Conclusion

It was concluded from current study findings that pulmonary vein flow Doppler can be a non-invasive substitute to cardiac catheterization for indirect assessment of pulmonary vascular resistance index and its response to oxygen inhalation.

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