BRONCHIAL SYMPATHETIC ACTIVITY IN CHRONIC BRONCHITIS

T. W. ASTIN

University Department of Medicine, The Royal Hospital, Sheffield

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SUMMARY

1. Measurements of airways resistance and lung volume were made in sixteen patients with chronic bronchitis and ten patients without chest disease before and after intravenous propranolol administration.

2. The airways resistance of the patients with chronic bronchitis increased significantly after propranolol administration but in the control subjects there was no significant increase.

3. In the patients with chronic bronchitis the increases in airways resistance were greater when the initial values were high.

4. In seven of the patients with chronic bronchitis and seven further control subjects airways resistance was measured before and after intravenous thymoxamine administration.

5. The airways resistance of the normal subjects was unchanged by thymoxamine administration, but that of the patients with chronic bronchitis decreased significantly.

6. The results are consistent with the existence of bronchial alpha receptors in man. In patients with chronic bronchitis there are greater degrees of both alpha and beta bronchial sympathetic activity than in normal subjects. The greater the severity of the condition the greater is the degree of beta sympathetic activity. In considering the factors causing airways obstruction in chronic bronchitis sympathetic activity should be taken into account.

Key words: chronic bronchitis, airways resistance, bronchial sympathetic activity, propranolol, thymoxamine.

The bronchial tree has a double nerve supply, the parasympathetic (vagal) and the sympathetic nervous system. The former is generally considered to have a bronchoconstrictor action in both animals and man (Loofbourrow, Wood & Baird, 1957; Butler, Caro, Alcala & DuBois, 1960). Stimulation of the sympathetic nerve supply to the bronchial tree in animals has been found to
cause bronchodilatation (Golla & Symes, 1913; Daly & Mount, 1951) although Hebb (1941) found bronchoconstriction in the guinea-pig.

There have been few formal studies of sympathetic activity in the bronchi of man and its contribution and significance in physiological and pathological processes has not been clearly established (Widdicombe, 1970). Alquist (1948) demonstrated that there were two types of sympathetic receptors, the alpha and beta receptors. Stimulation of the beta receptors causes bronchodilatation in animals and man. Evidence of resting beta sympathetic activity in normal human subjects has been found by some investigators but not by others. McNeill & Ingram (1966) and MacDonald, Ingram & McNeill (1967) reported increases in airways resistance in normal subjects with beta adrenergic blockade but this was not found in the studies by Zaid & Beall (1966), Marcelle, Bottin, Jachmes & Lecomte (1968) or Richardson & Sterling (1969).

Increases in resistance with beta adrenergic blocking drugs in asthmatic subjects have been described by McNeill (1964), Langer (1967) and Richardson & Sterling (1969) indicating that in asthma there is increased beta sympathetic activity.

Alpha receptor stimulation has been shown to cause bronchoconstriction in animals (Castro de la Mata, Penna & Aviado, 1962; Everitt & Cairncross, 1969; de Kock, 1970). Alpha receptor blocking drugs have been reported to inhibit the effects of histamine on the airways of man by Kerr, Govindaraj & Patel (1970) and by Bianco, Griffin, Kamburoff & Prime (1972), and this suggests that human bronchial muscle may have alpha receptors. de Kock (1970) and Simonsson, Andersson, Bergh, Skoogh & Svedmyr (1970) have found that alpha receptor stimulation after prior beta receptor blockade increased airways resistance in normal man and patients with asthma.

In patients with chronic bronchitis small but insignificant decreases in the FEV₁ (forced expiratory volume in 1 s) during propranolol infusion were found by Stone, Keltz & Samortin (1971); they considered that this reflected insensitivity of spirometric tests for detecting changes in airways resistance. Apart from this, there have been no formal studies of sympathetic activity in patients with chronic bronchitis, although it has been recognized clinically that beta adrenergic receptor blocking drugs cause impairment of ventilation in these patients. The present study was undertaken to investigate this by means of alpha and beta adrenergic blockade in a group of patients with chronic bronchitis; airways resistance was measured before and after the administration of the adrenergic blocking drugs. Similar measurements were made in a group of patients without chest diseases.

**PATIENTS AND METHODS**

Seventeen male patients (patients 1–17) without lung or heart disease were investigated; they were hospital in-patients undergoing investigations or treatment of conditions unrelated to the chest and had no history of chest disease and no clinical, spirometric or plethysmographic evidence of chest disease. Sixteen male patients with chronic bronchitis (patients 18–33) were studied; they all had a clinical diagnosis of chronic bronchitis based on a history of a productive cough for at least 3 months of each year for a period of 3 years or more.

Airways resistance (Raw) was measured by the method of DuBois, Botelho & Comroe (1956) by using a whole-body constant-volume plethysmograph. Measurements of Raw and the spontaneous lung volume at which Raw was measured (Vtg) were made during inspiration at a flow rate of 0.6 litre/s while the patient panted at about 2 Hz. The means of four measurements
of Raw and Vtg were calculated to give the values for a given occasion. Results were expressed as the product of Raw and Vtg, i.e. specific airways resistance SRaw.

**Beta adrenergic blockade**

Measurements of SRaw were made at three 15 min intervals after which an intravenous injection of 2 mg of propranolol was given. Further measurements of SRaw were made at three 15 min intervals thereafter.

In four patients with chronic bronchitis SRaw was measured before and after intravenous administration of atropine sulphate (1-2 mg); intravenous administration of propranolol (2 mg) was then given and further measurements of SRaw were made.

**Alpha adrenergic blockade**

Measurements of SRaw were made at three 15 min intervals after which thymoxamine (an alpha receptor blocking drug which has a weak anti-histamine action; 5 mg) was given intravenously. Further measurements of SRaw were made at 5, 8, 12, 18 and 25 min after the injection.

In one patient (patient 18) alpha blockade was obtained by using phentolamine (2 mg, intravenously).

Forced vital capacity (FVC) and forced expiratory volume in 0.75 s (FEV$_{0.75}$) were measured with a Poulton spirometer (McKerrow, McDermott & Gilson, 1960).

All subjects volunteered for the studies after being informed of the nature of the procedures.

**RESULTS**

The detailed results for each patient before and after the drugs are given in Tables 1-6 which are deposited with the Librarian, Royal Society of Medicine (Clinical Science Tables 42/50-56) from whom copies may be obtained on request. These tables give the values of the ages, spirometric data, Vtg and SRaw before and after propranolol and thymoxamine administration. The mean values are given in Tables 7, 8 and 9.

The mean age of the normal subjects was 54 years (SD 8) and it was 58 years (SD 6) in the patients with chronic bronchitis. The results of the spirometric tests indicate that the patients with chronic bronchitis had airways obstruction.

**Beta adrenergic blockade**

The mean results are given in Table 8 and Fig. 1.

The mean of the three measurements of SRaw and Vtg before propranolol administration was calculated and compared with the mean of the three measurements after propranolol administration; this decreases the effect of errors in measurement.

In the normal subjects (subjects 1-10) the mean SRaw before propranolol administration was 4.1 cmH$_2$O s (SD 0.7) and it was 4.3 cmH$_2$O s (SD 0.9) after propranolol administration, the mean increase of 0.2 cmH$_2$O s was not significant statistically. The mean Vtg did not change significantly after the propranolol administration.

In the patients with chronic bronchitis (patients 18-33) SRaw increased in each patient after propranolol administration; the mean SRaw before propranolol administration was 20.0 cmH$_2$O s (SD 8.1) and it was 23.9 cmH$_2$O s (SD 10.2) after propranolol administration, the
### Table 7. Mean values (±SD) of ages and spirometric tests

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>FVC (litres)</th>
<th>FEV&lt;sub&gt;0.75&lt;/sub&gt; (litres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without chest disease</td>
<td>54 ± 8</td>
<td>4.25 ± 0.68</td>
<td>3.10 ± 0.43</td>
</tr>
<tr>
<td>Patients with chronic bronchitis</td>
<td>58 ± 6</td>
<td>2.11 ± 0.69</td>
<td>0.88 ± 0.43</td>
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</tbody>
</table>

### Table 8. Mean values (±SD) of Vtg and SRaw before and after propranolol administration.

<table>
<thead>
<tr>
<th></th>
<th>Vtg (litres)</th>
<th>SRaw (cmH₂O s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without chest disease</td>
<td>Before propranolol 4.83 ± 0.49</td>
<td>4.1 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>After propranolol 4.96 ± 0.53</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>Patients with chronic bronchitis</td>
<td>Before propranolol 6.60 ± 1.02</td>
<td>20.0 ± 8.1</td>
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<tr>
<td></td>
<td>After propranol 6.48 ± 0.93</td>
<td>23.9 ± 10.2</td>
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</tbody>
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### Fig. 1. Values of SRaw before and after intravenous administration of propranolol. ●, Patients with chronic bronchitis; ○, subjects without chest disease.
mean increase of 3.9 cmH₂O s was highly significant (P < 0.001). The mean Vtg did not change significantly after propranolol had been given.

The increases in SRaw with propranolol are related to the initial values of SRaw in Fig. 2. It is seen that the patients with chronic bronchitis had greater increases than the normal subjects. The patients with bronchitis who had the highest initial resistances had the greatest increases in resistance after propranolol administration. There was a linear relationship between these parameters which was significant (r = 0.91, P < 0.001).

When propranolol was given after atropine administration, SRaw decreased after atropine administration and increased after propranolol administration in three patients (Fig. 3), but in one patient there was no increase in resistance with propranolol.

*Fig. 2. Relationship between the initial values of SRaw and the values after intravenous administration of propranolol.* ●, Patients with chronic bronchitis; ○, subjects without chest disease (r = 0.91, P < 0.001).

**Alpha adrenergic blockade**

The results are given in Table 9 and Fig. 4. The mean of the three measurements of SRaw and Vtg before thymoxamine administration were compared with the mean of the first three measurements after thymoxamine administration; it is seen from Fig. 4 that the maximum changes in SRaw after thymoxamine administration occurred during these first three measurements.

In the normal subjects (subjects 11–17) the mean SRaw before thymoxamine administration was 5.19 cmH₂O s (SD 0.38) and it was 5.33 cmH₂O s (SD 0.47) after thymoxamine administration the mean increase of 0.14 cmH₂O s was not significant statistically. The mean Vtg did not change significantly after thymoxamine administration.

In the patients with chronic bronchitis (patients 20, 21, 23, 25, 31, 32 and 33) SRaw decreased in each patient after thymoxamine administration; the mean SRaw before thymoxamine administration was 19.01 cmH₂O s (SD 5.13) and it was 16.38 cmH₂O s (SD 4.96) after thymoxamine administration, the mean decrease of 2.64 cmH₂O s was significant (P < 0.001). The mean Vtg decreased after thymoxamine administration by 0.26 litres which was significant (P < 0.02).
Fig. 3. Mean values (± SD) of SRaw of three patients with chronic bronchitis before and after intravenous administration of atropine sulphate (1.2 mg), and after intravenous administration of propranolol (2 mg).

Fig. 4. Values of SRaw before and after intravenous administration of thymoxamine. ●, Values of patients with chronic bronchitis; ○, mean values (± SD) for the subjects without chest disease.
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| TABLE 9. Mean values (± SD) of Vtg and SRaw before and after thymoxamine administration |
|-------------------------------------------------|-----------------|-----------------|
| Subjects without chest disease                  | Before thymoxamine | After thymoxamine |
| Mean values (litres)                             | 4.68 ± 0.55      | 4.71 ± 0.54      |
| SRaw (cm H₂O s)                                 | 5.2 ± 0.4        | 5.3 ± 0.5        |
| Patients with chronic bronchitis                | Before thymoxamine | After thymoxamine |
| Mean values (litres)                             | 4.90 ± 0.48      | 4.64 ± 0.62      |
| SRaw (cm H₂O s)                                 | 19.0 ± 5.1       | 16.4 ± 4.9       |

There was no significant relationship between the size of the initial SRaw and the decrease in SRaw after thymoxamine administration.

DISCUSSION

In the study of beta adrenergic blockade the dose of 2 mg of propranolol was chosen since it was anticipated that the airways resistance of the bronchitic patients might increase and it was desired to avoid serious respiratory embarrassment. This dose of propranolol may not have achieved complete sympathetic blockade; however, Simonsson et al. (1970) studied dose-response curves in asthmatic patients and found that a 5.0 mg dose of propranolol had no greater effect on airways resistance than a 0.05 mg one, suggesting an 'all or nothing' response. The present results indicate that considerable changes in resistance were achieved with a dose of 2 mg (up to 30%).

SRaw increased in the majority of the normal patients after propranolol administration but the increases were not significant statistically. This suggests that there is little resting beta sympathetic activity in normal subjects and agrees with previous findings in normal subjects (Zaid & Beall, 1966; Marcelle et al., 1968; Richardson & Sterling, 1969). However, since a small dose of propranolol was used in the present study the findings do not exclude resting beta sympathetic activity entirely.

The results in the patients with chronic bronchitis are in marked contrast to those of the normal subjects. They indicate that in chronic bronchitis there is a considerable increase in beta sympathetic activity above that in normal subjects. Further, the greater the severity of the airways obstruction the greater is the degree of this activity. The fact that propranolol still increased resistance after atropine administration in three out of four patients indicates that the increased resistance is due, at least in part, to a decrease of increased beta sympathetic activity and not solely to unopposed parasympathetic activity. This finding differs from that of MacDonald et al. (1967).

The study of alpha adrenergic blockade showed that this did not cause any change in resistance in the normal subjects. This does not exclude alpha receptor activity in normal man since de Kock (1970) and Simonsson et al. (1970) found evidence of alpha receptor activity in normal subjects only after prior beta adrenergic blockade. It does, however, seem that alpha receptor activity has little effect on the airways resistance in normal man.

In the patients with chronic bronchitis alpha blockade caused significant decreases in airways resistance (mean decrease 15%). This indicates that alpha receptors are present in the bronchial...
tree of man and that alpha sympathetic activity is increased in patients with chronic bronchitis as compared with normal subjects. Sympathetic alpha receptor activity is therefore one factor contributing to the increased airways resistance of patients with chronic bronchitis. The decreases in resistance obtained in the present study, although significant, were not large and were transient. This was probably due to the small dose of thymoxamine used (5 mg); however, it is noted that Kerr et al. (1970) found that 5 mg of intravenously administered phentolamine completely inhibited the decrease of FEV induced by histamine infusion. The true extent of alpha receptor bronchoconstriction in the patients in the present study is uncertain since a dose–response study was not made; it was considered inadvisable to give larger intravenous doses of thymoxamine because of circulatory side effects.

Widdicombe (1966) has suggested that the sympathetic nervous system normally has a minor role to play in the regulation of airways calibre. The present results support this but indicate that in chronic bronchitis it does have some effect.

Alpha sympathetic activity differed in the present study from beta sympathetic activity in that its degree was not related to the degree of initial airways resistance.

It is not possible to determine the site of sympathetic activity in the bronchial tree from the present results. Woolcock, Macklem, Hogg, Wilson, Nadel, Frank & Brain (1967) investigated the beta sympathetic activity in normal dogs by using a retrograde catheter to partition lung resistance into central and peripheral portions; the peripheral resistance increased after propranolol administration and they concluded that beta sympathetic activity is primarily in airways of 2 mm internal diameter and less. This may apply also to man.

The origins of the increased sympathetic activity are not known. It could be a nervous reflex or there may be increased sensitivity of sympathetic receptors in the airways of patients with chronic bronchitis but there is no evidence of either of these possibilities. Keller, Lohman & Schuren (1971) have reported concentrations of blood catecholamines greater than normal in patients with chronic bronchitis; this is a possible mechanism although the cause of the increased catecholamine concentrations is not known.

It has been shown that there is an increased parasympathetic activity in patients with chronic bronchitis (Astin, 1972). Thus both parasympathetic and sympathetic activity are increased in this condition and the degree to which they alter the airways resistance will depend on the resultant effect of their differing actions. In considering the factors which cause airways obstruction in chronic bronchitis the effect of bronchial parasympathetic and sympathetic activity should be taken into account.

ACKNOWLEDGMENT

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REFERENCES

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