Primary Spontaneous Pneumothorax: A Diffuse Disease of the Pleura

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\begin{abstract}
Primary spontaneous pneumothorax (PSP) is by definition not associated with any underlying lung disease. However, this does not mean that there is no underlying pathological process. It has become increasingly apparent over recent years that PSP is associated with diffuse and often bilateral abnormalities within the pleura and is not simply a disease caused by ruptured blebs/bullae. The pathological process includes emphysema-like changes, pleural porosity and inflammation. In this review, we summarise the recent advances in our understanding of the pathogenesis of PSP and discuss how this relates to management strategies for patients with PSP.
\end{abstract}

\begin{keywords}
Aetiology · Emphysema-like changes · Management · Pathogenesis · Pleural diseases · Pleural porosity · Pneumothorax · Thoracoscopy
\end{keywords}

\section{Introduction}
Pneumothorax is defined as air in the pleural space and can be classified as spontaneous or traumatic. Traumatic pneumothorax includes iatrogenic cases caused during procedures such as pacemaker insertion or other central venous cannulation procedures. Spontaneous pneumothorax can be subclassified as primary or secondary (table 1). Secondary spontaneous pneumothorax (SSP) occurs in association with a known underlying lung pathology such as chronic obstructive pulmonary disease. Primary spontaneous pneumothorax (PSP) occurs in patients with no apparent underlying lung disease (table 1). Spontaneous pneumothorax was first described in 1803. However, until 1932 it was thought to be always associated with tuberculosis until 1932 when 'spontaneous pneumothorax in the apparently healthy' was first described [1].

PSP is a significant clinical problem with an annual incidence of 18–28/100,000 in males and 1.2–6/100,000 in females leading to the use of many hospital bed days and associated morbidity for patients [2]. The incidence is significantly higher amongst individuals who smoke [3]. Despite a number of international guidelines having been published [2, 4, 5], there remains debate over the best management approach for initial treatment and re-
We will review here recent advances in our understanding of the aetiology of spontaneous pneumothorax and relate the importance of this to appropriate management strategies.

**Aetiology of Spontaneous Pneumothorax**

There is little debate about the aetiology of SSP. It is commonly associated with chronic obstructive pulmonary disease but also with other important underlying lung diseases, including cystic fibrosis, tuberculosis, diffuse parenchymal lung disease and lung cancer. Rupture of blebs/bullae on the visceral pleura allows air to pass into the pleural space during the phase of respiration when the intra-thoracic pressure is lower than atmospheric pressure (i.e. during inspiration). Tension pneumothorax occurs when the intra-pleural pressure becomes greater than atmospheric pressure throughout all phases of respiration. This is thought to be caused by a 1-way valve effect whereby air passes into the pleural space on inspiration when the pressure becomes negative, but is unable to escape on expiration due to closing of the valve. This is extremely rare in spontaneous pneumothorax but more commonly seen with traumatic pneumothoraces or with ventilated patients.

PSP, by definition, occurs in patients with no associated lung disease. However, it is important to note that this does not mean that there is no underlying pathological process. Indeed, a finding of abnormal pleura is very common in PSP patients if looked for carefully [7]. The abnormalities seen in PSP are summarised in table 2 and include blebs and bullae, which are otherwise known as emphysema-like changes (ELC). These are areas of weakness of the visceral pleura, which are prone to rupture allowing air to leak into the pleural space. Abnormalities can be visualized, radiologically with high-resolution computed tomography scans and macroscopically at thoracoscopy [7, 8].

High-resolution CT imaging reveals pleural abnormalities in approximately 80% of PSP patients. These changes are often bilateral. The literature is mixed as to whether the presence or extent of ELC is directly related to the risk of recurrence, with some case series suggesting no association [9, 10] and others going as far as to suggest that the presence of contralateral blebs/bullae is a risk factor for future pneumothorax and thus should be an indication for bilateral recurrence prevention [11, 12]. Given that contralateral pneumothoraces are generally more of a symptomatic nuisance than a life-threatening event, this may seem an extreme point of view except in high-risk professions such as pilots or divers. All these studies are observational and small in size, and the differences in results may be related to different patient populations and scanning protocols. The only clear conclusion that can be drawn is that there is a direct association between the presence of ELC and the occurrence (but not necessarily recurrence) of a pneumothorax.

The macroscopic appearance of the visceral pleura has been shown to be abnormal in patients with PSP, with 77% of patients with a first PSP having blebs or bullae.

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**Table 1. Classification of pneumothorax**

<table>
<thead>
<tr>
<th>Type</th>
<th>Aetiology</th>
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</thead>
<tbody>
<tr>
<td>PSP</td>
<td>No underlying lung disease (but blebs/bullae commonly present)</td>
</tr>
<tr>
<td>SSP</td>
<td>Associated with underlying lung disease (e.g. chronic obstructive pulmonary disease, cystic fibrosis, AIDS with emphysema)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Related to trauma to the thorax</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Secondary to transthoracic or transbronchial lung biopsy (10% risk), central venous catheterisation, supra-clavicular nerve block</td>
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</tbody>
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**Table 2. Pathological changes associated with PSP**

<table>
<thead>
<tr>
<th>Pathological abnormality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELC (blebs/bullae)</td>
<td>Macroscopically visible areas of weakness on visceral pleura Occasional seen to be the sight of air leak Present in approx. 80% of cases Often bilateral</td>
</tr>
<tr>
<td>Fluorescein-enhanced autofluorescence</td>
<td>Represent areas of pleural/sub-pleural abnormality not visible with white light Often present at sites distinct from ELC in PSP lungs and not in controls Provides evidence of diffuse pleural porosity</td>
</tr>
<tr>
<td>Distal airway inflammation</td>
<td>Inflammatory infiltration with lymphocytes and macrophages within walls of bronchioles Associated fibrotic changes and compensatory emphysema</td>
</tr>
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occurrence prevention. This, in part, accounts for the relatively low compliance with published guidelines [6].
seen at thoracoscopy [13]. This compares with the presence of blebs/bulla in 6% of patients undergoing thoracoscopy for essential hyperhidrosis [14]. Indeed, in this study, patients with ELC were more likely to be smokers and have a low body mass index, both of which are independent risk factors for PSP.

When studied with fluorescein-enhanced autofluorescence, areas of high-grade abnormality were frequently visualised separate from any area of abnormality seen with white light at thoracoscopy in patients with PSP, and high-grade abnormalities were not seen in control patients undergoing bilateral thoracoscopic sympathicolyisis for essential hyperhidrosis [15]. Importantly, areas of fluorescein leak, i.e. areas of potential air leak, were visualised in only a small proportion of patients with PSP, but these areas of leak were noted to be distinct from areas of ELC. This would strongly suggest that the pathological process associated with PSP goes beyond the presence of ELC and that the site of air leak is not always related to a ruptured bleb or bulla.

The microscopic appearance of areas of lung tissue resected from patients with PSP has been noted to show features of chronic distal airway inflammation with lymphocyte and macrophage infiltration alongside fibrotic changes [16] and compensatory emphysema. This suggests an inflammatory aetiology to the formation of ELC. This is further supported by the noted presence of respiratory bronchiolitis (RB) in close to 90% of cases of PSP who underwent surgical resection in a different study. However, all patients in this study were current smokers, a recognised cause of RB [17]. When studied with electron microscopy, the linings of some resected areas of ELC have been shown to have an almost complete absence of mesothelial cells and abnormal pores present [18]. This information along with the fact that air leaks have been seen with fluorescein enhancement away from any macroscopically abnormal pleura leads to the hypothesis that pleural porosity contributes at least in part to the aetiology of PSP and thus rupture of ELC is not a prerequisite for a pneumothorax. It has been proposed that distal airway inflammation associated with PSP leads to obstructive gas trapping and consequent increases in distal airway pressure, which possibly causes air leak into the pleural space [19].

Although the aetiology of the pathological changes seen in patients with PSP is poorly understood, there are some clinical associations between patient phenotype and risk of PSP. Smoking is a major risk factor for PSP with a lifetime risk of 12% in smokers compared with 0.1% in non-smokers [3]. Tall stature and low body mass index are also associated with higher rates of PSP. It is hypothesised that the RB develops in smokers and leads to the development of ELC in patients predisposed to this process. A tall thin body habitus possibly predisposes to this due to increased pressure gradient between the lung base and apex resulting in increased alveolar distending pressures at the apex [20].

Although the patho-aetiology of the pleural abnormalities associated with PSP are incompletely understood, it has become clear over recent years that PSP is certainly not a disease of patients with normal lungs, and most likely is related to a diffuse inflammatory process within the pleura and underlying lung. It remains unclear whether ELC, visualised with either CT or at thoracoscopy, are the absolute cause of the air leak, or are simply an associated phenomenon or bystander.

**Initial Management**

There are a number of published international guidelines relating to the management of spontaneous pneumothorax with differences between these guidelines highlighting the fact that, even now, the absolute optimal management strategy for spontaneous pneumothorax is not clear [2, 4, 5]. Overall, the initial management of PSP depends on the size of the pneumothorax and its physiological impact on the patient. Small pneumothoraces can simply be observed without intervention. Larger PSPs should be treated in most cases initially with simple aspiration and only if this fails with inter-costal small-bore drain [21, 22]. There is much interest in developing outpatient management pathways which are suitable for many patients with PSP [23].

**Recurrence Prevention**

The risk of recurrence of PSP after a first event is approximately 30%, increasing to 62 and 83% after second and third events, respectively [24]. Therefore, recurrence prevention is an important aspect of the management strategy for patients with spontaneous pneumothorax. There is debate in the field about the best approach for recurrence prevention and the two areas central to the debate are the timing of recurrence prevention and the technique used.

As a general rule, recurrence prevention is considered in patients who have had more than one pneumothorax or are at increased risk of complications from a further
pneumothorax (e.g. high-risk professions such as flying personnel) [2]. However, there is an argument in favour of intervening after a first event as recurrence prevention at this juncture leads to fewer recurrences and overall savings in terms of both cost and total hospital stay with either video-assisted thoracoscopic surgery (VATS) or local anaesthetic thoracoscopy [11, 25, 26]. This must, however, be weighed against the risks associated with surgical intervention, e.g. chronic pain and paraesthesia at the surgical site. Furthermore, in healthy individuals, PSP is generally the cause of mild-to-moderate, easily treated symptoms rather than serious morbidity or mortality, and this should be borne in mind when considering recurrence prevention in first episodes.

More hotly debated is the best technical approach to recurrence prevention. The options can be summarised as being between resection of ELC versus pleurodesis or the combination of the two, and between open thoracotomy versus VATS versus local anaesthetic thoracoscopy. It is in relation to this debate that a sound understanding of the pathological abnormalities associated with PSP is important. As previously mentioned, the abnormalities within the pleura of patients with PSP are diffuse [15]. Therefore, it seems counterintuitive to simply resect areas of abnormality only visible to the naked eye. Indeed, the literature supports this, in that patients who undergo only bullectomy have a significantly higher recurrence rate than those who undergo bullectomy combined with pleurodesis [27]. The stated ‘gold standard’ recurrence prevention intervention is open thoracotomy with resection of blebs/bullae and pleurectomy/pleurodesis [2]. This approach is associated with a recurrence rate of <1%. However, it is associated with an increase in complications such as pain following thoracotomy and longer hospitalization. VATS with bullectomy and pleurodesis is associated with a slightly higher recurrence rate of 5% but shorter hospital stay and lower complication rates [28, 29].

Medical thoracoscopy with talc poudrage has been shown to be both a safe and effective technique for recurrence prevention of both PSP and SSP [26, 30, 31]. Although there has been discussion about the risk of the acute respiratory distress syndrome with the use of talc for pleurodesis, it now seems pretty clear that graded large-particle talc does not lead to the acute respiratory distress syndrome, is safe in use and is the most effective sclerosing agent [31]. Talc poudrage with medical thoracoscopy has a long-term recurrence rate of 5% in experienced hands [30, 32], similar to published recurrence rates with VATS, the most commonly used approach in current practice. As the pathological process associated with PSP is a diffuse one, it makes perfect sense that the most important aspect of recurrence prevention also addresses the pleura in a diffuse manner [33]. However, there does seem to be an increased risk of recurrence in the subgroup of patients with bullae >2 cm in diameter when treated with talc poudrage alone [30]. Currently, there is no published literature directly comparing the efficacy and complication rates of VATS with local anaesthetic thoracoscopy despite separate studies suggesting similar recurrence rates between both techniques and lower costs with local anaesthetic thoracoscopy [25, 34].

Conclusions

It has become clear that PSP is not an entirely spontaneous event but is a disease associated with widespread, often bilateral, abnormalities within the pleura. There remains uncertainty over the optimal management strategy for recurrence prevention and as such our patients’ opinions should be sought after discussion of therapeutic options. There is a strong indication for a randomised controlled trial making a direct comparison between VATS and local-anaesthetic thoracoscopy for the prevention of PSP recurrence.

References

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