Left Ventricular Diastolic Function in Patients With Advanced Cystic Fibrosis*

Todd M. Koelling, MD; G. William Dec, MD; Leo C. Ginns, MD, FCCP; and Marc J. Semigran, MD

Objectives: To assess left ventricular systolic and diastolic function in adult patients with cystic fibrosis using radionuclide ventriculography.

Background: Although myocardial fibrosis has been described in autopsy specimens of patients with cystic fibrosis, the possibility that myocardial dysfunction may occur during life in adult patients with cystic fibrosis has not been explored.

Methods: To assess the possibility of cardiac dysfunction occurring in cystic fibrosis, we studied 40 patients with advanced cystic fibrosis with first-pass radionuclide ventriculography and compared them to 9 patients with advanced bronchiectasis and 18 normal control subjects.

Results: Indexes of right ventricular systolic function were similarly impaired in patients with cystic fibrosis and patients with bronchiectasis. Left ventricular ejection fraction of patients with cystic fibrosis, patients with bronchiectasis, and normal control subjects did not differ. Fractional left ventricular filling at 50% of diastole, an index of diastolic function, was significantly lower in patients with cystic fibrosis (54 ± 13%, mean ± SD) in comparison to patients with bronchiectasis (66 ± 4%, p = 0.009) or normal control subjects (69 ± 14, p = 0.0002). The contribution of atrial systole to total diastolic left ventricular filling was greater in patients with cystic fibrosis (38 ± 18%) than in patients with bronchiectasis (21 ± 4%, p = 0.01) or normal control subjects (25 ± 12%, p = 0.01).

Conclusions: Patients with advanced cystic fibrosis demonstrate impaired left ventricular distensibility when compared to normal control subjects and patients with bronchiectasis. Patients with cystic fibrosis may be at risk of heart failure due to right ventricular dysfunction or left ventricular diastolic dysfunction.

(CHEST 2003; 123:1488–1494)

Key words: cystic fibrosis; diastolic dysfunction; radionuclide ventriculography

Abbreviations: BSA = body surface area; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; VO₂ = oxygen consumption

Cystic fibrosis is a systemic disease characterized by progressive deterioration of organ function and the development of scarring and fibrosis. In the past 20 years, several case reports have described children with cystic fibrosis dying with signs and/or symptoms of left ventricular dysfunction who were later found to have myocardial fibrosis at autopsy.¹,² Despite this, left ventricular function has not been systematically investigated in patients with cystic fibrosis, although the effects of cystic fibrosis on the right ventricle have been well described by previous investigators, and include abnormalities of structure and systolic function.³–⁸

As the longevity of patients with cystic fibrosis is extended with the use of newer antibiotics, lung transplantation, and the possibility of successful gene therapy, a process of progressive fibrosis of myocardium may have functional significance and could lead to the development of heart failure in these patients. In order to determine if patients with cystic fibrosis, without symptomatic heart failure, would exhibit impairment of myocardial function, we compared indexes of systolic and diastolic function in these patients with a group of patients with bronchiectasis who did not have abnormal epithelial chloride conductance, and with a control population.

Materials and Methods

Patient Population

The study population was composed of 49 patients and 18 normal volunteers who served as control subjects. The patients...
were classified into two groups: 40 patients with advanced cystic fibrosis, and 9 patients with advanced bronchiectasis in whom diagnostic testing results for cystic fibrosis were negative. All patients had been referred to the Massachusetts General Hospital for consideration of lung transplantation. Data compiled for each patient or control subject included clinical history and physical examination, and the results of routine echocardiography with Doppler examination, exercise testing, radionuclide ventriculography, and spirometry. The frequency of prescription of supplemental oxygen by the patient’s physician was assessed.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed by previously reported methods. In brief, upright bicycle ergometry (pedal ergometer; Warren E. Collins; Braintree, MA) was used with a 12.5 W/min or 25 W/min incremental ramp protocol based on predicted exercise capacity, and was performed following an overnight fast with all patients breathing air. Breath-by-breath expired gas analysis was performed by a metabolic cart (Beckman OM1; Beckman Instruments; Fullerton, CA) interfaced to the ergometer. Peak oxygen uptake was defined as the highest oxygen consumption (VO2) measured during the last minute of symptom-limited exercise. The anaerobic threshold was determined by the V-slope method. Exercise testing was delayed if patients required a course of antibiotics until their pulmonary infection had improved.

First-Pass Radionuclide Ventriculography

Rest and exercise first-pass radionuclide ventriculography was performed at the time of bicycle ergometry. Patients were seated upright on the cycle ergometer facing a multicrystal nuclear camera (System 77; Baird Corporation; Bedford, MA). Images were acquired at 0.025-s intervals after central venous bolus administration of autologous erythrocytes labeled with 10 mCi 99mTc at rest and with 15 mCi at peak exercise. Left and right ventricular regions of interest were chosen based on maximum contribution, time to peak filling rate, and filling at 50% of diastole as depicted by color and identification of valvular planes. Time-activity curves were generated for each region of interest by imaging software (SIM-400; Scinticor; Milwaukee, WI). Only cycles with agreement between 99mTc and positron emission tomography (PET) were included in the analysis of the right ventricle in 34 of the 40 patients verified to be normal.

The clinical characteristics of the study populations are shown in Table 1. The mean age of patients with cystic fibrosis was similar to the bronchiectasis population and less than the control subjects. Patients with cystic fibrosis were smaller than the comparison populations, as assessed by body surface area (BSA). None of the patients with cystic fibrosis were known to have prior cardiac disease, nor were they receiving any cardiac medications. The arterial oxygen tension in the cystic fibrosis populations and the patients with bronchiectasis were similar, measured prior to exercise breathing air. However, supplemental oxygen was prescribed more frequently for patients with cystic fibrosis (2 L/min, n = 11; 3 L/min, n = 6; 4 L/min, n = 3; 5 L/min, n = 1) than for patients with bronchiectasis (3 L/min, n = 1) [Table 1]. Spirometry revealed that the patients with cystic fibrosis had more severe lung disease, with a lower vital capacity and FEV1 than the patients with bronchiectasis. The oxygen saturations and pulmonary function test results of the control subjects were verified to be normal.

Echocardiography

Echocardiography was technically satisfactory for analysis of the right ventricle in 34 of the 40 patients with cystic fibrosis and 8 of the 9 patients with bronchiectasis (Table 2). Left ventricular and left ventricular end-diastolic volume (LVEDV) was determined using a statistical analysis. Results are presented as mean ± SD. For all analyses, a two-tailed p value < 0.05 was considered statistically significant.

Study Population

The clinical characteristics of the study populations are shown in Table 1. The mean age of patients with cystic fibrosis was similar to the bronchiectasis population and less than the control subjects. Patients with cystic fibrosis were smaller than the comparison populations, as assessed by body surface area (BSA). None of the patients with cystic fibrosis were known to have prior cardiac disease, nor were they receiving any cardiac medications. The arterial oxygen tension in the cystic fibrosis populations and the patients with bronchiectasis were similar, measured prior to exercise breathing air. However, supplemental oxygen was prescribed more frequently for patients with cystic fibrosis (2 L/min, n = 11; 3 L/min, n = 6; 4 L/min, n = 3; 5 L/min, n = 1) than for patients with bronchiectasis (3 L/min, n = 1) [Table 1]. Spirometry revealed that the patients with cystic fibrosis had more severe lung disease, with a lower vital capacity and FEV1 than the patients with bronchiectasis. The oxygen saturations and pulmonary function test results of the control subjects were verified to be normal.

Table 1—Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cystic Fibrosis (n = 40)</th>
<th>Bronchiectasis (n = 9)</th>
<th>Control (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>29 ± 8†</td>
<td>33 ± 7</td>
<td>37 ± 12</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>44</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.5 ± 0.2†</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Supplemental O₂, %</td>
<td>52†</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>% predicted FEV₁, %</td>
<td>23 ± 8†</td>
<td>45 ± 38</td>
<td></td>
</tr>
<tr>
<td>% predicted FVC, %</td>
<td>39 ± 12†</td>
<td>61 ± 28</td>
<td></td>
</tr>
<tr>
<td>DLCO, mm/min/mm Hg</td>
<td>15 ± 5</td>
<td>14 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD; supplemental O₂ = percentage of patients receiving O₂; DLCO = diffusing capacity of the lung for carbon monoxide.

†p < 0.01 vs normal control.

‡p < 0.01 vs bronchiectasis.
atrial size, indexed to BSA, were no different between patients with cystic fibrosis and patients with bronchiectasis. The interventricular septal thickness of patients with cystic fibrosis (5.7 ± 0.7 mm/m²) was significantly larger than patients with bronchiectasis (5.1 ± 0.7 mm/m², p < 0.05). Left ventricular ejection fraction (LVEF) was normal and similar in the two groups of patients. The presence of right ventricular dilatation or hypokinesis was noted in a minority of patients and with similar frequency in the two groups of patients. Flattening of the interventricular septum during systole suggesting right ventricular pressure overload was also observed with similar frequency in the two groups, as was the presence of significant tricuspid regurgitation (milder or greater, by color Doppler echocardiography). Doppler echocardiographic measurement of the velocity of the tricuspid regurgitation jet revealed severe elevation of the estimated right ventricular systolic pressure (> 50 mm Hg) in two patients with cystic fibrosis. Because only a small percentage of patients had tricuspid regurgitation, the estimated right ventricular systolic pressures of the two groups of patients were not compared. No other echocardiographic abnormalities were noted.

### Cardiopulmonary Exercise Testing

The results of cardiopulmonary exercise testing in the study population are shown in Table 3. All patients exercised while breathing room air. The patients with cystic fibrosis had similar exercise tolerance to the patients with bronchiectasis, with both patient groups having less exercise capacity than control subjects as measured by peak workload, peak VO₂, and VO₂ at the anaerobic threshold. Each of the patients with cystic fibrosis and patients with bronchiectasis reached a pulmonary limit to exercise. Peak workload achieved by patients with cystic fibrosis was less than observed in patients with bronchiectasis, but no difference was seen with respect to peak VO₂ or VO₂ at the anaerobic threshold. The resting heart rate of the patients with cystic fibrosis was higher than either the patients with bronchiectasis (87 ± 23 beats/min) or the normal control subjects (82 ± 13 beats/min), although the heart rate at peak exercise did not differ. The mean systemic BP at rest was similar in all three groups; however, the systemic BP achieved at peak exercise was lower in the patients with cystic fibrosis than the patients with bronchiectasis. The PaO₂ of the patients with cystic fibrosis and patients with bronchiectasis was similar at rest and at peak exercise.

### Radionuclide Ventriculography

Right and left ventricular systolic function was assessed by radionuclide ventriculography performed at rest and peak exercise (Table 4). The rest and exercise right ventricular ejection fractions

---

**Table 2—Echocardiography Data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cystic Fibrosis (n = 34)</th>
<th>Bronchiectasis (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDD, mm/m²</td>
<td>29 ± 3</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>Left atrium, mm/m²</td>
<td>19 ± 3</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>Interventricular septum, mm/m²</td>
<td>5.7 ± 0.7†</td>
<td>5.1 ± 0.7‡</td>
</tr>
<tr>
<td>LVEF</td>
<td>65 ± 8</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>Right ventricle dilatation</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Right ventricle hypokinesis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Septal flattening</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Tricuspid regurgitation, milder or greater</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or %. LVIDD = left ventricular internal diastolic dimension.

†p < 0.05 vs bronchiectasis.

**Table 3—Exercise Data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cystic Fibrosis (n = 40)</th>
<th>Bronchiectasis (n = 9)</th>
<th>Normal Control (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak work, W</td>
<td>46 ± 24†</td>
<td>75 ± 38†</td>
<td>132 ± 45</td>
</tr>
<tr>
<td>Peak VO₂, mL/min/kg</td>
<td>16.7 ± 5.8†</td>
<td>15.8 ± 5.9†</td>
<td>24.5 ± 5.3</td>
</tr>
<tr>
<td>V̇O₂ anaerobic threshold, mL/min/kg</td>
<td>10.2 ± 3.1†</td>
<td>10.4 ± 4.1†</td>
<td>17.1 ± 4.5</td>
</tr>
<tr>
<td>Mean BP, at rest, mm Hg</td>
<td>79 ± 17</td>
<td>85 ± 7</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>Mean BP, at peak exercise, mm Hg</td>
<td>108 ± 17†</td>
<td>120 ± 14†</td>
<td>103 ± 18</td>
</tr>
<tr>
<td>Heart rate at rest, beats/min</td>
<td>107 ± 19†</td>
<td>87 ± 23</td>
<td>82 ± 13</td>
</tr>
<tr>
<td>Heart rate at peak exercise, beats/min</td>
<td>148 ± 16</td>
<td>135 ± 27</td>
<td>159 ± 16</td>
</tr>
<tr>
<td>PaO₂ at rest, mm Hg</td>
<td>68 ± 11</td>
<td>68 ± 8</td>
<td></td>
</tr>
<tr>
<td>PaO₂ at exercise, mm Hg</td>
<td>64 ± 11</td>
<td>61 ± 13</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ at rest, mm Hg</td>
<td>42 ± 7</td>
<td>41 ± 8</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.

†p < 0.001 vs normal control.

‡p < 0.001 vs bronchiectasis.
(RVEFs) were lower in the patients with cystic fibrosis and the patients with bronchiectasis when compared with the normal control subjects, and did not differ between the two patient populations. The observed decrease in rest and exercise RVEF persisted after the two cystic fibrosis patients with echocardiographic right ventricular systolic pressure > 50 mm Hg were excluded from analysis. Left ventricular dilation was also present in the patients with cystic fibrosis, as LVEDV indexed to BSA, at both rest and exercise, was 25% greater than in the control population.

The results of assessment of left ventricular diastolic function at rest by radionuclide ventriculography are shown in Table 5. Fractional left ventricular filling at mid-diastole was lower in the patients with cystic fibrosis than either the patients with bronchiectasis or normal control subjects, and the contribution of atrial contraction to left ventricular filling was higher. Neither peak left ventricular filling rate nor time to left ventricular peak filling indexed to the R-R interval differed in the study populations. These observations are consistent with a restrictive pattern of ventricular filling.

### Table 4—Radionuclide Ventricular Systolic Function Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cystic Fibrosis (n = 40)</th>
<th>Bronchiectasis (n = 9)</th>
<th>Normal Control (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEF at rest</td>
<td>0.34 ± 0.07†</td>
<td>0.36 ± 0.07†</td>
<td>0.44 ± 0.08</td>
</tr>
<tr>
<td>RVEF at exercise</td>
<td>0.35 ± 0.07†</td>
<td>0.39 ± 0.07†</td>
<td>0.47 ± 0.08</td>
</tr>
<tr>
<td>LVEF at rest</td>
<td>0.62 ± 0.08</td>
<td>0.61 ± 0.08</td>
<td>0.62 ± 0.06</td>
</tr>
<tr>
<td>LVEF at exercise</td>
<td>0.64 ± 0.11</td>
<td>0.70 ± 0.12</td>
<td>0.66 ± 0.08</td>
</tr>
<tr>
<td>LVEDVI at rest, mL/m²</td>
<td>81 ± 15†</td>
<td>77 ± 18†</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>LVEDVI at exercise, mL/m²</td>
<td>91 ± 19†</td>
<td>82 ± 12</td>
<td>76 ± 10</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD; LVEDVI = LVEDV/BSA.
†p < 0.05 vs normal control.
‡p < 0.01 vs normal control.

### Table 5—Radionuclide Ventricular Diastolic Function Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cystic Fibrosis (n = 40)</th>
<th>Bronchiectasis (n = 9)</th>
<th>Normal Control (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular filling at 50% of diastole</td>
<td>0.54 ± 0.13†</td>
<td>0.66 ± 0.04</td>
<td>0.69 ± 0.14</td>
</tr>
<tr>
<td>Atrial filling contribution</td>
<td>0.38 ± 0.18†</td>
<td>0.21 ± 0.08</td>
<td>0.25 ± 0.12</td>
</tr>
<tr>
<td>Left ventricular peak filling rate, end-diastolic volume/s</td>
<td>3.8 ± 1.1</td>
<td>3.5 ± 0.9</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>Time to left ventricular peak filling rate/R-R interval</td>
<td>0.25 ± 0.07</td>
<td>0.21 ± 0.08</td>
<td>0.22 ± 0.06</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†p < 0.01 vs bronchiectasis patients and normal control subjects.
‡p < 0.05 vs normal control.
§p < 0.001 vs bronchiectasis.

### Clinical Correlates of the Results of Radionuclide Ventriculography

Correlation of radionuclide indexes of right and left ventricular systolic and diastolic function with demographic data, physical examination findings, and pulmonary function data were performed using nonparametric techniques. RVEF at rest was found to correlate with FEV₁ (r = 0.37, p = 0.03). Both fractional left ventricular filling at 50% of diastole and atrial contribution to filling were found to correlate with resting heart rate (r = −0.54, p < 0.001, and r = 0.60, p < 0.001, respectively) and female gender (r = −0.51, p < 0.001, and r = 0.36, p = 0.02, respectively). There was no significant correlation between fractional left ventricular filling at 50% of diastole or atrial contribution to filling and supplemental oxygen use, PaO₂ at rest or exercise, right ventricular dilatation, right ventricular hypokinesis, or septal flattening by echocardiography, or RVEF at rest or exercise by radionuclide ventriculography. When patients with evidence of septal flattening by echocardiography were excluded from the analysis, the remaining patients with cystic fibrosis (n = 25) continued to show lower fractional filling at 50% of diastole (0.54 ± 0.12) and higher atrial filling contributions (0.36 ± 0.18) than patients with bronchiectasis (n = 8, 0.66 ± 0.04 and 0.21 ± 0.04, respectively; p = 0.01 for each).

### Discussion

This study shows that adult patients with advanced lung disease from cystic fibrosis demonstrate impairment of cardiac function when compared to patients with bronchiectasis and normal control subjects. While left ventricular systolic function was normal in both groups of patients, patients with cystic fibrosis had impaired left ventricular diastolic filling and were more reliant on the atrial contribution to filling when compared to patients with bronchiectasis or normal control subjects. We also observed that right
Ventricular systolic function both at rest and peak exercise was similarly compromised in patients with cystic fibrosis and patients with bronchiectasis. The abnormal diastolic indexes in patients with cystic fibrosis were found to be independent of arterial oxygen tension, echocardiographic assessment of right ventricular dilation or hypokinesis or interventricular septal flattening, or RVEF measured by radionuclide ventriculography. When patients with evidence of right ventricular pressure or volume overload assessed by echocardiography were excluded from the analysis, the abnormalities of diastolic function in the patients with cystic fibrosis persisted compared with normal control subjects or patients with bronchiectasis. These abnormalities of diastolic function are similar to those observed with a restrictive cardiomyopathy.\(^1\)\

**Ventricular Dysfunction in Patients With Cystic Fibrosis**

Although right ventricular dysfunction in patients with cystic fibrosis has been described by previous investigators,\(^3\)–\(^6\),\(^14\) left ventricular function has not been studied extensively. Tomlin et al\(^15\) described chronic cor pulmonale as a complication of fibrocystic disease of the pancreas in 1952. Allen et al,\(^16\) using echocardiography, identified increased right ventricular wall thickness and cavity size in 37 children with cystic fibrosis, observing that these abnormalities occurred in patients with mild as well as severe disease. Ryland and Reid\(^17\) identified right ventricular hypertrophy at postmortem examination in 83% of 36 patients with cystic fibrosis > 3 years old.

Our study expands on these observations, as we observed that abnormalities in right ventricular systolic function are present at rest and persist to peak exercise in patients with cystic fibrosis. Although 25% of the patients had RVEFs < 0.30, it is important to note that no patients with cystic fibrosis in the population had more than mild (1+/4) pedal edema, and only 8% had evidence of jugular venous distention. Only 2 of the 40 patients with cystic fibrosis required therapy with diuretic medications. None of the patients in this pretransplant population was recommended to have combined heart-lung transplantation. One potential cause of right ventricular systolic dysfunction may be an increase in afterload related to destruction of pulmonary parenchyma. In support of this, we found a correlation between F\(E_V\)\(_1\) and RVEF. We did not find a correlation between RVEF and pulmonary arterial systolic pressure estimated from the velocity of the tricuspid regurgitant jet; however, pulmonary arterial systolic pressure may not be an accurate measure of afterload in the presence of right ventricular dilation such as was observed in the patient population.

The etiology of the observed left ventricular diastolic dysfunction in patients with cystic fibrosis is potentially multifold. Right ventricular dilation may decrease left ventricular distensibility through the interventricular septum.\(^18\) The echocardiographic observation of septal flattening in some of the patients with cystic fibrosis supports this mechanism; however we did not observe an association of the presence of septal flattening with impaired indexes of ventricular filling. Other determinants of ventricular distensibility, such as tachycardia and increased levels of neurohormonal mediators, may have had a greater impact on ventricular filling and obscured the effect of the right ventricular pressure and volume overload on left ventricular function.

Studies of left ventricular function in patients with cystic fibrosis have given clues that the disease may be associated with a pathologic process that directly effects the myocardium. Several case reports have described children with cystic fibrosis with signs and/or symptoms of left ventricular dysfunction who were later found to have myocardial fibrosis at autopsy.\(^1\),\(^2\)

Allen et al\(^16\) showed that patients with cystic fibrosis and severe pulmonary disease had thickened septa, posterior walls, and aortas compared with normal subjects by two-dimensional echocardiography. Our study confirms that the interventricular septa of patients with cystic fibrosis are thickened as compared to the patients with bronchiectasis. Benson et al\(^19\) studied 31 patients with cystic fibrosis with exercise radionuclide ventriculography and found that only 2 patients had LVEF < 55% at rest, but 29% had impaired cardiac performance with exercise. More recently, Herout et al\(^20\) described skeletal and cardiac muscle pathologic changes in 26 children with cardiomyopathy and cystic fibrosis, 24 of whom subsequently died. Ambrosi et al\(^21\) studied 67 infants and children with cystic fibrosis and found that 17 patients had LVEFs < 0.45, and 35% of these had perfusion defects by scintigraphy compared to 8% of the patients with LVEFs > 0.45. They surmised that these abnormalities were due to myocardial fibrosis.

A more likely clinical manifestation of myocardial fibrosis would be the development of impaired left ventricular diastolic relaxation. Johnson et al\(^22\) studied 25 patients with cystic fibrosis using Doppler echocardiography, examining left ventricular filling patterns, and found that the proportion of atrial filling was higher in these patients compared to control subjects, and correlated with worsening pulmonary disease. Although the Doppler signal from atrial filling is inversely associated with left ventric-
ular relaxation, transmitral flow velocities have been shown to be closely related to both atrial filling pressure and left ventricular diastolic pressure.\textsuperscript{29} For this reason, we chose to assess the patients with cystic fibrosis with radionuclide ventriculography to assess left ventricular volumetric changes during diastole.

Causes of myocardial fibrosis in patients with cystic fibrosis are unknown. Zimmerman et al.\textsuperscript{14} reported on pathology findings in two patients dying of cystic fibrosis-associated cardiomyopathy in whom myocardial edema was found and lymph stasis was seen, suggesting that cystic fibrosis may be complicated by a disorder of cardiac lymphatic drainage. Others have hypothesized that the fibrosis seen on pathology samples occurs because of malnourishment and/or hypovitaminosis.\textsuperscript{2} Levels of neurohormonal mediators such as aldosterone and angiotensin II are increased in patients with cystic fibrosis, and these signaling molecules have previously been shown to cause myocyte hypertrophy and interstitial fibrosis.\textsuperscript{25,26} Certainly, chronic hypoxia can lead to myocardial fibrosis,\textsuperscript{27} and this may have occurred in the patients with cystic fibrosis we studied, as indicated by the need for supplemental oxygen in many of them. Finally, the fundamental abnormality of cystic fibrosis lies in chloride transport in epithelial cells. Whether this abnormality alters either myocyte calcium handling or myocardial collagen production is unknown.

The implications of the finding of diastolic dysfunction in this population are twofold. First, advances in medical therapy for patients with cystic fibrosis may lead to a population of patients in whom dyspnea may have both pulmonary and cardiac contributions. Secondly, patients who have successful lung transplantation and long-term survival from improved allograft preservation may eventually acquire symptomatic left heart failure from progressive left ventricular noncompliance. The study of ventricular function in cystic fibrosis patients after transplantation is warranted.

Limitations

This study is a review of cardiovascular findings in a population of patients under evaluation for lung transplantation. Because of the advanced degree of the lung disease in these patients, the results of this study cannot necessarily be extrapolated to the general population of patients with cystic fibrosis without further study. Further study of a broader age range of patients may allow demonstration of an association between diastolic parameters and age in our study.

The indexes of diastolic function used in this study were derived from changes in chamber volume over time measured by radionuclide ventriculography. These indexes have been shown previously to be dependent on loading conditions, ejection fraction, and heart rate.\textsuperscript{28–31} We found no significant differences among the groups with respect to BP or LVEF at rest. Patients with cystic fibrosis did have higher resting heart rates, on average, than control subjects or patients with bronchiectasis. Previous investigators have shown that higher heart rate increases the peak ventricular filling rate, increases the early diastolic filling contribution, and decreases the atrial filling contribution; however, despite the tendency of a higher heart rate to improve diastolic relaxation, the patients with cystic fibrosis were observed to have impaired diastolic filling parameters. Future assessment of diastolic function independent of loading conditions and heart rate may require the patients and controls to undergo micromanometer left-heart and right-heart catheterization simultaneous with radionuclide ventriculography and right atrial pacing.

We chose to compare indexes of myocardial systolic and diastolic function in patients with cystic fibrosis with a group of patients with bronchiectasis who did not have abnormal epithelial chloride conductance but in whom the pulmonary pathology is similar to that of cystic fibrosis. The patients with cystic fibrosis did have a greater degree of impairment of pulmonary function than the patients with bronchiectasis, and we cannot completely exclude the possibility that this contributed to the left ventricular diastolic dysfunction observed in the patients with cystic fibrosis; however, the differences in pulmonary function did not cause resting right and left ventricular loading conditions to differ, given the limitation imposed by the sample size to determine a difference. This supports our conclusion that our findings are characteristic of cystic fibrosis and not the greater degree of impairment of pulmonary function.

Summary

In this study, patients with cystic fibrosis were found to have normal left ventricular systolic function but significant diastolic dysfunction as evidenced by radionuclide ventriculography (percentage of filling at 50% of diastole, atrial filling contribution, and time to peak filling/R-R interval ratio). Progressive myocardial fibrosis as described in previous pathology reports of cystic fibrosis and/or ventricular interdependence may partially explain this finding.
REFERENCES