Abnormal Lung Function in Adults With Congenital Heart Disease: Prevalence, Relation to Cardiac Anatomy, and Association With Survival

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Background—Restrictive lung defects are associated with higher mortality in patients with acquired chronic heart failure. We investigated the prevalence of abnormal lung function, its relation to severity of underlying cardiac defect, its surgical history, and its impact on outcome across the spectrum of adult congenital heart disease.

Methods and Results—A total of 1188 patients with adult congenital heart disease (age, 33.1±13.1 years) undergoing lung function testing between 2000 and 2009 were included. Patients were classified according to the severity of lung dysfunction based on predicted values of forced vital capacity. Lung function was normal in 53% of patients with adult congenital heart disease, mildly impaired in 17%, and moderately to severely impaired in the remainder (30%). Moderate to severe impairment of lung function related to complexity of underlying cardiac defect, enlarged cardiothoracic ratio, previous thoracotomy/ies, body mass index, scoliosis, and diaphragm palsy. Over a median follow-up period of 6.7 years, 106 patients died. Moderate to severe impairment of lung function was an independent predictor of survival in this cohort. Patients with reduced forced vital capacity of at least moderate severity had a 1.6-fold increased risk of death compared with patients with normal lung function (P=0.04).

Conclusions—A reduced forced vital capacity is prevalent in patients with adult congenital heart disease; its severity relates to the complexity of the underlying heart defect, surgical history, and scoliosis. Moderate to severe impairment of lung function is an independent predictor of mortality in contemporary patients with adult congenital heart disease. (Circulation. 2013;127:882-890.)

Key Words: adult heart diseases ■ lung ■ scoliosis ■ surgery ■ survival

Physical activity requires coupling of the cardiovascular and respiratory systems for gas exchange, blood oxygenation, and oxygen transport to the working muscle. If either system is impaired, aerobic metabolism may also be impaired; patients typically experience shortness of breath and exercise limitation. In fact, shortness of breath is the most common symptom in patients with chronic heart failure12 and in adult patients with congenital heart disease (ACHD).3

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It has been reported that up to 60% of patients with chronic heart failure have ventilation and diffusion abnormalities with reduction of lung volumes on lung function testing.5,5 These abnormalities are due to respiratory muscle weakness, lung fluid imbalance, secondary pulmonary hypertension, and/or chronic interstitial edema, resulting in pulmonary membrane thickening and fibrosis. In the setting of chronic heart failure, a restrictive lung defect is also an independent predictor of mortality.6 Furthermore, even in healthy subjects, a reduction in lung capacity has been related to an increased risk of adverse cardiovascular events, including death, compared with subjects with normal lung function.7,8 Despite the obvious similarities between chronic heart failure and ACHD,9 no study has systematically investigated lung function in a large contemporary cohort of ACHD patients.10,11

Major therapeutic advances in recent decades have transformed the outcome of patients with congenital heart disease.12 However, patients are still afflicted by late morbidity and mortality.13 Improving risk stratification is thus providing...
prognostic information to patients and identifying high-risk subjects who could potentially benefit from special medical and/or surgical intervention. We hypothesized that abnormal lung function is prevalent among ACHD patients and that severity of reduction in forced vital capacity carries prognostic information in this growing patient cohort.

Methods

Study Population
A total of 1188 ACHD patients (all ≥14 years of age) undergoing lung function testing as part of routine clinical follow-up by conventional spirometry at our center between 2000 and 2009 were included. Freedom from death was ascertained in 2012. All patients gave informed consent; our local ethics committee approved the study.

Lung Function Measurement
Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were assessed according to the recommendations of the American Thoracic Society.¹⁴ Predicted values for lung flows were calculated with established reference equations,¹⁵ which adjust absolute values for age, sex, and height. Patients were classified into 3 groups based on predicted FVC values: group A, patients with normal lung function (predicted FVC >70%); group B, patients with mildly impaired lung function (predicted FVC, 70% to 60%); and group C, patients with moderately to severely impaired lung function (FVC <60%) based on published recommendations.¹⁵ Patients with a pure obstructive lung defect (FEV₁/FVC <0.7; n=59 patients) were excluded from analysis. However, patients with mixed lung dysfunction but predominantly reduced FVC (FEV₁/FVC ratio of 0.7–0.8 and predicted FVC <70%) were included.

Data Collection, Diagnoses, and Definition of Scoliosis, Pulmonary Hypertension, and Pulmonary Hypoperfusion
This was a retrospective study. Data on demographics, anthropometric measurements, New York Heart Association functional class, smoking status/history, and resting oxygen saturation at the time of the pulmonary function test were collected in all patients. Information on cardiac anatomy, type of previous cardiac surgery (palliative or reparative), number of previous sternotomies and thoracotomies, age at surgical repair, and current medications was obtained from surgical and medical records. Cardiotoracic ratio was measured by posteroanterior chest radiograph performed within 6 months from the lung function test; the presence of moderate to severe scoliosis (defined as a Cobb angle >30°) was also assessed from these films.¹⁶

Patients were classified into diagnostic groups according to the underlying cardiac lesion,¹⁷ whereas complexity was assessed according to the recent American College of Cardiology/American Heart Association guidelines.¹ Systemic ventricular magnetic resonance imaging within 6 months from lung function tests and was classified as normal or mildly, moderately, or severely impaired. Pulmonary hypertension was defined as evidence of systolic pulmonary artery pressure ≥40 mm Hg measured by Doppler echocardiography and/or a mean pulmonary artery pressure >25 mm Hg measured invasively. Echocardiographic data were obtained from the reports when available. If not available, a single echocardiographer (F.B.) reviewed the echocardiograms. Patients with lung hypoperfusion at birth were defined as those with tetrology of Fallot, pulmonary stenosis, pulmonary atresia, or a functionally univentricular heart with limited pulmonary blood flow requiring a systemic to pulmonary shunt.

Follow-up
Patients underwent routine clinical follow-up every 6 to 12 months after lung function testing (most of them annually) at our center. Follow-up was complete for all patients. Survival status and time of death were obtained from the National Health Service computer system, linked to a national database at the Office of National Statistics. All-cause mortality was defined as the primary end point to avoid unnecessary bias.

Statistical Analysis
All values are presented as mean±SD, percentage of the population, or median (interquartile range). Comparisons between groups were made with the Student t test or Mann-Whitney U test for continuous variables and by the χ² test for categorical variables as appropriate. Logistic regression analysis was used to identify univariate predictors of moderately to severely impaired lung function; backward stepwise logistic regression was used to identify independent predictors of moderately to severely impaired lung function. Variables with a value of P<0.10 at the univariate-model level were entered into a multivariate analysis. Kaplan-Meier curves with log-rank tests were plotted to compare outcome between patients with normal to mildly impaired lung function and patients with moderately to severely impaired lung function. Predictors of all-cause of mortality were assessed using Cox proportional-hazards regression analysis. Variables with values of P<0.10 in univariate analysis were candidates for a backwards stepwise (inclusion criterion, P≤0.05; exclusion criterion, P≥0.1) multivariate analysis, and those with values of P<0.05 were retained in the model. The following parameters were used for the multivariate model: age, cyanosis, New York Heart Association functional class III/IV, cardiomegaly, repaired versus un repaired/palliated, pulmonary vasodilators, moderately to severely impaired systemic ventricular function, previous thoracotomy, previous sternotomy, peak Vo₂/ V̇O₂ slope, complex anatomy, and age at repair. After the multivariate model was created, lung function and age were forced into the model as a covariate, and the P value was assessed for significance. For all multivariate models used, missing data were not imputed; therefore, missing data in any covariates led to the exclusion of the observation/subject from the respective multivariate analysis. A value of P<0.05 was considered significant. Statistical analysis was performed with SPSS version 17 (SPSS Inc, Chicago, IL) and R version 2.10.1 (http://cran.r-project.org/) statistical software.

Results

Patient Characteristics
Baseline and clinical characteristics, surgical history, and lung function results are shown in Table 1. Underlying diagnoses were the following: atrial septal defects in 44 patients (3.7%), ventricular septal defect in 43 patients (3.6%), aortic coarctation in 41 patients (3.5%), arterial switch for transposition of the great arteries in 21 patients (1.8%), atrioventricular septal defect in 45 patients (3.8%), congenitally correct transposition of the great arteries in 41 patients (3.5%), Ebstein anomaly in 63 patients (5.3%), Eisenmenger physiology in 60 patients (5.1%), Fontan circulation in 88 patients (7.4%), Mustard operation for transposition of the great arteries in 84 patients (7.1%), tetralogy of Fallot in 364 patients (30.6%), un repaired complex disease in 89 patients (7.5%), valvar disease in 174 patients (14.6%), and other diagnoses in 31 patients (2.6%). Cardiac lesions of high complexity were present in 45.7% of the population. Surgical repair/palliation was performed in 75.7% of patients with a median age at repair of 5.1 years (interquartile range, 2–12 years).

Prevalence of Abnormal Lung Function in the ACHD Population
The distribution of predicted lung flow values is shown in Figure 1. Overall, 52.8% of patients presented with a normal lung function (group A), 17.4% had a mildly impaired FVC (group B), and 29.7% had a moderately to severely reduced
Table 1. Baseline Characteristics, Surgical History, and Spirometry in Relation to Lung Function

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All patients (n=1188)</th>
<th>Normal (n=628)</th>
<th>Mildly Impaired (n=207)</th>
<th>Moderately to Severely Impaired (n=353)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>100</td>
<td>52.9</td>
<td>17.4</td>
<td>29.7</td>
<td>0.19/0.28</td>
</tr>
<tr>
<td>Age, y</td>
<td>33.2±13.1 (1188)</td>
<td>33.7±12.8</td>
<td>32.7±14.1</td>
<td>32.7±13.2</td>
<td>0.65/0.73</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>53.3 (1188)</td>
<td>55.6</td>
<td>55.4</td>
<td>54.7</td>
<td>0.09/0.12</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.0±10.6 (1188)</td>
<td>171.4±10.6</td>
<td>170.0±10.1</td>
<td>167.4±10.5</td>
<td>0.94/&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.8±4.7 (1188)</td>
<td>24.2±4.7</td>
<td>24.0±4.5</td>
<td>22.9±4.6</td>
<td>0.53/&lt;0.001</td>
</tr>
<tr>
<td>Smoker or ex-smoker, n (%)</td>
<td>10.9 (1188)</td>
<td>12.2</td>
<td>11.3</td>
<td>9.0</td>
<td>0.89/0.12</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>96.8±4.8 (1188)</td>
<td>97.5±3.8</td>
<td>97.1±3.9</td>
<td>95.6±5.9</td>
<td>0.20/&lt;0.001</td>
</tr>
<tr>
<td>Cyanosis, %</td>
<td>9.6 (1147)</td>
<td>6.1</td>
<td>8.9</td>
<td>16.3</td>
<td>0.24/&lt;0.001</td>
</tr>
<tr>
<td>NYHA III-IV, %</td>
<td>9.2 (1069)</td>
<td>5.5</td>
<td>9.0</td>
<td>15.8</td>
<td>0.13/&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe systemic ventricular dysfunction, %</td>
<td>8.2 (1148)</td>
<td>5.4</td>
<td>8.0</td>
<td>13.4</td>
<td>0.24/&lt;0.001</td>
</tr>
<tr>
<td>Cardiothoracic ratio, %</td>
<td>54.0±7.7 (935)</td>
<td>51.5±6.8</td>
<td>54.7±7.0</td>
<td>57.9±7.9</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe scoliosis, %</td>
<td>16.4 (935)</td>
<td>11.9</td>
<td>17.8</td>
<td>22.4</td>
<td>0.06/&lt;0.001</td>
</tr>
<tr>
<td>Diaphragm palsy, %</td>
<td>1.1 (1109)</td>
<td>0.2</td>
<td>1.6</td>
<td>3.3</td>
<td>0.99/&lt;0.001</td>
</tr>
<tr>
<td>Hiatal hernia, %</td>
<td>0.3 (1136)</td>
<td>0.5</td>
<td>0.5</td>
<td>0</td>
<td>0.99/0.19</td>
</tr>
<tr>
<td>Pulmonary hypertension, %</td>
<td>5.2 (1188)</td>
<td>4.0</td>
<td>4.8</td>
<td>7.6</td>
<td>0.60/0.001</td>
</tr>
<tr>
<td>Lung hypoperfusion at birth, %</td>
<td>45.9 (1170)</td>
<td>41.0</td>
<td>50.0</td>
<td>52.5</td>
<td>0.02/&lt;0.001</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>13.6 (1055)</td>
<td>10.3</td>
<td>14.4</td>
<td>19.4</td>
<td>0.21/&lt;0.001</td>
</tr>
<tr>
<td>ACEi/ARB, %</td>
<td>18.6 (1051)</td>
<td>17.4</td>
<td>17.5</td>
<td>21.3</td>
<td>0.91/0.19</td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>9 (1053)</td>
<td>6.2</td>
<td>12.8</td>
<td>11.9</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>9.8 (1052)</td>
<td>8.5</td>
<td>8.2</td>
<td>13.1</td>
<td>0.82/0.05</td>
</tr>
<tr>
<td>Inhalers, %</td>
<td>7.1 (1165)</td>
<td>7.8</td>
<td>5.0</td>
<td>7.2</td>
<td>0.18/0.73</td>
</tr>
<tr>
<td>Pulmonary vasodilators, %</td>
<td>5.1 (1188)</td>
<td>3.2</td>
<td>4.6</td>
<td>6.8</td>
<td>0.37/&lt;0.001</td>
</tr>
<tr>
<td>Surgical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaired, %</td>
<td>73.1</td>
<td>70.4</td>
<td>79.6</td>
<td>73.6</td>
<td>0.02/0.35</td>
</tr>
<tr>
<td>Palliated/unrepaired, %</td>
<td>26.9 (1041)</td>
<td>29.6</td>
<td>20.4</td>
<td>26.4</td>
<td>0.02/0.35</td>
</tr>
<tr>
<td>Previous thoracotomy, %</td>
<td>24.8 (1151)</td>
<td>17.4</td>
<td>27.2</td>
<td>37.5</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Previous sternotomy, %</td>
<td>70.1 (1161)</td>
<td>67.3</td>
<td>77.5</td>
<td>71.0</td>
<td>&lt;0.001/0.43</td>
</tr>
<tr>
<td>Multiple thoracotomies (≥2), %</td>
<td>5.7</td>
<td>2.0</td>
<td>7.31</td>
<td>11.3</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Multiple sternotomies (≥2), %</td>
<td>19.9</td>
<td>15.8</td>
<td>25.4</td>
<td>25.6</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Age at repair, y</td>
<td>5.2 (2.0–11.8)</td>
<td>4.6 (1.7–11.0)</td>
<td>5.9 (2.1–13.7)</td>
<td>6 (2.2–11.0)</td>
<td>0.08/0.21</td>
</tr>
<tr>
<td>Age at shunt, y</td>
<td>1.3 (0.3–5.0)</td>
<td>2 (0.3–5.0)</td>
<td>1.4 (0.3–4.2)</td>
<td>1 (0.3–5.4)</td>
<td>0.94/0.86</td>
</tr>
<tr>
<td>Time since repair/palliation, y</td>
<td>22.5 (15.7–30.1)</td>
<td>23.9 (15.6–30.6)</td>
<td>20.8 (14.6–27.4)</td>
<td>21.4 (14.8–30.1)</td>
<td>&lt;0.001/0.07</td>
</tr>
<tr>
<td>Previous surgery for scoliosis, %</td>
<td>1.3 (1137)</td>
<td>0.2</td>
<td>0.3</td>
<td>3.7</td>
<td>0.41/&lt;0.001</td>
</tr>
<tr>
<td>Lung function test</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FEV1, L</td>
<td>2.7±0.9 (1188)</td>
<td>3.1±0.7</td>
<td>2.5±0.6</td>
<td>1.8±0.6</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>FEV1, % of predicted</td>
<td>72.7±18.0 (1188)</td>
<td>85.6±11.2</td>
<td>68.6±6.9</td>
<td>52.1±10.3</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.0±1.1 (1188)</td>
<td>3.5±0.8</td>
<td>2.8±0.6</td>
<td>2.0±0.6</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>69.7±17.5 (1188)</td>
<td>83.1±10.4</td>
<td>64.8±2.8</td>
<td>48.8±8.8</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>0.89±0.08</td>
<td>0.88±0.07</td>
<td>0.90±0.08</td>
<td>0.91±0.08</td>
<td>&lt;0.01/&lt;0.01</td>
</tr>
<tr>
<td>Cardiopulmonary exercise test</td>
<td>22.8±8.9 (1170)</td>
<td>25.1±9.1</td>
<td>21.6±8.0</td>
<td>19.4±7.8</td>
<td>0.11/0.04</td>
</tr>
<tr>
<td>Peak V̇O2, mL·kg⁻¹·min⁻¹</td>
<td>62.3±27.8 (1170)</td>
<td>74.9±30.4</td>
<td>63.4±21.0</td>
<td>56.0±21.4</td>
<td>0.33/0.17</td>
</tr>
<tr>
<td>% Predicted peak V̇O2</td>
<td>36.8±14.9 (1170)</td>
<td>35.1±13.8</td>
<td>36.6±14.1</td>
<td>40.1±16.5</td>
<td>0.44/0.01</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; and NYHA, New York Heart Association functional class. Data are expressed as mean±SD when appropriate. Age at repair, age at shunt operation, and time from repair are expressed as median (interquartile range). Number of patients available on each variable is given in parentheses.

*Left P values compare patients with normal and mild restrictive lung defect; right P values compare normal patients and patients with moderate to severe restrictive lung defect.
FVC (group C; Figure 1). There was no significant difference in age, sex, and smoking history between the 3 groups. Patients from group C were more likely to have lower body mass index (22.9 versus 24.2 kg/m²) and lower oxygen saturation at rest compared with patients from group A (95.6% versus 97.5%; \(P<0.01\), as shown in Table 1). Moreover, group C patients were more likely to be cyanotic (proportion of patients with an oxygen saturation <90% at rest in room air, 16.3% versus 6.1%; \(P<0.01\)) and in New York Heart Association functional class III or IV (15.8% versus 5.5%; \(P<0.01\)) and to have moderate to severe systemic ventricular dysfunction (13.4% versus 5.4%; \(P<0.01\)). These differences were not present between groups A and B. Patients with reduced FVC had higher cardiothoracic ratio on chest x-ray compared with patients with normal lung function (\(P<0.01\)). Moreover, moderate to severe scoliosis was present in 16.4% of the entire study population. It was more prevalent in patients with moderately to severely impaired lung function (22.4% versus 11.9%; \(P<0.01\) versus patients with normal lung function).

The majority of patients (73.1%) had undergone surgical repair, whereas 26.9% of patients had either a palliative procedure (such as a Blalock-Taussig shunt or pulmonary artery banding) or no cardiac operation. There was no difference in the prevalence of moderately to severely impaired lung function among repaired patients (32.1%) compared with the remainder (26.8%; \(P=0.9\)).

The prevalence of moderately to severely impaired lung function was related to the complexity of the underlying cardiac lesion (Figure 2). Patients with unrepaired complex, or primarily cyanotic cardiac lesions, Eisenmenger physiology, Fontan circulation and tetralogy of Fallot presented with the lowest predicted FVC values (58.9±17.6%, 63.8±17.4%, 66.9±17.3%, and 67.1±17.6%; \(P<0.01\), respectively, compared with the remaining patients [73.7±17.6%]) and the highest prevalence of moderately to severely impaired lung function (56.2%, 50.0%, 34.1%, and 33.5%, respectively; \(P<0.01\) versus the remaining patients [20.9%]). Predicted FVC values were lower among cyanotic patients compared with noncyanotic patients (60.2±19.6% versus 70.9±15.6%; \(P<0.01\)). The prevalence of moderately to severely impaired lung function was 50.4% in cyanotic compared with 26.7% in noncyanotic ACHD patients (\(P<0.01\)).

### Predictors of Moderately to Severely Impaired Lung Function

Univariate and multivariate predictors of impaired lung function are shown in Table 2. By multivariate logistic regression analysis, diaphragmatic palsy (odds ratio [OR], 4.64; 95% confidence interval [CI], 1.24–17.40), enlarged cardiothoracic ratio (OR, 3.31; 95% CI, 2.27–4.83), moderate to severe scoliosis (OR, 3.18; 95% CI, 1.56–6.48), previous thoracotomy (OR, 1.89; 95% CI, 1.37–2.61), complex congenital heart disease (OR, 1.74; 95% CI, 1.28–2.36), and body mass index (OR, 0.92; 95% CI, 0.88–0.95) emerged as independent predictors of moderately to severely impaired lung function in our population. Cyanosis, moderate to severe systemic ventricle dysfunction, history of multiple sternotomies (≥2), and lung hypoperfusion at birth were not retained in this multivariate statistical model.

Predictors of moderately to severely impaired lung function were analyzed separately in repaired ACHD patients and unrepaired/palliated ACHD patients. Variables reaching significance on univariate logistic regression analysis for each group were entered into multiple regression models. History of previous thoracotomy, enlarged cardiothoracic ratio, moderate to severe scoliosis, diaphragmatic palsy, and complex congenital...
heart disease were independent predictors of moderately to severely impaired lung function in surgically repaired ACHD patients, whereas in unrepaired/palliated ACHD patients, complex congenital heart disease, moderate to severe scoliosis, enlarged cardiothoracic ratio, and previous thoracotomy were found to predict moderately to severely impaired lung function (Table 3). Cyanosis was not related to impaired lung function in either group.

Association Between Abnormal Lung Function and Survival
Median follow-up after lung function testing was 6.7 years. One hundred six patients died during this period (mortality rate, 1.3% per patient-year). Most deaths were observed in the complex unrepaired group (18 patients, 17.0%), the Fontan group (17 patients, 16.0%), the tetralogy of Fallot group (16 patients, 15.1%), the Eisenmenger physiology group (13 patients, 12.3%), and the congenitally corrected transposition of the great arteries group (8 patients, 7.5%). A moderately to severely impaired lung function was an independent predictor of survival in ACHD patients. Cox proportional hazards regression analysis showed that ACHD patients with moderately to severely impaired lung function had a 1.6-fold higher risk of death during follow-up compared with patients with a normal lung function (adjusted hazard ratio, 1.63; 95% CI, 1.01–2.63; \( P = 0.04 \); Table 4) after adjustment for other significant covariates. Figure 3 illustrates differences in survival between patients with normal-mildly impaired lung function and those with moderately-severely impaired lung function. No difference in survival was found between patients with normal and mildly impaired lung function (\( P = 0.13 \)).

Discussion
Our study shows that abnormal lung function is prevalent across the spectrum of ACHD and that its severity relates to worse outcome. Mildly impaired lung function was present...
in 17.4% of ACHD patients, whereas moderately to severely impaired lung function was seen in 29.7% of them. Patients with moderately to severely impaired lung function had a 1.6-fold higher risk of all-cause mortality in the medium term.

Predictors of Moderately to Severely Impaired Lung Function in ACHD Patients

Ventilatory function in the general population is largely related to age, body weight, and nicotine abuse. These factors were not found to predict lung function in our ACHD population, probably because of the relative young age and normal body weight in most patients included. Instead, the presence of significantly reduced FVC was found to relate to complexity of the underlying cardiac defect. The prevalence of moderately to severely impaired lung function varied from ≈15% to 20% in ACHD patients with simple cardiac defects to 30% to 50% in patients with cardiac defects of high complexity. Furthermore, diaphragmatic palsy and cardiomegaly, as assessed by cardiothoracic ratio on chest x-ray, were found to be the strongest predictors of moderately to severely impaired lung function in our population. Finally, the presence of abnormal lung function was related to surgical history and body mass index. Impairment of lung function likely reflects the complexity of the patient’s past cardiac operations and cardiac morbidities.

Potential Role of Cardiac Surgery

The presence of diaphragmatic palsy and history of previous thoracotomy in patients who had undergone reparative surgery were strong predictors of moderately to severely impaired lung function. Similarly, a previous thoracotomy and the presence of moderate to severe scoliosis were identified as factors associated with moderately to severely impaired lung function in unrepaired/palliated ACHD patients. Pulmonary function is often mildly and transiently impaired after sternotomy; residual ventilatory dysfunction has been described as late as 10 years after cardiac surgery. It has been suggested that cardiopulmonary bypass with temporal interruption or reduction of pulmonary blood flow may trigger an inflammatory response in the pulmonary vasculature, inducing damage to the alveolar membrane and blood air-gas exchange abnormalities. Evidence suggests that in patients undergoing cardiopulmonary bypass surgery at a young age, such a postoperative inflammatory response is exaggerated, with extensive tissue infiltration by white blood cells and increased cytokine expression. Furthermore, because many cardiac operations in our patients were performed in childhood or even in infancy, there is potential for inadequate thoracic cavity growth and maturation as a consequence of surgery. Diaphragmatic nerve palsy has also been reported after surgery for congenital heart disease (as high as 10%), and it may be
responsible for hemidiaphragm elevation and lung ventilatory mismatch.\textsuperscript{9,10} In our population, diaphragmatic nerve palsy was an independent predictor of moderately to severely impaired lung function, as shown in Table 3.

**Scoliosis**

Unrepaired/palliated ACHD patients with a Cobb angle >30° had a 5-fold increased risk of having ventilatory dysfunction with moderately to severely impaired lung function. Scoliosis in ACHD patients might be part of the underlying condition and/or a consequence of previous surgery. In our study, 16.2% of patients had moderate to severe scoliosis; the majority of these patients had moderately to severely impaired lung function. Possible mechanisms linking scoliosis and reduced lung volumes include abnormal development of the thorax; increased elastic force of the respiratory system, which opposes the muscle forces during maximum inspiration and expiration; and the effects of the deformity on the development of inspiratory or expiratory muscles.\textsuperscript{31-33} The reduction in lung volumes appears to be related to the degree of spinal curvature.\textsuperscript{34} Necropsy evidence suggests a reduced alveolar number with compensatory increased size of remnant alveoli in lung areas close to the spinal curvature.\textsuperscript{35}

**Cardiomegaly and Systemic Ventricular Dysfunction**

Cardiomegaly as assessed by enlarged cardiothoracic ratio emerged as a strong predictor of moderately to severely impaired lung function across our ACHD population. Patients with congestive heart failure, who often have cardiomegaly and left ventricular dysfunction, have been reported to have impaired ventilatory function and air-gas exchange, resulting primarily from respiratory muscle weakness, lung fluid imbalance, secondary pulmonary hypertension, and chronic interstitial edema with pulmonary membrane fibrosis.\textsuperscript{36–38} Patients with ACHD, like congestive heart failure patients, commonly have chronic ventricular volume and/or pressure overload, presenting with enlargement of the cardiac chambers, which is reflected by increased cardiothoracic ratios on chest x-ray. Systemic ventricular dysfunction, assessed qualitatively in our study, did not relate to abnormal lung function. We speculate that in our population, cardiomegaly on chest x-ray is more likely to relate to right heart enlargement and right ventricular failure. Examples to support this include Ebstein anomaly and Eisenmenger physiology, both characterized by progressive dilatation of the right atrium/ventricle with resultant reduced pulmonary venous return and right heart failure, and tetralogy of Fallot with severe pulmonary regurgitation, typically presenting with right heart dilatation.\textsuperscript{39}

**Relation Between Moderately to Severely Impaired Lung Function and Survival**

Our study demonstrates that moderately to severely impaired lung function (predicted FVC<60%) was an independent predictor of death among ACHD patients. Even after adjustment for variables such as worse New York Heart Association functional class and moderate to severe systemic ventricular dysfunction, moderately to severely impaired lung function remained an independent predictor of death. In contrast, patients with mild impairment of lung function had survival profiles similar to those patients with normal lung function. Severity of lung dysfunction reflects the complexity of the underlying cardiac defect and surgical history in ACHD and may relate to neurohormonal activation, which is known to be associated with an adverse outcome.\textsuperscript{40} Lower FVC values in healthy subjects\textsuperscript{7,8} and in the elderly\textsuperscript{41,42} are related to higher blood levels of inflammatory/oxidative stress markers and to higher risk of subsequent death. Patients with ACHD exhibit many features of the chronic heart failure syndrome, including inflammatory and neurohormonal activation.\textsuperscript{9} This could explain in part the association between lung function and survival reported.

**Study Limitations**

The study population was heterogeneous; we sought to assess the prevalence, predictors, and impact on survival of abnormal lung function across the spectrum of ACHD patients attending a tertiary care center. The diagnostic mix, however, is representative of current practice. Data on static lung volumes measured by plethysmography were not available for the scope of this study. However, forced expiratory and inspiratory lung flows in ACHD patients were recorded by trained physicians following the American Thoracic Society guidelines.\textsuperscript{43} Obstructive lung disease is rare in ACHD patients, and we elected to exclude patients with pure obstructive lung defects from further analysis. Even after their inclusion, however, patients with moderate to severe restrictive lung defect had a higher risk of death in follow-up compared with the remainder population (data not shown). Future, larger studies using plethysmography data may shed additional light on the mechanism/s of reduced FVC in ACHD patients, validate the prognostic value of the impaired lung function test reported here, and assess the potential impact of earlier repair of congenital heart disease in this population. Diaphragmatic palsy is likely to be incomplete because specific measures were not taken to look for this problem. Because of a lack of complete data, we were unable to study the predictive value of respiratory disease after adjusting for previously published predictors such as serum sodium or brain natriuretic peptide. Future, larger studies are required to address this question.

**Clinical Implications**

Given the high prevalence of lung defects in the ACHD population, close collaboration between cardiologists and pulmonologists is desirable. Collaboration with lung specialists should be considered, especially for patients with moderately to severely impaired lung function and patients with significant lung function abnormalities undergoing cardiac surgery, aiming to optimize treatment to reduce the risk of postoperative pulmonary complications. ACHD patients have an increased mortality risk; identifying high-risk patients who could benefit from specific medical and/or surgical intervention is essential in making individual treatment decisions and planning resource allocation. This study demonstrates the prognostic value of parameters of lung function testing in this population. Reduced FVC was found to be common in the ACHD population and its severity was related to outcome. In addition, moderately to severely impaired lung function was identified as an
independent predictor of death even after accounting for functional status, systemic ventricular dysfunction, and peak oxygen uptake. In contrast, restrictive lung defects rarely are so severe that ACHD patients die of respiratory failure. Rather, abnormal lung function was more likely to represent a proxy of more severe underlying heart disease but also to convey information on ventricular function, severity of heart failure, and inadequate pulmonary perfusion. Furthermore, the link between respiratory impairment and scoliosis suggests a possible cause-and-effect relation. Although speculative, we suggest that early diagnosis of scoliosis and appropriate treatment are warranted. Furthermore, contemporary patients presenting with congenital heart disease in infancy are likely to receive primary repair rather than palliation, and this may have a beneficial effect on scoliosis. We submit that lung function assessed by conventional spirometry—a simple and widely available test to measure lung flows—should be used as an adjunct to assess prognosis in this challenging patient population and that, when more than mild impairment of lung function is present, appropriate action should be taken. Further studies are required to identify diagnosis specific cutoff values for lung function parameters and to validate the prognostic value of lung function testing across the spectrum of ACHD. Until these data are available, clinicians should refrain from estimating mortality risk in a particular patient on the basis of lung function data alone.

Conclusions

Reduced FVC is prevalent in ACHD patients; its severity relates to the complexity of the underlying congenital defect and cardiac surgical history. Moderate to severe impairment of lung function is an independent predictor of mortality in ACHD patients, with a 1.6-fold increased risk of death in the medium term among this population. Pulmonary function testing looking for reduced FVC should be considered part of the noninvasive periodic assessment of ACHD patients.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Reduced forced vital capacity is prevalent among adult patients with congenital heart disease. Its severity relates to complexity of the underlying congenital heart defect and to past cardiac surgical history. Despite the heterogeneity of adult congenital heart disease, moderate to severe impairment of lung function was an independent predictor of mortality in our study, with a 1.6-fold increased risk of death in the medium term. We submit that lung function assessed by conventional spirometry, a simple and widely available test to measure lung flows, should be used as an adjunct to assess prognosis in this challenging patient population and that, when more than mild impairment of lung function is present, appropriate action should be taken. Whether a proactive treatment of lung disease and/or concomitant skeletal abnormalities alter prognosis remains speculative, but physicians need to be aware of respiratory and/or orthopedic complications and to be proactive in relevant aspects of care.
Abnormal Lung Function in Adults With Congenital Heart Disease: Prevalence, Relation to Cardiac Anatomy, and Association With Survival
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