

Bronchial responsiveness and the reproducibility of forced expiratory volume in one second

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VENABLES KM, GRANEK BJ, NEWMAN TAYLOR AJ. Bronchial responsiveness and the reproducibility of forced expiratory volume in one second. *Scand J Work Environ Health* 1993;19: 342–5. Although poorly reproducible spirometric tests, “test failures,” are associated with respiratory morbidity, it is not clear what causes them. Bronchial responsiveness was examined in relation to test failure for forced expiratory volume in 1 s ($FEV_{1.0}$) (1979 definition of the American Thoracic Society) in 249 bakers, 165 chemical industry workers, and 204 office workers. The first two groups were studied by the same methods and were combined. Test failure was observed in 4%, and for 38% the provocative dose of inhaled methacholine causing a 20% fall in $FEV_{1.0}$ relative to $FEV_{1.0}$ after the inhalation of normal saline (PD_{20}) was $\leq 120 \mu\text{mol}$ (7% with a PD_{20} of $\leq 8 \mu\text{mol}$). Test failure was not related to the level of PD_{20} . Of the office workers, 3% had test failure, 11% a PD_{20} of $\leq 8 \mu\text{mol}$ of histamine, and no significant relation was observed. The study does not exclude the possibility that bronchial responsiveness might be related to test failure in patients with airway disease or that a clearer relation might be demonstrable in a larger study, but it does suggest that it is not a major determinant of test failure.

Key terms: asthma, epidemiology, spirometry, test failure.

The most widely used reproducibility criterion for spirometry in recent years has been that published by the American Thoracic Society (ATS) in 1979 (1), which states that the best two values should be within 100 ml or 5% of the best, whichever is greater. Subjects who fail a reproducibility criterion are often excluded from analysis, but this exclusion may be a source of bias. Eisen and her colleagues have shown that poor reproducibility, or “test failure,” is an index of ill health (2–7) and is associated with respiratory symptoms, low forced expiratory volume in 1 s, an accelerated rate of decline in forced expiratory volume in 1 s ($FEV_{1.0}$), and higher mortality. The ATS now recommends that technically acceptable, but poorly reproducible, tests not be excluded (8).

It is not clear what causes test failure. We thought it could be explained by bronchial hyperresponsiveness, which is observed in airway disease, particularly in asthma (9), and which increases after viral infection (10). It would be a plausible explanation for the respiratory morbidity associated with test failure. We tested the hypothesis in surveys of working populations in which we had measured bronchial responsiveness.

Subjects and methods

Group 1 was 249 bakery workers studied to relate health indices to flour dust exposure (11). Group 2 comprised 165 chemical industry workers from a plant studied in a survey of the health of workers exposed to acid anhydrides (the study to be published in full elsewhere). Group 3 included 204 volunteer office workers who took part in a study of a symptoms questionnaire (12). Information on response rates, gender, smoking, and age is presented in table 1.

Groups 1 and 2 were studied within a few months of each other in 1986 by the same team of nine investigators using identical procedures, and they have been combined in this report. Two to five technically acceptable forced expiratory maneuvers were recorded with calibrated, leak-free Vitalograph® spirometers (Buckingham, England). Test failure was defined as an $FEV_{1.0}$ which did not meet the 1979 ATS reproducibility criterion, as already stated. Bronchial responsiveness was measured using DeVilbiss No 40 nebulizers (Pennsylvania, United States) as described by Yan et al (13) with the modified protocol described by James et al (14), which uses methacholine up to a maximum cumulative dose of 120 μmol . The provocative dose causing a 20% fall in $FEV_{1.0}$ relative to $FEV_{1.0}$ after the inhalation of normal saline (PD_{20}) was estimated by linear interpolation between the logarithms of the last two points on the dose-response curve. Of the 414 subjects, 53 (13%) were excluded from the analyses of test failure because more than five acceptable forced expirations were recorded and it was possible that some would have been classed as test failure if fewer expirations had been recorded.

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Group 3 was studied in 1988 by four investigators (from the team of nine in 1986), who recorded three to six technically acceptable forced expirations as already described and measured bronchial responsiveness as already described, except that the protocol described by Yan et al (13) was followed without modification using histamine up to 4 μmol . In the calculations of PD_{20} , extrapolation to 8 μmol was allowed (15). There were no exclusions from the analyses. An uncensored bronchial responsiveness variable was also derived by calculating the area under the dose-response curve by a method similar to that described by Townley et al (16), the units being change in $\text{FEV}_{1.0}$ as a percentage of $\text{FEV}_{1.0}$ after saline control multiplied by log micromoles of histamine ($\% \cdot \log \mu\text{mol}$).

Statistical significance was considered a probability of $\leq 5\%$.

Results

Fifteen (4%) of the 414 subjects in groups 1 and 2 were classed as test failure. The upper panel in figure 1 shows the distribution of PD_{20} in groups 1 and 2. Most of the subjects (257, 62%) did not show a fall in $\text{FEV}_{1.0}$ of 20% or more, even with the high dose of methacholine used. Thirty-one (7%) had a PD_{20} of $\leq 8 \mu\text{mol}$. The lower panel in figure 1 shows the percentage of subjects at each level of PD_{20} who (i) were classed as test failure, (ii) had more than five $\text{FEV}_{1.0}$ readings, or (iii) were classed as test success. There was no relation between bronchial hyperresponsiveness and test failure, even if it was assumed that a proportion of those with more than five $\text{FEV}_{1.0}$ readings could be classed as test failure.

In group 3, six subjects (3% of 204) were classed as test failure, and 23 (11%) had a PD_{20} of $\leq 8 \mu\text{mol}$.

Table 1. Characteristics of the subjects.

	Eligible (N)	Studied (N)	Analyzed (N)	Men (N)	Women (N)	Smoking ^a			Age ^a (years)	
						Current (%)	Former (%)	Never (%)	Mean	SD
Group 1	318	279	249	159	90	48	17	35	36	14
Group 2	186	184	165	155	10	41	32	28	44	12
Group 3	^b	211	204	72	132	17	23	61	39	13

^a Calculated for the subjects analyzed who had bronchial responsiveness measured.

^b Group 3 comprised volunteers.

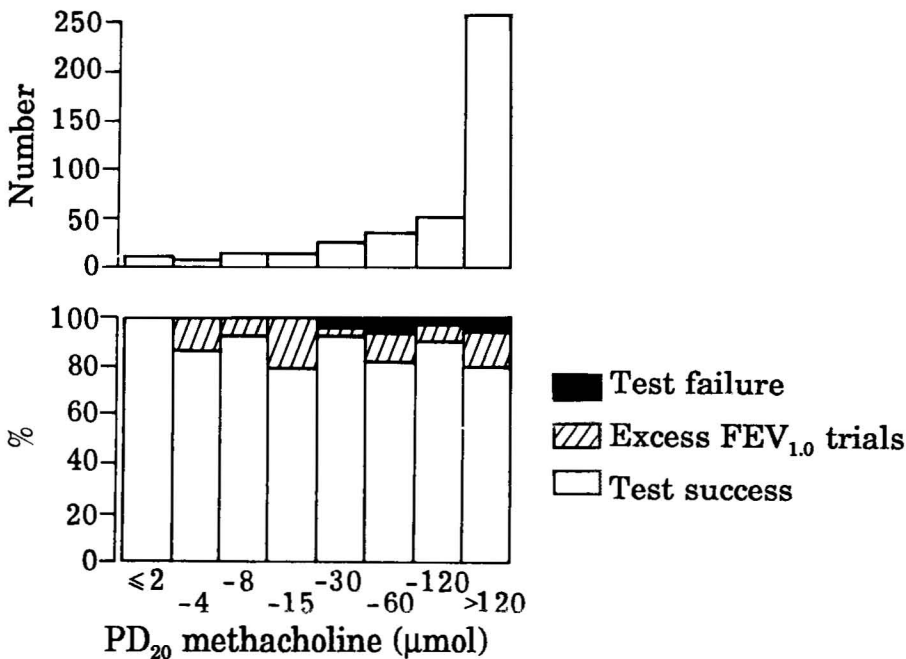


Figure 1. Distribution of bronchial responsiveness in groups 1 and 2 (upper panel) and category of reproducibility of forced expiratory volume in 1 s ($\text{FEV}_{1.0}$) by level of bronchial responsiveness (lower panel). (PD_{20} = provocative dose causing a 20% fall in $\text{FEV}_{1.0}$ relative to $\text{FEV}_{1.0}$ after the inhalation of normal saline)

Three of the six with test failure (50%) had a PD_{20} of $\leq 8 \mu\text{mol}$, compared with 20 of the 198 with test success (10%), but this difference was not statistically significant. When $FEV_{1.0}$ reproducibility as the difference between the best and next best $FEV_{1.0}$ (percentage of the best) was plotted on bronchial responsiveness as $\% \cdot \log \mu\text{mol}$, there was no clear relation (figure 2), particularly if one subject (at the upper left of figure 2) with the greatest bronchial responsiveness and poorest $FEV_{1.0}$ reproducibility was excluded as an outlier. Regression analyses of $FEV_{1.0}$ reproducibility in both groups of subjects, separately and combined, supported this impression, showing no consistent relation with bronchial responsiveness even though there was a consistent negative relation with the level of $FEV_{1.0}$ (mean of best and next best $FEV_{1.0}$) in accord with previous observations (4–6).

The subject mentioned as an outlier in figure 2 was a man 28 years of age with troublesome asthma who required intermittent oral steroid therapy, although not recently. He had not inhaled bronchodilators for 4 h when assessed. He showed a successive fall in $FEV_{1.0}$ with each forced expiration, appearing to bronchoconstrict with these maneuvers. His PD_{20} was $0.2 \mu\text{mol}$ in the test analyzed in this report, and it was similar when the test was repeated within a few days. A placebo inhalation test using only normal saline was carried out and showed no important change in $FEV_{1.0}$.

Those with test failure were older than those with test success, and a greater percentage smoked (table 2). These differences were not marked but were consistent across subgroups when the men and women, and group 1 and group 2, were considered separately (data not tabulated).

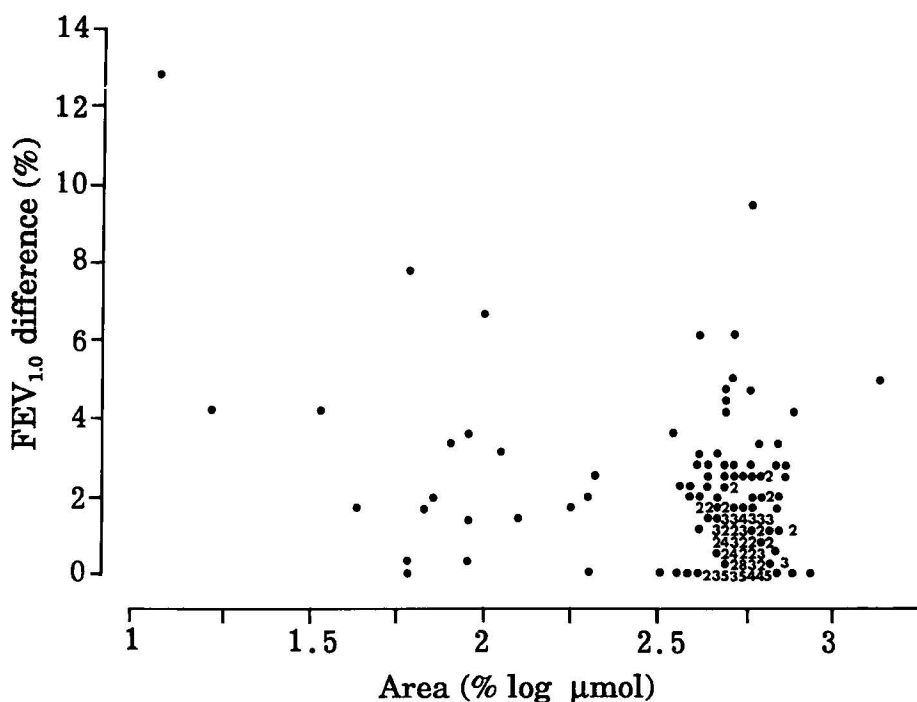


Figure 2. Reproducibility of forced expiratory volume in 1 s ($FEV_{1.0}$) compared with bronchial responsiveness in group 3.

Table 2. Gender, smoking, and age by reproducibility of the subjects' forced expiratory volume in 1 s.

	Women (%)	Smoking			Age (years)	
		Current (%)	Former (%)	Never (%)	Mean	SD
Groups 1 and 2						
Test success (N = 346)	22	47	21	33	39	14
Test failure (N = 15)	33	53	40	7	44	15
Group 3						
Test success (N = 198)	65	15	22	62	38	13
Test failure (N = 6)	50	67	33	0	50	11

Discussion

We believed that bronchial hyperresponsiveness was a plausible explanation for test failure, so any potential bias in our data recording was in favor of an association between the two variables. We have, however, failed to demonstrate a convincing relation between them.

The associations of test failure with older age and with smoking have been noted previously (4, 5, 7) and may be consequences of a low FEV_{1.0} in older people and in smokers. The ATS reproducibility criterion uses the 5% rule down to 2.0 l and therefore assumes that variance in FEV_{1.0} decreases with decreasing FEV_{1.0} down to 2.0 l, which may not be correct.

It is possible that groups 1 and 2 contained fewer subjects with hyperresponsive airways than the general population because these subjects had left after finding the work environment unpleasant (flour dust and chemicals, respectively). But any strong relation between PD₂₀ and test failure should be evident across the range of PD₂₀, and we used a sensitive high dose protocol and failed to find a relation. Furthermore, there was also no clear relation in group 3, a group of office workers without exposure to airway irritants. If anything, this group of volunteers could have contained more hyperresponsive subjects than the general population because we had encouraged people with a history of asthma to participate.

The subject who was an outlier in figure 2, whose case history is presented, was the type of patient with asthma who had led us to our original hypothesis that test failure was related to bronchial hyperresponsiveness. We cannot exclude the possibility that there is a relation between FEV_{1.0} reproducibility and bronchial responsiveness in patients with airway disease.

It is also possible that, although we studied over 600 persons altogether, a larger study is needed. Even in studies which had higher rates of test failure than ours, for example, 14% for Pennsylvania machinists (5) and 9% in a study in six cities in the United States (7), the numbers for analysis are still small. A study of working adults in Canada found that test failure was significantly associated with bronchial hyperresponsiveness in 143 men but not in 148 women (17). We believe the association would be more convincing if present in both genders. Although a larger study would have the power to demonstrate a weak but real relation, these data suggest that bronchial responsiveness is unlikely to be a major determinant of test failure, for which other explanations should be sought.

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