Transcatheter closure of atrial septal defects improves right ventricular volume, mass, function, pulmonary pressure and functional class: A MRI study

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Abstract

**Background:** An atrial septal defect (ASD) with significant left-to-right shunt leads to chronic volume overload of the right atrium (RA) and ventricle (RV) and in certain patients later on to pulmonary hypertension and right heart failure. Conflicting data exist about the progression of RV volume and function after closure of the interatrial defect. The aim of this study was to prospectively characterize by magnetic resonance imaging (MRI) changes in RV volume, function and mass following transcatheter closure of ASDs. Also we sought to evaluate the course of pulmonary pressure and functional class criteria.

**Methods:** In 20 patients with secundum type ASD and dilated RV diameter, MRI was performed to quantify RV end-diastolic and end-systolic volumes (RVEDV, RVESV), RV mass, tricuspid annular diameter (TAD) and RV ejection fraction (RVEF) before and also six and twelve months after transcatheter closure of the ASD. RV systolic pressure (RVSP) during follow-up was measured by transthoracic echocardiography (TTE).

**Results:** Functional class improved in the majority of patients after ASD closure. RVESV, RVEDV (p<0.001) and RV mass (p<0.01) decreased significantly during follow-up, although TAD did not. RVEF improved (p<0.05) and RVSP showed a significant reduction (p<0.001) following closure.

**Conclusion:** MRI studies showed significant improvement of RV volumes, mass and function after transcatheter closure of ASDs. Resolution of the RV leads to a decrease of pulmonary pressure resulting in a better functional class in the majority of patients.
Introduction

Atrial septal defects (ASD) are among the most common congenital heart lesions found in adult life <1>. Most infants and children with ASD are asymptomatic and physical findings may be unimpressive, making survival into adulthood normal. Long-term exposure to chronic right heart volume overload leads to dilatation of the right atrium (RA) and ventricle (RV) and in certain cases, due to an increased pulmonary flow, to deleterious effects such as pulmonary hypertension and right heart failure <2>. Patients may present symptoms of fatigue, dyspnea, recurrent lower respiratory tract infection, palpitations and thromboembolic events. It has been accepted that closure of the interatrial defect is the treatment of choice for an ASD with significant pulmonary to systemic flow ratio, especially if RV volume overload is present, even if the patient has few or no symptoms <1, 3>.

In recent years transcatheter closure of interatrial defects was introduced into clinical practice and became, next to the surgical approach, a secure, efficient and cost effective option for defect management <4, 5, 6>. In a study comparing surgical versus transcatheter closure of ASDs, the transcatheter approach proved superior. Myocardial function, both systolic and diastolic, was impaired by surgical closure but preserved after transcatheter occlusion <7>. Conflicting data exist, as to whether the course following ASD closure leads to an improvement of RV performance, or if it only prevents further deterioration <3, 7, 8, 9, 10, 11, 12, 13, 14>. For example, Eidem et al. described no significant change in RV performance in patients after surgical closure of ASDs <11>, however Salehian et al. <14> demonstrated that transcatheter closure of ASDs was associated with improvement of left ventricular (LV) and RV function.

A reason for divergent results regarding RV volume and function following closure may be caused by different ASD closure techniques and limitations of echocardiography in the quantitative assessment of the RV.

The aim of this study was to clarify whether after percutaneous ASD closure RV volume and mass resolves and RV function improves. Changes in RV end-diastolic and end-systolic volumes (RVEDV, RVESV), right ventricular ejection fraction (RVEF), RV mass and tricuspid annular diameter (TAD) were analyzed by magnetic resonance imaging (MRI), the most robust technique for morphological evaluation of the RV <15,16>. Finally, we sought to evaluate the course of pulmonary pressure and functional class criteria.

Methods

Study Population
20 consecutive patients referred for transcatheter closure of a secundum type ASD were included in this study. Before undergoing MRI, all patients gave written informed consent in accordance with ethical guidelines followed in our institution. To be eligible, patients had to be 18 years or older and echocardiographic estimation had to show a dilated RV diameter. None of the patients had additional coronary artery disease, valvular heart disease or pulmonary disease. Patient’s characteristics are shown in Table 1, along with baseline findings. The study protocol consisted of clinical assessments, evaluation of functional class criteria according the New York Heart Association (NYHA), transthoracic and transesophageal echocardiography (TTE, TEE) and MRI examinations before, six and twelve months after transcatheter ASD closure. Patients also had a complete hemodynamic evaluation via cardiac catheterization just before closure of the defect.
Transthoracic echocardiography
2-dimensional color Doppler TTE was performed before and also six and twelve months after ASD closure, using a Sonos 5500 ultrasound system (Agilent Technologies). The examination focused on the measurement of RV end-diastolic diameter (RVEDD) and right ventricular systolic pressure (RVSP). Two measurements of the RV were made in the apical four-chamber view: maximal RV long-axis dimension, defined as the distance between the RV apex and the mid-point of the tricuspid valve and RV short-axis dimension, defined as the maximal dimension from the right septal surface to the free wall perpendicular to the long axis. RVSP was estimated by use of the maximum velocity of the tricuspid regurgitant jet, the systolic pressure gradient between RV and RA was calculated by the modified Bernoulli equation. RA pressure was estimated by examination of the jugular venous pulse as described previously <17, 18>. Adding the transtricuspid gradient to the RA pressure (10 ± 5 mmHg) gave predictions of the RVSP <19>. All patients were in sinus rhythm at the time of their examinations.

Magnetic resonance imaging
MRI was performed for determination of RV volumes, function, mass and TAD. From ventricular apex to base ECG-triggered, breathhold, segmented k-space cine gradient echo sequences (1.5 T, Somatom Vision, Siemens) were obtained in the short axis view. Parameters were as follows: echo time: 3.8 ms, repeat time = RR interval, slice thickness: 10 mm, field of view: 35 × 35 cm, read matrix: 256, phase matrix: 128, frames: 16 (typical temporal resolution of 50 ms), flip angle: 40°, phase encode grouping: 6 to 10, 8 to 12 short-axis slices were needed to encompass the entire right ventricle. Manual tracing of epicardial and endocardial borders of contiguous short-axis slices at end-diastole (first cine phase of the R-wave triggered acquisition) and end-systole (image phase with smallest cavity area) allowed for calculation of RV mass, RVEDV and RVESV, from which RVEF could be derived. TAD was measured as maximum diameter of the tricuspid annulus in a stack of cine gradient echo sequences in the four-chamber view. For RV mass calculation, the myocardial volume was multiplied by the specific density of myocardium (taken as 1.05 g/cm³) <20>. The interventricular septum was treated as part of the left ventricle and excluded from RV mass measurements, the moderator band and evident trabeculations were included in the mass and excluded from the RV volume. Analysis of the scans was done with the investigator blinded to the previous results. In all individuals MRI was performed in the morning, patients had no oral intake between midnight and the scans. Volumes and TAD were normalized to body surface area. As normal values we used: RVEDV: 48.0-107.5 ml/m², RVESV: 13.1-47.2 ml/m², RVEF: 49.1-74.1 %, TAD: 13-20 mm/m², RV mass: 33-80g <16, 21, 22, 23, 24>.

Hemodynamic study and ASD closure
Hemodynamic study and percutaneous closure were performed under sedation and local anesthesia. The size, location, and relationship of the ASD to the surrounding structures were assessed by continuous TEE. Pulmonary to systemic flow ratio (Qp/Qs) was calculated by oximetry, using the Fick principle. The Amplatzer septal occluder (AGA Corp.) or the Cardia PFO / ASD Device (Cardia Inc.) was used for ASD closure as previously described <25, 26>. Postinterventional treatment included oral aspirin (100 mg/day) for 12 months, clopidogrel (75 mg/day) for 6 weeks and low dose heparin for the first 3 days (2×5000 IE s.c.) after intervention.

Statistical Analysis
The Wilcoxon matched-pairs test was used to compare pre- versus six or twelve months post-ASD closure variables. A value of p<0.05 was considered significant.
Results

Closure of an ASD was achieved in 14 patients with an Amplatzer device, median device size was $26 \pm 6$ mm, in 6 patients with a PFO-Star device, median device size was $22 \pm 5$ mm. At TTE and TEE performed periinterventional and after six and twelve months, no residual shunt was noted in the entire study group. Major complications did not occur. The mean age of the 20 patients (12 female, 8 male) was $43 \pm 13$ years (range 19-65). No patient was lost to clinical follow-up. Patient’s characteristics are shown in Table 1, along with baseline TTE, TEE and MRI findings.

Table 1

<table>
<thead>
<tr>
<th>Baseline Clinical and Hemodynamic Data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at closure (years)</td>
<td>$43 \pm 13$</td>
</tr>
<tr>
<td>Female gender</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>NYHA functional class &gt; I</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Stretch balloon size (mm)</td>
<td>$24 \pm 6$</td>
</tr>
<tr>
<td>Qp/Qs ratio ≥ 2:1</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Qp/Qs ratio &lt; 2:1</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Median Amplatzer device size (mm)</td>
<td>$26 \pm 6$</td>
</tr>
<tr>
<td>Median PFO-Star device size (mm)</td>
<td>$22 \pm 5$</td>
</tr>
<tr>
<td>RVSP at TTE (mmHg)</td>
<td>$33 \pm 8$</td>
</tr>
<tr>
<td>Patients with RVSP &gt; 30mmHg</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>RVEDD at TTE (mm)</td>
<td>$36 \pm 4$</td>
</tr>
<tr>
<td>RVEDV at MRI (ml/m² body surface area)</td>
<td>$127 \pm 17$</td>
</tr>
<tr>
<td>RVESV at MRI (ml/m² body surface area)</td>
<td>$81 \pm 18$</td>
</tr>
<tr>
<td>RVEF at MRI (%)</td>
<td>$37 \pm 9$</td>
</tr>
<tr>
<td>TAD at MRI (mm/m² body surface area)</td>
<td>$23 \pm 7$</td>
</tr>
</tbody>
</table>

Mean interval from transcatheter closure procedure to six months follow-up was 6.4 months (5.6-9.2) and to twelve months follow-up 12.8 months (11.2-14.8). TEE revealed sufficient closure of ASDs in all patients.

Functional status
Before ASD closure 12 patients were in NYHA I, 5 patients in NYHA II and 3 patients in NYHA III. Patient’s condition improved during follow-up, leading to a better functional class in 5 of 8 symptomatic individuals (Figure 1).

Echocardiography
Before ASD closure all patients had dilated RVEDD (36mm ± 4mm), measured by 2-dimensional TTE (inclusion criterion). Baseline RVSP was $33$mmHg ± 8mmHg however decreased significantly after 6 months to $27$mmHg ± 7mmHg and after 12 months to $24$mmHg ± 6mmHg ($p<0.001$). Before closure 6 patients showed moderate tricuspid regurgitation (TR). In 14 patients minimal up to mild TR was obvious. At the 6 months follow-up 17 patients had minimal up to mild TR, in 3 cases moderate TR persisted. TTE at 12 months after ASD closure showed moderate TR in 2 patients, in 18 individuals minimal up to mild TR was obvious. No patient showed worsening of TR.
Magnetic resonance imaging
Baseline measurements showed enlarged RV volumes in all individuals and dilated TAD in 13 patients (65%): RVEDV $127\text{ml/m}^2 \pm 17\text{ml/m}^2$, RVESV $81\text{ml/m}^2 \pm 18\text{ml/m}^2$, RVEF $37\% \pm 9\%$, RV mass $79 \pm 10\text{g}$ and TAD $23\text{mm/m}^2 \pm 7\text{mm/m}^2$ (see methods for normal values). At six months after closure a significant reduction of RVEDV to $103\text{ml/m}^2 \pm 20\text{ml/m}^2$ and of RVESV to $57\text{ml/m}^2 \pm 14\text{ml/m}^2$ was obvious ($p< 0.001$, Figure 2 and 3), RVEF significantly increased by 8%. RV mass and TAD showed slightly but no significant changes compared to baseline MRI measurements. Follow-up after 12 months assessed a further reduction of RVEDV to $99\text{ml/m}^2 \pm 18\text{ml/m}^2$ and of RVESV to $53\text{ml/m}^2 \pm 15\text{ml/m}^2$ ($p< 0.001$, Figure 3), RVEF improved by 9% compared to baseline measurements ($p<0.05$), RV mass was significantly reduced to $63\text{g} \pm 8\text{g}$ ($p<0.01$) and TAD slightly decreased ($21\text{mm/m}^2 \pm 6\text{mm/m}^2$, n.s., Figure 4).

Discussion
This is the first study to demonstrate changes of RV volumes, function and mass following ASD closure by MRI. A significant improvement of RV volumes and function occurs within six months after transcatheter ASD closure in adults. A further volume reduction and improving RVEF was obvious up to twelve months, however major changes occurred within the first six months following closure. Significant regression of RV hypertrophy could be demonstrated at the twelve months follow-up investigation. Pulmonary pressure decreased significantly in the change over time and patient’s condition increased during follow-up, leading to a better functional class in 5 of 8 symptomatic individuals. At baseline 65% of patients showed a dilated TAD. During follow-up after ASD closure we saw no significant changes in TAD. Dilated RVs seem to reshape quickly within six months, however TAD did not follow the changes of the right ventricle suggesting that fibrous cardiac tissue is less prone to remodel. Secondary TR seems to resolve with regression of RV volume load. We hypothesize that regression of TR during follow up is the result of RV resolution and not the result of structural changes of the valve annulus. This is believed because MRI measurements of TAD did not alter significantly following ASD closure.

Despite the obvious reduction of RV volumes, 30% of patients were still outside the normal range for RV volumes after twelve months.

Before this study conflicting data existed as to whether the course following ASD closure leads to an improvement of RV performance, or if it only prevents further deterioration <7, 9, 11, 12, 13>. After closure the diameter of dilated RVs seems to decrease, but objective measures of improved RV volumes and function had been lacking. Some authors described partial resolution up to normalization of echocardiographically measured RV diameter within different intervals following closure <3, 8, 10>. However, other authors reported that ASD closure is a relatively less effective procedure to restore RV enlargement and dysfunction especially after surgical repair in children <12, 9>.

These divergent results regarding RV volume and function following ASD closure may be caused by different closure and imaging techniques. While surgical closure of ASDs seems to result in persisting RV dysfunction up to several years <9,11, 12>, percutaneous ASD closure seems to lead to a faster resolution of RV dilatation <3, 7, 13, 28>. This delay of RV recovery after surgical closure could be explained by the trauma of operation, the use of cardioplectic
solution, adverse inflammatory responses <29, 30, 31> and transiently impaired cardiac output that accompany cardiopulmonary bypass <32, 33>.

Two studies comparing RV hemodynamics after surgical closure versus percutaneous closure of ASDs have been performed. One study showed normalization of RV volume and RVEF early after ASD closure, irrespective of whether this was achieved surgically or via transcatheter closure <8>. However Dhillon et al. demonstrated that RV function, both systolic and diastolic, is impaired by surgical closure but preserved after transcatheter device closure <7>. These findings may support the percutaneous approach to ASD closure in anatomically suitable defects.

Another reason for divergent results regarding RV performance following ASD closure is the limited accuracy of 2-dimensional echocardiography in quantifying RV parameters <34>. Estimation of RV volume and function are more difficult to obtain than similar measurements of LV mainly because the configuration of the RV is far more complex and not well approximated by simple geometric formulas <35>. In the present study MRI as noninvasive imaging technique was chosen for the evaluation of RV function because of its potential to obtain RV geometry and function with good accuracy and reproducibility <16, 36, 37, 38, 39>. To our knowledge, this is the first study investigating RV function, mass and volume after transcatheter ASD closure by MRI giving detailed information about the postinterventional changes of the RV. According to studies on safety of MRI in patients with cardiovascular implants, the used closure devices are not affected by MRI six months after implantation <40, 41>.

Our data suggest that the abolishment of left-to-right shunting after ASD closure decreases RV filling, thereby reducing pulmonary volume overload and pulmonary pressure leading to a better functional class. Giardini, who focused on left ventricular hemodynamics following ASD closure postulated an augmented LV filling, due to an abolished paradoxical movement of the interventricular septum. Hereby increasing LV stroke volumes lead to an improvement in peak oxygen pulse <42>. Also Salehian et al. <14> demonstrated that transcatheter closure of secundum type ASDs was associated with an improvement of LV performance and RV function, the latter in contrast to Eidem et al. <11>.

Firm conclusions if RV resolution is caused by passive changes in ventricular dynamics after shunt abolishment or by cellular and molecular remodeling can not be drawn out of this study. However the reduction in RV mass, indicated by the present data, suggests that an active structural alteration in the RV myocardium takes place. We speculate that after ASD closure both processes - an active structural alteration in the RV myocardium and a passive change of RV volumes by abolishment of the interatrial shunt – contribute to the resolution of RV volume and the improvement of RVEF.

Different MRI imaging options and orientations for RV volume and mass measurements have been described in the literature. For example, Alfakih et al. compared two orientations for RV volumetry. As result, data sets acquired in axial orientation seem to have a lower intra- and interobserver variability than the short axis orientation <43>. To assess RV mass some authors recommend imaging planes perpendicular to the RV outflow tract and turbo inversion recovery imaging. However compared with gradient echo images no significant difference between masses was found and repeatability of analysis was equally good with both methods <44>. Optimal MRI visualisation and quantification of RV volumes, mass and function has to be discussed.
Conclusion

MRI studies showed significant improvement of RV volumes, mass and function after transcatheter closure of ASD. Resolution of the RV following closure leads to a decrease of pulmonary pressure resulting in a better functional class in the majority of patients.

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Figure legends

Figure 1
On the left side the number of patients in different NYHA classes were shown at baseline and during follow-up after ASD closure. RVSP significantly decreased following transcatheter closure (right side, asterixs indicate significant changes (p<0.001)).

Figure 2
Short axis apex end-diastolic (left) and end-systolic (right) images covering both ventricles from base to the in a patient with ASD and RV dilatation. The epicardial (green) and endocardial (red) boundaries of the RV are traced for calculation of RVEDV, RVESV and RV mass.

Figure 3
Changes in RVEDV and RVESV after transcatheter closure of ASD. Asterixs indicate significant alterations (p<0.001).

Figure 4
Changes in RVEF, RV mass and TAD after transcatheter closure of ASD. Asterixs indicate significant alterations (**p<0.01, *p<0.05).
References


RVEDV (ml/m²)

baseline 6 months 12 months

RVESV (ml/m²)

baseline 6 months 12 months
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