Risk Factors for Pulmonary Hypertension in Adults After Atrial Septal Defect Closure

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Atrial septal defect (ASD) closure is performed to prevent pulmonary hypertension (PH), which is associated with poor outcome. This study investigated the prevalence of PH in adults before and after ASD closure and explored associations between patient characteristics and PH after ASD closure. Consecutive adult patients who underwent surgical or percutaneous ASD closure in the Erasmus MC, the Netherlands, were included (2000 to 2014). Echocardiograms before and after ASD closure were retrospectively assessed. Patients were categorized into 3 groups (no PH, possible PH, and PH) based on tricuspid regurgitation velocity (<2.9, 2.9 to 3.4, and ≥3.4 m/s) or mean pulmonary arterial pressure (<20, 20 to 24, and ≥25 mm Hg). Cox regression was performed to identify associations between patient characteristics and PH after ASD closure. Of the 244 eligible patients who underwent ASD closure, 198 (81%) had echocardiograms both before and median 15 (interquartile range 12 to 35) months after ASD closure (median age at closure 45 [interquartile range 30 to 57] years, 75% woman). The prevalence of PH was 13.1% (n = 26) before ASD closure and 5.0% (n = 10) after closure. New York Heart Association III to IV (hazard ratio [HR] 11.07, 95% confidence interval [CI] 3.12 to 39.29, p <0.001), pulmonary disease (HR 10.43, 95% CI 2.12 to 51.21, p = 0.004), cardiac medication use (HR 3.96, 95% CI 1.02 to 15.34, p = 0.047), right ventricular fractional area change (HR 0.87, 95% CI 0.81 to 0.93, p <0.001), and tricuspid annular plane systolic excursion (HR 0.75, 95% CI 0.59 to 0.95, p = 0.018) were significantly associated with PH. In conclusion, adult patients with low pulmonary pressures before ASD closure are not at risk of PH after closure. Nevertheless, PH remained prevalent in approximately 5% of patients. Especially those patients with high New York Heart Association functional class, presence of pulmonary disease, cardiac medication use and impaired RV function at baseline are at risk. **(Am J Cardiol 2019;123:1336−1342)**

Atrial septal defect (ASD) accounts for approximately 10% of congenital cardiac anomalies.[1] Increased pulmonary flow by left-to-right shunting can cause pulmonary hypertension (PH).[2] Left untreated, the consequent increase in pulmonary vascular resistance can lead to progressive deterioration of right ventricular (RV) function, right heart failure, and eventually death.[3,4] Therefore, in patients with a significant hemodynamic shunt causing RV volume overload, ASD closure is indicated, unless specific contraindications are present.[5] The reported prevalence of PH in adult patients with a closed ASD is widely varying from 5% to 50% in older studies.[6−16] Some studies even suggest that pulmonary pressures can further increase after ASD closure in individual patients.[17] PH associated with congenital heart disease is associated with a high mortality.[4] Identification of patient characteristics associated with the persistence or development of PH after ASD closure as well as further delineation of the clinical course of patients with PH after ASD closure is important, as it affects individual patient follow-up and therapeutic management. The objective of this study is to estimate the prevalence of PH before and after ASD closure. In addition, this study aims to investigate the association between patient characteristics and the presence of PH after ASD closure.

Methods

All consecutive adult patients who underwent surgical or percutaneous closure of an ASD ostium secundum or sinus venosus defect between 2000 and 2014 in our center were identified. Criteria for ASD closure agrees with the European Society of Cardiology (ESC) guidelines.[5] We excluded patients with a patent foramen ovale, significant pulmonary stenosis (>2.0 m/s or requiring surgery), Ebstein's anomaly, left heart surgery or percutaneous coronary intervention during the procedure, lung transplantation before ASD closure, and patients with other identifiable causes for PH such as chronic thromboembolic PH.

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All investigators take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

See page 1341 for disclosure information.

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Patient characteristics such as age at ASD closure, gender, height, weight, blood pressure, saturation, New York Heart Association (NYHA) functional class, cardiac medication, known pulmonary disease (chronic obstructive pulmonary disease or obstructive sleep apnea syndrome), type of procedure (percutaneous or surgical), residual lesions, and cardiac (re-)interventions were obtained from the electronic patient charts. The Erasmus MC medical ethics committee approved the study protocol and waived the need for written informed consent.

All transthoracic echocardiograms before and ≥6 months after ASD closure were retrospectively assessed. Right atrial (RA) and RV dimensions and area were primarily measured on a RV focused view. If this view was not available, these measurements were performed on the apical 4-chamber view. RV function was quantified with tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC). Tricuspid regurgitation (TR) and pulmonary regurgitation (PR) were quantified on color Doppler echocardiography. All measurements were performed in agreement with the current recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging.[18]

In this study, PH is defined as an echocardiographic high probability of PH as described in the guideline of Galiè et al.[19] Patients were categorized into 3 groups based on TR velocity (no PH: <2.9 m/s, possible PH: 2.9 to 3.4 m/s, and PH: ≥3.4 m/s) according to the ESC/European Respiratory Society guidelines for the diagnosis and treatment of PH.[19] When a TR velocity measurement was not available, categorization was based on the mean pulmonary arterial pressure (mPAP; no PH: <20 mm Hg, possible PH: 20 to 24 mm Hg, and PH: ≥25 mm Hg). The mPAP was calculated from the PR maximal velocity and the estimated RA pressure; RA pressure was estimated from the inferior vena cava size and respiratory variation.[18] RV systolic pressure and mPAP were calculated in accordance with the current recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging.[18] When both TR velocity and mPAP could not be measured, patients were categorized as possible PH based on the presence of enlarged RV dimensions, decreased RV function and/or signs of PH (systolic and diastolic septal flattening on the parasternal short-axis image at midventricular level)[20] by an expert cardiologist in the field of echocardiography and PH (A.E.v.d.B.).

Continuous variables were reported as mean ± standard deviation, or as median (interquartile range [IQR]) if data were skewed. Categorical data were presented as frequencies and percentages. Comparisons across the different PH categories (no PH, possible PH, and PH) were performed using the Chi-square Mantel-Haenszel trend test for categorical variables and linear regression for continuous variables. Cox proportional hazards regression was performed to identify associations between patient characteristics and PH after ASD closure. Proportional hazards assumption was checked in R (version 3.4.1) using log-minus-log plots for categorical variables and Schoenfeld residuals for continuous variables. Because of the limited number of patients with PH after ASD closure, multivariable Cox regression analysis was not performed. Statistical analysis was performed using SPSS version 21.0.0.1 (IBM Corp., Armonk, New York). Two-sided p values of <0.05 were considered statistically significant.

Results

We identified 281 adult patients with an ASD closure in our center, of whom 37 patients were excluded based on predefined criteria (Figure 1). Of the 244 eligible patients, 6 and 40 patients had missing echocardiographic data on RV pressures before or after the ASD closure, respectively. Therefore, 198 patients were included in the final study cohort. The 46 patients with missing RV pressures did not have significant differences in age at closure, body mass index, use of cardiac medication, NYHA class, type of procedure, or PH classification before ASD closure compared with the 198 patients included in the analysis. The ASD was closed percutaneously in 110 patients and surgically in 88 patients. Baseline characteristics of the study population (and for the separate PH classification groups) are specified in Table 1.

Figure 2 provides an overview of the PH classification before and after ASD closure. Before ASD closure, 121 patients (61.1%) were categorized as no PH. After ASD closure, in 174 patients (87.9%) no signs of PH were present. The prevalence of PH was 13.1% (n = 26) before and 5.0% (n = 10) after ASD closure. Median follow-up time was 15 (IQR 12 to 35) months. Of the 10 patients with PH after closure, 7 were suspected to have PAH and the other 3 were suspected of PH due to left ventricular diastolic dysfunction according to the ESC/European Respiratory Society guidelines for the diagnosis and treatment of PH.[19] Figure 2 also shows that RV pressures decreased in almost all patients after ASD closure. Only 1 patient (ASD closed at age of 63 years) had an increase in the pulmonary pressure, but this patient also had left ventricular diastolic dysfunction.

Before ASD closure, the classification of PH was based on TR velocity in 187 patients (94%), on PR velocity in 4 patients (2%), and on a combination of RV dimensions, RV function and signs of PH in 7 patients (4%). In 29 patients (15%) the PH classification after ASD closure was based on different variables (i.e., TR before ASD closure, and PR velocity or RV function after ASD closure), because reliable measurements of the TR maximal velocity were not always available.

Before ASD closure, 4 patients used PH medication. Three patients used a phosphodiesterase-5 inhibitor and 1 patient used a combination of a phosphodiesterase-5 inhibitor, an endothelin antagonist, and a prostacyclin analogue. Of the 10 patients classified as PH after ASD closure, 7 patients used a combination of a phosphodiesterase-5 inhibitor and an endothelin antagonist. 2 patients only used a phosphodiesterase-5 inhibitor.

In Table 2, the results of the Cox proportional hazards regression are displayed. Of all clinical, electrocardiographic and echocardiographic measurements that were evaluated, we found that NYHA class, presence of pulmonary disease, use of cardiac medication, TR maximum velocity, RV FAC, TAPSE, and PH before ASD closure were significantly associated with PH at follow-up. Of note, the estimates for some

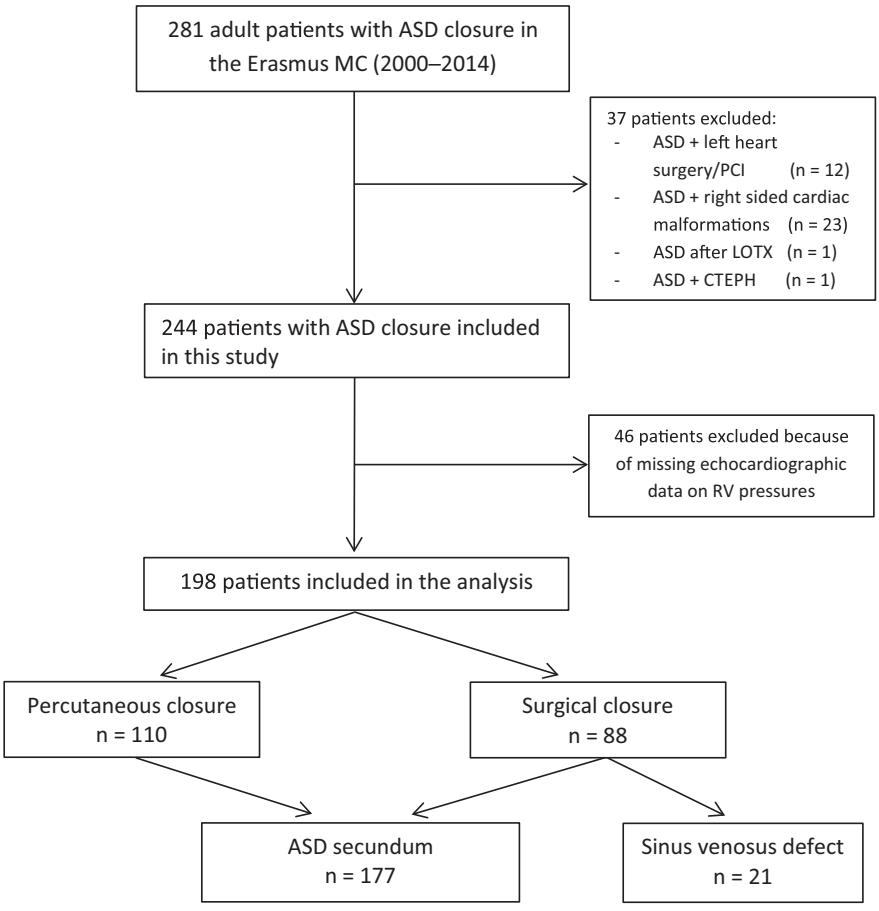

Figure 1. Flowchart of the patient selection.

of these variables (such as pulmonary disease and cardiac medication) are not precise and should be therefore interpreted with caution. Age at closure and the diameter of the ASD or sinus venosus defect were not found to be associated with PH after ASD closure.

Information on survival was available in all patients using the municipal registry. During a clinical follow-up of 8 (IQR 5.5 to 10.0) years from the ASD closure, overall 9 patients died. Of these patients, 5 were categorized as no PH, 1 patient as possible PH and 3 patients as PH after ASD closure. Causes of death were end stage heart failure (n = 4), sudden death (suspected cardiac; n = 1), malignancy (n = 1), gastrointestinal bleeding, presumably due to anticoagulants use (n = 1), euthanasia (in a patient with an infaust prognosis due to malignancy; n = 1), and unknown (n = 1). Reintervention after the ASD closure because of a significant rest shunt was performed in 2 patients (1%).

Discussion

The prevalence of PH in adult patients before ASD closure in our study was 13.1% and decreased to 5% after ASD closure. Factors associated with PH after ASD closure were PH before ASD closure, NYHA functional class III to IV, presence of pulmonary disease, cardiac medication use, RV FAC, and TAPSE.

Although pulmonary artery pressure (PAP) decreased after ASD closure in the majority of patients, 10 patients showed no change in PAP resulting in an overall PH prevalence median 15 months after ASD closure of 5%. This number is consistent with some previous studies, who also reported a prevalence of 5% in the adult population after ASD closure.[13,14] Other studies have reported a higher prevalence ranging from 12% to 50%.[6–8,10–12,15] These studies were mainly published in 1970 to 1990 and consisted of a small study population with the majority having surgical ASD closure. In these studies, before ASD closure the PH prevalence and NYHA functional class was also higher [6,7,11,15]; therefore, it is likely that this is a selection of more severe cases. There is no documentation on the type of patients who were lost to follow-up, but the percentage of patients lost to follow-up was clearly higher in these older studies (>25%) and selection bias could have occurred.

According to the guidelines of PH and the literature, the most recognized predictors of poor clinical outcome in patients with PH are TAPSE, pericardial effusion and RA area.[19,21] In our study, only 1 patient had significant pericardial effusion so this variable was not further analyzed in our study. RA area was not associated with the presence of PH in adults after ASD closure. Our study did show an association of the presence of pulmonary disease, NYHA class, RV FAC, TAPSE, and pulmonary pressures before

Table 1
Baseline characteristics of the study cohort (n = 198)

			PH classification before ASD closure			
	Valid cases	All, n = 198	No PH (n = 121)	Possible PH (n = 51)	PH (n = 26)	p for trend
Clinical characteristics						
Age at closure (years)*	198 (100%)	45 [30−57]	42 [27−52]	53 [44−64]	50 [36−66]	<0.001
Female	198 (100%)	148 (75%)	91 (75%)	39 (77%)	18 (69%)	0.650
NYHA class III−IV	198 (100%)	24 (12%)	7 (6%)	6 (12%)	11 (42%)	<0.001
Sinus venosus defect	198 (100%)	21 (11%)	15 (12%)	5 (10%)	1 (4%)	0.207
Surgical repair	198 (100%)	88 (44%)	52 (43%)	21 (41%)	15 (58%)	0.298
Pulmonary disease	198 (100%)	8 (5%)	4 (3%)	2 (4%)	2 (8%)	0.355
COPD	198 (100%)	7 (4%)	4 (3%)	2 (4%)	1 (4%)	-
OSAS	198 (100%)	2 (1%)	0 (0%)	0 (0%)	2 (8%)	-
Cardiac medication	198 (100%)	66 (33%)	27 (22%)	23 (45%)	16 (62%)	<0.001
ACE-inhibitor	198 (100%)	12 (6%)	5 (4%)	4 (8%)	3 (12%)	-
Beta blocker	198 (100%)	49 (25%)	19 (16%)	20 (39%)	10 (39%)	-
Diuretic	198 (100%)	33 (17%)	10 (8%)	14 (28%)	9 (35%)	-
Anti-arrhythmic	198 (100%)	12 (6%)	2 (2%)	6 (12%)	4 (15%)	-
Body mass index (kg/m^2)	198 (100%)	25 ± 5	24 ± 4	27 ± 5	25 ± 5	0.016
Systolic blood pressure (mm Hg)	197 (99%)	133 ± 19	123 ± 16	142 ± 21	139 ± 19	<0.001
O_2 saturation <95%	126 (64%)	16 (8%)	4 (6%)	6 (17%)	6 (32%)	0.002
Electrocardiography						
Heart rate (beats/min)	197 (99%)	73 ± 12	73 ± 12	74 ± 14	73 ± 11	0.998
Loss of sinus rhythm	198 (100%)	30 (15%)	13 (11%)	9 (18%)	8 (31%)	0.009
QRS duration (ms)	198 (100%)	109 ± 19	107 ± 18	110 ± 19	116 ± 24	0.021
PR interval (ms)	173 (87%)	164 ± 24	169 ± 23	171 ± 25	168 ± 31	0.114
Echocardiography						
Defect diameter (mm)	163 (82%)	21.5 ± 9.4	20.4 ± 8.6	21.2 ± 9.7	27 ± 11	0.007
RA pressure (mm Hg)	177 (90%)	6.5 ± 2.8	6.1 ± 2.5	6.6 ± 2.8	7.8 ± 3.9	0.012
RA pressure ≥15 mm Hg	177 (90%)	10 (6%)	4 (4%)	2 (5%)	4 (17%)	0.025
RA end-systolic area (cm^2)	159 (80%)	29 ± 11	26 ± 8	33 ± 13	38 ± 14	<0.001
RA end-systolic area >18 cm^2	159 (80%)	151 (76%)	95 (93%)	37 (97%)	19 (100%)	0.144
TR maximum velocity (m/s)	187 (94%)	2.8 ± 0.5	2.4 ± 0.3	3.0 ± 0.2	3.8 ± 0.4	<0.001
RV FAC (%)	154 (78%)	38 ± 8	39 ± 7	39 ± 10	31 ± 8	0.001
RV FAC <35%	154 (78%)	55 (28%)	27 (27%)	14 (38%)	14 (78%)	<0.001
RVEDD basal (mm)	154 (78%)	5.6 ± 0.9	5.4 ± 0.8	5.8 ± 1.0	6.2 ± 0.9	0.001
RVEDD basal >41 mm	154 (78%)	146 (95%)	94 (95%)	34 (92%)	18 (100%)	0.680
LV FS (%)	187 (94%)	38 ± 9	37 ± 9	40 ± 8	39 ± 9	0.205
LV systolic function	190 (96%)					0.412
Normal	190 (96%)	159 (84%)	100 (83%)	43 (91%)	16 (70%)	
Mildly impaired	190 (96%)	28 (14%)	18 (15%)	4 (9%)	6 (26%)	
Moderately impaired	190 (96%)	3 (2%)	2 (2%)	0 (0%)	1 (4%)	
Severely impaired	190 (96%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
TAPSE (mm)	106 (54%)	28.4 ± 6.3	28.7 ± 5.7	29.0 ± 6.9	25.4 ± 8.0	0.262
TAPSE <17 mm	106 (54%)	3 (3%)	2 (3%)	0 (0%)	1 (10%)	0.503

p value for trend was calculated using the Chi-square Mantel-Haenszel test for categorical variables and linear regression for continuous variables. For pulmonary disease en cardiac medication: no comparisons were made between subgroups. Legend:

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASD = atrial septal defect; COPD = chronic obstructive pulmonary disease; FS = fractional shortening; LV = left ventricular; NYHA = New York Heart Association; OSAS = obstructive sleep apnea syndrome; PH = pulmonary hypertension; RA = right atrial; RVEDD = right ventricle end-diastolic dimension; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

* Median (IQ_1 to IQ_3), other n (%) or mean ± SD.

closure with PH classification after ASD closure. These variables have also been reported as predictors for PH in previous studies.[10,12,17,22] Various studies have identified age at ASD closure as a predictor for PH.[12,17,23] Interestingly, in our study age at closure was not found to be associated with PH after ASD closure. In the study of Gabriels et al, besides adult patients, also patients with an ASD closure in their childhood were included.[17] Yong et al[12] and Humenberger et al[23] only included patients with an ASD repair at adult age, but these patients were much older than in our study cohort (mean age 54 ± 16 and 49 ± 18 years, respectively). The wider age range compared with our study may explain why these studies did find an association between age at closure and PH after ASD closure, in contrast to our study.

Patients with an ASD repair at adult age, especially those repaired at 40 years of age and older, should be followed on a regular basis during the first 2 years and then depending on the results every 2 to 4 years, according to the 2010 European Society of Cardiology guidelines for the

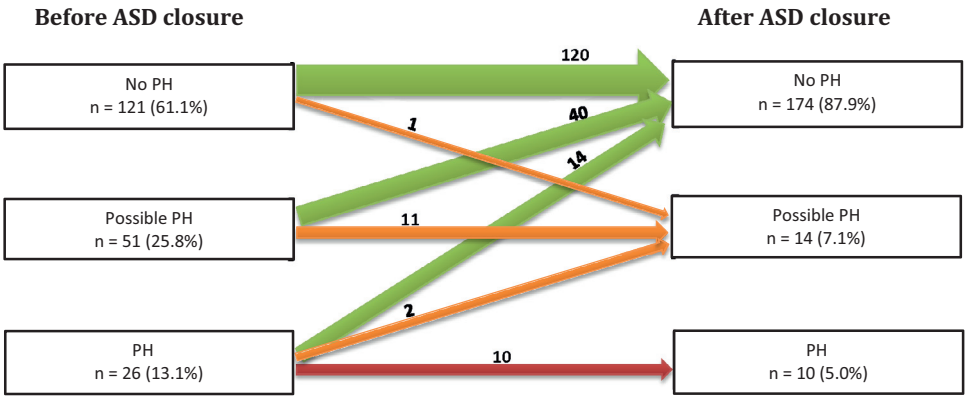

Figure 2. Classification of pulmonary hypertension before and after ASD closure. No PH: TR velocity <2.9 m/s or mPAP <20 mm Hg; Possible PH: TR velocity 2.9 to 3.4 m/s or mPAP 20 to 24 mm Hg; PH: TR velocity ≥3.4 m/s or mPAP ≥25 mm Hg. ASD = atrial septal defect; mPAP = mean pulmonary artery pressure; PH = pulmonary hypertension; TR = tricuspid regurgitation.

management of grown-up congenital heart disease.[5] No specific recommendations are made with regard to patient characteristics that further differentiate the need for clinical follow-up. The results of our study show that adult patients without signs of PH before ASD closure are not at risk for the development of PH after the repair and therefore follow-up is needed only with long intervals. In contrast, a substantial proportion of the patients with signs of PH before closure continued to have high RV pressures. Therefore, it is indeed important to regularly follow-up patients with elevated PAP or signs of PH before closure, while patients without PH can be checked with a low frequency. Special attention is warranted for those patients who have specific risk factors such as NYHA class III to IV, cardiac medication use, presence of pulmonary disease and RV dysfunction before the ASD closure as they have an increased risk of PH after ASD closure. Finally, these findings reinforce the current proactive treatment strategy that is recommended in the guidelines, advocating that the sooner one acts (in regard to pre-existing development of PH; and in regard to severity of PH reflected by NYHA class, RV dysfunction and pulmonary pressures), the better.

This study is vulnerable to different types of bias because of its observational and retrospective design. We

Table 2
Associations between patient characteristics and pulmonary hypertension after atrial septal defect closure

Variables	Valid cases	Hazard ratio	95% CI	p value
Clinical characteristics				
Age at closure (years)	198 (100%)	1.02	0.98−1.07	0.241
Female	198 (100%)	1.16	0.30−4.50	0.828
NYHA class III−IV	198 (100%)	11.07	3.12−39.3	<0.001
Sinus venosus defect	198 (100%)	0.04	0.00−166	0.450
Surgical repair	198 (100%)	1.34	0.39−4.63	0.644
Pulmonary disease (yes)	198 (100%)	10.43	2.12−51.2	0.004
Cardiac medication (yes)	198 (100%)	3.96	1.02−15.3	0.047
Body mass index (kg/m^2)	198 (100%)	1.03	0.92−1.16	0.589
Systolic blood pressure (mm Hg)	197 (99%)	0.99	0.96−1.03	0.601
O_2 saturation <95%	126 (64%)	1.98	0.38−10.3	0.416
Electrocardiography				
Heart rate (beats/min)	197 (99%)	1.02	0.98−1.07	0.368
Loss of sinus rhythm	198 (100%)	1.24	0.26−5.85	0.788
QRS duration (ms)	198 (100%)	1.01	0.98−1.04	0.600
PR interval (ms)	173 (87%)	1.00	0.97−1.04	0.863
Echocardiography				
Defect diameter (per mm)	163 (82%)	1.03	0.96−1.10	0.382
RA pressure (per mm Hg)	177 (90%)	1.10	0.92−1.32	0.293
RA end-systolic area (per cm^2)	159 (80%)	1.01	0.97−1.06	0.516
TR maximum velocity (per m/s)	187 (94%)	7.36	2.92−18.5	<0.001
RV FAC (per %)	154 (78%)	0.87	0.81−0.93	<0.001
RVEDD basal (per mm)	154 (78%)	1.44	0.70−2.94	0.318
LV FS (per %)	187 (94%)	1.02	0.95−1.10	0.580
LV systolic function (mild/moderately impaired)	190 (96%)	3.40	0.85−13.7	0.085
TAPSE (per mm)	106 (54%)	0.75	0.59−0.95	0.018
PH before ASD closure	198 (100%)	23.03	3.39−157	0.001

CI = confidence interval; others as defined in Table 1.

attempted to avoid selection bias by including all consecutive patients that underwent ASD closure between 2000 and 2014 in our center; however, echocardiographic data on RV pressures were not available in 46 patients. Although the baseline characteristics of these patients were not significantly different from the included study population, selective loss to follow-up may have occurred. Secondly, patients were categorized into PH groups based on echocardiographic measurements, which is less accurate for the diagnosis of PH than the reference standard, right heart catheterization. This was not routinely performed in all patients, because it is unethical to perform these invasive measurements in asymptomatic patients.[19] Some patients have been classified with different echocardiographic variables before and after ASD closure, but these were mostly patients without any signs of PH, and we expect that this has not largely influenced our conclusions. Third, the aim of this study was to focus on PH after ASD closure. Therefore, other late complications such as arrhythmia were not taken into account. The risk of these other late complications is also an important factor to take into account when determining the frequency and location of follow-up visits. Finally, multivariable Cox regression could not be performed, because the limited number of patients with PH after ASD closure (5%, n = 10). A larger sample size would lead to more precise confidence intervals and the possibility for multivariable analyses. Future studies should therefore involve collaborations with other institutions to increase the sample size.

In conclusion, adult patients with low pulmonary pressures before ASD closure are not at risk for the development of PH after ASD closure during a follow-up period of 15 months. These patients can be reassured and need less frequent follow-up. Nevertheless, PH remained prevalent in approximately 5% of adult patients after ASD closure. Especially those patients with high pulmonary pressures before ASD closure, high NYHA functional class, presence of pulmonary disease, cardiac medication use and impaired RV function at baseline are at risk and therefore require close follow-up after ASD closure.

Contributors

The investigators are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the report and its final contents.

Disclosures

The investigators have no conflicts of interest to disclose.

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