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The effect of *Pseudomonas aeruginosa* on pulmonary function in patients with bronchiectasis

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Abstract

Introduction

Bronchiectasis patients are susceptible to infection with *Pseudomonas aeruginosa.* Isolation is associated with more severe disease, greater airflow obstruction and worse quality of life. It is not known whether infection by *P. aeruginosa* is a marker of disease severity, or contributes to disease progression.

Methods

Consecutive non-cystic fibrosis adult bronchiectasis outpatients (n=163), with multiple sputum cultures and follow-up pulmonary function tests, were designated, according to isolation of *P. aeruginosa*, as "Never infected" (Group 1) (n=67), "Intermittently isolated" (Group 2) (n=82) and "Chronically infected" (Group 3) (n=14). Based upon change in percentage predicted FEV1 levels at least two years after presentation, longitudinal behaviour was characterised as "improvement" (≥10% rise), "decline" (≥10% fall) or "stability". Baseline pulmonary function tests and longitudinal behaviour were examined in relation to pseudomonas status.

Results

There was no difference between the groups in age, gender, smoking habit or length of follow up. Baseline FEV_1 levels were highest in Group 1 (77.4 (24.3)) (mean (SD)) and higher in Group 2 (67.3 (25.7)) than in Group 3 (55.2 (18.5)), $p<0.005$. The same significant trends were seen for baseline FEV_1/FVC ratios and DLCO levels. Subsequent longitudinal behaviour was linked to baseline FEV1 levels, which were lowest in patients with improvement, and lower in association with decline than with stability, $p<0.00005$. However, longitudinal behaviour did not differ between groups I, 2 and 3, either before or after adjustment for baseline FEV1 levels.

Conclusion

Infection by *P. aeruginosa* occurs in bronchiectasis patients with more severe impairment of pulmonary function but does not influence rate of decline in pulmonary function either before or after adjustment for baseline disease severity. Thus *P. aeruginosa* is a marker of severity but is not linked to accelerated decline in pulmonary function.

Keywords

Pseudomonas aeruginosa

bronchiectasis

pulmonary function

Introduction

Bronchiectasis is defined as chronic dilatation of one or more bronchi. This causes poor mucus clearance and susceptibility to bacterial infection. Once a treatable cause has been excluded, the management largely involves physiotherapy and treatment with appropriate antibiotics, for treatment of exacerbations and in some cases prophylaxis. Chronic bacterial infection is common in patients with bronchiectasis, and the bronchial inflammation this stimulates has been implicated in disease progression (1, 2) . *Pseudomonas aeruginosa* is an opportunistic pathogen, affecting only those with impaired lung defences, such as patients with cystic fibrosis, other forms of bronchiectasis and severe chronic obstructive pulmonary disease (3-6). In cystic fibrosis *P. aeruginosa* infection leads to a deterioration of pulmonary function and ultimately respiratory failure and death (1, 7, 8). Although *P. aeruginosa* can be isolated intermittently in bronchiectasis, once it becomes a chronic infection it is rarely eradicated despite intensive intravenous antibiotic therapy (1, 9). Chronic infection is associated with more extensive lung disease and more severe airflow obstruction (10), but it is not known whether *P. aeruginosa* is simply a marker of severe disease which has occurred due to another cause, or whether it contributes to disease progression.

The purpose of the present study was to assess whether *P. aeruginosa* infection in patients with bronchiectasis is associated with a greater rate of decline in pulmonary function.

Methods

In this study we included consecutive adult patients, who satisfied the following criteria, from outpatient clinics during a six month period:

- A diagnosis of bronchiectasis made by high resolution computed tomography (CT). Diagnostic criteria used were:
    - Lack of tapering or flaring
    - “Signet ring” sign
- Followed up at the Royal Brompton for greater than two years
- Two or more sputum cultures results available per annum
- Two or more pulmonary function tests at a minimum interval of two years
- A negative sweat test to exclude cystic fibrosis
- No other major parenchymal lung diseases

We reviewed case notes to identify *P. aeruginosa* isolation in sputum cultures. Sputum samples from clinics and hospital stays were processed using selective and non-selective techniques (11). Patients were designated as: Group 1 ("Never infected" with *P. aeruginosa*, n= 67); Group 2 (*P. aeruginosa* isolated at least once, but not on all occasions,"Intermittently isolated" n= 82); Group 3 (*P. aeruginosa* in all cultures, "Chronically infected" n= 14). Group 2 included a sub-group of patients developing chronic isolation of P. aeruginosa during follow-up (n=16). It is our practice to perform pulmonary function tests during a period of clinical stability and this was verified in the case notes. This is defined as lack of change in symptoms, and no change in treatment including a requirement for additional antibiotics, for four weeks prior to the lung function test. Patients are followed up at least annually in these clinics, whatever their disease severity, so all patients, under our care, who had appointments in this time were considered. Serial changes between the first and last pulmonary function tests were evaluated.

Percentage predicted forced expiratory volume in 1 second (FEV_1), percentage predicted residual volume (RV), percentage predicted corrected diffusion capacity, corrected for haemoglobin (DLCO) and FEV_1/FVC ratio were noted. FEV1 levels have the strongest correlation with the severity of morphologic abnormalities on HRCT (11, 12) and were designated as the primary end-point. Normal values for pulmonary function testing were validated in the study by Crapo et al(13). Since we do not know whether the rate of decline in bronchiectasis is continuous or whether discrete events, such as infections, lead to irregular periods of decline on a background of general stability, we have analysed pulmonary function trends to cover both possibilities. For the primary analysis, based upon our clinical experience that deterioration is usually discrete and not continuous. Serial change in percentage predicted FEV_1 from baseline to last measurement was characterised as "improvement" (>10% improvement from baseline value), "decline" (>10% decline from baseline value), and "stability" (final value within 10% of baseline value) (12). A secondary post hoc analysis of serial change in FEV1 expressed as mls/year (over the total follow up time) was also performed.

Patients were managed in our Unit by a set protocol which has not changed during the study. Infective exacerbations are treated with oral antibiotics guided by sputum microbiology, antibiotic sensitivities and patient antibiotic history. Failure leads to a clinic appointment and admission for intravenous antibiotics if required. Antibiotic prophylaxis is introduced if patients have >6 infective exacerbations per year despite optimal (eg physiotherapy) management. Oral antibiotics during the winter months (amoxycillin or doxycycline) for non-pseudomonas patients, and nebulised colomycin throughout the year for pseudomonas patients, are first-line treatments. Asthma and acid reflux were treated in the usual way if present. Inhaled steroids were assessed in an objective manner (lung function and sputum characteristics) and only continued if benefits are demonstrated; oral

corticosteroids are only used in severe exacerbations. At the time of the study long term macrolide antibiotics were not used as antibiotic prophylaxis.

All routine pulmonary function tests were performed in our department using the Jaeger Compact Masterlab pulmonary function equipment. Inhaled treatment is not taken on the day of the test. The spirometry was performed in a conventional way by carrying out maximal flow-volume loops in a graphical form of flow versus volume, recorded from a maximal forced expiration, starting from full inspiration, immediately followed by a maximal inspiration, this is performed as one manoeuvre. Several manoeuvres are performed and the results reported should be the greatest FEV1 and FVC from at least three technically acceptable manoeuvres, irrespective of the manoeuvre in which they occur, as per recommendations published by BTS and ARTP in 1994 (14). Jaeger equipment has been used for about 13 years; although some has been replaced the results obtained have always remained comparable. We perform biological control tests on a daily basis on normal staff members and we have seen no trend regarding a change in pulmonary function test results obtained for more than a decade. The same predicted values have been used by our department over the last twelve years (13,15).

Population data are expressed as means with standard deviations for normally distributed variables (age, time between pulmonary function tests, percentage predicted FEV1, percentage predicted DLco, FEV1/FVC ratio) and as median values with ranges for abnormally distributed variables (percentage predicted RV; serial changes in FEV1, expressed as mls/year). Group comparisons were made using t testing or analysis of variance for normally distributed variables, Wilcoxon's rank sum test or the Kruskal Wallis test for abnormally distributed variables and chi-squared statistics for all comparisons of proportion. A p value of <0.05 was taken to indicate statistical significance. Logistic regression models were constructed to determine whether 1) improvement and 2) decline were linked to *P. aeruginosa* status after adjustment for baseline FEV_1 levels. This was an important factor as those who had never isolated *P. aeruginosa* started with a higher FEV_1.

Results

Clinical data are compared between groups 1, 2 and 3 in Table 1; no significant or marginal sub-group differences were identified.

Patient Characteristics (Table 1)

	Group 1 (never isolated)	Group 2 (intermittent isolation)	Group 3 (chronic isolation)
Number	67	82	14
Age at first pulmonary function test (years) (SD)	43.6 (14.6)	45.1 (12.2)	49.4 (14.91)
Gender (M:F)	21 : 46	25 : 57	6 : 8
Smoking Habit (Yes:No:Ex)	2 : 54 : 11	0 : 66 : 16	0 : 11 : 3
Time between Pulmonary Function test (years) (SD)	9.9 (4.9)	11.0 (5.5)	8.8 (5.3)

Baseline Pulmonary Function tests

As shown in Table 2, baseline FEV_1 levels were highest in Group 1 and higher in Group 2 than in Group 3 ($p<0.005$) (Figure 1). Similar trends emerged for FEV_1/FVC ($p=0.02$) and DLCO ($p=0.02$), but not for RV (Table 2).

Group 2 patients developing chronic isolation of *P. aeruginosa* during follow-up (n=16) were seen for a mean time of 6.34 years (3.74; 2.1 – 21.1 years (SD; range)) before *P. aeruginosa* acquisition and for a mean time of 8.75 (5.3; 1.9 – 11.1 years (SD; range)) afterwards. They had lower baseline FEV_1 levels at baseline (58.6 (20.5)) (mean (SD)) ($p<0.01$) and higher RV levels (160.5 (65.8)) ($p<0.05$) than group 1 patients. However, percent predicted FEV1 levels did not differ significantly (paired t-test) before and after the acquisition of chronic *P. aeruginosa* isolation (58.6 (20.5) vs 59.4 (25.3)).

Pulmonary function test results at baseline (Table 2)

	% predicted FEV_1	FEV_1/FVC	% predicted RV	% predicted DLCO
Group 1	77.4 (24.3)	69.1 (13.7)	120 (74 to 258)	83.4 (13.9)
Group 2	67.3 (25.7)	63.1 (17.7)	126 (68 to 349)	78.8 (20.9)
Group 3	55.2 (18.5)	58.5 (12.6)	141 (86 to 264)	68.9 (22.5)
Trend across groups	*p<0.005*	*P=0.02*	*NS*	*p=0.02*

Results are shown as mean (SD), except for % predicted RV levels, which were positively skewed and are stated as median values with ranges.

Longitudinal behaviour in relation to baseline FEV1 levels

Analysis of changes in FEV_1 during follow up (Figure 2) showed that patients with improvement had the lowest baseline FEV_1 levels (53.7 (20.9) (mean (SD)); FEV1 levels were lower in association with subsequent decline (71.6 (20.6)) than with stability (77.9 (28.7)). Significance was shown in all comparisons, improvement vs decline ($p<0.005$), improvement vs stability ($p<0.00005$) and decline vs stability ($p<0.01$).

Longitudinal behaviour in relation to pseudomonas status

P. aeruginosa status was not linked to longitudinal behaviour. Neither "decline" [group 1 (21/67, 31%), group 2 (25/82, 30%), group 3 (5/14, 36%)] nor "improvement" [group 1 (13/67, 19%), group 2 (26/82, 32%), group 3 (3/14 (21%)] differed significantly between groups. These findings were not altered by analysis of absolute changes in FEV1 per year (median values: Group 1 = 24 mls; Group 2 = 17mls; Group 3 = 23mls), with no significant or marginal group differences on non-parametric analysis (Wilcoxon's rank sum test). The p value for groups 1 vs 2, 1 vs 3 and 2 vs 3 are 0.43, 0.68 and 0.92 respectively. When rate of decline in FEV1 (in mls/yr) was compared before and after acquisition of chronic P. aeruginosa there was no significant difference (-1.3 (4.3) vs 0.2 (3.8); mean (SD)), using Wilcoxon's rank sum test ($p=0.35$).

Examination of separate logistic regression models showed that neither decline nor improvement in FEV1 was linked to *P. aeruginosa* status after adjustment for baseline FEV1 status. An improvement of >10% in FEV1 was less frequent with a higher base-line FEV1 (odds ratio = 0.96; 95% confidence intervals 0.95, 0.98; $p<0.0005$), with no independent relationship to *P. aeruginosa* status (odds ratio = 0.93; 95% confidence intervals 0.51, 1.72; $p=0.83$). A decline of >10% in FEV1 was related to neither baseline FEV1 nor *P. aeruginosa* status.

Discussion

A vicious circle of bacteria stimulated host mediated lung damage caused by chronic inflammation has been proposed in bronchiectasis(16, 17). Systemic markers of inflammation are elevated in stable disease and are increased, together with sputum markers, during exacerbations. The level of chronic inflammation is thought to be responsible for disease progression and many of the symptoms that patients experience (18, 19). Therefore chronic bacterial infection might be expected to accelerate decline in pulmonary function.

P. aeruginosa is an opportunistic pathogen, affecting only those with an impaired host defence. In cystic fibrosis infection can occur at an early age, before severe bronchiectasis has developed, and various explanations have been put forward for this unique host-bacterial interaction (20-22). There is an exuberant inflammatory response

to the chronic bacterial infection (23), and a large number of exotoxins are produced by *P. aeruginosa* (24). There is a strong antibody response to *P. aeruginosa* in pulmonary secretions, saliva and serum, and immune complexes are thought to contribute to the inflammatory process (25).

The host-bacterial relationship in non-cystic fibrosis bronchiectasis is less clear. In most cases the severity of abnormality in the airways is not as severe as in cystic fibrosis, and there has been no suggestion of any unique host-bacterial interaction. Intermittent isolation is more common than reported in cystic fibrosis. The change from non-mucoid to mucoid phenotype does occur with chronic infection, but is found predominately in patients with severe disease (2). The isolation of *P. aeruginosa* in bronchiectasis might be more analogous to chronic obstructive pulmonary disease patients, where it has also been recognised as a pathogen in patients with very severe airflow obstruction (26-28). Evans et al (4) showed an association between *P. aeruginosa* and disease severity in bronchiectasis patients. This study showed a significant reduction in FEV_1 and FVC in those chronically infected with *P. aeruginosa* compared with those who had never isolated *P. aeruginosa*. They also observed an accelerated decline in FEV_1 and FVC in patients with chronic *P. aeruginosa* infection, but could not exclude the possibility of deterioration prior to *P. aeruginosa* isolation. Wells et al also found an association between colonisation and more severe disease but provided no longitudinal data (10).

Another study comparing severity of bronchiectasis on thin section CT scans with *P. aeruginosa* isolation from concurrent sputum samples by Miszkiel et al [30], showed a strong relationship between *P. aeruginosa* infection of concurrent sputum samples and increased severity and extensiveness of disease on CT. The *P. aeruginosa* group had more extensive CT features of bronchiectasis, a greater degree of bronchial wall thickening and dilatation, as well as evidence of a greater degree of small airways disease indicated by more extensive decreased attenuation.

In a study of eighty seven patients with non-cystic fibrosis (non-cystic fibrosis) bronchiectasis, in a stable phase of their illness, the quality of life of patients infected by *P. aeruginosa* was significantly worse than non-*P. aeruginosa* patients. This paper also showed the *P. aeruginosa* group had worse pulmonary function, but no significant differences were found between the groups for forced expiratory volume in one second (FEV_1) and peak expiratory flow rate unless the length of *P. aeruginosa* infection was considered. Patients infected by *P. aeruginosa* for more than 3 yrs had significantly worse FEV_1 ($p<0.03$) and bronchiectasis scores ($p<0.05$) than those infected with *P. aeruginosa* for less time (29).

An interesting observation in the present study concerns linkages between baseline FEV_1 and longitudinal behaviour. Patients exhibiting improvement or decline had lower baseline FEV_1 levels than those with stable disease, who had minor reductions in baseline FEV_1 (mean of 77%). Subsequent improvement was associated with the lowest mean baseline FEV_1 (performed in a stable phase of their disease). The authors believe that this apparent anomaly is probably due to the previous observation (12) that improvement in FEV_1 is largely due to clearance of mucus plugging. Therefore, treatment of an underlying condition, e.g. hypogammaglobulinaemia, regular physiotherapy and antibiotic treatment probably led to this improvement in a group of patients in whom major management improvements were attainable. It is important to consider that the lower baseline FEV_1 levels in the improvement group provide a larger abnormal pulmonary function signal and therefore a greater opportunity to observe improvement.

In the present study we have confirmed previous studies that *P. aeruginosa* isolation occurs in some patients intermittently, and since some of these patients were followed up for more than 10 years we have shown that the inevitable progression to chronic infection which occurs in cystic fibrosis does not necessarily occur in non-cystic fibrosis bronchiectasis. There is an association of chronic *P. aeruginosa* infection with more severe airflow obstruction which is present in patients who acquired *P. aeruginosa* during the study period and those with chronic infection, but not in the group with intermittent isolation. The association with more severe disease is also true for % predicted DLCO. However, in bronchiectasis, the severity of the airflow obstruction is not as severe as seen in COPD, where cases usually have $FEV_1 < 30\%$ predicted. *P. aeruginosa* has a high affinity for mucus, and it is possible that impairment of mucociliary clearance, and cough clearance, that occurs in bronchiectatic airways due to mucus hypersecretion, increased mucus viscosity and loss of cilia predisposes to the colonization (2). Another factor may be antibiotic treatment which may be given more frequently in bronchiectasis and drive the airway bacterial flora towards the more antibiotic resistant *P. aeruginosa* (4, 10, 29).

In our study we have not shown any difference in rate of pulmonary function decline between patients with and without *P. aeruginosa* infection. We have also been able to study a cohort of patients before and after *P. aeruginosa* acquisition and show no change in rate of decline in FEV_1. These results suggest that *P. aeruginosa* is a marker of disease severity, but does not account for the impairment in pulmonary function, nor accelerate the decline. Patients were not recruited prospectively with this specific study in mind, and there was therefore no strict protocol for the timing of sputum examination and lung function measurement. However we do have a protocol for culturing at least once each year, and performing lung function every three years. We tried to avoid unrecognised bias by enrolling consecutive patients from clinic who all had bronchiectasis at the outset. Changes in pulmonary function over time were, in most cases, small and yet there was a high prevalence of both decline and

improvement. *P. aeruginosa* does not appear any worse than other species in causing decline. We have previously hypothesised that patients with chronic *P. aeruginosa* infection have worse quality of life in part because they have more severe disease, but also because they are given more medication (e.g. nebulised antibiotics) and required more admissions to hospital (because ciprofloxacin is the only available oral antibiotic). It is possible that without this extra treatment patients might have an accelerated decline after *P. aeruginosa* infection. However our results do show that any accelerated decline after *P. aeruginosa* colonization can be prevented. Another concern is that progressive lung damage might occur due to *P. aeruginosa* infection without any change in pulmonary function. However this is unlikely to be clinically important if there has been no change in pulmonary function. This has recently been reported in cystic fibrosis (30). Our current practice is to only repeat CT scans, because of concerns about the radiation involved, if there is a change in clinical status.

In conclusion, our study shows that *P. aeruginosa* status in bronchiectasis is a marker of more severe airflow obstruction but is not associated with an accelerated decline in pulmonary function parameters, even after adjustment for baseline disease severity.

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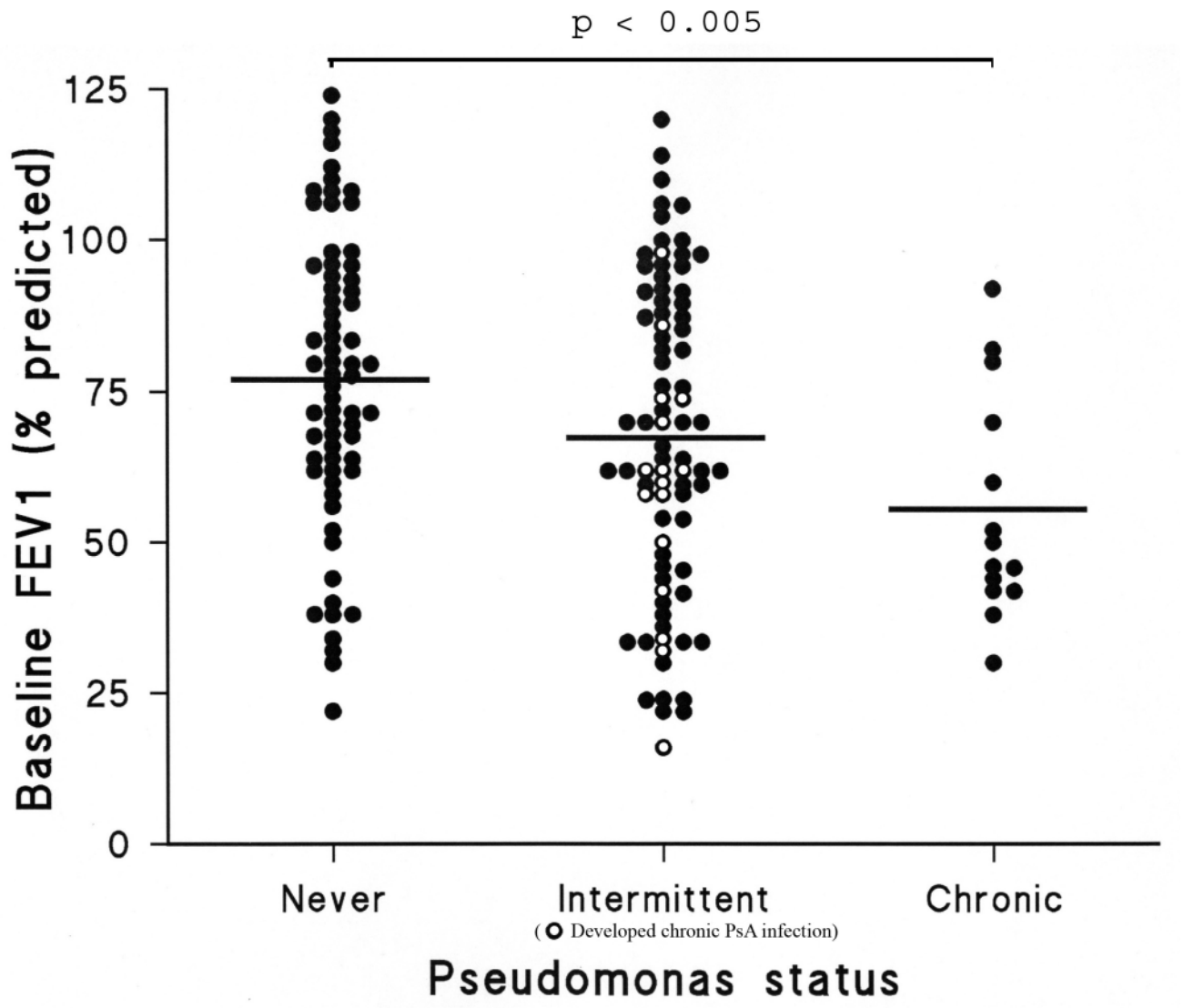

Figure 1. Comparison of baseline FEV1 with pseudomonas status.

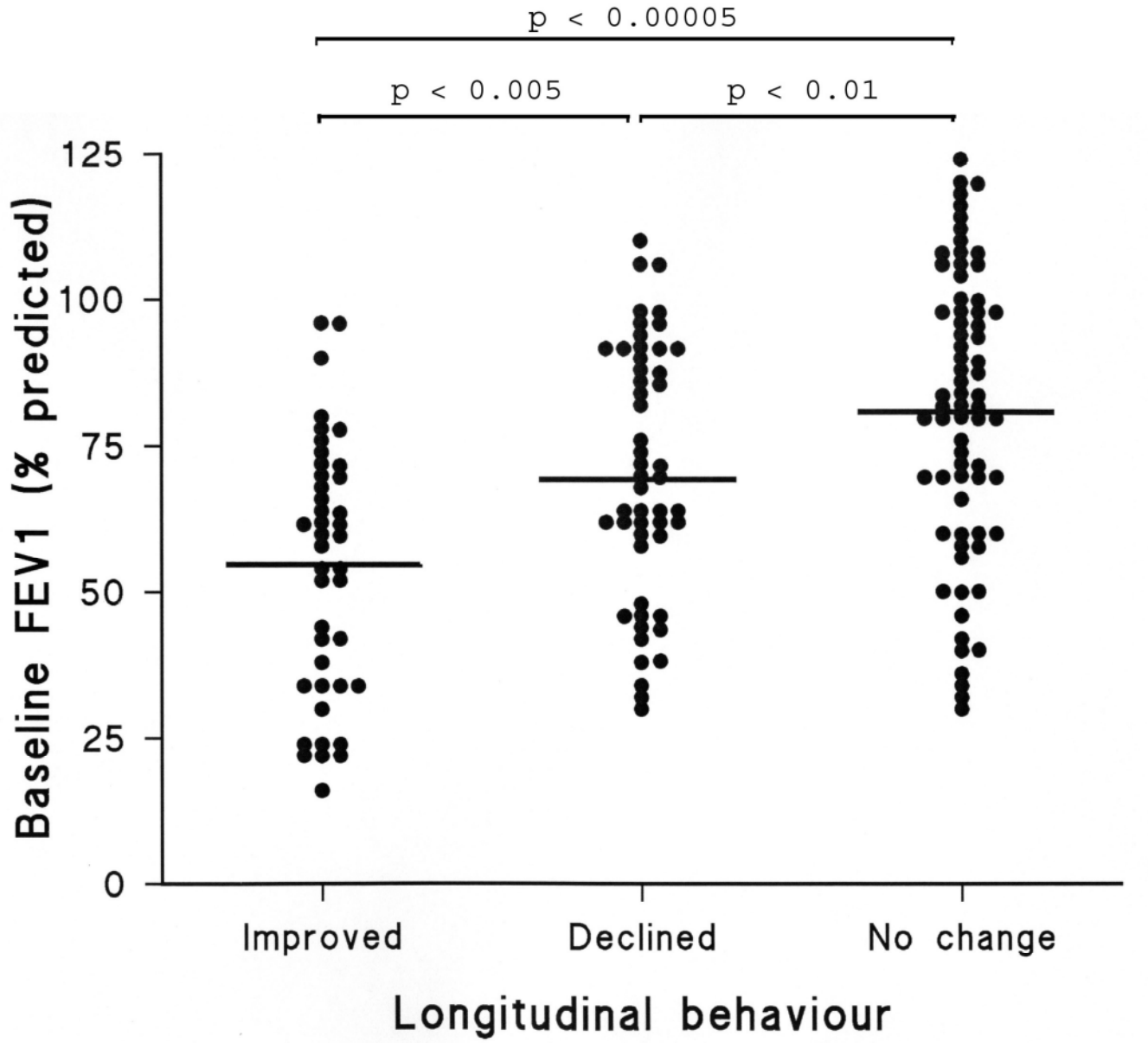

Figure 2. Comparison of baseline FEV1 with longitudinal behaviour, when analysed as decline or improvement of > 10% over time.