Use of Pulmonary Inhalants Remains Remarkably High After Atrial Septal Defect Closure

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Background: Post-repair atrial septal defects (ASD) patients are frequently discharged from follow-up, but the extent of pulmonary symptoms long-term post-repair is unknown.

Methods and Results: The national CONgenital CORvitia registry was linked to the national Drug Registry to investigate all ambulatory-dispensed pulmonary inhalants for 2006–2014. ASD patients were compared with age- and sex-matched referents from the general population. A total of 1,959 adult patients (age 42±17 years; 66% female; 1,223 [62%] repaired) were included. Compared with the referents, ASD patients had more inhalant use, even at long-term post-repair follow-up (OR=1.81 [95% CI 1.62–2.03]; P<0.001).

Conclusions: ASD patients had 2-fold higher inhalant use compared with referents even at long-term post-repair follow-up, suggesting persistent pulmonary functional impairment.

Key Words: Adult congenital heart disease; Atrial septal defects; Dyspnea; Pulmonary inhalants

Secundum atrial septal defects (ASD) are one of the most common congenital heart defects. Appropriate and timely diagnosis and treatment prevents complications of long-standing right ventricular volume overload such as irreversible pulmonary hypertension and right-sided heart failure. Patients may present late during adulthood because of symptom overlap with pulmonary diseases, such as asthma, with consequent long-term pulmonary inhalant use. Post-repair ASD patients are often discharged from follow-up, but little is known about the extent of symptoms at long-term post-repair follow-up. We aimed to compare pulmonary inhalant use in adults with open and repaired ASD in comparison with matched referents from the general population.

Methods

In this multicenter cohort study, adult secundum ASD patients included in the CONgenital CORvitia Dutch national registry for adult congenital heart disease patients were linked to the Dispensed Drug Registry of Statistics Netherlands for the years 2006–2014, which contains all ambulatory-dispensed drugs registered per patient per year according to the Anatomical Therapeutic Chemical (ATC) classification system. In this study, all pulmonary inhalants for obstructive airway diseases were included (ATC codes R03A-B). Patients were compared in a 1:10 ratio with age- and sex-matched referents from the general population who were enrolled at the time of patient inclusion. Follow-up ended at the latest CONCOR update or upon death (Cause of Death Registry Netherlands). All patients provided informed consent. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Medical ethics committees of all participating medical centers approved the study.

Statistical analyses were performed using R version 1.0.153 (R Foundation for Statistical Computing, Vienna, Austria). Logistic regression with generalized estimation equations with exchangeable working correlation was used to compare overall pulmonary inhalant use for ASD patients vs. matched referents, repaired vs. unrepaired patients, surgical vs. device repair, and patients with age at closure ≤25 years vs. >25 years. Where applicable, corrections were made for age, sex, and concomitant medication use. Registered skeletal comorbidities (pectus carinatum and excavatum, kyphoscoliosis) and syndromes with cardiac involvement (Down, Turner, Marfan, Noonan, Williams, 22q11 deletion) were assessed in relation to inhalant use. Data are presented as mean±standard deviation, median [25–75th percentile] or frequency (percentage).
repaired patients had undergone ASD closure 22 [10–37] years before study inclusion, and 1,096 (90%) were surgically closed. At baseline, 736 patients were unrepaired (age 44 ± 16 years), of whom 298 underwent closure within the study period (n=149 [50%] surgically) after 3.0 [1.0–5.0] years. ASD patients generally used 4 [2–6] different drug types per year, compared with 2 [0–4] used by the referents.

A two-sided P<0.05 was considered statistically significant.

**Results**

In total, 1,959 ASD patients were identified (age 42±17 years, 66% female, 1,223 [62%] repaired). Within the 9-year study period, patients were followed for 9 [7–9] years. The repaired patients had undergone ASD closure 22 [10–37] years before study inclusion, and 1,096 (90%) were surgically closed. At baseline, 736 patients were unrepaired (age 44±16 years), of whom 298 underwent closure within the study period (n=149 [50%] surgically) after 3.0 [1.0–5.0] years. ASD patients generally used 4 [2–6] different drug types per year, compared with 2 [0–4] used by the referents.
Prescribed cardiovascular and respiratory drugs are shown in Table S1.

Overall, the ASD patients had a higher percentage of pulmonary inhalant use than the matched referents (odds ratio (OR)=1.81 [95% confidence interval (CI) 1.62–2.03]; P<0.001, Figure A), with 13.8 years per 100 patient-years compared with 8.3 years per 100 person-years in the matched referents (see duration of inhalant use in Table S2). Inhalant use increased over the years with increasing age (OR/year=1.04 [95% CI 1.03–1.04]; P<0.001); however, the difference between ASD patients and their matched referents remained unchanged (Pinteraction=0.41). Inhalant use in ASD patients remained significantly higher than in referents when corrected for concomitant use of β-blockers or diuretics (OR=1.71 [95% CI 1.53–1.92]; P<0.001) and pulmonary antihypertensive drugs (endothelin-receptor antagonists/PDE-5 inhibitors; OR=1.81 [95% CI 1.62–2.02]; P<0.001).

No statistically significant difference in inhalant use was found between open and repaired ASD patients (OR=0.96 [95% CI 0.79–1.15]; P=0.56) or between surgical and device closure (OR=0.97 [95% CI 0.71–1.34]; P=0.87). When corrected for sex and age, no difference was seen between patients repaired at age ≤25 years compared with age >25 years (OR=1.03 [95% CI 0.73–1.44]; P=0.87), and both groups had significantly higher inhalant use than their matched referents (Figure B). Higher inhalant use was associated with the presence of skeletal comorbidity (n=23 [1.2%]; OR=2.44 [95% CI 1.14–5.20]; P=0.02), but not with the presence of syndromes (n=66 [3.4%]; OR=0.71 [95% CI 0.36–1.32]; P=0.28).

Of the 298 patients repaired within the study period, 52 (17%) used inhalants in the year of closure, which significantly reduced to 38 (14%) patients in the following year (paired McNemar P=0.04, Figure S1). However, inhalant use increased again in the years thereafter. Patients who underwent device closure had comparable use of inhalants as surgically repaired patients.

**Discussion**

ASD-associated dyspnea may arise from left-to-right shunting through cardiac and pulmonary volume and/or pressure overload. This was reflected by a significantly higher percentage of patients with pulmonary inhalant use compared with matched referents. After shunt closure, significantly lower inhalant use in the first year after closure may represent immediate symptom relief. However, this effect did not last in the years thereafter, when a similar percentage of patients used inhalants as before closure. Patients repaired at age ≤25 years who, according to current guidelines can be discharged from lifelong follow-up, had similarly high inhalant use as patients repaired at age >25 years when corrected for sex and age, suggesting that repair at young age did not prevent long-term inhalant use post-closure.

Several mechanisms may potentially cause continuous pulmonary inhalant use after ASD repair. Some studies observed persistent pulmonary vascular dysfunction with exercise impairment in a subgroup of post-repair ASD patients. Others reported high prevalence and incidence rates of pulmonary hypertension after ASD repair, suggesting late effects of previous left-to-right shunting even in patients repaired at age ≤25 years. A prospective study performed by the authors showed a 63% (95% CI 45–81%) prevalence of airway hyperresponsiveness in adult patients, which remained unchanged after device closure. Therefore, the present study results are supportive evidence of irreversible, possibly ASD-associated pulmonary function impairment in a subgroup of repaired adults, requiring the use of pulmonary inhalants for obstructive airway disease.

Several factors may have influenced pulmonary inhalant use as reported in this study. Firstly, ASD patients were generally more likely to use medication than matched referents (Table S1), possibly because of increased healthcare utilization. Possible interference with inhalant use includes shortness of breath, wheezing and cough, as side effects of β-blockers or as a result of congestive heart failure for which diuretics are prescribed. Also, pulmonary hypertension is known to potentially induce obstructive symptoms. However, when correcting for these drug types in our analyses, pulmonary inhalant use remained significantly higher in ASD patients compared with the general population. Secondly, smoking is associated with broncho-obstructive symptoms. Although smoking status could not be assessed in the current data, a previous study of this national registry reported significantly less and shorter smoking habits in adult congenital heart disease patients than in the general population, as supported by other studies. Therefore, smoking status cannot explain the increased inhalant use in ASD patients. Finally, all registered growth-impairing comorbidities that might have influenced thoracic size and function, only skeletal disorders were associated with higher inhalant use. With its prevalence of 1.2% in this ASD cohort, the potential effect on inhalant use in ASD patients is limited.

This study has several strengths and limitations. A major strength is the combination of a large cohort of ASD patients with data from national administrative databases, including both patients from secondary and tertiary centers and inclusion following national campaigns, as well as matched comparisons with the general population. Limitations inherent to these administrative databases were unavoidable, such as absence of data on duration, timing, and daily doses of pulmonary inhalant use. Noncardiac comorbidities and the prescribing physician’s specialty cannot be extracted from these data either. Future studies should investigate the possible underlying mechanisms of persistent pulmonary symptoms that require pulmonary inhalants after closure.

**Conclusions**

The present study shows twofold higher pulmonary inhalant use in adult ASD patients compared with age- and sex-matched referents from the general population. Repaired ASD patients have equally high use of pulmonary inhalants as unrepaired patients, irrespective of age at closure, which suggests dyspnea due to pulmonary function impairment even long after ASD closure. Attention to pulmonary function should be an integral part of clinical monitoring during long-term post-repair follow-up in ASD patients even after closure at a young age.

**Acknowledgments**

Disclosures: R.J.deW.: Academic Medical Center received an institutional unrestricted educational research grant from Abbott Vascular BV. All others: none disclosed. Funding: O.I.W. and B.J.B. are funded by the Netherlands Heart Foundation.
Circulation Journal Vol.82, November 2018

References

Supplementary Files
Supplementary File 1
Figure S1. Use of pulmonary inhalants in patients with ASD repaired within the 9-year study period.
Table S1. Use of cardiovascular drugs in ASD patients and age- and sex-matched referents
Table S2. Duration of pulmonary inhalant use in ASD patients and age- and sex-matched referents

Please find supplementary file(s);