Restrictive lung function in pediatric patients with structural congenital heart disease

Stephen M. M. Hawkins, MD,[a] Amy L. Taylor, PhD,[b] Stefan H. Sillau, MS,[c] Max B. Mitchell, MD,[d] and Christopher M. Rausch, MD[a,b]

Objectives: We sought to describe the prevalence of restrictive lung function in structural congenital heart disease and to determine the effect of cardiothoracic surgical intervention.

Methods: The data from a retrospective review of the spirometry findings from pediatric patients with structural congenital heart disease were compared with the data from 220 matched controls. Restrictive lung function was defined as a forced vital capacity of <80%, with a preserved ratio of the forced expiratory volume in the first second to forced vital capacity of >80%.

Results: Of the children with congenital heart disease, 20% met the criteria for restrictive lung function compared with 13.2% of the controls ($P = .03$). The prevalence in those with congenital heart disease without a surgical history was similar to that of the controls (odds ratio, 0.62; 95% confidence interval, 0.34-1.13). Restrictive lung function was more likely if surgical intervention had occurred within the first year of life (odds ratio, 1.96; 95% confidence interval, 1.08-3.55; $P < .0001$). Those who had undergone both sternotomy and thoracotomy had a greater prevalence of restrictive lung function than those who had undergone sternotomy or thoracotomy alone (54.2% vs 25.6% and 23.5%, respectively; $P < .0001$). The prevalence of restrictive lung function increased significantly with each additional surgical intervention (odds ratio, 1.61; 95% confidence interval, 1.29-2.01; $P < .0001$).

Conclusions: Restrictive lung function was more prevalent in those with congenital heart disease after cardiothoracic surgical intervention than in the controls or patients without surgical intervention. The prevalence was also greater with surgical intervention at an earlier age. The risk was equivalent when sternotomy alone was compared with thoracotomy alone but was significantly greater when both sternotomy and thoracotomy were performed. The risk increased with each additional surgery performed. (J Thorac Cardiovasc Surg 2014;148:207-11)

CHD

Restrictive lung disease is associated with intrinsic lung diseases that lead to inflammation and scarring of the lung parenchyma and with extrinsic lung diseases that lead to lung restriction and impaired respiration. A restrictive pattern has been shown to be associated with certain forms of structural congenital heart disease (CHD) in numerous small studies.[1-14] To our knowledge, pulmonary function testing in a large pediatric population with CHD has never been studied. In our clinical practice, it has been observed that patients with structural CHD, especially those who have undergone surgical intervention, are more likely to have a pattern of restrictive lung function (RLF) on spirometry consistent with restrictive lung disease. In those who do develop RLF, it has been unclear whether this has been related to the specific heart lesion, cardiothoracic surgical intervention, the type of surgical approach (sternotomy vs thoracotomy), or some other unrecognized etiology.

Since 2002, our center has routinely obtained spirometry testing for all patients before they undergo cardiopulmonary exercise testing (CPET). This has resulted in a unique database of pulmonary function testing for hundreds of pediatric patients with CHD who were able to undergo testing. We sought to describe the prevalence of RLF in those with CHD, with the hypothesis that RLF would be more prevalent in patients with structural CHD than in controls and that those who underwent surgical intervention for CHD would have a greater prevalence of RLF than those who did not undergo surgery. Furthermore, we evaluated whether the age at first surgical intervention, the number of surgical interventions, and the anatomic

From the Department of Pediatrics,[a] University of Colorado, Aurora, Colo; Division of Cardiology,[b] Children's Hospital Colorado, Aurora, Colo; Department of Biostatistics and Informatics,[c] University of Colorado, Aurora, Colo; and Department of Surgery,[d] University of Colorado, Aurora, Colo.

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Address for reprints: Christopher M. Rausch, MD, Department of Pediatrics, University of Colorado and Division of Cardiology, Children's Hospital Colorado, 13123 E 16th Ave, B100, Aurora, CO 80043 (E-mail: Christopher.Rausch@childrenscolorado.org).

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Abbreviations and Acronyms
CHD = congenital heart disease
CI = confidence interval
CPET = cardiopulmonary exercise test
FVC = forced vital capacity
FEV_1 = forced expiratory volume in 1 s
RLF = restrictive lung function

location of the CHD had an effect on the development of RLF.

METHODS

The Colorado Multiple Institutional Review Board approved the present single-center retrospective chart review (COMIRB protocol no. 11-0019), which was performed at our large, academic, pediatric tertiary care center. The study population included patients with structural CHD who had undergone CPET from December 2002 through January 2011. Patients with repair of anatomic defects by nonsurgical methods, such as intravascular intervention, were not included. Patients with nonstructural CHD, such as arrhythmias, were not considered. The control population was age- and gender-matched to the patients with CHD and included patients who had undergone CPET for any reason (eg, exertional dyspnea, chest pain) but had been found to have structurally normal hearts.

Baseline spirometry and CPET were performed using a metabolic cart and cycle ergometer (Care Fusion, Yorba Linda, Calif). Spirometry was performed according to the American Thoracic Society guidelines.[15] All CPET included measurement of metabolic gases, blood pressure, oxygen saturation, and electrocardiography according to the standard guidelines.[16] Spirometry provided the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and the FEV_1/FVC ratio. The FVC and FEV_1 are reported as the percentage predicted according to age, gender, and height. Normal spirometry findings were defined as FVC, FEV_1, and FEV_1/FVC ratio >80% of the predicted value according to age, gender, and height. RLF was defined as a reduced FVC of <80% predicted, with a preserved FEV_1/FVC ratio > 80%.[17]

A total of 1163 cases of pediatric patients with structural CHD who had undergone spirometry and CPET were available. The test results were excluded if poor patient technique during spirometry had been documented or incomplete data had been documented during the test. This resulted in 677 pediatric patients with CHD with 876 complete test results available for analysis. Many patients with CHD underwent several sessions of CPET and spirometry during the study period as part of their overall clinical management. Only the most recent test result was evaluated, unless otherwise specified.

The CHD population was subdivided into groups according to the anatomic location of the pathologic entity for the purpose of comparing lesions of dissimilar pathophysiology. The groups included left-sided lesions, right-sided lesions, septal defects, and other primary lesions. The surgical approach (ie, sternotomy or thoracotomy, or both), patient age at the first surgical intervention, and the total number of surgical interventions were recorded.

Statistical analyses were performed using Statistical Analysis Systems (SAS Institute, Cary, NC). When longitudinal data needed to be compressed into a single measurement, either the first or last chronological observation on a subject was used, within a set of criteria that depended on the specific question. The analyses were conducted using the available case data. Categorical variables were compared using 2-way frequency tables and chi-square and Fisher's exact association tests. For binary outcomes, logistic regression analysis was sometimes used. Proportions and odds ratios were computed, as needed. For continuous variables, standard descriptive statistics, such as the mean and standard deviation are presented. Because of the longitudinal nature of the data, mixed models regression methods were used for inferential statistics.

RESULTS

Data from the CHD and control populations included in the present study are listed in Table 1. Overall, the patients with CHD had a greater prevalence of RLF than did the controls (19.7% vs 13.2%), with a definite association between CHD and RLF ($P = .03$). When the patients with CHD were further divided into nonsurgical and surgical groups, a significantly greater prevalence of RLF was found in the postoperative CHD group (25.5%) than in the control group (13.2%) and nonsurgical CHD group (8.6%; $P < .0001$; Table 2). The odds ratio of RLF in the surgical CHD population compared with the nonsurgical CHD population and the control population was 3.64 (95% confidence interval [CI], 2.19-6.03) and 2.25 (95% CI, 1.44-3.51), respectively. The risk of RLF in the nonsurgical CHD group was not different from that of the controls (odds ratio, 0.62; 95% CI, 0.34-1.13).

The nonsurgical CHD group (233 patients who performed 244 tests) was stratified according to the anatomic location of the primary defect to assess whether RLF was associated with lesion type. The groups included left-sided lesions (n = 98), right-sided lesions (n = 41), septal defects (n = 32), and other lesions (n = 72). The analysis was limited to those patients who had undergone no surgical intervention before CPET to avoid surgical intervention as a confounding factor. Although RLF was somewhat more prevalent in left-sided (11.2%) than in right-sided lesions (7.3%), RLF was not significantly associated with lesion type in the nonsurgical population ($P = .96$).

Included in the nonsurgical CHD group were 11 patients who had previously undergone transcatheter intervention for their CHD. These included 5 patients who had undergone transcatheter device closure of an atrial septal defect, 4 patients with aortic coarctation stenting, and 2 patients with aortic coarctation balloon angioplasty. Of these 11 patients, 1 with atrial septal defect closure and 1 with balloon angioplasty demonstrated RLF.

Of the 444 postoperative CHD patients, 390 had clear documentation of the age at which they had undergone their first surgical intervention. The subanalysis demonstrated that the prevalence of RLF was greater when surgical intervention had occurred before 1 year of age (30.2%) compared with intervention after 1 year of age (18.1%). However, surgical intervention before 1 month of age did not greatly increase the prevalence (32.6%; $P = .016$; Table 3).

A comparison according to the cardiothoracic surgical intervention in the CHD population was performed to determine the effect of the first surgical approach (ie, sternotomy

TABLE 1. Demographics of control and CHD populations

Variable	Controls	CHD group
Tests (n)	220	876
Male gender (%)	61.1	67.4
Age (y)	13.9 ± 3.3	15.5 ± 7.7
BMI (kg/m^2)	21.1 ± 4.4	21.1 ± 6.6
Height (cm)	161.4 ± 15.8	157.9 ± 18.2
Weight (kg)	56.5 ± 18.8	54.3 ± 21.2

CHD, Congenital heart disease; *BMI*, body mass index.

or thoracotomy, or both) on the prevalence of RLF (Table 4). Of the 444 postoperative patients, 277 had undergone sternotomy alone, 81 thoracotomy alone, and 59 both approaches. One patient was excluded because of an unclear surgical status, and 27 had a known surgical history without clear documentation regarding which surgical approach had been used. The surgical approach was significantly associated with the development of RLF ($P < .0001$), with the greatest prevalence of RLF seen in patients who had undergone both sternotomy and thoracotomy (54.2%). No difference was found in the prevalence of RLF in the postoperative CHD patients when sternotomy alone was compared with thoracotomy alone ($P = .69$).

The influence that the number of surgical interventions an individual patient had undergone was also evaluated. Figure 1 demonstrates the effect the number of surgical interventions performed had on the prevalence of RLF, with more surgical interventions associated with greater rates of RLF. Despite the low numbers of patients with 3 or 4 surgical interventions, logistic regression analysis demonstrated that the odds of a patient with CHD having RLF increased by an estimated 61% (95% CI, 28.9%-101.2%).

DISCUSSION

Our study results have shown that pediatric patients with structural CHD were more likely to develop RLF but only in those who had undergone surgical intervention by sternotomy and/or thoracotomy. Surgical intervention at a younger age was associated with a greater risk, just as was the combination of both sternotomy and thoracotomy at initial surgical intervention. Furthermore, those who had undergone multiple surgical interventions were even more likely to develop RLF, with each procedure conferring additional risk. The anatomic site of CHD was not associated with RLF in the nonsurgical CHD population.

Ours was not the first study to demonstrate a restrictive pattern in a population after surgical intervention for CHD. Postoperative pediatric patients with atrial septal defects have been shown to have reduced expiratory reserve volume and FVC and decreases in lung compliance with sternotomy compared with percutaneous closure.[3,10,11,14] The lung volume and lung compliance have been shown to be decreased in a number of studies of both pediatric and adult patients with ventricular septal defects,[12] transposition,[7] tetralogy of Fallot,[1,2,6,9,18] and post-Fontan[5,19] surgical repair.

Several studies have found a lesion-specific prevalence of RLF without surgical intervention, including in adults with congenital pulmonary stenosis[4] and aortic stenosis.[13] In adults with aortic stenosis, a restrictive pattern was only seen in those with an elevated pulmonary capillary wedge pressure. Our data did not support a lesion-specific etiology for the development of RLF in the nonsurgical CHD pediatric population; however, we grouped the lesions into very basic anatomic subgroups. Thus, it is possible that certain lesions such as mitral stenosis behave physiologically differently than coarctation of the aorta, for example, and would have a different effect on the development of RLF. Few studies have demonstrated changes in lung compliance, although Schofield and colleagues[8] showed an inverse relationship among FVC, FEV_1, and FEV_1/FVC ratio as the mean pulmonary artery pressure increased in patients with atrial septal defects, suggesting that cardiopulmonary hemodynamics do play a role in lung function. The most thorough review of pulmonary function data from patients with CHD was performed by Pianosi and colleagues,[20] who concluded that changes in pulmonary function were lesion specific and that surgical intervention played a minimal role in the development of restriction, unless a complication leading to diaphragm paresis occurred. These findings contrasted with our results, which demonstrated a clear

TABLE 2. Prevalence of RLF in control and CHD populations*

Variable	Controls	Nonsurgical CHD	Surgical CHD
Total patients (n)	220	233	444
Patients with RLF (n)	29 (13.2)	20 (8.6)	113 (25.5)

Data in parentheses are percentages. *RLF*, Restrictive Lung function; *CHD*, congenital heart disease. *$P < .0001$; chi-square association test.

TABLE 3. Prevalence of RLF stratified by age at first surgical intervention*

Age at first surgical intervention	Patients (n)	RLF (%)	95% CI
<1 mo	46	32.6	24.9-40.4
1 mo to 1 y	35	30.2	21.8-38.5
>1 y	24	18.1	11.5-24.6

RLF, Restrictive lung function; *CI*, confidence interval. *$P = .016$; chi-square association test.

TABLE 4. Prevalence of RLF stratified by method of first surgical intervention*

First surgical intervention	Patients (n)	RLF (%)	95% CI
Sternotomy	277	25.6	20.5-30.8
Thoracotomy	81	23.5	14.2-32.7
Sternotomy with thoracotomy	59	54.2	41.5-66.9
Unknown	27	—	—

RLF, Restrictive lung function; *CI*, confidence interval. *$P < .0001$; chi-square association test.

CHD

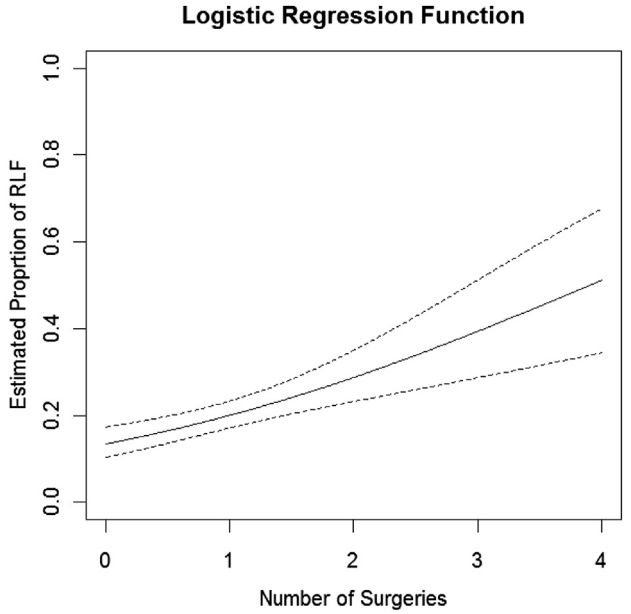

FIGURE 1. Logistic regression of the prevalence of restrictive lung function (*RLF*) in the congenital heart disease population according to the number of surgical interventions.

association between surgical intervention and the occurrence of RLF.

Evidence is conflicting regarding the effect of the point of the first repair on cardiopulmonary physiology. Samanek and colleagues[7] demonstrated that an earlier age at transposition of the great arteries correction was associated with a more pronounced reduction in lung compliance, and others[6] have reported that pediatric patients with tetralogy of Fallot corrected at a later age (2 to 12 years) had decreased lung compliance and vital capacity compared with those who had undergone correction at an earlier age (<2 years). Our data would support the former, with surgical intervention at a young age clearly associated with a greater prevalence of RLF. Those with the earliest interventions, before 1 month of age, did not seem to have risk additional to that of those who had undergone intervention by 1 year of age.

It would be expected that those with more severe forms of structural CHD would be recognized and surgically repaired at an earlier age and would undergo more complex, multistage procedures. The severity of CHD might to some extent be associated with the development of RLF. This theory was supported by our findings that RLF prevalence was greater with surgical intervention at an earlier age, with the combination of sternotomy and thoracotomy at the initial intervention, and after multiple interventions. That no difference was found when comparing sternotomy and thoracotomy alone, or when comparing surgical intervention before 1 month of age with intervention before 1 year of age, speaks against CHD severity as the sole cause. The most severe forms of CHD would be expected to require intervention before 1 month of age, although this is not absolute. However, in a heterogeneous population such as ours, with many forms of CHD, comparing the severity of 1 form to another would be difficult or impractical owing to the considerable physiologic differences.

Fredrisken and colleagues[5] suggested diaphragmatic palsy, a restrictive thoracic cage, and/or respiratory muscle weakness as possible etiologies of postoperative RLF development, although they showed no effect of the interval since repair and had only 12 months of follow-up data. It has been speculated that thoracotomy would be less likely to lead to diaphragmatic palsy and therefore would not lead to the same risk of RLF that sternotomy carries. However, repeated interventions of either type might convey similar risk. A restrictive thoracic cage is a highly suspected etiology, because this could be caused by a number of factors, including scarring of the chest wall, release of inflammatory mediators that might lead to scarring of the pleural surface, and a decreased range of motion of the costovertebral joints, either from inflammation or disuse in the postoperative period. Cardiopulmonary bypass has been associated with the release of proinflammatory mediators and with increased pulmonary vascular resistance, in particular.[21] Much like in our study, it remains unclear whether it is causality or simply association. To our knowledge, ours is the only study that compared the prevalence of RLF after thoracotomy to sternotomy and demonstrated no evidence of difference when stratified by these surgical approaches. Given the significant differences in manipulation of the pleural surfaces and scarring that occur during sternotomy and thoracotomy, the common aspects of surgical intervention must be considered as possible factors leading to RLF, such as operation time, length of mechanical ventilation, need for pain management, prolonged periods of hypoventilation, length of hospital stay, and length of recovery.

Our study was limited by its retrospective nature. Ideally, we would prospectively monitor pulmonary function testing in patients with particular forms of CHD. The patients with RLF did not undergo lung volume assessment, which would be necessary to confirm restrictive lung disease instead of a pattern of RLF. Also, there is the question of the clinical relevance of RLF without knowledge of patient symptoms. All patients involved presented for CPET because of symptoms; however, the severity and limitation of those symptoms were not evaluated. Also, the lack of a significant number of patients with spirometry obtained both before and after surgical intervention also limits the application of our findings. The inability to perform spirometry before early surgical repair of the more severe forms of CHD leaves the question of how CHD severity affects the

development of RLF unanswered. Obtaining infant pulmonary function testing would be ideal but is likely impractical in this population, for whom surgical intervention is performed urgently and/or very early in life.

Finally, the control population might not represent a ''healthy'' population, because those referred for CPET might have had symptoms because of some other etiology, albeit not of cardiac origin. Although these controls might not provide a truly representative indication of RLF prevalence, we have postulated that those referred for CPET for any reason would be more likely to have pathophysiologic features, including restrictive lung disease, and would make our findings even more pertinent if compared with a normal population.

We have concluded that surgical intervention is associated with the development of RLF in pediatric patients with structural CHD, regardless of the underlying CHD lesion. The prevalence of RLF increased if the initial intervention involved both sternotomy and thoracotomy, was performed at a younger age, and was followed by additional surgical interventions. The CHD severity might contribute to these findings. Pulmonary function testing for all those who have undergone any form of thoracic surgical intervention should be routinely performed. More research is needed in this field, in particular, of possible mechanisms for postoperative thoracic restriction and the comparison of pre- and postoperative pulmonary function testing in the pediatric CHD population. This might become more feasible as infant pulmonary function testing evolves.

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