


# Atrial septal defect in adults is associated with airway hyperresponsiveness

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## 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  $49 \pm 15$ y) who underwent spirometry and bronchoprovocation testing pre-and six-month postprocedurally, with additional bronchoprovocation at 2-year follow-up. Airway hyperresponsiveness was defined as  $\geq 20\%$  fall of forced expiratory volume in 1-second ( $FEV_1$ ) 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

## 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.<sup>1</sup> The association between ASD and asthma-like dyspnea, such as wheezing and chest tightness, is commonly acknowledged in the pediatric community,<sup>2</sup> 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.<sup>3</sup> Also, in a multi-center 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,<sup>4–9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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<sup>12</sup> 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.<sup>13</sup> Bronchoprovocation testing was performed according to the 2-minute tidal breathing method<sup>10,14</sup> using a MasterScreen Body plethysmograph (Jaeger). Changes in airway caliber were expressed as forced expiratory volume in 1 second ( $FEV_1$ ). After inhaling 0.9% isotonic saline, patients received doubling doses of methacholine chloride from 0.6 to 1.2 mg/mL until  $FEV_1$  decreased  $\geq 20\%$  from baseline or when a maximum of 19.6 mg/mL methacholine was administered. Airway hyperresponsiveness was defined as  $\geq 20\%$  of  $FEV_1$  decline from baseline following  $\leq 8.0$  mg/mL of inhaled methacholine.<sup>15</sup> 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  $FEV_1$  decline at the last methacholine concentration, divided by the cumulative methacholine dose administered.<sup>16</sup>

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  $FEV_1 < 70\%$  of predicted. Patients were instructed not to smoke  $< 2$  h prior to testing, use short-acting  $\beta_2$ -agonist  $< 8$  h, anticholinergic inhaler/antileukotrienes  $< 24$  h, long-acting  $\beta_2$ -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 dyspnea, (nocturnal) cough, and/or phlegm during winter, troubled breathing, diagnosed asthma, nasal allergies, hay fever,

and eczema.<sup>17</sup> 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.<sup>11</sup>

## 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<sup>18</sup> 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.<sup>19</sup>

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 x 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  $\pm$  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  $\geq 80\%$  was considered a significant statistical power for the reported prevalence of airway hyperresponsiveness in this study.

## 3 | RESULTS

### 3.1 | Study cohort

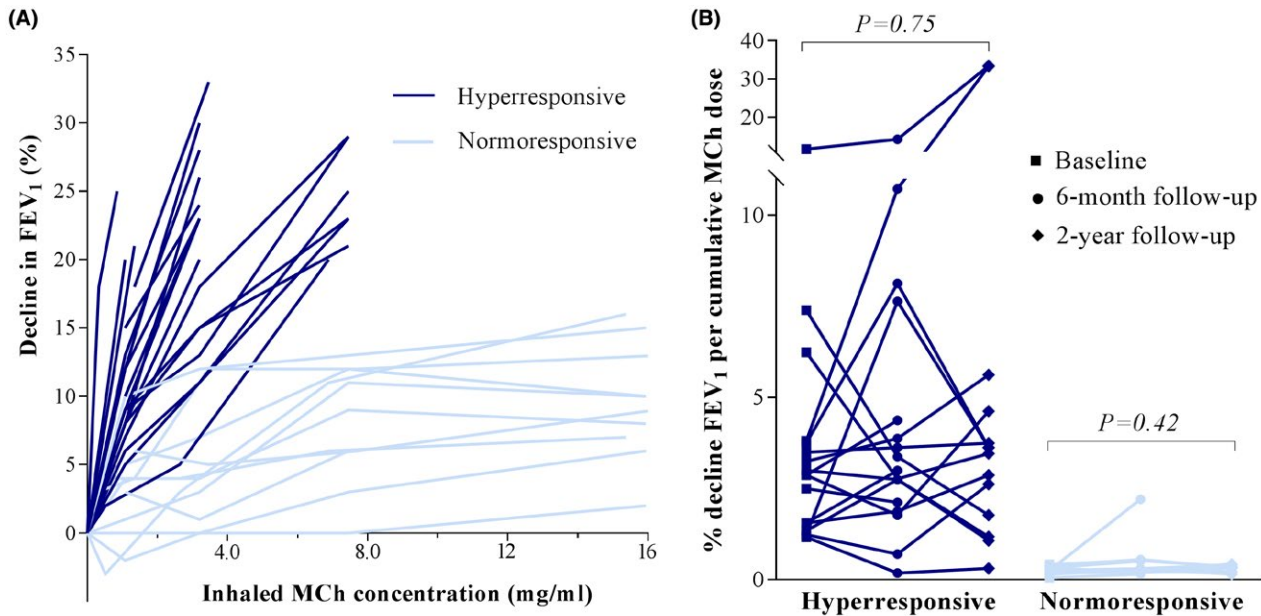
Following the Grown-Up Congenital Heart team decision, 41 adults were consecutively planned for percutaneous ASD closure in a 13-month period. Ten patients had incomplete baseline pulmonary assessment, therefore 31 ASD patients with complete preprocedural spirometry and bronchoprovocation testing formed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

Baseline characteristics are shown in Table 1. The mean age was  $49 \pm 15$  years, 65% were female, and 84% were repaired for right ventricular dilatation with a pulmonary-to-systemic-flow ratio of  $1.9 \pm 0.9$ . 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  $\beta_2$ -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  $FEV_1 < 70\%$ ), 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



**FIGURE 1** Airway hyperresponsiveness in adult secundum ASD patients. (A) Per patient baseline dose-response curve of percentage FEV<sub>1</sub> decline in response to the cumulative inhaled methacholine dose ( $n = 30$ ). Airway hyperresponsiveness was defined as  $\geq 20\%$  FEV<sub>1</sub> reduction from baseline following  $\leq 8.0$  mg/mL of methacholine. (B) Paired per patient methacholine dose-response slopes at baseline and at 6-month ( $n = 28$ ) and 2-year ( $n = 22$ ) postprocedural follow-ups. Abbreviations: FEV<sub>1</sub> = forced expiratory volume in 1 s; MCh = methacholine. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

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  $6.0 \pm 1.0$  months), as measured by spirometry and cardiac imaging, respectively.

At baseline spirometry, FEV<sub>1</sub> was  $3.0 \pm 0.9$  L/s (98%  $\pm$  15% predicted) with a FEV<sub>1</sub>/forced vital capacity index of  $0.8 \pm 0.07$  (99%  $\pm$  7.8% predicted). FEV<sub>1</sub> was associated with baseline symptoms of wheezing ( $r^2 = 0.22$ ;  $P = .008$ ). Postprocedural improvements in spirometry were seen most notably in FEV<sub>1</sub> (98%  $\pm$  15%-101%  $\pm$  14%;  $P = .04$ ), forced vital capacity (103%  $\pm$  16%-108%  $\pm$  15%;  $P < .001$ ) and inspiratory vital capacity (100%  $\pm$  16%-103%  $\pm$  15%;  $P = .03$ ). Low baseline spirometry values were associated with baseline exertional dyspnea ( $P < .01$ ) and its postprocedural resolution ( $P \leq .01$ ).

Following successful percutaneous closure, significant right atrial and ventricular reverse remodeling was observed. CMR-based right ventricular end-diastolic volume decreased from  $134 \pm 40$  mL/m<sup>2</sup>- $96 \pm 23$  mL/m<sup>2</sup> ( $P < .001$ ), 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 size ( $r^2 = 0.47$ ;  $P = .002$ ). 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<sub>1</sub> ( $r^2 = 0.24$ ;  $P = .03$ ), 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.<sup>11</sup> In the general adult population the prevalence of airway responsiveness is 10%-16% (max. 25%-35% as defined by a  $\leq 10\%$  FEV<sub>1</sub> decline),<sup>20,21</sup> and its risk factors include age, female gender, atopic constitution, respiratory tract infection, current smoking, and genetic predisposition.<sup>22</sup> The 63% (95%CI 45%-81%)

**TABLE 1** Baseline characteristics of the study cohort

	Total N = 31
<b>Demographics</b>	
Age, y	49 ± 15
Female	20 (65)
Body mass index, kg/m <sup>2</sup>	25 ± 4.3
Current smoker	4 (13)
Former smoker	10 (32)
Pack years	3.2 [0.7-23]
<b>Clinical history</b>	
Asthma	4 (13)
Atopic constitution <sup>a</sup>	11 (36)
Atrial arrhythmia	5 (16)
<b>Symptoms</b>	
Asthma-like symptoms <sup>b</sup>	10 (32)
NYHA class ≥II	22 (71)
<b>Respiratory medication</b>	
Current	4 (13)
Bronchodilators only	1
Corticosteroids added	3
Former	4 (13)
Bronchodilators only	3
Corticosteroids added	1
<b>ASD closure indication</b>	
Right ventricular dilatation	26 (84)
Paradoxical embolism	5 (16)
<b>ASD-related characteristics</b>	
Max. defect size, mm	20 ± 6.4
Pulmonary-to-systemic-flow ratio	1.9 ± 0.9
Systolic pulmonary artery pressure, mmHg	34 ± 7.8
Left atrial pressure, mm Hg <sup>c</sup>	10 ± 2.6

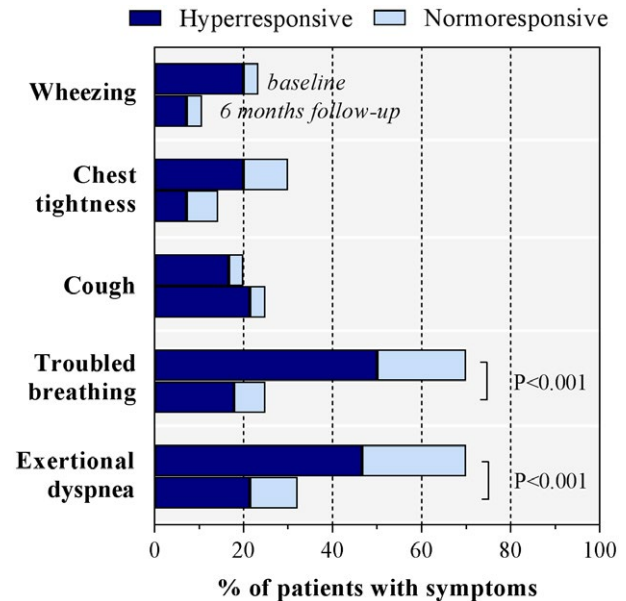
Data are presented as mean ±SD, frequencies (%), or median [25th-75th percentile]. Abbreviation: NYHA=New York Heart Association.

<sup>a</sup>≥1 of the following: allergic rhinitis, atopic eczema, or insect allergy.

<sup>b</sup>≥1 of the following: "wheezing without cold," "nocturnal dyspnea," "ever diagnosed with asthma."

<sup>c</sup>Direct periprocedural measurement during general anesthesia (n = 24).

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,<sup>23</sup> no evidence of such medical reaction was observed.



**FIGURE 2** Symptoms before and after ASD closure in hyperresponsive and normoresponsive patients. European Community Respiratory Health Survey-reported symptoms at baseline and 6-month follow-up (n = 29). Patients with asthma-like symptoms were more likely airway hyperresponsive. The extent of postprocedural symptom relief was similar in hyperresponsive and normoresponsive ASD patients. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Neither airway reactivity (dose-response slope) nor airway sensitivity (estimated by the methacholine concentration at which FEV<sub>1</sub> decreases ≥20%) improved at six-month or two-year follow-up after successful ASD closure. Our data are consistent with studies reporting unchanged airway hyperresponsiveness after treatment for mitral valve disease,<sup>24-26</sup> although some improvement in airway sensitivity was seen. A previous study in acute on chronic heart failure patients also showed no alteration in responsiveness despite adequate diuretic therapy and significant radiological improvement.<sup>27</sup> Thus, pathophysiology inherent to such cardiac diseases seems to maintain airway hyperresponsiveness despite adequate therapy, suggesting that flow-mediated pulmonary vascular distention in ASD patients may be a trigger rather than a cause of airway hyperresponsiveness.

## 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.<sup>11</sup> 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,



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

	n	Baseline	Follow-up	Δ	P value
<b>Spirometry</b>					
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 <sub>1</sub> /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
<b>Echocardiography</b>					
RA end-systolic area, cm <sup>2</sup> /m <sup>2</sup>	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	n/a	n/a
LA end-systolic volume, ml/m <sup>2</sup>	24	35 ± 14	35 ± 9.6	0.9 ± 13	0.74
<b>Cardiac magnetic resonance</b>					
RV end-diastolic volume, ml	21	249 ± 83	182 ± 62	-67 ± 51	<0.001
RV end-diastolic volume, ml/m <sup>2</sup>	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 <sup>2</sup>	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, mls	21	129 ± 40	147 ± 45	18 ± 14	<0.001
LV end-diastolic volume, ml/m <sup>2</sup>	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 <sup>2</sup>	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<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; RA, right atrial; RV, right ventricular; LA, left atrial; LV, left ventricular.

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<sub>1</sub> 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.<sup>28</sup> 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.<sup>29</sup>

#### 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,<sup>11</sup> ASD-associated asthma-like symptoms are not necessarily episodic over merely few hours to days, but can manifest with progressive

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 unrepaired ASD with the risk of complications from long-standing right ventricular volume overload,<sup>1</sup> as well as diagnostic delay of long-term postrepair pulmonary function impairment.<sup>30</sup>

#### 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.<sup>31</sup> 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

RJ de Winter: Academic Medical Center received an institutional unrestricted educational research grant from Abbott Vascular BV. All other authors: none declared.

## 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, BJB, 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.

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## REFERENCES

1. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation*. 2006;114(15):1645-1653.
2. Lockey RF, Ledford DK. *Pediatric Cardiac Conditions Coexisting and Differential Diagnosis. Asthma: Comorbidities, Coexisting Conditions, and Differential Diagnosis. Pediatric Cardiac Conditions Mimicking Asthma (differential diagnosis); Left-to-right Shunts*. New York: Oxford University Press; 2014:207-208.
3. Nassif M, Heuschen CB, Lu H, et al. Relationship between atrial septal defects and asthma-like dyspnoea: the impact of transcatheter closure. *Neth Heart J*. 2016;24(11):640-646.
4. Eichacker PQ, Seideman MJ, Rothstein MS, et al. Methacholine bronchial reactivity testing in patients with chronic congestive heart failure. *Chest*. 1988;93(2):336-338.
5. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med*. 1989;320(20):1317-1322.
6. Rolla G, Bucca C, Caria E, et al. Bronchial responsiveness in patients with mitral valve disease. *Eur Respir J*. 1990;3(2):127-131.
7. Rolla G, Bucca C, Brussino L, et al. Bronchial responsiveness, oscillations of peak flow rate and symptoms in patients with mitral stenosis. *Eur Respir J*. 1992;5(2):213-218.
8. Brunnee T, Graf K, Kastens B, et al. Bronchial hyperreactivity in patients with moderate pulmonary circulation overload. *Chest*. 1993;103(5):1477-1481.
9. Evans SA, Kinnear WJ, Watson L, et al. Breathlessness and exercise capacity in heart failure: the role of bronchial obstruction and responsiveness. *Int J Cardiol*. 1996;57(3):233-240.
10. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. *Eur Respir J Suppl*. 1993;16:53-83.
11. Asthma. Gf. Global Strategy for Asthma Management and Prevention. 2016.
12. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31(23):2915-2957.
13. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
14. Crapo RO, Casaburi R, Coates AL et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American thoracic society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161(1):309-329.

15. Cockcroft DW, Killian DN, Mellon JJ, et al. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy*. 1977;7(3):235-243.
16. O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis*. 1987;136(6):1412-1417.
17. Survey ECRH. ECRHS II Main questionnaire.
18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.
19. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30(6):1527-1533.
20. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2004;1(2):77-87.
21. Rijcken B, Schouten JP, Weiss ST, et al. The relationship between airway responsiveness to histamine and pulmonary function level in a random population sample. *Am Rev Respir Dis*. 1988;137(4):826-832.
22. Antosova M. Bronchial hyperreactivity: pathogenesis and treatment options. *Open J Mol Integr Physiol*. 2011;1:43-51.
23. Fahrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol*. 2003;24(2):113-124.
24. Rolla G, Bucca C, Brussino L, et al. Reduction of bronchial responsiveness to methacholine after mitral valve replacement. *Respiration*. 1991;58(2):81-84.
25. Nishimura Y, Maeda H, Yokoyama M, et al. Bronchial hyperreactivity in patients with mitral valve disease. *Chest*. 1990;98(5):1085-1090.
26. Gulec S, Ertas F, Tutar E, et al. Bronchial hyperreactivity in patients with mitral stenosis before and after successful percutaneous mitral balloon valvulotomy. *Chest*. 1999;116(6):1582-1586.
27. Pison C, Malo JL, Rouleau JL, et al. Bronchial hyperresponsiveness to inhaled methacholine in subjects with chronic left heart failure at a time of exacerbation and after increasing diuretic therapy. *Chest*. 1989;96(2):230-235.
28. Dollery CT, Dyson NA, Sinclair JD. Regional variations in uptake of radioactive CO in the normal lung. *J Appl Physiol*. 1960;15:411-417.
29. Plantier L, Marchand-Adam S, Boyer L, et al. Methacholine-Induced variations in airway volume and the slope of the alveolar capnogram are distinctly associated with airflow limitation and airway closure. *PLoS One*. 2015;10(11):e0143550.
30. van Riel AC, Blok IM, Zwinderman AH, et al. Lifetime risk of pulmonary hypertension for all patients after shunt closure. *J Am Coll Cardiol*. 2015;66(9):1084-1086.
31. Albu G, Babik B, Kesmarky K, et al. Changes in airway and respiratory tissue mechanics after cardiac surgery. *Ann Thorac Surg*. 2010;89(4):1218-1226.

### SUPPORTING INFORMATION

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

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