Lung function in bronchiectasis: the influence of Pseudomonas aeruginosa

S.A. Evans, S.M. Turner, B.J. Bosch, C.C. Hardy, M.A. Woodhead


ABSTRACT: Sputum isolation of Pseudomonas aeruginosa (PA) is associated with extensive disease in bronchiectasis. It is not known, however, whether infection with P. aeruginosa is the result or the cause of severe disease.

We compared spirometry in patients with bronchiectasis before and after infection with P. aeruginosa, with that of patients infected by other organisms. All patients (n = 12) with chronic colonization by P. aeruginosa (PA group) were studied. These were compared with other patients with bronchiectasis with no isolations of P. aeruginosa (n = 37, non-PA group).

In the PA group, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were lower than in the non-PA group. The PA group, however, also had lower values at the time of initial colonization with P. aeruginosa than the current values for the non-PA group. Change in FEV1 and FVC over time was faster in the PA group than in the non-PA group. Reduction of FEV1 and FVC over time in the PA group prior to P. aeruginosa colonization was intermediate, not being statistically different from either value above.

Our results confirm the association of chronic P. aeruginosa colonization with poor lung function, but conclude that patients with bronchiectasis who become colonized by P. aeruginosa have poorer lung function when first colonized than those colonized by other organisms. Decline in lung function is faster in those chronically colonized by P. aeruginosa than in those colonized by other organisms. It is not clear whether chronic P. aeruginosa colonization causes an accelerated decline in lung function or whether it is simply a marker of those whose lung function is already declining rapidly.

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The prognosis of patients with bronchiectasis is usually good except when associated with cystic fibrosis (CF). The decline in lung function over time for the majority is no greater than that predicted due to ageing. A minority of patients, however, show a more rapid deterioration, the cause of which has not been determined [1, 2].

Haemophilus influenzae and Streptococcus pneumoniae are the bacteria most commonly isolated from sputum in patients with bronchiectasis, but Pseudomonas aeruginosa (PA) is also found in about 10% of cases [3]. Chronic colonization with P. aeruginosa is associated with a rapid decline in lung function in CF [4], and it has been suggested that this organism is associated with extensive lung disease and severe airflow obstruction in non-CF bronchiectasis; however, data in man are scarce [5].

Animal models of bronchiectasis suggest that P. aeruginosa results in disease of greater severity than H. influenzae and Staphylococcus aureus [6].

The aim of the present study was to establish whether patients with bronchiectasis who have chronic colonization by P. aeruginosa have poorer lung function than those colonized by other organisms, and to compare the rate of lung function decline in these two groups.

Methods

Patients

Patients were identified from the Respiratory Medicine department's bronchiectasis register, in which all patients attending the department with this condition are recorded (patients in register n = 135; chronically infected by P. aeruginosa n = 12; intermittently infected by P. aeruginosa n = 4). For the purposes of this study, bronchiectasis was defined as chronic sputum production and either thickened dilated bronchi typical of cylindrical bronchiectasis or cystic lesions typical of saccular bronchiectasis on chest radiograph or thoracic computed tomography (CT) scan. Serial sputum cultures and pulmonary function tests were performed at out-patient follow-up, at three monthly intervals in most patients.

All patients (n = 12) with chronic colonization with P. aeruginosa (PA group) were studied (median of 348 isolations, range 3-48). Chronic colonization was defined as >3 isolations of P. aeruginosa from separate sputum
samples over >3 months. Ten patients were female (mean age 60 yrs, range 52–82 yrs), and two were male (aged 60 and 78 yrs). Where a subsequent sputum culture isolated another organism but not *P. aeruginosa*, patients were excluded from the PA group and regarded as intermittently colonized. Four patients fell into this category (mean age 60 yrs, range 54–67 yrs, including one patient with rheumatoid arthritis, one with tracheobronchopathia osteochondroplastica and one with amyloidosis and chronic renal failure) and were not included in the main study. Patients were not excluded if isolations showed another organism in addition to *P. aeruginosa*.

The PA group were compared with those with no isolations of *P. aeruginosa* (non-PA group), comprising all other female patients with bronchiectasis aged >50 yrs (n=34, mean age 62 yrs, range 51–79 yrs), and 6 males from the bronchiectasis register matched for age to those in the PA group. Medical records were obtained in 37 cases. Recent sputum cultures showed *H. influenzae* in 22 cases, *Moraxella catarrhalis* in 4, *S. pneumoniae* in 1, *Stenotrophomonas maltophilia* in 1, and growth of only "normal flora" in 9. The median number of sputum isolations in this group was 3 (range 2–13).

Clinical details and pulmonary function were retrieved from case records by a single observer (SAE).

### Lung function

Spirometry was measured using a wedge bellows spirometer (Vitalograph TM Ltd, Buckingham UK) by two pulmonary function technicians (SMT and BBJ). Measurements were repeated until the two highest measurements differed by <5% - the highest was accepted. Spirometry measured during exacerbations was not used for analysis, and measurements more than 5% lower than the following three monthly value were also excluded from analysis, on the assumption that such values may have been the result of either poor technique or an unidentified exacerbation.

### Deoxyribonucleic acid (DNA) analysis

Patients in the PA group had mouth wash cell samples examined for AF508, G542X, G551D, and 621+1(G>T). These mutations account for more than 88% of CF genes in the North West Region of the UK [7].

### Statistics

Pulmonary function was analysed both as absolute and percentage predicted [8]. The characteristics of the groups were compared using the Mann-Whitney U test.

### Results

Causes of bronchiectasis and associated conditions are displayed in table 1. Time since diagnosis was significantly different between the two groups (PA 28±16 (mean±sd) yrs versus non-PA 17±18 yrs; p=0.05).

### Smoking habit

None of the PA group was a smoker during the study period, eight being life-long nonsmokers and two past smokers, with prestudy data being unavailable in two. Six of the non-PA group smoked during follow-up, 12 were life-long nonsmokers and 10 past smokers, with prestudy data being unavailable in nine.

### Previous thoracic surgery

One patient in the PA group had had a lobectomy, and one a thoracoplasty and phrenic nerve crush, both before the study period. Three of the non-PA group had had lobectomies, all being before the study period.

### Antibiotic treatment

Three out of 10 patients from the PA group (data unavailable in two) were known to have received continuous antibiotic therapy for more than 3 months prior to *P. aeruginosa* colonization, compared to 4 out of 37 in the non-PA group (p=0.05). Four out of 12 patients received continuous antibiotic therapy for more than 3 months after *P. aeruginosa* colonization (oral or nebulized), compared to 4 out of 37 in the non-PA group (p=0.07). The frequency of antibiotic courses were similar in the two groups (3.6±2.8 versus 3.0±2.3 courses-yr⁻¹; p=0.1), but these data are almost certainly incomplete, as courses of antibiotics given by the patient's general practitioner are often not documented in the hospital records.

### Lung function

The mean length of time over which lung function was monitored was 10.2±5.5 yrs for the PA group and 8.9±2.6 yrs for the non-PA group (p=0.05). Lung function data in the PA group was monitored for a mean of 4.9±4.4 yrs while infected with *P. aeruginosa*, with lung function data prior to *P. aeruginosa* infection being available in eight patients.

A comparison of lung function in the PA and non-PA groups is presented in table 2. In the PA group, current FEV₁ and FVC at the time of data analysis were lower

### Table 1. Causes of bronchiectasis and associated conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>PA group (n=12)</th>
<th>Non-PA group (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-tuberculuous</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
<td><strong>72</strong></td>
</tr>
</tbody>
</table>

**PA:** *Pseudomonas aeruginosa.*

smokers, with prestudy data being unavailable in two. Six of the non-PA group smoked during follow-up, 12 were life-long nonsmokers and 10 past smokers, with prestudy data being unavailable in nine.
Table 2. – Pulmonary function and change of pulmonary function over time

<table>
<thead>
<tr>
<th></th>
<th>PA group</th>
<th>Non-PA group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=37)</td>
</tr>
<tr>
<td>Latest FEV₁ L</td>
<td>0.68±0.28*</td>
<td>1.21±0.59</td>
</tr>
<tr>
<td>% pred</td>
<td>33±15*</td>
<td>53±20</td>
</tr>
<tr>
<td>Latest FVC L</td>
<td>1.26±0.36*</td>
<td>2.07±0.8</td>
</tr>
<tr>
<td>% pred</td>
<td>50±14*</td>
<td>73±20</td>
</tr>
<tr>
<td>FEV₁ at time of PA colonization L</td>
<td>0.76±0.27</td>
<td>37±13²</td>
</tr>
<tr>
<td>% pred</td>
<td>52±17</td>
<td></td>
</tr>
<tr>
<td>FVC at time of PA colonization L</td>
<td>1.41±0.45</td>
<td></td>
</tr>
<tr>
<td>% pred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in FEV₁ mL·yr⁻¹</td>
<td>-52±61 post-PA</td>
<td>-14±58</td>
</tr>
<tr>
<td>% pred</td>
<td>-3.0±4.7 post-PA*</td>
<td>-0.1±1.4</td>
</tr>
<tr>
<td>Change in FVC mL·yr⁻¹</td>
<td>-161±208 post-PA*</td>
<td>3±8</td>
</tr>
<tr>
<td>% pred</td>
<td>-4.0±7.4 post-PA*</td>
<td>+0.2±2.2</td>
</tr>
</tbody>
</table>

Values are presented as means. PA: Pseudomonas aeruginosa; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value; FVC: forced vital capacity. *: p<0.05, compared to the non-PA group (see text). ²: p<0.05, compared to the latest values for the non-PA group.

than in the non-PA group. The PA group, however, also had lower values at the time of initial P. aeruginosa infection than the current values for the non-PA group. Lung function was not related to time from diagnosis (% FEV₁ against time from diagnosis r = -0.26 (p=0.12), %FVC against time from diagnosis r = -0.23 (p=0.18).

The four patients who were intermittently colonized by P. aeruginosa had comparatively well-preserved lung function (mean FEV₁ 1.56 L (59% pred), FVC 2.82 L (77% pred)).

Change in pulmonary function over time

Reduction in percentage predicted FEV₁ and FVC over time, was faster in the PA group after P. aeruginosa infection, than in the non-PA group. Reduction of percentage predicted FEV₁ and FVC over time in the PA group prior to P. aeruginosa infection (n=6) was intermediate to, and not statistically different from, either value above (FEV₁ -0.8±2.7% pred·yr⁻¹; FVC -1.9±4.9% pred·yr⁻¹). Assessment of pulmonary function using absolute values gave similar results. Change in pulmonary function over time was not related to time from diagnosis in either group.

The four patients who were intermittently colonized by P. aeruginosa had a moderate fall in FEV₁ (-38 mL·yr⁻¹ or -0.98% pred·yr⁻¹).

DNA analysis

Mouth wash samples sent for genetic analysis from the PA group (n=9; three patients having died before samples were obtained) were all negative for AF508, G542X, G551D, and 621+1(G>T).

Discussion

This study has shown that patients with bronchiectasis chronically colonized by P. aeruginosa have poorer lung function than those colonized by other organisms. It has also shown that such patients have an increased rate of lung function decline compared to patients infected by other organisms, the rate of decline being comparable to that seen in CF patients colonized by P. aeruginosa [9]. The decline in lung function observed in those colonized by other organisms is similar to that seen in normal subjects [1]. It was also found, however, that those patients colonized by P. aeruginosa had poorer lung function at the time of initial colonization, compared to those colonized by other organisms.

The possibility that P. aeruginosa itself might cause a rapid decline in lung function, is supported by animal studies of experimental bronchiectasis, where P. aeruginosa inoculated into the bronchial lumen distal to a partially ligated bronchus produced more severe bronchiectatic changes than when equal numbers of H. influenzae or S. aureus were injected [6]. P. aeruginosa is a good candidate to cause progressive lung damage, as it produces toxins and virulence factors (e.g. exotoxin A, exotoxin S, phospholipase C, lipase, leukocidin, lipopolysaccharide and alginate) and proteolytic enzymes (e.g. alkaline protease and elastase), which interfere with host defence mechanisms [10–13]. In addition, P. aeruginosa produces factors which lead to epithelial disruption and reduced ciliary function, which could contribute to progressive lung damage [14, 15].

Our finding that those patients colonized by P. aeruginosa had poor lung function at the time of initial colonization, compared to those infected by other organisms, suggests, however, that P. aeruginosa merely colonizes those patients who already have rapidly declining lung function, and does not directly contribute to this decline. Experimental data suggest that bronchial wall damage is a necessary prerequisite for P. aeruginosa to adhere to respiratory epithelium [16, 17]. Interestingly, in CF, while colonization with P. aeruginosa is associated with poor lung function and a poor prognosis [9, 18–20], a causal relationship has not been shown, with CF patients infected by P. aeruginosa having a similar rate of lung function decline to CF patients infected by other organisms [9].

Another possibility is that P. aeruginosa colonises those with already rapidly deteriorating lung function but then causes an additional acceleration in lung function decline. We were unable to demonstrate a change in the rate of lung function decline after infection by P. aeruginosa, however, but were limited by the small number of patients with lung function measurements available prior to P. aeruginosa colonization.

The final explanation, is that the observations made were due to confounding factors, and did not relate to infection by P. aeruginosa. Data on potential confounding factors were collected, and there is no reason to believe that the group differences found were due to these. The six patients who smoked during the follow-up period were all in the non-PA group, and a history of past smoking was also more common in this group. No patients underwent thoracic surgery during the follow-up period. The causes of bronchiectasis are incompletely understood, but the apparent causes and associated diseases were similar in both groups. "Missed" CF has been described in some patients with apparent idiopathic bronchiectasis, but the genotype studies performed in our patients make this an unlikely confounding factor in the present study. While the patients in the PA group had been diagnosed as having bronchiectasis for a greater length of time, there was...
no relationship between time since diagnosis and pulmonary function or change in pulmonary function, making this an unlikely confounding factor. A final confounding factor, which may be relevant, is that of antibiotic therapy. A history of long-term antibiotic therapy was not significantly more frequent in either group, suggesting that treatment effects are unlikely to account for the differences found. Whilst the PA group tended to have at least as much antibiotic therapy as the non-PA group, it may have been less effective because of the antibiotic resistance which is a feature of the organism.

Our study has several limitations, which should be noted. It could be argued that lung function is not the best measure of the clinical status of a patient with bronchiectasis. The extent of radiological disease, symptoms, or performance scores might be more relevant parameters. Secondly, the growth of P. aeruginosa as the predominant bacterium on sputum culture, does not exclude the simultaneous presence of other organisms that might contribute to the decline in lung function observed. Finally, the small size of the PA group does limit the conclusions that can be drawn from this study.

In conclusion, the results of the present study confirm the association of P. aeruginosa colonization in patients with bronchiectasis with severe airflow obstruction, but it was also demonstrated that patients with bronchiectasis who become colonized by P. aeruginosa have poorer lung function at the time of colonization than those colonized by other organisms. It therefore appears that P. aeruginosa selectively colonizes those patients with poor lung function. Whether P. aeruginosa has a role in any subsequent decline in lung function is unclear. Decline in lung function is faster in those colonized by P. aeruginosa compared with those colonized by other organisms, but it was not possible to demonstrate an accelerated decline in lung function after P. aeruginosa colonization compared with before. Further study would be useful in addressing this issue but would be difficult to perform in view of the patient numbers needed and the length of follow-up required.

P. aeruginosa may, therefore, have a causal role in the rapid decline in lung function seen in these patients, or it may be only a marker of those whose lung function is already declining rapidly. Although P. aeruginosa colonization occurs in only a small proportion of patients with bronchiectasis, its association with rapidly declining lung function means that a better understanding of the factors leading to colonization may be an important step in preventing severe lung damage in this group.

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References


