PROJECT REPORT

Submitted during the course of

DM Cardiology

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DM Trainee

DEPARTMENT OF CARDIOLOGY

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DECLARATION

I, Dr. Nishant Gangil hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram
Date

Dr Nishant Gangil
DM Trainee

Forwarded

The candidate, Dr Nishant Gangil, has carried out the minimum required project.

Thiruvananthapuram
Date

Prof. Dr Jaganmohan Tharakan
Head of Department of Cardiology
A Study on Pulmonary vein spectral Doppler pattern in isolated ostium secundum atrial septal defect patients and to analyse the change in Doppler pattern after device closure and on follow up.

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Atrial septal defect (ASD) is the second most common congenital heart disease, after ventricular septal defect. Though the standard treatment for ostium primum and sinus venosus ASDs is still surgical, in past two decades ostium secundum ASDs have come under the purview of transcatheter closure. Percutaneous closure offers numerous advantages over the conventional bypass surgery including lower complication rates and shorter hospital stays. Though there are infrequent reports of device thrombosis and device erosions, overall percutaneous closure of secundum ASD has become the treatment of choice in majority of centers.

Atrial septal defect provides an unique model of cardiac hemodynamics wherein one can understand the filling pattern of left ventricle and right ventricle along with venous return, both systemic and pulmonary, in to the respective atria. There are numerous past studies which have shown the changes in size of left and right sided cardiac chambers over long term follow up after ASD closure. Investigators have also shown regression of pulmonary hypertension after closure along with reduced incidence of atrial arrhythmias in such patients.
However, there are very few studies analysing the change in hemodynamics of atrial septal defect before and after closure, be surgical or percutaneous. With the advent of Doppler echocardiography, flow patterns in cardiac chambers and vessels can be reliably studied and extrapolated to enhance our understanding of the cardiac hemodynamics in various pathological conditions.

This study was formulated to understand the change in cardiac hemodynamics before and after ASD percutaneous closure by assessing the Doppler flow patterns in pulmonary veins and also to observe if the changes are persistent on short term follow up. And whether this can be used to derive some meaningful clinical outcomes.
OBJECTIVE

- To study and analyse the pulse Doppler flow pattern in pulmonary vein of isolated ostium secundum atrial septal defect patients before, immediately after percutaneous device closure and on short term follow up.

- To analyse if ASD shunt can be quantified from pulse Doppler flow pattern in pulmonary veins.
REVIEW OF LITERATURE

Atrial septal defect (ASD) occur as an isolated anomaly in 5-10% of all congenital heart defects. This interatrial communication can occur at four sites in decreasing order of frequency:

1. In the central portion of atrial septum in the position of foramen ovale, termed fossa ovalis or secundum defects, accounting for 50-70% of all ASDs. Anomalous pulmonary venous return is present in about 10% cases.

2. At the junction of interatrial septum and atrioventricular valves, termed as ostium primum defects. These defects account for 30% of all ASDs, if those that occur as part of complete endocardial cushion defect are included. Isolated primum ASDs account for 15% of all ASDs.

3. In the region of the junction of the superior vena cava (SVC) and the right atrium, termed sinus venosus defects accounting for 10% of all ASDs. The defect is most commonly located at the entry of the SVC into the right atrium (RA) – superior vena caval type and rarely at the entry of the inferior vena cava (IVC) into the RA – inferior vena caval type. The former is very commonly associated with anomalous drainage of the right upper
pulmonary vein into the RA and the latter is often associated with anomalous drainage of the right lung into the IVC – Scimitar syndrome.

4. Between the left atrium (LA) and the coronary sinus at its ostium into the right atrium, termed unroofing of the coronary sinus.

HEMODYNAMICS IN ATRIAL SEPTAL DEFECT

When there is an ASD, hemodynamic changes after delivery the circulatory changes after birth promotes changes in the fetal right to left shunting pattern to left to right shunting. The magnitude of the left to right shunt is determined by the size of the ASD and the relative resistances of the two ventricles.

The atria are low pressure chambers and the pressure difference between left and right sides are considerably lower than those seen in the ventricle. Large ASDs are the ones that have a diameter equal to or greater than mitral valve. If defect is large and non restrictive, both mean and phasic between the atria are equal. Because atrial pressures are similar, flow through the mitral and tricuspid valves and the magnitude and direction of shunt will be related to the relative inflow resistances of the left and right ventricles.

The inflow into the ventricles is determined by the compliance of that chamber which is related to muscle thickness. This explains why infants with ASDs rarely
have any symptoms, since left and right ventricular muscle masses are similar postnatally, they have equal compliances and therefore no atrial shunt occurs. Subsequently, pulmonary vascular resistance and right ventricular pressure fall, the right ventricular myocardium does not grow as rapidly as the left ventricular muscle after birth, the wall of right ventricle becomes thinner than that of the left and its compliance becomes relatively higher. The left to right shunt, therefore parallels these changes in the relative muscle mass.

However other than ventricular compliance, shunting across the ASD also depends on relative vascular resistances. Within a few hours of birth, some amount of shunting can be noticed despite the ventricular compliance being same. This can be explained on the basis of relative changes in vascular resistance after birth. The volume of the blood ejected by the ventricle depends on preload, myocardial contractility and afterload. Preload is determined by the filling pressure and by the compliance of the ventricular wall. Afterload is dependent on changes in pulmonary and systemic vascular resistances. Myocardial contractility immediately after birth is same on both sides.
PATTERN OF SHUNTING ACROSS ASD

Effect of Respiration

Inspiration produces negative intrathoracic pressure which causes an increased venous return to the right side of the heart. On the contrary, venous return from the pulmonary veins to the Left atrium decreases as the blood amount in pulmonary circulation is more. As a result, inspiration decreases left to right shunt and may cause a transient right to left shunt during this phase of respiration. During expiration, the intrathoracic pressure increases, there is fall in venous return to the right atrium while the PV flow to LA gets augmented. All this results in an increased left to right shunt and a decreased right to left shunt across the interatrial septal defect.

Effect of cardiac cycle

Shunting across ASD occurs maximum during ventricular systole, particularly late systole, which coincides with peak of v wave. This is analogous to the point of maximum difference between LA and RA pressure. A small right to left shunt may occur at the beginning of ventricular diastole which is due to rapid systemic venous flow into the atrium at this time, with passage of some IVC blood across the defect.
**Effect of posture**

In the erect position, because of pooling of blood in lower limb Inferior vena cava flow is reduced and thus there is negligible right to left shunting and vice versa.

**Effect of blood flow pattern**

Dye dilution studies, with selective injection of dye into the right and left pulmonary arteries, have shown that in secundum ASD there is greater shunting from the right pulmonary veins than from the left. Around 80% of the right PA flow shunts across the defect as compared with only 20-40% of left PA flow.

**ANATOMY AND PHYSIOLOGY OF PULMONARY VEINS**

Between the lung capillaries and the LA, there are the intra- and extraparenchymal pulmonary veins. There are usually four pulmonary veins including the right and left upper and lower veins. The right and left pulmonary veins connect, respectively, medially and laterally to the superior and posterior LA walls. The lower veins run below the inferior border of the right and left bronchi, and the upper veins run anterior to their bronchi. The right pulmonary
veins run behind the superior vena cava and right atrium and join the LA adjacent to the atrial septum.

**Normal Pulmonary Venous Flow**

There has been a lot of debate regarding the driving force behind the pulmonary venous flow to LA. Two mechanisms have been suggested for the control of pulmonary venous flow. One group of investigators holds that pulmonary venous flow should be attributed to forward transmission of pressure from the right ventricle through the pulmonary vasculature. A second group suggests that pulmonary flow is determined by a "suctioning effect" created by the left atrium and left ventricle throughout the cardiac cycle.

The argument against the former hypothesis is that if pulmonary venous flow were the result of transmission of a right ventricular systolic pressure pulse, then there should have been only one wave of pulmonary venous flow occurring at a specific time after right ventricular systole. However, the flow in normal subjects is double peaked and each phase occurs after the reduction in left atrial pressure associated with mitral flow.

A study of patients in whom atrial and ventricular phenomena are not synchronized constitutes a setting in which the relative contributions of atrial
and ventricular events to pulmonary venous flow can be assessed. If right ventricular events were the main determinants of pulmonary venous flow, these patients should have had a grossly normal pulmonary venous flow pattern. However this is not the case. In patients without atrial contraction (atrial fibrillation and sinoatrial standstill) pulmonary venous flow is of minimal amplitude during ventricular systole whereas flow during the period which followed mitral rapid filling, is recorded as a significant pulse of flow.

Rajagopalan et al.\textsuperscript{19-21} observed, in a canine preparation, that flow in the large extraparenchymal pulmonary veins is dominated by left atrial events. Thus, when the left atrial pressure was high, flow through the pulmonary veins was reduced, and when the pressure was low, flow into the left atrium increased.

Each of the pulmonary venous flow pulses, the first of which occurs during ventricular systole and the second of which occurs during diastole, contributes significantly to left ventricular filling. The systolic phase of pulmonary venous flow occurs while the mitral valve is closed and is a reflection of the reduced pressure in the left atrium that results from relaxation of the atrium at the end of ventricular diastole. Moreover, during the early phase of ventricular systole, the mitral valve descends slightly as a result of the contraction and shortening of the long diameter of the left ventricle. This movement contributes to the reduction in left atrial pressure that promotes flow from the pulmonary veins.
into the left atrium. After the rapid filling wave across the mitral valve, the pressure in the left atrium is reduced and flow from the pulmonary veins into the left atrium resumes in a second phase. This diastolic phase occurs during ventricular diastole, reaches a peak after the rapid filling wave, and diminishes before the atrial contribution to mitral flow. During this phase, the atrium acts as an open conduit through which blood flows directly from the pulmonary veins through the mitral valve into the left ventricle.

**Normal pulmonary venous colour Doppler pattern**

As recorded by transesophageal echocardiography, has four phases, with two forward peaks during ventricular systole, one forward diastolic peak and one reversed flow peak coinciding with atrial contraction.
However, appreciation of two systolic waves is difficult and mostly pulmonary Doppler may show only three waves.

1. The **Systolic (S) wave** is caused by antegrade ventricular systolic flow and is seen above the baseline. The velocity ($V_S$) is $30 - 80$ cm/sec. The S wave has 2 components most pronounced during increased P-R interval of ECG:
   - $S1$ due to atrial relaxation that is determined by LA pressure, contraction and relaxation.

S2 due to mitral annular descent and impacted by stroke volume and pulse wave propagation in the pulmonary arterial tree.

2. The **Diastolic (D) wave** is caused by antegrade ventricular diastolic flow and is seen above the baseline. The Velocity ($V_D$) is 20 – 70 cm/sec.

3. The **Atrial Systolic Reversal (AR) wave** caused by retrograde atrial systolic flow, is seen below the baseline. The Velocity ($V_{AR}$) is 10 – 25 cm/sec. Duration ($AR_{dur}$) is 30-160 msec.

Under normal conditions, systolic flow wave is same or slightly greater than the diastolic flow wave. The difference between duration of Ar wave and the A wave on pulse Doppler at mitral wave is less than 25msec. A greater difference suggest decrease in LV compliance.

With increasing age, the ratio of the systolic and diastolic wave increases as does the velocity of Ar wave. Similarly tachycardia due to increase in LV contractility increases the systolic wave while the contribution during the diastole decreases.
Figure 1: Spectral Doppler data acquired for blood flow through the right upper pulmonary vein. In the upper right, a two-dimensional TEE image of the modified bicaval view; the blue circle indicates the location of the sample volume which is placed within the right upper pulmonary vein. In the lower half of the image, a spectral Doppler trace shows the relationship between red blood cell velocity and time. The baseline is orange. D=diastolic wave, AR=atrial systolic reversal and S=systolic wave.
Relation between RV, pulmonary artery and PV and LA pressures

PV pressure and contour varies depending on recording site, so that a “family” of successive pressure curves is seen between the pulmonary artery and LA. At locations closer to the pulmonary venules and capillary bed, the PV pressure contour resembles a delayed pulmonary artery pressure, with mean pressure reduced by 4 to 5 mm Hg. Recording locations closer to the venoatrial junction have pressure contours more like LA pressure, with noticeable ‘a’ and ‘c’ waves. These ‘a’ and ‘c’ waves are largest in the atrium and delayed and smaller in proportion to the distance upstream in the pulmonary veins. The maximal PV pressure occurs in late systole (in conjunction with the peak LA V wave) and appears closely linked to RV pressure events and pulse pressure throughout the respiratory cycle. Overall this maximal systolic pressure decreases by one-half to two-thirds, traversing the pulmonary artery and capillary beds, with another 10% to 15% pressure decrease between the PVs and LA.  

PV flow velocity components and relation to hemodynamic pressure gradients

Pulmonary vein pressure and shape of the pressure waveform changes with the recording site, however there is relationship between the Pulmonary vein–Left atrium pressure gradient and pulmonary vein flow velocity (PVFV).
There are two occasions of maximal pressure gradient, one occurring in systole and the other in diastole. These are analogous in timing to four PVFV components:

- Pulmonary vein flow velocity in early systole (PVs1),
- Pulmonary vein flow velocity in late systole (PVs2),
- Pulmonary vein flow velocity in early diastole (PVd)
- Retrograde Pulmonary vein flow velocity at atrial contraction (PVa).

**Effect of respiration on PVFVs and hemodynamic pressure gradients**

In general, pulmonary vein flow velocity (PVFV) decreases with inspiration and increases on the first two beats of expiration, with the changes most marked for the PVa component. The respiratory changes in flow velocities are influenced by multiple hemodynamic factors. As intrathoracic pressure varies, PV pressure changes more than LA pressure. At the same time respiration also causes changes in RV stroke volume, changes more than LA pressure. At the same time respiration also causes change in RV stroke volume, which altered the PV pulse pressure, the PV–LA pressure gradient and LA filling and A wave pressure increase. \(^{35}\)
Effect of heart rate on PVFVs and hemodynamic pressure gradients

Changes in heart rate markedly affectes PVa and PVs1, with less effect on PVs2 and PVd. At slower heart rates PV and LA pressures equilibrated in mid-diastole, so that atrial contraction resulted in a reverse pressure gradient and reverse flow back into the PVs. However, at faster heart rates diastole was shortened so that atrial contraction only diminished but did not reverse PV flow. By altering the PVa, faster heart rates also affected PVs1, which increases as the PVa minimum became more positive. PV and LA pressures in late systole and early diastole were less affected by increasing heart rates, explaining the lesser effect on PVs2 and PVd.
PULMONARY VENOUS PULSE DOPPLER IN PATHOLOGICAL CONDITIONS

**Abnormal Relaxation:** In LV diastolic dysfunction due to relaxation abnormality, the mitral inflow E velocity decreases with an increase in deceleration time, which suggests shortened early diastolic LV filling rate. Whereas mitral inflow A velocity increases because of the more forceful atrial contractions during atrial systole secondary to Frank Starling mechanism. As a result, the pulmonary venous systolic fraction and the S2/D ratio increases, and the deceleration time of the D wave increases so that the increased volume of blood during systole could counteract impaired early LV filling.22,23

![Doppler Image](image.png)

**Pseudonormal Relaxation abnormality:** Due to the associated increase in LA pressure the early mitral inflow velocity increases which masquerades the relaxation abnormality. There is an increase in the mitral inflow E-wave velocity while the A-wave velocity decreases. The classic way to differentiate between pseudorelaxation abnormality and normal filling pattern is the presence of a normal or decreased S2 (“blunted” systolic pattern) and increased D velocities which produces a decreased systolic fraction and S2/D ratio and with a large Ar wave >35 cm/s.24
### Echocardiographic Classification of Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Diastolic Function</td>
<td>Impaired Relaxation</td>
<td>Pseudonormal</td>
<td>Fixed Restrictive</td>
</tr>
</tbody>
</table>

#### Mitral Inflow

- **Normal**: E/A > 1.5, DT > 140 ms
- **Stage I**: E/A < 1.5, DT > 140 ms
- **Stage II**: E/A > 1.5, DT < 140 ms
- **Stage III**: E/A > 1.5, DT < 140 ms

#### Mitral Inflow at Peak Valsalva Maneuver

- **Normal**: ΔE/A > 0.5
- **Stage I**: ΔE/A < 0.5
- **Stage II**: ΔE/A > 0.5
- **Stage III**: ΔE/A < 0.5

#### Pulmonary Venous Flow

- **Normal**: S-D, ARd < Adur
- **Stage I**: S-D, ARd < Adur + 30 ms
- **Stage II**: S-D, ARd < Adur + 30 ms
- **Stage III**: S-D, ARd < Adur + 30 ms

#### Color M-Mode Propagation Velocity

- **Normal**: Vp > 45
- **Stage I**: Vp < 45
- **Stage II**: Vp < 45
- **Stage III**: Vp < 45

#### Doppler Tissue Imaging of Mitral Annular Motion

- **Normal**: E/A > 10
- **Stage I**: E/A < 10
- **Stage II**: E/A > 10
- **Stage III**: E/A > 10

#### LV Relaxation

- **Normal**: Normal
- **Impaired**: Impaired

#### LV Compliance

- **Normal**: Normal
- **Impaired**: Impaired

#### Atrial Pressure

- **Normal**: Normal
- **Impaired**: Impaired
**Estimation of LV filling pressure:** Pulmonary venous flows have been used to clinically estimate mean LA pressure; LA pressure has been shown to have a negative correlation with pulmonary venous systolic fraction and S2/D ratio in those patients with pseudonormal and restrictive physiology. A systolic fraction <55% was found to be 91% sensitive and 87% specific in predicting a mean LA pressure >15 mm Hg. However, S2 velocity is not only affected by LA pressure, but also by LV contractility. There is a negative correlation between the S2 velocity and the LA pressure in patients with a low cardiac index because of the decrease in the systolic descent of the mitral annulus.

On the other hand, the difference between the PVF-AR wave duration and the mitral inflow atrial-wave duration has been reported to correlate with an increase in LV pressure during atrial contraction and LV end-diastolic pressure. The PVF-AR wave duration (exceeding mitral inflow A-wave duration by 30 ms) is reported to provide high sensitivity (82%) and specificity (92%) for the detection of LV end-diastolic pressure >20 mm Hg.
PULMONARY VENOUS FLOW IN ATRIAL SEPTAL DEFECT

Atrial septal defect dramatically alters cardiac hemodynamics during both ventricular systole and diastole. In patients with ASD, the entire pulmonary venous return does not cross the mitral valve (as is the case in healthy persons), but rather is divided between the flow across the mitral valve and the flow across the ASD.

Unlike healthy persons in whom the left atrium becomes a dead-end chamber during ventricular systole, patients with ASD have a left atrium that is in constant communication with the compliant, low resistance right side of the heart throughout the cardiac cycle. This persistent egress of blood from the left atrium via the ASD throughout the cardiac cycle allows for a continuous flow into the left atrium from the pulmonary veins.
In non restrictive ASD with large shunt, shunting occurs from left atrium to right atrium as the compliance of right sided chambers is more than the left sided chambers. As only a fraction of PV flow enters left ventricle through mitral valve due to blood flowing across ASD, the influence of left atrium on PV flow diminishes. Consequently, the PV flow becomes more dependent on the interatrial shunting. This relationship break between left sided cardiac chambers hemodynamics and PV flow causes distinct changes on spectral Doppler of PV.\textsuperscript{32,33} As a result, in contrast to normal pulse Doppler PV pattern, there are no clearly appreciable S and D waves. Infact a single continuous antegrade wave (CAW) is seen starting from ventricular contraction i.e. systole to the onset of atrial contraction i.e. diastole.\textsuperscript{32,33} This wave reflects the continuous runoff of blood from the LA into the RA throughout systole and most of diastole. In two studies, a CAW was detected on the PV Doppler in 95% and 100% of individuals with large and uncomplicated ASD, respectively.\textsuperscript{32,33}
METHOD AND MATERIAL

Setting: Department of Cardiology, SCTIMST, Trivandrum, India

Study period: April 1, 2014 to August 30, 2015

Study Design: Prospective Observational study

• All consecutive patients, irrespective of sex, who have undergone isolated secundum atrial septal defect device closure from April 1, 2014 were enrolled. This study aims to study the pulse Doppler flow pattern in pulmonary vein of atrial septal defect patients, before, immediately after device closure and after a minimum follow up period of 6 months and to analyse if ASD shunt can be predicted from pulmonary flow pattern.

Exclusion criteria:

• Atrial septal defect other than ostium secundum type.

• Patients with associated cardiac anamoly like pulmonary stenosis, ebstein anamoly of tricuspid valve, partial anamolous drainage of pulmonary vein, associated mitral valve disease.

• Patients who were not suitable for percutaneous device closure.

• Patients who did not give consent to participate in the study.
Study Protocol

- Patients were recruited at the time of preprocedural workup for atrial septal defect device closure.

- Suitable subjects were asked to give their consents for their potential participation in the study. Subjects who were less than 18 years of age, consent was taken from the guardian.

- All the subjects underwent transesophageal echocardiogram as per standard protocol of the institute during the time of percutaneous ASD closure. All patients were studied under general anaesthesia, as per the departmental regime. Prior to the closure, pulse wave Doppler of pulmonary veins was recorded.

- All the subjects subsequently underwent a cardiac catheterisation to measure pulmonary artery pressures and quantify and ASD shunt. Following successful device closure, pulse wave Doppler flow pattern in pulmonary veins were recorded as done prior to closure.

- For follow up data, all patients underwent repeat tranesophageal recording of pulse Doppler of pulmonary veins after a minimum of 6 months. Children who were below 14 years of age were studied under general anaesthesia after taking consent from the guardians while
subjects above 14 years of age were studied under local anaesthesia after taking consent from the patient and/or guardian(s).

**Method to study pulse wave Doppler of pulmonary veins:**

TEE examinations (Phillips IE33) were done immediately before and after ASD closure. At least 5 consecutive beats in sinus rhythm were recorded, and the average values were calculated. All echocardiographic recordings were made using a sweep speed of 100 mm/s, with an ECG (lead II) superimposed.

Pulmonary venous flows were recorded by placing a 2 mm pulse wave Doppler sample volume 1 cm within the orifice of the right upper pulmonary vein from the apical 4-chamber view. However, other pulmonary veins like left upper pulmonary vein was used in case of unsatisfactory tracing with right upper pulmonary vein. Parameters measured included:

1) Velocities
   - PVs=peak systolic velocity (m/s)
   - PVd=peak diastolic velocity (m/s)
   - PVar=peak atrial reversal velocity (m/s)

2) Pulmonary venous velocity-time integral (PV-VTI) (cm)
The presence of single continuous antegrade wave (CAW, defined as fused peak systolic and diastolic forward waves) and the absence of atrial reversal wave were also recorded.

Statistics

- The data was analyzed by the principal investigator. All data was handled with care to maintain patient confidentiality. Records were maintained in both computer and paper formats.
- Descriptive summaries will be presented as frequencies and percentages for categorical data, and as means and standard deviations for continuous variables. Continuous variables will be compared using Student’s t test or Mann-Whitney U test as appropriate. Group comparisons will be made using $\chi^2$ tests. Kaplan-Meier survival analyses will be performed to evaluate differences in freedom from thromboembolic events, bleeding events, and valve related deaths between the 2 groups. Univariate and multivariate analysis will be done from Cox proportional hazard model. All statistical analyses were performed using the SPSS statistical software package (release 16.0, SPSS Inc.; Chicago, III).
RESULTS

- The mean age of the study population was 20.57±17.42 years while the median age was 11.5 years. More than half of the study population was below 14 years of age and around 42% of patients being between 14-50 years of age.

- The male to female ratio in study population was 1:2.9. This ratio was maintained in both the age groups of less than 14 years of age and more than 14 years of age.

Table 1: Age and Sex distribution of the study population

<table>
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<th>Age</th>
<th>Male</th>
<th>Female</th>
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</thead>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
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</tr>
<tr>
<td>&lt;14</td>
<td>4</td>
<td>50.0</td>
<td>12</td>
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<tr>
<td>14-50</td>
<td>4</td>
<td>50.0</td>
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</tr>
<tr>
<td>&gt;50</td>
<td>0</td>
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<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>100.0</td>
<td>23</td>
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- The mean size of atrial septal defect 19.26±7.15 mm. The size of ASD was more in population above above 14 years of age as compared to less than 14 years of age, 14.19±3.43 mm and 24.67±6.01 mm, respectively.
The mean cardiac shunt across atrial septal defect (Qp/Qs) was 2.49±0.89 which was fairly similar in the both the age groups.

The peak pulmonary systolic pressure and mean pulmonary pressure in the study group were 25.06±5.36 mmHg and 18.39±4.3 mmHg respectively.

Table 2: Baseline hemodynamic characteristics of the study population

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<tr>
<th>Parameters</th>
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<td>14-50 (N=13)</td>
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<tr>
<td></td>
<td>mean</td>
<td>sd</td>
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<tr>
<td>BSA</td>
<td>14.99</td>
<td>2.99</td>
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<tr>
<td>ASD size</td>
<td>14.19</td>
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<tr>
<td>LA a</td>
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<td>1.82</td>
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<tr>
<td>LA v</td>
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<td>LA m</td>
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<td>Qp/Qs</td>
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<td>0.88</td>
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The sensitivity and specificity of a cardiac electrocardiogram (ECG) to predict Qp/Qs>1.5 in the study group were 73.07% and 63%, respectively. The sensitivity of electrocardiogram to predict high shunt
was significantly higher in patients below 14 years of age as compared to subjects above 14 years of age. However, the positive predictive value of ECG was 100% in predicting large shunt in the latter age group.

- Chest X-Ray (CXR) as a predictor of a large shunt had higher number of false positives as compared to ECG with a very low specificity and negative predictive value, albeit with a high sensitivity of 96.1%. This pattern of a very high sensitivity for Qp/Qs prediction and a low specificity and negative predictive value was seen across all age groups.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
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<tbody>
<tr>
<td>ECG</td>
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<td>&lt;14 years</td>
<td>92.3%</td>
<td>33.3%</td>
<td>85.7%</td>
<td>50%</td>
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<tr>
<td>&gt;14 years</td>
<td>53.8%</td>
<td>100%</td>
<td>100%</td>
<td>25%</td>
</tr>
<tr>
<td>Overall</td>
<td>73.07%</td>
<td>60%</td>
<td>90.4%</td>
<td>30%</td>
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<tr>
<td>CXR</td>
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<td></td>
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</tr>
<tr>
<td>&lt;14 years</td>
<td>100%</td>
<td>0%</td>
<td>81.25%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;14 years</td>
<td>92.3%</td>
<td>0%</td>
<td>85.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Overall</td>
<td>96.1%</td>
<td>0%</td>
<td>83.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 3: ECG and CXR as predictors of Qp/Qs ratio>1.5
- The mean peak pulmonary systolic velocity on pulmonary venous pulse Doppler was 59.16±21.29 cm/sec which was not significantly different across all age groups. The pulmonary venous pulse wave Doppler velocity time integral (VTI) was 24.06±6.28 cm and 28.33±10.08 cm in patients below and above 14 years of age respectively (p = 0.164).

- Pulmonary vein atrial reversal wave (Ar) wave was absent in majority of patients on baseline pulmonary vein Doppler, being appreciable in only 1 patient below 14 years of age and in 2 patients above 14 years of age.
Continuous antegrade wave (CAW) was seen in 16 patients (51.6%) out of 31 prior to ASD device closure, of which 7 were below 14 years of age and 9 were above 14 years.

Figure 2: Pulmonary Venous spectral Doppler in large atrial septal defect showing loss of distinct systolic and diastolic wave with presence of continuous antegrade wave (CAW)

- CAW as predictor of Qp/Qs >2.0 did not fare well as compared to ECG and CXR. Below 14 years of age, CAW had sensitivity and specificity of 45% and 29% to predict large shunt, respectively. However, in patients
above 14 years of age, CAW had positive predictive value of 50% to predict significant shunt.

**Table 4: CAW as predictor of Qp/Qs >2.0**

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAW &lt;14 years</td>
<td>44.4%</td>
<td>28.5%</td>
<td>44.4%</td>
<td>28.5%</td>
</tr>
<tr>
<td>&gt;14 years</td>
<td>27.2%</td>
<td>25%</td>
<td>50%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>35.0%</td>
<td>27.2%</td>
<td>46.6%</td>
<td>18.7%</td>
</tr>
</tbody>
</table>

- Pulmonary venous Doppler velocity time integral (VTI) indexed to body surface area (IVTI) predicted ASD shunt of >1.5 with sensitivity and specificity of 80% each whereas ASD shunt >2.0 could be estimated with sensitivity of 70% and 72.7% respectively.
Figure 3: Receiver Operating Characteristic Curve showing strength of Indexed Pulmonary Vein VTI to predict ASD shunt >1.5

Area under curve with 95% CI = 0.815 (0.670 - 0.971)
Cut off value of PV VTI - 21.05 cm/m²
Sensitivity 80.0% Specificity 80.0%
Immediately after ASD device closure, mean peak pulmonary systolic velocity decreased to 37.83±15.09 cm/sec which was significantly lower as compared to pre procedure systolic velocity \((p<0.001)\). Similar significant reduction were also seen in peak diastolic velocity after device closure with peak diastolic velocity coming down to 42.81±13.96 cm/sec \((p<0.001)\). Consequently, pulmonary venous Doppler velocity
time integral (VTI) indexed to body surface area (IVTI) also showed significant reduction from 1.54±0.62 cm to 0.89±0.54cm (p<0.001).

- This reduction of pulmonary systolic and diastolic mean peak velocity and pulmonary vein VTI was similar in patients above and below 14 years of age. The mean percentage reduction in systolic velocity was 31.12±17.87 vs 34.56±27.06 (p=0.698), in diastolic velocity was 31.02±17.72 vs 29.30±32.29 (p=0.864).

![Figure 5: Change in peak mean pulmonary systolic and diastolic velocity after device closure](image)
Heart rate was similar prior and immediately after device closure with no significant difference across all age groups. Mean heart rate prior and immediately after device closure was $96.90 \pm 16.91$ and $97.33 \pm 15.06$ ($p = \text{ns}$), respectively.

Continuous antegrade wave (CAW) which was present in 16 patients prior to device closure, disappeared in all the patients immediately after device closure. Post procedure, none of the patient had this pattern on pulse wave Doppler.

Atrial reversal wave (Ar) appeared in 14 patients immediately after device closure increasing from 9.7% to 45.2%. Mean peak Ar velocity in these patients was $20.44 \pm 6.19$ cm/sec with mean Ar VTI of $1.54 \pm 0.51$ cm.
Figure 7: Pulmonary Venous spectral Doppler before and after ASD device closure showing appearance of atrial reversal wave after procedure with reduction in systolic and diastolic velocities.
The mean follow up period was 7.86±1.97 months. On follow up, same parameters were recorded as was done immediately after post procedure. A total of 24 patients underwent follow up measurements.

On follow up after ASD device closure, mean peak pulmonary systolic velocity was 49.48±15.26 cm/sec which was significantly lower as compared to pre procedure systolic velocity (p<0.048). However, as compared to immediately after device closure, mean peak pulmonary systolic velocity showed a trend towards significant increment (p=0.052). This pattern of decrement of peak systolic velocity followed by increment at follow up was seen across all age groups.

Peak diastolic velocity on follow up was 53.45±15.27 cm/sec. Like systolic velocity, diastolic velocity was significantly lower immediately post procedure but then increased subsequently over follow up to pre procedure levels (0.298). This pattern of decrement followed by increment was seen in all patients whether less than 14 years or more than 14 years of age.

In contrast, IVTI decreased from the immediate post procedure level to 0.87±0.35 cm (p=0.737). However, this was significantly lower than the pre procedure indexed VTI i.e. 1.54±0.62 cm (p<0.001).
Figure 8: Change in pulmonary venous doppler velocities during the course of the study

Figure 9: Change in IVTI over the course of the study
On follow up, Ar was appreciable in 19 patients as compared to 14 patients immediately after device closure. The peak mean Ar velocity was 25.39±8.51 cm/sec while the VTI was 1.70±0.64 cm.

There was no significant difference in heart rate on follow up as compared to immediately after device closure (p=ns).

In patients below 14 years of age, while mean peak systolic velocity decreased immediately after device closure, on follow up this velocity increased by 37.79%. Similarly, diastolic velocity increased by 9.39% while
pulmonary vein VTI decreased by 9.39% and 18.01% respectively. In patients over 14 years of age, results were not significantly different. However, the increment in diastolic velocity was more pronounced in this group (p=0.03). The mean increment in systolic and diastolic velocity were 43.24% and 49.93%, respectively.

- In patients with cardiac catheterisation proven Qp/Qs shunt more than 2.0 as compared to patients with shunt of less than 2.0, ASD size showed a trend of larger in ASD in former group though it was not statistically significant (p=0.052). The mean size of ASD in former group was 21.1±7.1mm as compared to 15.91±5.9mm in latter.

- There was no significant difference between baseline mean peak systolic and diastolic velocity in patients with shunts more than 2.0 and less than 2.0.

- There was no significant difference in mean percentage fall of mean peak systolic and diastolic velocity immediately after device closure or on follow up. However, there was significant drop in IVTI immediately after device closure in the two groups (36.99±7.5 cm vs 24.61±6.8 ; p=0.05).
Figure 11: Sequential changes in pulmonary venous spectral doppler before and after procedure and on follow up.

Case 1:

Case 2:

Case 3:
DISCUSSION

To the best of the knowledge, our study is the first study which has assessed the changes in pulmonary vein pulse wave Doppler not only pre and post device closure but also on short term follow up.

In our study more than half of the patients were from paediatric age group with median age of the study population being around 11 years. However, similar studies had different patient population. Study by Lam et al\(^ {36}\) mainly involved adult patients with mean age above 32 years whereas study by Lin et al included both paediatric and adult patient like the current study. The gender ratio was, however, similar in all studies including our study which showed significant female predominance. \(^ {36-38}\)

The mean size of atrial septal defect in our study was around 20mm, with patients in pediatric group (<14 years) being 15mm and in adult group being 25mm which was fairly similar to other studies. \(^ {36,37}\)

The shunt across the ASD was more than 2.0 in two third of our study population which was also similar to other studies. While Lam et al involved patients equally with shunts less than and more than 2.0, Lin et al had pediatric patients with mean shunt less than 2.0 and adult patients with mean shunt of 2.5\(^ {36,37}\)
Our study did not involve many patients with pulmonary hypertension, being present in only 3 patients. This was in contrast to study by Lin et al where majority of patients had at least mild pulmonary hypertension\textsuperscript{37}.

Current study showed that electrocardiogram has a fair sensitivity and specificity to predict large shunt in ASDs whereas chest X-ray had high sensitivity with a low specificity to do the same. Previous study by Siddiqui AM et al also suggested a sensitivity and specificity of around 65\% to predict a shunt of more than 1.5.\textsuperscript{39}

The pattern of the pulmonary vein pulse wave Doppler showed a characteristic shape in which there was loss of distinct systolic and diastolic waves. Instead there was a single antegrade wave with two peaks starting from the onset of systole and extending till atrial systole, which has been previously termed as Continuous Antegrade wave (CAW).\textsuperscript{32,33} Our study showed that around 50\% of patients had similar pattern, though it was more indicative of the presence of an atrial septal defect rather than the shunt quantity.

The reason for such kind of pattern in ASD patients appears to be due to the presence of two outlets for left atrium as a result of which the gradient across pulmonary veins and left atrium is maintained during most parts of cardiac
cycle. Under normal circumstances, the first phase of systolic pulmonary vein flow is due to atrial relaxation immediately after atrial systole. This is followed by ventricular systole in which due to the right ventricular contractions, rate of pressure rise is greater in pulmonary veins as compared to left atrium. Eventually left atrial pressure rises and pulmonary vein flow declines for a brief period, starting again with onset of ventricular systole. In atrial septal defect patients, the left atrial pressure rise during ventricular systole is not sustained, as there is an interatrial communication. As a result there a gradient exists between pulmonary vein and left atrium even in late systole though to a lesser extent as compared to just after ventricular systole. Henceforth, the pulmonary vein pulse Doppler shows a continuous antegrade systolic flow which continues in the diastole. Though, the flow is continuous during most of the cardiac cycle, the systolic and diastolic peaks are well appreciable suggesting that the gradients between pulmonary vein and left atrium change during the cardiac cycle.

Absence of CAW pattern on pulmonary venous pulse wave Doppler neither confirms nor excludes atrial septal defect. Such pattern has been documented to be present in pulmonary vein stenosis, where again there is a continuous gradient between pulmonary vein and left atrium throughout the cardiac cycle. Similarly, patients with atrial septal defect can have distinct systolic and
diastolic waves if left atrial pressure are not affected by ASD, which is possible in case of small defects. However, though it seems plausible that presence of CAW pattern would suggest to predict a large shunt across ASD, as the size of defect in such patients would be large, in our study this was not the case. Presence of CAW could predict a large shunt in only around of the cases correctly which again proves that the shunt across ASD not only depends on the defect size but on the compliance of the two ventricles as well. There have been other studies which have studied pulse wave Doppler patterns of atrial septal defects patients and have not found any conclusive presence of such pattern. 36,37

In normal children, the pulmonary vein pulse wave Doppler shows distinct systolic and diastolic waves with the latter wave being more prominent and the S/D ratio being less than 1.40 However, our study clearly demonstrated that the systolic wave is atleast as prominent as diastolic wave with a mean S/D ratio >1. Previous studies have also suggested the systolic prominence in ASD patients.38,41 The explanation for such pattern could be understood by the application of Frank Starling law. Such patients are volume overloaded on right side due to the left to right shunt across ASD. As a result, there is a greater longitudinal myocardial fibre contraction of right ventricle which in turn leads to greater apical systolic displacement of the tricuspid valve, decreasing right
atrial pressure. This facilitates a ‘sucking effect’ where blood is sucked from the superior and inferior vena cavae and also from the left atrium. This flow from left atrium causes a dip in its pressure thereby facilitating the pulmonary venous flow to left atrium. Infact, other studies have showed systolic prominence of flow in SVC and IVC in ASD patients.42

Our study is the first one to analyse changes in pulmonary flow after ASD device closure on a short term follow up other than immediately before and after device closure. The results of this study showed that both the mean peak systolic and diastolic velocity came down significantly along with indexed pulmonary vein velocity time integral immediately after ASD device closure. This was concurrent with other similar studies which have assessed pulmonary flow immediately after ASD closure.36,37,43. Our study also showed that there was disappearance of CAW pattern in all patients, if present previously. This significant fall in all the parameters of pulmonary flow could be explained by cessation of the shunt flow across atrial septal defect. After device closure, LA becomes a closed chamber with only mitral valve as its outlet in contrast to two outlets prior to device closure. As a result, during late systole rate of pressure rise in LA is higher as compared to pre-procedure resulting in decreased amplitude of pulmonary vein systolic wave on pulse wave Doppler. Similarly during the diastole, LA can now empty only through mitral valve, and
therefore the LA pressure are higher as compared to the patients with ASD which again leads to reduced diastolic wave velocity.

Interestingly, the systolic and diastolic wave velocities increased on follow up pulse wave Doppler as compared to the immediate post procedure period. This finding has been observed for the first time to the best of the knowledge. However, it is difficult to explain the increase in systolic and diastolic velocities. The most plausible explanation, is an increase in LA compliance after ASD closure. Immediately after device closure, there is sudden overloading of left atrium which may lead to a decrease in pulmonary venous flow velocities. However, over a period of time left atrium may increase in its compliance and thus restoring the pulmonary flow velocities.

Normally, pulmonary venous Doppler shows an atrial reversal wave which occurs during late diastole due to the left atrial contraction which leads to transient reversal of flow in pulmonary veins. Our study found that patients with ASD usually do not have atrial reversal wave on pulse Doppler which could be explained by the fact that the atrial contraction would not increase left atrial pressure due to septal defect. As a result the flow in pulmonary veins may not get reversed. And as expected, after device closure, atrial reversal wave appeared in around half of the patient population and two third of patients on
follow up. This absence of atrial reversal wave and its reappearance after device closure was also observed in other studies.\textsuperscript{36,37,43}

Our study also attempted to link the pattern of pulmonary venous pulse wave Doppler with shunt quantification. Although, presence of continuous antegrade wave had a low sensitivity and specificity to predict large shunt, pulmonary venous velocity time integral was found to have better correlation for estimation of ASD shunt. However, pulmonary venous flow depends on a number of other factors like heart rate, body surface area and other factors. Thus, velocity time integral indexed to body surface area appeared to be a better correlate than absolute VTI. Like the study by Lam et al\textsuperscript{36}, our study also showed that a higher pulmonary VTI indexed to body surface area can predict a large shunt in ASD with a high sensitivity and specificity. And this parameter can be used with other echocardiographic parameters and non invasive investigations to decide on intervention in such patients.

In the current study, we have observed that PV-VTI is a simple and sensitive parameter for the quantification of Qp/Qs ratios in patients with secundum ASD. As a dimensionless parameter, it does not require geometrical assumptions or meticulous measurements of outflow tract dimensions and therefore minimizes errors. Therefore, we suggest including assessment of pulmonary venous velocity-time integral when evaluating patients with
suspected ASD. This may improve diagnostic sensitivity especially in patients with far-field drop-out artifacts at interatrial septum level.

More importantly, this novel dimensionless parameter provides additional information about the magnitude of left-to-right IAS in ASD patients.

Pulmonary veins have long been studied for assessing diastolic dysfunction including patients with restrictive cardiomyopathy. This study further strengthens the utility of pulmonary vein Doppler in a different subset of patients and holds a promising future.
CONCLUSION

➢ Patients with atrial septal defect have a distinguishable pulmonary vein pulse wave Doppler pattern which includes presence of continuous antegrade wave and a high pulmonary vein velocity time integral.

➢ PV-VTI can be used as a novel tool for assessing shunt quantity.

➢ The pulse wave Doppler pattern usually normalises immediately after device closure of atrial septal defect.

➢ These changes are seen in patients across all age groups, however the changes are slightly more pronounced in pediatric patients and in patients with large shunt.
REFERENCES


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