

The breath-by-breath assessment of the response to bronchodilator

Bruce J. Sobol, M.D.

With the assistance of

Anne Reed and Janet Waldie

Valhalla, N. Y.

A method is presented for the continuous breath-by-breath assessment of airway resistance. This method is uniquely suitable for following the response to the administration of bronchodilator in patients with bronchial asthma. The method produces no discomfort and requires no special maneuvers on the part of the subject. The method consists of breathing into a nonobstructive flowmeter in series with a resistance of low value that is rapidly added and removed. The change in flow with the intrusion of the resistor permits calculation of the subject's respiratory resistance (the largest component of this being airway resistance). Sixteen studies were carried out on 8 subjects. In those subjects with a response to bronchodilator, this response was evident in 10 to 30 seconds following the administration of the bronchodilator.

A simple device, the "shutter,"¹⁻³ which we have been using in routine pulmonary evaluation appeared to have a place in the assessment of the response to bronchodilators. The device is easily used, produces no discomfort, and requires no special maneuvers, merely normal breathing. Because of these features it is an ideal method for assessing the rapidity of onset of the response to bronchodilators in patients with bronchospastic pulmonary disease. A study currently underway in this laboratory involving the comparison of the time of onset and duration of action of isoproterenol and metaproterenol offered a unique opportunity to assess the shutter as a means of measuring the breath-by-breath changes in airway resistance. The applicability of the shutter to this type of investigation seemed demonstrated by this work and is, therefore, presented here.

METHODS

The device

The principles upon which the shutter is based have been discussed in detail in the past.^{1, 2} In brief, the shutter tests (TRR) in the following manner: A resistor is rapidly (10 times per second) introduced and removed at the mouth. In this brief period, one tenth of a second, the driving pressure of respiration, the alveolar pressure, cannot be altered either voluntarily or involuntarily. In the instant in time when the resistor is in series with the lung, flow

From the Cardiopulmonary Laboratory, Grasslands Hospital, Department of Medicine, New York Medical College.

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Reprint requests to: Dr. Bruce J. Sobol, Cardiopulmonary Laboratory, Grasslands Hospital, Valhalla, N. Y. 10595.

Special abbreviations used

EFR: expiratory flow rate
FEV₁: one-second forced expiratory volume
FVC: forced vital capacity
MEFR: maximum expiratory flow rate
MMF: maximum midexpiratory flow
TRR: total respiratory resistance

decreases in proportion to the resistance of the added resistor and the resistance of the lung. Since the resistance of the added resistor is known and the ratio of the two flows, with and without the added resistor, is obtained by means of a flowmeter, TRR is easily calculated. It should be pointed out that TRR includes not merely airway resistance but also tissue resistance. However, the major portion of TRR in patients with airway obstruction is airway resistance, and acute changes consequent to the administration of a bronchodilator can be attributed only to changes in airway resistance.

Fig. 1 presents the respiratory pattern in a normal individual and one with an elevated airway resistance. Under ordinary circumstances TRR is determined by measuring several ratios from several breaths and averaging them. The analysis is done separately for inspiration and expiration. For the work presented here, several complexes were calculated and averaged for *each* inspiratory cycle separately. This permitted a breath-by-breath determination of resistance. Expiration was not calculated since it is commonly incalculable in patients with elevated airway resistance.^{1, 2, 4}

The protocol

The device was used with each of the 2 drugs studied in the first 8 subjects of the study. Testing on the shutter was performed twice as a control value, once prior to spirometric testing and once following it. With the subject seated in front of the shutter, the bronchodilator was then administered in aerosol form. Zero time was taken as the instant of the second and last "whiff" of the aerosol. Immediately after this was accomplished, the patient turned his head to the shutter (the noseclip was already in place) and began to breathe into it. Only a matter of a few seconds elapsed between the second "whiff" and the beginning of testing. The subject breathed continuously on the device for 40 to 50 seconds. Testing was interrupted so that spirometric measurements could be made at one minute. Shutter measurements were then made again at 2, 4, 7, 10, and 14 minutes. Testing on these occasions was for 30 seconds or less. Spirometry was repeated at 3, 6, and 15 minutes.

RESULTS

Fig. 2 is an example of the breath-by-breath analysis of the inspiratory resistance prior to and for 14 minutes following bronchodilator. For the first 42 seconds the record of resistance is uninterrupted. Following this the record is discontinuous since interruptions were necessary to perform the spirometric tests.

The patient in Fig. 2 is not unique. A drop in resistance in 10 seconds was not uncommon, and definite decrease was evident in 7 of the 8 patients by 30 seconds. The eighth patient was near normal on the two occasions he was tested and had only minor improvement both in TRR and EFR. Fig. 3 gives the average value for the 8 patients for the per cent change in TRR for each of the study intervals.

Fig. 2 illustrates that there is considerable variability in resistance between breaths. This is in part due to the fact that the analysis is performed manually,

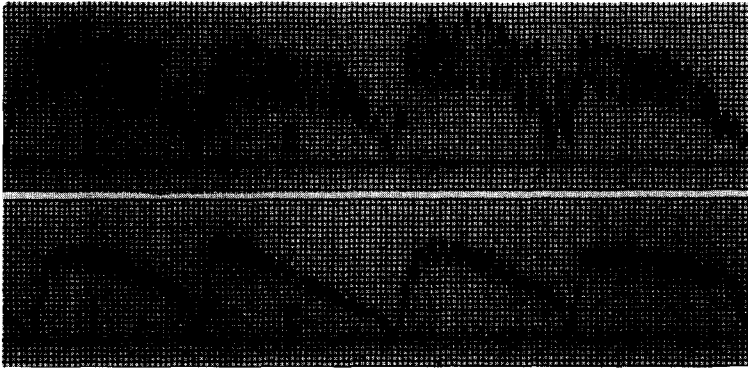


FIG. 1. The flowmeter used inscribes inspiration (I) and expiration (E) in the same direction. The first large upward deflection is inspiration, the second is expiration. These two large deflections have superimposed on them high-frequency oscillations. These oscillations closely resemble square waves. The upper portion of each high-frequency oscillation represents flow with no resistor in series with the mouth, the lower when the resistor is added at the mouth. The ratio of these two heights to the baseline permits the calculation of the subject's respiratory resistance.^{1, 2}

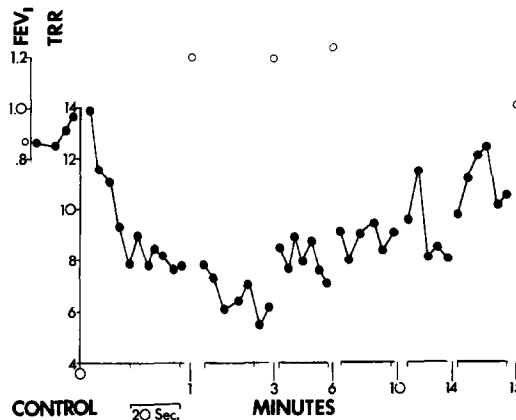


FIG. 2. The long vertical axis applies to TRR, in cm. H₂O/L./sec., solid circles, while the short axis refers to the FEV₁, open circles, liters. The abscissa is discontinuous since testing was interrupted to perform spirometry. This axis is in seconds where continuous; where broken the numerals indicate the elapsed minutes since the administration of bronchodilator. Each solid circle represents the inspiratory resistance of a single breath.

and some variation in measurement is inevitable. Furthermore, with high resistance and low flow rates small differences in measured heights of the flow complexes result in large differences in calculated resistance. These problems are less important when a series of breaths are averaged. However, in a breath-by-breath analysis the difficulties are compounded; some of the variability may be due to true biologic undulations in resistance, and the extent of this is unknown.

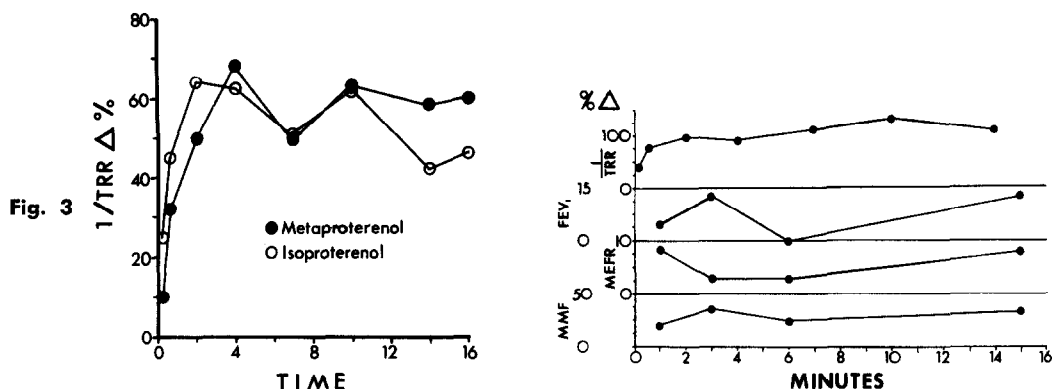


FIG. 3. Each point represents the average per cent change for all eight subjects. The abscissa is in minutes. However, the first two points were obtained at 10 and 30 seconds, respectively, after the administration of bronchodilator. The reciprocal of **TRR** was used so that the per cent change, plotted on the ordinate, is represented by an increase as resistance falls in response to bronchodilator. This is more in keeping with the directional change of the expiratory flow rates, as they improve with bronchodilator, seen in Fig. 4.

FIG. 4. **TRR** is shown as its reciprocal in order that improvement be represented as a rise in its value rather than a fall. This was done to make it comparable to the measures of expiratory flow, FEV_1 , **MMF**, and **MEFR**, all of which increase with improvement. Minutes are the minutes following the administration of the bronchodilator. Note that there tends to be some variability in response even between the measure of expiratory flow. The values shown are those of one subject.

In order to determine whether or not the rapid fall in airway resistance could be validated by more generally accepted techniques, 8 subjects with response to bronchodilator were tested by body plethysmography^{5, 6} as rapidly as the technician and patient could perform following the second "whiff" of bronchodilator and again 2 minutes later. The rapidity of the first measurement varied between 12 and 25 seconds (the ability to begin testing this rapidly after the door to the plethysmograph is closed is due to a modification that eliminated the necessity for an equilibration time in the box⁷). Of the 8 patients who had a response to bronchodilator by 2 minutes, 4 had a demonstrable response by the first determination, 15 to 25 seconds after the administration of the bronchodilator. A clear comparison between this method and the shutter is not possible because continuous determination is not possible. What per cent would have shown response by 30 seconds (7 out of 8 did by shutter) is, therefore, impossible to determine.

Although there was usually general agreement between the changes detected by the shutter and those of certain measures of expiratory flow, the FEV_1 , the **MMF**, and the **MEFR** (Fig. 4), this was not invariable, particularly as regards the **MMF** in those with large changes in **FVC**⁸—but perfect correlation at specific time intervals is impossible. In the first place, the two tests, spirometry and the shutter, were used at slightly different times. Secondly, there is only general agreement between the three measures of flow rate themselves (Fig. 4), and the degree of correlation between flow rate and shutter would vary with the flow rate chosen and the particular patient chosen. Nevertheless, as seen in Figs.

2 and 4, there is general agreement between flow rates and TRR. Both figures reflect a rough parallelism between all methods.

DISCUSSION

Previous work has indicated that the shutter accurately reflects airways resistance as measured by body plethysmography. In that study the correlation coefficient between the two methods was 0.88.² It is impossible to test patients simultaneously on the two devices. However, 4 of 8 additional subjects with a decrease in airway resistance following bronchodilator demonstrated that the onset of drug action can be as rapid by plethysmography as by the shutter. Although the onset of bronchodilation is demonstrable equally with this more conventional method, it takes considerable skill by the technician. In addition, repeated panting maneuvers, particularly when the subject is dyspneic, are exhausting for the patient. These factors limit the frequency of testing and make the plethysmograph unsuitable for continuous monitoring of the effects of bronchodilator. Spirometry also permits only intermittent testing and tends to be unpleasant and exhausting when repeated frequently. The forced expiratory effort commonly produces paroxysms of coughing. In addition, the forced expiratory maneuver itself can produce bronchospasm so that the true time course of bronchodilation cannot be determined.

The simple technique illustrated here offers a method of continuous evaluation of airway resistance. The use of the device is no more uncomfortable than breathing into a mouthpiece with a noseclip in place. Continuous observation could thus have been much longer than performed here and was limited only by the requirements of the protocol, interrupting the shutter test in order to perform the spiograms.

REFERENCES

- 1 Sobol, B. J.: A simple rapid technique for assessing airway resistance during quiet breathing, *Am. Rev. Resp. Dis.* **102**: 970, 1970.
- 2 Sobol, B. J.: Clinical experience with a new test of pulmonary function, *Chest* **60**: 137, 1971.
- 3 Sobol, B. J.: Further experience with a new test of pulmonary function. In press, *N. Y. State J. Med.*
- 4 Sobol, B. J.: A method of assuring maximal flow in forced expiratory maneuvers. In press, *Chest*.
- 5 Comroe, J. H., Jr., Botelho, S. Y., and DuBois, A. B.: Design of a body plethysmograph for studying cardiopulmonary physiology, *J. Appl. Physiol.* **13**: 430, 1959.
- 6 DuBois, A. B., Botelho, S. Y., and Comroe, J. H., Jr.: A new method for measuring airway resistance in man using a body plethysmograph: Values in normal subjects and in patients with respiratory disease, *J. Clin. Invest.* **3**: 327, 1956.
- 7 Sobol, B. J.: Methods for simplifying constant-volume body plethysmograph, *J. Appl. Physiol.* **27**: 295, 1969.
- 8 Sobol, B. J., Emirgil, C., and Wadhvani, B.: The response to bronchodilator in asthmatic subjects as assessed by pulmonary function tests, *J. ALLERGY* **46**: 65, 1970.