Effect of vagotomy on the breathing pattern and exercise ability in emphysematous patients

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Summary

1. The potential value of right vagotomy for the relief of breathlessness has been explored in five patients with emphysema. Two patients had symptomatic improvement, two had minor symptomatic improvement, and one was unchanged.

2. Exercise ventilation was not noticeably depressed by unilateral right vagotomy in the two patients investigated fully, but the pattern of breathing was altered. After vagotomy, breathing was deeper, and the rise in the frequency of breathing with exercise was depressed.

3. After right vagotomy the response to rebreathing carbon dioxide also consisted of slower deeper breaths.

4. Right vagotomy sometimes appears to remove an influence preventing slow deep breathing and exacerbating dyspnoea.

5. Results of bilateral pulmonary denervation, attempted in one patient, were complicated by the need for left thoracotomy, which removed any possible beneficial effects.

Key words: emphysema, exercise, vagotomy.

Introduction

Some patients with chronic lung disease become very dyspnoeic, in association with an apparently normal responsiveness of ventilation to respiratory stimuli. Inherited differences in the sensitivity of the respiratory apparatus in the brain stem or peripheral chemoreceptors has been invoked to explain this [1, 2]. It is possible that such patients have an increased excitatory input from pulmonary receptors affected by the disease process. Artificially produced pulmonary embolism, pneumonia, granuloma and collapse in animals causes hyperventilation with a particularly marked rise in the frequency of breathing [3–5]. This is abolished by vagotomy or local anaesthetic block of the vagus nerves, which prevents information from the lungs reaching the brain.

Vagotomy and local anaesthetic block of the vagus nerves in humans has been shown to depress the frequency of breathing and relieves breathlessness in certain patients with lung disease [6]. The present work was undertaken to explore the potential symptomatic benefit of vagotomy in a group of emphysematous patients, and to evaluate the contribution of vagal information to ventilation and the pattern of breathing in these patients.

Methods

General

The depth to which the patients were investigated varied largely for practical reasons. Some patients felt too ill to undergo protracted investigations and some could not find the time to make repeated visits for exercise tests. Routine pulmonary functions were measured with conventional apparatus (Vitalograph and body plethysmograph). Alveolar dead space ventilation for nitrogen was also assessed [7]. The procedure
of vagotomy was approved on ethical grounds only as a last resort in patients with crippling dyspnoea. This limitation excluded many patients who could manage regular and reproducible exercise tests and also excluded a control placebo (sham operation) group. The patients consented to the procedure after being told that it was experimental.

Exercise tests

We thought that adequate assessment of exercise ability required at least two visits to the laboratory for habituation before results were recorded. Once subjects were habituated, the interval between tests was never shorter than 1 week, to avoid training effects.

In those patients in whom exercise ability was assessed objectively, a progressive exercise test with a cycle ergometer (Elema–Schonander 380) was used. On the first visit to the laboratory the patient was introduced to personnel and became familiar with the apparatus. On the second visit full exercise tests were performed but the results discarded. Results from the third and subsequent visits were recorded. The exercise test consisted of increasing work loads, starting with no external load (equivalent to approximately 5 W work load), and increasing loads of 15 W every minute until the patient could exercise no more. Dyspnoea was the reason for termination of exercise in each case. From the known duration of exercise at each work load, the total work done could be calculated.

During the exercise tests, the patient breathed through a mouthpiece and valve. Expiratory flow was recorded with a heated Fleisch pneumotachograph (no. 4), the tubing between mouthpiece and pneumotachograph being lagged to keep expired air warm. End-tidal CO₂ and O₂ were recorded with a mass spectrometer (Centronic Q806), with sampling at the mouthpiece. Expiratory flow signal, CO₂, O₂ and ECG were recorded on tape (Racal, eight channel) for subsequent analysis.

Rebreathing test

The effect of rebreathing CO₂ was studied in one patient with a conventional rebreathing circuit. Initially the patient inspired 100% oxygen for at least 2 min before being switched into a circuit containing O₂/CO₂ (95:5, v/v). The patient continued to breathe via this circuit until forced to stop because of shortness of breath. End-tidal CO₂ never exceeded 10%. The pneumotachograph was calibrated with air and corrections were made for the high O₂ concentration [8]. Flow was recorded from a heated pneumotachograph and O₂ and CO₂ concentration via a mass spectrometer, with sampling at the mouthpiece. The signals were recorded on tape as for the exercise tests.

Signals from the tape were subsequently recorded at fast paper speed on a Gould Brush recorder. Expired flow was integrated electronically to give tidal volume. Breath by breath measurements of tidal volume (VT), inspiratory duration (Tᵢ), expiratory duration (Tₑ) and end-tidal CO₂ were made by hand. Breathing frequency, minute ventilation (Vₑ) and mean inspiratory flow rate (Vᵢ/Tᵢ) were computed from these. Values were averaged over half-minute intervals for both the exercise and rebreathing runs.

Local anaesthetic block

Local anaesthetic block of the glossopharyngeal and vagus nerves at the base of the skull [9, 10] was performed in all patients in the hope of assessing their likely response to vagotomy. It was argued that if temporary block of the vagus nerves relieved the sensation of breathlessness during exercise, then vagotomy should be useful. Such improved exercise tolerance was indeed obtained in all the patients. In retrospect, however, we did not find this to be a valid predictor of the results of subsequent pulmonary denervation. Anaesthetic block of the glossopharyngeal and vagus nerves is not quite analogous to section of the vagus nerves below the recurrent laryngeal nerve, since it involves paralysis of the vocal cords as well as changes in blood pressure produced by associated block of the carotid baroreceptor fibres. The fibres from carotid chemoreceptors are also blocked, although the reflex effect of this can be minimized by breathing a high concentration of oxygen. Realistic comparison of respiratory sensation in these circumstances is therefore difficult and results from this procedure are not presented.

Surgery

All five patients had right vagotomy below the origin of the recurrent laryngeal nerve to avoid paralysis of the vocal cord on that side; this complication did nevertheless occur in one case. Vagotomy can be performed on the right side via a neck incision since the recurrent laryngeal nerve joins the vagus relatively high up after hooking round the subclavian artery. Left vagotomy requires a thoracotomy and this was performed.
on only one patient. In this case the pulmonary branches of the vagus nerve were cut at the hilum. Strictly speaking, therefore, this was not a vagotomy.

**Results**

**Clinical details**

The pre-vagotomy pulmonary function tests of all the patients are shown in Table 1. They all had chronic airways obstruction with large lung volumes, and there was no improvement in their pulmonary function after inhaled salbutamol.

The following summarizes the clinical details and response to vagotomy.

Patient no. 1. Shortness of breath had been present over 10 years but this had become progressively worse over the preceding 2 years. His chest X-ray and pulmonary angiogram were consistent with emphysema of the upper zones. Right vagotomy produced good symptomatic improvement, enabling him to carry on with his job without difficulty. Objective assessment of his exercise ability was not made.

Patient no. 2. Dyspnoea had been progressive over 27 years and she was breathless on minimal exercise. Chest X-ray showed hyperinflation and the pulmonary angiogram was consistent with emphysema. There was moderate symptomatic improvement after right vagotomy, e.g. she was able to take up horse-riding again after many years during which this activity had produced crippling dyspnoea. Maximum exercise work load on a bicycle ergometer was only 15 W and did not show much improvement. Ten months after the operation, she developed a chest infection and died.

Patient no. 3. This man, with lung hyperinflation shown by X-ray, had been getting increasingly short of breath over a 10-year period and was able to climb only one flight of stairs slowly. Unfortunately there was no symptomatic improvement after right vagotomy nor any objective improvement in exercise ability (although this was measured only once before and after the operation). He died 12 months after the vagotomy when not in our care. Details of the cause of death were unobtainable.

Patient no. 4. This woman was getting increasingly short of breath over a period of 7 years and used a wheelchair outside the house. Lung function, assessed by spirometry on each visit for exercise test showed no change after vagotomy. Emphysema was evident post mortem. There was some objective improvement after right vagotomy and this was consistent with measured exercise ability (see Fig. 1). The mean total work of our exercise tests before vagotomy was 979 + 200 J and the mean of three, after vagotomy, was 1595 + 390 J. Although this was an approximate 50% increase her exercise ability was still very limited after vagotomy (a total work load of 1200 J is equivalent to 1 min at a work load of 5 W and 1 min at 15 W). The increase in ventilation with exercise was due to a rise in both $V_T$ and $f_R$, both before and after right vagotomy. The rise in $f_R$, both before and after right vagotomy was smaller than the rise before vagotomy, although the effect was not large. However, the tidal volume was increased after vagotomy both at the beginning and end of exercise. There was also a slight increase in ventilation after vagotomy.

Despite this improvement, she still continued to use her wheelchair most of the time when out of the house. She died from a chest infection 8 months after the vagotomy.

Patient no. 5. Increasing shortness of breath over the preceding 18 months had begun seriously to affect the life of this active man. Chest X-ray showed hyperinflation with a large retrosternal air space, and pulmonary angiography was compatible with emphysema. After right vagotomy there was a marked improvement in that he could undertake activities which would have been out of the question before the operation. In view of the good response, the pulmonary branches of the left vagus nerve were cut at thoracotomy 7 months after the right

<table>
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<th>Table 1. Pre-operative pulmonary function tests of five patients</th>
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vagotomy. This produced a slight further symptomatic improvement although the benefit was not marked. Objective assessment of his exercise ability (Fig. 2) demonstrated clear improvement after right vagotomy with little further improvement after left vagotomy.

Table 2 shows the effect of vagotomy on basic measurements of lung mechanics and gas exchange. Right vagotomy produced no discernible change in lung mechanics or percentage alveolar dead space ventilation for nitrogen, although there was a major improvement in symptoms and exercise ability. Left vagotomy (plus thoracotomy) produced a small rise in FEV₁,₀ and FVC but no changes in TLC, RV or percentage dead-space ventilation. The change in FEV₁,₀ and FVC after left vagotomy was not associated with improvement in symptoms and exercise ability.

**Effect of vagotomy on breathing pattern in patient no. 5**

Fig. 3 shows the effect of vagotomy on the frequency of breathing and tidal volume. Before vagotomy there was a marked rise in breathing frequency as exercise progressed. After right vagotomy the frequency was lower throughout the exercise period but still rose as exercise progressed. Surprisingly, the frequency was higher after the thoracotomy and left vagotomy at the lower level of exercise, but there was very little increase in the frequency with exercise.

Tidal volume showed only small changes with
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Exercise when the vagus nerves were intact. There was a small increase in the tidal volume at the lower levels of exercise, but this fell again as exercise progressed. After right vagotomy the tidal volume was higher at all levels of exercise, although a plateau level appeared to be achieved at about 1 litre. After left vagotomy the tidal volume fell to approximately the values found before the right vagotomy. However, the tidal volume did increase progressively with the duration of exercise to achieve a value at the end of exercise approximately the same as that found after left vagotomy.

Total ventilation with exercise (Fig. 4) was changed little by right vagotomy but was lower after left vagotomy. Similarly, mean inspiratory flow rate ($V_I/T_I$) was lower after bilateral vagotomy but not, apparently, after right vagotomy. At the lower level of exercise, the mean inspiratory flow rate after right vagotomy was higher than the pre-vagotomy rates.

The change in breathing frequency with exercise before vagotomy was due to a reduction in both $T_I$ and $T_E$. After right vagotomy the increase in breathing frequency was smaller, initially being due to a fall in $T_E$ and subsequently to a fall in both $T_I$ and $T_E$. Left vagotomy virtually abolished the decreases in $T_I$ and $T_E$ with exercise.

**Effect of vagotomy on the response to CO₂ in patient no. 5**

The various respiratory measurements were made breath by breath and averaged over
half-minute intervals. The mean values for the half minute immediately before the rebreathing circuit was switched in were recorded and also the value for the half-minute interval which had a mean end-tidal CO$_2$ nearest to 8%. The mean values of the two pre-vagotomy runs, five post-right vagotomy runs and the four post-left vagotomy runs are shown in Fig. 5. The mean end-tidal CO$_2$ values were similar in the three conditions: pre-rebreathing values were 4·1, 4·1 and 4·3% respectively and the rebreathing values were 8·2, 8·3 and 8·2% respectively.

Ventilation ($V_E$) and mean inspiratory flow rate ($V_I/T_i$) were depressed by vagotomy, both whilst oxygen was breathed and at high CO$_2$. Right vagotomy reduced the frequency of breathing both at low and high CO$_2$, although left vagotomy had little further effect. Tidal volume ($V_T$) was increased by right vagotomy but left vagotomy was associated with a fall in tidal volume, although this effect was only small at the higher CO$_2$.

The rise in the frequency of breathing produced by CO$_2$ before vagotomy was due to changes in both $T_i$ and $T_e$. The change in frequency with CO$_2$ after vagotomy was much diminished, but again changes in both $T_i$ and $T_e$ contributed.

**Effect of vagotomy on blood gas tensions**

In the group as a whole, there was a tendency for Pao$_2$ and Paco$_2$ to be higher after right vagotomy (Table 3).

Fig. 6 shows the effect of vagotomy in patient no. 5 on blood gases measured at rest and at peak exercise before and after right and left vagotomy. Blood was sampled via an indwelling arterial cannula with the patient breathing through the same circuit at rest and during exercise. On each occasion exercise produced a fall in Paco$_2$ and a rise in Pao$_2$. Although there was little change in total ventilation or mean Paco$_2$ after right vagotomy, both Pao$_2$ and Paco$_2$ improved on the occasion of the exercise test. Presumably this was due to an improved breathing pattern with slower
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Fig. 5. Effect of vagotomy on the response to rebreathing CO₂ in patient no. 5. The six groups are each of the same format, and show the effect of CO₂ on (a) frequency of breathing (f), (b) inspiratory duration (Tᵢ), (c) expiratory duration (Tₑ), (d) tidal volume (Vₕ), (e) mean inspiratory flow rate (Vᵢ/Tᵢ) and (f) ventilation (Vₑ). Values are shown with the vagus nerves intact (Vi), after right vagotomy (RV) and after bilateral vagotomy (R + LV). See the text for further details.

Fig. 6. Effect of exercise and vagotomy on blood gases of patient no. 5. Symbols are as identified in Fig. 3.
deeper breaths, reducing total dead-space ventilation. After left vagotomy the blood gas concentration deteriorated towards initial blood gas values. Although the improved breathing pattern had been maintained, left vagotomy was associated with a fall in total ventilation, which could have caused these changes in blood gases.

Discussion
These results suggest that certain patients with emphysema benefit from vagotomy although others do not. This variability in response is similar to that found by Guz et al. [6] in a group of patients with a wider spectrum of pathology. The reason for this difference in response is not obvious, but it is clearly important that this should be explored further if vagotomy is ever to become established as a potential treatment of breathlessness in patients with chronic lung disease.

One possible explanation for the response in some patients might be the removal of reflex bronchoconstrictor tone in the airways by vagotomy. The clear improvement in the symptoms of patient no. 5 after right vagotomy without change in measured lung function is against this interpretation. The more modest improvement in symptoms of patient no. 4 was also achieved without any change in her spirometry.

An alternative explanation is that vagotomy might reduce respiratory drive by removing stimulation from pulmonary receptors. The tendency for $\text{Paco}_2$ to rise after right vagotomy (Table 3) is consistent with such an interpretation. Although ventilation and mean inspiratory flow were reduced during exercise after bilateral vagotomy in patient no. 5, no such reduction was seen after unilateral vagotomy, despite the improvement in symptoms that this produced.

A further possible explanation for the response is the effect of vagotomy on the pattern of breathing. Slower, deeper breathing might explain the tendency for $\text{Pao}_2$ to rise (Table 3). Unilateral vagotomy was associated with an increase in $V_T$ in patients nos. 4 and 5. Breathing frequency, particularly towards the end of exercise, was clearly depressed after right vagotomy in these patients. The greater symptomatic improvement in patient no. 5 compared with patient no. 4 might be due to the greater effect of vagotomy on the frequency of breathing.

Presumably vagotomy alters the breathing pattern by removing afferent input from tracheo–bronchial or lung receptors, but which group or groups of receptors are responsible remains conjectural. Non-myelinated pulmonary and bronchial receptors (‘J receptors’) may be affected by pulmonary disease [3, 4] and since their discharge often produced fast breathing they could be responsible for the relatively fast rate of breathing seen with exercise in chronic lung disease [11]. Removal of their influence would thus slow breathing. The reflex effect of airway stretch receptors is relatively weak in normal man, but may be operative during hyperpnoea, producing an increase in the frequency of breathing [12]. How emphysema affects their sensitivity is unknown, but the lower tension on the tracheo–bronchial wall may lead to a reduction in their discharge and alter their influence. Epithelial receptors (irritant receptors) can increase the frequency of breathing but how their discharge would be influenced by emphysema is difficult to predict.

The increase in $V_T$ and tendency for slower breathing after vagotomy ensures improved alveolar ventilation at any given level of total ventilation and improved blood gases [13, 14]. Any risk of vagotomy depressing total ventilation, so inducing respiratory failure, would thus be opposed by an improved pattern of breathing. The reduction in wasted ventilation after vagotomy, particularly at the higher levels of exercise, could be responsible for the increase in exercise ability. This would be achieved by a fall in the oxygen cost of breathing, i.e. by a fall in the amount of oxygen required by the respiratory muscles to achieve oxygen uptake by the lungs.

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<th>Table 3. Arterial blood gas values in five patients</th>
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<td>The means of all values available when the patients were in a stable state are presented (i.e. no overbreathing). $\text{PCO}_2$ and $\text{PO}_2$ are in kPa.</td>
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One potential disadvantage of vagotomy is alteration of the cough reflex. The patients did not notice any change in their cough reflex, but none had a chronic cough. Cough reflexes from the lower airways might have been abolished on the side of the vagotomy, but whether this significantly influenced clearing of secretions from the lower airways is unknown. Three of the patients in this study died within a year of the vagotomy and in two cases this was known to be associated with chest infections. However, they all had severe chronic lung disease and, therefore, death from lung infection was not surprising. It is impossible to tell whether vagotomy influenced their final illness.

Right vagotomy is a relatively simple procedure. Since it does not require a thoracotomy it was well tolerated even by patients with fairly severe lung disease. Left vagotomy requires a thoracotomy and it may be that any benefit due to vagotomy would be matched by disadvantages resulting from the thoracotomy. We feel that this makes interpretation of the results of this procedure in patient no. 5 extremely difficult, and in the light of this experience we could conclude that it should not be repeated in other patients. Patients with predominant right lung pathology would presumably stand most to gain from vagotomy, but it is encouraging that patient no. 5 derived much benefit from right vagotomy despite bilateral disease. Patients with granulomatous or fibrotic lung conditions might benefit as much, or even more, than patients with emphysema but this has not yet been evaluated by objective exercise testing. Further careful exploration of the possible benefits of right vagotomy is justified in patients with severe lung disease and crippling dyspnoea.

References