Benefit of atrial septal defect closure in adults: impact of age

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Aims	To evaluate the effect of age on the clinical benefit of atrial septal defect (ASD) closure in adults.
Methods and results	Functional status, the presence of arrhythmias, right ventricular (RV) remodelling, and pulmonary artery pressure (PAP) were studied in 236 consecutive patients undergoing transcatheter ASD closure [164 females, mean age of 49 ± 18 years, 78 younger than 40 years (Group A), 84 between 40 and 60 years (Group B) and 74 older than 60 years (Group C)]. Defect size [median 22 mm (inter-quartile range, 19, 26 mm)] and shunt ratio [Qp:Qs 2.2 (1.7, 2.9)] did not differ among age groups. Older patients had, however, more advanced symptoms and both, PAP ($r = 0.65$, $P < 0.0001$) and RV size ($r = 0.28$, $P < 0.0001$), were significantly related to age. Post-interventionally, RV size decreased from 41 ± 7, 43 ± 7, and 45 ± 6 mm to 32 ± 5, 34 ± 5, and 37 ± 5 mm for Groups A, B, and C, respectively ($P < 0.0001$), and PAP decreased from 31 ± 7, 37 ± 10, and 53 ± 17 mmHg to 26 ± 5, 30 ± 6, and 43 ± 14 mmHg ($P < 0.0001$), respectively. Absolute changes in RV size ($P = 0.80$) and PAP ($P = 0.24$) did not significantly differ among groups. Symptoms were present in 13, 49, and 83% of the patients before and in 3, 11, and 34% after intervention in Groups A, B, and C. Functional status was related to PAP.
Conclusions	At any age, ASD closure is followed by symptomatic improvement and regression of PAP and RV size. However, the best outcome is achieved in patients with less functional impairment and less elevated PAP. Considering the continuous increase in symptoms, RV remodelling, and PAP with age, ASD closure must be recommended irrespective of symptoms early after diagnosis even in adults of advanced age.
Keywords	Transcatheter closure • Age at intervention

Introduction

Atrial septal defect (ASD) not uncommonly remains undetected until adulthood accounting for 25–30% of newly diagnosed congenital heart defects.[1] Atrial septal defect closure has become an established therapy that is performed in increasing numbers of adult patients.[2] Early surgical repair results in excellent long-term outcome, whereas results appear less favourable when intervention is delayed until adulthood.[3] In particular, controversial findings have been reported for surgery performed after the age of 40 years.[4,5] In small series, surgical closure was associated with symptom and possibly survival improvement even in patients older than 60 years.[6,7] The sole randomized trial performed in patients older than 40 years, however, found reduced morbidity but not mortality after surgical ASD closure.[8] Thus, the benefits of ASD closure in adults, particularly those of advanced age, remained uncertain.[9–11] More recently, transcatheter ASD closure has been shown to be feasible and safe in children and adults.[12–15] Being significantly less invasive and associated with fewer complications even in older adults,[16,17] it became an

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attractive therapy for the elderly. Patients with pulmonary hypertension may also benefit.[18,19] Furthermore, an improved exercise capacity was reported even for asymptomatic and mildly symptomatic adult patients.[20,21] Despite being a widely performed and accepted treatment modality, data on age-dependent benefits of this procedure are, however, limited, particularly in the elderly.

The aim of the present study was, therefore, to evaluate the effects of transcatheter ASD closure on functional status, arrhythmias, right ventricular (RV) size, and pulmonary arterial pressure according to the age at intervention in a large unselected cohort of adults.

Methods

Patient population

The study population consists of 236 consecutive adults (mean age 49 ± 18 years, 164 females) who underwent transcatheter ASD closure with the Amplatzer septal occluder (ASO; AGA Medical Corporation, Golden Valley, MN, USA). Of these, 78 were younger than 40 years (Group A), 84 were between 40 and 60 years (Group B), and 74 were older than 60 years (up to 82 years; Group C) at the time of intervention. Indication for closure was a significant left-to-right shunt (signs of RV volume overload), irrespective of the presence of symptoms. Patients with severe pulmonary vascular disease (>5 Wood units) even after vasoreactivity testing or after targeted treatment were not considered for ASD closure.

During the study period, transcatheter ASD closure was attempted in 237 patients, but one patient required surgery because of significant residual shunt (success rate 99.6%). Transcatheter ASD closure was not attempted in patients who had a balloon-stretched defect diameter of >36 mm or a native diameter of >25 mm (80% of the patients found to be ineligible for transcatheter closure) and in those with inadequate defect morphology (insufficient rim, multiple defects, complex aneurysm, and significant additional lesions). For these reasons, 16% of the patients referred to our institution had surgical ASD closure, whereas 84% had transcatheter closure during the study period.

Echocardiography

Transoesophageal echocardiography (TEE) was routinely performed in all patients screened for transcatheter closure to assess ASD morphology and exclude additional lesions such as an anomalous pulmonary venous connection.

A comprehensive transthoracic echocardiogram (TTE), including M-mode, two-dimensional, continuous-wave, pulsed-wave, and colour Doppler echocardiography, was performed before intervention and at each follow-up visit.

Right ventricular size was measured by taking the transverse diameter in the apical four-chamber view, and pulmonary artery pressure (PAP) was estimated from the tricuspid regurgitant velocity.[22] The shunt ratio (Qp:Qs) was obtained by the measurement of the velocity time integrals as well as the cross-sectional areas at the corresponding sites in the pulmonary artery and the left ventricular outflow tract.[23]

Invasive evaluation

Invasive evaluation was performed prior to intervention when patients presented with a non-invasively estimated systolic PAP of >50% of systemic pressure or >60 mmHg. In these patients, pulmonary vascular resistance (PVR) was carefully assessed. Only patients with PVR ≤5 Wood units either at baseline or after vasoreactivity testing with nitric oxide were considered for ASD closure.

In patients who were found to have a left atrial pressure of >15 mmHg during intraprocedural invasive evaluation, balloon occlusion of the ASD was performed and pressure measurement was repeated. In patients with a left atrial pressure increase of >10 mmHg, further heart failure treatment was requested before consideration for defect closure to reduce the risk of left heart failure after intervention.

Catheter intervention

All procedures were carried out under general anaesthesia with endotracheal intubation and guided by fluoroscopy and TEE. After haemodynamic assessment, all patients underwent balloon sizing of the defect. The ASO was chosen 2–4 mm larger than the stretched diameter.

Aspirin therapy (100 mg/day) was initiated at least 2 days prior to and maintained for at least 6 months after the intervention. Intravenous heparin was administered intraprocedurally.

Follow-up

The patients underwent serial follow-up examinations 1 day, 1 week, 3–6 months, 12 months, and then yearly after the intervention including clinical examination, TTE, and electrocardiography. Particular care was taken to determine the functional status and to obtain information regarding symptom development or any complications. Transoesophageal echocardiography was only performed on indication (suspected residual shunt 6 months post-interventionally, suspicion of embolism).

Statistical analysis

The distribution of continuous variables within age groups was assessed by the Shapiro–Wilk tests for normal distribution. These tests revealed significant deviations from the normal distribution in nearly all variables and subgroups. Thus, continuous variables were described by medians and inter-quartile ranges and compared between the three age groups by the Kruskal–Wallis tests. In the case of a significant three-group comparison, pairwise Wilcoxon's rank sum tests were performed. For dichotomous variables, these tests were replaced by χ^2 tests. Changes in RV size and PAP from baseline to subsequent follow-up assessments were evaluated by the analysis of variance for repeated measurements (RM-ANOVA), assuming a covariance of 'unstructured' type between subsequent measurements on the same patients. For comparison of age groups, we used the analysis of covariance (ANCOVA), using the change from baseline to 6 months follow-up value as a dependent variable, age group as a nominal fixed factor, and the baseline value as a covariate. The baseline-adjusted group means were computed by the LSMEANS method of SAS/PROC GLM; these baseline-adjusted group means refer to the expected values of the dependent variable in each group given an average baseline value. Comparisons between the three age groups were adjusted by the Tukey–Kramér method. Inspecting the distribution of residuals from RM-ANOVA and ANCOVA with original and log-transformed RV size and PAP revealed a slightly closer agreement with the normal distribution after log-transformation. However, there was no difference in the observed pattern of significances between both types of analysis. Thus, for better interpretability, only results on the original values of RV size and PAP are reported here. We also supply means and standard deviations for these parameters, despite slight deviation from the normal distribution, as these are compatible to the results of RM-ANOVA and ANCOVA. A Spearman's correlation was used to determine the

relationship between age, RV size, and PAP. The SAS System 9.2 (SAS Institute, Inc., Cary, NC, USA, 2008) was used for statistical analysis. All tests were two-sided, and P-values <0.05 were considered as indicating statistical significance.

Results

Baseline characteristics

Baseline patient characteristics are shown in *Table 1*. Defect size, device size, and shunt ratio did not significantly differ among age groups.

Limited exercise capacity and shortness of breath were the most frequently reported symptoms. Prior to intervention, 121 patients were symptomatic. The presence of symptoms markedly increased with age (*Table 1*). Although 75.3% of Group A patients were asymptomatic, 51.9% of those in Group B and 87.1% in Group C presented with symptoms [45.2% New York Heart Association (NYHA) III]. Overall, there was a significant increase in PAP with age, although even some elderly patients presented with still normal PAP (*Table 1* and *Figure 1*; $r = 0.65$, $P < 0.0001$). Pulmonary artery pressure was clearly related to functional class with PAP 33 ± 9, 42 ± 12, and 60 ± 20 mmHg for patients in NYHA classes I, II, and III, respectively ($P < 0.0001$). There was a statistically significant relation but only weak correlation between age and RV size ($r = 0.28$, $P < 0.0001$). Defect size correlated weakly with RV size ($r = 0.41$, $P < 0.0001$) and poorly with PAP; nevertheless, the relation was statistically significant ($r = 0.21$, $P = 0.007$).

Moderate tricuspid regurgitation (TR) was present in 23 patients (9.7%), of whom 18 were older than 60 years. Only seven patients (3%) had severe TR. All of them were older than 60 years, had elevated systolic PAP (60.6 ± 13.4 mmHg), and were mostly symptomatic requiring diuretic therapy (three patients in NYHA class III).

The invasively measured systolic, diastolic, and mean PAP as well as transpulmonary gradient significantly increased with age ($P < 0.0001$). Systolic PAP obtained by echocardiography in the awake patient was on average 10 mmHg higher than the invasively measured pressure during general anaesthesia. Right and left atrial mean pressures were significantly higher in the oldest patient group. We found no significant difference in RV end-diastolic pressures ($P = 0.21$).

None of the patients in Group A presented with atrial fibrillation (AFib). Paroxysmal AFib was present in 9.5 and 18.9% of the patients in Groups B and C, and persistent AFib was present in 2.4 and 32.4%, respectively.

Co-morbidities such as arterial hypertension and vascular disease were mainly present in patients older than 40 years (*Table 1*).

Catheter intervention and procedural complications

The median device size was 24 mm (22, 28 mm), median procedure time 40 min (30, 55), and median fluoroscopy time 7.3 min (5.6, 10.8) with no significant differences among age groups (*Table 1*).

No major procedural complications occurred. Transient ST-elevation with complete resolution, probably due to air embolization, was observed in two patients, uncomplicated groin haematoma in five, and one developed a femoral artery pseudoaneurysm

managed conservatively. Spontaneously resolving supraventricular arrhythmias were common during the procedure. At the end of the procedure, four patients had new AFib or atrial flutter. Of these, three converted spontaneously and one required medical conversion. One patient developed transient complete atrioventricular block not requiring permanent pacemaker implantation. One patient with a history of recurrent transient ischaemic attacks had a transient worsening of his neurological deficit without neuroradiological signs of new ischaemia. Intraprocedural pressure measurement revealed 15 patients with a left atrial mean pressure of >15 mmHg and 3 patients >20 mmHg before ASD closure. None of them increased by >10 mmHg during balloon occlusion, and all of them underwent successful closure without signs of left heart failure.

Early complications and residual shunts (first day to 3 months)

For arrhythmias see below. Six patients developed a small pericardial effusion, which disappeared spontaneously within 3 months. One patient developed gastrointestinal bleeding on oral anticoagulation given for AFib. No moderate or severe residual shunt was observed. Although a mild residual shunt was more common on day 1, only seven patients (3%) had a definite and three (1.3%) a questionable mild residual shunt 3 months post-interventionally.

Follow-up

Early follow-up data (3–6 months) were available for all patients. Three patients were lost to follow-up (2.3 ± 1.6 years). None of five observed deaths were related to ASD.

The following late complications (after 3 months) were observed: 5 years after implantation, one patient developed a large thrombus on the left atrial occluder disc, which embolized into all four extremities and the spleen requiring surgical embolectomy. The patient underwent chemotherapy for haematological disease before the event and eventually fully recovered.

Three cerebral events were observed. Two patients with an ischaemic event had no residual shunt or thrombus on the occluder. One patient receiving oral anticoagulation for AFib had minor cerebellar bleeding.

Early and late arrhythmias

Atrial fibrillation was recorded in 11 patients (Group B, 7; Group C, 4) within the first week. Four of these spontaneously converted to sinus rhythm, whereas four underwent successful electrical and three medical cardioversion. Additionally, four patients developed new AFib after 3–6 months—two of these were medically and two electrically cardioverted.

All 26 patients with pre-existing persistent AFib remained in AFib. In addition, one patient who had paroxysmal AFib at entry developed persistent AFib at follow-up. However, 10 of the 22 patients (5 of 8 in Group B and 5 of 14 in Group C) with paroxysmal AFib remained in sinus rhythm during follow-up.

Regression of right ventricular size and pulmonary artery pressure

Right ventricular diameter decreased from 43 ± 7 mm at baseline to 38 ± 6 mm ($P < 0.0001$) on the first post-interventional day,

Table I Patient characteristics at study entry

	All patients (*n* = 236)	Group A, age <40 years (*n* = 78)	Group B, 40–60 years (*n* = 84)	Group C, age >60 years (*n* = 74)	P-value A/B/C	A/B	A/C	B/C
Age (years)	49 ± 17.4	29 ± 6.7	50 ± 5.6	71 ± 6.1	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Gender (female), *n* (%)	164 (69.5)	48 (61.5)	55 (65.5)	61 (82.4)	0.0160*	0.6468	0.0058*	0.0183*
Echocardiographic data								
RV size (mm)	43 (39, 48)	41 (37, 46)	43 (38, 41)	45 (42, 50)	0.0007*	0.2006	<0.0001*	0.0141*
PA systolic pressure (mmHg)	37 (30, 48)	30 (26, 35)	35 (31, 41)	51 (42, 62)	<0.0001*	0.0005*	<0.0001*	<0.0001*
Qp:Qs	2.21 (1.7, 2.9)	2.11 (1.7, 2.6)	2.15 (1.6, 2.6)	2.45 (2.75, 3.1)	0.0893	0.9452	0.1116	0.0263*
Defect size (mm)	22 (19, 26)	23 (19, 26)	22 (17.5, 26.5)	22.5 (20, 28)	0.2397	0.2736	0.5995	0.0954
Moderate TR, *n* (%)	23 (9.7)	1 (1.3)	4 (4.8)	18 (24.7)	<0.0001*	0.2007	<0.0001*	0.003
Severe TR, *n* (%)	7 (3)	0	0	7 (9.6)	0.0003*	NA	0.0054	0.0039
Invasive data (mmHg)								
RA mean pressure	7 (5, 9)	7 (5, 8.5)	7 (5, 9)	8 (6, 11)	0.0194*	0.6346	0.0111*	0.0236*
RV end-diastolic pressure	9 (7, 11)	9 (7, 10)	9 (7, 11)	10 (8, 12)	0.2162	0.6998	0.0937	0.1911
PA systolic pressure	28 (23, 36)	24 (20, 27)	29 (23, 33)	36 (30, 50)	<0.0001*	0.0002*	<0.0001*	<0.0001*
PA diastolic pressure	11 (8, 14)	9 (8, 12)	10 (8, 14)	14 (9, 17)	0.0001*	0.0409*	<0.0001*	0.0048*
PA mean pressure	18 (15, 23)	15 (14, 18)	18 (16, 22)	23 (19, 30)	<0.0001*	0.0020*	<0.0001*	0.0001*
LA mean pressure	9 (7, 11)	9 (7, 10)	9 (7, 11)	10 (8, 14)	0.0259*	0.4481	0.0121*	0.0438*
Transpulmonary gradient	10 (7, 13)	7 (6, 9)	10 (7, 12)	13 (9, 17)	<0.0001*	0.0005*	<0.0001*	0.0042*
Clinical data								
NYHA I, *n* (%)	105 (46.5)	58 (75.3)	38 (48.1)	9 (12.9)	<0.0001*	<0.0001*	0.2203	<0.0001*
NYHA II, *n* (%)	88 (38.9)	18 (23.4)	38 (48.1)	32 (45.7)	0.0063	0.003	0.0081	0.8011
NYHA III, *n* (%)	33 (14.6)	1 (1.3)	3 (3.8)	29 (41.4)	<0.0001*	0.3481	<0.0001*	<0.0001*
Persistent atrial fibrillation, *n* (%)	26 (11)	0	2 (2.4)	24 (32.4)	<0.0001*	0.1703	<0.0001*	<0.0001*
Paroxysmal atrial fibrillation, *n* (%)	22 (9.3)	0	8 (9.5)	14 (18.9)	0.0003*	0.0051*	<0.0001*	0.0887*
Arterial Hypertension, *n* (%)	39 (16.5)	0	19 (22.6)	20 (27)	<0.0001*	<0.0001*	<0.0001*	0.5214
Diabetes mellitus, *n* (%)	9 (3.8)	0	4 (4.8)	5 (6.8)	0.08	0.051	0.0196*	0.5893
Hypercholesterolaemia, *n* (%)	18 (7.6)	1 (1.3)	3 (3.6)	29 (39.2)	<0.0001*	0.3481	<0.0001*	<0.0001*
Coronary artery disease, *n* (%)	11 (4.7)	0	4 (4.8)	7 (9.5)	0.083	0.051	0.00542	0.247
Peripheral arterial disease, *n* (%)	3 (1.3)	0	2 (2.4)	1 (1.4)	0.40	0.17	0.303	0.6361
Carotid artery disease, *n* (%)	4 (1.7)	0	1 (1.2)	3 (4.1)	0.1391	0.3337	0.0725	0.2529
Chronic obstructive pulmonary disease, *n* (%)	8 (3.4)	0	2 (2.4)	6 (8.1)	0.018	0.1703	0.0101	0.1013
Device size (mm)	24 (22, 28)	24 (22, 28)	24 (20, 29.5)	26 (22, 30)	0.3213	0.7207	0.1449	0.2679
Fluoroscopy time (min)	7.3 (5.6, 10.8)	7.15 (5.6, 10.4)	6.7 (5.5, 10.4)	8.55 (6.5, 12)	0.1471	0.8479	0.1090	0.0714
Procedure time (min)	40 (30, 55)	40 (30, 59)	40 (30, 56)	37 (30, 48.5)	0.8866	0.7233	0.6544	0.8456

Data are presented as mean ± standard deviation or median (inter-quartile range) where appropriate.
LA, left atrial; NYHA, New York Heart Association functional class; Qp:Qs, pulmonary to systemic flow ratio; PA, pulmonary artery; RA, right atrial; RV, right ventricular; TR, tricuspid regurgitation.
*Statistically significant difference.

36 ± 6 mm after 1 week, and 34 ± 6 mm after 3−6 months. At last follow-up, RV size remained stable with 34 ± 6 mm (*Figure 2*).

Pulmonary artery pressure decreased from 41 ± 16 to 35 ± 13 mmHg on day 1 and 34 ± 12 mmHg 3 months after ASD closure (*P* < 0.0001) remaining stable thereafter (33 ± 14 mmHg at last follow-up; *Figure 3*).

A decrease in RV size and PAP was observed in all age groups. The absolute changes did not significantly differ among groups (decreases in RV size 9 ± 7, 8 ± 7, and 8 ± 6 mm for Groups A, B, and C, *P* = 0.80; decreases in PAP 5 ± 8, 8 ± 9, and 9 ± 14 mmHg, respectively, *P* = 0.24). Consequently, older patients who had significantly larger RVs and higher PAPs before ASD closure ended up with larger ventricles and higher PAPs after intervention. The baseline-adjusted mean decreases in RV size for Groups A, B, and C were 10.1, 8.4, and 6.1 mm, respectively (*P* < 0.0001 for comparison of Groups A and C, *P* = 0.0163 for

comparison of Groups B and C, and *P* = 0.0903 for comparison of Groups A and B). The baseline-adjusted mean decreases in PAP in Groups A, B, and C were 11.6, 10.4, and 2.3 mmHg, respectively, and significantly differed between Groups A and C (*P* < 0.0001) and Groups B and C (*P* = 0.0001) but not between Groups A and B (*P* = 0.8210). A moderate correlation between age and PAP persisted post-interventionally (*r* = 0.63, *P* < 0.0001) and patients older than 60 years were most likely to be left with persistently elevated PAP. Although no patient in Group A and only five patients in Group B (6%) had a systolic PAP ≥40 mmHg, this was the case in 38 patients (51%) of Group C.

Tricuspid regurgitation

After ASD closure, the degree of TR decreased. Only 2 of originally 7 patients still had severe TR and 17 (originally 23) had moderate TR. They also improved with regard to functional status. Of the seven patients with originally severe TR, three were asymptomatic and four in NYHA class II after closure.

Functional status

Symptomatic improvement was observed across all age groups (*Figure 4*). After 3−6 months, all but two Group A patients who remained in NYHA class II were asymptomatic. In Group B, nine patients remained in NYHA class II, whereas 89% were asymptomatic. In Group C, however, 22 patients remained in NYHA class II and 3 in NYHA class III. Two of them suffered from marked persistent pulmonary hypertension, and one had advanced obstructive pulmonary disease. Nevertheless, even Group C patients improved markedly with 69% being asymptomatic post-interventionally when compared with 16% before.

Functional status was closely related to PAP. At 3−6 months, patients in NYHA classes I, II, and III had a systolic PAP of 31 ± 9, 47 ± 15, and 67 ± 3 mmHg, respectively. A PAP above 40 mmHg was present in 2 of 3 patients in NYHA class III, in 18
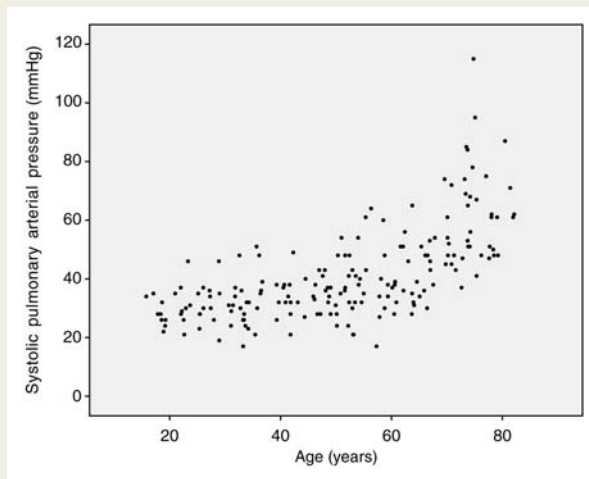
**Figure 1** Correlation between systolic pulmonary artery pressure and age (*r* = 0.65, *P* < 0.0001).
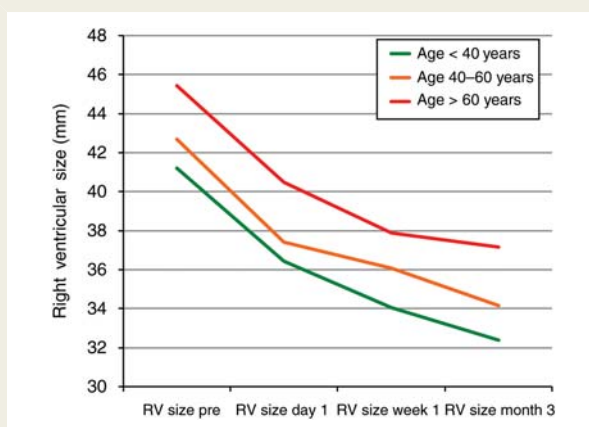
Figure 2 Right ventricular (RV) size before, 1 day, 1 week, and 3 months after atrial septal defect closure for patients younger than 40 years (green line), patients aged 40−60 years (orange line), and patients older than 60 years (red line).
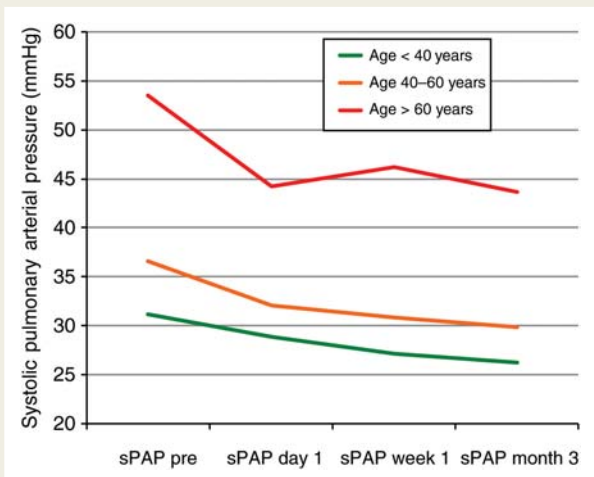
Figure 3 Systolic pulmonary artery pressure (sPAP) before, 1 day, 1 week, and 3 months after atrial septal defect closure for patients younger than 40 years (green line), patients aged 40−60 years (orange line), and patients older than 60 years (red line).
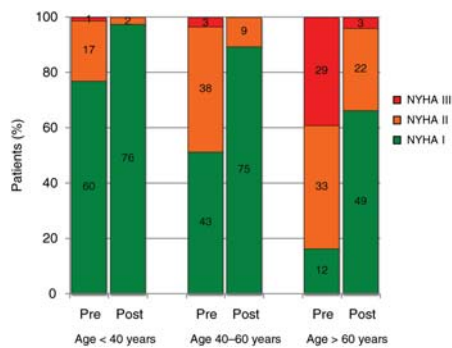
Figure 4 Symptomatic status before (pre) and after (post) atrial septal defect closure for patients younger than 40 years, patients aged 40−60 years, and patients older than 60 years.

of 30 in NYHA class II, and in only 23 of 203 asymptomatic patients.

However, 180 of 193 patients (93%) with a PAP <40 mmHg were asymptomatic, whereas this was only the case for 23 of 43 patients (54%) with PAP ≥40 mmHg.

At late follow-up, a slight worsening of the symptomatic status was observed, again being more likely in older patients.

Discussion

The benefit of ASD closure in adults, particularly those of advanced age, remains a matter of debate.[9−11] Transcatheter ASD closure has the advantage of being significantly less invasive and associated with shorter hospital stay than surgery.[24,25] In currently published series including the present one, no procedure-related death was observed.[15−17] In contrast, surgical ASD closure has been found to be associated with significant mortality at advanced age.[3,6,26,27] Although primarily low-risk patients were referred to surgery in the past, data of larger unselected series are now available including the elderly and patients with significant co-morbidities. Although some previous series documented the feasibility and safety of the procedure in older adults, data on the actual benefit remained so far insufficient and inconclusive: in the most recent and largest series including 144 patients older than 60 years, Majunke et al.[15] only report on the efficacy and safety of the procedure but no details about clinical benefits and changes in RV and PAP. Swan et al.[28] retrospectively analysed the results of ASD closure in 185 patients, 50 older than 60 years. They reported that RV size and PAP decreased in the older group but provide only short-term results, not including clinical outcome and effects of age. Similarly, Elshershari et al.[29] only reported short-term results for a group of 41 patients older than 60 years, allowing no conclusions with regard to age effects or factors associated with insufficient improvement. Yalonetsky and Lorber[30] studied only small groups of patients aged 40−60 years and above 60 years (23 patients in each group), reporting a greater reduction in PAP in the older group again without detailing the outcome.

The present study is to our best knowledge the first report of a large cohort of consecutive adult patients with a comprehensive analysis of the impact of age at intervention on the long-term effect of ASD closure on functional status, arrhythmias, and other adverse events as well as RV size and PAP.

The study confirms the feasibility and safety of transcatheter ASD closure in all age groups. Although one occurrence of late thrombus formation on the occluder with embolization in a patient with haematological disease may raise concern, this remained the only major complication in the long-term follow-up. Krumsdorf et al.[31] published a study with over 1000 patients, which focused on thrombus formation on different devices and found that in all occluders, with exception of the Amplatzer occluder (no incidence), there was a low incidence of thrombosis. Nevertheless, embolic events were extremely rare.

Arrhythmias

The incidence of AFib—one of the major causes of morbidity in patients with ASD—is closely related to age.[32] After surgery, AFib occurs more frequently in patients older than 40 years at the time of intervention,[32] and the rate of new-onset arrhythmias was reportedly similar to medically treated patients.[4,8] The different timing of arrhythmia onset, however, suggests different underlying mechanisms, scars playing an important role after surgery. Both acute and long-term effects on the interatrial septum and atria may be different after transcatheter closure. New-onset AFib early after transcatheter ASD closure has previously been reported.[33] In our series, 6% of the patients developed AFib within 3 months after the intervention. Sinus rhythm was restored in all of them emphasizing its transient nature potentially caused by early mechanical irritation of the septum. Of note, AFib has been reported to occur both after percutaneous ASD and patent foramen ovale closure.[34] Silversides et al.[35] reported that the likelihood of remaining free of arrhythmia after transcatheter ASD closure was greatest in patients younger than 40 years without a history of arrhythmia. A positive effect of transcatheter ASD closure on the long-term incidence of arrhythmia was described.[36] In agreement with our observations, the incidence of arrhythmias after closure was reduced in patients (particularly, the younger ones) with paroxysmal AFib but not in those with persistent AFib.[37] Thus, transcatheter ASD closure may trigger early transient arrhythmias, persistent AFib is unlikely to be affected, but paroxysmal arrhythmias may improve although that likelihood decreases with age.[34]

Functional status

Controversial data were reported regarding the effect of late surgical ASD closure on the functional status.[4,5] The present study demonstrates how the incidence and intensity of symptoms increase with age. Symptomatic improvement was observed across all age groups but was most impressive in older patients. Nevertheless, a significant portion of older patients remained symptomatic, and some patients deteriorated again during late follow-up.

Pulmonary hypertension

The prevalence of pulmonary hypertension in patients with ASD has been reported to be between 6 and 27%.[18,38−41] Two previous studies report successful transcatheter ASD closure in patients

with pulmonary hypertension. Although PAP remained elevated in a significant portion, some decrease associated with symptomatic improvement was reported.[18,19] However, these previous studies did not allow conclusions on age-related effects, and it remains unclear how many of these patients also had a severely increased vascular resistance.

In the present study, patients with severe pulmonary vascular disease were excluded. Nevertheless, the study clearly demonstrates that PAP increases continuously with age and that a significant portion of patients had severe pulmonary hypertension. A significant and similar decrease in PAP after ASD closure was observed in all age groups. However, older patients who had higher pre-interventional PAPs still had significantly higher PAPs after intervention and significantly less baseline-adjusted pressure decrease. The increase in PAP in these patients can be assumed to be partially due to a high pulmonary flow. However, although patients with severe pulmonary vascular disease were excluded, part of the patients had a more or less increased vascular resistance. All patients decreased with their PAP after ASD closure, at least partially due to the decrease in transpulmonary flow and probably also due to some decrease in PVR. Although we cannot provide invasive follow-up data, it is likely that persistent elevation of PVR must be assumed to be the reason for a still elevated PAP in part of the patients. Importantly, there was a close relation between PAP and functional status.

Similar to our results, Yong et al.[42] recently reported that patients with advanced pulmonary arterial hypertension responded with a significant decrease in PAP after interventional ASD closure but were less likely to reach normal PAPs and become asymptomatic.

Right ventricular remodelling

Atrial septal defect closure has been shown to result in a significant reduction in RV and an increase in left ventricular volumes.[43,44] A reduction in RV size occurs immediately after ASD closure with a further reduction within the following 3–6 months.[43,45] The improvement of both RV and LV functions has been reported.[46] Our findings demonstrate that a significant decrease in RV size can be expected even in elderly patients, although the latter present with larger ventricles before and after the intervention.

Mortality

So far, the only randomized study of surgical ASD closure in adult patients did not find a survival benefit but was limited by the exclusion of markedly symptomatic patients and a short follow-up. Nevertheless, observational studies suggest that surgical ASD closure confers a survival benefit: in one retrospective series[6] 84 patients with surgical ASD closure had an improved long-term survival in comparison with 95 medically treated patients.[4] Since transcatheter ASD closure can be performed with almost no mortality even in the elderly, an overall mortality benefit of the catheter intervention is even more likely. However, this will never be proven by a randomized trial since it would be unethical to perform such a study nowadays.

Study limitations

The major limitation of the present study is its non-randomized nature and the lack of a control group, making it impossible to study effects of ASD closure on survival. However, it can no longer be justified to perform a randomized trial on ASD closure even in the elderly. Exercise testing was not routinely performed since it is poorly standardized in the elderly. However, objective measures such as RV size and PAP were obtained. Functional improvement indeed went along with the changes of these variables. Finally, patients with severe pulmonary vascular disease (>5 Wood units even after vasoreactivity testing or targeted treatment) were excluded, making it impossible to draw conclusions for these patients.

Conclusions

Transcatheter ASD closure can be safely and successfully performed in adults at any age. Regression of RV size and PAP as well as symptomatic improvement can be expected across all age groups. However, the best outcome is achieved in patients with less functional impairment and less elevated PAP. Considering the continuous increase in symptoms, RV remodelling, and PAP with increasing age, ASD closure must be recommended irrespective of symptoms early after diagnosis even in adults of advanced age.

Conflict of interest: none declared.

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