ly in the different groups. Figure 2 depicts mean changes in test values that were induced by isoproterenol in each of the four groups. The vertical brackets around the means represent 95 percent confidence intervals, determined by multiplying the standard error of the mean change by the appropriate t value. Depicting the data in this manner makes its statistical significance readily apparent. Whenever the brackets overlap the horizontal 0 percent change axis, the change brought about by isoproterenol is not statistically significant. However, since one can be 95 percent confident that the true mean change of the population being sampled resides within the interval, the change brought about by isoproterenol is significant (P < 0.05) when the brackets do not overlap the 0 percent axis.

Figure 2 indicates that FEV₁ increased significantly in all four groups. Although the magnitude of the change is smaller in the groups starting out with normal FEV₁ than in group 4, the low variability of this measurement accounts for its uniformly significant increase.

CV/VC is seen to change significantly only in group 2, in which subjects started out with high closing volumes. Interestingly, CV/VC increased in the normal subjects of group 1 as well as in the group 3 subjects, although not significantly. Group 4 demonstrated a huge variability in CV/VC changes.

V₅₀ values significantly increased after isoproterenol in all four groups. However, a different pattern of increase was seen than with FEV₁. V₅₀ increased the most in group 1 subjects, who started out with normal V₅₀ values, than in the low V₅₀ subjects of group 3. The least response in V₅₀ was seen in the abnormal subjects of group 4.

Analysis of the V₂₅ data shows this parameter to be significantly increased only in group 2. This observation tends to support the contention that V₂₅ and CV/VC measurements reflect a similar locus of potential abnormality.

FVC is shown to significantly increase only in group 4, with very little change seen in subjects originally presenting with normal FEV₁ values. Contrasting the influence of isoproterenol on FVC values and FEV₁ values shows how these two parameters differ in their ability to delineate obstructive airway disease. FEV₁ appears to be a highly sensitive and consistent index of bronchodilator response, but its change with isoproterenol may not be able to discriminate the different degrees of abnormality. FVC, on the other hand, is less sensitive to isoproterenol but remains a useful diagnostic tool due to its tendency to increase after the drug only in cases of significant dysfunction.

An Evaluation of Tests Used to Measure Bronchodilator Drug Responses

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Bronchodilator effects were measured by spirometry and in the body plethysmograph in a double-blind crossover study involving 20 volunteer asthmatic subjects. The subjects inhaled medications from aerosol canisters containing fenoterol at 0.1 mg, 0.2 mg and 0.4 mg, as well as isoproterenol at 0.15 mg and an inert placebo in a random sequence on five test days. Bronchodilation was quantitated by measurements of FEV₁, FEF 25-75 and Gaw/VT for up to eight hours after administration of the medication. There was a maximum increase in FEV₁ of up to 80 percent, in FEF 25-75 of up to 120 percent and in Gaw/VT of up to 450 percent in response to the most active medication. These results

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might be interpreted as indicating that the most sensitive of these several measures of bronchodilation is Gaw/VL with FEF_{25-75} next and FEV₁ least sensitive. However, when these changes are examined in terms of the multiple of standard errors change, the three measures are remarkably comparable. The percentage of change of these three parameters from baseline at 30 minutes post aerosol inhalation given in Table 1 illustrate this point.

Considering the expected bronchodilator response to isoproterenol, FEF_{25-75} shows the most significant response (greatest number of standard errors change—6.15) with FEV₁ next (5.81) and Gaw/VL least significant (2.48). However, the response to 0.1 mg TBI1165a gives a significance order Gaw/VL > FEV₁ > FEF_{25-75}. The order of significance for the average of the four bronchodilator responses, when considered in this manner, is FEF_{25-75} > FEV₁ > Gaw/VL.

If an increasing response is expected from an increasing dose of fenoterol the order of significance from comparing the ratio of the difference of the means to the standard error of the differences of 0.1 mg to 0.2 mg doses shows FEF_{25-75} > Gaw/VL > FEV₁, and from comparing 0.2 mg to 0.4 mg doses a significance order of FEF_{25-75} > FEV₁ > Gaw/VL is obtained.

A look at responses at times other than 30 minutes post-inhalation revealed similarly inconsistent orders of significance for the three measures. Thus, no one of the three seems to be better than the others in revealing response to bronchodilator in a group of subjects with a history of reversible airways disease although this may not be true in individual cases.

Relative Value of Tests Used to Measure Bronchodilator Response

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Recently we completed a study in which the bronchodilator effect of varying doses of aerosolized fenoterol, isoproterenol, and placebo were compared. Since we had measured the forced expiratory volume in one second (FEV₁), the forced vital capacity (FVC) and the mid-half flow rate (FEF_{25-75}%) before and serially after the administration of bronchodilators, we analyzed our data to see which of these tests best separated the different therapeutic regimens.

Twenty adult patients with reversible airway disease were studied. Each patient was randomly given the following five drug regimens in a double-blind manner: fenoterol 400, 200, and 100 μg, isoproterenol 150 μg and placebo. Medications were administered via freon propellant in metered dose inhalers. The results were expressed as the time-weighted mean percent improvement over the four hours following drug administration.

The drug regimens could be ranked as follows (Fig 1): fenoterol 400 μg > fenoterol 200 μg > fenoterol 100 μg > isoproterenol 150 μg > placebo. When the percent mean improvement in the various tests was calculated, the greatest improvement was seen in the Gaw/VL followed by the FEF_{25-75}%, FEV₁, and FVC.

However, these percent changes do not take into account the inherent variability of the tests. This variability can be compensated for in the statistical procedure known as the analysis of variance. It is based on the principle that in the evaluation of a response to a treatment, some of the variance in tests is due to the treatment while some is due to other factors such as the measurement itself, and spontaneous variations not due to the treatment. The ratio of the variance attributable to the drugs divided by the variance not attributable to the drugs is known as the F value. The higher the F value, the more significant the results.

The order of the F values (Fig 1) is in marked contrast to that when the percent increase is considered. The FEV₁ has the highest F value followed by the Raw and the FVC. The Gaw/VL and the FEF_{25-75}% which have the highest percentage of mean improvement have relatively lower F values.

Higher F values should be associated with more statistically significant conclusions. Using five drug regimens, there are ten comparisons to make (Table 1). Use of the FEV₁ allows seven statistically significant conclusions to be made while no more than six conclusions can be made with any of the other tests. All significant conclusions available from any of the tests are available from the