

## VENTRICULAR FUNCTION ASSESSMENT IN PATIENTS OF ATRIAL SEPTAL DEFECT BY STRAIN IMAGING BEFORE AND AFTER CORRECTION

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### ABSTRACT

**Background:** Atrial septal defect (ASD) is a common congenital heart disease associated with volume overload of Right ventricle (RV) with variable effect on Left ventricle (LV). Two-dimensional (2D) Strain analysis is a new tool for objective analysis of myocardial function. This prospective study evaluated the systolic function of right and left ventricle by conventional 2D echo and strain echo and measured changes in cardiac hemodynamics that occurred in patients of ASD before and after correction.

**Patients and methods:** 2D echo and strain analysis of each patient before and at 48 hrs, 3 months and 6 months after correction was performed. Routine 2D echo parameters and global longitudinal strain of both ventricles were measured.

**Result:** Improvement in LV ejection fraction ( $p=0.0001$ ) and myocardial performance index (MPI) ( $p<0.0001$ ) occurred at the end of 6 months, whereas decrease in RV MPI ( $p<0.0001$ ) and tricuspid annular plane systolic excursion ( $p<0.0001$ ) became statistically significant after 3 months of ASD correction. In comparison to conventional 2D echo, global longitudinal strain of RV decreased significantly only after 48 hours of ASD correction while there was no improvement in left ventricular global longitudinal strain after 6 month of correction.

**Conclusion:** There was improvement in RV function with subtle change in LV function by strain imaging and most of these changes were completed within 6 months of ASD correction and nearly correlated with conventional 2DEchocardiography.

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### INTRODUCTION

Atrial septal defect is the most common cause of chronic right heart volume overload. Over time, atrial shunts tend to increase due to a physiological ASD enlargement and an age dependant decline of left ventricular compliance. Natural history studies have shown that right heart volume overload caused by Atrial shunt tend to increase progressively over time, thereby affecting cardiac performance even in asymptomatic patients [1, 2, 3]. Thus one of the targets of ASD closure is prevention of progressive cardiac enlargement in asymptomatic patients. The ideal ASD treatment should aim both to unload the right heart and also to normalize the left to right volumetric imbalance.

The previously mentioned studies have clearly shown the dramatic volumetric changes in both the atria and ventricles, both in adult as well as pediatric population with some minor differences on the timing of these changes and regarding the impact of age at closure on the speed and extent of the changes. These primarily reflect the changes in pre load and changes occurring in right and left ventricular function both in the presence of ASD as well as after its closure by surgical or

percutaneous route, which were subsequently analyzed independent of these volumetric changes.

The reported effects of ASD on left ventricular function are variable. In most echocardiographic studies, left ventricular systolic function was normal despite the RV volume overload [4, 5, 6, 7]. However, a reduced ejection fraction is often found in patients with ASD with severe right ventricular volume overload [8]. Cineangiographic studies suggest abnormalities of left ventricular function affecting the systole and diastole [9,10,11]. The effect of ASD on right ventricular function appears to be more consistent. Although delayed right ventricular contraction has been detected by radionuclide studies in the absence of conduction system defects [12], echocardiographic assessment has shown that right ventricular function to be normal or exagerrated.

Novel echocardiographic methods have been developed to quantify global as well as regional left ventricular (LV) function and are used for diagnostic and prognostic evaluation of various cardiovascular diseases. In contrast, quantitative assessment of right ventricular (RV) function is still challenging due to its complex anatomy and thin wall structure, and therefore not incorporated into daily clinical practice. Two-dimensional (2D) strain and SR (strain rate) analyses are Doppler-independent novel techniques that

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measure myocardial movement and deformation [13]. While this method has been used to assess LV function earlier, it has yet rarely been used to examine both LV and RV function simultaneously. Since RV function is an important prognostic factor in patients with congenital heart disease, the objective of the present study is to quantify both LV as well as RV function in patients with chronic RV volume overload due to an atrial septal defect (ASD) before and after its correction.

## MATERIALS AND METHODS

**Population:** After approval from the institutional ethics committee, and written consent of the patient or his or her guardian, 32 consecutive patients of ostium secundum ASD with a significant left to right shunt and age more than 2 years who underwent correction of ASD (percutaneously or surgically) between January 2015 to July 2016 were taken into study. The demographic details including age and sex were collected. ASD patients with any other cardiac co morbidities regardless of congenital or acquired heart diseases and patients with right-to-left shunting due to severe pulmonary hypertension were excluded.

### Echocardiography

All patients with Ostium secundum ASD underwent usual clinical and trans-thoracic echocardiography (TTE) assessment. Those patients in whom ASD closure was indicated were assessed for suitability of percutaneous closure by transthoracic echocardiography with 4 and /or 7 MHz probes (Vivid 6, General electronics) on outpatient basis. 2-D echocardiography was performed to determine the situs, apex position, atrioventricular connections, great vessel relation and abnormalities, ventricular dimensions and functions, state of cardiac valves, venous connections, and any intra cardiac shunts. M-mode echocardiography was performed to measure the cardiac chamber sizes and quantities left ventricular wall thickness, end systolic and end diastolic diameters and volumes and systolic function. Pulsed Wave Doppler echocardiography: Pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess left ventricle (LV) filling. A multitude of indices such as peak E and A velocity, their ratio, and deceleration times were derived from this velocity pattern and proposed as markers for diastolic function. A sample volume was placed between the mitral leaflet tips during diastole to record a crisp velocity profile. Tissue Doppler Echocardiography was performed to measure tissue velocities within LV myocardium & the Tei index (myocardial performance index).

Left and right atrial volume were estimated using the length-diameter ellipsoid method and were indexed to body surface area of the individual patient.

LV Tei index was measured by modified method using a built-in software by introducing the time interval from the end to the onset of the left ventricular inflow (a) and the LV ejection time (b) by TDI (Tissue Doppler Imaging) of the lateral mitral annulus and calculated automatically by following the equation  $(a-b)/b$ . In RV Tei index calculation, a=time interval between the end and onset of tricuspid annular diastolic velocity; b=RV ejection time.

RV TAPSE (Tricuspid Annulus Plane Systolic Excursion) was calculated using M-mode with cursor placed at the

junction of RV free wall and tricuspid valve. The amplitude of excursion of tricuspid annulus from the base towards the apex in systole was defined as TAPSE.

Standard Echocardiographic views like Apical 4-chamber, parasternal long axis, short axis and sub costal bi-caval were taken with TTE and in those patients with a poor echo window, transesophageal echocardiography was done to diagnose the ASD and study the hemodynamic effects of ASD on the heart before closure. Further echocardiographic follow up was done to detect changes in ventricular dimensions and myocardial deformations occurring at 48 hrs, 3 months and later at 6 months after surgical or percutaneous ASD closure. Routine post op echocardiography was performed at 1 month and after 12 month as per institutional protocol.

### Strain imaging

For longitudinal strain analysis, gray-scale images were recorded from the apical four-, two- and three-chamber views. A frame rate of 80-100 frames/sec was used for storage and analysis. The images were optimized to visualize the myocardial walls. The analysis was performed using the two-dimensional strain program. In brief, the endocardial border was manually traced at end systole. Tracking was automatically performed, and the analysis was accepted after visual inspection and when the software indicated adequate tracking. If tracking was suboptimal, the endocardial border was retraced. If satisfactory tracking was not accomplished within 5 minutes, the nontracking segments were excluded from the analysis. The end-systolic strain values were measured at aortic valve closure. The global longitudinal strain of LV (including the septum) and RV (free wall only) longitudinal strain was calculated by averaging all the measured segmental values; (as shown in figure 1A and B)

### Procedural details

The ASD was assessed by trans-thoracic echocardiography (trans-esophageal; if anatomy is not clear by trans-thoracic echocardiography). In this study, patients with at least 5mm of rim in all planes were considered for device closure. Amplatzer septal occluder (AGA Medical corp., Golden Valley, MN, USA) was used for the closure of ASD which is a self-expandable, double-disc device made from the nitinol wire mesh. The device size was at least 2mm bigger than the size of the defect. The defect which was not suitable for device closure was closed in CTVS department under cardiopulmonary bypass. Aspirin at the dose of 5mg/kg or clopidogrel at 3mg/kg were given to all patients after discharge for 6 months. Routine post op echocardiography was performed at 1 month and after 12 month as per institutional protocol.

### Statistical analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 20.0.1 and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables.

Where the data is normally distributed, Continuous variables were presented as mean  $\pm$  SD and compared using 2 tailed paired Student t test. Comparison between pre, post and follow up was made by one way ANOVA test (2 tailed) with post hoc analysis by tukey test.

P-value ≤ 0.05 was considered statistically significant.

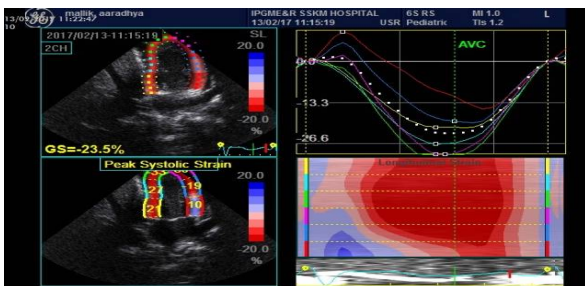
**RESULT & ANALYSES**

Age and sex distribution with regard to ASD size less than or greater than 20mm as shown in table 1:

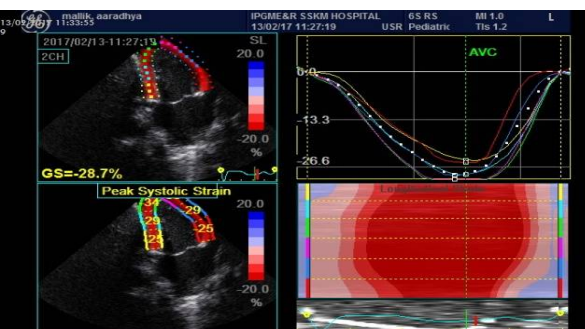
**Table 1** Age and sex distribution with regard to ASD size less than or greater than 20mm.

Male (n=32)	Female(n=32)	Age>15 yrs(n=32)	Age<15 yrs(n=32)	ASD size<20mm(n=32)	ASD size>20mm(n=32)
10(31.3%)	22(68.8%)	14(43.8%)	18(56.3%)	18(56.3%)	14(43.8%)

**Comparative changes in 2D - Echocardiography:** Changes in the LV and RV parameters are shown in figure 2. No significant change in LA volume (23.97±3.9 to 23.85±2.81, p=0.62) was observed, while decrease in RA volume was observed in 2D echocardiography which was statistically significant (35.85±2.80 to 31.86±3.03, p<0.0001) at 6 months. Similarly, there was significant improvement in LV end diastolic diameter (34.57±6.3 to 38.55±5.9,p=0.04), LV ejection fraction (53.91±5.13 to 59.28±4.64, p=0.0001) and LV myocardial performance index (0.36±0.02 to 0.32±0.02, p<0.0001) which were observed at the end of 6 month follow up in 2D echocardiography.



**Figure 1A** Global longitudinal strain imaging of Left ventricle in patient of atrial septal defect before correction. Apical four-chamber view is shown. Red, white and blue line represent different segment of left ventricle while dotted lines represents global longitudinal strain.



**Figure 1B** Global longitudinal strain imaging of Right ventricle in patient of atrial septal defect before correction. Apical four-chamber view is shown. Red, white and blue line represent different segment of right ventricle while dotted lines represents global longitudinal strain.

In comparison to LV parameters (as shown in the figure 2), there was decrease in RV diameter (38.58±4.73 to 33.86±4.68, p<0.0001), RV myocardial performance index (0.36±0.01 to 0.32±0.01, p<0.0001) and TAPSE (23.71±1.6 to 19.50±1.41, p<0.0001) as observed in 2D echocardiography

which became statistically significant only after 3 months of ASD correction. There was also significant fall in RV systolic pressure after 3 months of procedure.

**Comparative changes in strain imaging:** The global longitudinal strain of left and right ventricles were compared as shown in the table 2:

Decrease in the global longitudinal strain of LV was observed after 6 month of ASD correction (-19.61±1.44 to -18.70 ± 6.91) but this change was statistically non- significant (p=0.814); however the percentage decrease in LV global longitudinal strain was 6.9 % at the end of 6 month.

The result obtained in RV global longitudinal strain after correction of ASD was quite different in comparison to LV global longitudinal strain. RV global longitudinal strain decreased significantly in the first follow up at 48 hrs after correction of ASD (-26.10±4.27 to -24.33±3.46, p<0.0001) which was statistically significant. This observed improvement in RV global longitudinal strain persisted in subsequent follow up with maximum decrease (16.58%) in second follow up at the end of 3 months and at the end of 6 months as well.

**DISCUSSION**

Left and right ventricular systolic function abnormalities have been described in various congenital heart diseases especially in patients with intracardiac shunt. The complex anatomy of right ventricle along with variability in subjective assessment of ventricular function with transthoracic echocardiography limits the use of this technique for routine evaluation of ventricular function in today’s practice.

Atrial septal defect is characterized by chronic volume overload of the right ventricle with progressive increase in right ventricular dimensions and progressive pulmonary vascular changes over time which leads to pressure overload of right ventricle. This overloading of right ventricle leads to decreased left ventricular filling and decreased left ventricular preload due to shift of inter-ventricular septum towards the left side [14].

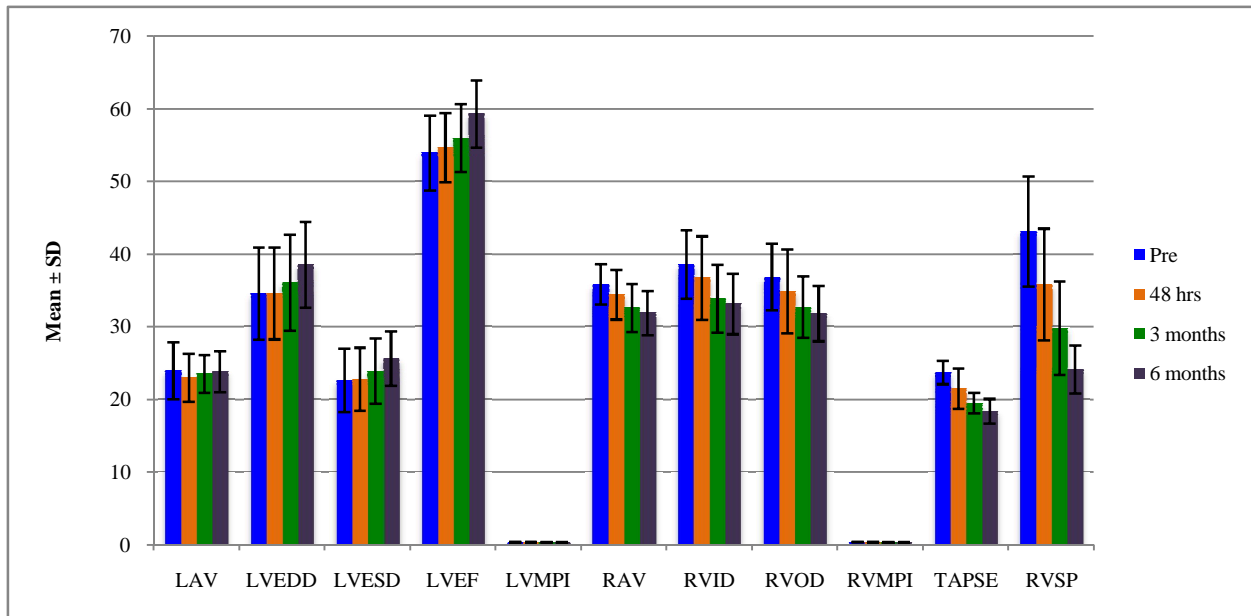
**Table 2** Showing the LV and RV global longitudinal strain in patients of atrial septal defect before (pre) and after correction in subsequent follow up at 48 hrs, 3 months and 6 months with percentage change in global longitudinal strain in each follow up. LVGLS=Left ventricular global longitudinal strain, RVGLS=Right ventricular free wall global longitudinal strain

	Pre		48 hrs		p-Value (1)	% change	3 months		p-Value (2)	% change	6 months		p-Value (3)	% change	p-Value (4)
	Mean	SD	Mean	SD			Mean	SD			Mean	SD			
<b>LVGLS</b>	-19.61	1.44	-18.61	1.44	0.600	0.38	-17.65	6.92	0.216	5.13	-18.70	6.91	0.287	9.38	0.8145
<b>RVGLS</b>	-26.10	4.27	-24.33	3.46	0.0001	6.77	-21.77	1.79	0.0001	16.58	-21.70	1.78	0.0001	16.84	0.0001

P Value (1): between preop and 48 hrs, P Value (2): between preop and 3 month, P Value (3): between preop and 6 month, P Value (4): overall



explained by improved LV filling [18] and decrease in LA preload after correction of ASD; although volume measurement may be difficult due to mass effect of the device in-situ after correction of the defect.



**Figure 2** Showing the echocardiographic data in patients of atrial septal defect before and after correction in subsequent follow up. LAV= Left atrial volume, LVEDD= Left ventricular end-diastolic diameter, LVESD= Left ventricular end-systolic diameter, LVEF= Left ventricle ejection fraction, LVMP= Left ventricle myocardial performance index, RAV= Right atrial volume, RVID= Right ventricle inflow diameter, RVOD= Right ventricle outflow diameter, RVMPI= Right ventricle myocardial performance index, TAPSE= tricuspid annulus systolic excursion, RVSP= Right ventricle systolic pressure

Although volume overload of the right ventricle is well tolerated in most of the patients [15] with atrial septal defect but it can be detrimental in some patients [16, 17].

Surgical or percutaneous closure of the defect causes reverse remodeling of the ventricles. However such adaptation may take long time, so the need of some functional parameters to assess reverse remodeling after percutaneous closure or corrective surgery is well attained by newer technical modalities such as strain imaging to detect subtle changes in the ventricular function during short and intermediate term follow-up of patients with atrial septal defect. Speckled-derived strain rate echocardiography is a new modality which improves the understanding of cardiac functions, though parameters for assessment are yet to be standardized for pediatric population [21].

The author feel that the strategies employed in the current study is novel and innovative. Global longitudinal strain is used for the assessment of both LV and RV systolic function simultaneously in patients with ASD and its comparison with conventional 2D echocardiography along with measurement of changes that occurred after closure of ASD (surgical or percutaneous) immediately post procedure and after short term follow-ups.

**Changes in atrial volume:** Though the RA volume in the present study was high to begin with but it decreased to a value ( $35.85 \pm 2.80$ )mm to ( $31.86 \pm 3.03$ )mm, ( $p < 0.0001$ ) which was statistically significant at the end of 6 months, which can possibly be explained by decrease in preload due to closure of left to right shunt.

The population in this study had a pre closure mean LA volume of  $23.9 \pm 3.9$ ml/m<sup>2</sup> with non significant decrease after correction of ASD. This decrease in LA volume can be

This decrease in LA volume might have some potential benefit in reducing the risk of atrial arrhythmias and other vascular complications like stroke probably by reducing the potentially available space for thrombus formation and organization in patients of ASD after correction of defect [19].

**Changes in LV parameters:** Very few studies have shown the effect of ASD correction on LV function and among them one study showed significant change in LV function at each follow up with maximum change at the end of 3 months [20]. In the present study, statistically significant and maximum improvement in LV end diastolic diameter and LV ejection fraction occurred at the end of 6 month. Similarly, the authors observed a significant decrease in LV MPI ( $0.36 \pm 0.02$  to  $0.32 \pm 0.02$ ,  $p < 0.0001$ ) after 6 month of ASD correction. This improvement in LV function can be explained by improved LV filling.

**Change in RV parameters and function:** RV dimensions showed a continuous fall in all studied population irrespective of the procedure used for the closure of ASD and this change has been demonstrated in all previous studies. There was a non-significant fall in RV diameter after 48 hrs of closure which became significant at the end of 3 months with continuous fall thereafter. Similarly there was improvement in RV MPI and TAPSE.

**Changes in strain imaging of LV and RV:** ASD predominantly affects right side of the heart. Here the authors aimed to identify any subtle change in echocardiographic parameters of both the ventricles and how they evolve by reverse remodeling after correction (surgical or percutaneous, as appropriate) during serial follow-ups. Till date no other study has shown the impact of ASD correction on LV function. Although in this study, the baseline LV strain values

were within normal limits but there was non-significant change in the LV global longitudinal strain observed after 6 months of follow up, with maximum decrease of 9.38% irrespective of the type of procedure used for correction which was statistically non-significant.

In comparison to LV, there are some literatures related to impact of ASD closure on RV deformation. Although there is some evidence in support of the use of RVGLS assessment for the free wall based on a limited number of single centre study (reference value  $>-20\%$  was normal) [21, 22, 23] but accepted guidelines have not been defined for strain and SR of the right ventricle until now. In this study, there is increase in RVGLS at the baseline because of chronic volume overload. There was statistically significant decrease in RV global longitudinal strain after 48 hrs of ASD correction and decrease to near normal values at 3 months of correction. Similar results has been shown by Jategaonkar *et al* study in 2009 [24] suggesting that early follow up period after ASD correction is sufficient to have an idea about the reverse remodeling effect of ASD correction on right ventricle.

The findings of the current study lead to the evolution that global longitudinal strain is a non-invasive tool for the objective assessment of myocardial deformation and impact of correction of the congenital heart defects on myocardial deformation. Being an objective assessment of longitudinal strain analysis, this method is free from performance variability among echocardiographers conferring it an universally accepted tool in predicting early myocardial deformation

#### LIMITATIONS OF THE STUDY

Theoretically, myocardial strain can be measured in all dimensions (longitudinal, radial, and circumferential). In this study we have only quantified the global longitudinal strain assuming that the contraction of the right ventricle is predominantly longitudinal. Apart from this major limitation, the number of patients included in surgical (12) and transcatheter (20) group are different, so it may affect the outcome after correction of ASD. Other limitations are small sample size and lack of age and sex matched control population in the present study.

#### CONCLUSION

Atrial septal defect causes hemodynamic alteration in right ventricular function with subtle changes in left ventricular function. Closure of ASD helps in improvement in ventricular systolic function due to alterations in the cardiac hemodynamics. This improvement in ventricular function occurred in all patients irrespective of the size of the defect, age of the patient and preoperative ventricular dimensions ; Although it took more time in patients with defect of larger size. So, Two-dimensional strain is a novel imaging technique for evaluation of global and regional myocardial function. There is improvement of myocardial function of both the ventricles as shown by strain imaging and most of these changes are completed within 6 month of ASD correction and nearly correlates with conventional two-dimensional Echocardiography. Such a validated tool can be used in volume overloaded conditions to predict early ventricular dysfunction and initiation of drugs to guide therapeutic remodeling on short term basis

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