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Lifelong Burden of Small Unrepaired Atrial Septal Defect: Results from the Danish National Patient Registry

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Abstract

Background: Adults patients with small, unrepaired atrial septal defects (ASD) have higher late mortality than the background population. In this nationwide study, we characterise the late natural history of adults with small, unrepaired ASD.

Methods: Using the Danish National Patient Registry, we included all Danish patients, diagnosed between 1953 and 2011 with an unrepaired ASD. Additionally, all patients, aged 18-65, were invited for clinical testing. Patients also completed a general health survey for comparison with the general population.

Results: We identified 723 patients with a small unrepaired ASD. Since the time of diagnosis, 182 patients had died, with an average lifespan of 63 years. The most common cause of death was heart failure. Furthermore, ASD patients had a higher burden of chronic disease than the general population (38.2% vs. 26.9%; p=0.005), particularly lung disease (3.6% vs. 0.9%; p=0.008). A total of 153 patients (mean age 32y) underwent additional testing. On echocardiography an open defect was verified in 19.6% (n=30) of the patients, of which half subsequently underwent intervention. Interestingly, 6-minute walking distance was markedly reduced ($p<0.0001$ compared to normative values) no matter whether the defect was open or closed by echocardiography. Finally, 25.5% of the patients often felt stressed or nervous as compared with 16.3% of the general population (p=0.004).

Conclusions: Patients with small, unrepaired ASD in adult life have reduced lifespan, more chronic diseases, impaired submaximal exercise capacity, and higher levels of stress than the general population. The current guidelines for intervention and follow-up may need to be reconsidered.

1. Introduction

Atrial Septal Defect (ASD) is the third most common type of congenital heart disease, with a total prevalence of 1.1 per 1000 live births in Denmark.[1] International recommendations for the closure of significant defects are well-established and the long-term outcomes have been considered benign with international recommendations suggesting these patients do not require specialized follow-up in adult congenital heart clinics.[2] However, using our national database we have recently shown that late mortality is increased, compared with the general population, both in those that have and have not undergone prior closure of ASD,[3] that there is a significantly increased risk of pneumonia, that does not normalize until 5 years after closure,[4] and that there is an 8-fold increase of later onset atrial fibrillation compared with population controls, independent of mode of closure (surgical or device).[5]

In this study we concentrate on the late outcomes of unoperated ASD. Patients with asymptomatic ASD without right ventricular enlargement, thromboembolic complications, or with a pulmonary to systemic flow ratio (Qp:Qs) less than 1.5, are typically not offered closure.[2,6] Such defects are presumably considered hemodynamically insignificant, and to be associated with normal life expectancy and co-incidence of comorbidities. However, these recommendations were developed in the absence of adequate long-term natural history data in unoperated patients with these small defects.

2. Methods

2.1 Study design and participants

This is a nationwide descriptive cohort study of all patients with an unrepaired ASD based on medical registries in Denmark. The cohort was identified in previous studies through the Danish National Patient Registry (DNPR), which includes complete and continuously updated data on all

residents living in Denmark since 1977.[4,5] The DNPR contains information on all inpatient and outpatient hospital contacts in Denmark, dates of admission and discharge, surgical procedures, and discharge diagnoses coded according to the International Classification of Disease (ICD). Two independent clinicians validated the ASD diagnosis through review of hospital records. Patients with defect closure, pulmonary arterial hypertension, or Eisenmenger syndrome were excluded, leaving only those with small, unrepaired, and hemodynamically insignificant ASDs, although we cannot exclude the possibility that some patients with larger defects chose not to undergo closure and are therefore also included. Every patient in Denmark who at one point was diagnosed with an unrepaired ASD was also invited to undergo additional testing. The examination included a questionnaire, echocardiography, spirometry, and a 6-minute walking test. Enrolment was conducted from December 2015 to February 2018. We used the DNPR to characterize the entire cohort and to compare the patients attending for additional testing with patients who did not respond to or declined the invitation. Baseline comorbidity was identified using the ICD diagnoses in the DNPR. Comorbidity was indexed in the Charlson Comorbidity Index, which includes diagnoses of heart, lung, cerebral, renal, and liver disease, as well as cancer, human immunodeficiency virus, and diabetes, for a total of 17 diagnoses. Patients were categorized into four groups depending on their score as follows: no coexisting comorbidity, mild comorbidity, moderate comorbidity, and severe comorbidity.

Inclusion criteria for the additional testing were a diagnosis of unrepaired ASD aged between 18 and 65 years. The exclusion criteria for the additional testing were as follows: severe mental or psychiatric disorder incompatible with inclusion, other congenital heart disease (except patent ductus arteriosus), persistent foramen ovale, and previous ASD closure.

This study complies with the Declaration of Helsinki and was approved by The Danish Data

Protection Agency (j.nr. 1-16-02-633-15) and by The Regional Committee on Biomedical Research Ethics of the Central Denmark Region (j.nr. M-2015-197-15). Written informed consent for the additional testing was obtained for all participants at the beginning of inclusion.

2.2 Questionnaire

We compared our patient group to the general population using the questionnaire from the Danish National Health Survey 2013.[7] This questionnaire was distributed to a random sample of 300,450 citizens in Denmark. A total of 162,283 individuals completed the questionnaire. A random sample of 22,930 people was drawn and matched by gender and age with the included ASD patients, resulting in a ratio of 150 citizens per patient. All included ASD patients received an identical questionnaire and received a brief instruction before answering. Unless asked for question clarification, there was no intervention from the investigators. The Danish National Health Survey includes questions on health-related quality of life, health behavior, morbidity, and social relations. It also includes several internationally validated scales such as the 12-Item Short-Form Health Survey version 2 (SF-12) and Cohen's Perceived Stress Scale.

2.3 Echocardiography

We used a standardized transthoracic echocardiogram protocol with focus on the atrial septum, to determine if a defect was still present, and the right ventricle. All tests were performed using a GE Vivid E9 (GE Healthcare, Horten, Norway) by a single highly trained echo-technician, and all images were reviewed by an interventional pediatric cardiologist.

2.4 Spirometry

Patients performed standard dynamic spirometry on an EasyOne$_{TM}$ diagnostic spirometer (NDD Medizintechnik AG, Switzerland). Recorded measurements were forced vital capacity (FVC), forced expiratory flow in one second (FEV1), and peak expiratory flow (PEF). FEV1, FVC, and PEF are presented as percentage of expected normal values for each patient. The FEV1/FVC ratio was calculated and adjusted for age, sex, and height. The selected outcome was the best out of three attempts. All tests were performed by one investigator in accordance with current guidelines at our institution.

2.5 6-minute walking test

We used the 6-minute walking test to assess submaximal exercise capacity. The test was conducted on a flat surface with a straight-lined course. Recorded outcomes were; achieved walking distance; transcutaneous oxygen saturation, and heart rate. Reference equations were used for each patient to compute the predicted walking distance for healthy adults.[8]

2.6 Statistical analyses

Continuous, normally distributed data were reported as mean ± standard deviation. The paired Student t test was used for normally distributed 6-minute walking test data. Categorical variables were summarized by percentages or frequencies. Comparisons of categorical baseline characteristics and questionnaire between patients and the general population were performed by Fisher's exact test. Statistical significances were defined as those with p-values below 0.05. All analyses were performed using Stata IC 15.1 (StataCorp LP, College Station, TX).

3. Results

3.1 Patient characteristics

The Danish ASD cohort is composed of 2277 validated patients with ASD who are above 18 years of age. Of these, 1554 underwent closure either surgically or by catheter, leaving a total of 723 patients with an unrepaired ASD. The age and date at diagnosis was available in all patients. Of the 723 patients in the unrepaired ASD cohort, a total of 182 patients had died, with an average lifespan of 63 years (table 1). Most deaths were due to cardiac causes, especially non-ischemic heart failure.

156 patients with ASD (mean age 31.9 years, 61.4% female) consented to additional testing (figure 1). Three patients were later excluded from analysis due to incidental findings that could impact measured variables (two ventricular septal defects and one Ebstein's anomaly), providing a final total of 153 patients. All patients were asymptomatic at the time of inclusion. Patient characteristics and questionnaire results are summarized in table 2. No differences in age, time of diagnosis, or comorbidities were found when comparing included patients and patients who did not respond to the invitation letter (table 3).

3.2 Questionnaire

The vast majority (97%) of questionnaires were fully completed (see table 2). There was no significant difference in the number of daily smokers, the diet, or drinking habits among ASD patients and the general population. Body mass index (BMI) was slightly higher in the ASD patients. A clear pattern was evident regarding physical functioning. A lower proportion of ASD patients rated their physical functioning as good, and they scored lower in the SF-12 physical health section. However, the percentage who scored "extremely low" was identical between the groups. The ASD patients' mental health was similar to that of the general population, even though more patients were found to have higher levels of stress, more patients felt anxious/nervous, and more patients felt tired. Patients reported more chronic diseases, especially stroke, angina, and lung

diseases. Contact with the general practitioner over the last 12 months was comparable between the groups.

3.3 Echocardiography

All echocardiographic data are shown in table 4. Most defects had spontaneously closed since the time of diagnosis; and, only 30 patients (19.6%) (mean age 36 y) had an open ASD. One patient had an ostium primum defect, and the remaining patients had ostium secundum defects. Unsurprisingly, overall, patients with spontaneously closed defects had smaller right heart structures compared to those with small, open defects, and one third of these had overtly dilated right heart chambers (n = 10) (mean age 37 y). In the entire cohort altogether, no right ventricular or left ventricular systolic or diastolic dysfunction was identified. Pulmonary artery pressure estimated by the tricuspid regurgitation gradient was not significantly different between the spontaneously and small open ASD group.

3.4 Interventions

Closure of the defect was recommended in half of the patients (n = 15), comprising 9.8% of the entire included cohort. The indication for closure was right ventricular dilatation in 10 patients, three patients had their defect closed due to a previous history of stroke, the patient with an ostium primum defect underwent surgery, and a further patient with gross pulmonary artery dilation opted for medical surveillance.

3.5 Spirometry

FEV1 were substantially lower in our patient group (89 ± 16 %) than the expected normal values, although within the normal clinical range. PEF values were also low (78 ± 25 %), with a mean

value just below normal range. FEV1/FVC ratio (0.77 ± 0.39) and FVC (97 ± 15 %) was within normal range. No differences were found between patients with an open defect and patients with a spontaneously closed defect.

3.6 6-minute walking test

A significant impairment in walking distance was evident when comparing patients (632 ± 90 m) with computed reference values for each patient (715 ± 94 m; $p<0.0001$). Only one patient experienced significant oxygen desaturation from 97% to 90%. There was no difference between patients with an open defect and patients with a spontaneously closed defect. One patient had recent hip surgery and was excluded from the test.

4. Discussion

This is the first nationwide cohort study examining the natural history of patients with a small, unrepaired ASD. The entire cohort was characterized using registries, and approximately half of the eligible patients were subjected to additional physical testing and health evaluation questionnaire. Our study shows that far from being a benign lesion, a small ASD diagnosed in adult life, even if it closes spontaneously, is associated with reduced lifespan, increased incidence of co-morbidities, impaired functional performance, and lower self-reported physical functioning compared to population norms.

Patients diagnosed with an unrepaired ASD had a mean age at death of 63 years. This is well below today's normal life expectancy in Denmark of 80.9 years.[9] Indeed, life expectancy at birth for Danes has not been below 63 years since 1926.[9] The adverse impact of ASD on longevity was highlighted by Campbell et al in 1970, who showed clearly that large unrepaired ASDs are associated with a reduced lifespan.[10] These data were taken as further support for the notion that

such defects should be closed in early life, to prevent late increased mortality. However, this theoretical advantage has been hard to prove given the, perhaps understandable, lack of randomized clinical trials of intervention versus medical therapy. Indeed, this topic was the subject of a recent systematic review by a Task Force of the American Heart Association/American College of Cardiology.[11] Their conclusion that "insufficient data are available to determine the impact of ASD repair on mortality rate in adults" was informed by prior studies, including our own,[3] showing that despite earlier closure late mortality exceeds population norms in these patients. That said, our earlier data suggested that while there was an increased hazard ratio for late death in patients with a previously closed defect,[3] it was significantly higher in those with an 'open' defect. Given that the current study showed that these small unoperated ASD's have a substantial spontaneous closure rate in adult life (almost 80% of 153 patients undergoing detailed echocardiography), and that the life-expectancy for the entire group was substantially reduced despite most of the patients not having a discernible defect, this poor late outcome may reasonably be attributed to the late consequences of the rather subtle effects of the ASD earlier in life, perhaps supporting the notion that even small defects may be benefitted by closure in early childhood.

The same can be said for the other measurable adverse effects that we found in our patients. The associations and abnormalities we found must be, in the majority of patients, a consequence of having had an ASD, rather than having a small ASD, given that only one fifth of our cohort had an ASD by echocardiography at the time of examination. Nonetheless, patients reported a higher level of chronic illnesses compared with the general population. Whereas it might be anticipated that arrhythmias and stroke were more common in patients with small ASD,[5,12] the increased burden of chronic lung diseases had not been described before. In this regard, lung function has not previously been examined in adults with a diagnosis of small ASD, and only once in adult patients with

significant ASD.[13] We demonstrated that FEV1 and PEF were lower in our patients than the expected normal values. Whether these abnormalities are related to an increased frequency or impact, of recurrent chest infections is not known, although our prior data has shown an increased incidence of pneumonia in patients with ASD, which only normalizes 5 years after closure.[4]

While speculative, these abnormalities of lung function may have a direct functional impact on functional performance. No matter what the cause, our findings from the 6-minute walking test were clear. Patients with a diagnosis of small ASD (whether present at the time of the test or not) had impaired submaximal exercise capacity compared with reference values. The pathophysiologic basis of this unexpected finding deserves further investigation, but it lends further support to the notion that there are late, unforeseen, functional consequences of having a diagnosis of small ASD that cannot be explained on the basis of contemporary hemodynamic effects.

Given all of these adverse consequences, including poorer patient-assessed physical functioning compared to that of the general population, it is perhaps surprising that mental health status was similar in ASD patients and the general population. Nonetheless, on more direct assessment of psychosocial health status compared to the general population a higher proportion of ASD patients felt more stressed, anxious, tired, and nervous. Furthermore, a significantly lower proportion of patients were employed, which could not be explained by differences in age, gender, or education. The impact of a diagnosis of a small ASD, clearly therefore has effects beyond physical functioning and, although perhaps inter-related, also impacts on patients' general feelings of wellbeing.

4.1 Limitations

We used transthoracic echocardiography to assess the size and presence of atrial septal defect. This technique may overlook small defects and persistent foramen ovale, and the true percentage of complete spontaneous closure might have been lower than the 80% we report, had transesophageal echocardiography been performed. However, this approach was not practically or ethically feasible and the discovery of tiny defects would not influence the overall interpretation of our data.

Unfortunately, earlier information on defect characteristics and shunt dimensions at time of diagnosis was not always available. Therefore, we had to rely on the clinical description, and the implication of size from the lack of advice to undergo closure, to assign these patients as having a 'small defect'. While, as discussed earlier, some patients with larger defects earlier in life may conceivably have been included in our overall cohort, the fact that only 10 of 153 patients had defects that warranted intervention, on the basis of right ventricular dilation, when we formally reassessed them, and none of those had an anatomically 'large' defect reassures us that the impact of such patients on our findings would be minimal.

Finally, interpretation of registry-based data inherently has some limitations. While the registration of the death dates in the Civil Registration System is considered to highly accurate,[14] the cause of death registered in The Danish Register of Causes of Death is only as precise as what the physician interprets and enters on the death certificate. Similarly, the diagnoses given in the DNPR are potentially affected by mis- and under- or over-reporting.[15] Given that ASD is a diagnosis of inclusion (unlikely to be diagnosed when not present) it is unlikely that they were over-reported, however we cannot be sure how many patients with ASD were not reported or remained undiscovered.

5. Conclusion

Small ASD that is considered insignificant and not warranting closure in early life cannot be

considered to be a benign lesion. Patients with a small, unrepaired ASD that persists into adult life have increased risk of premature death, chronic diseases, worse functional capacity, higher levels of stress, and lower scores on their self-assessed physical function than the general population. This is despite the fact that by the time of assessment the majority of defects have closed spontaneously. Our data suggest that not only might the criteria for the need for closure in early life need to be revisited, but also that ASD whenever diagnosed, whatever the size, and whether closed or not, warrants regular lifelong follow-up in specialized clinics aware of these adverse, and possibly modifiable, outcomes.

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Figure legends

Figure 1: Flowchart of patient inclusion

Table 1: Causes of death for small, unrepaired ASD patients

	Small, unrepaired ASD (n=723)
Deaths (n)	182
Mean age at death (years)	63.3±1.9 Range: 0.2-99.1
Mean age at diagnosis (years)	53.3±27.4
Cause of death	
Cardiac, non-ischemic	57
Heart failure	*23*
AF	*2*
Mitral Valve	*4*
Other	*28*
Cardiac, ischemic	29
Total Cardiac	**86 (47%)**
Infection	10
Stroke	10
Cancer	22
Diabetes/kidney disease	8
Chronic lung disease	11
Chromosome anomalies	10
Accident	5
Other	12

Unknown	8

Causes of deaths divided into categories. Other cardiac disease includes those listed only as death caused by ASD (n=22), cardiomyopathy (n=3), and pulmonary heart disease (n=3).

Table 2: Patient characteristics (compared with the Danish National Health Survey)

Variable	**Small Unrepaired ASD n=153**	**General population n=22.950**	***p*-value**
Sex (% female)	61.4	61.4	1.000
Age (year)	31.9	31.5	0.652
Height (cm)	171.6	173.2	0.030
Weight (kg)	74.8	73.7	0.372
BMI (kg/m^2)	25.2	24.5	0.040
Smoking daily (%)	17.7	15.3	0.430
Alcohol: Days a week	1.4	1.6	0.200
Alcohol: High Risk (>21 men, >14 women) (%)	6.0	11.0	0.070
Diet, self-estimated if healthy (%)	36.4	40.7	0.319
Self-estimated health (excellent/good) (%)	88.2	91.4	0.190
Self-estimated physical health (good) (%)	21.7	37.4	0.000
Contact with your general practitioner in the last 12 months? (%)	79.0	80.2	0.684
Do you have a chronic illness? (Yes) (%)	39.9	27.1	0.001
Cancer (%)	0.7	0.3	0.372
Diabetes (%)	0.7	1.7	0.526
Rheumatoid Arthritis (%)	1.3	2.4	0.592
Osteoarthritis (%)	6.5	6.5	1.000
Lung disease (emphysema, COPD, bronchitis)	3.3	1.1	0.033

Asthma (%)	9.2	5.7	0.080
Allergy (not asthma) (%)	27.5	22.8	0.176
Hypertension (%)	5.2	5.8	1.000
Stroke (%)	2.6	0.8	0.035
Angina (%)	3.3	0.4	0.001
Migraine or frequent headache (%)	16.3	18.8	0.348
High levels of stress (perceived stress scale) (%)	28.8	22.8	0.100
Do you often feel nervous/stressed? (%)	25.5	16.3	0.004
Last 2 weeks: Felt anxiety (%)	34.4	25.0	0.011
Last 2 weeks: Had difficulty sleeping (%)	40.8	37.4	0.401
Last 2 weeks: Felt sad, depressed, unhappy (%)	33.8	31.2	0.533
Last 2 weeks: Felt tired (%)	78.2	68.4	0.011
Last 2 weeks: Had headache (%)	41.7	43.2	0.720
SF-12: Physical Health	51.2	53.6	0.000
SF-12: Low Physical Health (<35.37) (%)	4.7	4.6	0.842
SF-12: Mental Health	48.1	48.6	0.581
SF-12: Low Mental Health (<35.76) (%)	10.9	11.9	0.799
Are you ever undesirable alone? (%)	2.6	5.9	0.115
Are you rarely in contact (in person, speaking, writing, etc.) with your family? (%)	2.0	3.1	0.650
Are you working? (No) (%)	34.6	22.5	0.001
Have you completed a higher education? (medium- or long-term programs) (%)	28.1	28.0	1.000

Table 3: Cohort characteristics and morbidities

	Included patients **n=153**	**Non-responders** **n=205**
Female n, (%)	94 (61.4)	81 (38.9)
Age 1/1/18 (years)	33.2 ± 12.1	38.7 ±13.9
Age at diagnosis (years)	8.8 ±13.6	8.9 ±13.4
Follow-up (years)	18.9 ±9.0	19.2 ±8.1
Charlson Morbidity Index		
Group 0	151	201
Group 1	2	5
Group 2	0	2
Chronic lung disease, n (%)	4 (3)	5 (2)
Diabetes, n (%)	1 (0.6)	3 (1)
Pulmonary heart disease, n (%)	1 (0.6)	4 (2)
Hypertension, n (%)	3 (2)	2 (1)
Ischemic heart disease, n (%)	3 (2)	2 (1)
Cerebrovascular events, n (%)	3 (2)	5 (2)
Arrhythmia, n (%)	2 (1)	6 (3)

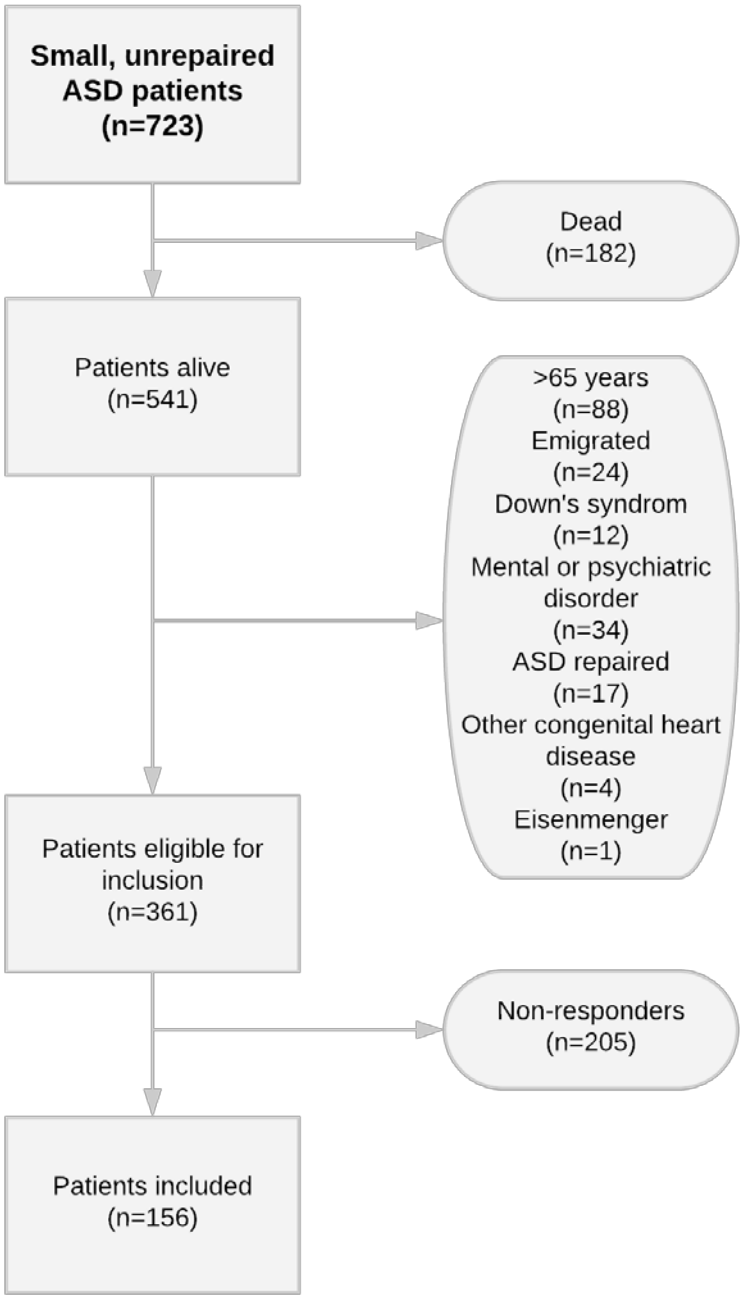
Table 4: Echocardiographic Measures

	Small unrepaired ASD (n=153)	**Spontaneously Closed ASD (n=123)**	**Small, open ASD (n=30)**	**P-value**
Ejection fraction (%)	62.5±3.9	62.5±3.2	62.1±6.2	0.6003
LV diameter (cm)	4.8±0.4	4.8±0.5	4.7±0.4	0.5620
LV areal (cm^2)	31.4±5.9	31.4±6.2	31.3±4.7	0.9271
TR (mmHg)	16±5.3	15.8±5.3	16.5±5.5	0.6417
PAAT (cm)	1.9±0.2	1.9±0.2	2.0±0.2	0.1506
LA areal (cm^2)	16.4±4.1	16.2±4.1	17.1±4.2	0.2772
RA areal (cm^2)	12.5±3.3	12.1±3.1	14.1±3.8	0.0027
RV areal (cm^2)	15.5±5.1	15.0±5.2	17.4±4.3	0.0189
- Men	17.8±6.2	17.8±6.8	18.1±3.2	-
- Woman	14.5±5.7	13.9±5.8	17.1±4.9	-
RV Fractional Area Change (%)	51.9±8.6	52.4±6.8	49.8±13.4	0.1418
RV E (m/s)	0.47±0.1	0.47±0.1	0.50±0.1	0.2197
RV diastolic area (cm^2)	31.1±4.2	30.5±3.7	33±5.6	0.0066
LV diastolic area (cm^2)	46±9.6	46.3±10.6	44.9±4.0	0.4994
RV/LV diastolic area, ratio	0.69±0.09	0.68±0.07	0.74±0.1	0.0013
TAPSE (mm)	24.5±3.8	24.5±3.8	24.4±3.7	0.9783
Global Longitudinal Strain (%)	-24.2±3.1	-24.1±3.2	-24.2±3.0	0.9026
Septal Thickness (mm)	7.9±1.2	7.9±1.2	8.0±1.1	0.8654

Posterior Wall Thickness (mm)	8.0±1.2	8.0±1.2	8.2±1.2	0.4422
LV E:A ratio	1.6±0.6	1.7±0.6	1.6±0.6	0.5699
LV E:E' ratio	5.1±1.3	5.1±1.3	5.2±1.3	0.6613
RV S' (m/s)	0.14±0.1	0.15±0.1	0.13±0.02	0.4615
RV A' (m/s)	0.16±0.15	0.16±0.15	0.16±0.15	0.9557
VCI diameter expiration/inspiration (cm) ratio	3.5±1.6	3.6±1.5	3.0±1.8	0.0903
Incidental findings				
- Gerbode defect	1			
- Ventricular septal defect	1			
- Persistent ductus arteriosus	1			
- Ebstein's anomaly	1			
- Atrial septal aneurysm	18 (11.8%)			

Echocardiographic outcome in all included patient. TR values were only measurable in 83 patients. P-values express the comparison between patients with spontaneously closed ASD and patients with small, open ASD. TR, tricuspid regurgitation. LV, left ventricle. LA, left atrium. RV, right ventricle. RA, right atrium. VCI, vena cava inferior.

Figure 1


Small, unrepaired ASD patients (n=723)
Dead (n=182)
Patients alive (n=541)
>65 years (n=88)
Emigrated (n=24)
Down's syndrom (n=12)
Mental or psychiatric disorder (n=34)
ASD repaired (n=17)
Other congenital heart disease (n=4)
Eisenmenger (n=1)
Patients eligible for inclusion (n=361)
Non-responders (n=205)
Patients included (n=156)