Forced oscillation technique and spirometry in cold air provocation tests

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Abstract

Background Impedance measurements by the forced pseudo random noise oscillation technique can be used to study the mechanical characteristics of the respiratory system. The objective of this study was to analyse the changes in impedance to a cold air provocation test in patients with asthma, and to correlate these changes with those in the forced expiratory volume in one second (FEV₁).

Methods The response to isocapnic hyperventilation with cold air was assessed by respiratory impedance measurements and spirometry in 60 patients with bronchial asthma in whom the provocative dose of histamine resulting in a 20% fall in FEV₁ (PD₂₀) was $\leq 8 \mu\text{mol}$.

Results Cold air provocation resulted in a mean(SD) fall in FEV₁ from 3.75(0.85) litres to 3.10(0.90) litres. The mean(SD) decrease in FEV₁ as a percentage of predicted was 15.4(3.8)%. The oscillatory resistance at 8 Hz increased from a mean(SD) of 0.367(0.108) kPa/l/s to 0.613(0.213) kPa/l/s and at 28 Hz the resistance increased from 0.348(0.089) to 0.403(0.099) kPa/l/s. Frequency dependence of resistance became significantly more negative. The reactance at 8 Hz decreased from a mean(SD) of -0.035(0.041) kPa/l/s to -0.234(0.199) kPa/l/s, and the resonant frequency increased from 12.5(4.9) Hz to 25.7(9.1) Hz. Significant correlations were calculated between the decrease in FEV₁ and changes in the various impedance parameters, especially between the decrease in FEV₁ and the increase in resistance at 8 Hz ($r = -0.66$), and the decrease in FEV₁ and the increase in the resonant frequency ($r = -0.63$).

Conclusion Cold air provocation in asthmatic subjects results in changes in the impedance of the respiratory system that correlate well with the changes in FEV₁. These changes in impedance reflect ventilatory inhomogeneities in the peripheral compartment of the bronchial tree. These observations show the value of this technique in the evaluation of induced bronchoconstriction, as both a quantitative and a qualitative analysis of the response is possible.

Bronchial hyperresponsiveness is one of the key elements in the pathogenesis of asthma, and the assessment of bronchial hyperresponsiveness has become an important diagnostic tool in the lung function laboratory. Bronchial hyperresponsiveness can be assessed using a variety of methods. The forced expiratory volume in one second (FEV₁) is generally used as an index of the response in bronchial challenge tests.¹ Spirometry, however, is dependent on effort, and requires a full inspiratory manoeuvre which may influence bronchial tone² and hence affect the outcome of bronchial provocation tests.

The measurement of the impedance of the respiratory system with the technique of forced oscillations³ has the benefit of being independent of effort, and it requires little or no cooperation from the patient. The method may therefore be well suited to provocation testing. With computerisation, the technique can easily be implemented, and the impedance of the respiratory system can be determined over a wide frequency range in a short period of time. The technique has been used in bronchial challenge tests by several investigators.⁴⁻¹⁰ Only a few studies have compared absolute changes in spirometric values with impedance data in induced bronchoconstriction.^{4,5,7,11,12}

The purpose of the present study was to evaluate the data obtained with the technique of forced oscillations in a provocation test with isocapnic hyperventilation with cold air in patients with bronchial asthma with documented bronchial hyperresponsiveness, and to correlate these data with spirometric indices.

Methods

SUBJECTS

We studied 60 asthmatic subjects (35 male) with a mean (SD) age of 27.9(10.7) years. All subjects had a characteristic history of recurrent attacks of dyspnoea with perceptible wheezing. Mean (SD) forced expiratory volume in one second (FEV₁) was 3.7(0.9) litres (97.2(14.6)% of predicted). All patients had evidence of bronchial hyperresponsiveness, reflected by a provocative dose of histamine resulting in a 20% fall in FEV₁ (PD₂₀) of $\leq 8 \mu\text{mol}$. Before the study all medication was withheld and short acting inhaled bronchodilators were stopped at least eight hours before the provocation test. Before provoca-

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tions of these various frequencies were applied in succession at the mouth or the chest. Originally, the measurements were performed during voluntary relaxation at the end of a normal expiration. Mead¹⁵ demonstrated that the forced oscillations can be superimposed on the normal breathing pattern.

The technique of forced oscillation used in this study is similar to the method described by Ländsér *et al.*¹⁶ The equipment consists of a loudspeaker which amplifies a signal generated by an oscillator, a high impedance side tube which enables the subject to breathe spontaneously and a screen type pneumotachograph (fig 1). In this technique a complex pseudo random noise oscillation signal is used, and various frequencies ranging from 4 to 52 Hz are applied simultaneously. Each frequency starts at a different randomly selected moment. This results in a small overall peak to peak size of the signal to improve the signal to noise ratio. The signal is applied at the mouth during spontaneous quiet breathing. Mouth pressure and flow are recorded by transducers with identical frequency characteristics (Validyne MP45). The recorded signals are fed directly without filtering into a Fourier analysing system, yielding impedance values for each of the investigated frequencies by means of spectral analysis. An ensemble averaging is performed over a time interval of eight seconds to filter out the disturbing signals produced by the breathing of the subject. A coherence function is calculated for each of the frequencies as a criterion for the validity of the measurements. A perfect coherence is indicated by 1.0, which means a complete absence of noise and alinearities in the obtained signals. Only those values with a coherence function ≥ 0.95 are retained. Under these conditions the error of the measurements is smaller than 10%.¹⁶

The relationship between pressure and flow is called the impedance. The impedance is divided into a resistance (R) and a reactance (X). The resistance corresponds with the total resistance in a resistance-inductance-capacitance ($R-I-C$) circuit. The total resistance of the respiratory system is the sum of three resistances in series: the resistance of the central airways, of the peripheral airways, and of the chest wall. The reactance depends on the compliant and inertia properties of the system: a negative reactance is found at lower frequencies as here the reactance is mainly determined by the capacitance of the system. At higher frequencies the reactance is influenced predominantly by the inertia qualities of the air within the airways.¹⁷ The reactance then becomes positive. The frequency at which the reactance equals zero is called the resonant frequency.

With the technique used in this study the input impedance is measured, indicating that pressure variations and flow measurements occur at the same site. An alternative approach is to measure the transfer impedance, in which case the pressure variations and flow measurements occur at different sites.

Figure 1 Schematic diagram of the apparatus. 1 = loudspeaker; 2 = side tube; 3 = pneumotachograph; 4 = pressure transducer; 5 = mouthpiece; 6 = bias flow.

INTERPRETATION OF FORCED OSCILLOMETRY DATA

Impedance data are influenced by the upper extrathoracic airways, the intrathoracic airways, alveolar gas, parenchymal lung tissue, and chest wall tissue. The mechanical properties of each of these components, their structural interactions, and the frequency range over which impedance measurements are obtained, determine to what extent these components influence impedance data. Michaelson *et al*¹⁸ showed that in patients with chronic obstructive airways disease (COPD), the impedance of the respiratory system is relatively high at low frequencies and decreases to a minimum at higher frequencies when compared with normal subjects. Clément *et al*¹⁹ compared the frequency dependence of the total respiratory resistance and reactance in patients with airflow obstruction with those in healthy subjects and reported that resistance decreases with increasing frequency and that the reactance is more negative in patients, resulting in increased values for resonant frequency. Similar findings in respiratory impedance have been described in induced bronchoconstriction.^{5-8 11}

The increase in resistance (especially at lower frequencies), the decrease in resistance with increasing frequency, and the more negative values of reactance, can be explained by airway obstruction extending to the peripheral airways according to Mead's two compartment lung model where two parallel units are represented by the expansible airways and the air spaces.²⁰ In the presence of an increase in peripheral airway resistance, inclusion of airway compliance into the lung model will result in negative frequency dependence of resistance. In patients with peripheral airway obstruction, the total respiratory resistance decreases with increasing frequency.

Patients with obstructive lung disease who exhibit frequency dependence of compliance also exhibit frequency dependence of resistance.²¹ This was interpreted as the effect of uneven distribution of the mechanical properties of the lungs. Nagels *et al*²² measured the resistance and reactance of the respiratory system in healthy subjects and in patients with COPD. They found that in healthy subjects, as well as in patients, the chest wall had a low resistance which decreased with frequency and increased with decreasing lung volume. They concluded that the observed frequency dependence of resistance and the simultaneous increase in resonant frequency can be simulated satisfactorily by Mead's two compartment model²⁰ assuming a large increase in peripheral airway resistance. Furthermore, increasing the central airway resistance twofold to threefold by narrowing the trachea does not result in frequency dependence of resistance,²³ and a two compartment model explains the changes in impedance.²⁴

The shunt properties of the upper airways may result in a loss of forced flow oscillations.²⁵⁻²⁸ This upper airway artefact

tends to underestimate the frequency dependence of the resistance and decreases the reactance. Therefore, the cheeks and the floor of the mouth are supported with the palms of the hands during the measurements.¹⁸

Thus the observations in patients with airflow obstruction of higher resistance values (especially at lower frequencies), a decrease in resistance with increasing frequency, decreased reactance values, and a high resonant frequency, can be explained by a high peripheral resistance in parallel with the compliance of the airways. In cases of high peripheral resistance, the resonant frequency is determined predominantly by airway compliance and inertia.

DATA ANALYSIS

With the forced pseudo random noise oscillation technique, the frequency dependent behaviour of the respiratory system can be measured simultaneously at different frequencies. The differences between the response of the system to low and high frequencies allow the division of the mechanical characteristics into a central and a peripheral compartment.

As a representation of low frequencies 8 Hz was chosen. The impedance at 4 Hz could not be used in our analysis as at this frequency the coherence coefficient was too often below 0.95. Snashall *et al*¹⁰ showed that in this way the error of the measurements is about 10%. Other investigators have used impedance values with a coherence function as low as 0.8^{8 29} or 0.9³⁰ in their analysis. Van Noord *et al*⁶ concluded from a study on histamine provocation in patients with asthma that the reciprocal value of the resistance at 6 Hz was the most suitable index of the technique of forced oscillations, and Lebègue *et al*³¹ showed that the concentration of histamine resulting in a 50% increase in the oscillatory resistance at 6 Hz had a sensitivity and specificity of 100% to separate groups of normal and asthmatic children. Wouters *et al*⁵ found a highly significant difference in the reciprocal value of the resistance at 8 Hz between normal subjects and patients with asthma after histamine provocation.

To represent higher frequencies 28 Hz was chosen. Several investigators have demonstrated that at frequencies above 24–28 Hz the negative frequency dependence of resistance disappears.

Thus, the resistance at low (8 Hz) and high (28 Hz) frequencies, the reciprocal value of the resistance at 8 Hz, the reactance at 8 Hz and the resonant frequency (frequency at which the reactance equals zero) were studied. The slope of the resistance versus frequency curve is represented by the equation:

$$\text{Frequency dependence of resistance (FD)} = R_{28} - R_{8/20}.$$

Values of FEV₁ and impedance before and after provocation were compared by the Student's paired *t* test, and Spearman's coefficients of correlation between FEV₁ as a percentage of predicted and the various impedance measures were calculated. *p*

Mean (SD) values of FEV₁ and impedance data before and after cold air challenge tests

	Before IHCA	After IHCA
FEV ₁ (litres)	3.75 (0.85)	3.10 (0.90)
FEV ₁ (% predicted)	97.2 (14.6)	81.8 (19.3)
Resistance at 8 Hz (kPa/l/s)	0.367 (0.108)	0.613 (0.213)
Resistance at 28 Hz (kPa/l/s)	0.348 (0.089)	0.403 (0.099)
Reactance at 8 Hz (kPa/l/s)	-0.035 (0.041)	-0.234 (0.199)
Resonant frequency (Hz)	12.5 (4.9)	25.7 (9.1)
Frequency dependence (kPa/l/s)	-0.00095 (0.0037)	-0.010 (0.0077)

IHCA—iscapnic hyperventilation with cold air; FEV₁—forced expiratory volume in one second.

All comparisons $p < 0.001$.

values below 0.05 were considered significant.

Results

The values for FEV₁, both absolute and as a percentage of predicted, and the values for the various impedance data used in the analysis, before and after the cold air challenge tests, are given in the table. Mean (SD) FEV₁ decreased from 3.75 (0.85) litres to 3.10 (0.90) litres ($p < 0.001$). The mean decrease in FEV₁ as a percentage of predicted was 15.4%, and the mean decrease as a percentage of the baseline values was 16.8% ($p < 0.001$).

Significant increases were observed in the mean (SD) resistance at 8 Hz from 0.367 (0.108) kPa/l/s to 0.613 (0.213) kPa/l/s, and at 28 Hz from 0.348 (0.089) kPa/l/s to 0.403 (0.099) kPa/l/s ($p < 0.001$). Frequency dependence of resistance (FD) decreased from -0.00095 (0.0037) kPa/l/s to -0.010 (0.0077) kPa/l/s ($p < 0.001$). The reactance at 8 Hz decreased from -0.035 (0.041) kPa/l/s to -0.234 (0.199) kPa/l/s ($p < 0.001$), with an increase in resonant frequency from 12.5 (4.9) Hz to 25.7 (9.1) Hz ($p < 0.001$).

Figures 2–5 show the relation between the changes in FEV₁ as a percentage of predicted (Δ FEV₁), and in the various impedance parameters. Significant inverse correlations were found between the decrease in FEV₁ and the increase in the resistance at 8 Hz ($r = -0.656$, $p < 0.001$) and between the decrease in FEV₁ and the increase in

resonant frequency ($r = -0.630$, $p < 0.001$). Correlations between Δ FEV₁ and the increase in the resistance at 28 Hz ($r = -0.458$, $p < 0.001$), and between Δ FEV₁ and the decrease in the reactance at 8 Hz ($r = 0.538$, $p < 0.001$) were also significant. There was a significant correlation between the decrease in the frequency dependence of resistance and the decrease in FEV₁ ($r = 0.596$, $p < 0.001$).

Discussion

Respiratory impedance measurements form a unique, non-invasive method, which is independent of effort, for the assessment of the response to bronchial provocation stimuli, providing insight into their pathophysiological effects on the respiratory system. An important advantage of the technique of forced oscillations is the fact that no forced respiratory manoeuvres are necessary for the measurements, so possible influences on bronchial tone are avoided.² In a recent study by Wilson *et al*,³² the effects of forced expiratory manoeuvres on the outcome of bronchial provocation testing have been clearly shown. These authors compared the response to methacholine challenge in normal subjects on two separate days; on one day impedance and FEV₁ were measured, while on the second day only impedance measurements were performed. No plateau was seen on the non-FEV₁ day, despite a mean fall in FEV₁ of 46%. On the non-FEV₁ day the increase in the resistance at 6 Hz was far greater than on the FEV₁ day. It was concluded from this study that forced expiratory manoeuvres as used in spirometry persistently reduce the bronchoconstrictor effect of methacholine. This could explain, in part, the plateau seen in other studies on bronchial challenge testing.

The sensitivity of the technique of forced oscillations in detecting induced bronchoconstriction has been evaluated by several authors.^{5 6 8 11 33 34} Van Noord *et al*⁶ concluded that the forced oscillation technique is a sensitive indicator of induced changes in airway calibre. The reciprocal of the oscillatory resistance at 6 Hz was found to be a suitable index with a sensitivity intermediate between that of specific airway conductance using body plethysmography, and FEV₁. Response evaluation measuring specific airway conductance, however, allows only a quantitative assessment of the response, whereas the technique of forced oscillations provides not only a sensitive method for diagnosing induced bronchoconstriction, but also for a qualitative analysis of the response.

In our study, provocation with cold air hyperventilation resulted in an increase in the resistance of the respiratory system, especially at lower frequencies, and thus frequency dependence of resistance became highly negative. Reactance also decreased, resulting in a marked increase in resonant frequency. These changes in the impedance of the respiratory system are consistent with the findings of

Figure 2 Relationship between the increase in the resistance at 8 Hz (Δ R8) and the decrease in FEV₁ (Δ FEV₁) as a percentage from baseline after cold air provocation in 60 patients with asthma ($r = -0.656$, $p < 0.001$).

Figure 3 Relationship between the increase in the reactance at 8 Hz (ΔX_8) and the decrease in FEV_1 (ΔFEV_1) ($r = -0.538$, $p < 0.001$).

Figure 4 Relationship between the increase in the resistance at 28 Hz (ΔR_{28}) and the decrease in FEV_1 (ΔFEV_1) ($r = 0.458$, $p < 0.001$).

Figure 5 Relationship between the increase in resonant frequency (Δf_0) and the decrease in FEV_1 (ΔFEV_1) ($r = -0.630$, $p < 0.001$).

Clément *et al*¹⁹ in patients with airflow obstruction.

Our results are in agreement with the findings of Decramer *et al*.⁷ Analogous changes in impedance have been reported after provocation with various other stimuli, both in children and in adults, in particular histamine,^{6 9-11 35} methacholine,^{33 36-38} carbachol,⁸ exercise,³⁹ and after allergen provocation.^{4 40} This observation suggests that the response is independent of the type of stimulus used.

Cold air hyperventilation leads to cooling of the mucosa of the airways and hyperosmolarity of the periciliary fluid. It is known that beyond the 14th airway generation the surface area of the respiratory mucosa is thought to be sufficient to humidify the inspired air in cold air hyperventilation.^{41 42} It is therefore easy to understand how this stimulus results in obstruction extending to the peripheral compartment of the bronchial tree.⁴³

In our study significant correlations were found between the changes in impedance and the changes in FEV_1 . Significant correlations between forced expiratory flow and oscillometric impedance values have been reported by various investigators. Wouters *et al*⁴⁴ found correlation coefficients between frequency dependence of resistance and resonant frequency on the one hand, and the forced vital capacity and FEV_1 on the other, ranging from 0.492 to 0.668. Similar values were reported by Peslin *et al*.⁴⁵

In histamine challenge tests in children, even stronger correlations between FEV_1 and impedance were reported by Lebègue *et al*,³¹ especially for resistance at lower frequencies and for frequency dependence of resistance. A possible explanation for the somewhat weaker correlations between the changes in FEV_1 and in frequency dependence of resistance and resonant frequency found in our study may be that provocation results in air trapping and thus in an increase in the functional residual capacity. Nagels *et al*²² showed that at higher lung volumes the resistance decreases and the reactance increases, resulting in a decrease in resonant frequency and lessening of the frequency dependence of resistance. In a study by Van den Elshout *et al*³⁹ on exercise induced bronchoconstriction, correlations ranging from 0.46 to 0.89 were found between the changes in impedance and in flow volume data. In contrast to the findings of others,^{6 31} use of the reciprocal value of the resistance at 8 Hz did not result in stronger correlations between the changes in impedance and in FEV_1 .

In this study, patients with bronchial asthma of wide ranging severity were challenged by isocapnic hyperventilation with cold air. The same provocative dose was used in all subjects. In view of the moderate response in terms of the decrease in FEV_1 , isocapnic hyperventilation with cold air can be considered a safe method in provocation studies.

We conclude that isocapnic hyperventilation with cold air in asthma patients results in a decrease in FEV_1 and an increase in oscillatory resistance, especially at lower

frequencies, a decrease in reactance at 8 Hz, and an increase in resonant frequency of the respiratory system as measured by the technique of forced oscillations. The changes in the impedance of the respiratory system represent an inhomogeneity in the peripheral compartment of the bronchial tree. These observations demonstrate the value of adding this technique to the evaluation of the response of the respiratory system to bronchoconstricting stimuli since, compared with forced expiration indices and body plethysmography, it is possible to partition the results into central and peripheral airway components.

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