REVERSIBILITY OF AIRWAYS OBSTRUCTION IN
CHRONIC BRONCHITIS

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SUMMARY

1. Airways resistance and lung volume were measured in twenty-five patients with chronic bronchitis and fifteen patients without chest disease before and after the inhalation of isoprenaline. Similar measurements were made on fourteen of these patients with chronic bronchitis and twelve other patients without chest disease before and after the intravenous injection of atropine sulphate.

2. There were significant decreases in airways resistance after isoprenaline inhalation and intravenous atropine both in patients with bronchitis and normal subjects but the decreases were greater in the patients with chronic bronchitis.

3. The decrease in resistance was proportional to the degree of initial airways resistance.

4. The results are considered to indicate that bronchial muscle contraction increases the airways resistance of patients with chronic bronchitis and contributes to the airways obstruction; its contribution increases with increasing severity of the condition. A significant part of the increased airways resistance in these patients is potentially reversible and nervously mediated.

Key words: chronic bronchitis, reversible airways obstruction, isoprenaline, atropine.

The factors that increase the airways resistance in patients who have chronic bronchitis with airways obstruction are not fully known. Possible causes are mucous gland hypertrophy, morbid anatomical changes in the bronchial walls, mucosal oedema, intraluminal secretions and bronchial muscle contraction. There is evidence of premature bronchial collapse on forced expiration but the extent to which this occurs on spontaneous breathing is uncertain. It is probable that all these possible causes contribute to the increased airways resistance in this condition. Although many investigators have shown that in normal man the bronchial muscle contributes to the airways resistance, as indicated by the decrease in airways resistance after...
the inhalation of isoprenaline (DuBois & Dautrebande, 1958; Butler, Caro, Alcala & DuBois, 1960; Nadel & Comroe, 1961) and the injection of atropine (Butler et al., 1960; Widdicombe, Kent & Nadel, 1962; Nadel & Widdicombe, 1963), it has not hitherto been shown conclusively that bronchial muscle contributes to the increased airways resistance in patients with chronic bronchitis.

Hossain & Heard (1970) used a quantitative point-counting method to show that there is an increased amount of bronchial muscle in patients with chronic bronchitis as compared with patients without this disease, and that this is due to hyperplasia of the muscle fibres. They considered this proliferation of bronchial muscle cells to be structural evidence of hyperactivity in life. These findings suggest that the airways obstruction in patients with chronic bronchitis may be due in part to bronchial muscle. If this is a significant factor in the pathogenesis of airways obstruction in chronic bronchitis it might be expected that the increased airways resistance would be reversible in part when bronchodilator drugs are given.

The present investigation was undertaken to assess the degree of reversibility of the airways obstruction in patients with this condition. Isoprenaline was given by inhalation in a large dose sufficient to cause a maximal relaxation of bronchial muscle and this was measured by changes in airways resistance after the inhalation of isoprenaline. Airways resistance was also measured before and after the intravenous injection of atropine sulphate, as this blocks the action of the vagus nerve on the bronchial muscle.

SUBJECTS AND METHODS

Twenty-five patients with chronic bronchitis and twenty-seven patients without chest disease were studied. The diagnosis of chronic bronchitis was made clinically by using the criteria of the Medical Research Council Committee on the aetiology of chronic bronchitis (1965). In accordance with these criteria all the patients had a cough and produced sputum. The forced expiratory volume/forced vital capacity % (FEV/FVC %) indicated the existence of obstructive airways disease. The subjects without chest disease were hospital in-patients undergoing investigations or treatment unrelated to the chest and had no clinical, spirometric or plethysmographic evidence of chest disease. All the subjects agreed to take part in the study after full explanation of its nature.

Values of airways resistance (R_{aw}) and the lung volume at which R_{aw} was measured (V_{tg}) were obtained with a whole-body constant-volume plethysmograph by the method of DuBois, Botelho & Comroe (1956). Resistance was measured on inspiration at a flow rate of 0.6 litre/s. The results were expressed as the product of R_{aw} and V_{tg}, specific airways resistance (SR_{aw}). V_{tg} was the spontaneous lung volume at which each patient panted for the measurement of resistance. Comparison with the known values of the functional residual capacities (FRC) of these patients has shown that in the majority of instances V_{tg} was close to FRC.

Minute volume, respiration rate and tidal volume were measured by the collection of expired air over a timed period; the expired gas volumes were corrected to BTPS.

Isoprenaline was given by a Wright's nebulizer with 1% isoprenaline (British Pharmacopoeia grade), air at a flow rate of 7 litres/min and a polythene face mask.

The following procedure was used; the resting minute volumes were measured and a measurement of SR_{aw} was then made. Each patient then inhaled isoprenaline by the above method for 5 min. A further measurement of SR_{aw} was made 15 min after the end of the inhalation.
This procedure was used for the twenty-five patients with chronic bronchitis and fifteen of the patients without chest disease.

In fourteen of the patients with chronic bronchitis and a further twelve patients without chest disease a second study was made. Airways resistance was measured three times at 15 min intervals after which 1·2 mg of atropine sulphate was given intravenously; further measurements of SRaw were made at three 15 min intervals after the injection.

Spirometric measurements were made using a Poulton spirometer (McKerrow, McDermott & Gilson, 1960).

RESULTS

The detailed results for each patient are shown in Tables 1–6 (Clinical Science Tables 42/33–42/38 respectively), which are deposited with the Librarian, Royal Society of Medicine, from whom copies may be obtained on request. These tables give the values of the ages, spirometric data, minute volumes, \( V_{tg} \) and \( SR_{aw} \) before and after administration of isoprenaline and atropine. The mean results are shown in Tables 7, 8 and 9.

Study with isoprenaline

The mean age of the patients with chronic bronchitis (Table 7) was 56·6 years (SD 8·3) and in the subjects without chest disease (subjects 1–15) it was 51·5 years (SD 9·2). Table 8 shows the values of the airways resistance and lung volume measurements before and after isoprenaline. In the patients with chronic bronchitis there was a mean decrease in \( SR_{aw} \) of 8·4 cmH\(_2\)O s \((34\%)\) which was significant \((P<0·001)\), and \( V_{tg} \) also decreased by a mean value of 0·203 litre, which was significant \((P<0·001)\).

In the patients without chest disease there was a mean reduction in \( SR_{aw} \) of 0·7 cmH\(_2\)O s \((16\%)\) which was significant \((P<0·001)\) and this was significantly less than the decrease of \( SR_{aw} \) in the patients with chronic bronchitis \((P<0·001)\). There was no significant change in the lung volume at which \( R_{aw} \) was measured in the patients without chest disease after they had inhaled isoprenaline.

The decrease in \( SR_{aw} \) was not identical in every patient (Fig. 1). The patients with the highest initial resistance had the greatest decrease after administration of isoprenaline. In Fig. 2 the decrease in \( SR_{aw} \) is related to the initial \( SR_{aw} \) and it is seen that there is a direct linear relationship, which is highly significant \((r = -0·95, P<0·001)\).

Many of the patients with chronic bronchitis showed a percentage decrease in \( SR_{aw} \) with isoprenaline that was similar to normal subjects but in those with very high initial values of \( SR_{aw} \) the percentage decrease was greater.

Study with atropine

The mean age of the patients with chronic bronchitis was 55·9 years (SD 9·5), and of the patients without chest disease (subjects 16–27) 49·3 years (SD 8·0). In this study the mean of the three measurements before atropine was compared with the mean of the three measurements after atropine to decrease the effect of errors in measurement.

The results are given in Table 9 and Fig. 3. There was a mean decrease in \( SR_{aw} \) with atropine of 8·5 cmH\(_2\)O s \((31\%)\) in the patients with chronic bronchitis and this was significant \((P<0·001)\). \( V_{tg} \) also decreased with atropine, by 0·635 litres, and this also was significant \((P<0·001)\). In
the patients without chest disease there was a mean decrease in SR$_{sw}$ of 0.7 cmH$_2$O s (18%) which was significant ($P<0.001$), but there was no significant change in V$_{1s}$.

**Table 7.** Mean values of ages and spirometric data

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>FVC (litres)</th>
<th>FEV$_{0.75}$ (litres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without chest disease</td>
<td>51.0</td>
<td>4.29</td>
</tr>
<tr>
<td>SD</td>
<td>9.2</td>
<td>SD 0.69</td>
</tr>
<tr>
<td>Patients with chronic bronchitis</td>
<td>56.6</td>
<td>2.04</td>
</tr>
<tr>
<td>SD</td>
<td>8.3</td>
<td>SD 0.78</td>
</tr>
</tbody>
</table>

**Table 8.** Mean values of V$_{1s}$ and SR$_{sw}$ before and after isoprenaline administration

<table>
<thead>
<tr>
<th>V$_{1s}$ (litres)</th>
<th>SR$_{sw}$ (cmH$_2$O s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without chest disease Before isoprenaline</td>
<td>4.528</td>
</tr>
<tr>
<td>SD</td>
<td>1.153</td>
</tr>
<tr>
<td>After isoprenaline</td>
<td>4.477</td>
</tr>
<tr>
<td>SD</td>
<td>1.204</td>
</tr>
<tr>
<td>Patients with chronic bronchitis Before isoprenaline</td>
<td>5.092</td>
</tr>
<tr>
<td>SD</td>
<td>1.464</td>
</tr>
<tr>
<td>After isoprenaline</td>
<td>4.888</td>
</tr>
<tr>
<td>SD</td>
<td>1.398</td>
</tr>
</tbody>
</table>

**Table 9.** Mean values of V$_{1s}$ and SR$_{sw}$ before and after atropine sulphate administration

<table>
<thead>
<tr>
<th>V$_{1s}$ (litres)</th>
<th>SR$_{sw}$ (cmH$_2$O s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without chest disease Before atropine</td>
<td>5.721</td>
</tr>
<tr>
<td>SD</td>
<td>0.876</td>
</tr>
<tr>
<td>After atropine</td>
<td>5.658</td>
</tr>
<tr>
<td>SD</td>
<td>0.820</td>
</tr>
<tr>
<td>Patients with chronic bronchitis Before atropine</td>
<td>6.619</td>
</tr>
<tr>
<td>SD</td>
<td>1.490</td>
</tr>
<tr>
<td>After atropine</td>
<td>5.956</td>
</tr>
<tr>
<td>SD</td>
<td>1.214</td>
</tr>
</tbody>
</table>

The size of the decrease in resistance after atropine administration was not the same in every patient. Those patients with chronic bronchitis who had the highest initial resistances showed the greatest decreases with atropine. This is seen in Fig. 4 where there is a significant direct
Fig. 1. Values of SR$_{sw}$ before and after isoprenaline. ●, Patients with chronic bronchitis; ○, subjects without chest disease.

Fig. 2. Relationship of the decreases in SR$_{sw}$ with isoprenaline to the initial values of SR$_{sw}$ ($r = -0.95, P < 0.001$). The symbols are as in Fig. 1.
FIG. 3. Mean values (± SD) of $SR_{aw}$ before and after intravenous administration of atropine sulphate. ●, Patients with chronic bronchitis; ○, subjects without chest disease.

FIG. 4. Relationship of the decreases in $SR_{aw}$ caused by atropine to the initial values of $SR_{aw}$ ($r = -0.58$, $P < 0.05$).
Reversible airways obstruction

The decreases in SR$_{aw}$ with atropine did not differ significantly from those with isoprenaline ($P>0.05$). In Fig. 5 the final resistances after isoprenaline and atropine are related to the initial resistances before these drugs and the regression lines for isoprenaline and atropine are shown. These results are expressed as the logarithmic values of SR$_{aw}$. The two regression lines are close together but at high resistances there is a separation of the regression lines indicating a difference in slope and this was a significant difference ($P<0.05$).

**DISCUSSION**

The results show that the airways resistance of patients with chronic bronchitis is reversible in part by the inhalation of isoprenaline. There is a greater reversible component of the airways resistance in patients with high resistances than in those with low resistances, and this is greater than in subjects without chronic bronchitis.

Isoprenaline stimulates \( \beta \)-adrenergic receptors and thus causes relaxation of bronchial muscle. It also causes pulmonary vasodilatation but this would be expected to increase rather than decrease airways resistance (Zamel, Faraco & de Freitas, 1966). It is therefore concluded from the present study that in patients with chronic bronchitis with airways obstruction the bronchial muscle must contribute to the increased airways resistance. The contribution is greater with increasing severity of the airways obstruction.

It is not possible to conclude from the present data whether the increased reversible component of resistance is due to an increase in muscle bulk or an increase in contractility per unit volume of muscle.
Variations in the amount of isoprenaline inhaled by different patients might have caused the differences in the degree of bronchodilatation but it is unlikely that the present results can be explained in this way. Most of an inhalation of isoprenaline is deposited and absorbed in the oropharynx and thus isoprenaline would reach the airways through the vascular system. Palpitations occurred in the majority of the patients during isoprenaline inhalation which indicates that a significant amount of the drug was absorbed into the systemic circulation. The dose of isoprenaline delivered from the nebulizer in the present study was 0.6 ml of a 1% solution, i.e. 6 mg.

In the patients with chronic bronchitis the lung volumes at which resistance was measured ($V_{eq}$) were decreased after isoprenaline administration but these decreases in volume could not have accounted for the decreases in $SR_{aw}$ since a reduced lung volume would tend to increase resistance. The values of $V_{eq}$ in these patients were close to the values of FRC and their decrease presumably indicates that the increased resistance causes a slight degree of air trapping in the lung.

The present results differ from those of Oppenheimer, Rigatto & Fletcher (1968), who found no relation between the severity of airways obstruction and bronchodilator response to isoprenaline as reflected by changes in specific airways conductance; the drug was given as two doses of 70 µg delivered from a pressurized aerosol. One explanation of this difference could be that the dose of isoprenaline given by these investigators was insufficient to cause a maximal relaxation of the bronchial muscle and therefore the degree of reversible airways was underestimated.

The patients in the present study had chronic bronchitis. In particular, it is emphasized that the bronchitis patients with the four greatest decreases in resistance after administration of isoprenaline all had raised arterial CO₂ pressures (mean $Pa_{CO_2}$ 67 mmHg, SD 15) and three had had repeated episodes of cor pulmonale.

The findings with atropine are similar to those of the isoprenaline study; greater decreases in resistance occurred with atropine in those subjects with high initial resistances than in those with low resistances. These decreases are probably due to muscular relaxation but it is difficult to be certain because atropine also diminishes the release of secretions from the bronchial mucous glands and might thus decrease resistance. Secretions must actually be in the lumen of the bronchial tree to increase resistance and there is no evidence that atropine causes their absorption. It is therefore unlikely that the observed decreases in resistance were effected by a decrease in the volume of secretions. These results with atropine indicate that the more severe the obstruction of the airways in chronic bronchitis, the greater also is the degree of vagal tonicity.

The mean decrease in resistance with atropine did not differ significantly from those with isoprenaline. This suggests that the increased resistance is nervously mediated. However, when the resistance values before and after administration of the drugs were compared there was a difference in the slopes of the regression lines for atropine and isoprenaline, indicating that at high resistances isoprenaline decreases resistance more than atropine. Thus when obstruction is very severe other factors in addition to parasympathetic nerve activity cause hyperactivity of the bronchial muscle.

Reversal of the airways resistance by bronchodilators may not be always beneficial. Olsen, Stevens & McIlroy (1967) and Bouhuys & Woestijne (1971) have shown that relaxation of bronchi can reduce their stability. The latter investigators found in normal subjects that whereas
isoprenaline increased airways conductance it only slightly increased or caused a decrease in maximum expiratory flow rates. As there was no change in elastic recoil of the lung they considered that this discrepancy could be accounted for by increased compressibility of airways due to muscular relaxation; this would permit collapse of airways when they were subjected to the increasing transmural pressure associated with a forced expiration.

Tests of the reversibility of airways obstruction are usually made with spirometric measurements and when these tests are used the airways obstruction of patients with chronic bronchitis is often found to be 'irreversible'. The present results show that this is not so. For the reasons given above, measurements of airways resistance are likely to give more accurate information about the reversibility of airways obstruction than tests made with forced expirations. The application of bronchodilator stimuli in adequate dosage is also important. It is suggested that further studies utilizing these methods may lead to a better understanding of the causes of airways obstruction in respiratory diseases.

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REFERENCES


