Pneumothorax in Cystic Fibrosis*

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Spontaneous pneumothorax is a common complication in patients with cystic fibrosis (CF). It is thought to occur more frequently in patients with more advanced disease. Recommendations on the management of pneumothorax in CF are based on retrospective analyses and reports from CF centers. The following is a review of what has been published regarding the incidence and management of pneumothorax in this population, with some comment on the pathogenesis of the complication.

Key words: cystic fibrosis; lung; pneumothorax; review

Abbreviation: CF = cystic fibrosis

Pneumothorax has long been listed as one of the complications of cystic fibrosis (CF), with the first case report having been published in 1966.1 The pathophysiology of spontaneous pneumothorax has been presumed to be due to the rupture of subpleural blebs through the visceral pleura, which occurs more frequently in older patients, probably because they have more severe disease, although other mechanisms may be more important. Our understanding of pneumothoraces in CF patients and their management is based on retrospective reports from large centers, typically over many years of observation, and generally mimics the management of primary spontaneous pneumothorax. The following is a review of the published literature on the subject, combining data when feasible, with an argument that current strategies of therapy should be reconsidered.

Epidemiology

The reported lifetime incidence of spontaneous pneumothorax in patients with CF ranges between 2.8% and 18.9%.2,3 Combining the results of the publications with larger populations between 1968 and 1989 produces an overall incidence of 6.4%.2–8 Rich et al6 reported an overall incidence of 6.4%, although it increased to 11% when considering only those patients 10 years of age. The annual incidence of pneumothorax determined by an analysis of the Cystic Fibrosis Foundation Registry database was 1% per year.9 The same analysis revealed that 5 to 8% of all patients will experience a pneumothorax at some time in their life. For those patients >18 years of age, 16 to 20% will experience a pneumothorax.9

The finding of an increasing incidence of pneumothorax later in life is consistent with the reports of age at initial pneumothorax. The earliest reported age of initial pneumothorax was 4 years,6,10 although the mean age of occurrence is typically in the mid-teenage years.2,4,6,7,10,11 The median age of survival for CF patients has increased over time (Fig 1), and it might be expected that the median age of initial pneumothorax would occur later as well, if we presume that it is related to the severity of the lung disease. The reported median age of initial pneumothorax2,4,5,7,11 did indeed increase (Fig 1), but not at the same rate as that seen for survival. Please note that the median ages of initial pneumothorax shown in Figure 1 are from retrospective reviews that were performed at large centers over a number of years, some of which are overlapping.

One study4 reported the results of pulmonary function testing of patients the year before they experienced their first pneumothorax. The mean FVC (±SD) was 51.1 ± 12% of predicted, with a range of 33 to 70% of predicted. The FEV1/FVC ratio for the same group was 57.6 ± 16.6%, with a range of 31 to 90%. Seddon and Hodson12 described 27 patients who underwent surgical pleurodesis for pneumothorax. All of their patients had an FEV1 < 50% of predicted, with a mean of 34% of predicted. Penketh et al3 reported on 46 patients with spontaneous pneumothoraces. All but two patients had FEV1 values < 50% of predicted. These findings suggested that most patients have

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moderate-to-severe pulmonary impairment at the time they experience a pneumothorax. The evidence to support airtrapping in these patients is reported by Stowe et al,8 whose patients had a residual volume/total lung capacity ratio of 0.56 (n = 46), and by McLaughlin et al, 13 whose patients had an average residual volume of 345% of predicted, an average total lung capacity of 122% of predicted, and an average maximum mid-expiratory flow of 14% of predicted (n = 19) prior to the initial pneumothorax.

There appears to be an equal risk of pneumothorax for men and women. Although the studies that report the rate of occurrence by sex1 –7,10,14 have revealed a tendency for more pneumothoraces in men than in women (163 vs 120, respectively), the difference did not achieve statistical significance. Similarly, there is an equal distribution of pneumothoraces between the right and left lungs.1,4 –7,10,14 There is a high rate (46%) of reported subsequent contralateral pneumothoraces.6 Smoking is a known risk factor for primary spontaneous pneumothorax,15 and there is no mention of tobacco use in the literature on spontaneous pneumothorax in patients with CF.

The recurrence of a pneumothorax is defined as one that occurs on the ipsilateral side > 7 days after a pneumothorax has resolved. The recurrence of pneumothoraces is common, with one report3 of a patient who experienced 11 separate episodes of pneumothorax. The overall average number of pneumothoraces per patient is 1.92.1–8,10,11,13,14,16

Pathogenesis

The cause of spontaneous pneumothorax in CF patients has not been clearly established. One explanation has attributed pneumothoraces to the rupture of subpleural blebs on the visceral pleura. This is supported in one study6 by the finding of blebs in 84% of patients who were undergoing pleurectomy by abrasion. However, an examination of the visceral pleura of CF patients, either at autopsy or after they had undergone pleurectomy, found that their visceral pleura were not different from those of patients without CF who also had experienced a spontaneous pneumothorax.17 The pleura of CF patients were often edematous with widely dilated lymphatics and were more intensely inflamed, but, in general they were structurally normal.

Cysts are commonly found in the lungs of CF patients, mostly bronchiectatic cysts but also interstitial and emphysematous cysts, and are most commonly found in the upper lobes.18 Many patients will have multiple cysts present on autopsy. Cysts have been found in the lungs of all CF patients who had experienced a pneumothorax but only in 60% of CF patients who had never experienced a pneumothorax.18 Interestingly, in that study, the two most severely cystic lungs were found in patients who had never had a pneumothorax. The development of pneumothorax does not correlate with the percentage of lung volume occupied by cysts, and there is a relative insensitivity of chest radiography to detecting cysts.18

An alternate explanation may be that there is increased volume and pressure in the alveoli due to mucus plugging and inflammatory changes of the more proximal airways. Airtrapping within the alveoli could lead to a rupture into the pleural space, although this is not required. An increase in alveolar pressure that exceeds the interstitial pressure would drive air into the interstitium, which could move into the hilar mediastinum. When mediastinal pressure increases, there could be a rupture of the mediastinal parietal pleura, causing a pneumothorax. This mechanism is similar to that suggested for primary spontaneous pneumothorax.19,20 This would be consistent with the finding of more frequent occurrences in patients with more severe airways disease and with airtrapping. It has been suggested that positive pressure applied to the airways may increase the risk of pneumothorax.21 Increased airway pressure may occur with mechanical ventilatory support, even in the form of therapy with noninvasive bilevel positive airway pressure and with certain methods of airway clearance that use devices to increase positive expiratory pressure. With respect to the latter, this type of therapy is used with great frequency in CF.
patients, but there is only one reported case of a child who experienced a spontaneous pneumothorax, occurring 4 h after a positive expiratory pressure therapy session.

**DIAGNOSIS**

The patient with spontaneous pneumothorax typically presents with acute onset of chest pain or dyspnea. In one report, chest pain was a presenting symptom in 50% of patients, while dyspnea occurred in 65%. Interestingly, hemoptysis was a presenting finding in 6 of 32 patients (19%) and was the sole finding in 1 patient. In that same report, 5 of 32 patients (16%) were asymptomatic at the time of diagnosis, 2 of whom had the pneumothorax identified on a routine chest radiograph.

The chest radiograph is the most important study in the diagnosis of pneumothorax. However, the chest radiograph may not be definitive, and a CT scan of the chest may be necessary to prove the diagnosis.

**MANAGEMENT**

The methods of managing spontaneous pneumothorax for CF patients has included observation, needle aspiration, closed thoracotomy using a chest tube, chemical pleurodesis with quinacrine, silver nitrate, tetracycline, and talc, and surgical pleurodesis by either parietal pleurectomy or pleural abrasion. The combined results of these reports are shown in Table 1. All of these published results are based on the retrospective analysis of charts and not as a result of controlled clinical trials. The choice of therapy was dependent on the size of the pneumothorax and the severity of symptoms. Thus, the choice of observation or needle aspiration was made more commonly in patients with small pneumothoraces or in those patients who were asymptomatic.

An initial lack of response to treatment and recurrence of pneumothorax is very high for observation, needle aspiration, and chest tube drainage, resulting in overall failure rates (ie, initial failure plus ipsilateral recurrence) of 68%, 90%, and 72%, respectively. These findings have prompted some authors to suggest that a more definitive procedure, such as chemical or surgical pleurodesis, be performed earlier. In addition, the occurrence of contralateral pneumothorax is reported to be so high (46%) that one author even suggested the consideration of prophylactic contralateral pleurodesis. The greatest success for chemical pleurodesis has been with quinacrine and talc. Quinacrine is no longer available, and the reported use of talc in this population remains limited. Nonetheless, there is extensive experience with talc pleurodesis, either by slurry or poudrage, in the treatment of primary spontaneous pneumothorax (ie, non-CF), with a reported recurrence rate of only 8%. The small numbers of patients reported to have been treated with silver nitrate and tetracycline still had a high recurrence rate, and these medications are not typically used anymore.

Surgical pleurodesis has a high success rate, but there is some concern about its use. Patients with severe lung disease were not considered to be candidates for a surgical procedure. The current recommendations are that the benefits of surgical pleurodesis for patients with persistent pneumothorax outweigh the risks of the procedure for most patients but that chemical pleurodesis should be used in those patients with extremely poor anesthetic risks, heart failure, or respiratory failure.

There also has been concern about the effects that pleurodesis may have on the patient’s candidacy for lung transplantation. In the earlier days of lung transplantation, the contralateral pleural space was obliterated to remove the risk of recurrent pneumothorax. Today, pleurodesis is reserved for patients who require an additional intervention after initial surgery.

**Table 1—Outcomes of Various Methods of Treating Pneumothorax**

<table>
<thead>
<tr>
<th>Method of Treatment</th>
<th>Patients, No.</th>
<th>Failure</th>
<th>Resolution</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>131</td>
<td>46 (35.1)</td>
<td>55 (45.9)</td>
<td>43 (30.6)</td>
</tr>
<tr>
<td>Needle aspiration</td>
<td>31</td>
<td>17 (54.8)</td>
<td>14 (45.2)</td>
<td>11 (37.8)</td>
</tr>
<tr>
<td>Chest tube</td>
<td>221</td>
<td>83 (37.6)</td>
<td>138 (62.4)</td>
<td>75 (34.3)</td>
</tr>
<tr>
<td>Chemical pleurodesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinacrine</td>
<td>33</td>
<td>9 (27.3)</td>
<td>24 (72.7)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>10</td>
<td>3 (30.0)</td>
<td>7 (70.0)</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>16</td>
<td>3 (18.8)</td>
<td>13 (81.3)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Talc</td>
<td>15</td>
<td>0 (0)</td>
<td>15 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parietal pleurectomy</td>
<td>118</td>
<td>4 (3.4)</td>
<td>114 (96.6)</td>
<td>9 (7.9)</td>
</tr>
</tbody>
</table>

*Values given as No. of patients (%). Failure = patients who required additional intervention; Recurrence = occurrence of ipsilateral pneumothorax > 7 days following resolution of a pneumothorax (percentage based on patients who had initial resolution).*
transplantation, it was thought that patients who had undergone a prior pleurectomy or pleurodesis had an unacceptably high rate of postoperative bleeding. An informal survey of CF centers found that many patients had been refused transplantation because of undergoing a previous pleural ablation and that most physicians had altered their approach to managing pneumothorax because of transplantation. Some have argued that a surgical pleurodesis is preferable to a chemical pleurodesis as there may be fewer diffuse adhesions that might complicate the transplant procedure. The current consensus is that pleurodesis is not an absolute contraindication to lung transplantation.

A consensus document on the pulmonary complications of CF offered an algorithm of management recommendations. They suggested that the observation of small (ie, < 20%), asymptomatic pneumothoraces is acceptable. For larger or symptomatic pneumothoraces, a chest tube should be placed. Surgery is offered to those patients who have persistent or recurrent pneumothoraces. Chemical pleurodesis is reserved for those who cannot tolerate surgery or who refuse surgery.

OUTCOMES

The prognosis for the patient after a spontaneous pneumothorax has been reported to be very poor, with death occurring approximately 30 months after the occurrence of the first pneumothorax. There are frequent reports of death occurring at the time of a pneumothorax or shortly thereafter, and it is thought to coincide with the finding that this complication tends to occur in patients with more severe lung disease. A history of pneumothorax was included in a prognostic scoring system, accounting for a maximum of 5% of total points, because of reports of its occurrence late in the course of disease. Boat et al reported that 7 of their 15 patients died an average of 7 months after their pneumothoraces. The eight survivors had been observed for an average of 15 months. Tribble et al had one patient die 36 months after a pneumothorax. Their four survivors had been observed for an average of 15 months. Lifschitz et al reported that 75% of their patients had died within 6 months after the pneumothorax. Although such results do seem ominous, there are also reports of patients surviving > 17 years after the pneumothorax.

Pulmonary function has been observed up to 1 year in patients who underwent surgical pleurodesis following pneumothorax. All patients had severe disease (FEV₁, < 50% of predicted). The average FEV₁ decreased by approximately 5% of predicted over the 12 months of the study.

SUMMARY

In conclusion, spontaneous pneumothorax is a relatively frequent complication in patients with CF. It is more likely to occur later in the course of airways disease, but there are no factors that will accurately predict those who will experience this complication. Although the current consensus suggests a conservative approach to management, either by observation or tube thoracostomy, the rate of lack of response to treatment or recurrence is so high that most patients will require pleurodesis for definitive treatment. The consensus statement recommended pleurodesis for those patients for whom air leakage persists or for those who have recurrent pneumothoraces. Surgical pleurodesis is preferred over chemical pleurodesis except for those patients who cannot tolerate a surgical procedure. This algorithm is similar to the current management of primary spontaneous pneumothorax in the United States. However, in light of the very high rate of recurrence of pneumothorax in patients with CF (> 50%), it would seem justified to offer pleurodesis even after the initial spontaneous pneumothorax. A multicenter trial of the management of spontaneous pneumothorax is needed to determine the optimum timing and method of treatment. Patients should be advised that there is a high rate of contralateral pneumothorax, and they should seek immediate medical attention for the acute onset of dyspnea and chest pain.

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