RESPIRATORY AND HAEMODYNAMIC RESPONSE TO CARBON DIOXIDE BREATHING IN PATIENTS WITH AND WITHOUT BRONCHIAL OBSTRUCTION

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SUMMARY

1. The effect of breathing a mixture of 5–6% carbon dioxide in air was examined in seven patients with obstructive bronchitis and in eight patients with lung disease but without bronchial obstruction.

2. Hyperventilation during CO₂ breathing was less marked in patients with bronchial obstruction than in the others. Cardiac output did not change in patients with airways obstruction but rose in the control group. The increase of arterial carbon dioxide tension, hydrogen ion concentration, pulmonary arterial and pulmonary wedge pressures \( P_{pa} \) and \( P_{paw} \) was comparable in both groups. The increase of \( P_{pa} \) and \( P_{paw} \) was proportional to the \( P_{a,co₂} \) but the change of cardiac output was not. The ventilatory response to CO₂ breathing was correlated with the spirometric measurements, but the haemodynamic changes were not.

3. No significant changes of pulmonary vascular resistance or of the \( P_{pa} - P_{paw} \) pressure gradient were observed. The increase of pulmonary arterial pressure during CO₂ breathing appears to be due to increased pulmonary wedge pressure.

4. The contribution of depressed myocardial function during CO₂ breathing to the response of cardiac output is discussed on the basis of a negative correlation between \( P_{a,co₂} \) and stroke volume during CO₂ breathing.

Decreased ventilatory response to CO₂ breathing in emphysema and bronchial obstruction has previously been described (Donald & Christie, 1949; Tenney, 1954; Cherniack & Snidal, 1956; Richards, Fritts & Davis, 1958; Brodofsky, MacDonnel & Cherniack, 1960; Flenley & Millar, 1967) though the complex mechanism is not completely explained (Cherniack, 1965). It is, however, less certain whether or not a similar difference exists in the haemodynamic response. With a view to contributing to this question we have examined the effect of CO₂ breathing on the pulmonary haemodynamics in patients suffering from chronic obstructive bronchitis and in those free from bronchial obstruction.

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METHODS AND SUBJECTS

A total of fifteen patients was examined. Seven suffered from chronic bronchitis according to the criteria of chronic productive cough and the spiographic signs of severe bronchial obstruction as judged from forced expiratory volume/vital capacity (FEV$_{1.0}$/VC) and residual volume/total lung capacity (RV/TLC) ratios. No patient had any cardiopulmonary disease except bronchitis. The remaining eight patients, who were considered as a control group, had a peripheral type of bronchogenic cancer (five subjects) or a history of chronic bronchitis without evidence of bronchial obstruction on spiography.

A right heart catheterization with a Courand catheter was performed in all patients in the supine position without premedication. The ventilation both of atmospheric air and CO$_2$ mixture was measured by using a mask connected to a Douglas bag. The dead-space of the system was 40 ml and its airflow resistance was 0·8 cmH$_2$O at a flow rate of 30 l/min, and 1·3 cmH$_2$O for 60 l/min as measured by the Jaeger body plethysmograph. The cardiac output was obtained by indicator dilution method by using an injection of 15 mg of Cardiogreen into the pulmonary artery and sampling from the femoral artery. Blood gases were analysed by the Astrup technique by using Radiometer equipment. Blood pressures were measured by Hellige tensometers and registered on a Multiscriptor recorder. The values of mean pulmonary arterial and wedge pressures were obtained by electrical integration during at least five respiratory cycles; electrical integration is regularly controlled by planimetry. The reference value for pulmonary arterial pressure was 10 cm above the catheterization table.

The pressures were measured, the blood for gas analysis was withdrawn and the dye-dilution was performed after 10 min stabilized ventilation breathing air and after 5 min CO$_2$ mixture breathing. At this time the continuously recorded pulmonary artery pressure had stabilized in all subjects; it corresponds to the data of Rokseth (1966). The electrocardiogram and respiratory rate were continuously recorded. A mixture of 5·1–5·9% CO$_2$ in air (5·59% on average with a standard deviation of 0·34%) was used for the inhalation. The composition of the mixture was controlled by a Kipp gas analyser immediately after the procedure.

Paired $t$-tests and the calculation of correlation coefficients were used for the statistical analysis.

RESULTS

Respiration. The minute volume of ventilation ($V_E$) increased after CO$_2$ in both groups (Table 1 and Fig. 1); its increase was less pronounced in the obstructive patients (by 63%) than in control subjects (by 120%). This difference is due to a larger increase of tidal volume (TV) in the latter group; the respiratory rate rose proportionally in all patients.

Arterial oxygen saturation (Sa$_{O_2}$) did not change. Both arterial CO$_2$ tension (Pa$_{CO_2}$) and hydrogen ion concentration ([H$^+$]$_a$) increased in all patients.

Circulation. Cardiac output (Q) did not change in the patients with bronchial obstruction but rose in the control group. The changes of heart rate and stroke volume (SV) were not significant. Pulmonary arterial pressure (P$_{pa}$) and pulmonary arterial wedge pressure (P$_{paw}$) rose in both groups and the difference between P$_{pa}$ and P$_{paw}$ did not change. Total pulmonary resistance (TPR, P$_{pa}$/Q) increased in patients with airways obstruction but not in the control group. Pulmonary vascular resistance [PVR, (P$_{paw}$/P$_{paw}$): Q] did not change.
Correlation between the variables. There was no significant relation between $P_{a,CO_2}$ at rest and any other variable during $CO_2$ breathing.

The changes of cardiac output were not significantly related to the increase of ventilation ($r = 0.369, P>0.10$) or to the $P_{a,CO_2}$. There was, however, a significant negative correlation between all values of $Q$ and $P_{a,CO_2}$ during $CO_2$ breathing ($r = -0.717, P<0.01$) and a similar correlation (Fig. 2) was obtained for stroke volume and $P_{a,CO_2}$ ($r = -0.739, P<0.01$).

![Graphs showing changes in respiratory and haemodynamic parameters during $CO_2$ breathing.](image)

**Fig. 1.** Individual changes in some respiratory and haemodynamic parameters during $CO_2$ breathing. ○, Patients from the control group; ●, patients with bronchial obstruction.

The changes of mean pulmonary arterial pressure were closely related to the increase of $P_{a,CO_2}$ ($r = 0.691, P<0.01$) and the same was true for the mean pulmonary arterial wedge pressure ($r = 0.514, P<0.01$). Both pressures showed no relation to the changes of cardiac output. $P_{pa}$ and $P_{paw}$ during $CO_2$ breathing were related to their value at rest; the higher the pressures were at rest, the higher their increase during $CO_2$ breathing ($r = 0.552$ and $0.514$ respectively, $P<0.01$).

$FEV_{1.0}/VC$ ratio was related to the change of ventilation ($r = 0.670, P<0.01$) but the correlations with the changes of cardiac output ($r = 0.186$), pulmonary arterial pressure ($r = 0.017$), pulmonary wedge pressure ($r = -0.335$) and pulmonary vascular resistance ($r = 0.107$) were not significant. The $RV/TLC$ index also showed a correlation with the increase of ventilation ($r = 0.500, P<0.05$) but not with any other variable.
TABLE 1. Respiratory and haemodynamic changes during CO₂ breathing

<table>
<thead>
<tr>
<th></th>
<th>Obstructive bronchitis</th>
<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>Air breathing</td>
<td>CO₂ breathing</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.7±5.3</td>
<td>—</td>
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<tr>
<td>FEV₁ (l/VC (%)</td>
<td>37.9±5.8</td>
<td>—</td>
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<tr>
<td>RV/TLC (%)</td>
<td>59.1±6.3</td>
<td>—</td>
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<tr>
<td>V̇E (l/min)</td>
<td>9.6±2.8</td>
<td>15.7±5.4†</td>
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<tr>
<td>Resp. rate (min⁻¹)</td>
<td>18±3</td>
<td>24±4†</td>
</tr>
<tr>
<td>TV (ml)</td>
<td>544±225</td>
<td>726±341†</td>
</tr>
<tr>
<td>SₐO₂ (%)</td>
<td>86±7</td>
<td>89±6</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>44±5</td>
<td>54±4‡</td>
</tr>
<tr>
<td>[H⁺]ₐ (nmol/l)</td>
<td>43±3</td>
<td>49±3‡</td>
</tr>
<tr>
<td>Q (l/min)</td>
<td>5.8±1.3</td>
<td>5.9±1.8</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>92±13</td>
<td>94±15</td>
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<tr>
<td>SV (ml)</td>
<td>65±20</td>
<td>63±21</td>
</tr>
<tr>
<td>Psa (mmHg)</td>
<td>26±9</td>
<td>33±14†</td>
</tr>
<tr>
<td>Pₚₐw (mmHg)</td>
<td>5.3±3.6</td>
<td>13.9±10.9*</td>
</tr>
<tr>
<td>P(ₚₐw-Pₚₐw) (mmHg)</td>
<td>20.6±5.7</td>
<td>18.8±12.2</td>
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<tr>
<td>TPR (units)</td>
<td>4.6±1.8</td>
<td>5.9±2.8*</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>3.7±1.8</td>
<td>3.1±1.9</td>
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The values are given as mean±one standard deviation. Statistical significance of the changes during CO₂ breathing: *P<0.05; †P<0.01; ‡P<0.001.

Fig. 2. Correlation between the values of arterial carbon dioxide tension and stroke volume during CO₂ breathing. ○, Patients from the control group; ●, patients with bronchial obstruction.
Haemodynamics during CO₂ breathing

DISCUSSION

Ventilation. Lower ventilatory response to CO₂ breathing in patients with bronchial obstruction has been repeatedly described and was also found in our patients. The ventilatory response in both our groups is lower than is usually observed. Probably it is due to the supine position of the patients in our experiment whereas ventilatory response is usually measured in sitting subjects.

Cardiac output and stroke volume. Various changes have been reported for cardiac output during CO₂ breathing: a slight increase (Grollman, 1930; Richardson, Wasserman & Patterson, 1961; McGregor, Donevan & Anderson, 1962; Tartulier, Deyrieux & Anterion, 1958; Fishman, Fritts & Cournand, 1960; Paul, Varmauskas, Forsberg, Sannerstedt & Widimský, 1964; Rokseth, 1966; Kilburn, Asmundsson, Britt & Cardon, 1969) or no change (Lim & Brownlee, 1968; Daum, Krofta, Nikodýmová, Stíkša, Tlustý, Dráb & Švorčík, 1967; Frank, Jordan, Kiefhaber & Zinn, 1958). The differences seem not to be due to different diagnoses of the examined subjects, and they are not related to the increase of Pa,CO₂. Rokseth (1966) found a relationship in one of three groups of patients between the changes of cardiac output and the hyperventilation during CO₂ breathing. Therefore, a different response of cardiac output to CO₂ in the patients with and without bronchial obstruction seems to be due neither to bronchial obstruction itself (no correlation with FEV₁₋₀/VC and RV/TLC ratio) nor to the degree of hyperventilation. The same conclusion may be derived from the data of Kilburn et al. (1969) by using their values of maximal mid-expiratory flow rate as a sign of bronchial obstruction, and from the data of Lim & Brownlee (1968).

Another possibility to be considered is a depressant effect of CO₂ on the heart muscle. The patients with bronchial obstruction reached a higher Pa,CO₂ value during CO₂ breathing than the control group. Further, a negative correlation exists during CO₂ breathing between all values of Pa,CO₂ and those of cardiac output and stroke volume. Thus, it is probable that cardiac depression after CO₂ plays a role in the response of cardiac output.

Pulmonary arterial and pulmonary artery wedge pressures. The pulmonary arterial pressure rose in both groups, its increase being more pronounced in patients with resting pulmonary arterial hypertension than in normotensives, and it is closely related to the increase of Pa,CO₂.

An increase of Pₚₐₕₐₜ has been noted by all authors with the exception of Kilburn et al. (1969) but interpretations have differed. (a) It may reflect the changes of left atrial and left ventricular filling pressures. (b) It may reflect an increased alveolar pressure during hyperventilation particularly in the patients with airways obstruction. (c) It may be due to pulmonary venous constriction. The last explanation is improbable since no evidence of venous constriction has been found in isolated lungs or in animal experiments.

The possibility of increased alveolar pressure as a major determinant of Pₚₐₕₐₜ has been discussed by Harris et al. (1968). They found an increase of Pₚₐₕₐₜ during slightly hypercapnic hyperventilation in the patients with chronic bronchitis but not in the controls. In fact, large respiratory variations of Pₚₐₕₐₜ may be observed in obstructive bronchitis both at rest and during exercise hyperventilation; they follow closely the respiratory swings of mean oesophageal pressure (Lim & Brownlee, 1968; Lockhart, Tzareva, Nader, Leblanc, Schrijen & Sadoul, 1969). On the other hand, Attinger (1960), Frank et al. (1958), Fishman et al. (1960) and Rokseth (1966) found no consistent elevation of mean oesophageal pressure during CO₂
breathing and, from the individual results of Rokseth (1966), we may see that $P_{\text{paw}}$ rose significantly in the patients in whom mean oesophageal pressure did not change or was slightly decreased. Moreover, Lockhart, Nader, Tzareva & Schrijen (1970) did not find a significant increase of $P_{\text{paw}}$ during isocapnic hyperventilation in the subjects with obstructive bronchitis whereas $P_{\text{paw}}$ rose significantly in the same subjects during an identical degree of hyperventilation due to exercise.

The assumption that the increase in wedge pressure is directly related to left heart filling pressure has been subjected to criticism. These pressures are almost identical in healthy subjects and in patients with left heart diseases (Sapru, Taylor & Donald, 1968) but the identity is rarely verified in obstructive bronchitis. Nevertheless, Lockhart et al. (1969) found an excellent correlation between $P_{\text{paw}}$ and left ventricular end-diastolic pressure both at rest and during exercise in seven bronchitic patients. In our experiment we measured $P_{\text{paw}}$ simultaneously with left atrial pressure in three subjects and found the pressures almost identical both before and during CO$_2$ breathing. On the other hand, $P_{\text{paw}}$ in chronic bronchitis may differ in different places of wedging (Ježek & Herles, 1969) and we must carefully consider the identity of $P_{\text{paw}}$ and left heart filling pressure in individual cases, considering also the technical conditions of wedging analysed by Bell, Haynes, Shimomura & Dallas (1962). If an increase of $P_{\text{paw}}$ in our patients really corresponds to the elevation of left ventricular end-diastolic pressure, it might contribute to our assumption of cardiac depression during CO$_2$ breathing.

Pulmonary vascular resistance. Though CO$_2$ breathing produces pulmonary vasoconstriction in the isolated lung and in a majority of animal experiments, the results obtained in human subjects are not consistent. An increase of PVR was noted by Kilburn et al. (1969) and by Harris, Segel, Green & Housley (1968) in chronic bronchitis, by Paul et al. (1964) and Rokseth (1966) in mitral stenosis, but no changes of PVR were observed in healthy subjects by Harris et al. (1968) and in lung disease by Rokseth (1966) and Daum et al. (1967). Our results agree with those authors who did not observe an increase of PVR. The different results mentioned above cannot be explained by various concentrations of inspired CO$_2$ as seen from the data of individual authors; moreover in another paper we studied the effect of various CO$_2$ concentrations and we found the PVR unchanged on average in concentrations from 3 to 9% (Herles, Ježek & Boudik, 1966) though $P_{\text{pa}}$ and $P_{\text{paw}}$ rose in proportion to the concentration of inspired CO$_2$ and to the resulting $P_{\text{a,co}_2}$. Therefore, our results suggest that the major determinant of pulmonary artery pressure increase during CO$_2$ breathing is the increase in pulmonary wedge pressure, and not an increase in pulmonary vascular resistance.

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REFERENCES


Haemodynamics during CO₂ breathing


