Atrial septal defect in adults is associated with airway hyperresponsiveness

Martina Nassif MD1 | Reindert P. van Steenwijk MD, PhD2 | Jacqueline M. Hogenhout B Health2 | Huangling Lu MD1 | Rianne H.A.C.M. de Bruin-Bon B Health1 | Alexander Hirsch MD, PhD1,3 | Peter J. Sterk MD, PhD2 | Berto J. Bouma MD, PhD1 | Bart Straver MD, PhD4 | Jan G.P. Tijssen PhD1 | Barbara J.M. Mulder MD, PhD1,5 | Robbert J. de Winter MD, PhD1

1Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
2Department of Respiratory Medicine, Academic Medical Center, Amsterdam, The Netherlands
3Department of Cardiology and Radiology, Erasmus Medical Center, Rotterdam, The Netherlands
4Department of Pediatric Cardiology, Academic Medical Center, Amsterdam, The Netherlands
5Netherlands Heart Institute, Utrecht, The Netherlands

Correspondence
Robbert J. de Winter, MD PhD FESC, Academic Medical Center- University of Amsterdam, Department of Cardiology, Room B2-137, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: r.j.dewinter@amc.uva.nl

Abstract

Objective: The association between secundum atrial septal defects (ASD) and asthma-like dyspnea with consequent long-term pulmonary inhalant use, is poorly understood in adult ASD patients. Airway hyperresponsiveness is suggested to be the underlying mechanism of cardiac asthma from mitral valve disease and ischemic cardiomyopathy. We hypothesized that airway hyperresponsiveness may also be found in adult ASD patients. Our aim was to study airway responsiveness in adult ASD patients before percutaneous closure and at short- and long-term postprocedural follow-up.

Methods: This prospective study included 31 ASD patients (65% female, mean age 49 ± 15y) who underwent spirometry and bronchoprovocation testing pre-and six-month postprocedurally, with additional bronchoprovocation at 2-year follow-up. Airway hyperresponsiveness was defined as ≥20% fall of forced expiratory volume in 1-second (FEV1) following <8.0 mg/mL of inhaled methacholine.

Results: Airway hyperresponsiveness was found in 19/30 patients (63%[95%CI 45%-81%]; post hoc statistical power = 89%). Asthma-like symptoms wheezing, chest tightness, and cough were more frequently reported in airway hyperresponsive patients. Airway responsiveness was not influenced by successful percutaneous ASD closure, corresponding to persistence of asthma-like symptoms postclosure. Regardless of airway responsiveness, postprocedural right-sided reverse remodeling significantly improved dyspnea and pulmonary function.

Conclusions: This study is the first to report a high prevalence of airway hyperresponsiveness in a cohort of unrepaired adult ASD patients, and confirms the association between asthma-like symptoms and ASD in adults. Attention to symptoms and pulmonary function should be given during clinical follow-up of adult ASD patients, both before and long after repair.

KEYWORDS
adult congenital heart disease, airway hyperresponsiveness, asthma, atrial, device closure, dyspnea, heart septal defects

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1 | INTRODUCTION

Secundum atrial septal defects (ASDs) are the second most common congenital heart defects, and may manifest late into adulthood with symptoms of dyspnea or palpitations. The association between ASD and asthma-like dyspnea, such as wheezing and chest tightness, is commonly acknowledged in the pediatric community, yet unequally established in adult cardiology. The prevalence of asthma-like symptoms and pulmonary inhalant use in an adult ASD study cohort has recently been suggested in a questionnaire-based study of 80 adult ASD patients in which one-third of patients reported wheezing and chest tightness and 20% used bronchodilators. Also, in a multicenter population-based study (unpublished data), use of pulmonary inhalants was found to be twice as high in adult ASD patients compared to the general population, both before and long after shunt repair. As of now, however, the possible underlying mechanism of asthma-like dyspnea with consequent long-term pulmonary inhalant use in adult ASD patients still remains unclear.

Among cardiac diseases, asthma-like symptoms known as “cardiac asthma” are extensively described in patients with chronic heart failure with or without mitral valve disease, and airway hyperresponsiveness has been suggested to be the underlying mechanism of these symptoms. Airway hyperresponsiveness is characterized by more sensitive and increased airway narrowing to nonspecific stimuli that normally lead to little or no airway response. Unlike in bronchial asthma, airway hyperresponsiveness can exist without a (family) history of atopy like allergic rhinitis or atopic eczema, or evidence of eosinophilic airways inflammation. Since ASD patients may present with asthma-like dyspnea, we hypothesized that airway hyperresponsiveness may also be found in adult ASD patients. Hence, our aim was to study airway responsiveness in adult ASD patients before percutaneous closure and at short- and long-term postprocedural follow-ups.

2 | METHODS

2.1 | Study design

In this prospective observational study, we evaluated consecutive adult patients with secundum ASD referred for percutaneous closure in the Center for Congenital Heart Disease Amsterdam Leiden within a period of 13 months (2014-2015). Indication for ASD closure was decided by our Grown-Up Congenital Heart team based on current guidelines. Pulmonary function testing and echocardiographic imaging were performed pre- and at six-month postprocedural follow-up as routine clinical work-up. Pulmonary function testing was repeated at 2-year postprocedural follow-up as part of this study. Additional cardiovascular magnetic resonance (CMR) imaging was performed at the physician’s discretion. The study cohort comprised patients who had complete baseline pulmonary testing and who underwent successful percutaneous ASD closure. This study conforms to the 1975 Declaration of Helsinki and all patients provided informed consent according to local medical ethical regulations.

2.2 | ASD closure

Percutaneous ASD closure was performed conform current guidelines and under general anesthesia for transesophageal echocardiographic guidance of device placement. Routinely, heparin and aspirin were administered at the start of the procedure and an Amplatzer Septal Occluder (Abbott Vascular BV, Santa Clara, California) of appropriate size was implanted. Postprocedural therapy included a 6-month dual antiplatelet regimen of daily aspirin 100 mg and clopidogrel 75 mg after a 600-mg loading dose.

2.3 | Methacholine challenge testing

Standardized spirometry was performed on a MasterScreen PFT (Jaeger, Wurzburg, Germany) and predicted values were based on age, sex, and height. Bronchoprovocation testing was performed according to the 2-minute tidal breathing method using a MasterScreen Body plethysmograph (Jaeger). Changes in airway caliber were expressed as forced expiratory volume in 1 second (FEV₁). After inhaling 0.9% isotonic saline, patients received doubling doses of methacholine chloride from 0.6 to 1.2 mg/mL until FEV₁ decreased ≥20% from baseline or when a maximum of 19.6 mg/mL methacholine was administered. Airway hyperresponsiveness was defined as ≥20% of FEV₁ decline from baseline following ≤8.0 mg/mL of inhaled methacholine. The dose-response curve served as quantitative index of airway responsiveness to visualize potential changes from the hyperresponsive patients toward the normal range of all patients. A 2-point dose-response slope (DRS) was calculated as the percentage FEV₁ decline at the last methacholine concentration, divided by the cumulative methacholine dose administered.

As per clinical protocol, patients were excluded from bronchoprovocation testing if they had a myocardial infarction >3 months, chronic heart disease or epilepsy with medical therapy, were pregnant or breast-feeding, or had FEV₁ <70% of predicted. Patients were instructed not to smoke <2 h prior to testing, use short-acting β₂-agonist <8 h, anticholinergic inhaler/antileukotrienes <24 h, long-acting β₂-agonist, or combination with inhaled corticosteroids/theophyllines/antihistamines/chromones <48 h, long-acting antimuscarinics <4 days, and the test was postponed in case of respiratory tract infections <3 weeks. To minimize confounding, postprocedural bronchoprovocation testing was kept identical to baseline in terms of diluent steps and the hour of the day on which the test was performed.

2.4 | Questionnaire

The validated Dutch version of the European Community Respiratory Health Survey (ECRHS) was conducted before any spirometry, enquiring about symptoms of wheezing not associated with the flu, (nocturnal) chest tightness, resting/exercise/nocturnal cough, and/or phlegm during winter, troubled breathing, diagnosed asthma, nasal allergies, hay fever,
and eczema. All questions refer to symptoms in the previous 12 months or 6 months, at baseline and follow-up, respectively. Asthma definition and classification were based on the Global Initiative for Asthma guidelines.

2.5 | Imaging

Two-dimensional echocardiography and CMR were performed at baseline and 6-month follow-up as part of the outpatient visits. Echocardiographic views were acquired on a Vivid 9 (GE Healthcare, Horten, Norway) based on recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging and were analyzed offline. Right atrial size was measured in the dedicated apical 4-chamber view by single-plane area measurements, and right systolic function was assessed by the velocity of the tricuspid annular systolic motion. Right ventricular single-plane and left atrial and ventricular biplane volumes and left ejection fraction were measured using the disk summation technique. Postprocedural pulmonary capillary wedge pressure was estimated by the E/e’ ratio as formulated by Nagueh et al.

CMR images were acquired on a clinical 1.5 or 3.0 Tesla scanner (Siemens, Erlangen, Germany or Philips, Best, The Netherlands) with a phased-array cardiac receiver coil. Functional imaging was performed using retrospectively electrocardiographically gated steady-state free precession cine imaging with breath holding. Contiguous short-axis slices were acquired, covering the entire left and right ventricle from base to apex, to examine global ventricular function (typical scan parameters: slice thickness 6 mm with interslice gap 3 mm, matrix 192 × 192, temporal resolution 30-55 ms, flip angle 75°). Analyses of right- and left-sided end-diastolic and end-systolic volumes were done by manual endocardial contouring (excluding papillary muscles and trabeculae) on short-axis frames from which ejection fraction was also derived. Analysis was performed offline with dedicated software (MASS v.5.1 2015-EXP beta; Medis, Leiden, The Netherlands) by an experienced imaging cardiologist (AH) who was blinded to all patient characteristics and outcome measures.

2.6 | Statistical analysis

Baseline characteristics, hemodynamics, and pulmonary function parameters are presented as mean ± standard deviation, median [25th-75th percentile], or frequency (percentage) according to distribution. Paired pre- and postprocedural variables were tested using the two-tailed paired t test, Wilcoxon signed-rank test, or McNemar’s test where appropriate. The Friedman test was used to compare dose-response slopes at pre- and 6-month and 2-year postprocedural follow-ups. Differences between hyper- and normoresponsive patients were tested using the Mann-Whitney U or Fisher’s exact test. Correlations were linearly tested unless mentioned otherwise. A two-sided P value < .05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, New York).

The primary outcome of this study was airway hyperresponsiveness at baseline before ASD closure. Secondary outcomes include airway responsiveness at 6-month and 2-year postprocedural follow-up, and ventilatory and hemodynamic changes from baseline to 6 months after percutaneous ASD closure. This hypothesis-generating study did not allow for sample size specification. Instead, a post hoc power analysis was conducted using G*Power software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) set at alpha error 0.05 (one-sided) and a 35% prevalence of airway hyperresponsiveness in the general population. A power of ≥80% was considered a significant statistical power for the reported prevalence of airway hyperresponsiveness in this study.

3 | RESULTS

3.1 | Study cohort

Following the Grown-Up Congenital Heart team decision, 41 adults were consecutively planned for percutaneous ASD closure in a 13-month period. Ten patients had incomplete baseline pulmonary assessment, therefore 31 ASD patients with complete preprocedural spirometry and bronchoprovocation testing formed the study cohort (Figure S1).

Baseline characteristics are shown in Table 1. The mean age was 49 ± 15 years, 65% were female, and 84% were repaired for right ventricular dilatation with a pulmonary-to-systemic-flow ratio of 1.9 ± 0.9. Based on the Global Initiative for Asthma guidelines, 4(13%) patients had diagnosed asthma (n = 2 mild, n = 2 moderate) and 11(35%) patients had a self-reported history of either allergic rhinitis, atopic eczema, or insect allergy. Ten (32%) patients had symptoms of wheezing, chest tightness, and/or nocturnal dyspnea. An episode of resting dyspnea was present in 21 (68%) patients, and exertional dyspnea was reported by 22 (71%) patients. Four patients were on current respiratory medicine (n = 3 corticosteroids, n = 1 short-acting β2-agonist) and another two used low-dose oral glucocorticoids for comorbidity.

3.2 | Airway responsiveness

Of the 30 patients with bronchoprovocation testing (n = 1 excluded for FEV1 <70%), 19 patients had airway hyperresponsiveness, corresponding to a prevalence of 63% (95%CI 45%-81%) in this study population. This yielded a post hoc statistical power of 89%. The dose-response curve of all individual patients is shown in Figure 1A.

Figure 1B shows the dose-response slope at baseline and at 6-month and 2-year postprocedural follow-up. At baseline, the hyperresponsive patients featured a dose-response slope of 2.87 [1.34-3.74] compared to a slope of 0.25 [0.18-0.32] in the 11 normoresponsive patients (P < .001). Both in hyperresponsive and normoresponsive patients the dose-response slopes at post-procedural follow-up remained unchanged from baseline (P = .75 and P = .42, respectively). Patient symptoms before and 6 months after closure are
shown in Figure 2. Numerical differences between hyperresponsive and normoresponsive patients were observed for wheezing (6 [32%] vs. 1 [9%]), cough (5 [26%] vs. 1 [9%]), ever used respiratory medicine (6 [32%] vs. 1 [9%]) and the combination of asthma-like symptoms (8 [42%] vs. 1 [9%]; \( P = .07 \)). Irrespective of responsiveness status, significant postprocedural improvement was seen in symptoms of troubled breathing and exertional dyspnea (both \( P < .001 \)), while wheezing and chest tightness reduced only slightly (Figure 2).

### 3.3 | Effect of closure

Table 2 shows the paired ventilatory and hemodynamic changes from baseline to 6-month postprocedural follow-up (mean follow-up 6.0 ± 1.0 months), as measured by spirometry and cardiac imaging, respectively.

At baseline spirometry, \( FEV_1 \) was 3.0 ± 0.9 L/s (98% ± 15% predicted) with a \( FEV_1/forced \) vital capacity index of 0.8 ± 0.07 (99% ± 7.8% predicted). \( FEV_1 \) was associated with baseline symptoms of wheezing \(( r^2 = 0.22; P = .008 \)). Postprocedural improvements in spirometry were seen most notably in \( FEV_1 \) (98% ± 15%-101% ± 14%; \( P = .04 \)), forced vital capacity (103% ± 16%-108% ± 15%; \( P < .001 \)) and inspiratory vital capacity (100% ± 16%-103% ± 15%; \( P = .03 \)). Low baseline spirometry values were associated with baseline exertional dyspnea (\( P < .01 \)) and its postprocedural resolution (\( P < .01 \)).

Following successful percutaneous closure, significant right atrial and ventricular reverse remodeling was observed. CMR-based right ventricular end-diastolic volume decreased from 134 ± 40 mL/m²-96 ± 23 mL/m² (\( P < .001 \)), corresponding to right ventricular stroke volume reduction \(( r^2 = 0.68; P < .001 \)). Systolic pulmonary artery pressure decline correlated with reduction in both right atrial \(( r^2 = 0.56; P < .001 \)) and ventricular \(( r^2 = 0.47; P = .002 \)). Right ventricular end-diastolic volume reduction was associated with resolution of troubled breathing \(( r^2 = 0.31; P = .01 \)) and exertional dyspnea \(( r^2 = 0.24; P = .03 \)), as well as improvement in \( FEV_1 \) \(( r^2 = 0.24; P = .03 \)), forced vital capacity \(( r^2 = 0.37; P = .004 \)) and inspiratory vital capacity \(( r^2 = 0.39; P = .004 \)).

### 4 | DISCUSSION

This study is the first to report a high prevalence of airway hyperresponsiveness in a cohort of unrepaired adult ASD patients. Asthma-like symptoms were more frequently reported in airway hyperresponsive patients. Parallel to the unchanged airway responsiveness after successful percutaneous ASD closure, asthma-like symptoms did not significantly improve postclosure. Regardless of airway responsiveness, postprocedural right-sided reverse remodeling significantly improved dyspnea and pulmonary function.

#### 4.1 | Airway hyperresponsiveness

Increased airway responsiveness to nonspecific stimuli is one of the major defining features of asthma, but not pathognomonic for it.\(^{11}\) In the general adult population the prevalence of airway responsiveness is 10%-16% (max. 25%-35% as defined by a ≤ 10 \( FEV_1 \) decline),\(^{20,21}\) and its risk factors include age, female gender, atopic constitution, respiratory tract infection, current smoking, and genetic predisposition.\(^{22}\) The 63% (95%CI 45%-81%)
The prevalence of airway hyperresponsiveness in this study is significantly higher than expected from the prevalence in the general population and cannot be accounted for by conventional risk factors of hyperresponsiveness. Only a few patients in this cohort were current smokers, and the testing season had no influence on airway responsiveness. None of the patients had comorbid lung disease or recent pulmonary infection during bronchoprovocation. Patients’ concomitant medication excluded responsiveness-affecting ones such as ACE-inhibitors, beta-blockers or diuretics to influence results. Although aspirin can incidentally exacerbate respiratory disease, no evidence of such medical reaction was observed.

### 4.2 Asthma-like symptoms

The Global Initiative for Asthma guideline defines asthma by respiratory symptoms such as wheezing, chest tightness, cough and shortness of breath that vary in duration and intensity, accompanied by variable airflow limitation. In the present study, wheezing, chest tightness, and cough were indeed predominantly reported by hyperresponsive ASD patients, and parallel to the unchanged airway responsiveness postclosure, these asthma-like symptoms did not significantly resolve after shunt repair (Figure 2). Therefore, the present study confirms the association between secundum ASD and asthma-like symptoms.
and additionally provides data that suggests that airway hyperresponsiveness is one of the possible underlying mechanisms.

### 4.3 Effects of ASD closure

The most frequently reported symptoms in this study cohort were troubled breathing and exertional dyspnea which, regardless of airway responsiveness, resolved significantly after successful closure. The corresponding improvement in FEV$_1$ and forced and inspiratory vital capacity significantly correlated with reverse right heart remodeling and systolic pulmonary artery pressure decline at 6-month follow-up. With or without the presence of pulmonary hypertension, left-to-right shunts are known to increase pulmonary apical perfusion by capillary recruitment. Indeed, the observed significant reverse remodeling after percutaneous closure may suggest that spatial reduction in pulmonary vascular volume and peripheral airway caliber improves vital capacity.

### 4.4 Clinical implications

The present study reports a high prevalence of airway hyperresponsiveness in a cohort of adult ASD patients, and proposes airway hyperresponsiveness as a possible mechanism for asthma-like symptoms that potentially require pulmonary inhalant use, both before and long after closure. Characteristic nonspecific triggers for bronchospasm such as cold or dry air, abrupt temperature changes, smoke, and exercise may induce asthma-like symptoms in ASD patients, regardless of repair status. Unlike in bronchial asthma, ASD-associated asthma-like symptoms are not necessarily episodic over merely few hours to days, but can manifest with progressive

**TABLE 2** Ventilatory and hemodynamic parameters before and 6 months after successful ASD closure

| Parameter                                           | n  | Baseline       | Follow-up      | Δ               | P value |
|-----------------------------------------------------|----|----------------|----------------|-----------------|---------|
| **Spirometry**                                      |    |                |                |                 |         |
| Forced expiratory volume in 1 s, %pred              | 29 | 98 ± 16        | 101 ± 14       | 2.3 ± 6.1       | 0.05    |
| Forced vital capacity, %pred                        | 29 | 103 ± 16       | 108 ± 15       | 5.1 ± 6.7       | <0.001  |
| FEV$_1$/FVC ratio, %pred                            | 29 | 100 ± 8        | 98 ± 9         | -2.1 ± 4.8      | 0.02    |
| Peak expiratory flow, %pred                         | 29 | 105 ± 22       | 108 ± 21       | 2.9 ± 11        | 0.15    |
| Max. expiratory flow at 50% of expiration, %pred    | 29 | 83 ± 25        | 78 ± 27        | -4.3 ± 16       | 0.16    |
| Inspiratory vital capacity, %pred                   | 29 | 100 ± 16       | 103 ± 15       | 3.3 ± 7.5       | 0.03    |
| Maximal vital capacity, %pred                       | 29 | 101 ± 16       | 106 ± 14       | 4.6 ± 7.1       | 0.002   |
| **Echocardiography**                                |    |                |                |                 |         |
| RA end-systolic area, cm$^2$/m$^2$                   | 27 | 25 ± 9.8       | 18 ± 4.8       | -7.0 ± 7.6      | <0.001  |
| Tricuspid annular systolic motion velocity, cm/s    | 9  | 14 ± 2.7       | 12 ± 1.7       | -1.3 ± 2.2      | 0.11    |
| Systolic pulmonary artery pressure, mm Hg           | 23 | 34 ± 7.8       | 27 ± 4.5       | -6.8 ± 8.6      | 0.001   |
| Pulmonary capillary wedge pressure, mm Hg           | 25 | n/a            | 13 ± 2.7       |                 |         |
| LA end-systolic volume, ml/m$^2$                    | 24 | 35 ± 14        | 35 ± 9.6       | 0.9 ± 13        | 0.74    |
| **Cardiac magnetic resonance**                      |    |                |                |                 |         |
| RV end-diastolic volume, ml                         | 21 | 249 ± 83       | 182 ± 62       | -67 ± 51        | <0.001  |
| RV end-diastolic volume, ml/m$^2$                   | 21 | 134 ± 40       | 96 ± 23        | -38 ± 30        | <0.001  |
| RV end-systolic volume, ml                          | 21 | 104 ± 41       | 83 ± 34        | -21 ± 26        | 0.001   |
| RV end-systolic volume, ml/m$^2$                    | 21 | 56 ± 21        | 44 ± 14        | -13 ± 16        | 0.002   |
| RV stroke volume, ml                                | 21 | 145 ± 47       | 101 ± 30       | -44 ± 30        | <0.001  |
| RV ejection fraction, %                             | 21 | 59 ± 6.1       | 56 ± 5.6       | -3.0 ± 3.8      | 0.002   |
| LV end-diastolic volume, ml/s                       | 21 | 129 ± 40       | 147 ± 45       | 18 ± 14         | <0.001  |
| LV end-diastolic volume, ml/m$^2$                   | 21 | 69 ± 16        | 78 ± 19        | 9.3 ± 6.9       | <0.001  |
| LV end-systolic volume, ml                          | 21 | 45 ± 16        | 52 ± 22        | 6.5 ± 9.3       | 0.005   |
| LV end-systolic volume, ml/m$^2$                    | 21 | 24 ± 8         | 27 ± 10        | 3.1 ± 4.9       | 0.009   |
| LV stroke volume, ml                                | 21 | 84 ± 26        | 96 ± 26        | 12 ± 10         | <0.001  |
| LV ejection fraction, %                             | 21 | 65 ± 5.5       | 66 ± 6.5       | 0.4 ± 5.3       | 0.72    |
| LV cardiac output, L/min                            | 21 | 5.9 ± 2.2      | 6.2 ± 1.9      | 0.3 ± 1.0       | 0.20    |

Data are presented as mean ±SD. Abbreviations: %Pred, percentage of predicted value; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; RA, right atrial; RV, right ventricular; LA, left atrial; LV, left ventricular.
dyspnea over the course of months. Also unlike bronchial asthma, these symptoms can manifest later in adult life, without a positive (family) history of asthma and atopy. Such better understanding of ASD-associated dyspnea may potentially prevent therapeutic delay of unrepaird ASD with the risk of complications from long-standing right ventricular volume overload, as well as diagnostic delay of long-term postrepair pulmonary function impairment.

4.5 Study strengths and limitations

Percutaneous ASD closure provides a unique model to validate the assumption that observed pulmonary function changes at follow-up can be fully attributed to left-to-right shunt closure, unlike surgical closure which can influence pulmonary function by the cardiopulmonary bypass and surgical scar. Consequently, no control group was provided since patients had paired testing and their postprocedural state was considered similar to controls. Also, postprocedural bronchoprovocation testing was performed up to 2 years after ASD closure, allowing for observation of potential long-term changes in airway responsiveness.

Although the primary study outcome was supported by sufficient post hoc statistical power, this study included a small number of adult ASD patients. Analyses of possible predictors of airway hyperresponsiveness were therefore beyond the scope of this study. Symptom reporting bias may have been present, though questionnaires were conducted before spirometry and were double-blinded of baseline questionnaire answers. Future studies should continue to investigate the possible underlying mechanisms of persistent pulmonary symptoms that require pulmonary inhalants after closure, as well as elucidate the mechanisms of coexisting airway hyperresponsiveness in ASD patients.

5 CONCLUSIONS

This is the first study to show an association between secundum ASD and airway hyperresponsiveness, and confirms the association between asthma-like symptoms and ASD in adults. Parallel to unchanged airway responsiveness after successful percutaneous ASD closure, asthma-like symptoms may persist after repair. Regardless of airway responsiveness, ASD closure reduces general dyspnea by benefitting right-sided hemodynamics and spirometry. Attention to symptoms and pulmonary function should be given during clinical follow-up of adult ASD patients, both before and long after repair.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

MN, RPvS, HL, PJS, BJMM, and RJdW contributed substantially to the study concept and design. MN and JMH acquired the data. MN, RPvS, RdBB, AH, PJS, BJF, BS, JGPT, BJMM, and RJdW substantially contributed to data analysis and interpretation. MN has drafted the submitted article. MN and JGPT provided statistical analysis. All authors have critically revised the submitted article for important intellectual content, and provided final approval of the version to be published.

ORCID

Martina Nassif http://orcid.org/0000-0001-7482-8482

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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