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A STUDY OF SUPERIOR VENACAVA, HEPATIC VENOUS PULSE WAVE DOPPLER IN OSTIUM-SECUNDUM ATRIAL SEPTAL DEFECT PATIENTS -- BEFORE AND AFTER DEVICE CLOSURE.

PROJECT REPORT

Submitted during the course of

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DECLARATION

I, Dr. Amitabh Poonia , hereby declare that the project in this book, titled **"A STUDY OF SUPERIOR VENACAVA, HEPATIC VENOUS PULSE WAVE DOPPLER IN OSTIUM-SECUNDUM ATRIAL SEPTAL DEFECT PATIENTS -- BEFORE AND AFTER DEVICE CLOSURE. "** was undertaken by me under the supervision of the Faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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A STUDY OF SUPERIOR VENACAVA, HEPATIC VENOUS PULSE WAVE DOPPLER IN OSTIUM-SECUNDUM ATRIAL SEPTAL DEFECT PATIENTS --- BEFORE AND AFTER DEVICE CLOSURE.

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Amitabh poonia

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ABBREVIATIONS AND ACRONYMS:

ASD - Atrial septal defect

A-WAVE – Diastolic flow reversal wave during atrial contraction

DC - Device closure

D-WAVE- Diastolic forward flow wave

EXP. - Expiration

HV- Hepatic veins

INSP. - Inspiration

IVC – Inferior venacava

OS-ASD- Ostium secundum atrial septal defect

RA- Right atrium

RV- Right ventricle

SVC- Superior venacava

S- WAVE- Systolic forward flow wave

VTI- Velocity-time integral

V- WAVE- Systolic flow reversal wave

INTRODUCTION

Atrial septal defect (ASD) is the second most common congenital heart disease, after ventricular septal defect. [1, 2] Atrial septal defect provides a unique model of cardiac hemodynamic wherein one can understand the filling pattern of left ventricle (LV), right ventricle (RV) along with pulmonary and systemic venous return 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.[3, 4] Investigators have also shown regression of pulmonary hypertension after closure along with reduced incidence of atrial arrhythmias in such patients.[5-7]

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. Various studies[8-11] in the past has shown that there are peculiar changes in systemic or pulmonary venous flow pattern in various underlying cardiac pathology including ASD which not only correlates with the amount to left to right in

ASD but also with the state of underlying ventricular function, chamber compliance and pressures.

Though the standard treatment for ostium primum and sinus venosus ASDs is still surgical, in past two decades ostium secundum ASDs (OS-ASD) have come under the purview of transcatheter closure[12, 13] and percutaneous closure of secundum ASD has become the treatment of choice in majority of centers in suitable cases. Percutaneous closure offers numerous advantages over the conventional bypass surgery including lower complication rates and shorter hospital stays.[14] It is also reported and emphasized that after surgical closure of ASD the underlying altered hemodynamic of ASD does not becomes fully normal, and a restrictive filling pattern of right heart develops and persists on long term follow up.[15-17] Though there are infrequent reports of device thrombosis[18] device erosions[19], residual shunt, the filling pattern of right heart after percutaneous device closure has rarely studied.[20]

This study was formulated to understand the change in cardiac hemodynamics before and after ASD percutaneous closure by assessing the Doppler flow patterns in hepatic veins (HV), superior venacava (SVC) 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.

AIMS AND OBJECTIVES

- To study the superior venacava and hepatic venous flow patterns in OS-ASD patients and understand the hemodynamics in the presence of atrial septal defect.
- To study the effect on Hepatic veins and Superior venacava flow patterns after device closure and on 6 months follow up.
- To analysis the effect of defect size/used device size on the flow pattern.

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 venacava (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.

Anatomy, physiology and Doppler flow of hepatic veins

Anatomy: --

The hepatic veins are the largest visceral tributaries of the inferior vena cava. They originate in the liver, returning blood from the liver and drain into the inferior vena cava. Their minor tributaries-right hepatic vein in the right lobe, middle hepatic vein in the left lobe, and left hepatic vein in the left lobe-empty into the inferior vena cava at the level of the diaphragm.[21.]The normal diameter of the hepatic veins is 0.5 to 1.1 cm.

Pulsed-wave Doppler examination of the hepatic veins: --

The hepatic veins are best imaged by use of the subxiphoid approach. Usually, the right hepatic vein is visualized and the pulsed-wave Doppler sample volume placed within the vein approximately 1 to 2 cm from its junction with the inferior vena cava.[22] Normal flow Doppler of hepatic veins is shown in ***Figure 1***.

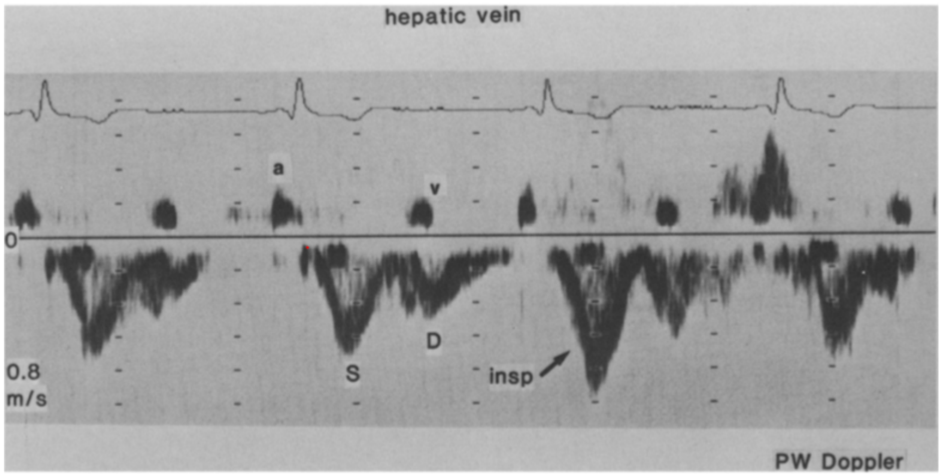

Figure 1. *Flow Velocity curve of a normal hepatic vein. Forward (negative) flow is evident during both systole (S wave) and diastole (D wave; systolic flow is greater than diastolic flow). There is a small reversal at the time of atrial contraction (A wave) and a small reversal may be seen at end-systole (V wave). Note the increase in forward flow with inspiration (insp; arrow). PW, Pulsed wave.*

Blood flow within the hepatic vein is continuous throughout the cardiac cycle; that is, flow occurs throughout systole and diastole. Normal hepatic venous flow is characterized by four distinct waveforms[22, 23]: (1) systolic forward flow (S-wave), (2) ventricular (systolic) flow reversal (V-wave), (3) diastolic forward flow (D-wave), and (4) atrial reversal of flow (A-wave).

Systolic forward flow (S-wave) occurs as a result of right atrial relaxation and the descent of the tricuspid annulus toward the cardiac apex with ventricular systole. Flow is directed away from the transducer and, therefore, is displayed below the zero baseline.

Diastolic forward flow (D-wave) starts with opening of tricuspid valve, the rapid filling phase of diastole, and ends with the onset of atrial contraction. Diastolic forward flow velocity is usually slightly lower that the systolic forward flow velocity. As for systolic forward flow, diastolic forward flow is directed away from the transducer and, therefore, is displayed below the zero baseline.

Atrial flow reversal (A-wave) refers to the retrograde flow of blood back into the hepatic veins secondary to atrial contraction. The A wave is small in normal individuals and may not be recorded in a small percentage of individuals.[23] Atrial flow reversal is directed towards the transducer, therefore, appears above the baseline.

Ventricular flow reversal (V-wave) refers to the retrograde flow of blood back into the hepatic vein occurring in late systole which corresponds to the atrial V wave on the right atrial pressure curve. Out of all above 4 waves, this is the wave which presents least commonly. The velocity of this flow is slightly lower than the atrial flow reversal velocity. When present, this flow is directed toward the transducer and, therefore, is displayed above the zero baseline.

Respiratory variation of hepatic venous flow:

It is important to recognize that the flow velocities of the hepatic veins vary throughout respiration. During inspiration, there is an increase in the systolic and diastolic forward velocities.[22] Ventricular flow reversal is usually more evident during expiration and decrease in size/disappears during inspiration.[22]

Anatomy, physiology and Doppler flow of superior venacava.

Anatomy:

The superior vena cava returns the blood from the upper half of the body and opens into the cranial and posterior part of the right atrium. Its orifice faces caudalward and ventralward so that the blood entering the atrium is directed toward atrioventricular opening. There is no valve at its opening.[21]

Pulse Doppler Examination of the Superior Vena Cava:

The Doppler interrogation of the superior vena cava (SVC) is best achieved from the suprasternal notch or from the right supraclavicular fossa. The optimal signal is usually obtained by placing the Doppler sample volume at a depth of between 5 and 7 cm.[22] Correct placement of the sample volume may be facilitated by the use of CFI. With CFI, blue laminar flow down the SVC toward the right atrium can be readily appreciated in most cases. In children the SVC Doppler can be obtained through the subxiphoid approach, where the optimal signal is usually obtained by placing the Doppler sample volume at 1-2 cm. proximal to the SVC-RA junction.

Normal SVC flow is also continuous throughout the cardiac cycle and characterized by three or rarely four distinct waveforms, similar to previously described waveform of hepatic veins[23]: (1) systolic forward flow (S-wave), (2) diastolic forward flow (D-wave), and (3) atrial reversal of flow (A-wave). Rarely, a fourth waveform, representing ventricular flow reversal (V-wave), is seen. Ventricular flow reversal is usually absent in the normal individual except with expiration[23, 24] When present, this flow is directed toward the transducer and, therefore, is displayed above the zero baseline. In the normal heart, the largest amount of antegrade blood flow is during systolic forward flow (S-wave) phase.[25]

In SVC flow the mechanism behind the genesis of different wave pattern is similar to previously described mechanism in hepatic venous flow. It should be noted that the systolic and diastolic forward flow velocities within the SVC are higher than those obtained from the hepatic veins. In contrast, reverse flow velocities of the hepatic vein are more prominent than those of the SVC. Possible explanations for this increase in hepatic venous flow reversals include variations in the pressure difference between the abdominal and thoracic cavities, and/or the closer proximity of the hepatic vein to the right atrium.[24, 26] The pulsed-wave Doppler tracings of the SVC are similar to those obtained from the hepatic veins except that the A and V wave reversals are usually less prominent.[21, 24, 26] Although not studied formally, this may be because of pressure differences in the abdominal and chest cavities with respiration.[21]

Respiratory variation of SVC flow:

As for the hepatic vein, flow velocities of the SVC vary throughout respiration. During inspiration, there is an increase in the systolic and diastolic forward velocities. Ventricular flow reversal is usually more evident during expiration and decrease in size/disappears during inspiration.[22]

Relationship of Magnitude between the S and D Waves.

In the normal hepatic vein waveform, the S wave is larger than or equal to the D wave.[25] The main two factors are responsible for this; one, large compliance and capacity of the right atrium to accommodate large amount of blood when the tricuspid valve is closed, two, the powerful systolic movement of the tricuspid annulus toward the cardiac apex causes a further increase the RA capacity leading to a large antegrade rush of blood toward the heart along with the pressure gradient.

Many studies has supported the view ,that systolic acceleration of blood flow into the right atrium originated from both atrial relaxation and downward displacement of the closed tricuspid floor.[27]

In heart diseases, like right ventricle systolic or diastolic dysfunction, right heart failure which cause elevated RV or RA pressure, decreased RV or RA compliance or decreased systolic apical movement of tricuspid valve, a greater antegrade blood flow will be seen during diastole.[28] This also gives a decreased or even a retrograde S wave. As the ventricle begins to relax and the tricuspid annulus returns to its original position, blood is forced out of the atrium again back into the IVC and liver, giving a retrograde V wave. Finally, during cardiac diastole, with the tricuspid valve open and the myocardium resting, blood flows passively from the liver into the right side of the heart, yielding the larger or only antegrade wave, the D wave.

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 pressures 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 and atrial compliance. 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.

Characteristic of flow Doppler through atrial septal defect: ---

Through the subcostal view with the pulsed-wave Doppler sample volume in the right atrium adjacent to the suspected defect, a characteristic audio and spectral flow velocity profile of the left-to-right shunt can be obtained. The spectral display consists of low velocity (0.2 to 1.0 m/sec) flow that peaks in late ventricular systole, reaches a second peak in early diastole, declines in mid diastole, and is accentuated with atrial systole.[21]

Many studies [8, 29, 30] has been conducted in the past to analyse the flow pattern through the ASD. It was concluded that apart from a minute right-to-left shunt in early systole, the shunt occurs from left to right throughout late systole and diastole, but displays in the typical pattern 3 distinct waves of acceleration: a late systolic (S) wave prolonged into early diastole, a mid-diastolic (D) wave, and a late diastolic (A) wave during atrial contraction.[8] ***(Figure 2.).***

The respective amplitude of these 3 waves varies appreciably depending on respiration, heart rate, and other factors. The S and D waves may be fused, giving rise to a large shunting wave encompassing late systole, early, and mid-diastole.[8]

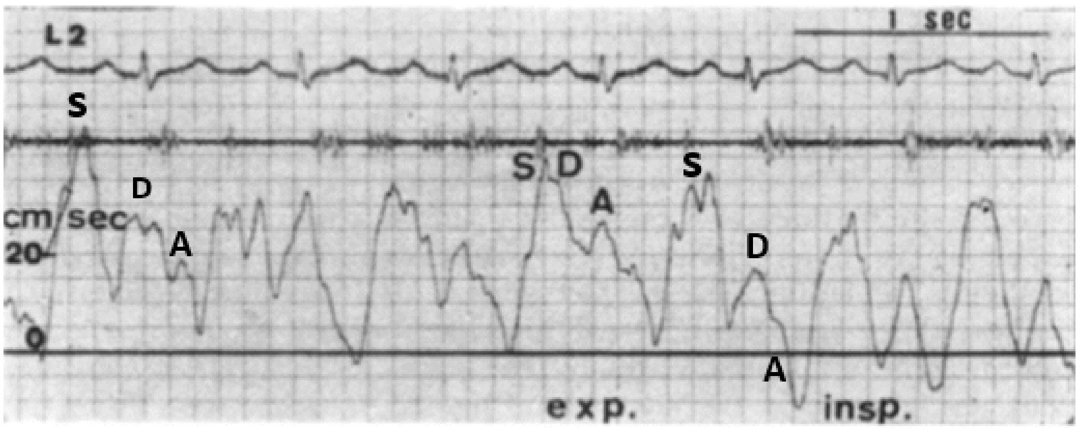

Figure 2. *Flow velocity tracing of an atrial septal defect shunt, recorded by Doppler catheterization. The left-to-right shunt has three major components: S, late systolic and early diastolic, D, mid-diastolic, and A, end-diastolic. Some of the S and D wave are fused. The negative early systolic wave is present only during inspiration (two last complexes) which decreases the positive velocities, and increases the negative ones.*

It is noteworthy that a general agreement in above mentioned major findings was there in many of major studies[30, 31] though these were at some variance with each other. Gamble and coworkers[29] using fiber-optics, found a three-wave pattern, whereas Levin and collaborators[30] studying the interatrial pressure gradient as well as biplane cineangiocardiography, reported a double wave pattern. The discrepancy between the findings of these authors can be explained by the possibility of occurrence of both the patterns. The variability of the shunt velocity pattern could also explain some of the variations encountered at the level of the jugular venous flow velocity trace.

Effect of ASD shunt flow on systemic venous return:

It is very logical to anticipate that ASD - a disease that obviously interferes with the filling of the right atrium would be likely to disturb venous return and therefore affect the pattern of the systemic venous flow velocity waves. Flow of systemic venous return and ASD in various cardiac cycle phase is shown in **figure 3.**

Many studies[8, 20,] has conducted to analyse the flow pattern of systemic and pulmonary venous return in the presence of underlying ASD and found that in the patients with ASD the basic anomaly in the flow starts at end-systole. In typical cases, the curve, after a normal ascent during early and midsystole suddenly shows a premature, more or less precipitous, descent, i.e. occurring before its normal timing. The trace then falls down, crosses the zero line before, at the time of, or closely after the pulmonary component of the second heart sound. Thereafter the curve displays an entirely negative wave, more or less deep, triangular in shape.

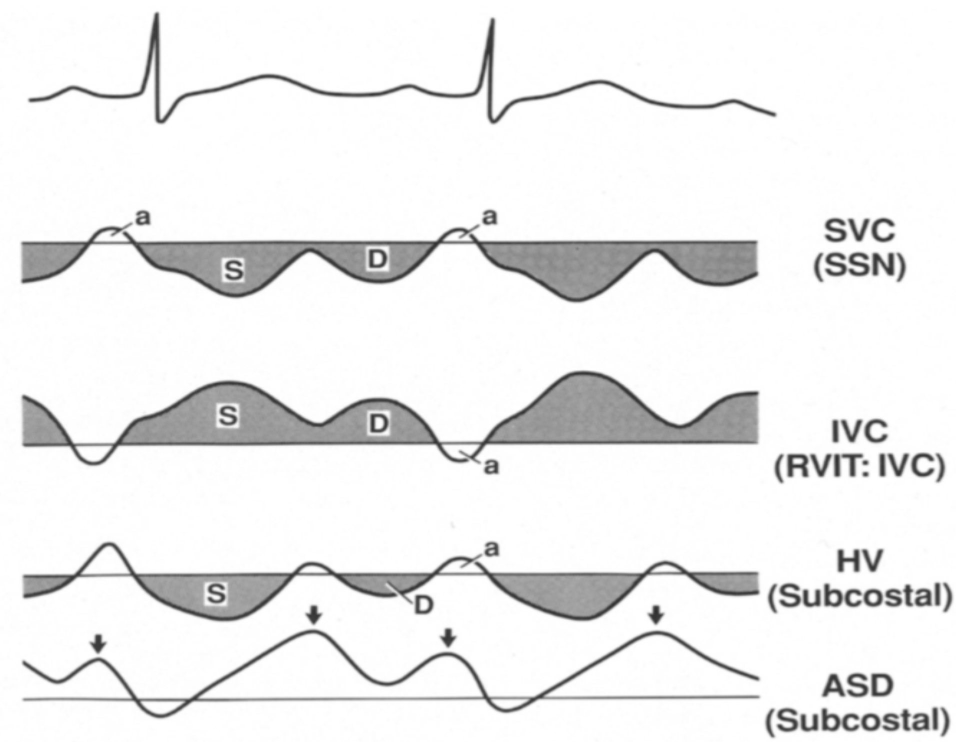

Figure 3. *This schematic figure shows the electrocardiogram and the normal pulsed-wave Doppler waveforms for right atrial venous inflow as well as the spectral waveform for an atrial septal defect (ASD). Note the similarities in the timing of the peak flow velocities for the superior vena cava (SVC), inferior vena cava (IVC) , and hepatic vein (HV), which occurs in midsystole and early diastole (shaded areas of SVC, IVC, and HV). The peak flow velocity in an ASD occurs during late systole and with atrial contraction (arrows). The nadir of ASD flow occurs in early ventricular systole, whereas venous inflow begins to peak. Also, remember that in response to inspiration, flow will decrease across the ASD, whereas venous flow will increase (not illustrated). SSN, Suprasternal notch; RVIT, right ventricular inflow tract.*

It is followed by a positive d wave, usually decreased in amplitude (in the typical pattern). The end-diastolic a wave is also in typical cases clearly diminished in amplitude compare to healthy individuals and can even become positive. The amplitude of the V and A waves may be equal, and even the V point may appear below the level of trough of the A wave as shown in ***figure 4.***

This pattern may be subject to some variations. The summit of the S wave may be of normal timing or the d wave may have a normal height or the A wave may not be decreased. But in all cases, the basic anomaly remains consisting of the amputation of the s wave in late systole, the crossing of the zero line in the neighbourhood of the second heart sound (pulmonary component), and the occurrence of a clear-cut negative, triangular wave of late systolic and/or early diastolic timing.

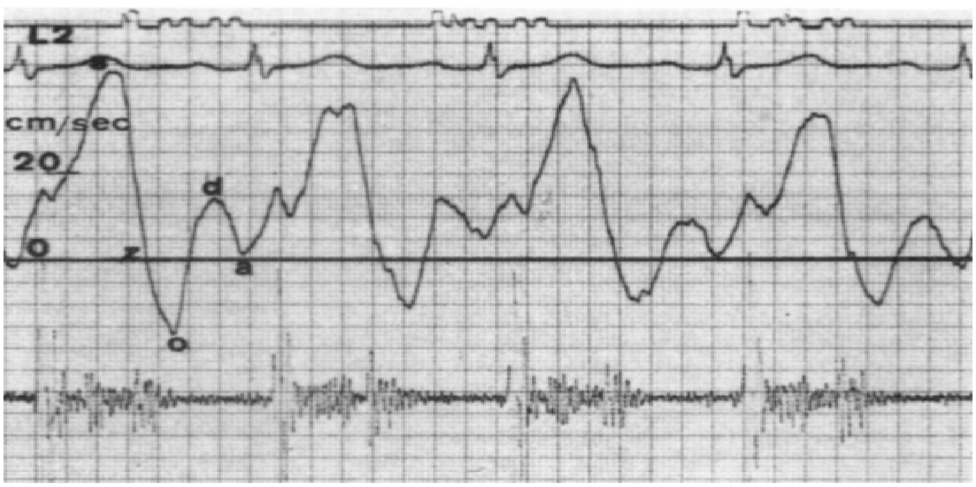

Figure 4. *Jugular venous flow velocity in atrial septal defect. The summit of the S wave clearly occurs earlier than normally. Note the precipitous fall of the descending limb of the S wave, the appearance of a deep negative wave encompassing late systole and early diastole, and the small amplitude of the d wave. The A wave is no longer negative.*

In summary, the systemic venous flow velocity curve consists of a general decrease of the end-systolic, mid-diastolic, and sometimes presystolic parts of the traces, and, most important, of an end-systolic and/or early diastolic negative wave.

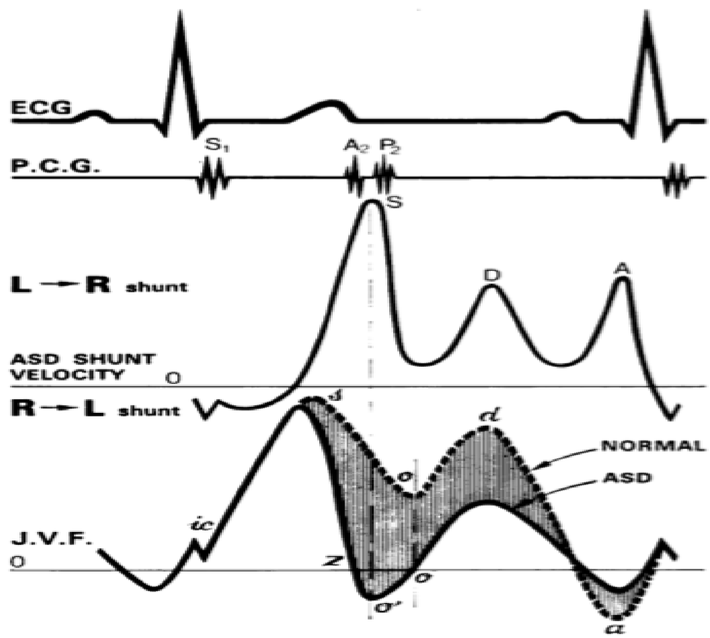

Figure 5. *Schematized relation between jugular venous flow velocity and shunt velocity curves in atrial septal defect in sinus rhythm. From top to bottom: electrocardiogram, phonocardiogram shunt velocity, and jugular venous flow velocity traces. In dotted line, the normal pattern; in bold line, the atrial septal defect pattern. Hatched area stresses the difference of velocity waveform of jugular venous flow velocity between normal and atrial septal defect cases. The atrial septal defect shunting pattern chosen here is a three wave pattern. The premature summit of the S wave lines up with the beginning of the S curve of the shunt. The jugular venous flow velocity curve of a patient with atrial septal defect appears roughly to be derived from the normal pattern by subtracting the amplitude of the atrial septal defect shunting velocity curve, except for the end-diastolic part. The S and D waves correlate well with the anomalies of the jugular venous flow velocity curve.*

Interpreted in terms of hemodynamics, these findings suggest a slowing down of the inflow into the right atrium at three different periods of the cycle: late systolic, mid-diastolic, end diastolic, and, most important, a reversal of flow at end-systole and/or early diastole ***(Figure 5).***

It seemed reasonable to assume that these effects of slowing down and reversal of blood flow were intimately related to, and most probably provoked by, the eruption of blood into the right atrium from the left atrium, through the septal defect, competing with, and thus impeding, the normal filling procedure of the right atrium from the caval system.

Figure 5 shows the satisfactory relation between the jugular venous flow and the atrial septal defect shunt velocity traces: the jugular venous flow velocity curve appears to be drawn from the normal pattern after 'subtraction' of the atrial septal defect shunt velocity curve, except for the a wave. In other words, the timing and pattern relation of both curves seem to support the assumption of a direct haemodynamic influence of the shunt flow upon the venous return, and in particular as seen from the jugular venous flow.

There is no direct evidence to account for the discrepancy of the juglar a and shunt A waves. One could indeed anticipate that the shunt wave during atrial contraction would enhance the normally occurring backflow into the cavae, which is not the case, since the A wave is usually decreased in depth. Only a hypothesis can be proposed. It has been suggested [31] that during atrial contraction the right atrium may be divided into two parts separated geographically by a 'watershed'. Above this line, blood flows back into the caval system, and below it, it flows down towards the right ventricle. It could be assumed that the pathological alterations of the right atrium may induce a shift of the line of 'watershed' towards the orifices of the cavae. This hypothesis was never been investigated further.

Patients with right heart diseases and without atrial septal defect. Most exceptionally the above-mentioned pattern could be elicited. Even in cases of tricuspid insufficiency, where the S wave may be biphasic, the overall pattern is different, in particular the amputation of the S wave starts in early systole, the S wave is decreased, and the d wave is considerably increased.

Respiratory variations of ASD and systemic venous flow:

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 respiration on ASD shunt flow (shown in **figure 2**) is also well studied in various studies in the past and found that the Inspiration decreases and expiration increases the magnitude of the positive shunt velocities, and have the opposite effects on the negative ones.[8, 20]

The effect of respiration on systemic venous return flow has somewhat reverse of what is seen on ASD shunt flow. In systemic venous in inspiration there is increase in the S and D waves similar to the pattern of normal healthy individuals.[8, 20] In some instances during inspiration the systolic flow reversal decreased to disappear so that the traces looks like a normal pattern. But in all cases, at end expiration, the typical anomalous pattern can be elicited. In rare instances, the whole systemic venous flow velocity curve is situated well above the zero line, due to the superimposition of continuous flow to the pulsatile flow.

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.

Diagnostic value of the venous flow velocity curve.

For many years attempts have been made to prove the diagnosis of atrial septal defect by non-traumatic techniques, especially the recording of the jugular venous pulse. The occurrence of a tall, peaked V wave, clearly over-topping the summit of the A wave (V/A ratio more than 1) has been shown to be highly consistent with the diagnosis of atrial septal defect with normal pulmonary arterial pressure.[32, 33] the reliability of such an abnormnal pattern is usually considered as very high, but the frequency of its occurrence remains controversial, and reported from 100% [32] to, less than 50%.[33]

It should be keep in mind that the jugular venous pulse curve reflects the absolute value of the pressure within the internal jugular vein (and in the right atrium), which may not be affected by the interatrial shunt, especially if the latter is not very large. The reason for this is that the magnitude of the shunt is not related to the pressure in the right atrium, but to the interatrial pressure gradient.

On the other hand, the jugular venous flow velocity curve reveals the alterations of the instantaneous velocity of blood flow, a much more sensitive parameter to haemodynamic disturbances because it is precisely determined by pressure gradient.[27] The juglar flow velocity assessment is the more sensitive parameter compare to JVP assessment to diagnose the presence of ASD.

Cardiovascular change after closure of ASD.

After ASD closure the resolution of all the underlying abnormalities are expected, however it does not always happens. It is reported that after closure of ASD normalization of cardiac chambers does not occurs in many of the patients including children[3, 34, 35, 37] and adults.[4, 6, 36-39] In contrast to the regression of right heart enlargement and increased left ventricular volume, left atrial size does not seem to react on ASD catheter closure and children do not differ from adults in this aspect.[3, 4, 6, 34-39]

In a short-term study in young patients (mean age 22 years) right atrial size diminished markedly while left atrial size remained unchanged after catheter closure of the ASD[6]. However, it seems that the right heart remodelling is an early event which diminishes in rate and is more or less finished after 6 months[6].

It has been reported that after surgical closure the Doppler flow anomalies did not disappear completely but only partially regressed or worsen, in spite of complete closure. This embarrassing finding has been attributed to the fact that after the surgical closure of the atrial septal defect, the right atrium, keeping its anomalous compliance[33] or altered by surgery does not return to a normal anatomical and haemodynamic state.

This reversal pattern was more severe in immediate post-surgery which improve a little on follow up but still diastolic filling remains larger than systolic filling. The findings were explained of the basis of two hypothesis. One, a large pericardium patch (which is a non-compliant, fibrous structure), post-surgical edema and scar on incision site cause a decrease in the compliance of RA leading to decrease in systolic filling and a compensatory increase in diastolic filling (as during diastolic filling RA acts as conduit only). Two, a sudden decrease in left to right shunt decrease pre-load and creates negative inotropic effect on RV leading to lesser apical movement of tricuspid valve decreases the RA capacity and decrease systolic filling. Other studied has confirmed convincingly that the first hypothesis appears more correct as the effect on tricuspid valve apical movement and RV contractions is not significantly different in post-surgical ASD closure.

In a recent study[20], it is shown that systemic venous flow pattern changed not after catheter closure but after open-heart surgery although the size and shunt volume of ASD in the catheter closure group were smaller than those in the surgical group. In all cases in the surgery group, D waves were larger than S waves and D/S was more than 1 after the treatment.

These changes in flow velocity pattern from the normal dominant systolic flow to dominant diastolic flow were first described as an alteration in jugular venous flow velocities after open-heart surgery[10, 40]. Wranne et. al.[41] reported that the abnormal pattern of SVC flow is present up to 6 months after surgery (the end of follow-up), although it is not as pronounced as in the early postoperative period.

The operation of ASD produces right atrial trauma and edema and increases right atrial stiffness, which in combination with poor preservation of the right atrium could affect both atrial contractility and relaxation, thereby decreasing systolic forward flow.

Wranne et al.[41] suggested that the change in venous pattern may be secondary to the decrease in tricuspid annulus motion. Ochi et al.[42] reported that atrial relaxation rather than systolic descent of the tricuspid annulus was the predominant factor determining systolic forward flow in the SVC.

It is reported that the flow velocity of the SVC both in the catheter group and in the surgery group increased during inspiration before the therapy.[20] However, the change of flow velocity during respiration became smaller after the therapy in the surgery group. It may be because there is less reserve ability in the right atrium of patients who underwent open-heart surgery.

ASD closure device is made up of nitinol alloy with mash fiber embedded into it. The metallic device is also a noncompliant rigid structure and a decreased RA compliance is expected in device closure patients similar or near similar to the surgical patch closure patients, but the effect on RA compliance in ASD device closure patients are rarely studied. In a smaller study[20] of 10 device closure and 30 surgical closure patients it was found that device closure has no impact on RA compliance while patch closure does. It needs a larger study to confirm the finding prior to reach on a conclusion.

In the present study we have studied the normal Doppler pattern in ASD patients and the change in pattern in post device closure.

As mentioned earlier that left to right shunt in ASD competing with, and thus impeding, the normal filling procedure of the RA. Because the left to right shunt occurs predominantly during systolic phase and causing impairment in

RA filling more during systolic than diastolic phase, a smaller D wave, larger S wave and a larger D/S ratio compare to normal people can be expected in ASD patients. By closing the defect a reversal of the pattern can be expected if the device or the patch closure does not have any impact on the RA compliance/RV functions.

Materials and methods

Setting: Department of Cardiology, SCTIMST, Trivandrum, India

Study period: January 01, 2017 to December 30, 2017

Study Design: This is a prospective Observational study (approved by the Institutional Ethics Committee, No: - SCT/IEC/1007/DECEMBER 2016)

Inclusion criteria:

All consecutive patients, irrespective of age, sex who have undergone isolated ostium secundum atrial septal defect device closure from January 01, 2017 to December 30, 2017 were enrolled. This study aims to study the pulse Doppler flow pattern in hepatic veins, superior venacava of atrial septal defect patients, before, immediately (within 24 hours) after device closure and after a minimum follow up period of 6 months.

Exclusion criteria:

- Atrial septal defect other than ostium secundum type.
- Patients with associated other intra-cardiac shunt, or valvular lesion.
- Patients who were not suitable for percutaneous device closure.
- Patients who did not give consent to participate in the study.
- Patients with underlying right or left ventricular dysfunction

- Patients with more than moderate pulmonary hypertension.
- Patients with more than mild tricuspid regurgitation.

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.
- Hepatic venous and superior venacava flow Doppler was recorded in all patients after admission for device closure, using i-33 Phillip's echocardiography machine.
- The Doppler interrogation of hepatic venous flow was done from the subcostal long axis view of the inferior vena cava (IVC). The PW Doppler sample volume (2 mm gate) was placed 1 to 2 cm into the hepatic vein proximal to its junction with the IVC.
- The Doppler interrogation of superior venacava flow was done either from the subcostal long axis view or from right supraclavicular fossa. During measuring doppler from subcostal long axis view the doppler sample volume (3-5 mm gate) was positioned at 1 to 2 cm proximal to

SVC-RA junction while during measuring from the suprasternal notch or from the right supraclavicular fossa the pulse wave Doppler sample volume (3-5 mm gate) was positioned at a depth of 5 to 7 cm into the SVC.

- Electrocardiogram and respirometer were used during echocardiography to localize the phases of Doppler flow and to see the respiratory variation of flow.
- The flow was measured in the form of peak flow velocities, mean flow velocities and velocity time integral (VTI).
- Late phase of expiration and early phase of inspiration phases were taken to see the respiratory variation of the flow.

Statistical analysis

- The data was analysed 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

In this study total 50 patients completed full follow up and were included in final calculation. Baseline demographic profile of study population is shown in **table 1**. The mean age of the study population was 19.14±18.8 years while the median age was 9 years. Pediatric age group (<14 years) was the major group with 33 patients and 17 patients were in adult age group (>14 years).

Female sex was the predominant study population including 32 patient while male patients were 18 with a female: male ratio of 1.78 **(Figure 6).**

Mean weight of the patients was 34.37+/-19.65 kilogram, mean height 131.86+/-21.95 centimeter and mean body surface area was 1.1+/-0.40 sq. meter.

Mean atrial septal defect (ASD) size was 16.1+/-5.55mm and the mean size of used device was 19.42+/-6.14mm. To neutralize the effect of wide range of body size and body surface area an indexed ASD size was calculated. Mean indexed ASD size was 15.66+/-5.35cm/sq. meter and mean indexed ASD device size was 19.03+/-6.47mm/sq. meter.

Depending upon availability of suitable size different devices were used for defect closure including cocoon device in 17 patients, AGA in 15 patients, heart-R in 7 patients, pushmed in 8 patients, amplatzer in 1 patient, figulle flex II in 1 patient and occlutech in 1 patient **(Figure 7).**

Table 1. *Baseline demographic profile of study population*

	MEAN (+/- SD)
MALE	18
FEMALE	32
AGE(YEARS)	19.14 (+/-18.87)
WEIGHT(Kg.)	34.37 (+/-19.65)
HEIGHT (cm.)	131.86 (+/-21.95)
BODY SURGACE AREA (Sq. meter)	1.1 (+/-0.40)
ASD SIZE(mm)	16.1 (+/-5.55)
INDEXED ASD SIZE(mm/Sq. meter BSA)	15.66 (+/-5.35)
DEVICE SIZE(mm)	19.42 (+/-6.14)
INDEXED DEVICE SIZE(mm/Sq. m. BSA)	19.03 (+/-6.47)
COCOON	17
AGA	15
HEART R	7
PUSHMED	8
OTHER DEVICES	3
PEDIATRIC AGE GROUP	33
ADULT AGE	17

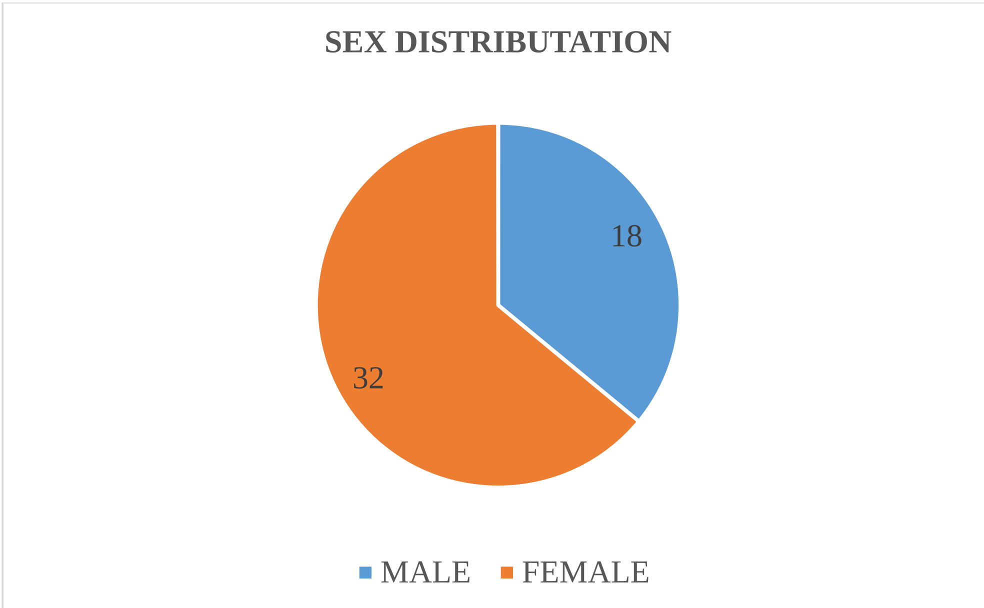

Figure 6. *Sex distribution*

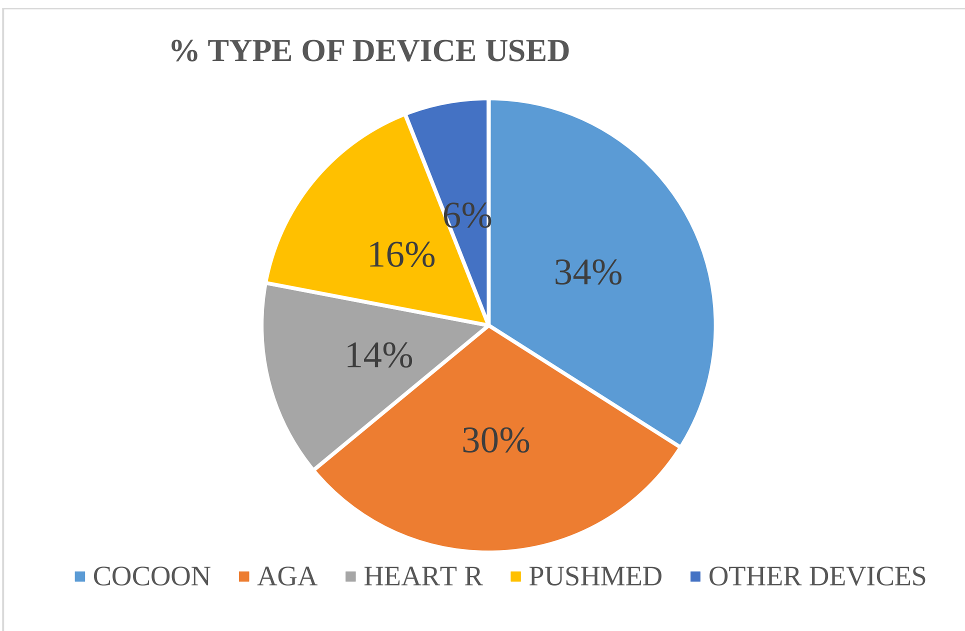

Figure 7. *Different used device for ASD closure*

Hepatic venous flow Doppler:

In all patients' hepatic veins Doppler flow S wave and D wave VTI in expiration and inspiration are shown in **table 2 and figure 8.** In hepatic veins systolic flow VTI was larger than diastolic flow VTI and after device closure both S and D waves VTI was increased but statistically not significant except expiration D-VTI which increased significantly. At 6 months follow up flow of both S-VTI and D-VTI was significantly higher than pre closure state.

Both S and D-VTI were significantly higher in inspiration than expiration, similar respiratory variation was maintained after device closure and 6 months follow up.

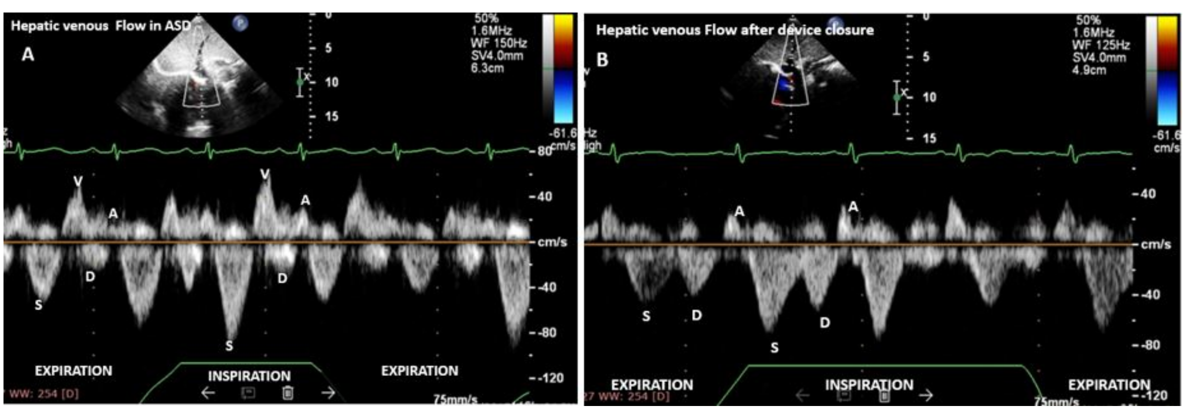

Figure 8. *Hepativ venous flow dopper before and after device closure. S; systolic forward flow (S-wave), V; systolic flow reversal (V-wave), D; diastolic forward flow (D-wave), and A; diastolic atrial reversal of flow (A-wave).*

Superior venacava flow Doppler:

In all patients' SVC Doppler flow S wave and D wave VTI in expiration and inspiration are shown in **table 2 and figure 9.** In ASD patients SVC systolic flow VTI was larger than diastolic flow VTI and except expiratory S-VTI (which not changed significantly) remaining other flow VTI increased significantly immediately after device closure which further increased on follow up study.

In ASD patients the effect of respiration on SVC flow was not as prominent as on hepatic veins flow, there was no significant respiratory variation in both the waves but after device closure and on follow up there was a significant inspiratory increase in S-VTI while D-VTI showing no significant respiratory variation.

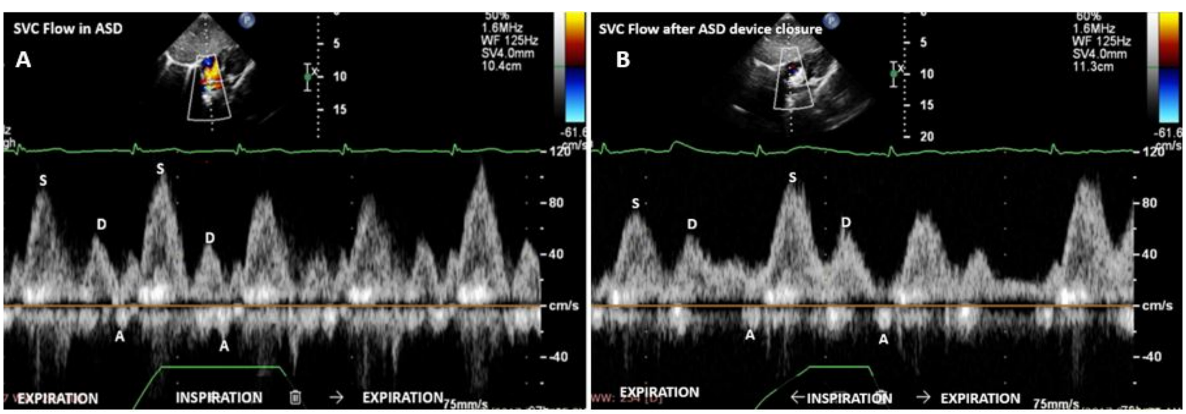

Figure 9. *Superior venacav flow dopper before and after device closure (from subcostal window). S; systolic forward flow (S-wave), D; diastolic forward flow (D-wave), and A; diastolic atrial reversal of flow (A-wave).*

Table 2. *Hepatic veins and superior venacava (SVC) Doppler flow S wave and D wave VTI during expiration and inspiration.*

	MEAN+/-SD (cm.)	**PRE**	**POST DC**	**p-value**	**6 MONTHS DC**	**p-value**
HEPATIC VEINS	EXPIRATION S-VTI	7.36 (+/- 4.22)	8.54 (+/-3.67)	0.12	9.78 (+/-4.4)	0.004
	INSPIRATION S-VTI	12.76 (+/-6.52)	12.50 (+/-5.62)	0.81	15.57 (+/-7.06)	0.03
		p=<0.01	p-<0.01		p-<0.01	
	EXPIRATION D-VTI	4.46 (+/-1.77)	6.26 (+/-5.46)	0.03	6.58 (+/-3.98)	0.001
	INSPIRATION D-VTI	6.34 (+/-5.01)	7.55 (+/-4.56)	0.21	9.92 (+/-5.79)	0.003
		p-<0.01	p-0.02		p-<0.01	
SVC	EXPIRATION S-VTI	15.49 (+/-6.9)	13.9 (+/-3.06)	0.11	13.5 (+/-3.66)	0.07
	INSPIRATION S-VTI	16.87 (+/-4.20)	18.87 (+/-4.36)	0.03	16.27 (+/-4.37)	0.44
		p = NS	p-<0.01		p-<0.01	
	EXPIRATION D-VTI	6.79 (+/-3.36)	8.38 (+/-3.64)	0.01	8.84 (+/-3.53)	0.005
	INSPIRATION D-VTI	6.37 (+/-2.70)	8.79 (+/-4.99)	0.001	9.38 (+/-3.35)	<0.01
		p-NS	p=NS		p-=NS	

Relative diastolic to systolic flow (D/S ratio) in HV and SVC flow:

Ratio of D/S VTI was calculated and compared as shown in **table 3.** In hepatic veins the mean (+/-SD) ratio of expiratory D/S was 0.68 (+/-0.31), inspiratory D/S was 0.51 (+/-0.26) which increased to 0.71 (+/-0.35), 0.66 (+/-0.49) immediately post device closure and to 0.71 (+/-0.39), 0.67 (+/-0.39) at 6 months follow up study respectively (**Figure 10**).

Post device closure inspiratory increase in D/S was statistically significant while expiratory increase was not. The ratio of post closure D/S to pre closure D/S was >1 indicating that diastolic flow increased more than systolic flow after ASD closure.

Table 3. *Relative diastolic to systolic flow (D/S ratio) in Hepatic veins and superior venacava (SVC) flow*

	RATIO (Mean+/-SD)	**PRE**	**POST DC**	**p-value**	**6 MONTHS DC**	**p-value**
HEPATIC VEINS	EXPIRATORY D/S	0.68 (+/-0.31)	0.71 (+/-0.35)	NS	0.71 (+/-0.39)	NS
	INSPIRATORY D/S	0.51 (+/-0.26)	0.66 (+/-0.49)	0.03	0.67 (+/-0.39)	0.005
		p-value <0.01	p =NS		p =NS	
SVC	EXPIRATORY D/S	0.47 (+/-0.20)	0.62 (+/-0.28)	<0.01	0.66 (+/-0.22)	<0.01
	INSPIRATORY D/S	0.40(+/-0.18)	0.48 (+/-0.26)	0.01	0.61 (+/-0.26)	<0.01
		p-value 0.01	p-value <0.01		P =NS	

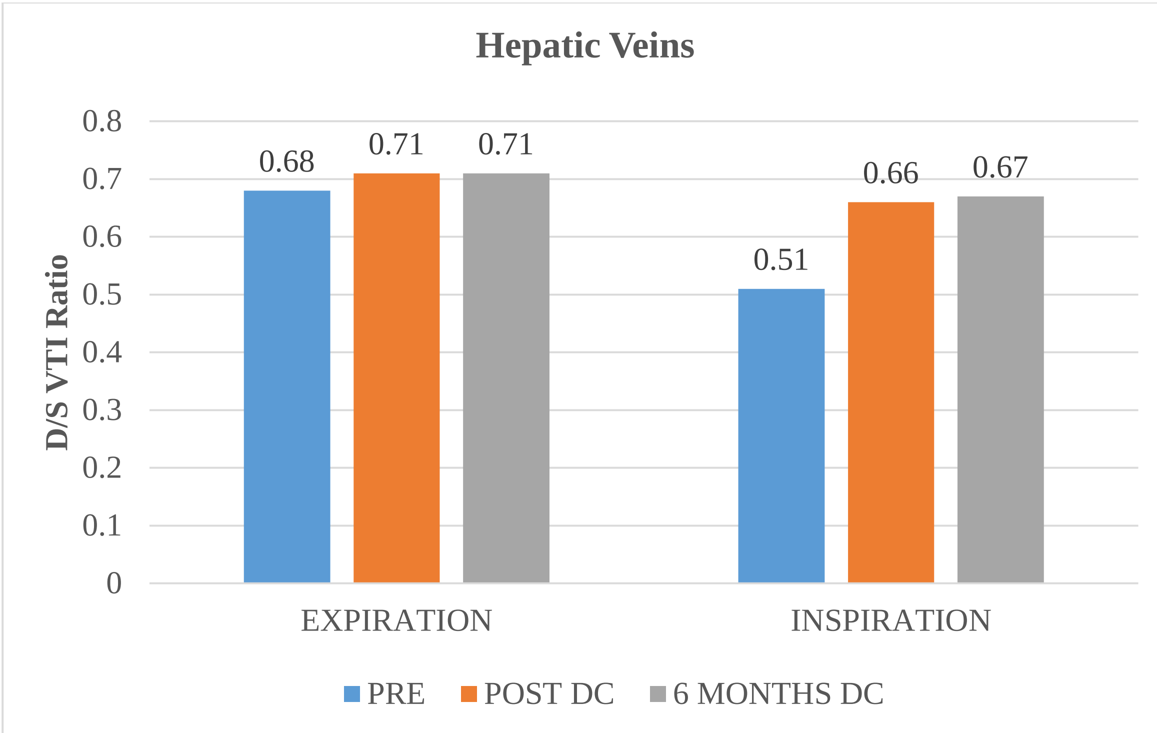

Figure 10. *Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

In hepatic veins inspiratory D/S was significantly lower than expiratory D/S and ratio of inspiratory D/S to expiratory D/S was <1 indicating that with inspiration S-VTI was increasing more than the D-VTI. Respiratory effect on D/S ratio was not significant after device closure **(Figure 11)**.

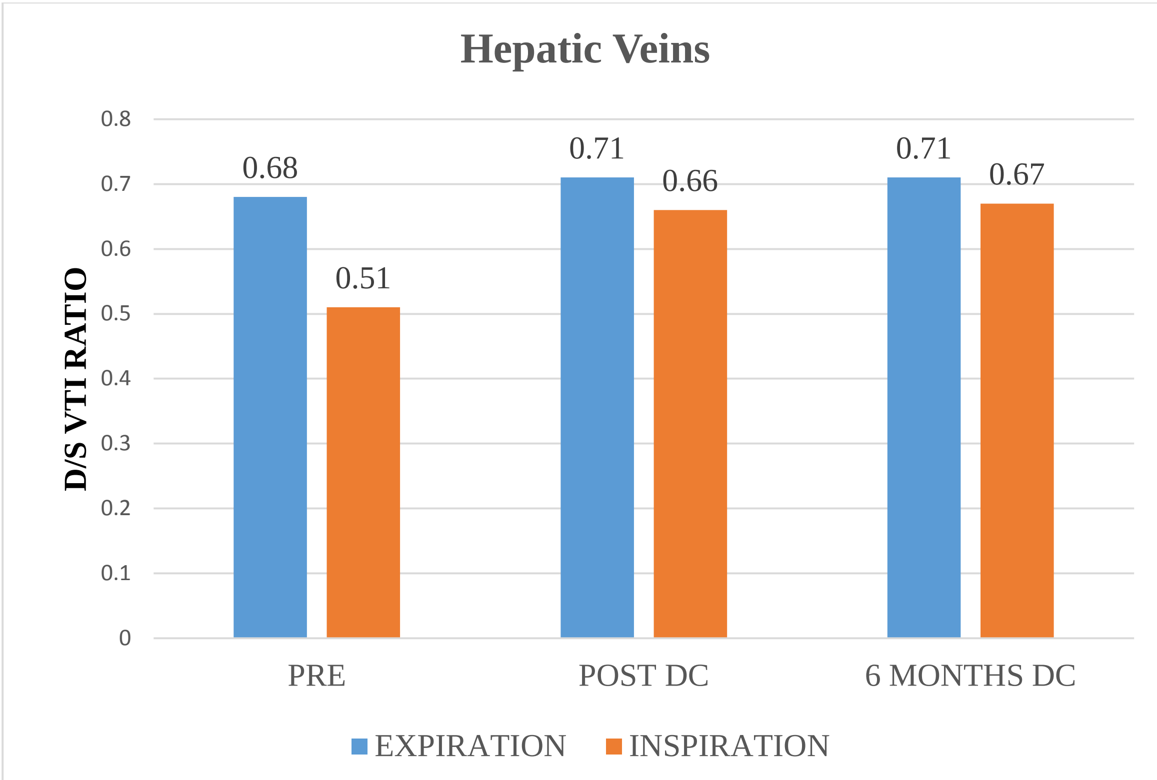

Figure 11. *Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins. Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

In SVC the mean (+/-SD) ratio of expiratory D/S was 0.47 (+/-0.20), inspiratory D/S was 0.47 (+/-0.18) which increased to 0.62 (+/-0.28), 0.48 (+/-0.26) immediately post device closure and to 0.66 (+/-0.22), 0.61 (+/-0.26) at 6 months follow up study respectively **(table 3, figure 12)**. Post device closure increase in D/S ratio was statistically significant in both the phases of respiration. The ratio of post closure D/S to pre closure D/S was >1 indicating that diastolic flow increased more than systolic flow after ASD closure.

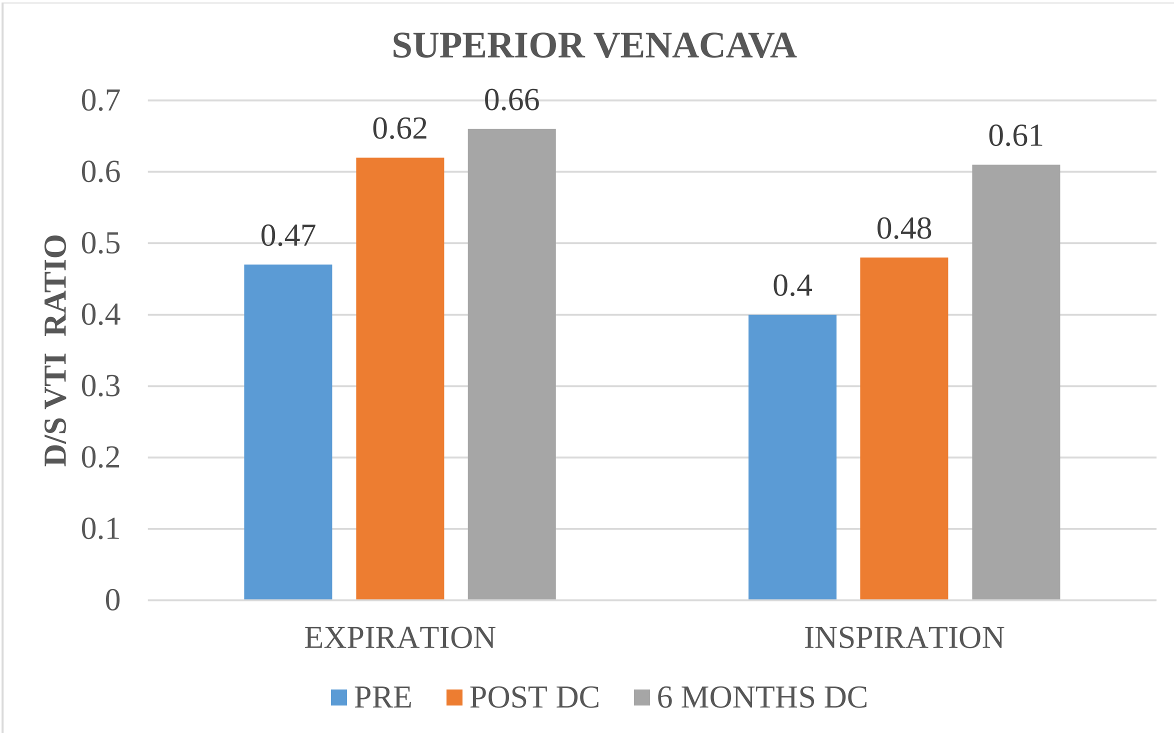

Figure 12. *Diastolic to systolic flow (D/S ratio) VTI in superior venacava. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

In SVC inspiratory D/S was significantly lower than expiratory D/S and the ratio of inspiratory D/S to expiratory D/S was <1 indicating that with inspiration S-VTI was increasing more than the D-VTI **(Figure 13).** Respiratory effect on D/S ratio was similar and significant after device closure but on follow up study the respiratory effect on D/S was not statically significant.

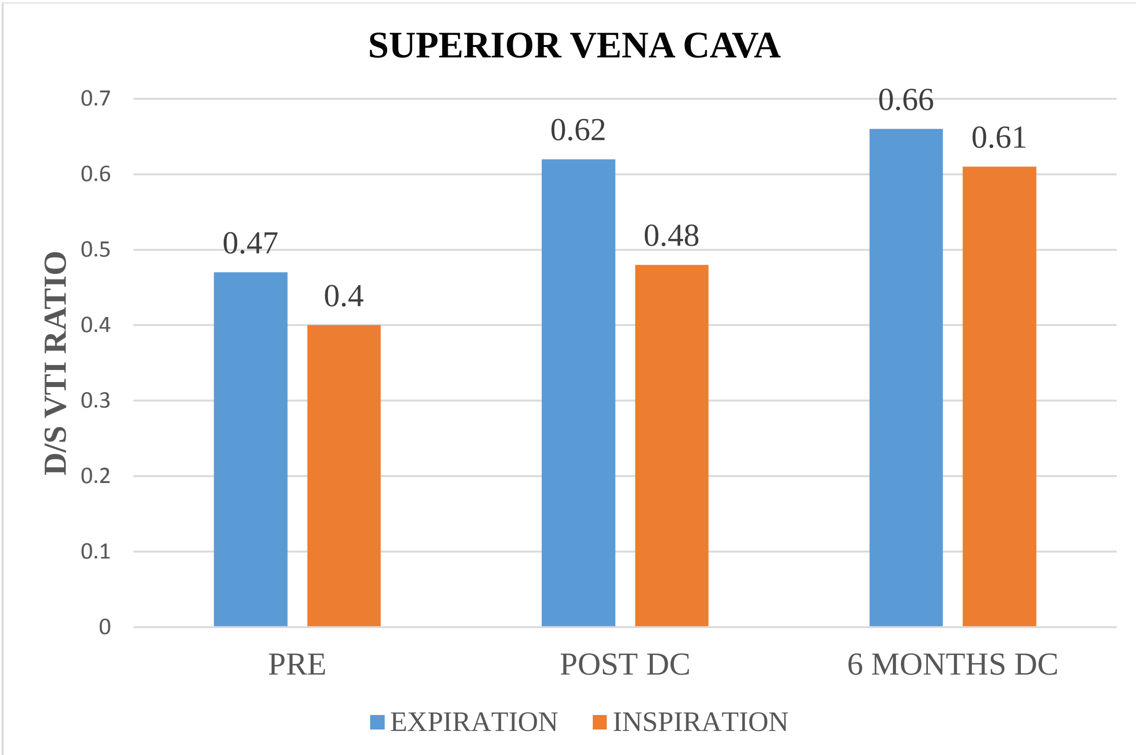

Figure 13. *Diastolic to systolic flow (D/S ratio) VTI in superior venacava. Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

V and A wave flow reversal:

In ASD patients S-wave and D-wave were consistently present in all the studied patients but the flow reversal waves (V and A waves) were not. In hepatic venous flow Doppler the well recognizable V-waves were seen in 19 patients during expiration and 26 patients during inspiration, while A-wave in 46 patients during expiration and 48 patients during inspiration. In SVC flow Doppler V-waves were seen in only 3 patients during expiration and 5 patients during inspiration, while A-wave in 39 patients during expiration and 42 patients during inspiration seen **(Table 4).**

Table 4. *V and A wave VTI Mean (+/- SD) and the number of patients in which well recognizable V-waves and A wave were recorded.*

		PRE		POST DC		6 MONTHS DC	
		No. of patients	MEAN (+/-SD)	No. of patients	MEAN (+/-SD)	No. of patients	MEAN (+/-SD)
Hepatic veins	V-VTI EXPIRATION	19	3.66+/-1.34	7	3.79+/-1.53	7	3.17+/-1.60
	V-VTI INSPIRATION	26	4.87+/-2.05	7	4.20+/-1.54	6	2.79+/-1.21
	A-VTI EXPIRATION	46	2.69+/-1.26	38	2.40+/-1.18	32	2.03+/-1.14
	A-VTI INSPIRATION	48	4.57+/-7.61	39	3.71+/-3.05	30	3.17+/-2.30
SVC	V-VTI EXPIRATION	3	3.03+/-0.82	2	3.29+/-0.82	0	NA
	V-VTI INSPIRATION	5	3.50+/-0.52	2	2.97+/-1.68	0	NA
	A-VTI EXPIRATION	39	2.30+/-0.64	27	2.14+/-1.06	18	1.66+/-0.51
	A-VTI INSPIRATION	42	2.63+/-0.90	29	2.27+/-1.14	18	2.19+/-0.80

Mean (+/- SD) of V and A-wave in hepatic veins and SVC is shown in **table 4**. The hepatic venous flow reversal of V and A phase was larger than the SVC flow reversal of the respective waves. Both the flow reversal waves were equal or larger during inspiration than expiration and similar respiratory variation was noticed after device closure and follow up study. Overall the mean V-VTI wave was larger than A-VTI during their respective respiratory phase in ASD patient, after device closure and on follow up study.

Division of all patients in two groups:

Total study population was divided into two groups.

Group 1. Patients with indexed ASD size less than 15mm.

Group 2. Patients with indexed ASD size more than 15mm.

Baseline demographic profile of patients in both the groups are shown in **table 5**. Group 1 contained total 20 patients including 11 females and 9 male patients while group 2 contained total 30 patients including 21 female and 9 male **(Figure 14).** Mean age of the study population in group 1 was 23.7+/-19.4 years while in group 2 was 16.1+/-18.18 years. In group 1, ten patients were of pediatric age group and ten patients of adult age group with a 1:1 ratio while in group 2, total 23 patients were of pediatric age group and only 7 patients of adult age group with 3.2:1 ratio.

In group 1 mean (+/-SD) weight 41.86+/-20.13kg, mean height 142+/-19.68cm, mean body surface area was 1.27+/-0.38 sq.m, while in group 2 mean weight 29.38+/-17.95 kg, mean height 125.1+/-21.03 cm, mean body surface area was 0.99+/-0.37 sq.m.

Table 5. *Baseline demographic profile of patients in both the groups*

	Group 1	**Group 2**
MALE	9	9
FEMALE	11	21
AGE(YEARS)	23.7+/-19.4	16.1+/-18.18
WEIGHT(Kg.)	41.86+/-20.13	29.38+/-17.95
HEIGHT (cm.)	142+/-19.68	125.1+/-21.03
BODY SURGACE AREA(Sq.m.)	1.27+/-0.38	0.99+/-0.37
ASD SIZE(mm)	12.75+/-3.99	18.3+/-5.38
INDEXED ASD SIZE(mm/sq.m)	10.36+/-2.44	19.2+/-3.50
DEVICE SIZE(mm)	16.1+/-5.43	21.63+/-5.63
INDEXED DEVICE SIZE(mm/sq.m)	13.05+/-3.21	23.02+/-4.77
COCOON	7	10
AGA	6	9
HEART R	1	6
PUSHMED	4	4
OTHERS	2	1
No. of PEDIATRIC AGE GROUP	10	23
No. of ADULT AGE	10	7

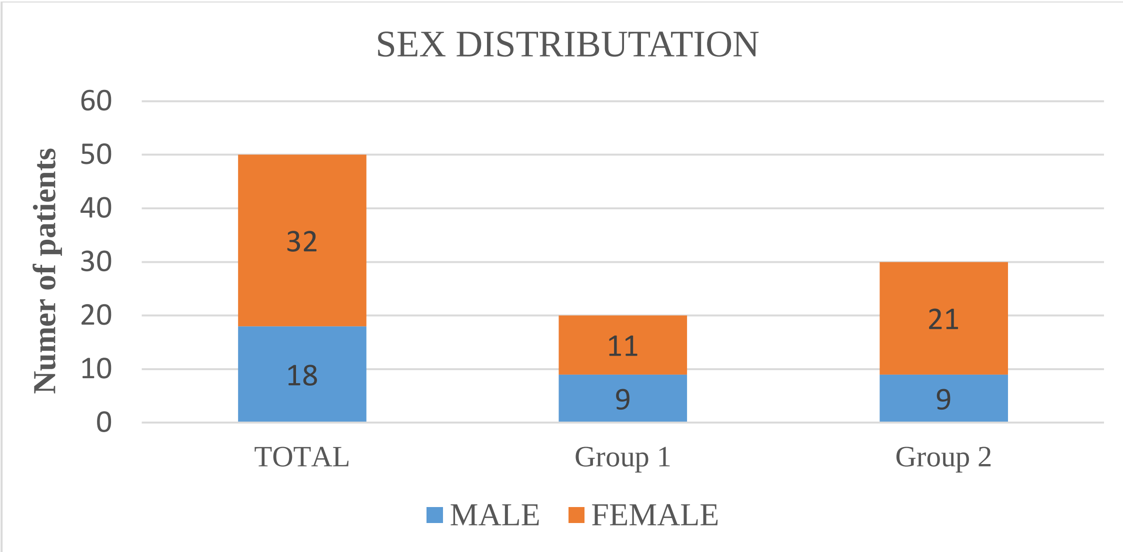

Figure 14. *Sex distribution in total, group 1, group 2 patient.*

In group 1 mean (+/-SD) atrial septal defect size was 12.75+/-3.99 mm and the mean size of device was 16.1+/-5.43 mm while in group 2 mean atrial septal defect size was 18.3+/-5.38 mm and the mean size of device was 21.63+/-5.63 mm.

In group 1 mean indexed ASD size was 10.36+/-2.44 mm/sq.m and mean indexed ASD device size was 13.05+/-3.21 mm/sq.m., while in group 2 mean indexed ASD size was 19.2+/-3.50 mm/sq.m and mean indexed ASD device size was 23.02+/-4.77 mm/sq.m.

Systemic venous flow pattern in group 1.

In group I patient's hepatic venous and superior venacava flow S wave and D wave VTI in expiration and inspiration are shown in **table 6**. After device closure S and D wave VTI changes of both the systemic veins were statistically non-significant till 6 months follow up except a significant increase in inspiratory S and D-VTI of SVC in immediate post device closure study.

Table 6. *Group 1 patient's hepatic venous and superior venacava flow S wave and D wave VTI during expiration and inspiration.*

	MEAN+/-SD (cm.)	**PRE**	**POST DC**	**p-value**	**6 MONTHS DC**	**p-value**
HEPATIC VEINS	EXPIRATION S-VTI	8.1 (+/-5.9)	7.77 (+/-2.88)	NS	9.31 (+/-4.27)	NS
	INSPIRATION S-VTI	13.48 (+/-7.66)	10.7 (+/-4.75)	0.1	15.35 (+/-8.14)	NS
		p <0.01	p <0.01		p<0.01	
	EXPIRATION D-VTI	4.69 (+/-1.86)	5.18 (+/-2.38)	NS	5.53 (+/-3.65)	NS
	INSPIRATION D-VTI	7.99 (+/-6.98)	5.70 (+/-2.56)	0.2	8.65 (+/-6.29)	NS
		p-value 0.04	p=NS		p=0.01	
SVC	EXPIRATION S-VTI	16.2 (+9.17)	13.6 (+3.21)	NS	12.74 (+/-3.55)	NS
	INSPIRATION S-VTI	16.4 (+/-4.14)	19.29 (+4.75)	0.007	14.58 (+/-4.09)	NS
		p =NS	p=<0.01		p=0.009	
	EXPIRATION D-VTI	7.32 (+/-3.92)	7.44 (+/-3.82)	NS	7.89 (+/-3.97)	NS
	INSPIRATION D-VTI	6.77 (+/-2.12)	8.49 (+/-4.75)	0.04	7.74 (+/-3.03)	NS
		p =NS	p =NS		p =NS	

In hepatic veins both S and D-VTI were significantly higher in inspiration than expiration, similar respiratory variation was maintained after device closure (except D-VTI which increased non-significantly) and 6 months follow up.

In ASD patients the effect of respiration in SVC was not as prominent as in hepatic veins flow, there was no significant respiratory variation in both the waves but after device closure and on follow up there was a significant inspiratory increase in S-VTI while D-VTI showing no significant respiratory variation.

Systemic venous flow pattern in group 2:

In group 2 patient's hepatic venous and SVC flow VTI are shown in **table 7**. The hepatic venous flow D and S wave VTI was little lesser in group 2 patients compare to group 1 patients. Hepatic venous D and S wave VTI after device closure was increased significantly, this increase was more prominent on 6 months follow up study compare to immediate post device closure study.

SVC flow S wave VTI was not changed significantly while D-VTI was increased significantly after device closure, which was also more prominent on follow up study compare to immediate post device closure study.

Table 7. *Group 2 patient's hepatic venous and superior venacava flow S wave and D wave VTI during expiration and inspiration.*

	MEAN+/-SD (cm.)	PRE	POST DC	p-value	6 MONTHS DC	p-value
HEPATIC VEINS	EXPIRATION S-VTI	6.87 (+/-2.59)	9.06 (+/-4.09)	0.008	10.09 (+/-4.54)	<0.01
	INSPIRATION S-VTI	12.28 (+/-5.73)	13.71 (+/-5.9)	NS	15.72 (+/-6.39)	0.009
		p<0.01	p=<0.01		p=<0.01	
	EXPIRATION D-VTI	4.3 (+/-1.72)	6.99 (+/-6.74)	0.03	7.27 (+/-4.09)	<0.01
	INSPIRATION D-VTI	5.25 (+/-2.73)	8.78 (+/-5.19)	<0.01	10.77 (+/-5.38)	<0.01
		p=0.05	p=0.05		p=0.002	
SVC	EXPIRATION S-VTI	15.03 (+/-5.0)	14.11 (+/-2.99)	NS	14.01 (+/-3.71)	NS
	INSPIRATION S-VTI	17.18 (+/-4.2)	18.59 (+/-4.14)	NS	17.40 (+/-4.25)	NS
		p=0.009	p<0.01		p=<0.01	
	EXPIRATION D-VTI	6.43 (+/-2.9)	9.0 (+/-3.44)	0.006	9.47 (+/-3.12)	0.002
	INSPIRATION D-VTI	6.09 (+/-3.0)	8.98 (+/-5.22)	0.01	10.48 (+/-3.14)	<0.01
		p=NS	p=NS		p=NS	

In hepatic veins both S and D-VTI were significantly higher in inspiration than expiration, similar respiratory variation was maintained after device closure and 6 months follow up.

In ASD patients of this group, the effect of respiration in SVC was not as prominent as in hepatic veins flow. S-VTI was increasing significantly with respiration while D-VTI showing no significant respiratory variation in ASD patients and the similar pattern was maintained after device closure and follow up.

Relative diastolic to systolic flow (D/S ratio) in systemic veins in group 1:

Ratio of hepatic venous and SVC D/S VTI in group 1 patients are shown in **table 8, figure 15 and figure 16**. In both hepatic veins and SVC the mean ratio of expiratory D/S and inspiratory D/S were not changed significantly after device closure and in follow up study.

Both in hepatic veins and SVC the inspiratory D/S was lower but statistically non-significant than expiratory D/S and similar respiratory effect was observed after device closure and follow up **(Figure 17 and 18**).

Table 8. *D/S VTI Ratio of hepatic venous and superior venacava in group 1 patients*

		PRE	**POST DC**	**p-value**	**6 MONTHS DC**	**p-value**
HEPATIC VEINS	EXPIRATORY D/S	0.66 (+/-0.29)	0.67 (+/-0.18)	NS	0.63 (+/-0.41)	NS
	INSPIRATORY D/S	0.59 (+/-0.33)	0.58 (+/-0.25)	NS	0.58 (+/-0.24)	NS
		p=NS	p=NS		p=NS	
SVC	EXPIRATORY D/S	0.50 (+/-0.24)	0.57 (+/-0.32)	NS	0.62 (+/-0.23)	NS
	INSPIRATORY D/S	0.43 (+/-0.16)	0.47 (+/-0.28)	NS	0.55 (+/-0.23)	0.059
		p=NS	p=NS		p=NS	

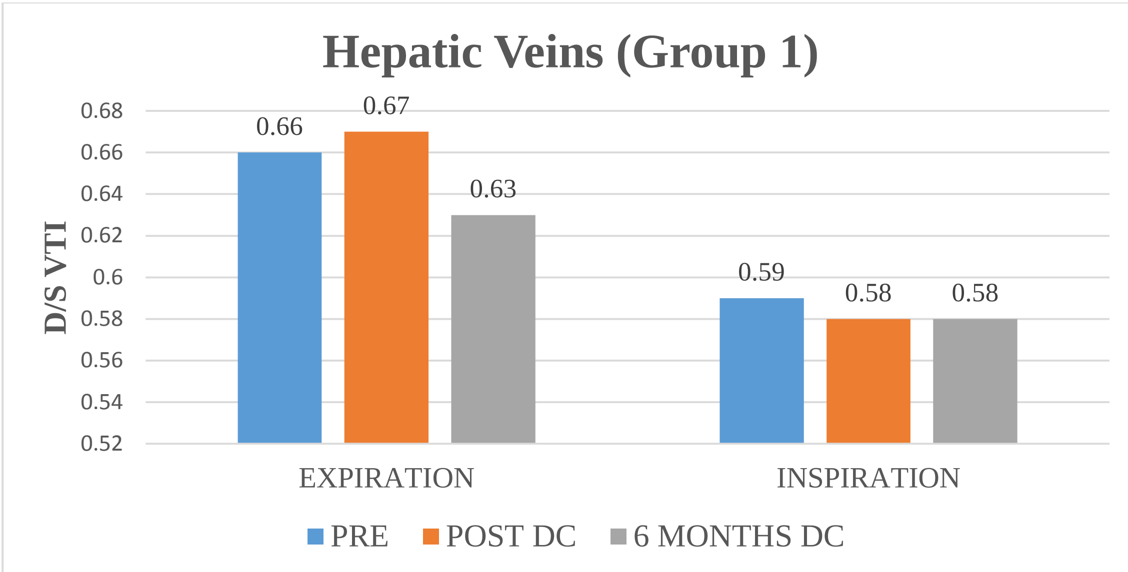

Figure 15. *Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins in group 1 patient. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

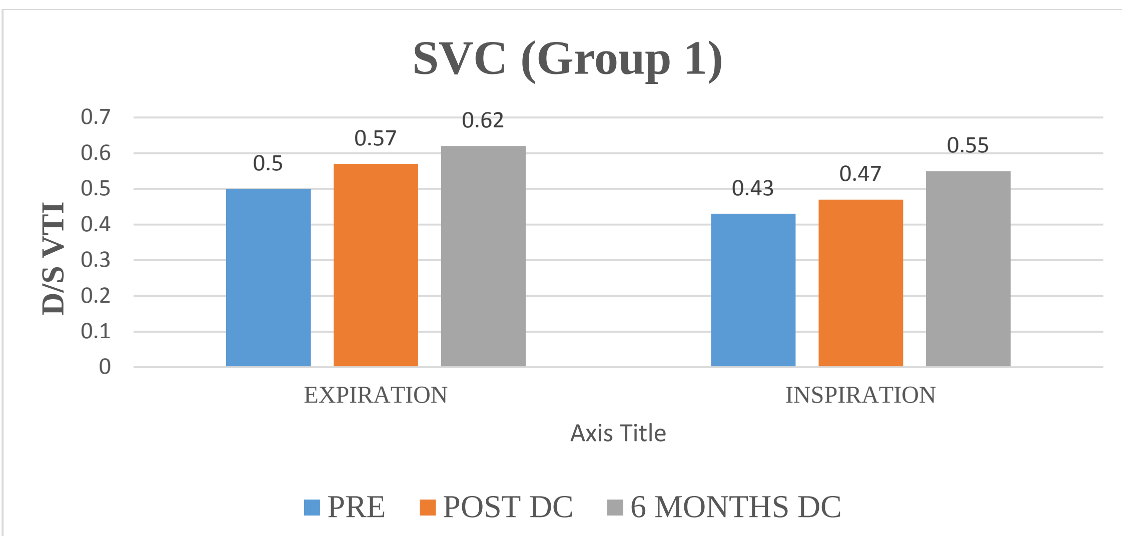

Figure 16. *Diastolic to systolic flow (D/S ratio) VTI in superior venacava in group 1 patient. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

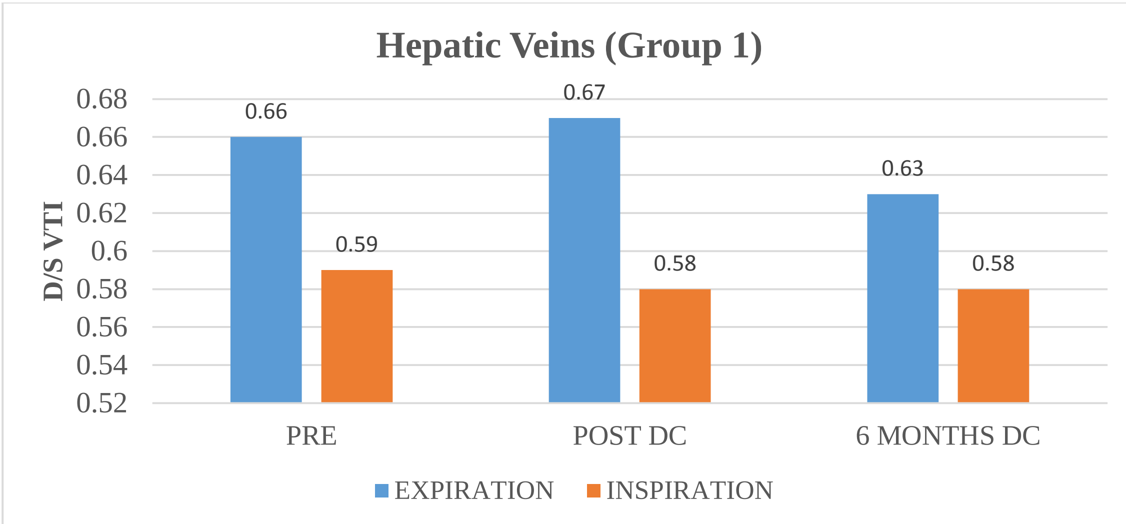

Figure 17. *In group 1 patients, Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins. Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

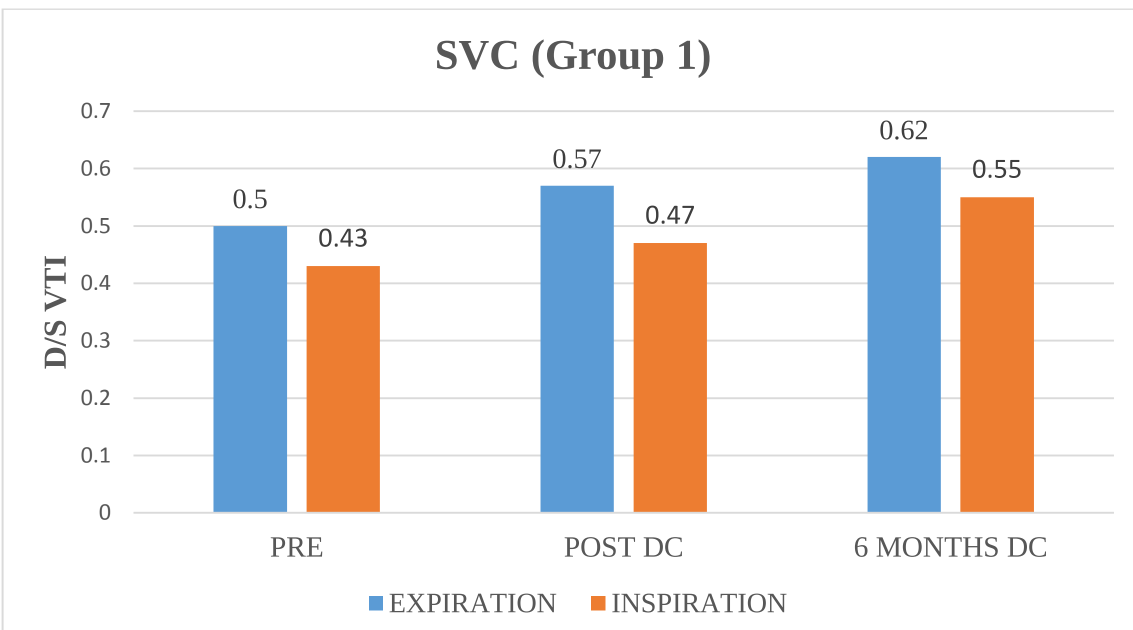

Figure 18. *In group 1 patients, Diastolic to systolic flow (D/S ratio) VTI in Superior venacava. Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

Relative diastolic to systolic flow (D/S ratio) in group 2:

Ratio of hepatic venous and SVC D/S VTI in group 2 patients are shown in **table 9 and figure 19, 20).** In hepatic veins the mean ratio of expiratory D/S was 0.69 (+/-0.34), inspiratory D/S was 0.45 (+/-0.19). Expiratory D/S ratio increased to 0.73+/-0.42 immediate post procedure and to 0.76+/-0.37 at 6 months follow up, this increase was statistically not significant. Inspiratory D/S ratio increased significantly to 0.72+/-0.59 immediate post procedure and to 0.74+/-0.46 at 6 months follow up.

Table 9. *D/S VTI Ratio of hepatic venous and SVC in group 2 patients*

	D/S Ratio	**PRE**	**POST DC**	**p-value**	**6 MONTHS DC**	**p-value**
HEPATIC VEINS	EXPIRATORY D/S	0.69 (+/-0.34)	0.73 (+/-0.42)	NS	0.76 (+/-0.37)	NS
	INSPIRATORY D/S	0.45 (+/-0.19)	0.72 (+/-0.59)	0.01	0.74 (+/-0.46)	0.001
		p=<0.01	p=NS		p=NS	
SVC	EXPIRATORY D/S	0.45 (+/-0.17)	0.65 (+/-0.24)	<0.01	0.69 (+/-0.21)	<0.01
	INSPIRATORY D/S	0.37 (+/-0.19)	0.49 (+/-0.25)	0.02	0.65 (+/-0.28)	<0.01
		p=0.02	p=0.002		p=NS	

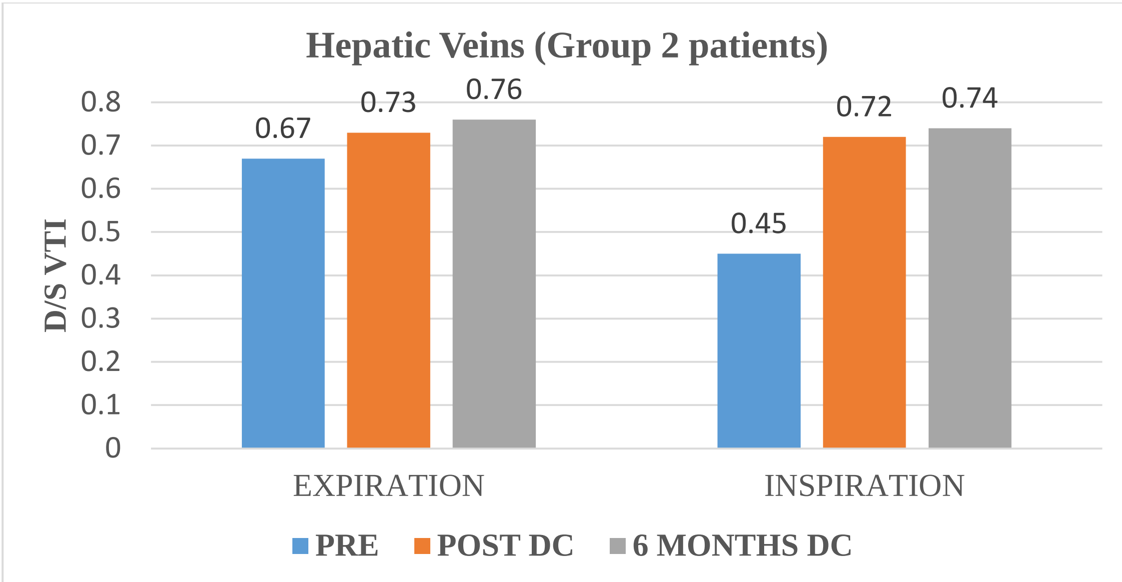

Figure 19. *Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins in group 2 patient. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

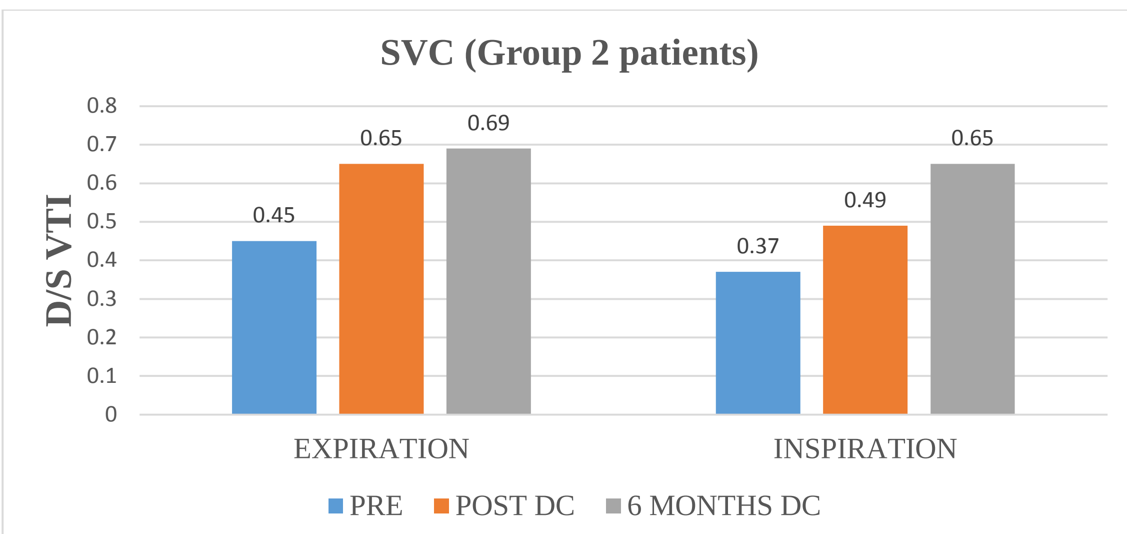

Figure 20. *Diastolic to systolic flow (D/S ratio) VTI in superior venacava in group 2 patient. Separately during expiration and inspiration, comparative change of D/S from pre device closure to post device closure and 6 months follow up are shown.*

In hepatic veins inspiratory D/S was significantly lower than expiratory D/S and ratio of inspiratory D/S to expiratory D/S was <1 indicating that with inspiration S-VTI was increasing more than the D-VTI. Respiratory effect on D/S ratio was not significant after device closure **(Figure 21.)**

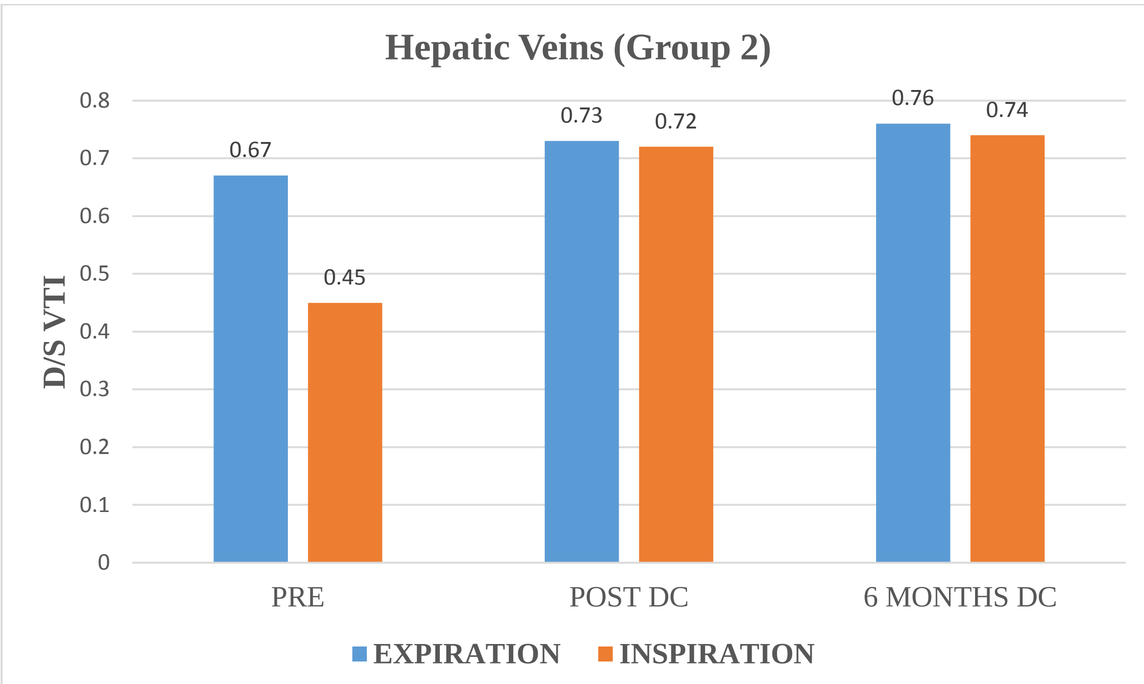

Figure 21. *In group 2 patients, Diastolic to systolic flow (D/S ratio) VTI in Hepatic veins. Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

In SVC inspiratory D/S was significantly lower than expiratory D/S and the ratio of inspiratory D/S to expiratory D/S was <1 indicating that with inspiration S-VTI was increasing more than the D-VTI. Respiratory effect on

D/S ratio was similar and significant after device closure but on follow up study the respiratory effect was not statically significant **(Figure 22).**

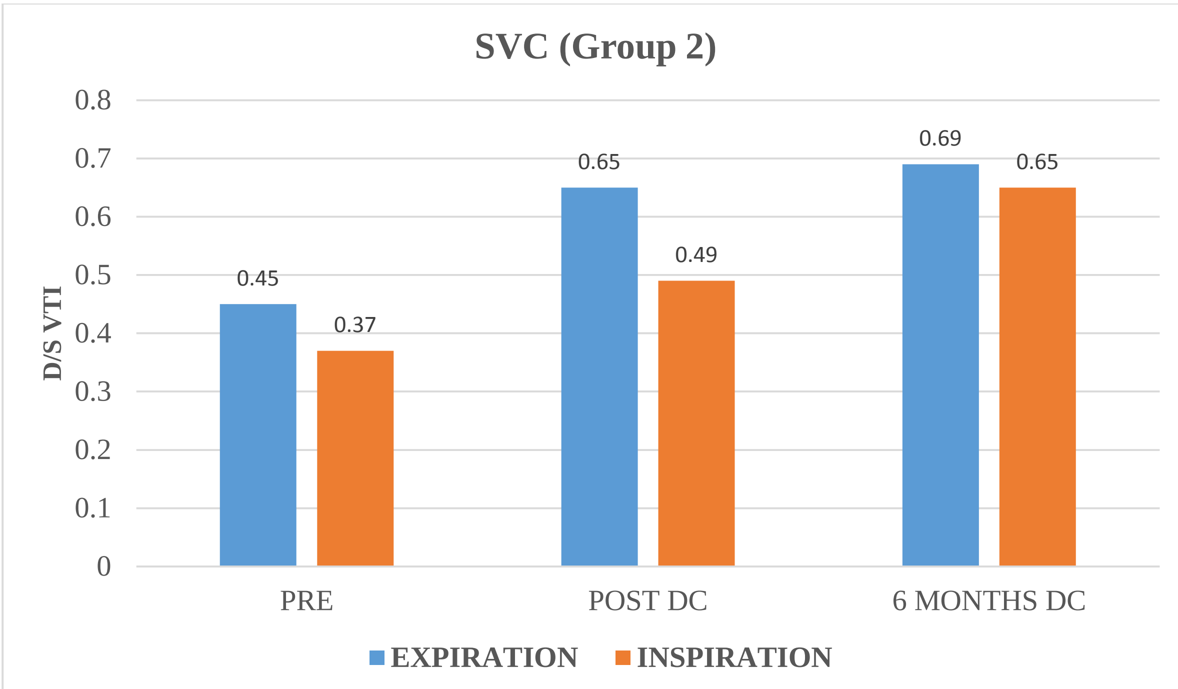

Figure. 22 *In group 2 patients, Diastolic to systolic flow (D/S ratio) VTI in superior venacava (SVC). Relative respiratory change in D/S ratio pre device closure, post device closure and 6 months follow up are shown.*

In group 2 patients it was noted that in 12 out of 30 patients (40%) post device closure diastolic forward flow was equal or larger than the systolic forward flow in inspiration or both the phases of respiration. Various pattern of systemic venous flow after device closure is shown in **figure 23.**

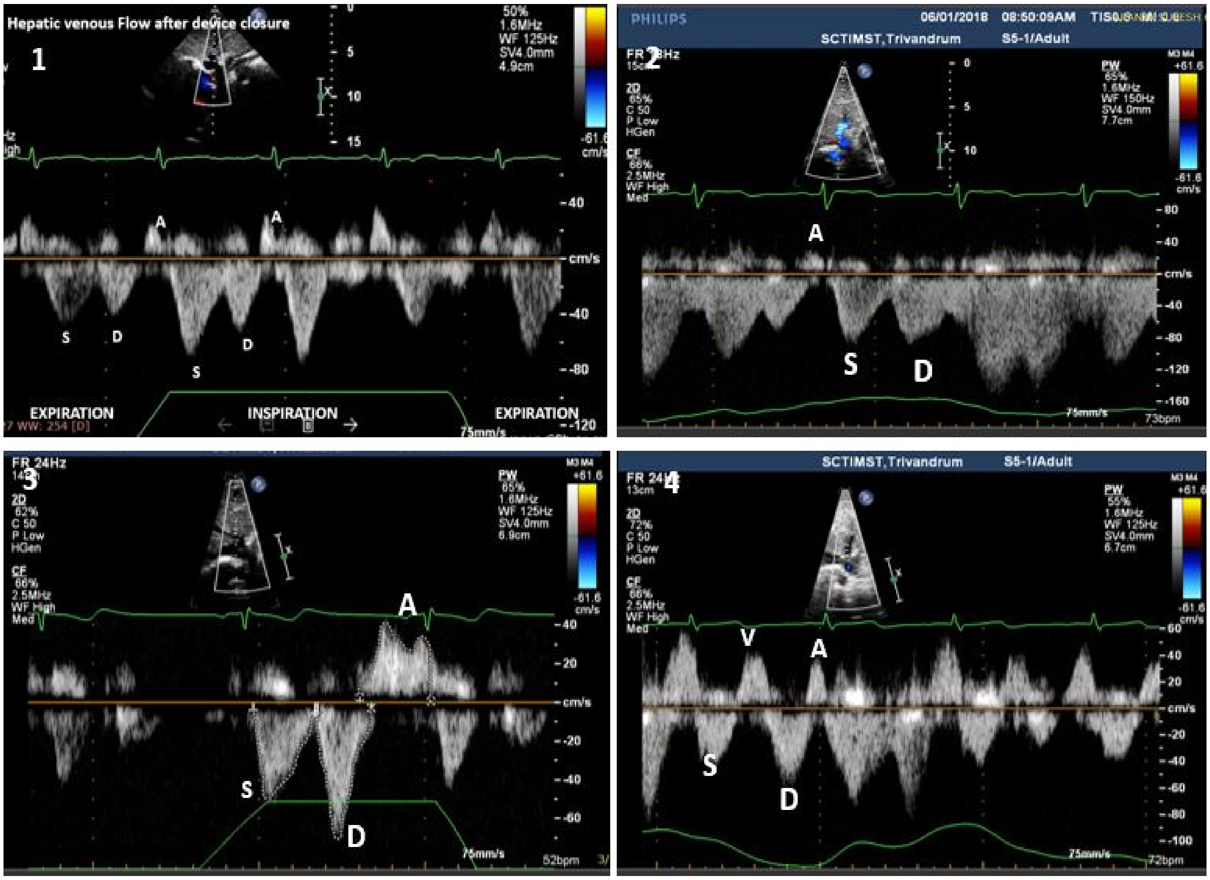

Figure 23. *Various pattern of Hepatic venous flow after device closure.* ***1****. S>D during expiration, S>D during inspiration, A wave larger during inspiration than expiration, no V wave.* ***2****. S>D during expiration, S=D during inspiration, very small A wave, no V wave.* ***3****. S>D during expiration, D>S during inspiration, large A wave during inspiration, no V wave.* ***4.*** *D>S during expiration and inspiration. Both V and A (V>A) waves are present during expiration, while during inspiration only a large A wave is present.* ***S****; systolic forward flow (S-wave),* ***V;*** *systolic flow reversal (V wave), D; diastolic forward flow (D-wave), and* ***A****; diastolic atrial reversal of flow (A-wave).*

DISCUSSION

To the best of our knowledge, this study is the largest prospective study which assessed the hemodynamic changes in systemic venous flow pattern by doppler in patients with atrial septal defect and in patients following ASD device closure with their short term (6 months) follow up.

In this study a total of 50 patients who completed 6 months follow up were included for final analysis. Majority were female patients with female to male ratio of 1.77:1. The sex distribution was similar to previous studies on ASD patients.[3-6, 20]

In our study, patients with wide age range were included, youngest was 4 years old and oldest was 66 years old, with majority in pediatric age group (<14 years). The mean size of atrial septal defect in our study was similar to other studies.[3-5, 20] Considering wide variation in body size, to correct for the effect of body size of patients on the flow hemodynamics, the septal defect size was indexed with body surface area.

I. Flow pattern in hepatic veins

Flow pattern in ASD patients prior to device closure:

In patients with ASD, four distinct waves were present in the hepatic venous flow doppler. Two forward flow waves (S wave and D wave) in which the direction of flow was towards the heart and two flow reversal waves (V wave and A wave) in which the direction of flow was away from the heart.

The hepatic venous systolic forward flow was higher than diastolic forward flow and D/S ratio was less than 1. Similar pattern has been reported in healthy individuals[21, 22] as well as in ASD patients[8, 29, 30] in the past.

Increase in forward flow during inspiration was noted. Both S-VTI and D-VTI increased significantly during inspiration. This flow pattern in ASD patients was similar to in other studies[8, 20] and was similar to the normal respiratory variation pattern of normal persons[21, 22].

In patients with ASD, the D/S ratio decreased significantly during inspiration. Decrease in D/S ratio occurred as the increase in systolic flow was more than the increase in diastolic flow during inspiration. This inspiratory increase in systolic forward flow more than the diastolic forward flow was reverse of the normal flow pattern where diastolic forward flow increases more than systolic forward flow.

This abnormal pattern occurs possibly because of two mechanisms acting either singly or together. Firstly, the smaller left to right shunt during inspiration[8] causes less interference with systemic venous return and leads to greater increase in systolic flow compared to diastolic flow. (as the interference was higher to the systolic flow compared to diastolic flow). Secondly, during inspiration RV receives higher volume of blood from systemic venous return in diastole which leads to more vigorous contraction during systole (understood by the application of Frank Starling law) and more apical displacement of the tricuspid valve creating larger space in RA to accommodate increased systolic forward flow.

Overall the mean systolic flow reversal (V-VTI wave) was higher than late diastolic flow reversal (A-VTI wave) during their respective phases of respiration in ASD patients. This pattern of flow reversal waves was similar to previously reported flow patterns in ASD patients.[8, 32, 33]

Both the flow reversal waves in inspiration were either equal or larger compared to that during expiration. This finding was contrary to previously reported pattern in ASD patients.[8] This pattern was also opposite to the previously reported pattern in normal individuals[22] in whom the V and A wave flow decreased during inspiration.

Changes in flow patterns post device closure in hepatic veins

In hepatic veins, increase in systemic venous flow during both systole and diastole was noted after device closure compared prior to device closure. This increase in venous flow velocity was more apparent at 6 months post device closure compared to immediate post procedure. This increase in systemic venous flow return was expected because of an increase in systemic flow (Qs) after device closure.

Post device closure, overall the systolic forward flow was higher than diastolic forward flow and D/S ratio was <1. The D/S ratio increased after device closure significantly and the ratio of D/S ratio post device closure to pre device closure was >1. This pattern indicated that the diastolic flow increase was higher than the systolic flow increase after device closure, which was more apparent during inspiration.

In a study[20] by K. Ichihashi et al, a significant increase in relative diastolic forward flow after surgical closure was reported and not after device closure. Although a similar pattern of diastolic increase was noted in their study but probably because of a smaller sample size (10 patients in device closure group) these changes were not statistically significant masking the actual fact.

In our study, the post device closure change in D/S ratio was similar to the change in D/S ratio reported in post-surgical closure patients[8, 15, 16, 20] but to a lesser extent. In post-surgical closure patients, the increase in diastolic flow compared to increase in systolic flow was so prominent that the diastolic flow was higher than systolic flow, but in patients post device closure the overall diastolic flow remained equal or less than systolic flow.

Rather than higher increase in systolic flow compared to diastolic flow, a relatively higher increase in diastolic flow indicated that either a decrease in RA compliance or an impairment of RV systolic function occurred. Similar Tricuspid annular plane systolic excursion (TAPSE) pre and post device closure ruled out the possibility of RV dysfunction. Hence, decrease in RA compliance post device closure was the only possible mechanism to explain these changes.

Prior to device closure, both S and D-VTI were significantly higher during inspiration than during expiration. Similar variations in respiratory phase was maintained after device closure and at 6 months follow up. Similar to the pattern pre device closure, inspiratory D/S post device closure was lower than expiratory D/S (although statistically not significant) and ratio of inspiratory D/S to expiratory D/S was <1. Decrease in D/S ratio indicated that the increase in systolic flow was more than the diastolic flow during inspiration.

II. Flow pattern in superior venacava

Flow pattern in ASD patients prior to device closure.

The S and D waves were consistently present in all patients. Well recognizable V-wave was recorded only in 3 patients during expiration and 5 patients during inspiration, while A-wave was recorded in 39 patients during expiration and 42 patients during inspiration.

In SVC, the systolic forward flow was higher than diastolic forward flow, D/S ratio was less than 1. Also the SVC flow in ASD patients was larger during both systolic and diastolic phases compared to hepatic venous flow. Similar pattern has been reported in normal individuals[21, 22, 23] and in ASD patients[8, 20] in the past.

Similar to normal healthy individuals, in ASD patients the effect of respiration on SVC flow pattern was not as prominent as on hepatic vein flow pattern and there was no significant respiratory variations in both the waves individually.

Inspiratory D/S was significantly lower than expiratory D/S and the ratio of inspiratory D/S to expiratory D/S was <1 indicating that during inspiration the increase in systolic forward flow was more than the increase diastolic forward flow. This relative increase in systolic flow more than diastolic flow was similar to hepatic venous flow pattern and was reverse to that seen in normal healthy individuals as reported in previous studies.[21-23]

The SVC flow reversal during systolic and diastolic phases were less marked compared to the hepatic venous flow reversal during the respective phases. Overall the systolic flow reversal was larger than late diastolic flow reversal during their respective respiratory phases in ASD patients. This pattern was opposite to the previously reported pattern in normal individuals where the A-wave reversal is larger than the V-wave reversal.[21, 22] This pattern in flow reversal waves was similar to the previously reported flow pattern in ASD patients.[8, 15, 16, 32, 33]

The effect of respiration was less prominent on SVC flow reversal wave than hepatic venous flow reversal waves, both the flow reversal waves were equal or larger during inspiration than expiration. This finding was contrary to previously reported pattern in ASD patients.[8] This pattern was also reverse of the previously reported pattern in normal individuals[21, 22] in which the V and A waves decrease with inspiration.

Changes post device closure verses pre device closure in SVC flow waves:

In SVC, except for expiratory S-VT rest of the other forward flow velocities increased significantly immediately after device closure with further increase seen on follow up. Compared to pre device closure, where there was no significant respiratory variation in both the waves, immediately following device closure and on follow up there was a significant increase in S-VTI during inspiration while D-VTI showed no significant respiratory variation.

In SVC the expiratory D/S and inspiratory D/S ratio increased significantly immediate post device closure and at 6 months follow up. The ratio of post device closure D/S to pre closure D/S was >1 indicating that diastolic flow increased more than systolic flow after ASD closure. In our study, the post device closure change in D/S ratio was similar to that reported in post-surgical closure patients[8, 15, 16, 20] but to a lesser extent.

After device closure, the increase in both systolic and diastolic flow with relatively higher increase in diastolic flow more than systolic flow was similar to the hepatic venous flow pattern.

Similar to the pre-device closure state, the Inspiratory D/S was significantly lower than expiratory D/S immediate device closure but on follow up, the effect of respiration on D/S was not statistically significant. The ratio of inspiratory D/S to expiratory D/S was <1 indicating that with inspiration S-VTI increases more than the D-VTI. This pattern of respiratory variation has been reported in ASD patients' post-surgical closure as well.[20]

Similar to in normal individuals, the effect of respiration on SVC flow in ASD patients was not as prominent as on hepatic venous flow and these observations were similar to that seen in other studies. There was no significant respiratory variation in both the waves, but after device closure and on follow up there was a significant increase in S-VTI during inspiration.

A relative increase in systolic flow more than diastolic flow was similar to hepatic venous flow pattern and this was opposite to that seen in normal individuals as reported in previous studies.

III. Immediate post device closure verses on 6 months follow up

It was seen that at 6 months follow up after device closure, the systolic forward flow was similar or higher than that seen at immediate post procedure, while diastolic forward flow was persistently higher on follow up than immediate post device closure. The post to pre device closure D/S ratio was higher at 6 months follow up compared to immediate post closure.

This pattern of relatively more increase in diastolic flow compared to systolic flow after device closure was similar to the previously reported pattern seen in post ASD surgical closure patients.[8, 15, 16, 20] Rather than normalization of the flow pattern at 6 months follow up further increase in change in the flow patterns was observed.

These changes noted on follow up were different from pattern seen in studies on post-ASD surgical closure patients [20, 41] where the changes in flow pattern became less obvious on follow up. Surgical closure of ASD results in right atrial injury, inflammation and edema increasing the stiffness of the right atrium, thereby decreasing systolic forward flow[20, 41]. On follow up the decrease in edema and inflammation improves the RA compliance and the flow changes.[20, 41]

While post procedure edema or inflammation was not a concern in post device closure patients, possibility of increased stiffness in interatrial septum and the surrounding area due to rigid mechanical device and peri-device adhesions on follow up can be considered to lead to further deterioration of flow changes.

Some degree of dehydration due to procedure related blood loss, prolonged fasting state and effect of general anaesthesia also have been contributed to low flow velocities in immediate post procedure period.

IV. Flow pattern in different groups

In group 1 and group 2 patients the pattern of changes in S or D wave, D/S ratio, pre to post device closure ratio of D/S and inspiratory to expiratory ratio of D/S was similar but the extent of change was different. In group 1 patients, these changes were less prominent and statistically not significant while in group 2 these changes were greater to the extent of statistical significance.

In 12(40%) of 30 patients of post device closure patients belonging to group 2, diastolic forward flow was equal or larger than the systolic forward flow in inspiration or both the phases of respiration mimicking the flow pattern of post-surgical closure patients.[20,41]

Overall it indicates that a large atrial septal defect has a higher degree of shunt related hemodynamic changes. Similarly a large device can produce major changes in hemodynamics post device closure, resulting in a higher degree of decrease in RA compliance leading to greater restriction to systolic inflow to RA.

Limitations

- Shunt assessment by cardiac catheterization was not done in all patients hence not included in analysis.
- This study being a single center study, an observational bias can confound the findings.
- Six months follow up is too short to assess the reversal of hemodynamic effects of a congenital defect.

Conclusion

- In the systemic venous flow pattern of ASD patients, systolic forward flow (S-VTI) is larger than diastolic forward flow (D-VTI). Total flow increases after device closure but the increase in diastolic flow is higher than increase in systolic flow.
- In ASD patients, both systolic and diastolic forward flow increase with inspiration but Systolic flow increase is more than that of Diastolic flow.
- Large atrial septal defects have a higher degree of shunt related hemodynamic changes.
- Large mechanical device can decrease the RA compliance leading to major changes in hemodynamics post device closure.

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Annexures…

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/1007/DECEMBER-2016 07.10.2017

Dr. Amitabh Poonia
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Amitabh Poonia,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "A STUDY OF SUPERIOR VENA CAVA – INFERIOR VENA CAVA PULSE WAVE DOPPLER IN OSTIUM-SECUNDUM ATRIAL SEPTAL DEFECT PATIENTS--- BEFORE AND AFTER DEVICE CLOSURE" (IEC/1007) on 17th December, 2016.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 24.11.2016 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co- Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 22.09.2017 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Copy of IEC Recommendation Letter dated 06.01.2017*
7. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 17th December, 2016 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Justice Gopinathan. P.S	BSc. LLB	Male	Legal Expert (Chairperson)	No
2.	Dr. Harikrishna Varma PR	PhD	Male	Biomedical Scientist	Yes
3.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro-Enterologist)	No
4.	Dr. Rema M. N	MD	Female	Pharmacologist	No
5.	Dr. R V G Menon	PhD	Male	Lay Person	No
6.	Smt. Sathi Nair	MA	Female	Lay Person	No
7.	Dr. K R S Krishnan	ME, PhD	Male	Biomedical Scientist/Engineer	No
8.	Dr. Kala Kesavan. P	MD	Female	Pharmacologist	No
9.	Dr. Christina George	MD	Female	Psychiatrist	No
10.	Dr. P. Manickam	PhD	Male	Scientist - Epidemiologist	No
11.	Dr. Mala Ramanathan	MSc, PhD, MA	Female	Ethicist/Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

M Ramanathan

Mala Ramanathan
Member Secretary, IEC

Page 2 of 2

Performa of the study:

AGE-

SEX-

WEIGHT-

DIAGNOSIS-

ASD SIZE AND TYPE-

DEVICE USED-

SIZE OF DEVICE -

ECHO:-

ASD SIZE-

SUPERIOR VENA CAVA DOPPLER PARAMETERS: --

EXPIRATION

INSPIRATION

PEAK FORWARD FLOW VELOCITY-

S- WAVE

D-WAVE –

PEAK REVERSAL FLOW VELOCITY-

A-WAVE -

V-WAVE -

FORWARD FLOW VELOCITY INTEGRAL

S-WAVE

D WAVE

TOTAL

REVERSAL FLOW VELOCITY INTEGRAL

A WAVE

V WAVE

TOTAL

HEPATIC VENOUS DOPPLER PARAMETERS: --

EXPIRATION INSPIRATION

PEAK FORWARD FLOW VELOCITY-

S- WAVE

D-WAVE –

PEAK REVERSAL FLOW VELOCITY-

A-WAVE -

V-WAVE -

FORWARD FLOW VELOCITY INTEGRAL

S-WAVE

D WAVE

TOTAL

REVERSAL FLOW VELOCITY INTEGRAL

A WAVE

V WAVE

TOTAL

On follow up visit at 6 month the similar echocardiography details as mentioned above will be collected.

INFORMED CONSENT FORM

Participant's name:

Date of Birth / Age (in years):

I______________________________________, declare that (Please tick boxes)

- I have read the information provided to me in the patient information sheet regarding the study "A STUDY OF SUPERIOR VENA CAVA – INFERIOR VENA CAVA PULSE WAVE DOPPLER IN OSTIUM-SECUNDUM ATRIAL SEPTAL DEFECT PATIENTS---- BEFORE AND AFTER DEVICE CLOSURE". [ ]
- I have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
- I voluntarily agree to take part in this study [ ]
- I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].
- I received a copy of this signed consent form [ ]

Signature / Thumb impression

Of the Patient / Legally acceptable representative:

NAME:

DATE:

Name of witness:

Relation to participant:

Signature:

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked are answered.

Date: Signature:

Place: Name:

കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രം

രോഗിയുടെ പേര്............... ....

വയസ്സ്............... സ്ത്രീ/പുരുഷൻ...........

ഞാൻ .... പ്രഖ്യാപിക്കുന്നു.
(ദയവായി ബോക്സിനുള്ളിൽ ടിക് ചെയ്യുക)

- ഞാൻ, ഓസ്റ്റിയം-സെക്കുണ്ടം എട്രിയൽ സ്പാറ്റിയൽ ഡിഫക്ട് രോഗികളിൽ ശസ്ത്രക്രിയനടത്തിയതിനു മുൻപും ശേഷവും സുപ്പീരിയർ വീനകാവ, ഇൻഫീരിയർ വീനകാവകളിലെ പൾസ് തരംഗ ഡോപ്ളർ പ്രവാഹ നിരീക്ഷണം വിലയിരുത്തുന്നതിനുള്ള പഠനത്തെക്കുറിച്ച് രോഗികൾക്കു നൽകുന്ന കാര്യവിവരണപത്രം വായിച്ചു. [ ]
- എനിക്കുള്ള സംശയങ്ങൾ ദൂരീകരിച്ചു. [ ]
- ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതിന് എന്റെ മാത്രം തീരുമാനമാണെന്നും എനിക്ക് എപ്പോൾ വേണമെങ്കിലും ഇതിൽ നിന്നും പിൻമാറാം എന്നും ഞാൻ മനസ്സിലാക്കുന്നു. അത് എന്റെ ചികിത്സയെയോ എന്റെ നിയമ അവകാശങ്ങളെയോ ബാധിക്കുകയില്ലയെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഈ പഠനത്തിൽ ഞാൻ സ്വയമേവ പങ്കെടുക്കുന്നു. [ ]
- പഠനത്തെപ്പറ്റികൂടുതലറിയണമെങ്കിലോ പങ്കാളിയുടെ അവകാശങ്ങളെപ്പറ്റി അറിയണമെങ്കിലോ എനിക്ക് പ്രധാന ഗവേഷകനെ ബന്ധപ്പെടാനുള്ള നമ്പറുകൾ തന്നിട്ടുണ്ട്. [ ]
- ഈ സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് കിട്ടി. [ ]

രോഗിയുടെ/നിയമപരമായി അംഗീകൃതമായ പ്രതിനിധിയുടെ ഒപ്പ് (തള്ളവിരലടയാളം) ....

തീയതി :................/.........../ ഒപ്പിട്ടയാളിന്റെ പേര്.................

സാക്ഷിയുടെ പേര്......

പങ്കാളിയുമായുള്ള ബന്ധം...........

ഒപ്പ് ....

(സമ്മതം വാങ്ങുന്നയാൾ)

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

തിയതി

സമ്മതപത്രം വാങ്ങുന്ന ആളുടെ പേര്

സ്ഥലം

ഒപ്പ്

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
1	AGE	SEX	WEIGHT	HEIGHT	BSA	ASD SIZE MAX	INDEXED ASD	DEVICE	DEVICE SIZE	EXPIRATIONPI	EXPIRATION PI	EXPIRATION PI	EXPIRATION PI	INSPIRATION P	INSPIRATION P	INSPIRATION P	INSPIRATION P	EXPIRATION PI	EXPIRATION PI	EXPIRATION PI	EXPIRATION PI
2	44	M	70	151	1.713	10	5.837711617	COCOON	12	32		5.84	3.42	40.7		31.1	2.66	11.3		3.96	3.29
3	65	F	62	156	1.639	10	6.101281269	AGA	14	5.91		2.34	3.26	7.32		11.4	2.81	7.05		4.4	2.97
4	32	M	55	173	1.626	12	7.380073801	OCCLUTECH	15	9.15		5.35	2.56	12.2		2.97	2.48	15.8		7.82	1.82
5	28	F	58	151	1.559	13	8.33867864	PUSHMED	16	6.65		3.69	2.7	9.44	2.75	6.27	3.54	12.5		5.66	2.47
6	34	F	64	153	1.649	14	8.489993936	COCOON	18	6.34		4.6	3.27	4.51		2.14	2.72	11.2		3.34	3.1
7	13	F	41	143	1.276	11	8.620689655	COCOON	14	5.74	2.67	8.41	1.68	14.2	2.93	10.2	1.19	16.6		8.6	2.42
8	32	M	60	174	1.703	15	8.807985907	COCOON	18	10.3		7.46	1.81	11.3		4.48	1.77	9.9		7.4	1.39
9	7	M	17	114	0.733	7	9.549795362	COCOON	8	7.38		3.94	3.03	16.6		5.72	7.5	15.2		10.1	2.21
10	9	F	24	133	0.942	9	9.554140127	AGA	12	6.9		2.08	1.05	17.1		3.96	1.2	14.1		4.93	
11	9	M	24	126	0.916	9	9.825327511	AGA	12	7.35	5.1	3.56	4.86	13.9	4.71	6.46	8.08	16.6	2.76	4.98	2.37
12	54	F	55	153	1.53	17	11.11111111	HEART R	20	4.28		1.99	4.95	5.62		2.43	3.03	11.4		5.92	2.85
13	8	F	27	124	0.964	11	11.41078838	AGA	14	7.78	2.1	4.5	1.7	17.7	8.3	2.6	1.47	23.7		8.51	2.34
14	60	F	69	154	1.717	20	11.64822365	COCOON	32	6.25		4.55		5.89		4.18		17.6		4.58	
15	8	F	19.3	124	0.815	10	12.26993865	AGA	12	7.2	2.4	5.72	2.01	8.21	2	4.3	1.4	17.3		4.5	0.98
16	16	F	57	160	1.59	20	12.57861635	AMPLATZER	22	6.85	5.83	4.57	2.99	15.9	3.44	20.3	53.4	50.4	3.27	7.91	1.99
17	9	F	9	119	0.79	10	12.65822785	COCOON	12	5.53	2.5	2.66	2.82	9.4	6.2	5.16	7.62	12.9		6.25	1.19
18	5	M	21	116	0.823	11	13.36573512	PUSHMED	15	5.28		5.84	2.45	15.6	4.12	8.42	4.4	23.9		19.8	
19	28	M	51	168	1.543	21	13.60985094	PUSHMED	25	4.9	3.32	3.76	2.9	11.9	3.29	5.63	3.51	8.64	2.06	3.93	2.07
20	7	M	30	125	1.02	14	13.7254902	AGA	17	11.3		8.22	1.81	15.9		12.7	2.1	11		13.1	
21	6	M	19	119	0.792	11	13.88888889	PUSHMED	14	4.85	3.32	4.69	3.21	16.3	3.21	9.35	5.1	16.7		10.8	2.8
22	54	F	50	150	1.44	21	14.58333333	AGA	22	7.56		4.65	3.74	7.71		3.17	4.41	16		5.85	
23	56	M	60	161	1.64	24	14.63414634	AGA	28	3.61		2.61	2.59	9.39		6.84	4.98	4.65	4.01	3.24	2.32
24	5	M	15.7	103	0.67	10	14.92537313	COCOON	16	5.75	4.26	2.75		8.18	7.38	2.64	3.44	18.2		4.86	2.36
25	36	F	77	153	1.808	28	15.48672566	COCOON	32	11.9		6.6	2.49	4.91		1.71	2.43	6.72		4.62	2.18
26	49	F	65	154	1.67	26	15.56886228	PUSHMED	30	11.5	3.12	2.11	3.14	18.6		8.86	3.35	15.9		3.46	3.01
27	7	M	14	106	0.642	10	15.57632399	HEART R	14	4.91		2.52	1.11	7.3	5.18	3.33	3.06	16.6		5.63	1.85
28	10	M	26	136	0.991	16	16.14530777	HEART R	18	4.87		6.35	2.25	15.8		5.15	4.1	12.8		8.53	3.29
29	5	F	17	116	0.74	12	16.21621622	HEART R	14	5.75		4.32	3.99	15.7		6.69	5.58	16.3		6.43	2.95
30	37	F	58	150	1.554	26	16.73101673	HEART R	28	9.52	6	8.13	6.88	9.57	6.1	8.71	7.32	11.9		3.14	
31	5	F	21.7	115	0.832	14	16.82692308	PUSHMED	18	6.47	3.53	2.75	1.03	11.7	2.76	2.27	1.35	14.4		3.6	1.85
32	12	F	36	151	1.23	21	17.07317073	COCOON	26	3.69	2.49	2.35	2.18	10.8	3.55	3.9	2.51	12.3		4.93	1.46
33	9	F	28	126	0.989	17	17.18907988	COCOON	18	4.56		3.92	1.97	27.4		5.07	1.42	8.98		4.39	2.04
34	12	F	42	161	1.37	24	17.51824818	AGA	28	7.08	3.54	3.95	2.65	9.89	8.71	7.18	7.12	10.4		8.56	2.9
35	26	F	48	152	1.42	25	17.6056338	COCOON	30	6.56		4.44	2.96	12.9	5.99	3.29	4.48	10.2		3.49	2.4
36	7	F	21.2	119	0.84	15	17.85714286	FIGULLE FLEX I	18	6.12		3.43	0.77	16		5.47	1.63	23.1		15.7	4.54
37	66	F	49	139	1.375	25	18.18181818	AGA	28	8.78		2.14	5.88	10.7		5.74	4.12	28.4		14.5	3.39
38	6	F	17.9	118	0.768	14	18.22916667	AGA	25	7.45	4.42	2.51	1.33	11.3	5.09	2.82	1.97	13.1		3.7	2.23
39	5	F	18	117	0.765	14	18.30065359	AGA	14	5.42		3.99	1.61	11.6		5.05	2.04	12.7		6.82	
40	4	F	11	96	0.54	10	18.51851852	AGA	12	2.13	4.28	4.21	3.63	4.15		3.61	1.24	16.7		4.98	2.35
41	8	M	26	130	0.968	21	21.69421488	HEART R	24	5.33		2.42	1.45	11.5		4.45	2.59	19.2		7.53	1.87
42	6	M	14	103	0.63	14	22.22222222	AGA	18	6.62		7.39	3.06	13.7		11.5	3.66	18.2		6.17	1.94
43	5	F	16	100	0.667	15	22.48875562	PUSHMED	17	10	3.23	6.36	1.73	8.65	6.81	2.99	4.06	16.8		7.2	1.4
44	10	F	32.5	137	1.11	25	22.52252252	COCOON	28	7.95		6.02	1.73	11.1	5.33	3.13	7.02	16.1		9.91	2.24
45	7	F	25	120	0.913	21	23.00109529	COCOON	22	13.3		6.91	2.29	29.9	2.39	13	2.33	19.9		8.04	
46	4	F	13	88	0.564	13	23.04964539	COCOON	17	9.62		5.85		18.6	1.98	8.87	1.7	21		5.82	1.86
47	7	M	17.4	110	0.73	17	23.28767123	PUSHMED	20	5.27		5.05	3.16	11	4.01	5.41	4.2	17.1		5.54	
48	5	F	23	125	0.894	21	23.48993289	AGA	24	8.4		5.03		15.8		5.69		8.5		6.34	
49	6	M	13	107	0.62	15	24.19354839	COCOON	18	5.23		4	1.58	7.03	7.48	3.18	1.04	13.9		5.75	1.9
50	8	F	15	110	0.677	17	25.11078287	COCOON	20	5.48	1.76	3.08	1.83	9.09	4.8	3.12	2.61	19.6		6.17	
51	6	M	16	105	0.68	18	26.47058824	HEART R	22	5.35	5.67	3.16	4.44	8.46	3.56	4.53	3.66	11.2		7.96	3.44

	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP
1	INSPIRATION P	INSPIRATION P	INSPIRATION P	INSPIRATION P	EXPIRATION P(	EXPIRATION P(	EXPIRATION P(	EXPIRATION P(	ISNPIRATION P	INSPIRATION P	INSPIRATION P	INSPIRATION P	EXPIRATION P(	EXPIRATION P(	EXPIRATION P(	EXPIRATION P(	INSPIRATION P	INSPIRATION P	INSPIRATION P	INSPIRATION P	EXPIRATION 6 E
2	17		5.55	3.42	8.39		8.55	2.49	18.5		3.82	2.26	13.4		3.78	3.66	22.7		3.18	4.01	
3	16.9		6.4	3.61	10.1		8.18	2.32	8.35		6.19	1.83	10.1		4	2.3	16.9		7.13	2.94	9.08
4	15.8		7.82	1.82	8.07		3.67	2.25	8.86		5.04	2.63	18.3		7.63	1.41	20.7		12.2	1.91	8.6
5	13.9	3.52	7.95	1.88	6.63		5.02	2.82	8.21		7.48	2.57	14.9		7.22	1.62	19.6		11.2	1.6	8.92
6	11.5		4.55	2.6																	22.2
7	21.5		8.74	2.69	12.7		6.2	2	11.9		7.18	1.47	12.6		10.2	1.87	17.8		5.98	1.63	9.49
8	8.93		6.84	1.4	2.96		2.09	2.63	4.99		4.86	2.43	4.98		5.16	1.49	13.2		12.1	2.34	7.67
9	15.5		6.64	1.89	7.68		6.45	1.5	10.3		5.58	4.76	16.4		9.99	2.06	19.2		7.96	1.89	6.38
10	17.9		4.3																		12.3
11	15.8	2.81	5.97	1.99	7.06	2.75	5.63	1.59	7.79		3.39	3.69	14.3		6.53	2.15	15.9		9.79	2.26	6.69
12	23.9		8.06	4.42	8.39		5.08	3.45	11.1		4.11	3.08	16.8		3.23	2.08	32.2		6.86	3.12	
13	23.2		5.41	2.64	16.1		11.7	1.67	24.5		14.2	1.7	16.8		6.55	2.12	21.8		8.25	2.15	10.8
14	20.2		3.67		9.09		3.6	2.82	7.88		6.29	8.67	11.6		1.72	3.37	18.7		3.75	1.94	4.27
15	16.9		8.1	1.8	8.47		5.61	3.68	9.21		3.5	7.61	16.9		11.4		15.5		10.7		
16	13.6	4.01	10.3	2.68	7.49	4.8	5.02	2.18	5.83	5.25	6.77	2.91	14.9	3.87	15.4	2.06	13	4.16	15	2.21	
17	15.4		4.86	2.14																	10.6
18	13.7		8.42		4.5		1.87	1.38	5.94		4.22	4.03	11.4		14.5		10.8		7.18	1.58	5.47
19	8.47	3.75	2.8	2.04																	15.8
20	19.5		8.99	1.7	5.24		3.17	1.5	5.8		3.62	1.23	10.5		11.2	1.31	20.9		9.63	1.32	9.33
21	18.3		10.1	3.31																	3.57
22	16.6		8.62		10.8		4.53	5	14.1		4.91	5.53	15		5.73	2.21	19.8		5.39	2.53	
23	6.84	3.45	6.24	3.32																	
24	19.9		4.06		6.96	6.01	3.44	3.64	11.8	4.58	2.47	6.28	15.1		5.84	1.27	18.4		4.67	1.61	7.39
25	20.9		5.57		14.4		2.61	1.31	20.2		1.35	1.8	13.5		12.1		18.8		1.72	1.83	
26	18		5.8	2.9	11	1.89	2.6	2.89	15.3	2.84	6.22	6.61	15.1	2.71	7.62	1.67	21	1.79	2.98	1.78	15.8
27	17.7		4.25	1.89																	10.4
28	18.1		8.29	3.12	3.3		3.01	1.45	6.42		6.47	0.976	11.1		8.21	1.46	19.7		6.18		9.95
29	15.1		5.1	2.23	5.96		4.73	1.29	15.1		7.63	2.62	12.8		8.83	1.73	14.9		6.74	1.36	
30	13.2		4.83		12.8	3.2	12	3.53	14.1	3.8	14	3.94	11.8		4.44	1.33	14.8		4.17	0.923	7.85
31	17.3		2.91	2.24	8.03		3.09	2.24	17.3		4.4	1.55	11.8		8.73	2.23	23.3		6.65	3.54	17.7
32	12.7		7.19	2.89	4.98		3.87	1.39	11.6	3.01	6.7	3.36	9.88		2.7	1.18	12.5		5.76	1.63	
33	15.9		7.54	2.71	7.48		3.4	1.62	13.1		6.77	1.92	10.5		9.66		11		3.53		10.7
34	11.7		8.87	2.7	6.55	2.54	3.95	2.6	9.63	2.3	5.29	2.13	9.7		5.83	2.21	11.3		8.03	1.65	
35	11.2		2.86	2.77																	
36	20.9		17.7		15.2		13.9	2.78	31.4		22.3	5.51	15.4		7.26		22.7		10.8		
37	17.2		4.01	5.94	20.7		12	3.55	3.17		11.3	17.1	10.7		3.36	2.7	21.1		16.7		6.57
38	14.9		3.81	2.34	3.58		1.58	0.982	9.52		6.27	1.86	15.1		6.24	1.98	19.3		3.7	1.67	
39	15.8		5.71		6.9		3.27	1.49	10.5		4.21	3.98	10.9		9.82		15.5		8.81		6.38
40	12.4		4.14	2.04																	
41	22.3		5.9	2	4.13		2.09	2.24	4.28		1.58	1.18	18.3		12.9	3.82	15.9		9.56	3.01	6.62
42	18.9		7.21	2.46	15.3		10.4	7.27	18.7		13	8.45	15.4		8.09	6.13	20.4		11.1	6.74	2.89
43	18.9		6.12	1.61	6.5		3.35	1.33	10.5		9.48	1.2	14.6		10.7	1.98	21.7		10.5	1.54	5.64
44	24		12.4	4.25																	
45	25.9		4.37		9.35		6.14	2.18	22.7		13.8	2.24	16.1		13.1	2.02	25.1		8.62		20.6
46	21		6.13	2.57	9.57		3.97	2.1	20.7		13.4	2.01	16.8		8.86	1.46	19.9		7.21	1.83	
47	20.4		5.81		5.22		3.15	2.02	13.1		4.9	2.09	21		8.87		21.7		4.55		6.84
48	13.5		2.61		7.61		4.61		18.6		10.3		21.7		8.19		25.6		11		9.58
49	16.2		3.32	1.69	4.08	4.28	3.23	2.09	5.52	6.44	2.09	5.87	11.3		7.41	1.04	9.76		6	2.27	
50	23.9		5.32		9.54		6.47	1.97	12.7		7.04	2.03	15		4.9		19.5		4.66		7.58
51	14.2		6.1	2.79																	

	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH	BI	BJ	BK
1	INSPIRA'	INSPIF	INSPIRA	INSPIR	EXPIRATI	EXP	EXPIRA	EXPIRATI	INSPIF	INSPI	INSPIRA	INSPIRA	PRE IVC EXPIRA	PRE IVC INSPIR	PRE IVC INSPIR	PRE SVC EXPIRA	PRE SVC INSPIF	PRE SVC INSPIF
2													0.1825	0.764127764	4.187001447	0.350442478	0.326470588	0.931595365
3	6.8		7.4	2.25	7.05		4.52	1.22	7.69		7.7	2.12	0.395939086	1.557377049	3.933375368	0.624113475	0.378698225	0.606777838
4	13		2.37	2.6	9.36		4.57	1.6	10.6		5.02	2.1	0.584699454	0.243442623	0.41635514	0.494936709	0.494936709	1
5	12.4		7.19	2.47	16		10.3	2.03	14.1		5.45	2.44	0.554887218	0.664194915	1.196990836	0.4528	0.571942446	1.263123777
6	37.3		27.9	8.06	9.03		7.09		11		9.11		0.72555205	0.474501109	0.653986311	0.298214286	0.395652174	1.326737829
7	20		9.27	3.72	12.3		6.72		13.5		5.91		1.465156794	0.718309859	0.490261426	0.518072289	0.406511628	0.784661979
8	9.14		7.05	1.86	6.1		5.6		9.2		9.3		0.724271845	0.396460177	0.547391397	0.747474747	0.765957447	1.024726855
9	15.3		6.3	1.07	11.9		6.75	1.26	15.1		9.82	1.91	0.533875339	0.344578313	0.645428414	0.664473684	0.428387097	0.644701373
10	16.8		11.6		18.8		6.63		21.3		6.94		0.301449275	0.231578947	0.768218623	0.34964539	0.240223464	0.687048852
11	13.8		8.9	7.9	15.3		15.9		15.7		8.32		0.484353741	0.464748201	0.95952227	0.3	0.377848101	1.259493671
12													0.464953271	0.432384342	0.929952252	0.519298246	0.337238494	0.649411964
13	24		11.8	2.04	13.3		7.63	1.62	15.6		12.4	1.24	0.57840617	0.146892655	0.25396108	0.35907173	0.233189655	0.649423599
14	3.59		2.04	2.46	14.5		12.1		21.6		10.9		0.728	0.709677419	0.97483162	0.260227273	0.181683168	0.698171127
15													0.794444444	0.523751523	0.659267651	0.260115607	0.479289941	1.84260355
16													0.667153285	1.27672956	1.91369748	0.156944444	0.757352941	4.825611661
17	19.9		18.9	1.74	12.6		11.5		17.2		13.2		0.481012658	0.54893617	1.141209406	0.484496124	0.315584416	0.651366234
18	17.6		16	5.63	14.5		10.5	0.86	15		8.15	1.65	1.106060606	0.53974359	0.487987355	0.828451883	0.61459854	0.741863894
19	23		8.1	1.65	11.8		6.8		11.2		5.04		0.767346939	0.473109244	0.61655194	0.454861111	0.330578512	0.726768027
20	6.21	2.79	3.47	1.29	15.4		12.8		18.3		12.1		0.727433628	0.798742138	1.098027514	1.190909091	0.461025641	0.387120767
21	20.3		7.05	6.55	19.9		15		15.6		8.82	1.31	0.967010309	0.573619632	0.593188745	0.646706587	0.551912568	0.85342036
22													0.615079365	0.411154345	0.668457387	0.365625	0.519277108	1.420245083
23													0.72299169	0.728434505	1.007528185	0.696774194	0.912280702	1.309291748
24	14.8		8.33		13.5		9.15		19.1		5.97		0.47826087	0.322738386	0.674816626	0.267032967	0.204020101	0.764025891
25													0.554621849	0.348268839	0.627939271	0.6875	0.266507177	0.387646803
26	17.1		6.8		15		2.15		16.9		5.93		0.183478261	0.476344086	2.596188147	0.217610063	0.322222222	1.480732177
27	7.37		2.33	3.99	18.3		5.92		20.9		6.14		0.513228289	0.456164384	0.888796477	0.339156627	0.240112994	0.707970818
28	21.7		12.2	1.58	15.2		11		22.7		10		1.303901437	0.325949367	0.249980066	0.66640625	0.45801105	0.687285045
29													0.751304348	0.42611465	0.56716649	0.394478528	0.337748344	0.856189427
30	7.85		14.3		7.4		8.8		8.47		6.16		0.853991597	0.910135841	1.065743322	0.263865546	0.365909091	1.386725536
31	30.2		3.87	1.5	15		13.6	1.94	27		14.6	3.12	0.42503864	0.194017094	0.456469308	0.25	0.168208092	0.67283237
32													0.636856369	0.361111111	0.567021277	0.400813008	0.566141732	1.412483429
33	20.3		15.7	3.23	9.28		7.7	1.61	19.7		6.62	2.7	0.859649123	0.185036496	0.215246537	0.488864143	0.474213836	0.970031948
34													0.557909605	0.725985844	1.301260703	0.823076923	0.75811965	0.921079958
35													0.676829268	0.25503876	0.376814023	0.342156863	0.255357143	0.746316005
36													0.560457516	0.341875	0.609992711	0.67965368	0.846889952	1.246061012
37	5.86		15.4		5.55		2.42	2.06	5.69		10.1	4.08	0.243735763	0.536448598	2.200943314	0.51056338	0.233139535	0.456631917
38													0.336912752	0.249557522	0.740718542	0.282442748	0.255704698	0.90533285
39	13.3		4.89	7.83	14.6		11.8	1.06	15.8		9.11		0.736162362	0.435344828	0.591370668	0.537007874	0.361292405	0.672974127
40													1.976525822	0.869879518	0.440105314	0.298203593	0.333870968	1.119607462
41	13.5		7.73		16.6		8.39		20.2		10.2		0.454033771	0.386956522	0.852263744	0.3921875	0.264573991	0.674610973
42	14		13.3		12.5		10.7		14		11.8		1.116314199	0.839416058	0.751953221	0.339010989	0.381481481	1.125277628
43	19.3		8.73	1.78	15.9		7.68		21.7		9.66		0.636	0.34566474	0.543498019	0.428571429	0.323809524	0.755555556
44													0.757232704	0.281981982	0.372384843	0.61552795	0.516666667	0.839387824
45	24.3		13.7	2.24	14.5		6.73	1.37	16.6		8.52	1.7	0.519548872	0.434782609	0.83684641	0.404020101	0.168725869	0.417617511
46													0.608108108	0.476888172	0.784205496	0.277142857	0.291904762	1.053264605
47	10.8		4.3	1.86	17		10.1	1.47	16.5		8.49	1.98	0.958254269	0.491818182	0.513243924	0.323976608	0.284802922	0.879087917
48	20.2		18.2		16.8		16.1		21.2		14.2		0.598809524	0.360126582	0.601404233	0.745882353	0.193333333	0.259200841
49													0.764810356	0.452347084	0.591443812	0.413669065	0.204903272	0.495415996
50	7.86		3.3	1.37	20.5		10.1	2.85	22.3		8.64	1.31	0.562043796	0.343234323	0.61068964	0.314795918	0.222594142	0.707106189
51													0.590654206	0.535460993	0.906555795	0.710714286	0.429577465	0.604430604
52																		

	BL	BM	BN	BO	BP	BQ	BR	BS	BT	BU	BV	BW
1	POST IVC EXPIR	POST IVC INSPII	POST IVC INSPII	POST SVC EXPIF	POST SVC INSP	POST SVC INSP	6 MONTHS IVC E	6 MONTHS IVC II	6 MONTHS IVC II	6 MONTHS SVC I	6 MONTHS SVC I	6 MONTHS SVC II
2	1.019070322	0.206486486	0.202622412	0.729850746	0.140088106	0.191940758	0.17	0.46	2.705882353	0.3	0.29	0.966666667
3	0.80990099	0.741317365	0.915318507	0.396039604	0.421893491	1.065281065	1.034140969	1.088235294	1.052308463	0.641134752	1.00130039	1.561762777
4	0.454770756	0.568848758	1.25084727	0.416939891	0.589371981	1.413565825	0.262790698	0.182307692	0.693737236	0.488247863	0.473584906	0.969968209
5	0.757164404	0.911084044	1.203284305	0.484563758	0.571428571	1.179263949	0.521300448	0.57983871	1.112292751	0.64375	0.386524823	0.600426909
6	0.61	0.5	0.819672131	0.26	0.3	1.153846154	0.617117117	0.747989276	1.212070214	0.785160576	0.828181818	1.054792922
7	0.488188976	0.603361345	1.235917593	0.80952381	0.335955056	0.415003305	1.232876712	0.4635	0.37595	0.546341463	0.437777778	0.801289683
8	0.706081081	0.973947896	1.379371183	1.036144578	0.916666667	0.884689922	0.370273794	0.771334792	2.083147132	0.918032787	1.010869565	1.101125776
9	0.83984375	0.541747573	0.645057575	0.609146341	0.414583333	0.680597264	0.959247649	0.411764706	0.429257978	0.567226891	0.650331126	1.146509688
10	0.54	0.21	0.388888889	0.21	0.11	0.523809524	0.400813008	0.69047619	1.722689076	0.352659574	0.325821596	0.923898342
11	0.797450425	0.435173299	0.545705771	0.456643357	0.61572327	1.348367958	1.704035874	0.644927536	0.378470633	1.039215686	0.529936306	0.509938709
12	0.605482718	0.37027027	0.611529049	0.192261905	0.213043478	1.108089918	0.31	0.31	1	0.3	0.23	0.766666667
13	0.726708075	0.579591837	0.797557998	0.389880952	0.378440367	0.970656208	0.612037037	0.491666667	0.80332829	0.573684211	0.794871795	1.38555634
14	0.396039604	0.79822335	2.015513959	0.148275862	0.200534759	1.352443726	0.585480094	0.568245125	0.970562674	0.834482759	0.50462963	0.604721457
15	0.662337662	0.380021716	0.573758276	0.674556213	0.690322581	1.023372949	0.35	0.3	0.857142857	0.25	0.27	1.08
16	0.670226969	1.161234991	1.732599619	1.033557047	1.153846154	1.116383616	0.33	0.7	2.121212121	0.3	0.34	1.133333333
17	0.5	0.4	0.8	0.35	0.21	0.6	0.28490566	0.949748744	3.333555193	0.912698413	0.76744186	0.840849343
18	0.415555556	0.71043771	1.709609464	1.271929825	0.664814815	0.522681992	1.230347349	0.909090909	0.738889639	0.724137931	0.543333333	0.75031746
19	0.71	0.37	0.521126761	0.4	0.2	0.5	0.286075949	0.352173913	1.231050404	0.576271186	0.45	0.780882353
20	0.604961832	0.624137931	1.031698031	1.066666667	0.46076555	0.431967703	0.879957128	0.558776167	0.635003854	0.831168831	0.661202186	0.79550888
21	1	0.61	0.61	0.45	0.85	1.888888889	0.546218487	0.34729064	0.635809019	0.753768844	0.565384615	0.750076923
22	0.419444444	0.34822695	0.830209948	0.382	0.272222222	0.712623618	0.91	0.7	0.769230769	0.56	0.73	1.303571429
23	0.9	0.99	1.1	0.92	1	1.086956522	0.92	0.82	0.891304348	0.79	0.99	1.253164557
24	0.494252874	0.209322034	0.423512022	0.386754967	0.253804348	0.656240694	0.554803789	0.562837838	1.014480883	0.677777778	0.312565445	0.461162132
25	0.18125	0.066831683	0.368726528	0.896296296	0.091489362	0.102074908	0.95	0.7	0.736842105	0.79	0.59	0.746835443
26	0.236363636	0.406535948	1.719959779	0.504635762	0.141904762	0.28120235	0.337974684	0.297660819	1.176599426	0.143333333	0.350887574	2.448052842
27	0.95	0.97	1.021052632	0.97	0.84	0.865979381	0.352884615	0.31614654	0.895892103	0.323497268	0.293779904	0.908137204
28	0.912121212	1.007788162	1.104884031	0.73963964	0.313705584	0.424133006	0.662311558	0.562211982	0.848863311	0.723684211	0.440528634	0.608730477
29	0.793624161	0.505298013	0.636696862	0.63984375	0.452348993	0.65572674	0.97	0.8	0.824742268	0.78	0.67	0.858974359
30	0.9375	0.992907801	1.059101655	0.376271186	0.281756757	0.748813002	2.012738854	1.821656051	0.905063291	1.189189189	0.727272727	0.611570248
31	0.384806974	0.25433526	0.66094244	0.739830508	0.285407725	0.385774474	0.745762712	0.128145695	0.171831728	0.906666667	0.540740741	0.596405229
32	0.777108434	0.577586207	0.743250468	0.273279352	0.4608	1.686186667	0.9	0.72	0.8	0.77	0.85	1.103896104
33	0.454545455	0.516793893	1.136946565	0.92	0.320909091	0.348814229	0.604672897	0.773399015	1.279037011	0.829741379	0.336040609	0.404994396
34	0.603053435	0.549325026	0.910906056	0.60103028	0.710619469	1.18223428	0.78	0.9	1.153846154	0.9	0.85	0.944444444
35	0.97	0.86	0.886597938	0.94	0.76	0.808510638	0.89	0.55	0.617977528	0.73	0.75	1.02739726
36	0.914473684	0.71019108	0.776611832	0.471428571	0.475770925	1.009211053	0.7	0.67	0.957142857	0.77	0.95	1.233766234
37	0.579710145	3.56466877	6.149053628	0.314018692	0.791469194	2.520452494	0.639497717	2.627986348	3.811450399	0.436036036	1.775043937	4.070865227
38	0.441340782	0.658613445	1.492301251	0.412345033	0.191709845	0.46391324	0.55	0.5	0.909090909	0.6	0.58	0.966666667
39	0.473913043	0.400952381	0.846046308	0.900917431	0.563387097	0.630898101	0.60031348	0.367669173	0.612461964	0.808219178	0.576502278	0.712398412
40	2.4	1	0.416666667	0.9	0.83	0.922222222	1.7	0.99	0.582352941	0.75	0.6	0.8
41	0.506053269	0.364158879	0.729486205	0.70491803	0.601257862	0.852947199	0.732628399	0.572592593	0.781559374	0.505421687	0.504950495	0.999067726
42	0.679738562	0.695187166	1.022727273	0.525324675	0.544117647	1.035774013	0.92733564	0.95	1.024440299	0.856	0.842857143	0.984646195
43	0.515384615	0.902857143	1.751812367	0.732876712	0.483870968	0.660235152	0.992907801	0.452331606	0.455562546	0.483018868	0.44516129	0.921622984
44	1.6	0.87	0.54375	0.88	0.9	1.022727273	0.78	0.58	0.743589744	0.8	0.8	1
45	0.656684492	0.607929515	0.925755858	0.813664596	0.343426295	0.422073538	0.229126214	0.563786008	2.460591477	0.464137931	0.513253012	1.105820011
46	0.414830036	0.647342995	1.560471653	0.527380952	0.362311558	0.687001599	0.7	0.85	1.214285714	0.67	0.59	0.880597015
47	0.603448276	0.374045802	0.619847328	0.422380952	0.209677419	0.496417791	0.416666667	0.398148148	0.955555556	0.594117647	0.514545455	0.866066607
48	0.605781866	0.552763441	0.91413010	0.377419355	0.4296875	1.138488248	0.313152401	0.900990099	2.877161716	0.958333333	0.669811321	0.698933552
49	0.791666667	0.378623188	0.47826087	0.655752212	0.614754098	0.937479259	0.86	0.83	0.965116279	0.71	0.57	0.802816901
50	0.678197065	0.554330709	0.817359345	0.326666667	0.238974359	0.73155416	0.296833773	0.419847328	1.414418999	0.492682927	0.387443946	0.786396128
51	1.1	0.98	0.890909091	1.1	0.9	0.818181818	0.7	0.71	1.014285714	0.8	0.6	0.75
52												

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