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Bronchodilator response in the lung health study over 11 yrs

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ABSTRACT: Long-term changes in bronchodilator response in people with mild chronic obstructive pulmonary disease were assessed in this study.

Changes in forced expiratory volume in one second (FEV_1) in response to isoproterenol was measured in 4,194 participants in the Lung Health Study annually for 5 yrs, and again 11 yrs after study entry. Responses were quantitated in terms of mL (absolute), as per cent of the pre-bronchodilator value (relative), and as a per cent of the predicted normal value (% predicted).

At baseline, the mean pre-bronchodilator FEV_1 was 75.4% predicted, and responses were small. Relative and percentage predicted responses were similar in males and females; and correlated positively with methacholine reactivity, and negatively with smoking intensity and age. Baseline bronchodilator responses did not correlate with subsequent decline in FEV_1. There was a substantial increase in response over the first year of the study, largely due to smoking cessation, with larger increases in those who stopped smoking. After the first year absolute responses changed little in those who maintained smoking cessation, but increased in those who did not. Mean relative and percentage predicted responses increased in all participants throughout the study. There was substantial annual variability of absolute response, and it was poorly reproducible in individual participants.

In conclusion, smoking cessation increased bronchodilator response, and response did not predict the rate of decline of forced expiratory volume in one second.

KEYWORDS: Forced expiratory volume in one second, methacholine reactivity, smoking

Spirometric assessment of bronchodilator responsiveness in chronic obstructive pulmonary disease (COPD) was recommended by most early COPD guidelines [1, 2]. The American Thoracic Society [1] and the more initial Global Initiative for Obstructive Lung Disease (GOLD) guidelines [2] identified a significant response as >200 mL and >12% of the pre-bronchodilator value. Both imply that this occurred in COPD and that its prevalence increased with serial testing because of poor reproducibility [1]. More recent guidelines [3–5] either do not refer to bronchodilator response as a diagnostic criterion or state that it is not significant unless ''large'' [5]. However, recent clinical trials, particularly of inhaled steroids, have excluded patients with significant bronchodilator responses [6, 7], presumably to lower the risk of unknowingly including patients with asthma or features of asthma.

Data regarding bronchodilator response in COPD have generally examined patients with severe or moderately severe disease, and few have involved serial measurements [8, 9]. In this respect the Lung Health Study (LHS) [10] is a unique data set. It recruited nearly 6,000 smokers with mild-to-moderate airways obstruction and followed >4,000 of them for 11 yrs with spirometric measurements before and after bronchodilator administration. These data permit characterisation of bronchodilator response in relatively mild COPD, its variability, its changes with time and smoking habit, and its relationship to rate of decline in lung function.

For editorial comments see page 6.

METHODS

The LHS [10–12] was a trial of smoking cessation and bronchodilator (ipratropium) therapy in volunteer smokers aged 35–59 yrs with airway obstruction (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <70%) who were not otherwise ill, and who had baseline values of FEV_1 of 55–90% of the predicted normal [13]. Of the original 5,887 participants, >90% were followed with annual spirometry for the 5 yrs of the original study [10]. After the original

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study, telephone contact was maintained with most participants, and ~11 yrs after enrollment 4,194 were re-examined, 77% of those not known to be dead [11]. Both the original 5-yr study and the 11-yr follow-up were approved by ethics committees at all participating institutions.

Results were analysed according to the original LHS treatment group assignment; usual care (UC) and special intervention (SI). The latter was a combination of groups that were assigned either to ipratropium or placebo therapy. Both received the smoking cessation programme and had similar quit rates, and neither had received any further study-related interventions. Participants were also divided into three groups according to smoking habit. Sustained quitters (SQ) were biochemically-validated nonsmokers at each follow-up visit from year one through to year 11 who gave a history of abstinence during all of those years. Continuous smokers (CS) reported smoking at all follow-up visits from year one through to year 11. Intermittent quitters (IQ) reported smoking at some but not all follow-up visits. Due to uncertainties regarding dose of cigarettes, the IQ group was not considered in some analyses.

Spirometry was performed with a rolling seal spirometer (Spirotech 500; Spirotech, Atlanta, GA, USA), with an intensive quality-control programme [14]. Measurements were made before and 10 min after two puffs of isoproterenol (200 μg total dose) from a metered dose inhaler. Participants discontinued bronchodilators 12 h before testing. The largest values for FEV_1 and FVC from multiple efforts were reported. Bronchodilator response was derived from FEV_1 measurements and did not influence study entry. Response (the difference between the pre-bronchodilator and post-bronchodilator values) was quantified in three ways; as an absolute number (absolute), as a per cent of the pre-bronchodilator value (relative), and as a per cent of the predicted normal FEV_1 (% predicted). Methacholine reactivity was measured at baseline [15].

Data from the original cohort, who were followed for 5 yrs, were compared with those of the cohort with the 11-yr follow-up to ensure that there were no differences between them. Otherwise, data from the 11-yr cohort are reported.

Standard descriptive statistics based on percentages for categorical data, means and standard deviations (SD) for quantitative variables were used. Univariate analysis employed Chi-squared for categorical variables and unpaired t-tests and ANOVA for quantitative variables. Multivariate analysis was used to assess the effect of baseline covariates (age, sex, treatment group, smoking habit and methacholine reactivity) on baseline responses. The relationship between baseline response and subsequent decline of FEV_1 was assessed with multivariate linear models considering the same baseline covariates. To measure the variability of absolute response from years one to five, residuals were calculated from a longitudinal, mixed-effect model for repeated response. Intercept was entered as a random effect, and smoking status and daily cigarette use entered as time-dependent covariates. The residuals were squared, square roots taken and reported as root mean squared error (RSME) analogous to the SD. This estimate of variation considers systematic changes in response during the evaluation period. All multivariate models included the following covariates: age, sex, treatment group, baseline smoking habit, methacholine reactivity and baseline FEV_1.

RESULTS

Table 1 shows the original baseline characteristics of the cohort that was examined at 11 yrs. Though this group had different baseline characteristics from those who were not examined at 11 yrs, the differences were accounted for by variations in age and smoking habits [11]. At baseline, all three responses were distributed normally. The mean±SD relative bronchodilator response was 4.32±5.01% and the mean absolute response was 111±129 mL, while the mean percentage predicted response was 3.14±3.56%. These figures did not differ from those of the 5-yr cohort.

Table 2 shows results of multivariate analysis of response in relation to other baseline characteristics. While absolute responses were larger in males, this was not true of relative or percentage predicted responses. Responses were negatively correlated with age and smoking habit, in the form of both baseline cigarettes·day^{-1} and pack-yrs exposure. Responses were positively correlated with methacholine reactivity. Baseline responses did not relate to treatment group or to subsequent smoking habit.

Baseline bronchodilator responses were not significantly related to the subsequent decline in post-bronchodilator FEV_1 when baseline data were excluded from the assessment of decline, which was, therefore, measured from year one to 11.

Figure 1 shows bronchodilator response as a function of time in the SI and UC groups.

TABLE 1 Baseline data: 11-yr cohort

Variable	
Male	61.9
Age yr	50.1±7.4
SI treatment group	67.2
Baseline cigarettes·day^{-1}	30.8±12.7
Pack-yrs	39.9±18.6
LHS 3 smoking status	
Sustained quitters	17.7
Intermittent quitters	57.1
Continuous smokers	25.5
FEV_1	
Pre-BD L	2.64±0.60
Post-BD L	2.75±0.63
FEV_1	
% pred pre-BD	75.4±8.73
% pred post-BD	78.5±9.01
Methacholine reactivity	
5 mg·mL^{-1} % reactors#	33.6
25 mg·mL^{-1} % reactors#	71.8

Data are presented as mean±SD or %. SI: special intervention; LHS: lung health study; FEV_1: forced expiratory volume in one second; BD: bronchodilator. #: reactors showed a decline in FEV_1 of ⩽20% in response to the indicated (or lower) doses.

TABLE 2 Bronchodilator response by demographic variables

Variable	Absolute		Relative		% predicted	
	Response	p-value	Response	p-value	Response	p-value
Sex						
Females	86.6	<0.001#	4.20	0.308#	3.07	0.299#
Males	127.3		4.36		3.19	
Group						
SI	112.2	0.776#	4.33	0.534#	3.16	0.543#
UC	111.0		4.23		3.09	
LHS 3 smoking status						
SQ	116.0	0.519#	4.41	0.712#	3.23	0.601#
IQ	111.8		4.30		3.15	
CS	108.9		4.21		3.06	
Methacholine Reactivity						
No response	107.1	<0.001#	3.62	<0.001#	2.82	<0.001#
25 mg	103.6		3.70		2.79	
10 mg	109.7		4.30		3.12	
5 mg	115.6		4.82		3.41	
1 mg	151.3		6.73		4.57	
Diluent	93.8		4.55		3.02	
Age	-0.200¶	<0.001+	-0.134¶	<0.001+	-0.157¶	<0.001+
Baseline cigarettes·day^{-1}	-0.032¶	0.013+	-0.044¶	0.001+	-0.057¶	<0.001+
Pack-yrs	-0.108¶	<0.001+	-0.089¶	<0.001+	-0.109¶	<0.001+

SI: special intervention; UC: usual care; LHS: lung health study; SQ: sustained quitters; IQ: intermediate quitters; CS: continuous smokers. #: p-value for ANOVA test of response differences within groups; ¶: correlation; +: p-value for correlation of response by variable of interest.

All three responses showed a substantial and significant increase during the first year of the study. After the first year, relative response increased progressively and significantly throughout follow-up, while absolute response leveled off between years one and five, and increased slightly, but significantly, between years five and 11. Response as per cent predicted tended to level off between years one and five in both groups, and then increased between years five and 11. The changes in all three responses in the first year were significantly larger in the SI group than in the UC group ($p=0.02$).

Figure 2 shows the same data as a function of smoking habit. Over the first year the increase in response was largest in the SQ group and smallest in the CS group, and was significant in all groups. After the first year, there was no significant change in absolute response in the SQ group, while in the IQ and CS groups absolute response did not change between years one and five, and then increased slightly, but significantly between years five and 11. Relative response increased progressively and significantly in all three smoking groups, with the least change after the first year occurring in the SQ group. Response as per cent predicted showed a similar pattern to the absolute response, except that the increase between years five and 11 was more striking in all three groups. The results over the first 5 yrs in the 11-yr cohort (figs. 1 and 2) were essentially the same as those in the larger 5-yr cohort.

When all participants were considered, the increase in response correlated significantly ($p<0.001$) with the decrease in daily cigarette use, but the relationship was dependent on participants who stopped smoking entirely. In participants who did not stop smoking entirely there was no significant relationship between bronchodilator response and change in smoking intensity at the end of the first year of the study. In the IQ group, the current authors examined year-to-year changes in response as a function of changes in smoking habit. Responses were larger in those who quit in the preceding year than in those who relapsed to smoking, but the difference was not significant. Increases in both absolute and relative response during the first year related positively to baseline methacholine responsiveness in the SQ and IQ groups, ($p<0.001$ for both responses), but not in the CS group.

Figure 3 shows the frequency distribution of RMSE, representing the variability of absolute responses as measured at years one to five, when the mean response was 143 mL. The average value of RMSE was 77.1 mL, and the distribution was somewhat skewed towards higher values, with a median of 69.5 mL (interquartile range 49.2–95.7 mL). Variability was significantly ($p=0.017$) less with increasing age and also correlated negatively with baseline FEV_1 expressed as percentage of the predicted normal ($p=0.001$). Variability correlated positively with baseline pack-yrs smoked and methacholine reactivity ($p<0.001$ for both). In the cohort as a whole, increased variablility was associated with greater loss of lung function between years five to 11 in multivariate regression ($p<0.0001$). This was true in both IQ ($p=0.0098$) and CS ($p=0.0002$), but not in SQ ($p=0.0645$).

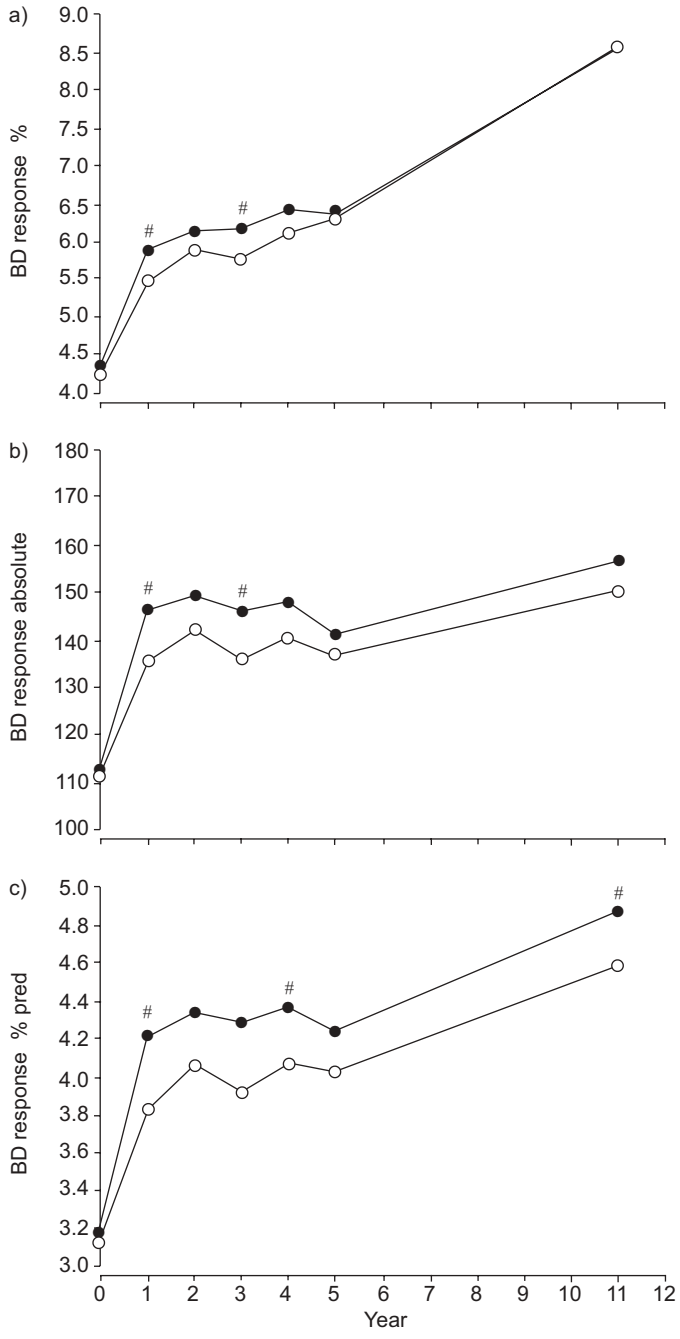

FIGURE 1. Bronchodilator (BD) responses in the special intervention (●) and usual care (○) groups over 11 yrs. a) shows relative responses, b) shows absolute responses, and c) shows responses as a percentage of predicted. #: significant differences among groups.

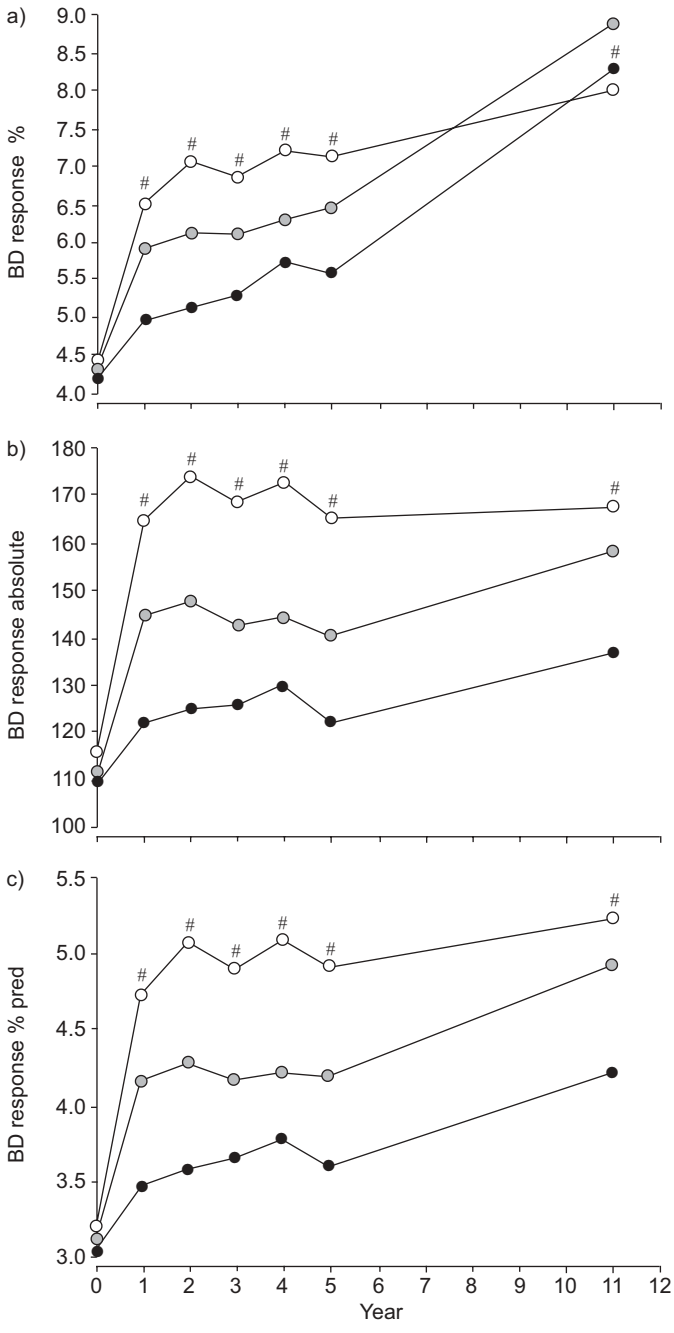

FIGURE 2. Bronchodilator (BD) responses as a function of time in sustained quitters (○), intermittent quitters (●), and continuing smokers (●). a) shows relative responses, b) shows absolute responses, and c) shows responses as a percentage of predicted. #: significant differences among groups.

DISCUSSION

The 11-yr cohort examined was a biased sample of the original 5-yr cohort. Subjects who did not participate in the 11-yr follow-up were more likely to be young, male, and noncompliant with smoking cessation and follow-up. However, their baseline lung function did not differ from the 11-yr participants, and differences in symptoms and rate of decline of FEV_1 during the initial 5 yrs were explained by differences in smoking habits [11]. Finally, bronchodilator response over the first 5 yrs of the study did not differ between the 11-yr cohort and the 5-yr cohort.

Generally speaking, bronchodilator responses were small and less, on average, than those designated as significant by early COPD guidelines [1, 2]. Out of 4,194 participants, ~20% demonstrated an initial response that was >200 mL, but responses of >15% of the pre-bronchodilator value or 12% of the predicted normal value were uncommon, occurring in

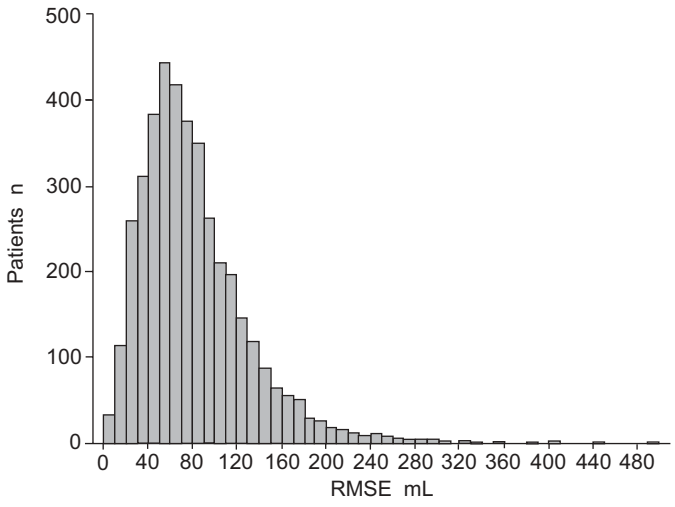

FIGURE 3. Frequency distribution of root mean squared error (RMSE), an analog of the standard deviation, of absolute response for years one to five.

2.58% and 1.17% of the participants, respectively. Intra-individual responses were quite variable (fig. 3), with RMSE averaging 56% of the average absolute response. Due to this variability, responses were poorly reproducible. Of participants who had an absolute response of <200 mL at the first annual visit, ~20% had larger responses at subsequent testing during annual visits 2–5, while of those with responses of ⩾200 mL at the first annual visit ~45% had responses of <200 mL at subsequent annual visits.

Relative and percentage predicted baseline responses were similar in males and females, though absolute responses were larger in males. Presumably, responses were similar when body size was considered. All three responses declined with age; to the current authors knowledge this has not been previously reported. Responses correlated negatively with smoking, which has been observed in the past [8]. Responses were positively correlated with methacholine reactivity, which has also been noted previously [15]. Such a correlation might have been expected, as both responses are thought to reflect differences in airway smooth muscle tone and/or excitability. However, there is evidence that bronchodilator response and methacholine response were not closely equivalent (table 3).

TABLE 3 Comparison of bronchodilator response and methacholine reactivity

	Bronchodilator response	Methacholine reactivity
Sex difference	No	Yes
Age related	Yes	No
Related to baseline smoking	Yes	No
Influence of smoking cessation	Increases	Decreases
Effect of disease progression	Increases	Increases
Predicts decline of FEV_1	No	Yes

FEV_1: forced expiration volume in one second.

There was a pronounced sex difference in methacholine reactivity in the LHS, with females having greater reactivity than males [16]. This was not true of bronchodilator response. Baseline methacholine responses did not correlate with age, while bronchodilator responses did, and bronchodilator responses related much more strongly to smoking habit than methacholine responses [15]. Smoking cessation had opposite effects on the two responses, increasing bronchodilator response while tending to decrease methacholine reactivity [17]. However, disease progression increased both methacholine reactivity and bronchodilator response as judged by data in the CS group. Finally, the baseline level of methacholine reactivity was a strong predictor of subsequent loss of lung function [18], not the case for bronchodilator response.

The most striking finding of this study is the increase in bronchodilator response observed over the first year of the LHS. This occurred in both treatment groups, but was greater in the SI group than the UC group (fig. 1), and was substantially larger in those who quit smoking than in those who did not (fig. 2). The difference between the SI and UC groups was largely due to the larger fraction of SQ participants in the former. Thus, it appears that smoking cessation was associated with an increase in bronchodilator response. This was supported by the fact that baseline response was negatively associated with cigarette use, both in the present and a previous study [8]. It should be noted that participants in the CS group, who did not stop smoking, also had a small increase in response over the first year, but the present authors think it likely that some of these people decreased or stopped smoking at the beginning of the LHS, and that these changes were not captured at the end of the first year year when the measurements were made. It cannot be demonstrated that response changed in the IQ participants as they stopped and started smoking during the study; although the changes were in the right direction, they were not significant. In spite of these caveats, the current authors believe that the best interpretation of the first year increase in response is that it was due to smoking cessation. Complete cessation had a much more powerful influence on response than partial cessation, in that the latter did not relate to bronchodilator response.

Obviously, the authors cannot be certain of the mechanism underlying the above change in bronchodilator response, but believe that the best explanation is a decrease in an acute inflammatory process related to daily cigarette consumption. This argument has been used to explain the small increase in post-bronchodilator FEV_1 associated with smoking cessation [8]. The present data indicate that >50% of that increase was accounted for by an increase in bronchodilator response; that is, the increase in pre-bronchodilator FEV_1 with smoking cessation is considerably smaller than the increase in the post-bronchodilator value.

Increases in relative and percentage predicted responses between years five to 11 (figs. 1 and 2) were almost certainly related to decline in denominators, which is pre-bronchodilator FEV_1 and its predicted normal value. However, absolute responses also increased from years five to 11 in the IQ and CS groups. In the CS group, these changes were likely to be due to progression of disease, while in the IQ they were probably related to a combination of disease progression and to further

smoking cessation [10]. However, the average response at 11 yrs was 4.79% predicted (SD=4.05), which is very close to the mean response observed in the Intermittent Positive Pressure Breathing (IPPB) study [8], whose participants were roughly the same age as those in this study, but had considerably worse airways obstruction. It is, therefore, not clear that, on average, this response index changes greatly with disease progression.

This study did not find that bronchodilator response, however expressed, related to a subsequent decline in FEV1. Since the baseline measurement was used to assess response, data was used from the first annual visit as the initial point in estimating rate of decline. The authors result was in agreement with data from the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study [9], but conflicted with those of the IPPB study [8], which reported that COPD patients with large bronchodilator responses had a relatively slow decline of lung function. In both studies, values used in assessing the initial response were not used in computing rate of decline. The current authors believe that the present results and those from the ISOLDE study are most likely to be correct, and that IPPB results were likely to be related to a residual effect from bronchodilator therapy mandated by study design, so that post-baseline FEV1 values were contaminated by concurrent therapy. If present, this effect would have been larger in more responsive subjects and, therefore, would have tended to decrease the rate of decline.

An index of variability of intra-individual bronchodilator response analogous to the SD was derived, utilising absolute response from years one to five, a period when the average response changed relatively little. As expected, there was considerable variability; RMSE averaged 56% of the mean value (fig. 3). The positive correlation of variability of response with methacholine reactivity may have been explicable on the basis of both reflecting the degree of airway smooth muscle tone. Variability of response has previously been noted to correlate negatively with baseline FEV1 [8], but relationships between variability and age, pack-yrs and rate of FEV1 decline in smokers have not been noted to the authors knowledge, and are not easy to interpret.

In conclusion, in a large cohort of patients with mild-to-moderate chronic obstructive pulmonary disease, it was found that large bronchodilator responses were uncommon, but response tended to increase over time. Response increased more in people who stopped smoking than in those who did not. There was no relationship between bronchodilator response and subsequent rate of decline of pulmonary function.

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