Use of An Impedance Meter for Measuring Airways Responsiveness to Histamine*

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We compared spirometry (FEV₁) and airway impedance (z) in the assessment of airway responsiveness to histamine. Airway impedance was measured by the oscillator technique during quiet breathing; both measurements were made twice after each increment of histamine during the challenge. Percentage change in impedance was related to percentage change in FEV₁ according to: \( \Delta z = 1.09 - 2.66 \Delta FEV₁ \), \( r = -0.73, p<0.01 \), i.e., impedance increased on average 2.7 times as much as FEV₁ fell. The cut-off point for the standard test is the histamine concentration giving a 20 percent fall of FEV₁ (PC₂₀FEV₁). The corresponding cut-off value chosen for impedance was a 30 percent increase (PC₂₀z) \( (PC_{20}z) = 0.74 \ (PC_{20}FEV₁) - 0.48, r = 0.74 \), where \( r \) is the Spearman rank correlation coefficient. Thus, impedance is a more sensitive index than FEV₁, because a smaller dose of histamine gave a diagnostic result. Impedance is a practical alternative to FEV₁, being less arduous for the patient and requiring little cooperation.

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The oscillator method for measurement of airway resistance was described by DuBois et al. 35 years ago, but has never found as prominent a place in practice. Following the modification and development of the method by Franetzki et al., apparatus using the oscillation method became commercially available for clinical and experimental use as the Siregnost PD5. This apparatus applies an oscillating flow at the mouth and records the amplitude, and if required, phase of the resultant oscillating pressure. Although respiratory impedance is the sum of airway, lung, and chest wall resistance and reactance, in practice, the main factor is central airway resistance which is accurately measured from the amplitude of pressure oscillation. Measurements are made during quiet breathing with little cooperation required from the subject, and therefore, the method has been of interest to pediatricians. Duiverman et al. found the technique satisfactory for histamine and methacholine challenges in children, and Solymar et al. in an indirect comparison with FEV₁, found the oscillator method to be slightly more sensitive. Two studies in adults have made direct comparisons between the impedance method and test of forced expiration during bronchial challenge and claimed either poor sensitivity of the impedance method or a poor correlation shown in some subjects between the two techniques. The interpretation of these studies is difficult, however, because they used non-standard challenge methods.

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Clinical methodology for methacholine and histamine challenge using cumulative and noncumulative dose-response techniques have been standardized, with most workers now using the PC20 test described by Cocksroft and associates. Since impedance measurement potentially offers advantages over spirometry, we have compared impedance and FEV₁ during standard histamine challenge.

METHODS

We studied 15 male and 9 female asthmatic outpatients; their mean age was 38 (range 12 to 72). The patients were non-smokers and had no evidence of any respiratory disorder other than asthma. We excluded patients in whom the FEV₁/FVC ratio was under 70 percent, those with a large response to the lowest histamine concentration, and those who were unable to use the spirometer. We also excluded patients in whom baseline variation of FEV₁ was excessive because we suspected that they were unreliable performers of the forced expiratory maneuver. All medications were stopped 18 hours prior to the study. All subjects were volunteers who agreed to take part after having the nature of the experiments and their purpose explained to them. The experiments were approved by the Ethical Committee of King Edward VII Hospital, where they were performed.

The method of challenge was that of Cocksroft and colleagues, with additional measurements of airway impedance (z). The procedure commenced with duplicate baseline measurements of first z and then FEV₁. Impedance was measured using apparatus that applied oscillating airflow at 10 Hz to the mouth during quiet breathing (Siregnost PD5). Readings were made at end expiration over a period of 30 s. The measurement was made by comparing the amplitude component of respiratory impedance with that of a reference tube of known impedance. A pen recorder was used to continuously display the impedance signal. This allowed easy identification of short-term obstruction occurring in the mouth or larynx. The FEV₁ was measured using a dry spirometer.

After baseline measurements, the subject inhaled from a Wright nebulizer (via a facemask) an aerosol of 0.93 percent NaCl (diluent used for histamine) for 2 min. Duplicated measurements of z and FEV₁ were made 30, 90, and 180 s later. The subject then inhaled histamine aerosol (0.03 mg/ml) for 2 min, and measurements were repeated in the same manner. Every 5 min, histamine concentration...
in the nebulizer was doubled until the lowest value recorded for FEV<sub>1</sub> was 20 percent lower than the lowest value after inhalation of diluent, or the maximum histamine concentration of 16.0 mg/ml had been reached. All tests were conducted at approximately the same time during the afternoon.

In order to assess the coefficients of variation for \( z \) and FEV<sub>1</sub> in ten of our subjects (5M and 5F), we made single measurements of these variables at 5-min intervals over a period of 60 min (the maximum time course of histamine challenge).

### Results

A total of 111 paired measurements of \( z \) and FEV<sub>1</sub> were obtained from 24 challenges. In general, \( z \) increases as FEV<sub>1</sub> fell with the development of bronchial narrowing. There was a significant negative correlation between these changes (\( r = -0.73; p < 0.01 \)) (Fig 1). \( z \) tended to increase proportionally more than the fall in FEV<sub>1</sub>, and therefore, most points in the relationship shown in Figure 1 lie above the line of identity. Although small changes in FEV<sub>1</sub> (±15 percent) were seen on occasions without significant changes in \( z \), falls in FEV<sub>1</sub> >20 percent (the endpoint of the PC<sub>20</sub> test) were always associated with >40 percent increase in \( z \). However, very large changes in \( z \) were often associated with insignificant changes in FEV<sub>1</sub>; and overall impedance changes were greater than changes in FEV<sub>1</sub>. Hence, the slope of the relationship (\( z = 1.09 - 2.66 \) [FEV<sub>1</sub)]) was significantly (\( p < 0.05 \)) greater than the line of identity.

Coefficient of variation (CV) for \( z \) was 4.9 percent and for FEV<sub>1</sub> 3.25 percent. Thus, the 20 percent decrease in FEV<sub>1</sub> used as a cut-off for the PC<sub>20</sub> test represents a change six times greater than the CV of the measurement. Therefore, the appropriate cut-off for \( z \), approximately equivalent to six times its CV is 30 percent, and in order to compare these methods of measurement, we have related PC<sub>30</sub> to PC<sub>20FEV<sub>1</sub></sub> (Fig 2). In all but one case, the points in this relationship fall below the line of identity, indicating that PC<sub>30</sub> is usually less than PC<sub>20FEV<sub>1</sub></sub>. The PC<sub>30</sub> was only one half of PC<sub>20FEV<sub>1</sub></sub> in nine cases, a quarter in six cases, and an eighth in one. The close and significant relationship between measurements (Spearman rank correlation coefficient = 0.88) indicates that despite the absolute differences between PC<sub>30</sub> and PC<sub>20FEV<sub>1</sub></sub>, similar conclusions about individual sensitivities are reached.

### Discussion

This study has demonstrated a close correlation between measurements of bronchial responsiveness to histamine derived from impedance measurement and FEV<sub>1</sub>. Impedance measurement is, however, a more sensitive method, usually demonstrating a significant change before it is registered by FEV<sub>1</sub>. Hence, a lower histamine exposure is required.

The PC<sub>20</sub> method, using FEV<sub>1</sub>, has established its place in clinical investigation, and owing to its rugged simplicity and cheapness, will no doubt continue to hold its place. For this reason, we have used the PC<sub>20</sub> test as our "gold standard" against which to assess the
impedance method. The result of our comparison suggests that its measurement is an acceptable alternative for measuring bronchial response. Done this way, the test is less arduous for the patient and allows study of individuals who are incapable of performing a reliable forced expiratory maneuver. The Siregnoost PD5, although more expensive than spirometers, is eminently portable and easy to use. In the wider context of the use of bronchial challenge in scientific studies in normal and asthmatic individuals, the impedance method probably has further advantages in avoiding artefacts of the FEV1 technique. During the development of bronchoconstriction in normal and mildly asthmatic subjects, the deep breath involved in performing a forced expiratory maneuver reduces or abolishes the bronchoconstriction.10 This greatly reduces the sensitivity of the FEV1 technique in these subjects, such that in many normal subjects, a response cannot be obtained.11 However, in more severe asthmatic subjects, this bronchodilator mechanism fails, and in some subjects, the FEV1 maneuver either causes bronchoconstriction itself or exacerbates it.12 The use of FEV1, therefore, tends to amplify the differences between normal and asthmatic subjects which may be an advantage in a clinical test designed to diagnose asthma, but is a disadvantage in a research test designed to measure bronchial responsiveness to an exogenous agent. Other alternatives to the FEV1 which avoid deep breath maneuvers include the body plethysmograph and the partial flow-volume technique.11

Using the same impedance apparatus, Davidson et al8 have shown close correlations between z and both airway resistance (measured in a body plethysmograph) and total respiratory resistance (measured with the Mead-Whittenberger technique). Respiratory impedance affects both the amplitude and phase of the oscillating pressure that results from the application of an oscillating flow. In practice, it is the amplitude component that is important and is highly correlated with airway resistance measured in the body plethysmograph.9 At an oscillating frequency of 10 Hz, the influences of lung and chest wall impedances are almost eliminated. Like airway resistance, impedance is a negative function of lung volume, and measurements were made during quiet tidal breathing at around FRC. With developing bronchoconstriction, lung volume tends to increase, and this will, to some extent, offset the impedance increase.

In conclusion, the impedance method for measuring airway response is an attractive alternative to FEV1. In most patients, a lower histamine dose will be required to produce a significant response, but the overall conclusion about the patient’s responsiveness will be similar to that derived from FEV1. The ease of measurement of z has advantages in children and adults who are incapable of performing a reliable forced expiratory maneuver.

REFERENCES


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