The Use of Expiratory Forced Flows for Determining Response to Bronchodilator Therapy

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Two hundred seventeen patients were studied before and after administration of isoproterenol by IPPB. In 35 patients, lung specimens were examined within 12 months after the study. Patients with elevated bronchial gland-bronchial wall ratio (Reid index) showed significantly more improvement in forced expiratory flows after bronchodilator therapy, as compared to patients with normal Reid index. There was no difference in response to therapy in patients with emphysema of less than 20 percent, as compared to patients with emphysema of more than 20 percent. Patients with severe reduction in lung recoil pressure had lesser improvement after therapy in forced expiratory flows, as compared to patients with moderate reduction in recoil pressure or normal recoil pressure. In 39 patients inspiratory pulmonary resistance and forced expiratory flows were measured before and after therapy. In all these 39 patients, airway resistance showed comparable improvement regardless of the value for recoil pressure. The lack of response in expiratory flows is attributed to the increased collapsibility of the large airways and not to lack of response to therapy.

Isoproterenol is widely used as a bronchodilator in treatment of patients with chronic obstructive pulmonary disease (COPD). Changes in flow rates after administration of bronchodilators have been advocated as a test to determine the "reversibility" or "irreversibility" of the disease process, to predict which patients will receive benefit from nebulized bronchodilators, and in some reports lack of response to isoproterenol has been used as a criterion for a diagnosis of emphysema. Others have reported patients with COPD and emphysema (judged on roentgenographic evaluation) as having no changes in forced expired volume in one second (FEV₁) after bronchodilator therapy, but significant improvement in inspiratory flow rate. Curtis et al studied the response to bronchodilators in patients with COPD over several years, and found almost all will show improvement in FEV₁ after use of bronchodilators on one or more occasions. Some patients may show improvement on one study and no change on another. A recent study reported patients responding to bronchodilators had elevated airway resistance, and those with normal airway resistance had no change in flow rates after such therapy.

In this report 217 patients were studied before and after administration of isoproterenol through intermittent positive pressure breathing machine (IPPB). In 35 patients lung specimens were available within 12 months after the study, and the response to treatment with bronchodilators was correlated with morphologic emphysema and bronchial gland hyperplasia. Lung recoil pressure and the single breath method diffusing capacity for CO were utilized to divide the patients into those with severe emphysema (50 percent or more), and those without emphysema or with mild emphysema (20 percent or less), and the two groups were compared to ascertain the differences in response to isoproterenol inhalation.

Materials and Methods

All patients in this study had FEV₁ below 80 percent normal. They were referred to the pulmonary function laboratory for evaluation of lung disease, or were a part of a long-term followup study of COPD. The patients were examined and a questionnaire pertaining to the respiratory tract was

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FIGURE 1. Calculation of midflow rates from maximum expired flow volume curves (MEFV) and forced vital capacity (FVC) curve in one patient. Upper portion are curves before treatment and lower portion after treatment. Solid lines were not corrected for lung volume, but drawn for each curve separately. Broken lines in the lower curves were drawn at the same volume, assuming no change in total lung capacity.

completed by the examining physician. The study was done in clinically stable patients, and administration of bronchodilators was discontinued ten hours before the test. After completion of bronchodilator therapy, the patient was asked by the technician whether he "improved" or not. During this study only four technicians administered the treatment and did the spirometric studies. All these technicians received adequate training before proceeding on their own.

All patients had three forced vital capacity (FVC) curves before the study on a 13.5 L Collins spirometer. Subsequently, they received eight drops of isoproterenol (Isuprel 1:200), diluted by 16 drops of saline, nebulized by IPPB (Bennett PR2). This lasted an average of 10 to 15 minutes. Five minutes after the IPPB was finished, three FVC curves were repeated. Forced expired volume in one second (FEV1) and maximum mid-expiratory flow rate (FEF25-75) were calculated from the record and the highest values used for the study.

On another day, and within a period of a few days, 186 patients had single breath diffusing capacity for carbon monoxide and total lung capacity (TLC) by the closed helium method, 155 patients had lung recoil pressure at total lung capacity (Pst), and 173 patients inspiratory pulmonary resistance. To correct lung recoil pressure for lung volume, percent normal TLC was divided by the value for recoil pressure at total lung capacity (% N TLC/Pst). Methods of pulmonary function and source of normal values have been described in detail previously. Pleural pressure was measured by esophageal balloon, and inspiratory pulmonary resistance was measured at mid-inspiration. Volume and flow were measured by hi-fi Med Science spirometer.

In 25 randomly selected patients airway resistance at 0.5 L/sec of flow and lung volumes by constant volume body plethysmograph,13 recoil pressure at total lung capacity, work of breathing and maximum expiratory flow volume curves (MEFV) were done before and after administration of isoproterenol, in addition to the FVC curve. In an additional 14 patients inspiratory pulmonary resistance was determined before and after use of bronchodilators, in addition to the studies just mentioned. Work of breathing was calculated from volume-pressure loops recorded on an X-Y recorder. For the MEFV curves, flow and volume from the Ohio Medical spirometer were recorded on a Tektronix storage oscilloscope and photographed. Since flow rates change with lung volume, midflow from the FVC curve (FEF25-75) and from MEFV (V max 50 percent VC) were calculated at the same lung volume, assuming there was no change in total lung capacity (Fig 1). Normal values for TLC and FEV1 were taken from the VA Cooperative Study.12 Inspiratory pulmonary resistance above 4 cm of water per liter per second was considered abnormal.

In 35 patients, lung specimens were available within 12 months after the study. There were 5 lobectomies, 12 pneumonectomies, and 18 lungs from autopsies. The surgical specimens were from patients with bronchogenic carcinoma, but the tumor masses were small and did not interfere with

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FIGURE 2. Changes after isoproterenol expressed as percent of pretreatment in 25 patients who had all the tests shown. Horizontal lines are the mean for each test. FEV1, forced expired volume in one second; FEF25-75 mid-expiratory flow measured from FVC curve and corrected for volume; V max 50 percent VC, mid-expiratory flow measured from flow-volume curves and corrected for volume; Gaw/tGV conductance per liter of thoracic gas volume; inspiratory resistance, inspiratory pulmonary resistance.
normal, emphysema is severe, and when both are normal there is either no emphysema or emphysema is less than 20 percent of lung parenchyma.

**Results**

Changes after use of isoproterenol for various tests in 25 patients are shown in Figure 2. The percent increase in FEV₁ was less than for mid flows, work of breathing, and airway resistance. Mean improvement in FEV₁ was 11 percent; FEF₂₅₋₇₅, 22 percent; V max 50 percent VC, 24 percent; work of breathing, 27 percent; inspiratory resistance, 40 percent; GW/TGV, 16 percent. Seven of 25 patients showed a decrease in conductance. All of these seven patients had evidence of airway collapse even at low flow rates of 0.5 L/sec in that the record showed they reached flow plateaus at this flow. In these 25 patients, total lung capacity and recoil pressure showed no significant change from pretreatment value. As expected, vital capacity increased and residual volume and functional residual capacity decreased.

For the patients as a whole, percent increase for FEF₂₅₋₇₅ (corrected for volume) and FEV₁ had high correlation (r = .71, Fig 3). The percent increase in FEF₂₅₋₇₅ was more than twice that for FEV₁, however. For the rest of the results FEF₂₅₋₇₅ was used to assess the change after isoproterenol inhalation. The volume corrected FEF₂₅₋₇₅ will be referred to as isovolume FEF₂₅₋₇₅.

Figure 3. Improvement in mid flow rates (FEF₂₅₋₇₅) and forced expired volume in one second (FEV₁). Increase in FEF₂₅₋₇₅ was slightly above twice that for FEV₁; however, the correlation coefficient was high (r = .71) and significant (P<.001). Patients with decrease in flow rates after treatment were omitted.

Quantitation of emphysema, nor the pulmonary function studies. The lungs were inflated and fixed by formalin steam. Emphysema was quantitated by the point-counting method, and bronchial gland hyperplasia by the bronchial gland-bronchial wall ratio (Reid index). Patients were also divided into those with mild or no emphysema (20 percent or less) and those with severe emphysema (50 percent or more) on bases of physiologic methods. This separation is possible by the use of the single breath diffusing capacity and recoil pressure at total lung capacity. When both are ab-

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21549/)

**Figure 4.** Changes in the isovolume midflow rates and morphologic emphysema and bronchitis. Horizontal lines are mean values. The difference between patients separated on the basis of Reid index was significant (.05>P>.02). The difference between patients separated on the basis of emphysema (portion on left) was not significant (.70>P>.60).
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Figure 5. Patients with reduced diffusing capacity (less than 3.5 ml/L) and reduced lung recoil pressure (Pst) (%N TLC/Pst, more than 6) were considered to have severe emphysema (50 percent or more). Patients with normal DL and Pst were considered to have mild or no emphysema (20 percent or less). Horizontal lines are mean values. The difference was statistically significant (P<.001).

Figure 5 separates the patients on physiologic bases into those with severe emphysema and mild or no emphysema. Those with severe emphysema had a 25 percent increase in flow rates after administration of isoproterenol, and patients with mild or no emphysema had 44 percent improvement in FEF_{25-75} (P<.001).

Further analysis showed this difference to be due to the patients who had severe reduction in Pst (%N TLC/Pst greater than 10). Patients with normal recoil pressure (Pst) and moderate reduction in Pst had a similar increase in FEF_{25-75} after isoproterenol therapy, but in patients with severe reduction in Pst improvement in FEF_{25-75} was significantly less (Fig 6) (P<.01). In 39 patients with Pst measurements inspiratory pulmonary resistance was measured before and after treatment in addition to FEF_{25-75}. In this group of 39 patients, those with severe reduction in Pst had lesser response in midflow, but equal improvement in inspiratory resistance after treatment, as compared to those with normal or moderately reduced Pst (Fig 7). Thus, the lack of improvement in FEF_{25-75} cannot be attributed to irreversible airway disease in these patients. Patients with elevated airway resistance had a similar increase in forced expiratory flow rates to those with normal airway resistance (Fig 8).

Thirty-six patients were restudied after an interval of 12-36 months. The mean increase in FEF_{25-75} on the first study was 36 percent, and on the second study 26 percent. Considering greater than 20 percent increase in FEF_{25-75} after use of isoproterenol as representing good response, and below 20 percent as poor response, 25 patients responded well on the first study and 11 patients responded poorly. Of the 25 patients who showed good response on the first study, 12 showed poor response on the second study, and of the 11 patients with poor response on the first study four showed good response on the second study.

The difference between the first and second study was not statistically significant, but this may suggest that response to isoproterenol therapy is diminished later in the course of the disease. To examine this point further, changes in FEF_{25-75} after use of isoproterenol were plotted against FEV\textsubscript{i} percent of normal. The changes in flow rates, after isoproterenol therapy were not related to the severity of the disease as judged by FEV\textsubscript{i} except in patients with minimal evidence of airway obstruction. The increase in FEF_{25-75} was identical in patients with

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Figure 6. Changes in isovolume FEF_{25-75} related to recoil pressure measurement. Horizontal lines are mean values. The difference between the two groups on the right side of the figure is significant (P<.01).
FIGURE 7. Changes in inspiratory resistance and isovolume FEF25-75 in 39 patients who had both measurements before and after isoproterenol inhalation related to recoil pressure measurement. Improvement in FEF25-75 was significantly less in patients with severe reduction in recoil pressure, as compared to patients with more normal recoil pressure. Inspiratory pulmonary resistance showed equal improvement in all groups.

FEV1 of 10 to 60 percent normal and averaged 35 percent. The 21 patients with FEV1 of 60 to 80 percent of normal had only 10 percent increase in flow rates after isoproterenol administration.

"Wheezing" and "attacks of bronchospasm" are usually associated with reversible airway obstruction. In Figure 9, patients with COPD and wheezing on auscultation of the chest during spontaneous breathing are compared to those without wheezing, and patients with COPD and a history of "asthmatic attacks" to those without such a history. Only patients seen and examined by the author were included in this evaluation to minimize observer variability. A patient was considered to have "asthmatic attacks" if he gave a history of episodic periods of wheezing and shortness of breath. Patients with "wheezing" on auscultation and those with "asthmatic attacks" had a higher increase in FEF25-75, as compared to patients without these findings. It should be noted that wheezing was frequently present in these patients (128 of 155 had wheezing). Figure 10 shows changes in flow rates which were virtually identical in patients who stated they improved after the treatment, as compared to those who stated they did not (25 and 32 percent).

DISCUSSION

The degree of change in function studies after administration of isoproterenol can vary, depending on the interval between treatments, duration between treatment and performance of the test, and the test used. Bronchodilator therapy was stopped ten hours before the study in all patients in this series, and post-treatment tests done 20 to 30 minutes after beginning of treatment when maximal response is reported to occur. Maximum midflow rate (FEF25-75) adjusted for changes in lung volume, was used to assess response to therapy in this series. When compared with maximum midflow rate from flow volume curves, the results are comparable (Fig 2). Bouhuys, et al. reported flow rates measured at the same lung volume to be the most sensitive test in assessing the response to bronchodilators when the diseased airways are the small airways, which is the case in COPD. Ideally, measurements of flow rates are best done in conjunction with determination of total lung capacity; however, total lung capacity showed no change after use of isoproterenol in 25 patients in this series, and this experience is similar to others.

Response to Bronchodilator Therapy and Emphysema

In 35 patients the response to bronchodilators, assessed on one occasion, did not differentiate patients with morphologic emphysema of less than 20 percent from those with more extensive emphysema.
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Figure 9. In the group as a whole, patients with history of episodic wheezing and shortness of breath “asthma attacks,” and patients with wheezing on auscultation of chest during spontaneous breathing, showed greater improvement after treatment as compared to patients without such findings. For both portions of the graph, the difference was significant (P<.02).

It is desirable to have such correlation on a larger number of patients. Recently we have shown that separation of patients into those with severe emphysema (more than 50 percent) from those with mild or no emphysema (20 percent or less) can be made by physiologic tests. Therefore, the patients were divided on the bases of Pst and DL/L into those with severe emphysema (more than 50 percent), and those with no emphysema or mild emphysema (20 percent). The improvement in FEF25-75 was significantly less in patients with physiologic evidence of severe emphysema. This was due to the small change in FEF25-75 in patients with severe reduction in Pst (%N TLC/Pst ≥ 10), while the response in patients with moderate reduction in Pst (%N TLC/Pst 6-9) was similar to patients with normal Pst. Both groups of patients with moderate and severe reduction in Pst should have severe emphysema (more than 50 percent). Furthermore the lack of improvement in flow rates in patients with severe reduction in Pst cannot be interpreted as lack of response to therapy in these patients, since inspiratory pulmonary resistance showed equal improvement with use of isoproterenol in them, as compared to patients with more normal Pst. Both groups of patients with moderate and severe reduction in Pst should have severe emphysema (more than 50 percent). Furthermore the lack of improvement in flow rates in patients with severe reduction in Pst cannot be interpreted as lack of response to therapy in these patients, since inspiratory pulmonary resistance showed equal improvement with use of isoproterenol in them, as compared to patients with more normal Pst. Both groups of patients with moderate and severe reduction in Pst should have severe emphysema (more than 50 percent). Furthermore the lack of improvement in flow rates in patients with severe reduction in Pst cannot be interpreted as lack of response to therapy in these patients, since inspiratory pulmonary resistance showed equal improvement with use of isoproterenol in them, as compared to patients with more normal Pst.

Figure 10. Changes in flow rates after isoproterenol were virtually identical in patients who stated they noticed improvement and those who did not (.70>P>.60). Saunders observed no change in FEV1 after bronchodilator treatment in patients with emphysema but increase in inspiratory flow rates. Another cause for the little improvement in flow rates after
isoproterenol could be reduction in recoil pressure after therapy as reported by McFadden et al.22

These authors delivered large doses of isoproterenol, which presumably caused muscular relaxation and dilatation of the terminal lung units. When they used smaller concentrations of isoproterenol, as the one used in this study, lung recoil pressure did not change. In 25 patients in this series there were no systematic changes in lung recoil at TLC. Therefore, in this study, reduction in recoil pressure after use of bronchodilators cannot be implicated as the cause of the minimal change in flow rates observed in some patients.

It is clear that measurements of forced expiratory flow rates may increase, decrease, or show no change after bronchodilator therapy, depending on whether bronchodilation of small airways or increased collapsibility of large airways predominate.

Changes in Airway Resistance after Bronchodilator Therapy

Inspiratory pulmonary resistance is not affected by changes in collapsibility of the large airways and should be a useful test to measure bronchodilator response. This is especially the case in patients with severe reduction in recoil pressure. A recent report by Bouhuys et al16 showed no change in airway resistance after administration of bronchodilators, while midflow rates showed significant improvement. Thus, in some patients changes in small airways may not be reflected by measurements of airway resistance alone. For a more adequate evaluation of the effect of bronchodilator treatment, both expiratory mid flow rates and airway resistance should be used.

Airway resistance by body plethysmography is measured at low flow rates and usually before flow plateaus occur. Under these conditions airway resistance is comparable to inspiratory pulmonary resistance.23 In some patients with severe COPD, flow plateaus occur even at flow rates of 0.5 L/sec, and measurement of airway resistance in these patients can show considerable variability24 and may be influenced by increased collapsibility of large airways. In seven patients, specific conductance decreased after bronchodilator therapy (Fig 2). All these patients showed flow plateaus at flow of 0.5 L/sec. In such patients inspiratory pulmonary resistance should be a more reliable test for measuring the response to bronchodilators. It should be mentioned that with body plethysmography, it is possible to measure both inspiratory and expiratory resistance separately.

Clinical Relevance of Determining Response to Bronchodilators

Clinically, the response to bronchodilator therapy did not correlate with the patient's own assessment of benefit from the treatment. In general, patients with wheezing and with episodes of bronchospasm can be expected to show more improvement in flow rates after therapy, as compared to patients without such findings. Enormous variability was present between patients, however. In addition, patients who do not show improvement on one occasion may show improvement on another, and according to Curtis et al,8 almost all patients with COPD will show good response when tested on more than one occasion. Assessed on one occasion, the response to bronchodilator therapy cannot be relied upon to determine the reversibility or irreversibility of COPD, nor to predict the clinical benefit from such therapy. Crompton25 did not find the response to isoproterenol to be helpful in selecting patients likely to benefit from steroid therapy. It is possible that multiple assessments of the response to bronchodilator therapy might be of more clinical value.

REFERENCES


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Illusion of Depth on the Flat Surface of a Painting

The genius who broke the spell of Byzantine conservatism was the Florentine painter Giotto de Bondone (1266-1337). Giotto’s most famous works are wall-paintings or frescoes (so called because they must be painted on the wall while the plaster is still fresh, that is, wet). It is easy to see the similarity of Giotto’s figure of Faith to the works of the Gothic sculptors. But it is no statue. It is a painting which gives the illusion of a statue in the round. We see the foreshortening of the arm, the modeling of the face and neck, the deep shadows in the flowing folds of the drapery. Nothing like this had been done for a thousand years. Giotto had rediscovered the art of creating the illusion of depth on a flat surface. For Giotto this discovery was not only a trick to be displayed for its own sake. It enabled him to change the whole conception of painting. Instead of using methods of picture writing he could create the illusion as if the sacred story were happening before our very eyes. Painting, for him, is more than a substitute for the written word. We seem to witness the real event as if enacted on the stage. Giotto was a contemporary of the great Florentine poet Dante, who mentions him in his Divine Comedy.