The Significance of Volume-Adjusting the Maximal Midexpiratory Flow in Assessing the Response to a Bronchodilator Drug*

Carl B. Sherter, M.D., F.C.C.P.;** John J. Connolly, M.D.;†
and Donald P. Schilder, M.D.‡

Forced expiratory spiromgrams were obtained before and for six hours after 25 subjects ingested ephedrine and placebo in a double-blind crossover study. Significant changes in the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV₁,₀) were noted on days when ephedrine was administered, while the mean forced expiratory flow during the middle half of the FVC (FEF₂₅-₇₅%) failed to indicate significant bronchodilation. When FVC increases after therapy with a bronchodilator drug, one is no longer measuring flow during the same volume segment and driving pressure (static transpulmonary pressure [Pst]) as before administration of the bronchodilator drug. Volume-adjusting the FEF₂₅-₇₅% after therapy to the same volume and Pst over which flow is being measured in the tracings before bronchodilator therapy yielded highly significant increases in flow after administration of the bronchodilator drug.

The mean forced expiratory flow during the middle half of the forced vital capacity (FEF₂₅-₇₅% or maximal midexpiratory flow rate) has been a useful measurement of obstruction to airflow since its introduction by Leuallen and Fowler.¹ Macklem and Mead,² working on dogs, demonstrated that small airways contribute little to flow resistance at high lung volume, but at lower lung volumes, the contribution of small airways increases. The FEF₂₅-₇₅% is the mean flow in the middle half of the forced vital capacity (FVC) and reflects an increasing contribution of the small airways to airway resistance. McFadden et al³ demonstrated that the FEF₂₅-₇₅% was a more sensitive measurement of obstruction to airflow than the forced expiratory volume in one second (FEV₁,₀). Furthermore, these authors³ noted that after their patients had been treated for one month, they maintained an abnormal, relatively unchanged total lung capacity (TLC), whereas their values for residual volume (RV) and FEF₂₅-₇₅% were statistically improved. Conversely, Olsen et al⁴ noted that immediately after therapy with a bronchodilator drug, the FEF₂₅-₇₅% frequently decreased when other indices of obstruction improved. This was seen in patients who increased their values for vital capacity (VC) after therapy. Olsen et al⁴ pointed out that in these patients, flow was not being measured during the same segment of volume before and after bronchodilator therapy, and these investigators⁴ suggested a method of volume-adjusting the FEF₂₅-₇₅% (isovolume FEF₂₅-₇₅%).

Data collected before and after oral administration of ephedrine during the course of a recent double-blind crossover study of bronchodilator drugs provided an opportunity to further evaluate the FEF₂₅-₇₅% adjusted for increases in VC as an index of bronchodilation. The results of that evaluation are presented herein.

MATERIALS AND METHODS

Twenty-five patients with reversible obstruction of the airways were selected from the outpatient population of our clinic. The purpose of the study was explained, and informed consents were obtained. Each patient demonstrated greater than 25 percent improvement in their FEV₁,₀ after inhaling 2 ml of a 1:800 solution of isoproterenol nebulized over a five-minute period by a modified nebulizer (Deutraband D-31). The mean age of the patients was 49 years, with a range of 20 to 73 years. Twenty-four were men, and one was a woman. All patients were clinically stable at the time of testing.
Therapy with all medications, including steroids, was closely controlled. For two weeks prior to and during the week of study, steroids were administered in a single dose at 6 P.M. Therapy with all other medications was withheld for at least 12 hours prior to each day of study. All patients fasted (except for water) for 12 hours before and 4 hours after ingestion of the drug. After the four-hour measurements, the patients ate a light meal.

The study utilized a double-blind crossover technique. On each of two days of study, the patient received an oral dose of either placebo or 25 mg of ephedrine. Each patient received both agents. To minimize the effects of natural variation of obstruction of the airways, both days of study were confined to one five-day period, and the studies were started at the same hour each day.

The bronchodilator effect was assessed by measurements of the FVC, the FEV1.0, the FEF25-75%, and the isovolume FEF25-75%. All studies were performed on a 13.5-L water-filled spirometer (Collins), and normal values were taken from the Veterans Administration-Army cooperative study.6 Lung volumes were measured using Boyle's law in a volume-displacement body plethysmograph.

The isovolume FEF25-75% (Fig 1) was measured on the curve after bronchodilator therapy by setting the maximal inspiratory point at zero volume and by setting the 25 percent and 75 percent points at the same volumes as were measured on the tracing before bronchodilator therapy. Thus, on the forced expiratory spirogram obtained after treatment, flow is not measured over the middle one-half of the FVC but rather over a segment of volume that more closely corresponds to the segment measured prior to treatment. The best of at least three forced expiratory spiograms are used from each period of measurement.

Each patient had complete studies at 15 and 30 minutes before administration of the drug, at 30 minutes after administration, and then hourly for six hours. The TLC was measured at 30 minutes before and at 30 minutes after administration of the drug. In seven patients the TLC was measured at each period of time; in others, measurements were taken at least at two additional times. The paired t-test was used to compare the mean percentage of change from baseline for therapy with ephedrine vs placebo at each increment of time.

**Results**

The mean baseline values for the population under study, expressed as the percentage of predicted values (±1 SE), are as follows: TLC, 136 ± 4 percent; FVC, 70 ± 4 percent; FEV1.0, 49 ± 4 percent; and FEF25-75%, 26 ± 4 percent. There was less than a 5 percent difference between mean baseline values on the days of study.

Figure 2 is a plot of FVC (percent of change from baseline) against time after ingestion of ephedrine.

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**Figure 1.** Isovolume FEF25-75% is measured by matching maximal inspiratory points of tracings before and after bronchodilator therapy. Points at 25 percent and 75 percent of curves after bronchodilator therapy are matched to those measured on tracing before bronchodilator therapy. Thus, on tracing after bronchodilator therapy, one is not measuring flow in middle 50 percent of that breath, but rather during same segment of volume as on forced expiration before bronchodilator therapy (modified from Olsen and Hale*).

**Figure 2.** Percent change in FVC from baseline (100 percent) before and after single orally administered doses of ephedrine and placebo in 25 subjects with reversible obstruction of airways. Statistically significant (P < 0.05) differences are noted at 60 minutes and are sustained throughout 360-minute period. Vertical bars include ± 1 SE.

**Figure 3.** Percent change in FEV1.0 from baseline (100 percent) before and after single orally administered doses of ephedrine and placebo. At 300-minute interval, differences between values after administration of ephedrine and placebo are not significantly different, but differences were significant at all other observations after 30 minutes.
and placebo. Compared with placebo, ingestion of ephedrine produced significant (P < 0.05) bronchodilation in one hour, which was sustained throughout the six hours of testing. At peak effect (180 minutes), the differences were highly significant (P < 0.01). Similar results are noted in Figure 3, a plot of FEV₁₀ expressed as percentage of change from baseline. At the 300-minute interval the difference between data after ingestion of ephedrine and placebo was not statistically significant, but the difference was significant at all other observations. In Figure 4, the FEF25-75% (expressed as percent change from baseline) is plotted against time. Although the means on the days when ephedrine was administered are higher than those on days when placebo was given, at no time are the values significantly different.

In Figure 5, isovolume FEF25-75% is plotted as percentage of change from baseline. The differences between data after ingestion of placebo and ephedrine are significant at all observations (P < 0.01 at 30 minutes; P < 0.0001 at 180 minutes). There were no significant changes in TLC for any patient.

**Discussion**

It seemed paradoxical to us that while we were studying a relatively weak bronchodilator drug, the FVC and FEV₁₀ should change significantly while the FEF25-75% changed little. At different lung volumes, values for elastic recoil pressure (and thus airway driving pressure) are different, and this difference may obscure or enhance a true change in resistance to flow. In all subjects, there were no significant differences in measured TLC before and 30 minutes after ingestion of ephedrine. In the seven subjects, additional measurements of TLC during the testing period also yielded no significant differences. These findings confirm the lack of significant change in TLC noted by McFadden et al. Therefore, our subjects' maximal inspiratory points did not change before and after therapy with ephedrine. The FVC did increase, with a concomitant decrease in RV. Measuring FEF25-75% as the mean flow over the segment of 25 to 75 percent of the FVC before and after ingestion of ephedrine would measure flow over different absolute lung volumes with different elastic recoil pressures and sizes of airways. Thus, these two determinations of FEF25-75% would not be directly comparable. In this population, these differences were enough to render comparison of FEF25-75% before and after ingestion of a bronchodilator drug useless.

Setting the maximal inspiratory point as zero volume and measuring the mean flow over the same segment of volume after bronchodilation as before allows direct comparison of maximal midflows. Indeed, the FEF25-75% adjusted to an isovolume segment (isovolume FEF25-75%) became a highly sensitive index of bronchodilation. At 30 minutes, only isovolume FEF25-75% indicated significant bronchodilation. At the time of peak response (180 minutes), FVC (P < 0.01) and FEV₁₀ (P < 0.001)
were highly significant, while isovolume FEF25-75% demonstrated the highest significance (P < 0.0001). The FEV\textsubscript{1.0} loses significance at 240 minutes but regains it at 300 minutes. The increases in FVC remain significant throughout the six-hour period of measurement. Changes in isovolume FEF25-75% remain highly significant at each interval of time.

In the course of this study,\textsuperscript{7} a far more potent orally administered sympathomimetic amine, terbutaline, also was given. Bronchodilation was so pronounced that midflow rates that were not adjusted for volume were highly significant. The increase in FVC and the decrease in RV were equally dramatic, and, again, the volume-adjusted midflow demonstrated much more significant bronchodilation than nonadjusted midflow rate.

Olsen and Hale\textsuperscript{8} noted that in 24 of 100 consecutive patients given a bronchodilator drug, isovolume FEF25-75% increased when FEF25-75% did not. McFadden et al\textsuperscript{9} described a group of patients with disease predominantly of the small airways who had normal values for FVC and FEV\textsubscript{1.0}. Their mean values for FEF25-75% and RV were significantly abnormal. After one month of therapy, the mean TLC and FEV\textsubscript{1.0} were unchanged, but FEF25-75% and RV improved significantly. With a decrease of RV at the same TLC, the VC must have improved. It can be argued that if FEF25-75% were adjusted for volume, even greater improvement would have been noted.

We agree with Olsen and Hale\textsuperscript{8} that FEF25-75% should be volume-adjusted to changes in FVC in all patients who are given a bronchodilator drug. Although the significance of this measurement was noted in 1966\textsuperscript{4} and again in 1968,\textsuperscript{8} it has not become widely accepted. Our data support the previous observations. Thus, the isovolume FEF25-75% becomes a highly sensitive measurement of bronchodilation and is frequently significant when FVC and FEV\textsubscript{1.0} have improved too little to be sure whether the patient has responded to the bronchodilator therapy.

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