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A different view on predictors of pulmonary hypertension in secundum atrial septal defect

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ABSTRACT

Background/objectives: Pulmonary arterial hypertension is an important complication in hemodynamically relevant atrial septal defects (ASD) and negatively affects outcome. This retrospective study aimed at (1) estimating the prevalence of pulmonary hypertension (PH) in patients with secundum ASD and (2) identifying predictors of PH development or persistence after ASD closure.
Methods: Consecutive patients with an isolated secundum ASD from the Belgian Registry on Adult Congenital Heart Disease were studied. Demographic, clinical, echocardiographic and invasive hemodynamic measurements were analyzed. PH was defined upon the echocardiographic PH probability (tricuspid regurgitation velocity ≥ 2.9 m/s).
Results: PH prevalence in the entire ASD population (295 patients, 68.8% females, mean age 46 ± 21 years) was 15.9% compared to 13.3% in patients after ASD closure. PH after ASD closure was significantly related to mortality ($p = 0.001$), atrial arrhythmia ($p < 0.001$) and right heart failure ($p = 0.019$). Age at repair was the most important predictor for PH (HR 1.11). In the highest tertile of age at repair (>55 years), PH prevalence was the highest (34%) and mean pulmonary artery pressure (mPAP) at catheterization before was related to PH after closure (HR 1.09). Twenty patients in the PH group had mPAP <25 mm Hg before closure.
Conclusions: PH in closed secundum ASD patients is not uncommon. Its prevalence was the highest when the defect was repaired above 55 years of age. Clinical outcome was worse. PH may even develop despite normal mPAP before closure. The present findings raise the question whether the cutoff value for mPAP before closure should be age-adjusted.

1. Introduction

Atrial septal defect (ASD) is one of the most common congenital heart defects, with a worldwide prevalence of around 2 per 1000 live births [1]. ASD type secundum (with the defect located in the mid atrial septum, in the fossa ovalis) accounts for 75% of all ASD. There is a female predominance of 2:1 [2].

Pulmonary arterial hypertension (PAH) may develop in response to a chronic volume overload of the pulmonary circulation, caused by a left-to-right shunt. It is an important complication in patients with hemodynamically relevant ASD and negatively affects outcome [3,4]. Its prevalence in ASD has been estimated around 10%. A remarkably higher percentage of patients with open ASD have PAH, compared to patients who underwent ASD closure [4,5]. ASD closure has shown to reduce right ventricular volume, improve right ventricular function and lower pulmonary artery pressure (PAP) [6,7]. However, remodeling of the right heart and changes in the pulmonary vasculature in patients with late ASD closure are not completely reversible [7–9].

Although early closure may prevent PAH development, many ASD are still detected later in adulthood when patients develop symptoms of right heart dysfunction and pulmonary vascular disease (PVD) [2]. Chronic volume overload of the pulmonary circulation is thought to cause irreversible changes of the medium-sized and small arteries [10,11]. Interestingly, not all patients with chronic volume overload will develop PAH and in some patients the progression rate of PAH is much faster [2,9,12]. This suggests a multifactorial cause of PVD, with a likely role for genetic factors, which are still largely unknown at present. To prevent this natural evolution of PVD and to better understand which patients are susceptible for developing PAH, we need better mapping of its predictors.

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The aim of the present study was to estimate the prevalence of PAH in the Belgian adult population with secundum ASD and to identify predictors of its development or persistence after ASD closure.

2. Methods

2.1. Patient selection

All patients with an isolated secundum ASD were selected from the Belgian Registry on Adult Congenital Heart Disease (ACHD). The registry was started in 2005 in collaboration with ten university/academic centers in Belgium and currently includes almost all congenital shunt lesions followed up in our country. Only a minority of patients with CHD in Belgium are followed at peripheral centers. Patients dismissed from follow-up in the seventies and eighties after closure of simple and small shunt lesions are currently contacted for check-up and inclusion in the registry. Demographic, clinical and biochemical data, electrocardiographic, echocardiographic, invasive hemodynamic measurements, and, if applicable, data on closure were obtained from the patient's records. Follow-up consisted of evaluations in each participating center. Each participant signed informed consent for registry inclusion. The Ethics Committee of each hospital approved the follow-up protocol (Belgian protocol number: B32220071280. Approval date: 19th of November 2007. http://www.uzleuven.be/commissie-medische-ethiek). The registry is maintained by an independent data manager (Alabus AG, Switzerland).

Exclusion criteria included concomitant congenital heart disease or the presence of pulmonary valve stenosis. Patients with Eisenmenger's syndrome associated with a secundum ASD were not excluded from primary analysis.

Data were retrospectively analyzed for all patients selected and three time points were considered. (1) First visit, as the first patient contact with the physician who diagnosed the defect. (2) Initial repair, as the date of ASD closure (if applicable), or heart catheterization. (3) Latest follow-up visit.

2.2. Echocardiography

All patients underwent transthoracic and/or transesophageal echocardiography (TTE and/or TEE) at baseline, mainly focusing on shunt characteristics. Defect size was defined as the maximal ASD diameter. At latest follow-up, TTE was performed according to the 2006 guidelines for chamber quantification [13]. TTE included two-dimensional, M-mode, pulsed wave, continuous wave and color Doppler measurements. Right atrial (RA) and right ventricular (RV) dilatations were graded as normal, mild, moderate or severe, based on absolute measurements (apical 4-chamber view, long-axis at end-systole and short-axis at the midventricular level at end-diastole, respectively) and observer impression. Tricuspid regurgitation (TR) was graded semi-quantitatively on color Doppler echocardiography. The PH probability at latest follow-up was estimated based upon the tricuspid regurgitation velocity (TRV), obtained by transthoracic echocardiography. Three different PH categories (no, possible and likely) were defined, following the ESC/ERS guidelines on pulmonary hypertension [3]. Patients with no or only trivial TR were assumed to have no PH, based on the absence of indirect echocardiographic signs for PH [3,14].

2.3. Invasive evaluation

Eighty-six percent of patients underwent invasive hemodynamic measurements prior to ASD closure. In 96% of patients with percutaneous ASD closure, invasive hemodynamic measurements before closure were performed. PAP and shunt ratio (Qp:Qs) were measured for each patient. As such, PH at baseline was defined invasively, based upon mPAP ≥ 25 mm Hg, according to the PH guidelines [3]. Pulmonary capillary wedge pressure (PCWP) was not a standard measurement and only performed if mean and diastolic PAP were elevated.

2.4. Follow-up

Patients with ASD closure were reassessed at day 1, 1 month and 6 months after ASD closure and yearly thereafter, unless abnormal evolution was noted. Patients without closure were normally followed on a yearly base. Follow-up was mainly done by non-invasive examinations (clinical examination, electrocardiography, TTE, exercise testing when indicated). A new heart catheterization was only performed in a few patients, solely based on clinical or echocardiographic indications.

2.5. Statistical analysis

The statistical analyses were performed with the software program SPSS (version 22.0, Chicago, USA). For continuous variables, data are reported as means ± standard deviation, or as medians + interquartile ranges (IQR) if normal assumption was not valid. Discrete variables are presented as frequencies and/or proportions. Comparative statistics were performed between the PH group (TRV ≥ 2.9 m/s) and non-PH group (TRV ≤ 2.8 m/s). Comparison of two means was done by a two-tailed Student's *t*-test or, when normality was not assumed, by a Mann–Whitney test. Levene's test was performed to assess for equal variances. Proportions were compared by the Chi-square test (or Fischer's exact test in case of small sample size). COX regression analysis was performed to identify predictors of PH. Because of the arbitrary division in a PH and non-PH group, linear regression analysis was done to predict the PH probability (no, possible or likely PH as the dependent variable of the regression model) and validate this binary division with cutoff at TRV 2.9 m/s. PH-free survival and overall survival were plotted by the Kaplan–Meier method with comparisons by log-rank statistics. Because of the important weight of age at repair in the regression model, further analysis was done on tertiles of age at repair. In a last step, data were compared between four subgroups, classified by mPAP at catheterization before closure of <25 mm Hg versus ≥25 mm Hg and the presence versus absence of PH at latest follow-up. Comparison of several means was done by the one-way analysis of variance. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient baseline characteristics and follow-up

The data of 324 adult patients with secundum ASD were collected from the Belgian Registry on ACHD. Twenty-nine patients were excluded. Two hundred ninety-five patients were analyzed, of which six (2%) patients had Eisenmenger's syndrome (Fig. 1). Ninety-two (31.2%) patients were male, and 203 (68.8%) female. Mean age at latest follow-up was 46 ± 21 years. Median follow-up time was 4.9 (IQR 0.8–11.1) years. Two hundred seventy-three patients underwent ASD repair, of which 182 were closed percutaneously. Mean age at initial ASD repair was 39 ± 24 years. The frequency table of age at ASD repair shows a typical bimodal distribution with most closures during the first years of life or after the age of 50 years (Fig. 2). Five patients needed redo surgery because of residual leakage.

Eighty-four percent of patients were in sinus rhythm at latest visit, compared to 92.9% at first visit. At latest follow-up, 25 (8.5%) patients had atrial fibrillation and 12 (4.1%) were in pacemaker rhythm. Main pacemaker indications encompassed high-degree atrioventricular block and sick sinus syndrome. Eight patients had suffered from a cerebrovascular accident (CVA) during follow-up. Eight (2.7%) patients died, of which six (75%) had PH.

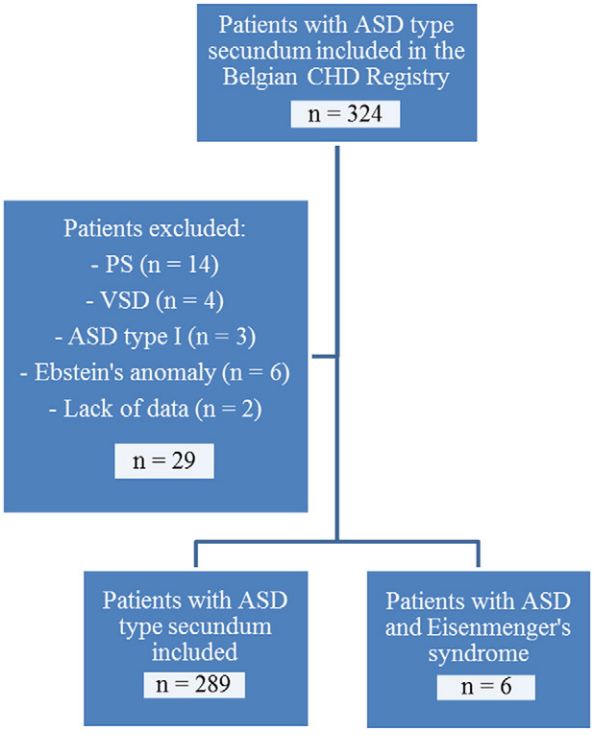

Fig. 1. Flowchart of patient inclusion. CHD = congenital heart disease; PS, pulmonary stenosis; VSD, ventricular septal defect.