# Impact of Pulmonary Hypertension on Survival Following Device Closure of Atrial Septal Defects

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**Pulmonary hypertension (PH), defined as mean pulmonary arterial pressure ≥25 mm Hg, may be a complication of a secundum atrial septal defect (ASD). This study sought to evaluate the impact of PH at time of ASD device closure on patient survival. A prospectively collected database of ASD closures was utilized. Patients were stratified by age above and below the cohort median (48 years). Survival was analyzed by preprocedural PH status, age cohort, and echocardiographic resolution of PH at 3 months postdevice closure. PH was present in 48 of 228 patients (21.1%) and was more common in the older cohort (31.3% vs 10.6%, p <0.01). ASD size was unrelated to the presence of PH (p = 0.33). Older patients had more medical co-morbidities including diabetes (p = 0.02), hyperlipidemia (p <0.01), and systemic hypertension (p <0.01) compared with younger patients. PH did not impact survival in patients ≤48 years, but PH was associated with fivefold increased risk of death in patients >48 years (p < 0.01). Patients with preprocedural PH and RVSP ≥40 mm Hg at 3-month follow-up continued to have an increased risk of mortality (p <0.01), whereas those with resolution of PH had similar survival to those without PH at time of closure. In conclusion, PH is common in adults with unrepaired ASDs and appears unrelated to defect size. PH in older adults and its persistence closure are strong predictors of a worsened clinical outcome. These patients may benefit from additional risk assessment and advanced medical therapies to mitigate this risk.**  **(Am J Cardiol 2019;124:1460−1464)**

An atrial septal defect (ASD) represents ~25% of congenital heart defects diagnosed during adulthood.[1] Possible long-term complications of an ASD are pulmonary hypertension (PH), right ventricular (RV) failure, atrial arrhythmias, and paradoxical emboli.[1,2] PH is observed in approximately 20% of patients with an ASD.[3−5] ASD closure can lead to a reduction in pulmonary arterial pressure, regression in RV dilatation, and symptomatic improvement.[6−8] There are inconsistent findings regarding the benefit of ASD closure in patients of advanced age, with some studies cautioning against closure.[9,10] In contrast, other literature has shown ASD repair to significantly improve 10-year survival and limit deterioration of cardiac function in patients >40 years of age compared with medical treatment alone.[11] Many of these studies compare surgical closure to medical management. Today, percutaneous closure is the treatment of choice for secundum-type ASD, as it is less invasive and associated with fewer complications.[12,13] Our aim is to evaluate the impact of transcatheter ASD closure on survival stratifying by PH status, age of intervention, and echocardiographic change.

## Methods

A prospectively collected database of ASD closures performed between 2000 and 2011 was analyzed. This database was collected at the Cleveland Clinic and contains consecutive patients 18 years of age or older who underwent transcatheter closure of a secundum ASD. No patients in this study had shunt inversion at baseline. This study was approved by the Duke University Institutional Review Board and individual informed consent was deemed unnecessary. The authors had direct access to the primary data and take responsibility for its integrity. The data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

PH was defined by mean pulmonary artery pressure ≥25 mm Hg during cardiac catheterization immediately preceding device closure.

ASD size was assessed using balloon diameter required to occlude flow, measured by either intracardiac echocardiography or fluoroscopy. If both measures were present, the average of the 2 values was used. Device closure was completed with Amplatzer (Abbott, St. Paul, Minnesota), Helex (W.L. Gore & Associates, Inc., Newark, Delaware) or CardioSEAL (NMT Medical Inc., Boston, Massachusetts) septal occluders.

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Baseline clinical data included age at the time of intervention, race, gender, tobacco use, hypertension, diabetes, body mass index, and hemodynamic parameters. Patients were stratified by age at or below (≤48 years, Group A) or above (>48 years, Group B) the cohort median. The cohort median was chosen to evaluate differences in outcome between older and younger patients. We additionally examined survival by echocardiographic resolution of PH at 3 months following ASD closure, with PH resolution defined as right ventricular systolic pressure (RVSP) <40 mm Hg on echocardiogram. The definition of an RVSP threshold of 40 mm Hg as a definition for PH has been used in multiple previous clinical and epidemiological studies.[14,15]

All analyses were performed using Stata Version 12.1 (StataCorp. College Station, Texas). Comparison of dichotomous variables was performed using chi-square test or Fisher's exact test as appropriate. Comparisons of continuous variables between groups were performed using 2-sided t-tests. Kaplan-Meier survival analysis was used to examine survival. Nelson-Aalen cumulative hazard function was used to estimate cumulative risk of mortality. Statistical significance was assumed for p value <0.05. Categorical variables are reported as n (%), and continuous variables are expressed as mean ± standard deviation.

## Results

The study population consisted of 228 consecutive adults (mean age 49.1 ± 16.2, median 48, range 18 to 84 years) who underwent transcatheter ASD closure. PH was present in 48 patients (21.1%). Table 1 displays the baseline clinical data.

Of the 228 patients in this cohort, 113 were younger than or equal to the median age (48 years) of the cohort (Group A) and 115 were older than 48 years (Group B) at the time of intervention. In the older cohort of patients, PH was more likely to be present (31.3% vs 10.6%, p <0.01). Older patients had similar sized ASDs (18.3 ± 6.9 vs 19.1 ± 6.3 mm, p = 0.35) but more medical co-morbidities including diabetes (10.4% vs 2.7%, p = 0.02), hyperlipidemia (49.6% vs 12.4%, p <0.01) and systemic hypertension (55.7% vs 15.0%, p <0.01).

The mean RVSP at 3 months after ASD closure in our cohort was 32.4 ± 11.2 mm Hg. There was a significant difference in both RVSP and rate of change of RVSP at 3 months postdevice closure in our PH and no PH cohorts (p <0.01 for both). Mean RVSP at 3 months in our PH group was 39.5 ± 7.8 versus 30.1 ± 11.2 mm Hg in the no PH group (p <0.01). Overall, 34.7% of our cohort had an RVSP ≤40 mm Hg at 3 months postclosure. There tended to be fewer preprocedural PH patients with an RVSP ≤40 mm Hg at 3 months compared with those without preprocedural PH (22.9% vs 37.8%, p = 0.06).

Over a mean follow-up time of 7.4 ± 3.3 years (range 0.05 to 13.8 years), there were 19 deaths. Older age (Group A: 2/111 vs Group B: 17/98 patients died, p <0.01) and the presence of PH (PH: 10/48 vs no PH: 9/171 patients died, p <0.01) significantly increased the risk of subsequent mortality. The mean age of those who died during follow-up was 67.6 ± 14.1 years (range 30 to 84 years). The average time from ASD closure to death was 4.4 ± 3.0 years (range 0.05 to 10 years). There was an increase in mortality seen with the presence of PH alone (Figure 1). When examining survival between the older and younger subgroups, the

Table 1
Baseline characteristics stratified by presence of pulmonary hypertension

| Variable | Overall (n = 228) | Pulmonary hypertension (PH) | | |
|---|---|---|---|---|
| | | Yes (n = 48) | No (n = 180) | p Value |
| Male | 71 (31.1%) | 13 (27%) | 58 (32.2%) | 0.50 |
| Age at ASD closure (years) | 49.1 ± 16.2 | 60.6 ± 16.9 | 46.1 ± 14.6 | **<0.01** |
| Race | | | | 0.09 |
| White | 144 (63.4%) | 36 (75%) | 108 (60.3%) | |
| Black | 12 (5.3%) | 3 (6%) | 9 (5.0%) | |
| Other | 71 (31.3%) | 9 (19%) | 62 (34.7%) | |
| Diabetes mellitus | 15 (6.6%) | 6 (13%) | 9 (5.0%) | 0.09 |
| Hyperlipidemia* | 71 (31.1%) | 20 (42%) | 51 (28.3%) | 0.08 |
| Hypertension | 81 (35.5%) | 30 (63%) | 51 (28.3%) | **<0.01** |
| Tobacco use | 40 (17.5%) | 9 (19%) | 31 (17.2%) | 0.80 |
| BMI (kg/m$^2$) | 26.8 ± 6.1 | 29.7 ± 8.9 | 26.0 ± 4.9 | **<0.01** |
| ASD size (mm) | 18.7 ± 6.6 | 19.6 ± 8.0 | 18.5 ± 6.2 | 0.33 |
| Device type | | | | 0.33 |
| Amplatzer | 174 (77.0%) | 40 (85%) | 134 (74.9%) | |
| Cardioseal | 12 (5.3%) | 2 (4%) | 10 (5.6%) | |
| Helex | 40 (17.7%) | 5 (11%) | 35 (19.5%) | |
| Cardiac index (L/min/m$^2$) | 3.3 ± 1.2 | 2.9 ± 0.7 | 3.4 ± 1.2 | 0.16 |
| Qp:Qs prior to closure | 1.9 ± 0.7 | 1.8 ± 0.7 | 1.9 ± 0.7 | 0.82 |
| Mean PA (mm Hg) | 20.0 ± 7.9 | 32.0 ± 7.5 | 16.8 ± 3.9 | **<0.01** |
| Systolic PA (mm Hg) | 34.1 ± 12.8 | 53.3 ± 12.8 | 29.0 ± 6.2 | **<0.01** |
| Diastolic PA (mm Hg) | 12.8 ± 6.1 | 20.9 ± 6.3 | 10.7 ± 3.9 | **<0.01** |
| Right ventricular systolic (mm Hg) | 34.8 ± 13.2 | 52.0 ± 14.1 | 30.2 ± 8.3 | **<0.01** |

ASD = atrial septal defect; PA = pulmonary artery; PH = pulmonary hypertension; Qp:Qs = pulmonary flow to systemic flow ratio.
* Hyperlipidemia was defined by the diagnosis having been recorded in the medical record by a provider.

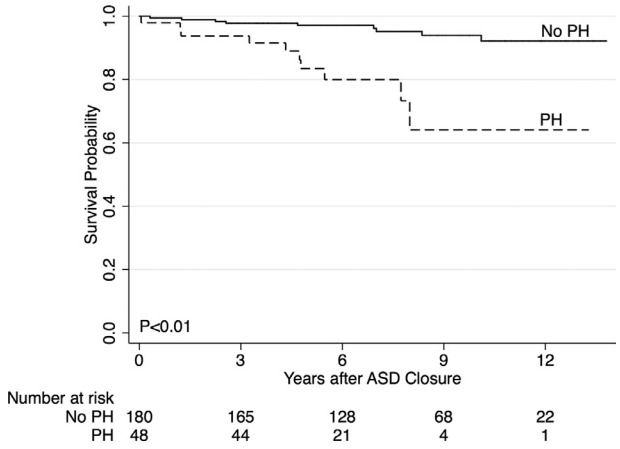


Figure 1. Kaplan-Meier survival analysis by presence of pulmonary hypertension at the time of device closure. The p value is shown for log-rank test. ASD = atrial septal defect; PH = pulmonary hypertension.

presence of PH increased mortality by fivefold over 10 years of follow-up in the older cohort (p <0.01; Figure 2), while having no impact on younger patients.

Mortality was also examined by those who had early resolution of PH, defined as an RVSP ≤40 mm Hg at 3 months

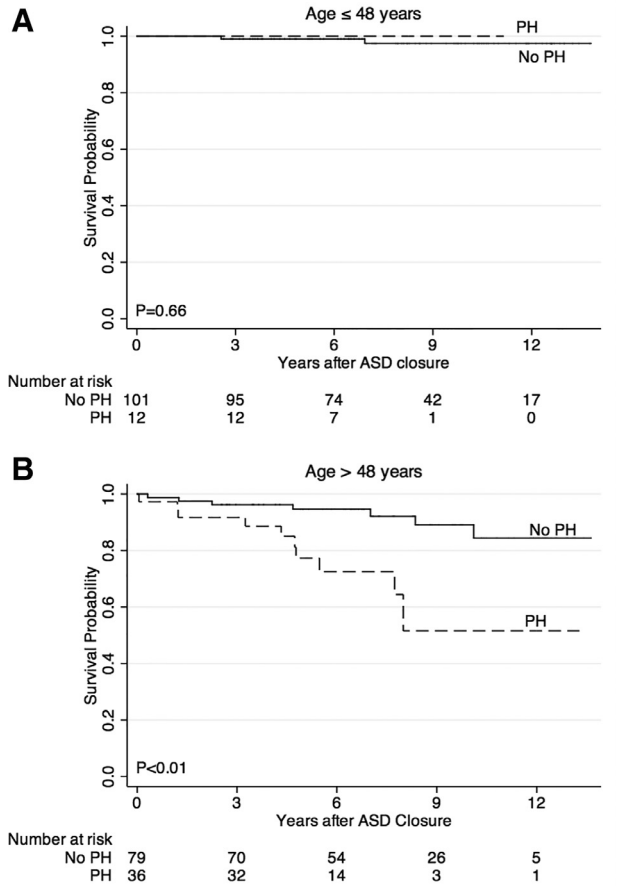


Figure 2. Kaplan-Meier survival analysis by age and the presence of pulmonary hypertension at the time of ASD closure. Patients ≤48 years are shown in Panel A. Patients >48 years are shown in Panel B. The p values are shown for log-rank test. ASD = atrial septal defect; PH = pulmonary hypertension.

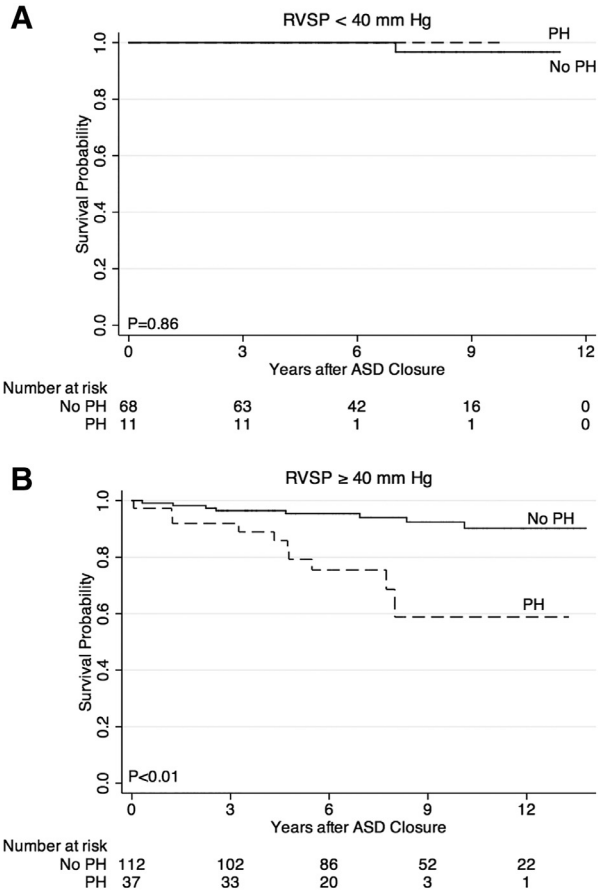


Figure 3. Kaplan-Meier survival analysis by echocardiographic resolution of pulmonary hypertension and the presence of pulmonary hypertension at the time of ASD closure. Patients with echocardiographic resolution of PH (RSVP <40 mm Hg) at 3 months are shown in Panel A. Patients with RVSP ≥40 mm Hg at 3 months are shown in Panel B. The p values are shown for log-rank test. ASD = atrial septal defect; PH = pulmonary hypertension; RVSP = right ventricular systolic pressure.

postclosure. Resolution of PH mitigated the impact of preprocedure PH on mortality. In those who did not have echocardiographic resolution of PH by 3 months, a significantly increased risk of mortality remained (p <0.01; Figure 3).

One year following ASD closure, 17 patients (13.4%) had a residual shunt seen on bubble study. The presence of preprocedural PH did not impact whether a residual shunt was present (p = 0.74).

## Discussion

We studied the impact of PH on patients who underwent percutaneous ASD closure. Our cohort of ASD patients had an overall incidence of PH as well as sex ratio (2:1 female to male) that is consistent with previously published data.[3,16–18] Our study has 3 main findings. First, ASD size is not associated with PH. Second, older patients with PH before ASD closure have higher mortality. Lastly, PH patients with ongoing echocardiographic evidence of PH at 3 months post-ASD closure have an increased risk of mortality.

ASD size was not found to be associated with PH in our cohort. This differs from previous literature that correlates

larger ASD size to the prevalence and severity of PH.[5,19] PH occurring independently of ASD size suggests that other underlying risk factors lead to the development of PH, such as an underlying genetic predisposition. This would reinforce the previously described "two-hit" hypothesis.[20,21]

Our second main finding is that the presence of PH at the time of ASD closure impacts survival only in older patients. There are very few randomized trials performed to examine morbidity and mortality following ASD closure in patients over 40 years old. The presence of PH in patients ≤48 years old in our study did not impact survival; however, the presence of PH in the older cohort increased mortality more than fivefold. This is consistent with previous studies that suggest more favorable long-term outcomes when ASD closure is performed at a younger age.[9] Although high mortality is observed with ASD closure in older patients with PH, it is important to recognize the lack of a comparator group in this study design. Thus, it is unclear whether device closure itself had detrimental effects in these patients, or whether outcomes would have been poor (or even worse) without ASD closure. We recognize that other medical comorbidities not examined in our study often accompany older age, and can both affect long-term outcomes and complicate PH. The fact that the older cohort had higher mortality despite closure suggests that some degree of irreversible pulmonary vascular changes had likely occurred in these patients in addition to the well-described, age-related physiological increase in pulmonary pressure.[22,23]

Lastly, there appears to be a survival benefit for PH patients who have echocardiographic resolution of PH (to RVSP <40 mm Hg) at 3 months postclosure. It is imperative that further studies examine the risk factors and characteristics of PH patients who do not have normalization of RVSP pressure after device closure. We hypothesize that duration of PH before closure affects the probability of pressure normalization postprocedure. One way to assess success of postprocedure normalization of RSVP may be preclosure hemodynamic assessment of reversibility of PH with vasoactive agents. It is possible that those patients with limited change in hemodynamics with vasoactive agents will be less likely to have normalization of RVSP postclosure, leading to potentially worse clinical outcomes.[24]

Identifying those patients that will benefit from ASD closure is important. We know that those with an ASD have higher mortality compared with the general population, and closure of the defect has been shown to lower mortality risk.[25] Our results support an aggressive approach to device closure in younger patients with an ASD, even if PH has developed. Risk may potentially be further modified with the use of advanced medical therapies for PH, though this approach requires further research. Previously published data suggests that advanced medical therapies for PH may offer patients with "irreversible" pulmonary vascular changes improvement in pulmonary vascular resistance and symptoms.[26–29] Since most of the cohort in this study was collected at a time when the availability of targeted PH pharmacotherapy was in its infancy, future studies are needed to investigate whether these therapies, either before or after ASD closure, favorably impact clinical outcomes. Studies should focus on older patients, given the significant risk observed in our study. These patients may in fact benefit from a "treat to close" strategy. In this situation, the patient is treated with vasoactive medication until the pressures are more favorable for device closure. Other options for these patients with high pulmonary pressures include the use of fenestrated occluders, which reduce the degree of left to right shunting, while continuing to provide a "pop-off valve" for the right side should hemodynamic compromise occur.[30,31]

Limitations of this study include that the analysis was performed retrospectively, although patients were enrolled in a prospective manner. Additionally, these data are from an academic referral center; therefore, not all patients were able to return for follow-up at each suggested study interval and long-term follow-up data was not available for all of our patients.

In summary, PH is a major co-morbidity for those with an ASD and is a strong predictor of future mortality in older patients who underwent device closure. Furthermore, younger patients experience more favorable clinical responses, supporting a more aggressive approach to transcatheter closure of ASDs in this population. Additionally, we found there that there is a significantly increased risk of mortality in those PH patients who do not show echocardiographic resolution of PH 3 months following device closure. Patients with an ASD and PH may benefit from additional risk assessment or advanced medical therapies to mitigate mortality following closure.

## Disclosures

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