THE EFFECTS OF BRONCHODILATORS ON PULMONARY VENTILATION AND DIFFUSION IN ASTHMA AND EMPHYSEMA

BY

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Impairment of ventilation and of the distribution of inspired air in asthma and emphysema has been reported by many authors (Beitzke, 1925; Kountz and Alexander, 1934; Darling, Courand, and Richards, 1944; Baldwin, Courand, and Richards, 1949; Bates and Christie, 1950; Beale, Fowler, and Comroe, 1952), and is the result mainly, if not entirely, of obstruction of the airway. Antispasmodics can relieve the obstruction in asthma, and have also been recommended in emphysema (Baldwin and others, 1949; Christie, 1952). Corticotrophin and cortisone-like substances have been used with benefit in acute and chronic asthma (Bordley, Carey, Harvey, Howard, Kattus, Newman, and Winkenwerder, 1949; Friedlaender and Friedlaender, 1951; Savidge and Brockbank, 1954; Medical Research Council, 1956), and occasional good results have been claimed for them in emphysema (Lukas, 1951; Galdston, Weisenfeld, Benjamin, and Rosenbluth, 1951). Gas exchange in emphysematous lungs is also defective, and this has been further studied in recent years by the new and more accurate techniques of measuring the diffusing capacity for oxygen or carbon monoxide which have become available (Donald, Renzetti, Riley, and Courand, 1952; Filley, MacIntosh, and Wright, 1954; Bates, Boucot, and Dormer, 1955; Shepard, Cohn, Cohen, Armstrong, Carroll, Donoso, and Riley, 1955; Bates, Knott, and Christie, 1956; Ogilvie, Forster, Blakemore, and Morton, 1957). Shepard and others (1955) and Bates and others (1956) have shown that, while both ventilation and diffusing capacity are usually impaired in emphysema, the impairment may affect either one or other of these tests of function disproportionately. As was noted by Donald and others (1952), reduction of the gas-blood interface by tissue destruction, and impairment of distribution of inspired air by airway obstruction, may both contribute to impairment of the diffusing capacity. The proportionate responsibility of these two factors is, however, unknown. Little has been published on the diffusing capacity in asthma. Bates (1952) measured the percentage uptake of carbon monoxide in 13 young asthmatics aged 12-19 years and found an abnormally low figure in only one. Ogilvie and others (1957) mention one asthmatic patient whose diffusing capacity was normal.

The objects of the present investigation were to examine the effects of two drugs, isoprenaline and prednisone orally, on the ventilation and diffusing capacity in patients with asthma and emphysema, and to attempt to assess the degree to which airway obstruction can depress the diffusing capacity in these disorders. The bronchodilator action of isoprenaline is well established (Rossier, 1949; Gilson and Hughes Jones, 1955), and the beneficial action of prednisone in asthma, and occasionally in emphysema, has been mentioned above.

SELECTION OF PATIENTS

All the subjects of this investigation suffered from asthma or emphysema. Most gave a history of wheezing, but a few were included in whom there was no such history although ventilatory tests showed evidence of airway obstruction. In patients classified as asthmatic the dyspnea and wheezing were intermittent, though four were included in whom the breathlessness, previously intermittent, had become constant in recent months. In a few infective cases chronic bronchitis was also present with sputum containing bacterial pathogens, but in general bronchitis was not a dominant symptom. At least one of the following features was also usually found: a family history of asthma, history of other allergic disorders such as paroxysmal rhinorrhoea, hay fever, or naso-polyp, and eosinophilia in the blood or sputum.
The patients classified as emphysematous were all persistently breathless on exertion, although the severity of this symptom often varied from time to time. All but one gave a history of long-standing chronic bronchitis with episodes of purulent sputum usually containing pathogens. The exception was a 39-year-old man who complained of increasing dyspnoea on exertion since leaving the Army in 1946. He had an unproductive cough and wheezed only in foggy weather. Other common findings were radiological evidence of emphysema (hyperinflation of the lungs, low flat diaphragm, large main pulmonary arteries with poor peripheral vessels, bullae), chronic central cyanosis, and pulmonary P waves in the electrocardiogram. The asthmatics were on the whole younger (range 17–55 years) than the emphysematous group (range 39–78 years). It was impossible to decide whether "asthma" or "emphysema" was the appropriate group for some patients.

**Grading of Wheezing.**—Wheezing may be caused by true bronchospasm, perhaps associated with mucosal oedema, or by airway obstruction from other causes, such as bronchial damage from chronic infection, collapse of bronchial walls during expiration due to loss of elasticity of the lung, or, as is seen in fatal cases of status asthmaticus, from blocking of the small peripheral bronchi by plugs of inspissated mucus. It was graded as follows:

**Severe.**—Breathing laboured at rest, expiratory wheeze, generalized rhonchi.

**Moderate.**—Breathing not laboured at rest, expiratory wheeze, generalized rhonchi.

**Slight.**—Prolonged expiration, scattered rhonchi.

It is to be noted that airway obstruction severe enough to cause dyspnoea at rest may be present without any wheeze, the only auscultatory sign sometimes being weak breath sounds. Patients in status asthmaticus were excluded from the investigation because they were too ill to carry out the tests.

**Methods**

The ventilatory test selected was the forced expiratory volume at one second (Gaensler, 1951), because it gives information equivalent to that provided by the maximal ventilatory volume and is less exhausting for the patient. Now generally known as the FEV₁, it was measured on the spirogram obtained from a spirometer of the type described by Bernstein, D'Silva, and Mendel (1952) at a peripheral drum speed of 16 mm. per second (Gandevia, Hume, and Prime, 1957). The mean was taken of three satisfactory tracings.

The diffusing capacity for carbon monoxide (Dₘ) was estimated by the steady-state technique of Bates and others (1955) on a simplified circuit devised by Prime (MacNamara, Prime, and Sinclair, 1959). This method is based on the assumption that the CO tension of the end-tidal sample is equivalent to the mean alveolar CO tension. The Dₘ is then calculated by dividing this figure into the rate of uptake of CO and is expressed as ml./min./mm. Hg. However, in normal subjects, as Bates points out, the end-tidal CO tension is likely to be lower than the mean alveolar CO tension, and the value for Dₘ will be correspondingly high. In patients with an uneven distribution of inspired air, such as is found in asthma and emphysema, the end-tidal CO tension may be higher or lower than the mean alveolar CO tension, and the magnitude of the error thus introduced cannot be known. Duplicate estimations of Dₘ showed surprisingly good agreement in the present series even in the presence of moderately severe airway obstruction, suggesting that the error due to uneven distribution does not vary greatly over short periods. Although the method of Filley and others (1954) probably reduces this error, it has the disadvantage of requiring arterial puncture, and this severely limits its applicability in the field of clinical research. Bates’s technique, on the other hand, does not require arterial puncture, is simply and quickly performed, and can be repeated frequently at short intervals so that duplicate estimations can be made.

Before the isoprenaline test the Dₘ was estimated with the patient sitting, duplicate estimations being made in most cases and the mean value taken. The FEV₁ was recorded and the patient then inhaled an aerosol of 1% isoprenaline solution given through a bright inhaler for one and a half minutes at a flow rate of eight litres per minute. The amount of solution inhaled during this time was approximately 0.75 ml. In most cases tachycardia and palpitation developed, breathing was often subjectively easier, and rhonchi fewer. After eight minutes the Dₘ and FEV₁ estimations were repeated.

The dosage of prednisone is described later.

**Results**

**Isoprenaline.**—Forty-seven patients were investigated, 38 men and nine women. There were no essential differences in the results as between the sexes. Twelve patients, eight men and four women, were certainly asthmatics. All the remainder are classified below as cases of chronic bronchitis and emphysema, although in six (two men and four women) there was doubt as to the group in which they should be placed. At the time of testing wheezing was moderately severe in four, moderate in 14, slight in 14, and absent in 15 patients. Among the last group wheezing had been present in the recent past in 10 and had not been observed at any time in five. The effects on FEV₁ and Dₘ will be described separately.
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TABLE I

EFFECT OF ISOPRENALINE AEROSOL ON FEV₁ AND Dₒ IN 47 PATIENTS WITH ASTHMA OR CHRONIC BRONCHITIS AND EMPHYSEMA

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>No. Cases</th>
<th>Mean Age (Range) in Years</th>
<th>Mean FEV₁ before Isoprenaline (Range in ml.)</th>
<th>Mean Increase in FEV₁ after Isoprenaline (Range in ml.)</th>
<th>Mean Dₒ before Isoprenaline (Range in ml./min./mm. Hg)</th>
<th>Mean Dₒ after Isoprenaline (Range in ml./min./mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All</td>
<td>9</td>
<td>40-9 (26-55)</td>
<td>1,140 (650-2,245)</td>
<td>500 (260-860)</td>
<td>11-7 (6-18-7)</td>
<td>12-3 (6-22-7)</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>12</td>
<td>54-2 (39-70)</td>
<td>765 (340-1,835)</td>
<td>290 (130-695)</td>
<td>9-2 (3-17-3)</td>
<td>8-4 (2-9-17-9)</td>
</tr>
<tr>
<td></td>
<td>Chronic bronchitis and emphysema</td>
<td>3</td>
<td>29-3 (17-47)</td>
<td>1,560 (415-3,435)</td>
<td>230 (70-630)</td>
<td>17 (7-27-8)</td>
<td>13-6 (6-8-17-5)</td>
</tr>
<tr>
<td>II</td>
<td>All</td>
<td>23</td>
<td>53-5 (43-63)</td>
<td>1,030 (385-2,555)</td>
<td>80 (-50 to +220)</td>
<td>10-2 (2-9-17-7)</td>
<td>9-8 (3-0-15-2)</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic bronchitis and emphysema</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Group I—Every patient had an increase of 25% or more in FEV₁ after isoprenaline.
Group II—".. ."  less than 25% in FEV₁ "..."

A. Effect on FEV₁.—The results shown in Table I are divided into two groups according to the magnitude of the response to isoprenaline, an increase of 25% being taken as the arbitrary dividing line. The mean increase in FEV₁ was greater in the asthmatic patients in each group, though there was a wide variation among the means. The most important point shown in Table I is the absence of any significant increase in mean Dₒ even when there was a significant improvement in FEV₁ after isoprenaline.

Table II shows that younger patients responded better than older, the reason being that eight of the nine patients under the age of 41 were asthmatics.

TABLE II

RESPONSE TO ISOPRENALINE IN RELATION TO AGE OF PATIENTS

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>% Increase in FEV₁ after Isoprenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;25%</td>
</tr>
<tr>
<td>17-40</td>
<td>7</td>
</tr>
<tr>
<td>41-70</td>
<td>14</td>
</tr>
</tbody>
</table>

The response in relation to the severity of wheezing is shown in Table III.

TABLE III

RESPONSE TO ISOPRENALINE IN RELATION TO DEGREE OF WHEEZING

<table>
<thead>
<tr>
<th>Degree of Wheezing</th>
<th>% Increase in FEV₁ after Isoprenaline</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;25%</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Slight</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Nil</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

The best results were obtained in those patients with slight or moderate wheezing, and these two groups included 10 of the 12 asthmatics. In the severe group there was one asthmatic, a girl aged 24 years with long-standing infective asthma, who, in spite of marked airway obstruction (FEV₁ 415 ml) which responded poorly to isoprenaline, had a normal Dₒ of 15 ml./min./mm. Hg. With the exception of one asthmatic boy aged 17 years who was free from bronchospasm on the day of the test and responded with an increase in FEV₁ of less than 25%, all the patients with no wheezing, i.e., the "nil" group in Table III, were suffering from chronic bronchitis and varying degrees of emphysema. In only one was the increase in FEV₁ impressive in absolute terms, a man aged 38 years who had been breathless on exertion for 11 years and wheezed only in foggy weather. His FEV₁ increased from 965 ml. to 1,360 ml. and he was thus the only patient in the series who had no auscultatory signs of bronchospasm and showed a large increase in FEV₁ after isoprenaline.

The results confirm the bronchodilator action of isoprenaline. Its comparative failure in the severe group suggests that part of the airway obstruction was due to some mechanism other than bronchospasm, or that isoprenaline as given in this investigation was not powerful enough to release severe bronchospasm.

B. Effect on Dₒ.—That there is a relationship between FEV₁ and Dₒ is shown in Fig. 1, where the values for log FEV₁ and for Dₒ before treatment are plotted for each of 63 patients with asthma or chronic bronchitis and emphysema. It will be seen that when the FEV₁ is low the Dₒ is likely also to be low. In view of this it might be expected that an increase in Dₒ would occur after isoprenaline in those patients whose FEV₁ improves considerably, but there is no indication of this in Table I. With such a wide scatter around the means, however, a real correlation might be concealed. Therefore, in Fig. 2 are plotted the percentage changes in FEV₁ and in
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for the percentage change in minute volume after isoprenaline varied from \(-47\%\) to \(+102\%\), with a mean of \(+10.4\%\). It therefore seems that changes in resting \(D_L\) after isoprenaline are associated with unpredictable changes in minute volume and are unrelated to changes in FEV\(_1\).

It will be observed that the regression line of Fig. 3 cuts the abscissa very slightly to the left of the origin, and that the points for 10 of the 12 asthmatics lie to the right of the regression line. Therefore, if the asthmatics were excluded, the regression line would shift further to the left and would cut the abscissa still more on the negative side of the origin. This suggests the possibility that in emphysema, if the minute volume were kept unchanged, isoprenaline by aerosol might actually cause a slight fall in mean resting \(D_L\) over a sufficient number of patients.

PREDNISONE.—Prednisone was given to 13 patients and corticotrophin to one, in whom routine antispasmodics had failed to give adequate relief. All had a history of wheezing at some time. Cases 1–5, 10, 13, and probably 14 (see Table IV and below) were asthmatics, and the remainder were suffering from chronic bronchitis and severe emphysema. When steroid treatment was begun wheezing was moderate in Cases 2, 3, 13, and 14, absent in Cases 11 and 12, both of which were, however, very breathless on exertion, and in the remainder was severe. Before

\[ D_L \text{ after isoprenaline for all 47 patients. It is clear that there is no correlation, and this is equally true of asthmatics and of patients suffering from chronic bronchitis and emphysema.} \]

Because MacNamara, Prime, and Sinclair (1959) have shown a direct relationship between minute volume and \(D_L\) at rest, the percentage changes in these values after isoprenaline for all 47 patients were plotted in Fig. 3, from which it is evident that there is a highly significant degree of correlation. There is no evidence that isoprenaline, under the conditions of the present investigation, has any consistent action on the minute volume,
prednisone or corticotrophin was given care was taken to exclude contraindications, especially evidence of coronary disease, a history suggestive of peptic ulceration, or a family history of diabetes mellitus. The initial daily dose of prednisone varied from 30 mg. to 100 mg. Doses above 50 mg. were given for one day only and then usually rapidly reduced by 10 mg. a day to 20 mg. daily or less. Tests were carried out before and at intervals ranging from 36 hours to six weeks after beginning treatment.

The results for Cases 1-12 are shown in Table IV, while Cases 13 and 14 are described briefly below. The patients fall into two groups. In Cases 1-5 there was marked clinical and objective improvement, whereas in Cases 6-12 there was little response; although the $D_L$ in Cases 6 and 11 and the FEV$_1$ in Case 9 increased appreciably, there was little clinical improvement. Even excluding the 78-year-old patient, the average age was lower for the group responding well (36.2 years as against 45.3), and the mean duration of symptoms shorter (9.1 years compared with 27.3). Case 10, the only asthmatic who did not respond to prednisone, was the girl with infective asthma mentioned previously. Her wheezing was hardly improved by 50 mg. daily of prednisone for two weeks.

Case 13 was a 38-year-old man who had suffered from asthma since the age of 7 years. He was admitted to hospital during a relapse, and, because moderate wheezing persisted after treatment with routine antispasmodics, he was given a short course of corticotrophin (40 units of the gel twice daily, rapidly reduced), on which treatment wheezing was almost abolished. His results were as follows:

In this case therefore corticotrophin added somewhat to the substantial measure of improvement already achieved by routine antispasmodics.

Case 14 was a 55-year-old man who only nine months previously had suddenly developed persistent shortness of breath, followed many weeks later by wheezing. After seven days' treatment with 20 mg. prednisone daily, moderate wheezing persisted. The dose of prednisone was therefore increased to 80 mg. for one day and reduced by 10 mg. daily thereafter. Wheezing was almost immediately abolished, and on the seventh day, at a dose again of 20 mg., the $D_L$ and FEV$_1$ estimations were repeated. The results were as follows:

This patient was subsequently discharged, still free from bronchospasm, on a maintenance dose of 10 mg. prednisone daily.

In all, therefore, seven patients responded well to prednisone or corticotrophin. Of these, four had previously been tested with isoprenaline, an increase of more than 25% in FEV$_1$, occurring in three. Among the seven patients who responded poorly to prednisone, five had been tested with isoprenaline, an increase of more than 25% in FEV$_1$, occurring in only one.

Three features differentiate the increase in $D_L$ among patients responding well to prednisone from any increase in $D_L$ following isoprenaline. With prednisone the increase was much greater; it was associated with a considerable increase in
FEV₁, and there was a striking absence of any proportionate increase in minute volume.

**Discussion**

In interpreting the significance of changes in DL, a distinction must be drawn between those cases in which an increase in DL is accompanied by a proportionate increase in minute volume, and those in which the minute volume remains substantially unchanged or even falls. The former association, first noted by MacNamara, Prime, and Sinclair (1959), is found to occur regularly with the present technique of estimating DL. The reason for this increase is not altogether clear, but presumably, as in exercise, hyperventilation is bringing into use the respiratory reserve. When, however, for the same minute volume a much greater quantity of gas is transferred from the inspired air into the blood, a real improvement in lung function is clearly implied. Such is the case in those patients whose DL improves on prednisone.

The reason for the failure of isoprenaline to increase the DL when it produces an increase in FEV₁ is not clear. There seems to be no obvious explanation in the pharmacology of isoprenaline, which is said to cause brief vasodilatation and more prolonged tachycardia with an increase in the cardiac output (Dautrebande, 1952; Sollmann, 1957). If the cardiac output rises it is difficult to envisage any general pulmonary vasoconstriction which might reduce the gas-blood interface and thus decrease the uptake of CO. In emphysematous patients the improved FEV₁ after isoprenaline may represent the ventilation of additional alveoli which are not well perfused with blood. In asthmatics, however, it seems more probable that any freshly ventilated alveoli would be well perfused, and yet the failure of DL to increase after isoprenaline is just as pronounced in asthma as in emphysema. Alternatively it is possible that the bronchodilator action of isoprenaline does not extend as deeply as the smallest bronchioles, any increase in FEV₁ representing a greater volume of bronchial and bronchiolar, but not of additional alveolar, space. If so, the magnitude of the increase—up to 860 ml.—is surprising. Again, there may be a fallacy in assuming that an increase in FEV₁, which, as its name implies, is a measure of forced expiration, is necessarily reflected in improved ventilation at rest. However, it may be noted that in Cases 3 and 4 considerable increases in DL on prednisone were associated with but moderate increases in FEV₁, 540 ml. and 390 ml. respectively.

The results with prednisone and corticotrophin were clear cut. All the asthmatics except one responded very well, while all patients with chronic bronchitis and emphysema, and the girl with long-standing infective asthma, responded poorly. There seems little doubt that prednisone and corticotrophin act by abolishing bronchospasm and perhaps mucosal oedema or hypersecretion, but the mechanism by which these effects are brought about is not clear. The work of Citron and Scadding (1957) has greatly clarified the problem of the variable action of cortisone on the delayed, tuberculin type of sensitivity reported by previous authors (Long and Favour, 1950; Carey, Harvey, Howard, and Winkenwerder, 1950). Reports regarding its effect on the immediate, histamine type of sensitivity reaction, however, remain conflicting. Goth, Allman, Merritt, and Holman (1951) found that injecting dogs with the surface-active agent Tween 20 caused a liberation of histamine from the tissues and a consequent fall in blood pressure, and this effect was repeated with further injections of the same substance. Cortisone did not prevent the fall in blood pressure after the first dose of Tween 20, but did prevent a fall after a second dose. The authors interpreted these findings as evidence that cortisone is unable to counteract the effects of histamine already formed in the tissues, but that it prevents the synthesis of further histamine. Schayer, Davis, and Smiley (1955) found that rat skin, when incubated with 14C L-histidine, converted a small percentage to 14C histamine which remained in a bound condition in the skin. Pre-treatment of the rats with cortisone impaired this conversion. Lovell, Goodman, Hudson, Armitage, and Pickering (1953), in a series of experiments in man, confirmed the suppressive action of cortisone on the delayed type of sensitivity reaction, but concluded that it had little or no effect on the immediate skin reaction to histamine. Holti (1956) has criticized the work of Lovell and others, on the grounds that they measured weals only up to 10 minutes after pricks with histamine solution, and that they did not compare prick tests at identical skin temperatures. Holti made careful measurements of weals 10 and 20 minutes after pricking histamine solutions into the skin, with strict control of skin temperature, and showed that oral cortisone, while its effect after 10 minutes was slight, exerted a clear-cut suppressive action at 20 minutes. This effect was more evident with large doses of cortisone. These findings may have some bearing on the mode of action of cortico-
steroids in asthma, though it must be admitted that antihistamines have little effect in asthma.

While in the present series the history was of value in forecasting the likely response to prednisone, the auscultatory signs differed little in character or severity as between successes and failures. A good response to prednisone seemed more likely in patients whose FEV₁ increased by over 25% after isoprenaline.

The action of prednisone on the Dₜ in asthmatics is evidence that airway obstruction can depress the diffusing capacity. By analogy, in cases of emphysema, although reduction of the capillary bed by tissue destruction is no doubt one important factor in impairment of the Dₜ, it seems probable that airway obstruction also plays a significant part. It is of interest that as long ago as 1925 Beitzke, on the basis of histological examination of normal and emphysematous lungs, together with experiments on the mixing of plain and coloured water by to-and-fro piston action in glass tubes of different shapes, suggested that the impairment of gas exchange in emphysema was due less to reduction of the alveolar surface area than to poor mixing of inspired and alveolar air.

Two final points may be noted in connexion with the response to prednisone. In Cases 6 and 11, although there was little clinical improvement and the FEV₁ remained substantially unchanged, the Dₜ increased significantly, suggesting that improved ventilation may not be the whole explanation of the action of prednisone. The results in Case 14 show that when moderate doses of prednisone fail to abolish bronchospasm, a short course with a heavy dosage may succeed, and the spasm may thereafter be controlled by a small maintenance dose.

CONCLUSIONS

In 47 patients with asthma or emphysema, isoprenaline, even when it caused a considerable increase in the forced expiratory volume at one second (FEV₁), did not increase the diffusing capacity for carbon monoxide (Dₜ), changes in which were associated with unpredictable changes in minute volume.

Prednisone or corticotrophin caused clinical and objective improvement in six asthmatics, but had little effect on one case of long-standing infective asthma and on seven cases of chronic bronchitis and emphysema. In patients responding well, a pronounced increase in Dₜ occurred, associated with a considerable increase in FEV₁ and without any proportionate change in minute volume.

Bronchospasm can markedly depress the Dₜ. A normal Dₜ may, however, be found in association with moderately severe bronchospasm.

In assessing the significance of changes in Dₜ at rest, the minute volume must be taken into account; a proportionate change in minute volume considerably reduces the significance of any alteration in Dₜ.

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