Closure of atrial septal defect in the adult. Cardiac remodeling is an early event.

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Abstract

Background: Study aimed to describe the extent and the temporal profile of cardiac remodeling after atrial septal defect closure in the adult.
Methods: Prospective and longitudinal echocardiographic assessment of right and left heart size before and after (1 day -1 week/1/4/12 months) surgical or catheter-based atrial septal closure in 39 adults (age 54 ± 15 years).
Results: Right ventricular and atrial sizes were markedly reduced, left ventricular size increased and left atrial size remained unchanged after closure. Older age and a history of atrial fibrillation reduced the potential to normalize right and left atrial size after closure. The greater part of the changes occurred very early, in the 1st day/1st week. From then on the speed of change gradually diminished and after 4 months no important changes were observed. The mode of closure did not influence the degree or the pace of the remodeling.
Conclusion: Cardiac remodeling after atrial septal closure in the adult is a common and early event that seems by and large completed within the first half year after closure. The ventricles seem to have a higher capacity of remodeling than the atria in this setting. The mode of closure does not seem to significantly impact remodeling.

Key words: Congenital heart disease, atrial septal defect, adult, closure, remodeling

Introduction

Atrial septal defect is one of the most common congenital cardiac malformations discovered in adult life. Closure of the defect has been a remedy for five decades and even when performed in adults and in middle-aged patients there are symptomatic and prognostic benefits (1,2). By closure the volume overload of the right heart is reduced and left ventricular loading improved, thereby increasing systemic cardiac output.

However, the extent and particularly the time profile of the cardiac remodeling after atrial septal defect closure is less well known. The aim with this study was to describe the extent and the pattern, in particular the temporal profile, of cardiac remodeling after closure of an atrial septal defect of the secundum type in adults.

Methods

During the period September1997 – February 2003 44 adult patients with an atrial septal defect of the secundum type had the defect closed at Lund University hospital. The basis of this report is the 39 patients who had a follow-up according to the routines of the service. Administrative, practical and personal reasons was the cause for not having this follow-up. Baseline characteristics are given in table 1. Besides a pre-closure assessment they were regularly followed post-closure by means of echocardiography and clinical evaluation including NYHA functional classification. In 10 patients the defect was closed surgically while in 29 it was done by percutaneous catheter technique using an Amplatzer® ASD closure device. There was no residual shunting of importance after closure. The reason for surgical closure was: Multiple defects, large defects, patient preferences but also, in the early part of the period that catheter closure was not an option in our service.

Six patients were in chronic atrial fibrillation. Another nine patients had a history of paroxysmal atrial fibrillation but demonstrated sinus rhythm during the entire follow-up. The 24 patients without a history of arrhythmia were significantly younger than those who had experienced an arrhythmia (table 2). Nine patients (23 %) had a history of or were treated for systemic essential hypertension and there was a trend towards a higher frequency of atrial fibrillation among them compared to normotensives (67 % vs 30 %, p=0.06). No patient had a history of myocardial infarction or angina pectoris. Pre-closure stress test was performed in 23 of the 39 patients without findings making ischemic heart disease likely. The majority of the patients had only a right heart catheterization. However, in four patients scheduled for surgical closure coronary angiography was performed with normal findings in three and 3-vessel disease in one. That patient had concomitant CABG at the time of the repair of the atrial septal defect.

As controls served 32 patients referred for echocardiography because of chest pain or suspected cardiac embolic source. Clinically and echocardiographically the controls had no signs of cardiac disease or a shunt lesion.

Transthoracic echocardiography was performed in a standard fashion (Hewlett-Packard Sonos 5500) by one of the authors. Conventional M-mode measurements were obtained. From an apical 4-chamber view the area of the heart chambers was measured when the heart chamber had a maximal size (end-diastole for the ventricles and end-systole for the atria). The obtained values were indexed according to body surface area (BSA), which was given from height (H, in cm) and weight (W, in kg): BSA in m^2= (H+W-60)/100. Valvular morphology and function was systematically assessed. Regurgitant lesions were semi-quantified on the basis of width and length of the color flow jet. The velocity of the tricuspid regurgitation, converted to a pressure gradient, served as an indicator of the pressure

levels in the pulmonary circulation as there was no patient with a right ventricular outflow obstruction. Echocardiography was performed before and at four occasions after closure of the atrial septal defect. The first post-closure exam was performed the day (mean 1.1 day) after closure in those who had their defect closed by catheter or approximately one week (mean 6.1 days) after closure in the surgical cases. The subsequent exams were performed around one month (mean 1.5 months), four months (mean 4.5 months) and one year (mean 16.1 months) post-closure. Due to administrative reasons only 28 of the 39 patients had a 4-month check-up. In one patient data on chamber areas the day after closure was not obtained. Before closure, as a part of the clinical management, the size and morphology of the atrial septal defect had been assessed by transesophageal echocardiography. If the defect was oval the diameter was defined as the average of the long and short axis distance. In one patient, due to multiple defects the defect diameter could not be determined. In all but one patient the pulmonary-systemic flow ratio had been investigated by means of either heart catheterization or radionuclide angiography.
All investigations were part of the routine clinical management and constitute an important component of our continuous quality improvement program. Informed consent was obtained.

Statistical analysis

Paired and unpaired t-tests were applied when appropriate. The Chi-2 test was used for categorical variables. A p-value < 0.05 was adopted as statistically significant. The Statview® statistical software was used for analysis.

Results

There were no significant baseline differences between the patients who had their defect closed by catheter and those who had it surgically closed regarding age, sex, arrhythmia, defect size or other hemodynamic variables (table 1). By definition all the controls had a normal heart rhythm, normal valvular functions and a normal pressure level in the pulmonary circulation. Right heart chambers and the left atrium were markedly larger and the left ventricle substantially smaller in patients at baseline (pre-closure) compared to controls. Age did not significantly differ between patients and controls while female gender was dominating in the patient group but not among the control subjects. Among patients a history of atrial fibrillation, when compared to those free from arrhythmia, did not influence pre-closure atrial and ventricular sizes (table 2).

As demonstrated in figure 1 and table 1 closure of the atrial septal defect resulted in a dramatic reduction of the right ventricular and atrial areas. The same was true for the parasternal right ventricular end diastolic dimension (fig. 2). Parallel to this there was also a marked reduction of the right ventricular – right atrium pressure gradient (fig. 3). The left ventricle increased significantly in size after closure, whether measured as an area or as a dimension (LVIDD). However, closure did not affect left atrial size.

Regarding the temporal profile (fig. 1-3) it was obvious that when changes occurred they came early. Compared to the findings before closure right ventricular end diastolic dimension, right ventricular and right atrial areas were highly statistically significantly ($p<0.001$) reduced at the first test after closure (1^{st} day/1^{st} week). Between that exam and the second, one month later, there was a further significant but less prominent reduction of the right heart chamber areas and right ventricular end diastolic dimension (RVIDD $p<0.0001$, RV area $p= 0.002$ and RA area $p=0.01$). Thereafter, during the further course no significant changes of right ventricular and right atrial area occurred from one

occasion to another. The right ventricular – right atrium pressure gradient that had fallen markedly ($p<0.001$) the day, or week for surgical cases, after closure did not significantly change later on. The temporal pattern of the left ventricular changes, although going in an opposite direction, followed by and large those of the right heart.
At the "one-year" examination after closure there was no statistically significant differences in right ventricular – right atrium pressure gradient, left ventricular area or left ventricular diastolic dimension (LVIDD) between patients and controls (table 1). In contrast, right ventricular and right atrial areas as well as right ventricular diastolic dimension (RVIDD) were all still significantly larger than in controls. The relative reduction in right ventricular area (% of baseline) was positively correlated to the pre-closure right ventricular area, the larger right ventricular area before closure the larger reduction ($r=0.46$, $p=0.004$). A similar analysis for right atrial area revealed no such correlation ($r=0.09$ $p=0.58$). The left atrial area which did not change at all after closure was significantly larger than that of controls at the one-year exam. At the "one-year" evaluation, in contrast to the pre-closure findings, a history of atrial fibrillation was associated with significantly larger right and left atrial areas and left atrial dimension (table 2). Right and left ventricular areas at the final exam were not influenced by a history of atrial fibrillation.

If the mean value of the chamber areas of the controls + 2 SD was defined as the upper limit of normality, 32 of the 39 patients (82%) had a normal-sized right ventricle and 28 of 39 patients (72%) had a normal-sized right atrium one year after closure. Sex, age, size of the defect, QP/QS, history of atrial fibrillation, right ventricular area or right ventricular – right atrium pressure gradient prior to closure did not significantly influence the potential to normalize right ventricular area one year post-closure. In contrast, failure to normalize the right atrial size was associated with higher age at closure (65 vs. 50 years, $p=0.005$), a history of atrial fibrillation, larger pre-closure right atrium (18.1 vs. 14.3 cm^2 / m^2, $p=0.002$) and higher right ventricular – right atrium pressure gradient at the one year test (26 vs. 21 mm Hg $p=0.01$). Only 40 % of the patients with a history of atrial fibrillation had a right atrium of a normal size at the final exam, compared to 92 % of those without a history of arrhythmia (table 2). The degree of tricuspid regurgitation one year after closure was not significantly associated with right atrial size at that time; however, those two who had a moderate tricuspid regurgitation also had a dilated right atrium. A normal-sized left atrium was found in 22 patients one year after closure of the defect. A persistent dilated left atrium, as opposed to normal size, at one-year follow-up was related to age at closure (64 vs. 47 years, $p<0.001$) and a history of atrial fibrillation (table 2) but not to ASD size, QP/QS, left ventricular area/dimension or left ventricular wall thickness at the last test. Only 20 % of the patients who had experienced atrial fibrillation had a normal left atrial area at the one-year test (table 2). At the final test coexistent right atrial enlargement was found in 53 % of the patients with an abnormal left atrial area.

The functional capacity was significantly improved ($p=0.01$) one year after closure of the atrial septal defect (table 3). At that time 34 of the 39 patients were in NYHA functional class I or had improved their functional capacity compared to pre-closure. In the remaining five individuals two had an unchanged functional capacity equivalent to NYHA functional class III, however due to non-cardiac restrictions (emphysema and muscular fatigue). In spite of that, both of them admitted that closure of the defect had given them symptomatic relief. The magnitude of heart chamber resolution or change of left ventricular size did not significantly differ between those who had improved compared to those with an

unchanged NYHA class. However, 16 patients were in NYHA class I pre-closure making improvement in NYHA class impossible.

The method of closing the defect – surgery or catheter - did not affect the rate or the extent of changes in any respect. At the final exam there were no significant differences between the surgical and the catheter-closed group regarding any chamber area, dimension or right ventricular – right atrium pressure gradient.

Discussion

The present study shows that closure of an atrial septal defect in adult life is associated with a striking reduction of the right heart enlargement which characterizes an atrial septal defect of importance. This is not controversial. Similar findings have been reported in adult as well as pediatric series on atrial septal defect 12 – 32 months after closure (3-8). However, there is a subgroup of patients, even in pediatric series, in whom right atrial or ventricular size do not become normal. This was the case in 28% and 18%, respectively, in our study and is in line with a previous study on adults with an atrial septal defect reporting a persistent right ventricular enlargement in 29 % of the patients one year after catheter-closure (7). In a recently presented 21-33 year follow-up study on patients with an atrial septal defect surgically closed during childhood more than 20 % had right ventricular dilatation and 33 % had right atrial enlargement illustrating that closure even in early life does not guarantee a complete normalization of the heart chamber sizes (9). In that study the prevalence of right ventricular dilatation was unchanged when compared to the findings 11 years earlier while the frequency of right atrial enlargement showed a statistically insignificant trend to increase with time. Thus, it seems that when the initial remodeling has taken place things are rather stable. We were not able to identify any risk factor for failure to normalize the right ventricular size after closure and thereby opposing the findings in an earlier small study which suggested that high age and a high degree of pre-closure right ventricular dilatation negatively influenced the potential for resolution of right ventricular enlargement after closure. Regarding the right atrium, we show that failure to normalize its size is associated with higher age at closure, a finding which gain support from an earlier report (4). A dilated left atrium, another hallmark of an atrial septal defect, did not respond to closure of the defect. This is consistent with the findings from a study on young adults and children (mean age 22.7 years) who had their atrial septal defect closed by means of a catheter (8). As for right atrial dilatation the prevalence of left atrial dilatation at the final exam was associated with older age and a history of atrial fibrillation. Parallel to the changes on the right side of the heart, the typically small left ventricle of the atrial septal defect normalized its size when the defect was closed, consistent with the findings of others (5,6,8).

Thus, it seems that the ventricles more readily adapt to the altered hemodynamics than the atria do and that older age and the occurrence of atrial fibrillation are associated with a more pronounced incapability to remodel the atria. There are several potential explanations for this. As age also is a marker of the duration of the excessive volume load pre-closure it may reflect the burden of a longstanding volume load causing irreversible structural changes. The geometrical, anatomical and physiological properties of the atria may make them more vulnerable than the ventricles to this volume load. Furthermore, one has to consider age-related cellular and physiological mechanisms that may hamper remodeling. The pressure levels in the pulmonary circulation may have some importance as failure to normalize right atrial size was associated to a somewhat higher pulmonary artery pressure at

the final test. The potential impact of impaired ventricular diastolic function, not assessed in our study, must also be taken into account and should be addressed in future studies. Moreover, one can not rule out that there are inborn atrial functional properties, as a part of the malformation itself, facilitating atrial enlargement. Age influenced the incidence of atrial fibrillation as well as the potential to normalize atrial sizes. The occurrence of atrial fibrillation could therefore be interpreted as a signal of permanent structural atrial abnormalities secondary to the mechanisms described above. However, one must also consider the possibility that atrial fibrillation starts or facilitates a process causing irreversible structural changes in the atria. Our data suggest that the left atrium, of unclear reasons, is even more vulnerable to this than the right atrium. These unresolved questions are of particular interest as the prevalence of atrial fibrillation among the middle-aged and elderly with an atrial septal defect is very high and does not seem to be affected by closure of the defect (2,10,11). Right atrial stretch in an atrial septal defect may cause electrophysiological alterations (12). However, regarding atrial fibrillation our results could indicate that the left atrium is a locus as important as the right atrium? If atrial remodeling more easily takes place in a young individual it might support early closure in order to avoid late atrial arrhythmias. The effect on long-term clinical outcome of the ability to normalize the right heart size is to a large extent unknown. In a small study on adults with surgically closed atrial septal defects and a more than 30-year follow-up it seemed that normalization of the radiological heart size was associated with an improved outcome (11). We demonstrate that closure of an atrial septal defect in the adult gives symptomatic relief and improves functional class. However, we are not able to relate this improvement or the functional class at the one-year test to the degree of altered chamber sizes or the potential to normalize any heart chamber.

The resolution of the right heart enlargement starts very early after closure and the speed of the changes are declining with time. Earlier longitudinal studies like ours are rare and small, therefore information is scant (4,6-8). Straight comparison are difficult because these reports either have a retrospective design, have lost or does not report on a majority of patients at follow-up or has a case mix of both children and adults. However, in all three studies designed with a 24 hour test post-closure the most marked changes were observed within this period, supporting our findings. Later on, as in the present study, the changes continued but at a lower and gradually declining speed. Although the present study is unable to differ if the remodeling is functional or structural it is reasonable to believe that the early immediate alterations in heart chamber sizes after closure of the defect are functional to a high degree while later changes tend to have a more structural background. Although not proven, because none of these longitudinal studies, including ours, have had a duration longer than two years, it seems that no significant changes occur regarding heart chamber size after six to twelve months post-closure of an atrial septal defect.

The mode of closure did not influence cardiac remodeling in our study. However, the finding should be interpreted with caution because of the small numbers. Furthermore, we did not quantitatively assess ventricular function. In pediatric series right ventricular function, rather than size, has been assessed early after surgical and catheter-based closure (13,14). Surgical closure, in contrary to catheter closure, seemed to have detrimental effects on right ventricular systolic and diastolic function in the early post-closure period. The reason for the negative influence of surgery has been supposed to be the cardio-pulmonary by-pass, however the long-term impact of it was not addressed and is still unknown. In the brief report by Du and colleagues catheter closure was inferred to be superior when compared

to surgically closed historic controls (6). However, in that study many patients were lost to follow-up and the basis for the comparison seems not very valid.

In conclusion, cardiac remodeling after atrial septal closure in the adult is a common feature and it is a very early event that seems by and large completed within the first six months. A great majority of adult patients with atrial septal defect experiences normalization of the right heart size and the pulmonary arterial pressure level after closure of the defect. The ventricles seem more capable to remodel than the atria in this setting. The significance of this finding, in the context of late atrial arrhythmias, warrants further evaluation. The process of remodeling is apparently not affected by the mode of closure.

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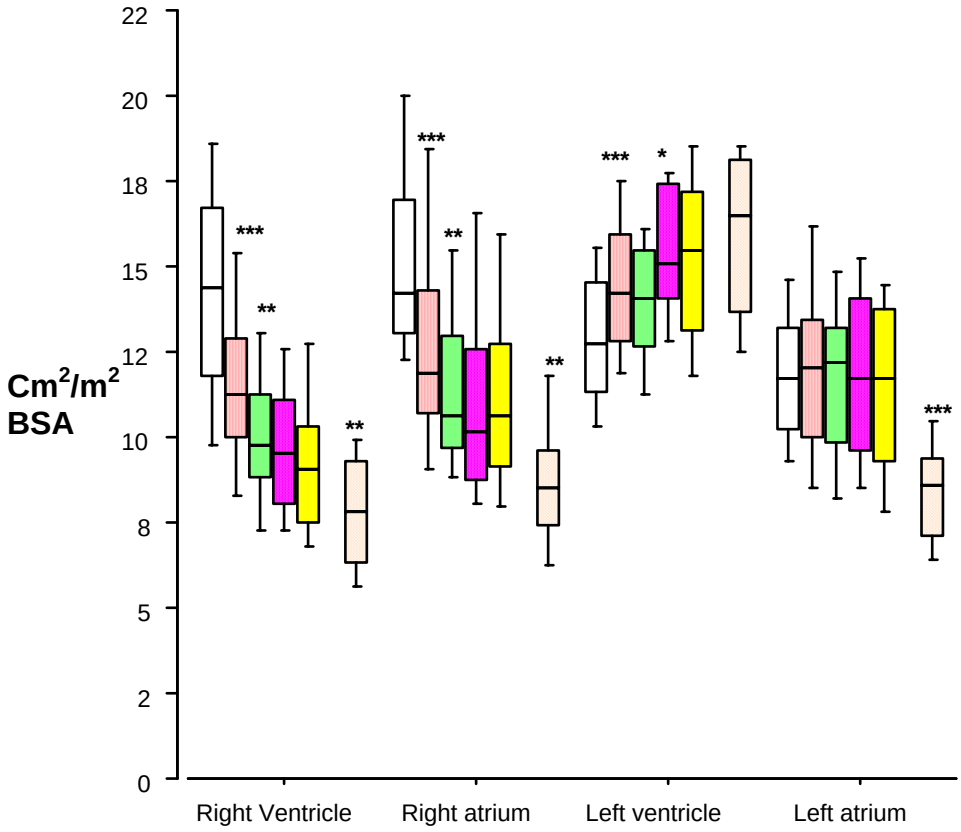
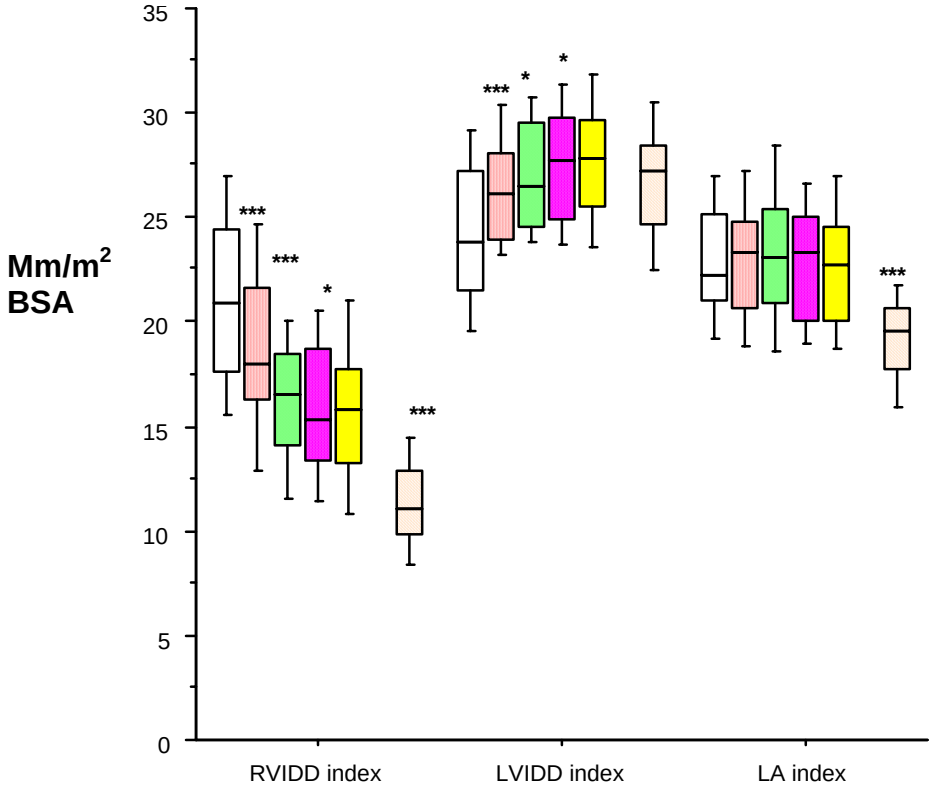
Figure 1



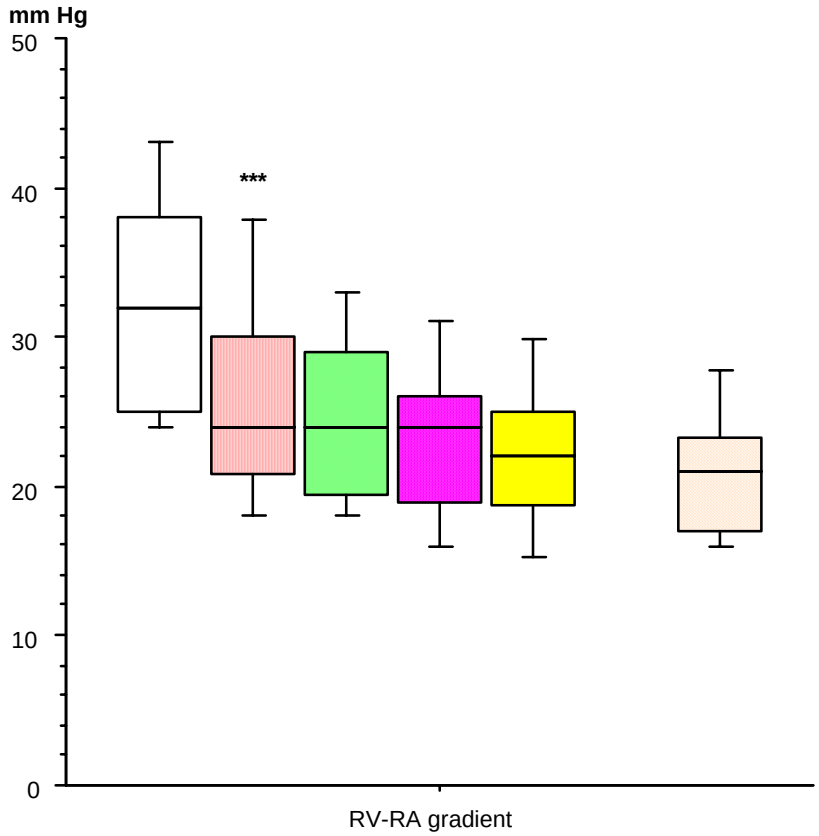
Heart chamber areas indexed to body surface area (BSA) in patients before and after closure of the atrial septal defect and in controls. Box-plots indicate 10th, 25th, 50th, 75th and 90th percentiles.
From left to right: Pre-closure, 1st day/1st week post-closure, one month post-closure, four months post-closure, one year post-closure and controls.
*** = p< 0.001, **= p< 0.01, *= p<0.05 when compared to the test occasion just before (paired t-test), for controls the comparison refers to the final test of the patients, one year post-closure (unpaired t-test).

Figure 2



Right and left ventricular parasternal dimension (RVIDD and LVIDD) and left atrial parasternal dimension (LA) indexed to body surface area in patients before and after closure of the atrial septal defect and in controls. Box-plots indicate 10th, 25th, 50th, 75th and 90th percentiles.
From left to right: Pre-closure, 1st day/1st week post-closure, one month post-closure, four months post-closure, one year post-closure and controls.
*** = p< 0.001, **= p< 0.01, *= p<0.05 when compared to the test occasion just before (paired t-test), for controls the comparison refers to the final test of the patients, one year post-closure (unpaired t-test).

Figure 3



Right ventricular – right atrial pressure gradient in patients before and after closure of the atrial septal defect and in controls. Box-plots indicate 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles.
From left to right: Pre-closure, 1^{st} day/1^{st} week post-closure, one month post-closure, four months post-closure, one year post-closure and controls.
*** = $p < 0.001$ when compared to the test occasion just before (paired t-test).

Table 1

	ASD N=39 Pre-closure	ASD Catheter closed N=29	ASD Sugically closed N=10 1-year post-closure	Controls N=32	ASD N=39
Gender, male/female	9/30	5/24	4/6	16/16	
Age, years, mean ± SD (range)	54 ± 15 (19-73)	56 ± 15	50 ± 14	47 ± 17 (18-73)	
Sinus rythm/history of atrial fib-rillation	24/15	18/11	6/4	32/0	
QP/QS	2.7	2.8	2.6	-	
ASD diameter, mm, mean ± SD #	17±5	17±4	18±6	-	
RV area, cm^2/m^2, mean ± SD	14.3 ± 3.2***	14.8 ± 3.5	12.8 ± 1.8	7.8 ± 1.7	9.3 ± 2.2**
RVIDD, mm//m^2, mean ± SD	21 ± 5***	21 ± 4	21 ± 6	11 ± 2	16 ± 4***
RA area, cm^2/m^2, mean ± SD	15.4 ± 3.6***	15.8 ± 3.8	14.3 ± 2.5	8.6 ± 1.9	11.4 ± 3.6**
LV area, cm^2/m^2, mean ± SD	12.8 ± 2.4***	13.0 ± 2.1	12.1 ± 3.3	15.9 ± 2.6	15.4 ± 2.6^{NS}
LVIDD, mm/m^2, mean ± SD	24 ± 3**	24 ± 4	24 ± 3	27 ± 3	27 ± 3 ^{NS}
LA area, cm^2/m^2, mean ± SD	11.8 ± 2.2***	12.2 ± 2.3	10.8 ± 1.9	8.5 ± 1.8	11.7 ± 3.4***
Tricuspid regurgitation ***None-trivial/Mild/Moderate***	8/28/3	6/20/3	2/8/0	30/2/0	23/14/2
Pulmonary regurgitation ***None-trivial/Mild***	33/6	25/4	8/2	32/0	36/3
RV-RA pressure gradient mm Hg, mean ± SD †	33 ± 9*** (n=38)	33 ± 9	32 ± 8	21 ± 4 (n=17)	22 ± 6 ^{NS} (n=37)

Table 1.

Characteristics of controls and patients before and one year after closure of the atrial septal defect. Heart chamber sizes are given indexed to body surface area. ASD = atrial septal defect. QP/QS = pulmonary - systemic flow ratio. RV= right ventricle. RVIDD=right ventricular enddiastolic dimension. RA=right atrium. LV=left ventricle. LVIDD= left ventricular enddiastolic dimension. LA=left atrium.
one patient not assessed because of multiple defects. † not obtainable in all subjects. Significance levels refer to comparison between controls and ASD patients pre- and post-closure. NS=no statistical significant difference, ***p<0.001 and ** p<0.01.

Table 2

	AF (n=15)	Sinus (n=24)	p
PRE-CLOSURE			
Atrial septal defect size, mm	17 ± 6	17 ± 4	NS
Age, years	65 ± 8	48 ± 15	<0.001
Left atrial dimension, mm/m^2 BSA	24 ± 4	22 ± 3	NS
Left atrial area, cm/m^2 BSA	12,4 ± 2,5	11,5 ± 2,1	NS
Right atrial area, cm/m^2 BSA	16,6 ± 4,5	14,6 ± 2,7	NS
POST-CLOSURE			
Left atrial dimension, mm/m^2 BSA	24 ± 4	21 ± 3	<0.05
Normal left atrial dimension, % of pat.	33	79	<0.01
Left atrial area, cm/m^2 BSA	14,0 ± 3,9	10,3 ± 2,2	<0.001
Normal left atrial area, % of pat.	20	79	<0.001
Right atrial area, cm/m^2 BSA	13,9 ± 4,2	9,8 ± 2,0	<0.001
Normal right atrial area, % of pat.	40	92	<0.001

Atrial sizes before and one year after atrial septal defect closure related to the occurrence of atrial fibrillation. AF = patients who had a history of chronic or paroxysmal atrial fibrillation. Sinus = patients without a history of arrhythmia. P-values refer to unpaired t-test between the groups.

Table 3

		NYHA one-year post closure			
		I	II	III	Total
NYHA	I	16	0	0	16
pre-closure	II	12	3	0	15
	III	4	2	2	8
	Total	32	5	2	39

Distribution of NYHA functional class before and one year after closure of the atrial septal defect.