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Maximal mid expiratory flow detects early lung disease in Alpha-1 Antitrypsin Deficiency.

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Take Home Message

Mean mid-expiratory flow indicates early disease, worse health status and predicts decline in AATD patients without COPD.

Abstract

Pathological studies suggest loss of small airways precedes airflow obstruction and emphysema in COPD. Not all Alpha 1 Anti-trypsin deficiency(AATD) patients develop COPD and measures of small airways function might be able to detect those at risk.

MMEF, FEV_1, FEV_1/FVC ratio, health status, presence of emphysema (CT densitometry) and subsequent decline in FEV_1 were assessed in 196 AATD patients.

FEV_1/FVC, FEV_1 %predicted and lung densitometry, related to MMEF %predicted (r^2=0·778, p<0·0001; r^2 =0·787, p<0·0001, r^2 =0·594, p<0·0001, respectively) in a curvilinear fashion. Patients could be divided into those with normal FEV_1/FVC and maximal mid-expiratory flow (MMEF)(Group 1), normal FEV_1/FVC and reduced MMEF(Group 2) and those with spirometrically-defined COPD(Group 3). Patients in Group 2 had worse health status than Group 1 (Total SGRQ (median) 23·15 [IQR7·09-39·63] versus 9·67 [IQR 1·83-22·35]; p=0·006) and had a greater subsequent decline in FEV_1 (median change in FEV_1=-1·09% predicted/year [IQR=-1·91--0·04] versus -0·04%predicted/year [IQR =-0·67-0·03]; p=0·007).

A reduction in MMEF is an early feature of lung disease in AATD and is associated with impaired health status and a faster decline in FEV_1.

Introduction

The early detection and prevention of COPD are key objectives both scientifically and clinically. COPD is defined physiologically by the presence of airflow obstruction (FEV_1/FVC ratio<70%) and disease severity is stratified by FEV_1 impairment[1], however, there is increasing recognition that FEV_1 and FEV_1/FVC ratio lack sensitivity to identify early disease or patients at risk of subsequent decline without serial testing over a prolonged period of time[2, 3]. Therefore, there has been a revival of interest in assessing the small airways of the lungs. The cross-sectional micro-Computed Tomographic (CT) imaging studies of Hogg and colleagues[4, 5] reported major loss of small airways prior to the development of abnormal spirometry or emphysema in COPD patients. They hypothesised that reduced small airways function (by narrowing and reduction in number) precedes the decline in FEV_1 and the development of emphysema in the very early stages of COPD. This is important as emphysema can be present with normal spirometry[6, 7], is a predictor of mortality even in patients without COPD[8] and also relates to the subsequent decline in FEV_1[9, 10], which itself is a major predictor of mortality for COPD patients[11] and may not be influenced by current inhaled therapies[12].

Understanding the relationship of small airways dysfunction (SAD) to the presence and subsequent progression of lung disease may be of central importance in the early detection of COPD. However, only a proportion of smokers develop COPD[13] and only a proportion of patients with COPD develop emphysema[14] and so studying an unselected, "at risk" population to determine the relationship between SAD and the subsequent onset of emphysema and COPD would be demanding as a proof of principle study. Here, alpha-1 antitrypsin deficiency (AATD) serves as a useful model. AATD is a genetic susceptibility to COPD, where a significant proportion of smokers develop COPD at a younger age than non-AATD COPD, characterised by a predominant emphysema phenotype[15].

Importantly a proportion of AATD patients who have never smoked also develop airflow obstruction and emphysema, although some do not[16] and currently we are unable to predict those at risk of decline. Family testing identifies siblings/progeny earlier in the disease process, often before COPD and emphysema are detectable, allowing the whole time course of the disease process to be observed.

We hypothesised that a proportion of never smoking AATD patients would have evidence of SAD without COPD, and those patients would experience more lung symptoms and would be at greater risk of subsequent progression.

The current study aimed to determine the relationship of the maximal mid-expiratory flow (MMEF- a spirometric parameter that when reduced is suggestive of SAD[17] and is readily available from the flow volume loop) to FEV_1 and FEV_1/FVC ratio, health status and CT defined emphysema. Of particular interest were subjects with both an FEV_1 and FEV_1/FVC ratio within the "normal range" to determine whether the presence of SAD might precede conventional airflow obstruction. In addition, follow up spirometry was analysed to relate the initial presence of SAD to subsequent decline in FEV_1. Percent predicted values were utilised as these are already adjusted for age, sex, height and ethnicity; thus accounting for these major determinants of lung function. In this proof of principle study, only never smoking AATD patients were included to determine the natural history of this disease and avoid the potential impact of variable smoking histories on lung physiology.

Materials and Methods

Study Subjects

ADAPT includes the UK registry for individuals with AATD. The programme was approved by the South Birmingham Research and Ethics Committee (Ref number; 3359a) and all patients provided written, informed consent. Patients were recruited either through medical referral (index) or family screening (non-index). For this study, >95% of index patients were screened for AATD due to a past medical history of respiratory symptoms, including an awareness of breathlessness greater than expected, cough or recurrent chest infections. Less than 5% of patients were identified by the presence of abnormal and unexplained liver function tests but not liver disease. Patients with significant structural lung disease (such as bronchiectasis) were excluded. Asthma is known to effect small airways function[18] and this was specifically screened for symptomatically as previously described[19].

Patients participating in this study had annual assessments that included post-bronchodilator full lung function, blood biochemistry and haematology, and health status using the St.

George's Respiratory Questionnaire (SGRQ). Patients also had a high resolution CT scan at baseline for qualitative and quantitative assessment where this had not been undertaken by the referring clinicians.

Methods

Initial baseline data was collected for lifelong never-smokers with a PiZZ AATD genotype. Measures of lung function were assessed on the same day as the clinical and health status data. Spirometry data included FEV_1, FEV_1/FVC and MMEF. FEV_1 and MMEF were expressed as % predicted to differentiate between natural decline in lung function due to ageing (where absolute values decrease but % predicted remains stable) and decline due to disease (where both absolute and % predicted values decrease). The FEV_1/FVC ratio was expressed as a percentage and the gas transfer coefficient (Kco) was documented as % predicted.

MMEF was chosen as it is the most readily accessible spirometric parameter that may relate to small airways function. However, the utility of MMEF in this carefully selected group of AATD patients is unclear. In the current study a cut-off of 80% predicted was pragmatically chosen for MMEF as this is compatible with previous studies (for example,[20, 21]) and meant that those described as "normal" for the purposes of this study were less likely to include patients with small airways dysfunction.

Decline in lung function was primarily determined by the change in % predicted for age, sex, height, and ethnicity using linear regression determined for all annual data points (provided ≥4) for each patient. Rapid decliners were defined as those whose lung function decline (FEV_1 change) was > −1.0% predicted per year as described previously[22].

All lung function tests were performed on Jaeger Masterscreen Pro lung function system (Jaeger Ltd, Hochberg, Germany) according to the Association for Respiratory Technology and Physiology/British Thoracic Society guidelines for quality control[23]. Predicted values for all tests were calculated from the European Community for Steel and Coal reference equations[24].

For high resolution CT scans (GE Prospeed Scanner; General Electrical Medical Systems; Milwaukee, WI), 1 mm slices were taken at 10 mm intervals through the thorax at full inspiration. Mean lung density was recorded in Hounsfield Units (HU), with a value less than -950 HU used as a threshold consistent with the presence of macroscopic emphysema[25]. CT data was included only where it was available and suitable for quantifiable analysis at the start of the study (at the time of baseline MMEF and lung function data) and is expressed as the PD15 (percentile point indicating the density of the lowest 15% of the voxels).

Analysis

The main outcome measures included the spirometric parameters FEV_1, FEV_1/FVC and MMEF. Secondary outcome measures included Kco and lung densitometry. T-tests, Mann-Whitney U tests and Kruskal Wallis were used to compare categories and spline modelling was used to determine the strength of any relationship. Chi-Squared tests were used to compare categorical data between groups. The predicted positive and negative value of MMEF to detect a rapid decline in lung function in patients with no physiological evidence of COPD was calculated using standard methods[26]. A p value of $<0{\cdot}05$ was taken to be statistically significant for all analyses.

Results

A total of 196 never-smoking PiZZ AATD patients were identified and divided into three physiological groups; Group 1 (n=43) had FEV_1/FVC>70% and MMEF$\geq$80% predicted (no SAD, no COPD); Group 2 (n=40) had FEV_1/FVC>70% and MMEF<80% predicted (SAD but no COPD) and Group 3 (n=113) had FEV1/FVC<70%, thus meeting physiological diagnostic criteria for COPD[27]. No patients had an MMEF$\geq$80% predicted and evidence of COPD. Demographic data and lung function of patients in the three physiological groups are shown in Table 1. There were a greater proportion of females in Group 2 (SAD but no COPD) compared to Group 1 (no SAD and no COPD, p=0·035) and Group 3 (COPD, p=0·002). The average age increased across groups with Group 1 patients being the youngest (p<0·001 for the difference across all groups). There was a greater proportion of index patients in Group 3 compared to Group 1 (p<0·001) and Group 2 (p<0·001). The prevalance of asthma was approximately 10% across this population and there were no differences in prevalence between groups (see table 1).

Group 2 (SAD, no COPD) had worse lung function than Group 1 (no SAD, no COPD), including FEV_1% predicted (p=0·011), FEV_1/FVC (p=0·009), Kco% predicted (p=0·055) and, by definition, MMEF% predicted (p<0·001). In turn, Group 3 (COPD) had worse lung function than Group 2 (p<0·001 for all indices, including FEV_1% predicted, FEV_1/FVC, Kco % predicted and MMEF % predicted).

Table 1 – Demographic Data

Variables	Group 1	Group 2	Group 3
Number of Patients	43	40	113
Males : Females	20 : 23	10 : 30 ǂ¥	60 : 53
Age (yr)	38·1 ± 13·1	49·1 ± 13·1 ǂ	60·4 ± 9·4 ǂ§
Index : Non-Index	20 : 23	21 : 19	96 : 17 ǂ§
FEV_1 % Predicted	118·7 ± 13·7	105·6 ± 15·6 ǂ	65·0 ± 23·7 ǂ§
FVC (%)	114.8 (107.4 – 129.3)	109.8 (99.4 – 126.9)	117.9 (100.4 – 135.0)
FEV_1/FVC (%)	86·0 ± 5·7	79·2 ± 5·5 ǂ	44·6 ± 12·7 ǂ§
MMEF % Predicted	110·7 ± 19·7	60·1 ± 12·6 ǂ	17·5 ± 11·4 ǂ§
Kco % Predicted	93·4 ± 18·5	83·5 ± 15·5	67·3 ± 20·7 ǂ§
Δ FEV_1 (ml/yr)	-27.9¥§ (-49.1 - -4.87)	-52.7 ǂ (-78.5 - -22.7)	-57.3 ǂ (-83.3 - -27.3)
Serum AATD level	4.4 (3.05 – 4.98)	3.9 (2.8 – 4.6)	4.2 (3.28 – 5.03)
Asthma, n (%)	4 (9.3)	4 (10)	5 (4.4)

Patient demographics are summarised for the 3 groups with mean ± SD unless otherwise stated. Change in FEV1 is the decline based on 4 measurements taken over 3 years and expressed as median and range. AAT level is serum level (measured in umol/l and is given as the median and range. Asthma is the number in each group with a Consultant physician confirmed diagnosis. Differences between groups are indicated by the symbols; ǂ Significantly different from Group 1: § Significantly different from Group 2:¥ Significantly different from Group 3

Relationship between lung function measurements

There was a strong (r^2=0·778, p<0·0001) relationship between the FEV_1/FVC ratio and MMEF % predicted (Figure 1) and for FEV_1 % predicted and MMEF % predicted (r^2=0·787, p<0·0001). There was a weaker though significant relationship (r^2=0·198, p<0·0001) between Kco % predicted and MMEF % predicted.

Health Status

Health status was assessed at baseline using the SGRQ. The median total SGRQ score was greater (indicating worse health status) in Group 2 (SAD, no COPD: median 23·15, IQR 7·09-39·63) than Group 1 (no SAD, no COPD: median 9·67, IQR 1·83-22·35, p=0·006) (Figure 2A). The same trend was seen for the individual domains with a median of 29·49, IQR 5·96-51·00 and 5·84, IQR 0·00-26·97, respectively for activity (p<0·001) (Figure 2B) and 15·38, IQR 1·90-26·40 and 3·89, IQR 0·00-11·60, respectively for disease impact (p=0·028) (Figure 2C). However, there was no significant difference (p>0·05) between SGRQ symptom scores for Group 1 (median 29·17, IQR 5·23-45·61) and Group 2 (median 37·77, IQR 17·07-59·59) (Figure 2D). SGRQ scores were even greater in Group 3 (COPD) compare to Group 2 for total score (median 38·25, IQR 27·06-53·72, p<0·0001), activity (median 53·62, IQR 35·60-66·19, p<0·0001), disease impact (median 24·80, IQR 14·11-40·50, p<0·001)) and symptoms (median 54·74, IQR 42·38-68·57, p=0·002).

Lung Function Decline

The rate of FEV_1 decline (% predicted) following baseline measurement was measured over at least 3 years to ensure at 4 or more data points for analysis[16]. The median decline was greater in Group 2 (SAD, no COPD: median change in FEV_1 -1·09% predicted/year, IQR -1·91 to -0·04) than Group 1 (no SAD, no COPD: median change in FEV_1 -0·04% predicted/year, IQR -0·67 to 0·03) (p=0·007). The median decline in FEV_1 in Group 3 (COPD) was similar (p>0·05) to that in Group 2 (-1·41% predicted/year, IQR -2·27 to -0·22) as shown in Figure 3.The decline in FEV_1 expressed as ml/year is shown in Table 1.

85% of AATD patients without COPD and an MMEF ≥80% predicted did not subsequently decline rapidly (an 85% negative predictive value). The positive predictive value was 57%.

CT Densitometry

Quantitative CT densitometry was available for 109 patients. There was a significant relationship of mean lung density in Hounsfield Units (HU) to MMEF % predicted (Figure 4) (r^2=0·594, p<0·0001). Although numbers are low, all patients with MMEF > 80% predicted had no evidence of emphysema (n = 3, Median PD15 (Interquartile range, IQR) -904.6 (-922.76 - -876.75). 11 patients had a reduced MMEF (<80% predicted) with the PD15 above the -950 HU threshold (median PD15 (IQR); -902.8(-913.05 - -873.35), with no macroscopic

emphysema. 95 patients had macroscopic emphysema (determined as the PD15 <-950HU, Median PD15 (IQR) -957.93 (-968-63—942.22) and all of these had severely reduced MMEF (≤20% predicted).

Discussion

The current paper describes unique data from a cohort of never-smoking individuals with AATD who have never received augmentation therapy, showing that subjects without spirometric evidence of COPD include some with reduced values for MMEF (defined here as <80% predicted), potentially suggestive of impaired small airways function. Those with an MMEF <80% predicted already have evidence of reduced health status despite their FEV_1 and FVC being within the normal range and subsequently demonstrated a more rapid decline in FEV_1.

MMEF appears of questionable value in an unselected population[28], but the usefulness of a spirometric parameter maybe different in different populations. The subjects included in the present work are never smoking AATD PiZZ patients, a highly selected population, and these data suggest MMEF may be useful to identify subgroups in this cohort with specific characteristics and to predict disease progression.

Differences in the shape of the forced expiration curve have been noted as early as 1976, where a "kink" in the spirogram was associated with a higher prevalence of emphysema in patients with airflow obstruction[29] and lower maximal expiratory flow measurements at 75%, 50% and 25% of FVC were seen in PiMZ AATD non-smokers compared to PiMM patients[30]. Since this time there has been little further information about small airways function in AATD although a recent study demonstrated an overall trend for more rapid decline in MMEF in PiMZ individuals over 11 years compared to those with the PiMM and PiMS phenotypes, whilst FEV_1 and FEV_1/FVC declined at the same rate in all groups (although values were expressed as absolute change and not % predicted)[31]. Studies of small airway function in non AATD COPD are also limited. Gold 0 COPD patients (those with a normal FEV_1/FVC but considered "at risk") had lower MMEF %predicted than normal subjects[32]. In addition, MMEF/FVC has been used as a diagnostic parameter for early stage COPD in smokers with otherwise normal spirometry[33]. Collectively, these studies support

the concept that MMEF may be useful in detecting early pathological changes in COPD and support our findings in AATD. However the utility of MMEF or other potential measures of small airways function would also need to be assessed in a non-AATD COPD cohort and patients at risk of COPD to determine more generalised utility.

What constitutes an abnormal MMEF is uncertain. The normal range for MMEF based on standardised residuals/z-scores is broad [34] and in a general population reporting MMEF using z-scores is not clinically useful over and above the traditional spirometric parameters such as FEV_1/FVC[28]. In the current study a cut-off of 80% predicted was pragmatically chosen for MMEF as this is compatible with previous studies (for example,[20, 21]) but patterns were similar if a cut off of 75% or 70% predicted were chosen. Moreover, choosing an 80% predicted cut-off for MMEF means that a greater number of patients with SAD are likely to be included in Group 2. The 70% fixed FEV_1/FVC ratio definition of COPD was also chosen to align this paper with the current GOLD strategy and enable easier comparison with other published work in this area.

The average age of the patients studied here ranged from 40 years for those in Group 1 to 50 years for those with MMEF values suggestive of SAD (Group 2) and 60 for those with COPD (Group 3). Lung function data, however, is presented as % predicted (therby accounting for age differences) and thus the decline in lung function could relate to the early stages of airway remodelling in Group 2 that precede more significant airflow limitation associated with COPD (Group 3). There was also a trend towards lower gas transfer in Group 2, which may reflect early emphysematous change. Patients in Group 2 (SAD, no COPD) also had impairment of health status compared to those with higher MMEF (Group 1). Although this may be at variance with earlier work in AATD that used a different symptom questionnaire[35] it is consistent with more recent work that has shown patients with GOLD Stage 0 COPD[27] can also have reduced quality of life[36]. The presence of worse symptoms in patients with mild spirometric COPD has also been shown in our previous work[37] and, collectively, the data in the current study supports a subtle decline in health status in tandem with early deterioration in lung physiology. Prospective studies would be needed to confirm this.

The predictive value of MMEF in this study suggests it may be an effective screening tool to select those most at risk of a fast decline in this group of patients. If this were confirmed in

prospective studies, these tests might identify a physiological subgroup (with evidence of SAD) that require closer monitoring, and perhaps earlier interventions when considering suitability for future therapeutic trials (such as alpha-1 antitrypsin augmentation). There are other tests of small airways function but MMEF was chosen in this proof of principle study as it is readily available in most physiology centres. Prospective studies might identify even more informative measures.

From a pathophysiological viewpoint, the data provide support for the cross-sectional studies of Hogg and colleagues[4]. Observational studies of lung specimens from patients with COPD (10 of whom had features typical of AATD—panlobular emphysema ,younger and lower smoking history) and emphysema has highlighted major loss of small airways in the absence of emphysema, leading to the hypothesis that this is a precursor of alveolar destruction. Currently, pathological changes cannot be studied prospectively but the physiological data presented here is consistent with this concept. A proportion of our patients underwent quantitative CT scan density analysis at baseline and there was a relationship to MMEF values. Density relationships to the presence of emphysema have been studied extensively in the past and the best data compared to pathological specimens remains that by Gevenois and his colleagues[38] who determined that a threshold of -950HU showed the best correlation with emphysema. Our data was analysed as the PD15 which is used in most modern publications and reflects the threshold of the least dense 15% of voxels. It is therefore not entirely comparable with the pathological threshold described by Gevenois which indicated <7% of voxels below this threshold, but is similar to the values of <10%[39] and <13%[40] found in normal subjects, and all subjects with PD15 below this threshold in our study had marked impairment of MMEF. Importantly, there was a significant proportion of patients with reduced MMEF who had a PD15 well above this threshold, suggesting the presence of SAD without emphysema. As patients with AATD who develop COPD almost invariably have emphysema, the data suggest significant loss of and/or impairment of airflow in the small airways does occur before emphysema becomes apparent. The age difference between our physiological groups also supports this as a natural temporal progression pathologically and confirms the importance to express values as % predicted in such studies. However, it should be noted that not all patients with AATD develop COPD and emphysema[25] and early evidence of SAD may differentiate these diverse outcomes. Our current data reflects an average result for the whole lung rather than regional assessment of the upper and lower zones which may more closely reflect different distribution patterns of emphysema known to

have different physiological effects especially in established disease[41]. This would be important for definitive interpretation in future prospective studies of AATD patients without COPD

Apart from age and lung function, the only other clear differences between the groups were sex in Group 2 (with a higher percentage of females having an MMEF ≤80% predicted without COPD) and a higher percentage of non-index cases in Groups 1 and 2. Index status is to be expected, since family screening tends to identify patients with more preserved lung function than found in index cases[42]. It is unclear why more females were present in Group 2 than Group 1 or 3. There is no published literature to suggest AATD females experience a faster decline than men. While this could reflect sampling bias, this observation requires follow up to determine its significance. Other studies have also looked at sex and respiratory symptoms, small airways responses and hyper-responsiveness and there are conflicting results (for example,[43, 44]); this subject appears far less understood and far more complex than initially thought but we have utilised percent predicted results in our analysis as these take into consideration sex and height differences in lung function to try and overcome the inherent size difference in the lungs of our patients.

The current study has excluded current or ex-smokers, which is both a strength and a weakness. Studying never smokers allows the natural history of AATD alone to be defined as smoking accelerates the development of COPD in AATD and a faster pathological progression. In addition most individuals stop smoking on diagnosis of AATD thereby altering the natural history. Our current cohort of over 900 AATD subjects and the group with normal spirometry includes no active smokers and only 21 ex-smokers; too small a proportion to analyse meaningfully. This study does not include information of passive smoke exposure or occupational history. While both factors may affect small airways function and lung development in childhood in some patients with AATD, the main question addressed here is whether current evidence of small airways dysfunction might impact on health status or subsequent FEV_1 decline in this population. Thus whatever the preceding time course involved, tests consistent with SAD act as a marker of faster subsequent decline.

MMEF is affected by loss of elastic recoil (seen in emphysema), which results in expiratory airflow limitation due to dynamic airways compression. However, we have shown that a number of patients have severely reduced MMEF but no evidence of emphysema on CT scan.

We suggest that this could reflect small airways dysfunction but interpretation without pathology will require a more comprehensive long term study.

In summary, the implications of our findings in AATD are two-fold. First, we now have physiological evidence to support the previous histological studies that SAD is an early feature of lung disease in AATD and precedes the development of emphysema and COPD[5]. MMEF % predicted may be a useful marker of early disease in these patients.
Second, AATD patients with a reduced MMEF appear more likely to be "rapid decliners"[16] than those with preserved small airway function. Therefore, MMEF may be a more sensitive physiological marker of AATD patients at risk of decline than FEV_1/FVC. There are also potential implications in non AATD-COPD, where re-evaluation of MMEF% predicted may provide a screening tool to identify patients at risk of developing emphysema and COPD prior to changes in FEV_1 and FEV_1/FVC ratio.

Figure legends

FIGURE 1.

FEV_1/FVC ratio is plotted against MMEF % predicted. Each point represents data from a single patient (n=196) with all measurements taken on the same day. Groups 1, 2 and 3 are highlighted.

FIGURE 2.

The charts show median, IQR and minimum/maximum bars for total SGRQ scores (A) and individual domain scores for activity (B), disease impact (C) and symptoms (D) for Groups 1, 2 and 3. P values are shown for each comparison.

FIGURE 3.

The chart shows median, IQR and minimum/maximum bars in the annual change in FEV_1 (expressed as % predicted) for Groups 1, 2 and 3. Values were calculated from the regression line of annual serial measurements of 4 data points or more. A lower value indicates a faster rate of decline. The median FEV_1 percent predicted decline in Group 1 was approximately zero, suggesting these patients experienced an FEV_1 decline in keeping with that expected with age alone. Patients within Groups 2 and 3 experienced a decline in FEV_1 greater than seen with age alone, suggesting disease progression.

FIGURE 4.

The chart shows mean lung density (HU) versus MMEF % predicted. Each point represents data from a single patient (n=109). Patients with reduced MMEF (<80% predicted) but a lung density above that typical of macroscopic emphysema (>950 HU) are shown by the shaded area.

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Author contributions.

JAS conducted tests of physiology, analysed and prepared the manuscript, AI, SH and RE helped collate clinical information and undertook some aspects of analysis. BGC oversaw all lung physiology, data interpretation and assisted with manuscript preparation. RAS and ES designed and coordinated studies, assisted with data interpretation and finalised the manuscript.

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Declaration of Interests

JAS, AMI, SMH, RE, BCC and ES have no conflicts of interest to declare. RAS has participated on Ad boards for Boehringer Ingelheim, Zealand, Dyax, Chiesi, AstraZeneca and CSL Behring and has non-commercial grant income from CSL Behring.

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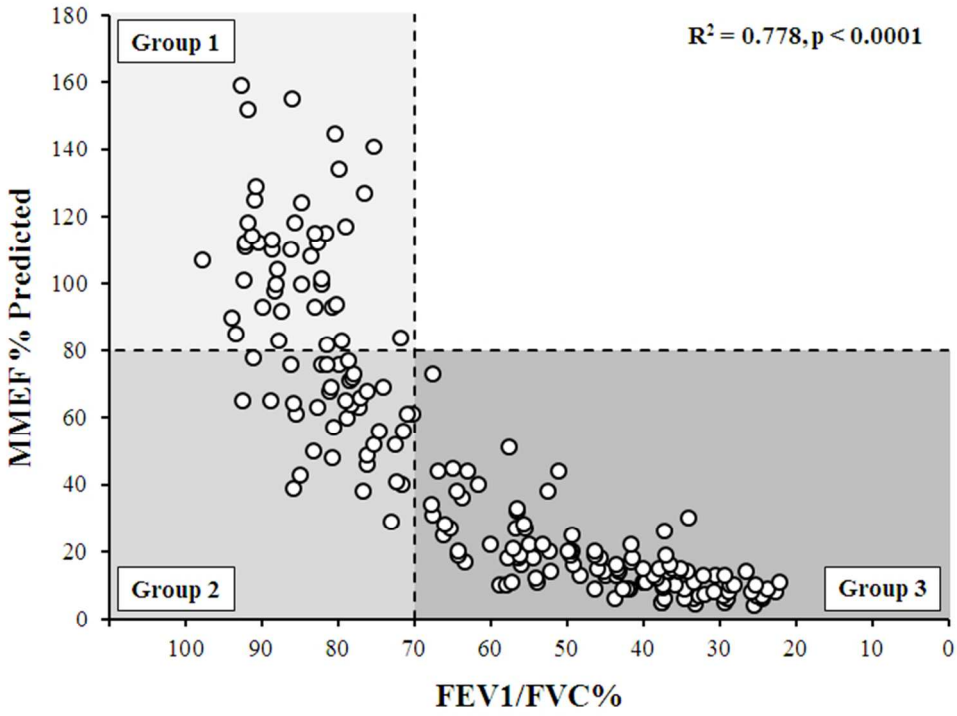

FIGURE 1.
FEV1/FVC ratio is plotted against MMEF % predicted. Each point represents data from a single patient (n=196) with all measurements taken on the same day. Groups 1, 2 and 3 are highlighted.

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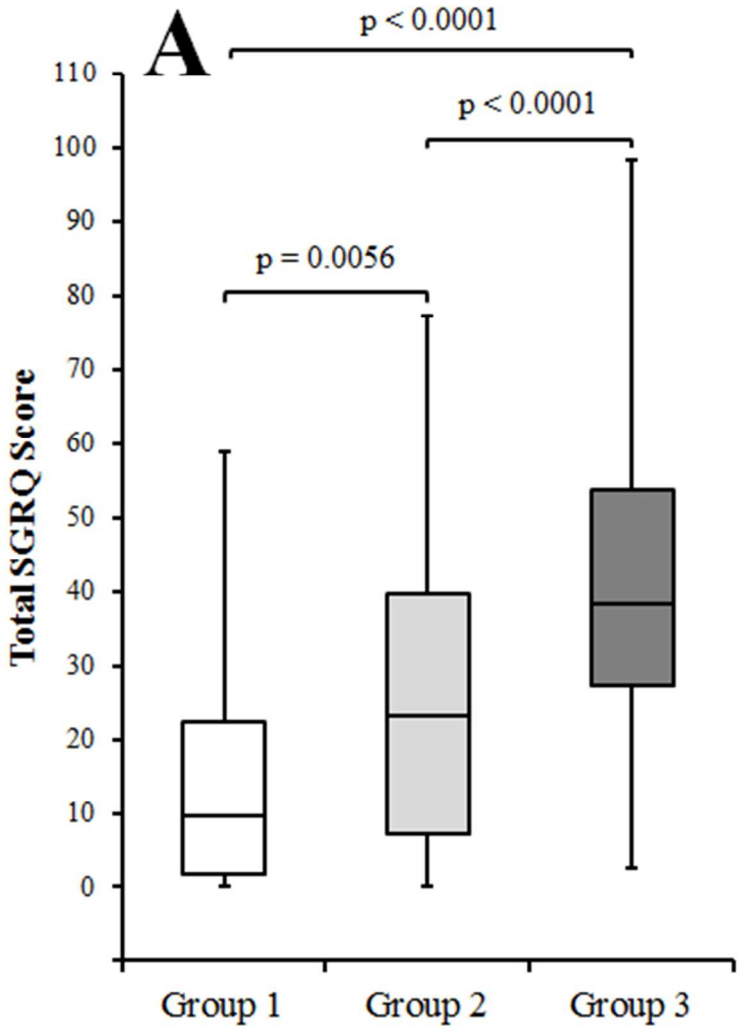

FIGURE 2.
The charts show median, IQR and minimum/maximum bars for total SGRQ scores (A) and individual domain scores for activity (B), disease impact (C) and symptoms (D) for Groups 1, 2 and 3. P values are shown for each comparison.

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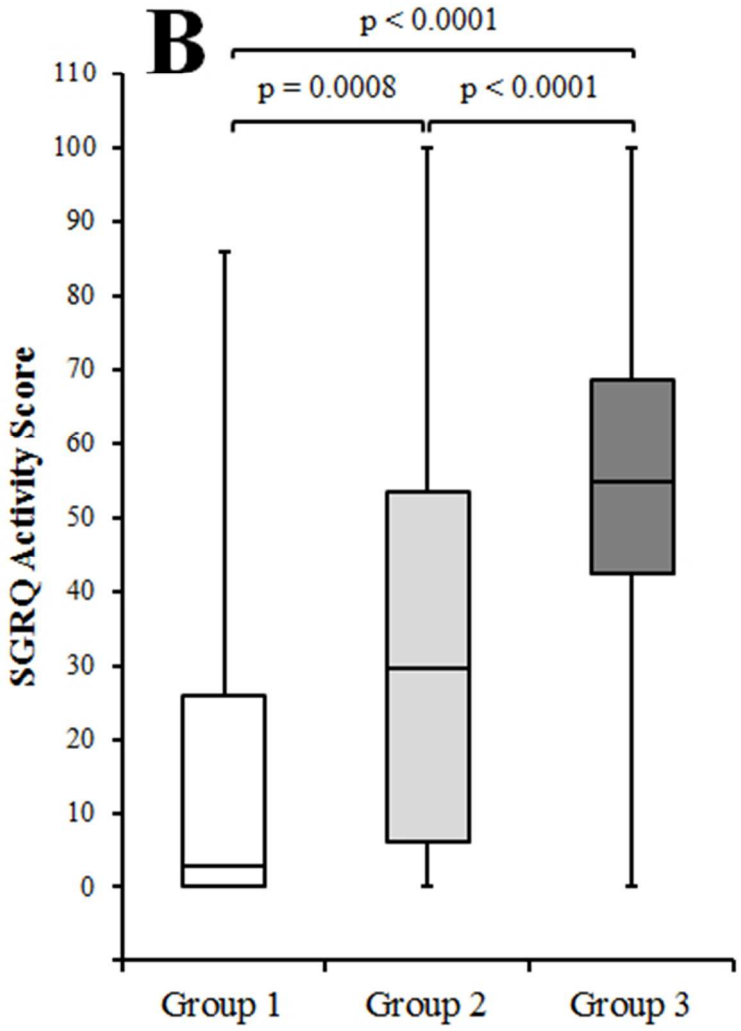

As for figure 2A

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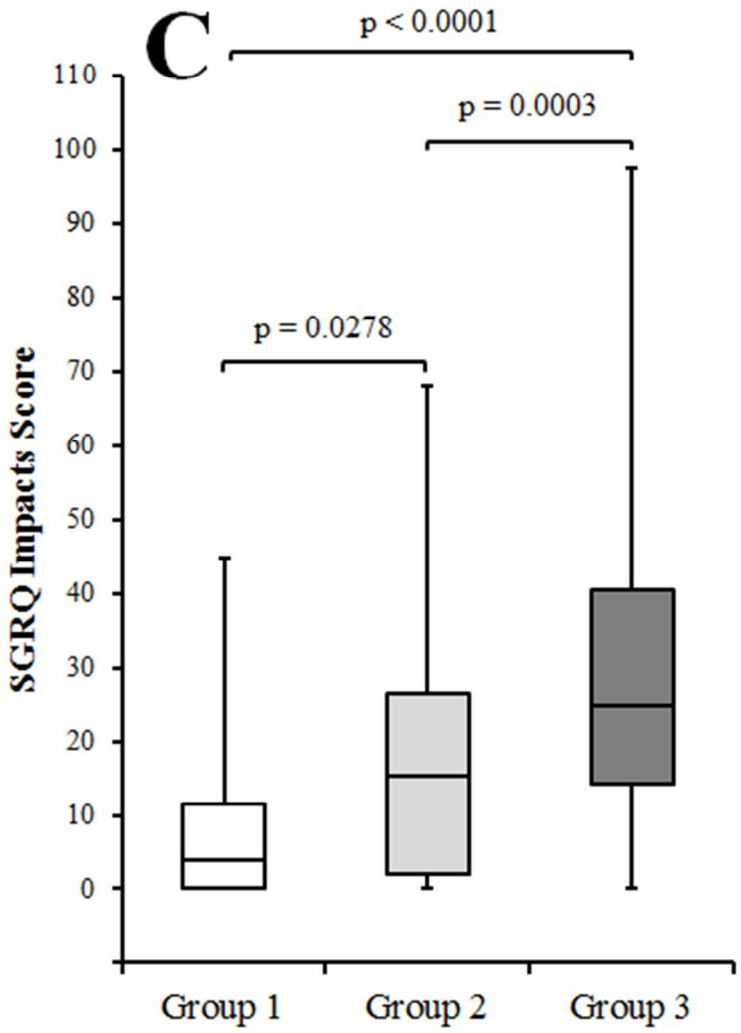

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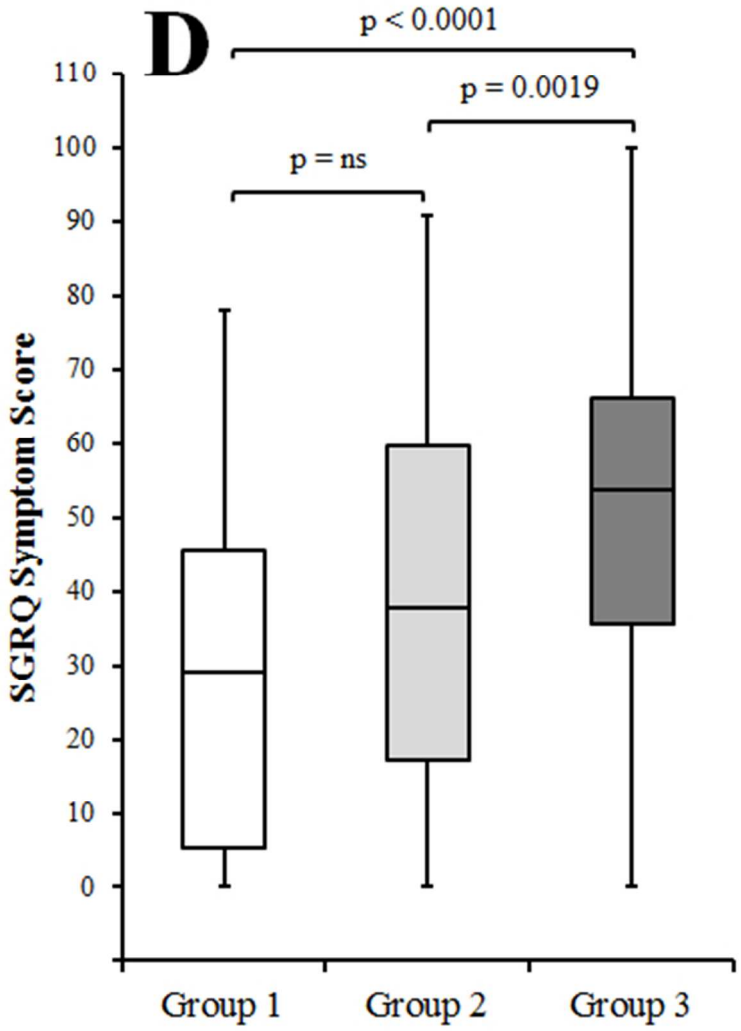

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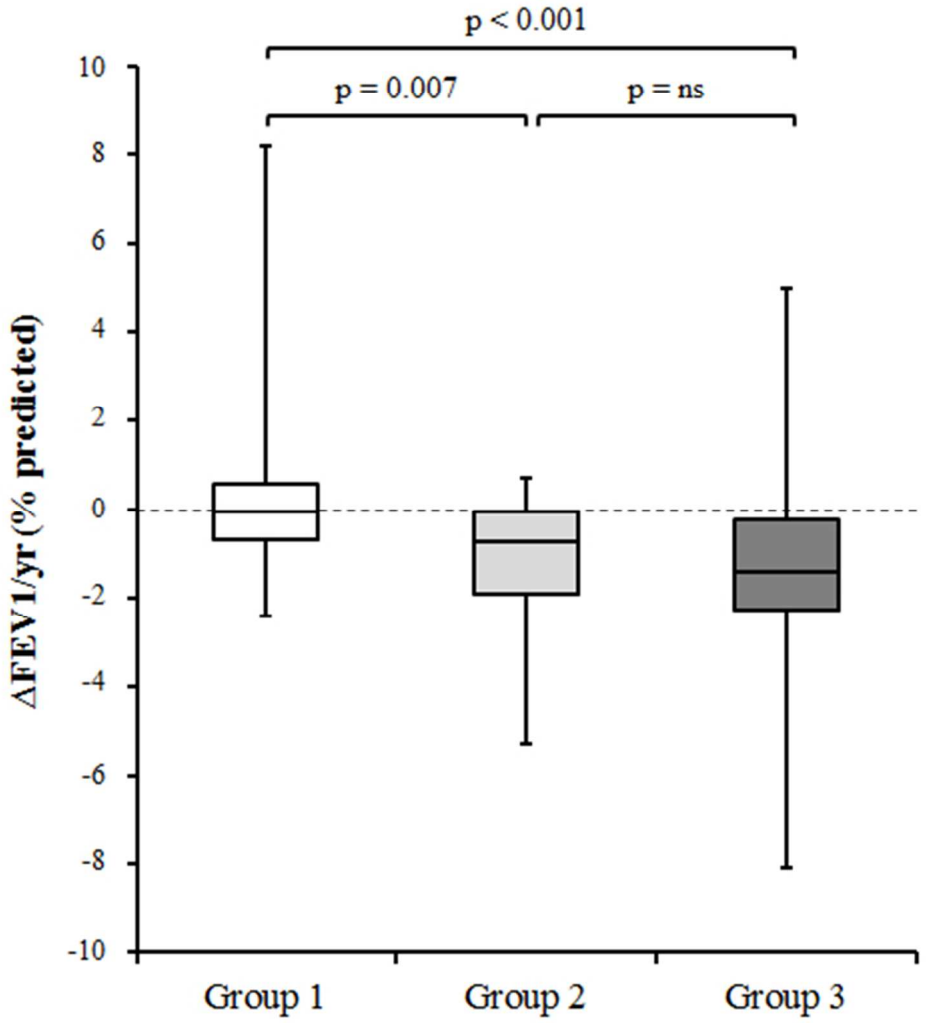

FIGURE 3.
The chart shows median, IQR and minimum/maximum bars in the annual change in FEV1 (expressed as % predicted) for Groups 1, 2 and 3. Values were calculated from the regression line of annual serial measurements of 4 data points or more. A lower value indicates a faster rate of decline. The median FEV1 percent predicted decline in Group 1 was approximately zero, suggesting these patients experienced an FEV1 decline in keeping with that expected with age alone. Patients within Groups 2 and 3 experienced a decline in FEV1 greater than seen with age alone, suggesting disease progression.

128x138mm (96 x 96 DPI)

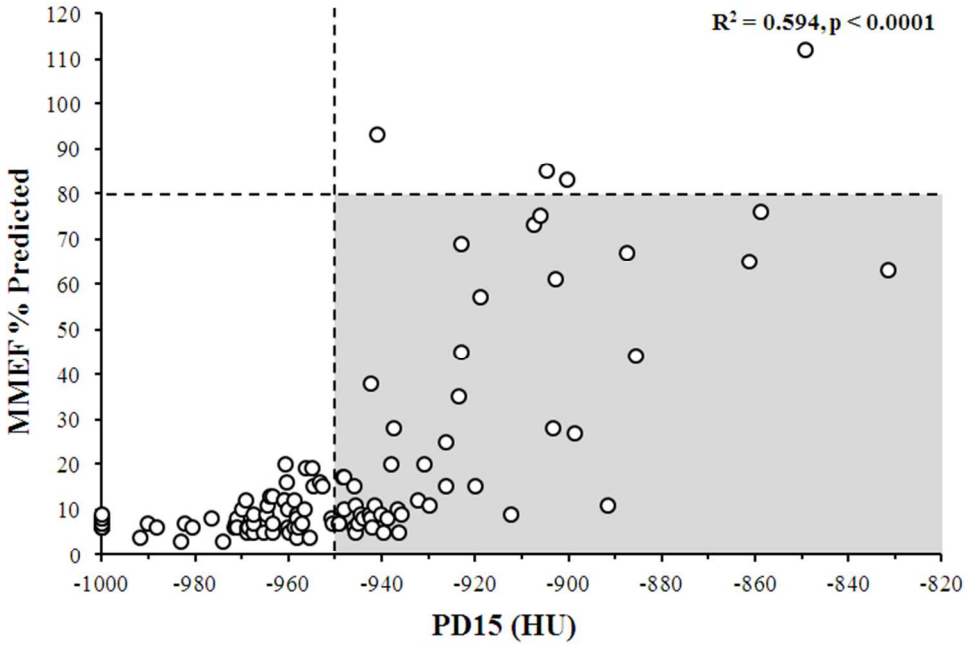

FIGURE 4.
The chart shows mean lung density (HU) versus MMEF % predicted. Each point represents data from a single patient (n=109). Patients with reduced MMEF (<80% predicted) but a lung density above that typical of macroscopic emphysema (>950 HU) are shown by the shaded area.

207x140mm (96 x 96 DPI)