Restricted Pulmonary Function in Cystic Fibrosis

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Some patients with cystic fibrosis have reduced pulmonary volumes, indicating a restrictive pattern of pulmonary disease. We identified ten patients with pulmonary functional evidence of restriction among 158 patients with cystic fibrosis followed at the University of California San Diego Medical Center in 1984 and 1985. We characterized the radiographic, pulmonary functional, and clinical characteristics of these restricted patients compared to matched nonrestricted patients. Pulmonary volumes were measured by three different techniques: plethysmography; nitrogen washout; and radiography. Except for plethysmographic pulmonary volumes, there were no significant differences between the matched restricted and nonrestricted patients. Radiographic pulmonary volume tended to overestimate gas volume measured by the other techniques. Differences among these techniques (thought to represent air-space filling) correlated best with radiographic evidence of air trapping and bronchial markings and not with parenchymal lesions. Serial pulmonary function tests demonstrated changes in pulmonary volume in several patients and a trend toward improvement in pulmonary volume in the restricted patients over time. We conclude that restricted pulmonary function does not necessarily indicate more severe disease in patients with cystic fibrosis and may be reversible in some. The mechanism of restriction may be related more to radiographic evidence of airway disease than to parenchymal abnormalities. (Chest 1985; 94:575-79)

Pulmonary function in patients with cystic fibrosis is characterized primarily by airflow obstruction and hyperinflation of static pulmonary volumes. Elevation in the ratio of residual volume to total lung capacity (RV/TLC) correlates with severity of disease. The TLC calculated from body plethysmographic measurements of thoracic gas volume is usually normal or elevated. The TLC by gas dilution techniques (helium dilution of nitrogen washout) may be lower than by plethysmography because of noncommunicating gas volume.

Nevertheless, some patients with cystic fibrosis have restricted pulmonary function with reduction in TLC even when measured by body plethysmography. This has been reported occasionally and is thought to represent a severe stage of disease.

We conducted this study (1) to better characterize the clinical, radiographic, and pulmonary functional features of restricted patients compared to a matched control group of nonrestricted patients with cystic fibrosis; and (2) to elevate possible mechanisms of restriction.

**Materials and Methods**

**Patients**

Twenty patients were selected retrospectively for this study by matched-pair design from 158 patients with cystic fibrosis who received an annual examination during 1984 and 1985 at the University of California San Diego Medical Center. Results of pulmonary function tests of all patients were reviewed to identify restriction by the following criteria: (1) vital capacity (VC) less than or equal to 75 percent of predicted; and (2) TLC by body plethysmography (a) less than or equal to 80 percent of predicted or (b) less than or equal to 85 percent of predicted with airflow obstruction (ratio of the forced expiratory volume in one second [FEV1]/FVC less than 80 percent of predicted; mean forced expiratory flow over the middle half of the FVC [FEF25-75%] less than 65 percent of predicted). The latter criterion was used to define restriction because patients with cystic fibrosis and airflow obstruction typically have measurements of TLC by plethysmography above predicted values (mean values, 109 to 125 percent of predicted in three published series). Thus, even though 85 percent of predicted would be within 95 percent confidence limits for a normal population, it would be considered abnormally low for a patient with cystic fibrosis who has flow obstruction. Patients with evidence of other causes of restrictive pulmonary disease (eg, previous pulmonary resection, pleural effusion, or concurrent pneumonia) were excluded.

Ten patients met the previously specified criteria for restriction ("restricted patients"): six with TLC less than or equal to 80 percent of predicted and four with TLC less than or equal to 85 percent of predicted and airflow obstruction. For each of the ten restricted patients, a control "nonrestricted patient" was selected from the remaining 148 patients matched as closely as possible with respect to sex, age, height, and weight, respectively.

For each of the 20 patients, anteroposterior and lateral chest roentgenograms were selected as close as possible to the date of the pulmonary function tests. In addition, for those patients who returned for the subsequent annual examination in 1985 and 1986, standardized clinical evaluations were performed, and results of repeat pulmonary function tests were obtained.

**Pulmonary Function Tests**

Spirometry was performed on a spirometer (Ohio 842) according to recommendations of the American Thoracic Society's Snowbird Conference before and after bronchodilator administration. Absolute pulmonary volumes were measured by three techniques: (1) body plethysmography using a constant-volume plethysmograph (Collins); (2) open-circuit nitrogen washout; and (3) radiographic

*From the Departments of Medicine, Pediatrics, and Radiology, University of California, San Diego. Supported in part by National Institutes of Health grant RR00827 from the Division of Research Resources for the Clinical Research Center. Manuscript received December 2; revision accepted February 12. Reprint requests: Dr. Ries, UCSD Medical Center, 225 Dickinson Street, San Diego 92103.
TLC by planimetry,\textsuperscript{16} plethysmographic airway resistance (Raw),\textsuperscript{11} and maximal inspiratory pressure\textsuperscript{14} were also measured. Reference values used were those of Knudson and co-workers\textsuperscript{15} for spirometry and those of Polgar and Promadhat\textsuperscript{14} (age less than or equal to 16) or Naimark and co-workers\textsuperscript{15} (age over 16) for pulmonary volumes.

**Chest Radiographic Grading**

Posteroanterior and lateral chest roentgenograms were graded on two separate occasions by an experienced chest radiologist (P.J.F.) using a scoring system modified from that described by Brasfield and co-workers.\textsuperscript{16} A grade was assigned for each of the following specific characteristics: air trapping (0 to 4); bronchial wall markings (0 to 4); small nodular or cystic lesions (0 to 4); large air-space lesions (0 to 5); and general severity (0 to 4) (0 = normal; 4 = most severe).\textsuperscript{16,18} Grades for each of the five categories were summed and subtracted from 25 to obtain a total score of 4 (most severe) to 25 (normal). On the first reading, each patient's films were examined separately. On the second reading, the set of 20 roentgenograms was sorted without knowledge of the initial scores according to severity for each of three criteria: bronchial markings; nodular lesions; and general severity.

**Clinical Scoring**

Patients who returned for the 1985-86 annual examination were evaluated and graded on the categories of physical examination, activity and nutrition on a scale of 1 to 25 (1 = most severe disease; 25 = normal).\textsuperscript{19} This scale is modified from the one originally published by Shwachman and Kuleczycz.\textsuperscript{20} The scores for each category were summed to give an overall clinical score of 3 (most severe) to 75 (normal).

**Statistical Methods**

Results for restricted and nonrestricted patients were compared by paired t-test for general characteristics of patients and pulmonary function tests (continuous variables) and Wilcoxon's signed-rank test for clinical and radiographic grades (discrete variables). Correlations involving clinical and radiographic grades were performed by Spearman's rank correlation. Analysis of changes in pulmonary function over one year of follow-up was performed by two-way analysis of variance of group (restricted and nonrestricted) vs time (1984-85 and 1985-86 test results).

**RESULTS**

**Pulmonary Function Tests**

General characteristics and results of selected pulmonary function tests of the restricted and matched nonrestricted patients are summarized in Table 1. There were no significant differences between groups for age, height, and weight, the variables used for matching. A significant difference was observed only
Table 2—Radiographic-Gas Volume Differences in Restricted and Matched Nonrestricted Patients with Cystic Fibrosis*

<table>
<thead>
<tr>
<th>Data</th>
<th>Restricted</th>
<th>Nonrestricted</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC(R-P), L</td>
<td>0.62±0.98</td>
<td>−0.07±0.49</td>
<td>0.11</td>
</tr>
<tr>
<td>TLC(R-N), L</td>
<td>0.82±1.05</td>
<td>0.15±0.96</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Results are expressed as mean±SD.
†Comparison of groups by paired t-test.

for plethysmographic TLC (TLC[P]), which was used in the selection of restricted patients. Plethysmographic RV and FRC were lower in the restricted group but not significantly different from the nonrestricted patients. The TLC by nitrogen washout (TLC[N]) was measured in only six restricted and eight nonrestricted patients. In five pairs of matched subjects, TLC(N) was not significantly lower in the restricted group. Radiographic TLC (TLC[R]) was also not significantly different between the groups. In addition, there were no differences in VC or expiratory flow rates (reduced in both groups), Raw (elevated in both groups), maximal inspiratory pressure (normal), or change in FEV₁ after bronchodilator.

Chest Radiographic Grades

There were no significant differences between restricted and nonrestricted patients for any of the radiographic criteria scored (Table 1). Reproducibility of the radiographic grading was assessed by correlating the radiologist’s two readings for the three criteria graded on the second reading. Correlations between the first and second radiographic grades were 0.90 for bronchial markings, 0.84 for nodular cystic lesions, and 0.91 for general severity.

Clinical Scores

Mean clinical scores were higher in all categories for the restricted patients (representing less severe disease), but the differences were statistically significant only for the activity scores (Table 1). Correlation for all patients between total clinical score and total radiographic grade was 0.46 (p<0.05).

Radiographic-Gas Volume Differences

Even though the restricted patients were selected on the basis of decreased TLC(P), TLC(R) in these same patients was not significantly different between groups. We postulated that measurements of TLC(R) would overestimate the TLC(P) or TLC(N) in patients with a significant amount of abnormal air-space filling. Therefore, we subtracted TLC(P) or TLC(N) from TLC(R) to estimate the amount that air-space filling might be contributing to the restrictive process. The differences between radiographic and gas volumes (TLC[R-P] and TLC[R-N]) were higher in the restricted patients, as expected, but the difference did not reach statistical significance because of the high variance within groups (Table 2).

The differences between radiographic and gas volumes were also correlated with specific radiographic findings. These results, summarized in Table 3, demonstrated highly significant correlations between TLC(R-P) and TLC(R-N) with the scores for air trapping and bronchial markings in the restricted patients only, but not with radiographic evidence of parenchymal lesions (nodular or air-space lesions).

Serial Studies

Seventeen of the 20 patients (including seven matched pairs) had pulmonary function tests repeated during their 1985-86 annual examination, one year after the initial study. One restricted patient died prior to repeat assessment. Two nonrestricted patients did not have repeat tests (one due to an exacerbation of disease and one was lost to follow-up).

Results of repeat pulmonary function tests in seven matched pairs showed a trend toward improvement in the restricted patients but not in the control subjects. The TLC increased 0.52 L (4.75 to 5.22 L) in the restricted and decreased 0.09 L (5.88 to 5.79 L) in the nonrestricted patients (p = 0.08 for time, p = 0.12 for group, and p = 0.02 for interactive effects). The VC increased an average of 0.45 L (2.63 to 3.08 L) in the restricted and decreased 0.19 L (2.62 to 2.43 L) in the nonrestricted patients (not significant for time and group effects; p = 0.04 for interactive effect). Indices of expiratory flow demonstrated a trend of improvement in the restricted patients and a decline in control subjects, but these changes were not statistically significant.

There were marked changes in pulmonary volume

Table 3—Correlations between Initial Radiographic Grades and Radiographic-Gas Volume Differences*

<table>
<thead>
<tr>
<th>Data</th>
<th>TLC (R-P)</th>
<th></th>
<th>TLC (R-N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restricted (n = 10)</td>
<td>Nonrestricted (n = 10)</td>
<td>Restricted (n = 6)</td>
<td>Nonrestricted (n = 8)</td>
</tr>
<tr>
<td>Air trapping</td>
<td>0.78†</td>
<td>0.47</td>
<td>0.93†</td>
<td>0.36</td>
</tr>
<tr>
<td>Bronchial markings</td>
<td>0.72‡</td>
<td>0.20</td>
<td>0.92†</td>
<td>0.44</td>
</tr>
<tr>
<td>Nodular cystic lesions</td>
<td>−0.28</td>
<td>−0.19</td>
<td>0.13</td>
<td>0.23</td>
</tr>
<tr>
<td>Air-space lesions</td>
<td>−0.27</td>
<td>−0.19</td>
<td>−0.61</td>
<td>−0.22</td>
</tr>
<tr>
<td>Overall severity</td>
<td>0.43</td>
<td>0.20</td>
<td>0.49</td>
<td>0.25</td>
</tr>
<tr>
<td>Total score</td>
<td>−0.45</td>
<td>−0.25</td>
<td>−0.62</td>
<td>−0.32</td>
</tr>
</tbody>
</table>

*Spearmann rank correlations; †p<0.01; ‡p<0.05.
over one year in individual patients. Three of the nine restricted patients with repeat tests were no longer restricted one year later (increases in TLC[P] of 0.80, 0.83, and 1.09 L). None of the nonrestricted patients became restricted one year later.

Because of the improvement in pulmonary volumes for restricted patients one year later (1985-86), we also examined pulmonary volumes of 16 patients with available pulmonary function tests in 1983-84, one year earlier. Two of eight restricted patients were not restricted in 1983-84 (one of whom was also not restricted two years later in 1985-86), and two of eight nonrestricted patients were restricted one year earlier in 1983-84. These changes in serial pulmonary volume were not associated with any consistent changes in blind ratings (PJ.F.) of serial chest roentgenograms over the same period.

**Discussion**

The results of this study indicate that restricted pulmonary function may be more common than previously reported in patients with cystic fibrosis. Among 158 patients, we identified ten with restriction (6 percent prevalence). Otherwise, restricted patients were remarkably similar to the matched control group of nonrestricted patients with respect to clinical and chest radiographic ratings. The restrictive defect did not appear to represent a more severe stage of disease, as has been proposed by others.2

Results of pulmonary function tests revealed significant differences between groups only for TLC(P), which was used in selecting restricted patients. The TLC(R) and TLC(N) were not significantly different between groups; however, nitrogen washout volume was performed in only five matched pairs. There were no differences in measurements of expiratory flow, Raw, maximal inspiratory pressure, or VC (reduced in both groups).

The discrepancy between groups for pulmonary volumes measured by the three different techniques highlights the important differences among these methods. Although the three methods produce equivalent results in normal subjects, each method measures a different theoretic volume which may differ with disease.10,23,24 Gas dilution techniques (nitrogen washout or helium dilution) measure communicating gas volume, the volume of gas which mixes with the reference gas. Body plethysmography measures compressible gas volume, the total volume of intrathoracic gas. This includes noncommunicating air space not measured by gas dilution or washout methods. Radiographic techniques estimate intrathoracic volume from the area bounded by the thoracic cage, diaphragm, and mediastinum.

In obstructive disease with noncommunicating air space, gas dilution measurements may underestimate both radiographic and plethysmographic volumes.23,24 In restrictive processes in which gas is replaced by fluid or abnormal tissue (eg, edema, fibrosis, pneumonitis), the radiographic thoracic volume may be larger than the gas dilution or plethysmographic volume.61,62 In restrictive conditions which do not affect the pulmonary parenchyma directly (eg, respiratory muscle weakness), the three techniques should be comparable.

In this study, we proposed that restriction would be due to scarring and infiltration of the pulmonary parenchyma and, therefore, expected to find differences between the radiographic and gas volumes in the restricted patients. Although these differences did exist and, on average, were in the expected direction, there was considerable variability within groups, and the differences did not reach statistical significance.

We also expected to find that the radiographic-gas volume differences in the restricted patients would correlate with radiographic grades of pulmonary parenchymal lesions (air-space or nodular cystic lesions) as a reflection of severity. Surprisingly, the radiographic-gas volume differences were highly correlated only with radiographic ratings of air trapping (hyperinflation) and bronchial markings. These findings suggest that the mechanism of restriction in these patients with cystic fibrosis is not related directly to the extent of air-space-filling lesions and raises the interesting possibility that the restriction may be related more to airway disease. The fact that maximum inspiratory pressure was not different between groups indicates that inspiratory muscle weakness was also not a cause of restriction.

The primary pulmonary lesion is cystic fibrosis is obstruction of the small airways by inflammation and mucous plugging.25 Restrictive changes have been observed occasionally in patients with other airway diseases, including asthma26,27 and bronchiolitis obliterans28,29 and may be related to diffuse inflammatory obstruction of small airways. A similar mechanism in cystic fibrosis might explain the significant correlations observed between radiographic-gas volume differences and bronchial marking grades on the chest roentgenograms reflecting generalized airway inflammation.

The results of serial pulmonary function tests from the previous (1983-84) and subsequent (1985-56) years also raises interesting questions about the mechanism of restriction and the implication of restriction regarding severity of disease. Three of nine restricted patients were no longer restricted on testing one year later, and two of eight were not restricted one year earlier. It is unlikely that the reduced plethysmographic pulmonary volume was due to measurement error, since nine of the ten restricted patients were restricted in at least two of the three years examined. In the nonres-
restricted patients, none of eight was restricted one year later, while two of eight were restricted one year earlier. Chest radiographic ratings did not change consistently over this period. Group data over one year of follow-up demonstrated a trend toward increase in expiratory flow and pulmonary volume in the restricted patients but not in the controls. These findings suggest that the restrictive process may be reversible in some patients and, therefore, does not necessarily represent an irreversible stage of disease.

In summary, we conclude that restricted pulmonary function may be observed in some patients with cystic fibrosis. It does not appear to indicate more severe disease than a nonrestricted pattern and may be reversible in some patients. In addition, restriction detected by plethysmographic measurements of pulmonary volume may not be evident on radiographic measurements of thoracic cage volume. In some restricted patients, there is a large difference between radiographic measurements and plethysmographic or nitrogen-washout measurements of gas volume. In this study, these radiographic-gas volume differences were highly correlated in the restricted patients with radiographic evidence of air trapping (hyperinflation) and bronchial markings, but not with parenchymal lesions. Although the mechanism of the restrictive defect is unclear, these preliminary observations suggest a possible relationship to airway disease such as small airway obstruction.

ACKNOWLEDGMENTS: We thank Dory Roy for technical contributions and Ms. Carol Howard for secretarial assistance.

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