Effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects

F J J van den Elshout, C L A van Herwaarden, H Th M Folgering

Abstract
The effects of hypercapnia and hypocapnia on respiratory resistance were studied in 15 healthy subjects and 30 asthmatic subjects. Respiratory resistance (impedance) was measured with the pseudo-random noise forced oscillation technique while the subjects rebreathed from a wet spirometer in a closed respiratory circuit in which end tidal carbon dioxide tension (Pco₂) could be controlled. Hypercapnia was induced by partially short circuiting the carbon dioxide absorber, and hypocapnia by voluntary hyperventilation. The circulating air was saturated with water vapour and kept at body temperature and ambient pressure. A rise of end tidal Pco₂ of 1 kPa caused a significant fall in respiratory resistance in both normal and asthmatic subjects (15% and 9% respectively). A fall of Pco₂ of 1 kPa did not cause any significant change in impedance in the control group. In the asthmatic patients resistance increased by 13%, reactance fell by 45%, and the frequency dependence of resistance rose 240%. These findings confirm that hypcapnia may contribute to airway obstruction in asthmatic patients, even when water and heat loss are prevented.

Many specific and non-specific bronchoconstrictor challenges are used to measure bronchial reactivity, including allergens, irritants, cholinergic drugs, mediators, exercise, and hyperventilation. For exercise and hyperventilation challenge respiratory heat loss and increased osmolarity of the airway mucosa are probably the most important factors contributing to bronchoconstriction, though hypcapnia may also contribute. Ventilation is increased in both hypcapnia, when this is induced experimentally by voluntary hyperventilation, and hypercapnia, which stimulates ventilation. The increase in ventilation may obscure the effects of Pco₂ on airway resistance, by increasing respiratory heat loss or osmolarity changes.

Acute and chronic airways obstruction in patients with asthma or chronic obstructive lung diseases is often accompanied by hyperventilation. It is still uncertain whether patients with bronchial hyperresponsiveness to histamine are also hyperresponsive to hypcapnia and hypercapnia.

The aim of the present study was to investigate the effect of change in end tidal Pco₂ on airway calibre without the confounding effects of heat and water loss from the airway mucosa. The forced oscillation technique was used because the measurements obtained with this method are collected during spontaneous breathing. Forced expiratory manoeuvres, which may influence bronchial function, were thus avoided.

Methods
EQUIPMENT
Oscillatory respiratory impedance (impedance) was measured with the pseudo-random noise forced oscillation technique using the apparatus developed by Landser et al (Oscillaire, Jones, Chicago). A loudspeaker generates pressure changes at the mouth in the form of a pseudo-random noise signal containing all harmonics of 4–52 Hz superimposed on spontaneous breathing. Mouth pressure and airflow signals are recorded by two identical differential transducers (Validyne MP 454). Fourier analysis allows the calculation of impedance at 4–52 Hz from the data, which were collected over eight seconds. The validity of the measurements was evaluated by a coherence function that assessed the amount of noise and linearity in the signals, only data with a coherence function of 0.95 or more were retained. The impedance data were subdivided into resistance and reactance and were computed over the range 4–52 Hz in steps of 4 Hz. Resistance (Rrs), computed as the ratio of the in phase components of pressure and flow, is determined by the resistive properties of the respiratory system (airways, lung tissue, and chest wall). Reactance (Xrs) was computed as the ratio of the components of pressure and flow, which are 90° out of phase. This part of impedance is determined by the elasticity and mass inertia of the airways, lung tissue, and thorax and the inertia of the air within the bronchi. The variables measured in this study were (1) total respiratory resistance (Rrs) at each frequency tested (4–8–12... 52 Hz) and the average value for all frequencies; (2) total respiratory reactance (Xrs) at each frequency tested and the average value for all frequencies; (3) resonant frequency—that is, the frequency at which the reactance is zero; (4) frequency dependence of the resistance, defined in this study as the ratio (Rrs 12 Hz–Rrs 52 Hz)/Rrs 52 Hz.

The Oscillaire apparatus was connected to a wet spirometer (Pulmotest, Godart, De Bitt, Utrecht, Holland) to form a closed respiratory
effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects

![Diagram](image)

**Figure 1** Oscillatory resistance apparatus connected to a wet spirometer to form a closed respiratory circuit to which oxygen was supplied and in which carbon dioxide could be absorbed.

The effects of hypercapnia (the subjects breathing quietly) and hypocapnia (the subjects breathing quietly after one minute of voluntary hyperventilation) on the respiratory circuit resistance were studied separately in 15 healthy subjects and five patients with asthma to determine the effects of carbon dioxide on the respiratory resistance. The results obtained with Oscillaire alone (I) were compared by paired analysis with the differences between measures with Oscillaire connected to the spirometer in the normocapnic (A) and hypercapnic (B) conditions. The measurements were made with the Oscillaire connected to the spirometer and the spirometer circuit kept in the BTPS condition. The temperature was maintained at 37°C by a heating element and water saturation of air at 90% or more. The subjects had their cheeks and submental muscles supported and they wore a nose clip during the impedance measurements.

Subjects

Forty-five subjects were studied: 15 healthy subjects and 30 patients with a history of asthma and bronchial hyperresponsiveness to histamine (the provocative concentration of histamine causing a decrease in the forced expiratory volume in one second (FEV₁) of 20% or more was less than 8 mg/ml)²⁶. The characteristics of the subjects are shown in table 1.

The patients used inhaled medication only (beta agonist or corticosteroids or both) and this was discontinued at least eight hours before testing. Patients who had had a respiratory infection in the past six weeks were excluded.

The study was approved by the local ethical committee and informed consent was obtained from all subjects.

**Procedure**

To establish whether connecting the spirometer to the Oscillaire changed the measurements, impedance was measured with the Oscillaire alone in 15 subjects (seven healthy subjects and eight patients) and, a few minutes later, with the Oscillaire connected to the wet spirometer circuit. In a further 10 subjects (five healthy subjects and five patients) the humidity of the air in the spirometer circuit was measured continuously during the whole procedure.

All subjects and patients were studied in three different conditions: (1) normocapnic (all carbon dioxide was absorbed in the closed circuit); (2) hypercapnic (with the carbon dioxide absorber partially shortcircuited); (3) hypocapnic (the subjects breathing quietly immediately after one minute of voluntary hyperventilation).

**DATA ANALYSIS**

The data from three adequate measurements were averaged for each of the three conditions (hypocapnia, normocapnia, and hypercapnia). The average values of Rsrs and Xrs calculated at intervals of 4 Hz in the range 4-52 Hz were plotted against the frequency at which they were measured. The changes in impedance data from normocapnic (A) to hypercapnic and hypocapnic conditions (B) were calculated for each individual as [(A-B)/(A)] × 100%. For statistical analysis Wilcoxon's test for paired observations was used. The differences between the two groups were tested with the Mann-Whitney U test.

**Results**

**Preliminary Studies**

There were no significant differences between the results obtained with the Oscillaire alone (I) and those obtained with the Oscillaire connected to the wet spirometer circuit (II). The data measured with I and II were compared by means of a two way linear regression analysis and analysis of variance. The coefficient of correlation ranged from 0.94 to 0.98, with a slope of 0.95 to 1.03, an intercept of −0.03 to +0.05 (p < 0.0001). The SE to the regression line varied from 0.02 to 0.06 (2-7%).

The relative humidity of the circulating air was above 90% within two minutes in the five healthy subjects and five patients when they were breathing in the closed respiratory circuit.
Table 2  Mean (SEM) values and changes in end tidal carbon dioxide tension (Pco2, kPa) in normocapnic, hypocapnic, and hypercapnic conditions in the two groups of subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Asthmatic</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pco2</td>
<td>ΔPco2</td>
<td>Pco2</td>
<td>ΔPco2</td>
</tr>
<tr>
<td>Normocapnia</td>
<td>5.3 (0.18)</td>
<td>+1.1 (0.08)</td>
<td>6.0 (0.23)</td>
<td>+1.0 (0.07)</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>4.2 (0.19)</td>
<td>-1.0 (0.11)</td>
<td>5.9 (0.13)</td>
<td>-1.0 (0.07)</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>4.2 (0.19)</td>
<td>-1.0 (0.11)</td>
<td>3.8 (0.11)</td>
<td>-1.0 (0.08)</td>
</tr>
</tbody>
</table>

*Significant difference between normal and asthmatic subjects: p < 0.05 (Mann-Whitney U test).

All further measurements were therefore taken after at least two minutes' closed circuit breathing.

HYPERCAPNIC AND HYPOCAPNIC STUDIES

During voluntary hyperventilation there was a mean (SEM) increase in functional residual capacity (FRC) of 0.5 (0.03) l in the healthy subjects and patients, and this disappeared within two to three breaths of stopping hyperventilation, at a time when end tidal Pco2 was still low. No significant change in FRC was observed during hypercapnia in either group.

The normal subjects had a higher resting end tidal PCO2 (5.3 kPa) than the asthmatic subjects (5.3 v 4.8 kPa, p < 0.05: table 2). Mean end tidal Pco2 fell by about 1 kPa during hyperventilation and rose by about 1 kPa during rebreathing (table 2). Neither the changes nor the final end tidal Pco2 values differed significantly between the two groups.

In the control group all the resistance values fell during hypercapnia (fig 2a, table 3). The other impedance results did not change significantly during hypercapnia or hypocapnia (figs 2a and 2b, table 3).

In the patients hypercapnia also caused a significant decrease in resistance measured at 4–20 Hz (fig 2c). The increase in reactance (table 3) and the changes in the other impedance data (resonant frequency and frequency dependence of resistance) were not significant. Hypocapnia induced an increase in

\[
\text{Rrs (cm H}_2\text{O/l/s)}
\]

\[
\text{Xrs (cm H}_2\text{O/l/s)}
\]

\[
\text{Oscillatory frequency (Hz)}
\]

Figure 2  Mean (SEM) values for respiratory resistance (Rrs) and reactance (Xrs) plotted against oscillatory frequency for the control group (a and b) and for patients with asthma (c and d) in normocapnic (\(\bullet\)), hypercapnic (\(\triangle\)), and hypocapnic conditions (\(\square\)).

*\(p < 0.01, \) *\(p < 0.05\) in the comparison with normocapnic condition (Wilcoxon's rank sum test).

Conversion to SI units: 1 cm H2O = ≈ 0.1 kPa.
### Table 3: Mean (SEM) changes in resistance measured at 8 Hz (Rrs8) and mean reactance for all frequencies (Xrs(av)) in asthmatic patients and normal subjects during hypoxemia and hypocapnia

<table>
<thead>
<tr>
<th></th>
<th>Hypoxemia</th>
<th>Hypocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Asthmatic</td>
</tr>
<tr>
<td>Rrs8</td>
<td>−14.6% (8)**</td>
<td>−9.3% (2.8)**</td>
</tr>
<tr>
<td>Xrs(av)</td>
<td>−13.3% (7.0)</td>
<td>+21.3% (8.6)</td>
</tr>
</tbody>
</table>

Significance according to Wilcoxon’s test: **p < 0.01; ***p < 0.001, in the comparison with the normocapnic condition.

Discussion

By using this circuit respiratory impedance can be measured while the subject breathes from a spirometer, as we observed previously.\(^7\) Change in functional residual capacity and minute ventilation can be observed directly. Functional residual capacity is often increased in an attack of asthma.\(^8\) In this study all impedance data were obtained at the same FRC, so no correction was made for lung volume.

The air in the circuit was kept in the BTPS condition to exclude possible effects due to water or heat loss from the airway mucosa. This probably explains why the changes during our hyperventilation were smaller than those in previous studies, in which the subjects breathed room air or cold air.\(^9\)\(^10\)

Hypoxemia caused a decrease in airway resistance in both groups, the changes at 4–12 Hz being statistically significant in the patients. This is in accordance with the results of previous studies, where measurements of resistance of 6 or 8 Hz have been the most sensitive and reproducible indices of change in airway diameter in bronchial challenge tests or in chronic airways obstruction.\(^11\)\(^12\) The central chemoreceptors of the medulla are thought to play a part in the reflex constriction and relaxation of the airways.\(^23\) Reported direct effects of hypoxemia on airway calibre have been contradictory, increased resistance,\(^24\)\(^25\) decreased resistance,\(^26\) and no effect\(^27\) all having been described. Hypoxemia possibly decreases bronchial muscle contractility directly. Hypoxemic acidosis has been found to cause a reduction in bronchial (but not tracheal) muscle contractility in the isolated bronchus of the dog.\(^28\)

A reduction in end tidal PCO\(_2\) of 1 kPa by voluntary hyperventilation caused no significant changes in impedance in the control group. In the asthmatic subjects resistance at 4–12 Hz rose. The concomitant decrease in the reactance values at all frequencies and the average value confirmed the presence of increased airway obstruction.\(^14\) The frequency dependence of resistance (a decrease in resistance with increasing frequency) is thought to indicate peripheral airway obstruction.\(^29\) Frequency dependence was enhanced in our patients, which suggests that hypoxemia causes peripheral airway narrowing in patients with asthma.

Hypocapnia, achieved by hyperventilation or by occlusion of the pulmonary artery, may cause bronchoconstriction by vagal reflex pathways or by a direct effect on bronchial smooth muscle. Hypocapnia caused increased activity of both the slowly adapting stretch receptors and the irritant receptors in anaesthetised dogs, and airway calibre consequently decreased. These effects were reversed by the administration of carbon dioxide, which resulted in reflex bronchodilation.\(^30\)\(^31\) Several investigators have shown that carbon dioxide tension in the airway rather than in tissue or blood was the stimulus.\(^31\)\(^32\)

In dogs a decrease in end tidal PCO\(_2\) of nearly 2 kPa after pulmonary arterial occlusion caused an increase in resistance of about 20% and fall in compliance of 18%. Vagotomy diminished the increase in resistance but did not affect the fall in compliance, which suggests a direct smooth muscle effect.\(^31\) These results are in keeping with our finding of an increase in resistance of 13% due to a fall in PCO\(_2\) of 1 kPa.

We conclude that hypoxemia decreases airway resistance measured by the forced oscillation technique in both healthy and asthmatic individuals. Hypoxemia appeared to increase both central and peripheral airway resistance in the asthmatic patients but not in the healthy subjects. These results suggest that an enhanced response to hypoxemia (and hypocapnia) is a component of the increased hyperreactiveness in asthmatic patients. Hypocapnia, which occurs in an early stage of an asthmatic attack as a result of hyperventilation,\(^10\)\(^33\) is an additional stimulus for bronchoconstriction, independent of drying and cooling of the airways.

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