Pulmonary Arterial Hypertension in Patients With Transcatheter Closure of Secundum Atrial Septal Defects
A Longitudinal Study

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Background—Pulmonary arterial hypertension (PAH) may develop in patients with atrial septal defects (ASD); however, little is known about associated risk factors and its evolution after transcatheter ASD closure.

Methods and Results—We conducted a cohort study on 215 adults with attempted transcatheter ASD closure from 1999 to 2006. Patients were classified according to baseline systolic pulmonary artery pressures as having no (I, <40 mm Hg), mild (II, 40 to 49 mm Hg), moderate (III, 50 to 59 mm Hg), or severe (IV, ≥60 mm Hg) PAH. Independent predictors of moderate or severe PAH were older age (odds ratio [OR], 1.10 per year; \( P<0.0001 \)), larger ASD (OR, 1.13 per millimeter; \( P=0.0052 \)), female sex (OR, 3.9; \( P=0.0313 \)), and at least moderate tricuspid regurgitation (OR, 3.6; \( P=0.0043 \)). At 15 (interquartile range, 8 to 43) months post–ASD closure, patients with higher baseline pressures were more likely to experience a ≥5-mm Hg decrease (33.7%, 73.9%, 79.2%, and 100.0% in groups I to IV, \( P<0.0001 \)), with a larger magnitude of reduction (0, 8, 17, and 22 mm Hg; \( P<0.0001 \)). However, normalization of pressures (<40 mm Hg) occurred less frequently in patients with more advanced PAH (90.2%, 71.7%, 66.7%, and 23.5%, \( P<0.0001 \)). Among patients with moderate or severe PAH, independent predictors of normalization were lower baseline pressures (OR, 0.91 per mm Hg; \( P=0.0418 \)) and no more than mild tricuspid regurgitation (OR, 0.14; \( P=0.0420 \)).

Conclusion—In adults with ASDs, severity of PAH is modulated by age, sex, defect size, and degree of tricuspid regurgitation. Patients with moderate or severe PAH may benefit from substantial reductions in pulmonary artery pressures after transcatheter ASD closure, although the PAH values remain elevated in a sizeable proportion. (Circ Cardiovasc Intervent. 2009;2:455-462.)

Key Words: heart defects, congenital ■ heart septal defects ■ hypertension, pulmonary

Pulmonary arterial hypertension (PAH), defined as pulmonary arterial systolic pressures (PASP) ≥40 mm Hg, has been noted in 6% to 35% of patients with secundum atrial septal defects (ASD). In the setting of congenital heart disease, pulmonary vascular histopathologic changes include medial hypertrophy, intimal proliferation fibrosis, and, in more severe forms, plexiform lesions and necrotizing arteritis. Clinically, PAH in unoperated patients with ASDs has been associated with increased mortality, functional limitations, and atrial tachyarrhythmias. After surgical closure, preoperative PAH remains predictive of mortality, heart failure, and arrhythmias. When the anatomy is favorable, transcatheter ASD closure has now largely supplanted surgery as the treatment of choice, with a <1% risk of major complications and up to 95% success rates.

Despite the high reported prevalence of PAH in patients with ASDs and its associated morbidity and mortality, there is a paucity of data regarding risk factors for the development of PAH and the evolution of pulmonary pressures postclosure. Our objectives were to determine the prevalence and severity of PAH in adults referred for transcatheter ASD closure, identify predictors for PAH before ASD closure, and quantify changes in pulmonary pressures and associated clinical features after closure.

Materials and Methods

Study Population
The study cohort consisted of consecutive patients with secundum ASD referred for transcatheter closure at our institution between January 1999 and December 2006. Patients were excluded if a baseline PASP had not been quantified by transthoracic echocardiography or if they had previous successful surgical or transcatheter ASD closure, coexisting congenital heart defects, or identifiable causes for PAH, including mitral valve disease, a left ventricular ejection fraction <50%, known seropositivity to human immunodeficiency virus, pulmonary thromboembolic disease, interstitial lung disease requiring PAH-specific therapy, portal hypertension, obstructive sleep apnea, or severe chronic obstructive pulmonary disease defined as a forced expiratory volume in 1 second <1.0 L or dependency on home oxygen therapy. The study was conducted in

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Transcatheter ASD Closure

Transcatheter ASD closure was conducted under general anesthesia, with fluoroscopic and transesophageal echocardiographic guidance in all patients, after obtaining written informed consent. Procedures were performed using previously described techniques, including ASD sizing with a compliant balloon (AGA Medical, Plymouth, Minn) and closure with an Amplatzer Atrial Septal Occluder (AGA Medical). Procedural success was defined as the successful deployment of an atrial septal occluder at the end of the procedure.

Clinical Variables and Follow-Up

Data collection was conducted retrospectively with a detailed review of medical records, including pre- and postprocedural echocardiography and cardiac catheterization studies, and clinical variables were defined a priori. Intraprocedural hemodynamic measures (under general anesthesia) included pulmonary to systemic flow ratios (Qp:Qs) and right and left atrial, pulmonary arterial, and aortic pressures. The Qp:Qs was calculated using the Fick principle as (\(SaO_2 - SvO_2\))/(\(SaO_2 - SpO_2\)), whereby \(SaO_2\), \(SpO_2\), and \(SvO_2\) were, respectively, the aortic, pulmonary arterial, and mixed venous oxygen saturations obtained without supplemental oxygen. It assumes equivalency of the aortic and pulmonary venous oxygen saturations. The mixed venous saturation was derived from oxygen sumes equivalency of the aortic and pulmonary venous oxygen saturations.

Continuous variables are expressed as mean±SD deviation or median and interquartile range, depending on normality of distribution. Discrete variables are expressed as frequencies and percentages. Comparisons between continuous variables were performed using 1-way ANOVA or nonparametric Kruskal-Wallis tests as appropriate. Discrete baseline clinical, echocardiographic, and hemodynamic variables were compared using \(\chi^2\) tests. Univariate and independent factors associated with a ≥5-mm Hg reduction in PASP and normalization of PASP post-ASD closure were assessed by logistic regression. Variables associated with \(P<0.1\) in univariate analyses were considered in multivariate models with stepwise backward selection. In addition, all multivariate regression models controlled for the time interval between the intervention and follow-up echocardiography. Chamber dilation, NYHA functional class, and presence of atrial tachyarrhythmias before and after ASD closure were compared by Cochran Q tests. To correct for multiple comparisons (ie, 4 pairwise comparisons for each variable), reported \(P\) values were adjusted using the Bonferroni method. Probability values \(<0.05\) were considered statistically significant. Statistical analysis was performed with SPSS version 16.0 (Chicago, Ill). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Study Population

During the study period, transcatheter ASD closure was attempted in 321 patients. Twenty-eight patients were excluded because of prior surgical ASD closure (N=6), coexisting congenital defects (N=12), and other medical conditions (N=10; 5 with left heart or mitral valve disease, 3 with history of pulmonary embolism, 1 with pulmonary fibrosis, and 1 with severe chronic obstructive pulmonary disease). Of the 293 eligible patients, 78 (26.6%) did not have an available PASP at baseline because of lack of sufficient tricuspid regurgitation. Therefore, the study was conducted on the remaining 215 patients. A secondary sensitivity analysis did, however, include the 78 patients without a baseline PASP.

Baseline Characteristics

Baseline clinical, echocardiographic, and cardiac catheterization data are summarized in Table 1. Baseline echocardiography was performed a mean of 10.5±7.6 months (range, 0.03 to 41 months) before attempted transcatheter ASD closure. Of the 215 patients, 108 (50.2%; 95% CI, 43.3 to 56.7) had some degree of PAH, with 62 (28.8%; 95% CI, 22.9 to 35.1) having mild, 27 (12.6%; 95% CI, 7.7 to 16.3) moderate, and 19 (8.8%; 95 CI, 5.0 to 12.6) severe PAH. The overall mean age was 53.9±15.7 years (range, 18 to 82 years), and it increased with the degree of PAH (\(P<0.0001\)). Univariate and multivariate baseline characteristics associated with moderate or severe PAH are listed in Table 2. Patients classified as having NYHA III or IV symptoms exclusively had functional class III symptoms. Of the 22 (10.3%) patients with respiratory disease, 10 had asthma and 12 had mild or moderate chronic obstructive pulmonary disease. At catheterization under general anesthesia, all but 3 patients had a pulmonary artery to aortic systolic pressure ratio <0.67. PASP estimates by echocardiography correlated well with values derived by cardiac catheterization (\(r=0.67, P<0.0001\)) and with pulmonary vascular resistance (\(r=0.59, P<0.0001\); Figure 1).
A sensitivity analysis conducted on the entire cohort (N = 293) that assumed normal PASP values when they could not be ascertained by echocardiography yielded concordant results with regards to independent variables associated with moderate or severe PAH, ie, older age (OR, 1.10 per year; 95% CI, 1.05 to 1.15; P < 0.0001), female sex (OR, 5.6; 95% CI, 1.4 to 23.6; P = 0.0180), ASD size (OR, 1.14 per mm; 95% CI, 1.04 to 1.26; P = 0.0062), and at least moderate tricuspid regurgitation (OR, 4.2; 95% CI, 1.6 to 11.2; P = 0.0041).

### Echocardiographic Follow-Up After Transcatheter ASD Closure
Transcatheter ASD closure was successful in 194 (90.2%) patients with a mean device size of 23.5 ± 6.2 mm (range, 8 to 40 mm). The 21 patients with failed transcatheter closure...
subsequently had successful surgical ASD closure and were excluded from follow-up analyses. The median duration of follow-up post-ASD closure was 15 (interquartile range, 8 to 43) months and was comparable in the 4 categories of PAH severity \( (P = 0.3261) \). A measured PASP was available in 186 (95.9%) patients, including all those with moderate or severe PAH before ASD closure.

The median reduction in PASP on follow-up was 5 (interquartile range, 1 to 13) mm Hg, with 106 (57.0%) patients having a decrease in PASP \( >5 \) mm Hg. Univariate and multivariate factors associated with a reduction in PASP \( \geq 5 \) mm Hg are summarized in Table 3. Figure 2 shows the magnitude of reduction in PAH (A) and proportion of patients with normalization of PASP postclosure (B), according to the baseline category of PAH. A reduction in PASP \( \geq 5 \) mm Hg was noted in 33.7%, 73.9%, 79.2%, and 100.0% of patients with no, mild, moderate, and severe baseline PAH, respectively \( (P < 0.0001) \). Among the 41 patients with moderate or severe PAH at baseline and successful ASD closure, the median reduction in PASP was 18.0 (interquartile range, 11.5 to 23.5) mm Hg. Normalization of PASP occurred in 141 (75.8%) patients, including 48.8% of those with moderate or severe PAH. Among patients with moderate or severe PAH, independent factors associated with normalization were a lower baseline PASP (OR, 0.91 per mm Hg; 95% CI, 0.86 to 0.99; \( P = 0.0418 \)) and absence of at least moderate tricuspid regurgitation at baseline (OR, 0.14; 95% CI, 0.02 to 0.93; \( P = 0.0420 \)).

The proportion of patients with right ventricular dilation, right atrial dilation, and at least moderate tricuspid regurgitation before and after transcatheter ASD closure is shown in Figure 3.

Clinical Follow-Up

Figure 4 shows the NYHA functional class before and after transcatheter ASD closure according to whether patients had no, mild, moderate, or severe PAH at baseline. The proportion of patients with NYHA functional class 3 or 4 symptoms was reduced by 79.6% (Cochran’s Q \( P < 0.0001 \)). Functional deterioration occurred only in 2 patients, both of whom had NYHA functional class II symptoms at baseline and PASP \( \geq 50 \) mm Hg before ASD closure. A modest reduction in atrial tachyarrhythmias was noted (37.5%, \( P < 0.0001 \), pre-

| Table 2. Features Associated With Moderate or Severe PAH at Baseline |
|-------------------------|----------------|----------------|
| Characteristics         | OR*            | 95% CI         |
| Univariate              |                |                |
| Age, y                  | 1.08           | 1.05 to 1.11   |
| Female                  | 2.4            | 1.0 to 5.7     |
| ASD size, mm            | 1.06           | 1.01 to 1.13   |
| NYHA class 3 or 4       | 4.6            | 2.1 to 10.0    |
| Atrial tachycardia      | 2.3            | 1.1 to 4.6     |
| Respiratory disease     | 5.8            | 2.3 to 14.5    |
| Hypertension            | 2.3            | 1.2 to 4.6     |
| Coronary artery disease | 2.4            | 1.0 to 5.6     |
| Dilated left atrium     | 2.9            | 1.4 to 5.9     |
| At least moderate atrium| 6.7            | 3.1 to 14.6    |
| Multivariate            |                |                |
| Age, y                  | 1.10           | 1.06 to 1.14   |
| Female                  | 3.9            | 1.1 to 13.2    |
| ASD size, mm            | 1.13           | 1.04 to 1.23   |
| At least moderate atrium| 3.6            | 1.5 to 8.8     |

*For continuous variables, ORs correspond to a 1-unit increase, ie, years for age and millimeter for ASD size.

| Table 3. Features Associated With a ≥5-mm Hg Reduction in Pulmonary Arterial Systolic Pressure After Transcatheter ASD Closure |
|-------------------------|----------------|----------------|
| Characteristics         | OR*            | 95% CI         |
| Univariate              |                |                |
| Age, y                  | 1.02           | 1.00 to 1.04   |
| Body surface area, m²   | 0.15           | 0.04 to 0.59   |
| Baseline PASP, mm Hg    | 1.16           | 1.10 to 1.21   |
| Moderate or severe PAH  | 7.7            | 2.9 to 20.8    |
| Pulmonary vascular resistance, dyne/s/cm⁻⁵| 1.006 | 1.001 to 1.011 |
| ASD size, mm            | 1.08           | 1.02 to 1.15   |
| Op:Qs                   | 1.8            | 1.3 to 2.5     |
| Dilated right ventricle | 8.7            | 1.0 to 73.9    |
| Dilated right atrium    | 7.2            | 0.8 to 63.5    |
| At least moderate tricuspid regurgitation | 1.8     | 1.0 to 3.5 |

*For continuous variables, odds ratios correspond to a 1-unit increase.
dominantly driven by a $52.3\%$ reduction ($P<0.0001$) among patients with no baseline PAH.

Discussion
The prevalence of PAH in our cohort of patients referred for transcatheter ASD closure was $50.2\%$, of whom $21.4\%$ had at least moderate PAH. However, $78$ patients were excluded because of insufficient tricuspid regurgitation to quantify PASP. In a conservative analysis, which assumes that excluded patients with trivial or no tricuspid regurgitation did not have PAH, $36.7\%$ prevalence is obtained. This figure is consistent with previous reports.$^{2–5,17}$

Patients with at least moderate PAH were more likely to be older, female, have larger ASDs, and have at least moderate tricuspid regurgitation. In patients with ASDs, age as a risk factor for PAH has previously been reported.$^{3,4,9,12,19}$ This may reflect the longer duration of shunting, physiological increase in PASP associated with aging,$^{20}$ and/or interactions with comorbidities. The association between female sex and PAH is also supported by a literature that highlights hormonal differences and pregnancy effects.$^{2,9,18}$ Because PAH may cause right ventricular and tricuspid annular dilation,$^{21}$ the association between at least moderate tricuspid regurgitation and PAH seems intuitively plausible.

The larger sample size in our study allowed us to detect the previously unreported association between ASD size and PAH.$^{4,9}$ Although the exact pathogenesis of PAH in patients with ASD is not clearly defined, it has been postulated that...
increased pulmonary flow leads to pulmonary endothelial damage with resultant leukocyte activation and release of mediators, ultimately causing vasoconstriction and eventual vascular hypertrophy. Pulmonary flow is determined by the size of the ASD and differences in compliance between right and left ventricles. Larger ASDs are modestly associated with higher degrees of left to right shunting, with consequently greater propensity for developing PAH. Indeed, we observed that patients with severe PAH had higher Qp:Qs ratios than those with lower baseline pressures (Table 1). However, these values were obtained under general anesthesia and may not accurately reflect the true magnitude of shunting in an ambulatory setting.

We quantified a notable reduction in PASP in patients with PAH after transcatheter closure, consistent with previous observations. Importantly, our study design also allowed us to elucidate factors associated with a response. Herein, we report that a higher baseline level of PAH severity is independently associated with a more frequent and greater reduction in PASP after ASD closure. Complete normalization of PASP was noted in two thirds of patients with moderate PAH and nearly 25% of those with severe PAH. These findings suggest that in the setting of an ASD, a large reversible component to pulmonary vascular changes is common in patients with PAH. This observation is consistent with a recent large US-based registry suggesting that PAH associated with congenital heart disease is more likely to be responsive to vasodilatory challenge than other forms of PAH.

Although these findings are encouraging, it is worthwhile emphasizing that most patients with severe PAH who undergo transcatheter ASD closure will remain with elevated pulmonary pressures, despite a reduction from baseline values. This suggests some degree of associated irreversible changes that are more prominent in patients with severe PAH. Interestingly, in 1 series, the prevalence of “irreversible pulmonary vascular disease,” ie, Heath-Edwards grade 4 to 6 by histopathology of lung biopsy specimens, was observed in only 6% of 75 patients who underwent surgical ASD closure. Other independent factors associated with a reduction in PASP after transcatheter ASD closure were younger age and smaller size (ie, body surface area). It seems intuitive that younger patients have lesser degrees of irreversible pulmonary vascular disease. In a series of patients with surgical ASD closure, younger age was associated with more favorable long-term outcomes. Although obesity is associated with elevated PASP, to our knowledge it has been not previously linked to degree of reversibility of pulmonary vascular changes or likelihood of response to PAH therapy.

Other salutary effects associated with ASD closure include a reduction in right atrial and ventricular dimensions and degree of tricuspid regurgitation. No left atrial changes were quantified by our study. Positive remodeling changes may be appreciable as early as 24 hours post-ASD closure. Benefits are less pronounced in patients with higher degrees of PAH, potentially reflecting residual defects with permanent structural changes.

We also observed a significant improvement in NHYA functional class after ASD closure, consistent with previous series of patients with surgical or transcatheter closure. Consistently, improvements were less marked in patients with higher degrees of PAH. Finally, a reduction was noted in the prevalence of atrial tachyarrhythmia after ASD closure, although not among those with moderate or severe PAH. Similarly, De Lezo et al reported a 41% relative risk reduction in the incidence of atrial tachyarrhythmia after ASD closure, whereas no reduction was noted in patients with more severe forms of PAH. Therefore, our results support the notion that severity of PAH may influence the propensity for atrial tachyarrhythmias by modulating the degree of residual structural and hemodynamic sequelae that persists after ASD closure.

Clinical implications of our findings are substantial. First, our results support the notion that transcatheter ASD closure may be safely undertaken, despite underlying PAH. Indeed, a greater magnitude of reduction in PASP is noted in patients with more severe forms of PAH, with some experiencing complete normalization of pressures. Nevertheless, residual sequelae is commonly seen in patients with more severe baseline PAH and may include persistent PAH, right-sided chamber enlargement, tricuspid regurgitation, ongoing dyspnea, and atrial tachyarrhythmias. Patients with residual PAH after transcatheter ASD closure should be monitored closely and considered for medical therapies targeting PAH, as indicated. Second, older age was independently associated with the development of at least moderate or severe PAH and a lesser response to ASD closure. This supports an overall earlier approach to ASD closure. Finally, although ASD size was not traditionally thought to bear prognostic relevance, the independent association with the development of at least moderate PAH identified in our study suggests a more aggressive approach to closure or monitoring those with larger defects. Further studies are, of course, required to prospectively validate clinical outcomes associated with tailored management strategies.

Limitations

Our study is retrospective in nature and, therefore, subject to nonuniformity in medical management that could potentially influence the evolution of PASP, cardiac dimensions, and clinical features after transcatheter ASD closure. Echocardiographic assessment rather than catheterization was selected to measure PASP. This approach was deemed preferable, given the necessity for serial studies and underestimation of pressure measurements under general anesthesia. This resulted in the exclusion of nearly one third of the total eligible cohort on the basis of insufficient tricuspid regurgitation to estimate PASP. Of these 78 patients, only 3 had a mean pulmonary artery pressure >25 mm Hg at catheterization, the current World Health Organization definition of PAH, with values of 26 mm Hg in 1 and 27 mm Hg in 2. However, a sensitivity analysis that assumed that PASP was normal when it could not be estimated by echocardiography suggested that our results were robust to these selection criteria. Right ventricular systolic pressure derived from echocardiography may lead to an overestimation of PASP because of a potential pressure decrease across the pulmonic valve in high flow states. Patients were not subjected to open-lung biopsies for quantification of pulmonary vascular hypertrophy. For calcu-
lation of the Qp:Qs, we assumed equivalency of the pulmonary venous and aortic oxygen saturations, which may lead to an underestimation in cases where there are elements of right to left shunting. Mixed venous oxygen saturation was derived exclusively from the superior vena cava, which may potentially overestimate Qp:Qs. In the balance, this definition was deemed preferable to incorporating inferior vena cava saturation. The latter would introduce a differential error resulting from tricuspid regurgitation of variable severity in the context of left-to-right shunting. Finally, our results should not be generalized to patients with ASDs not considered for transcatheter closure, including those with Eisenmenger syndrome and most with a PASP to aortic systolic pressure ratio exceeding 0.67.24

Conclusion

At least moderate PAH is common in adults with ASDs referred for transcatheter closure and is independently associated with older age, female sex, and larger ASD size. Transcatheter ASD closure is safe and effective in reducing PASP, even in patients with severe PAH (albeit PASP <2/3 of systemic pressures). Increased severity of PAH is associated with greater reduction in PASP and a greater proportion of patients with a decrease in PASP ≥5 mm Hg. Transcatheter ASD closure is also associated with symptomatic improvement and positive cardiac remodeling effects. Nevertheless, a higher degree of residual PAH, right-sided chamber enlargement, and symptoms may persist in those with more severe PAH before closure. In patients with at least moderate PAH, pressures are more likely to normalize in the absence of at least moderate tricuspid regurgitation. Younger adults experience more favorable responses, which supports an earlier approach to transcatheter closure.

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Disclosures

None.

References


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