Ventilation and breathlessness on maximal exercise in patients with interstitial lung disease after local anaesthetic aerosol inhalation

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SUMMARY

1. The ventilatory response to maximal incremental exercise and the accompanying sensation of breathlessness were studied after the inhalation of 0.9% sodium chloride (saline) and 5% bupivacaine aerosols in six patients with interstitial lung disease.

2. The adequacy of airway anaesthesia induced by bupivacaine aerosol was confirmed by the absence of the cough reflex to 5% citric acid aerosol on completion of exercise.

3. All subjects first performed a trial exercise test to familiarize them with the procedure and to assess the degree of arterial oxygen desaturation on exercise. In subsequent tests, supplementary oxygen was given to maintain the saturation at 95% or above.

4. Airway anaesthesia had no effect on the ability to perform exercise as assessed by maximum workload, CO₂ production or heart rate. No significant changes were seen on the pattern of breathing, minute ventilation or end-tidal Pco₂ on exercise. There was, however, a small but statistically significant increase in ventilation related to CO₂ production (Ve/VO₂) at the end of exercise.

5. There was a tendency for breathlessness to be increased by airway anaesthesia but this did not reach statistical significance.

6. These results provide no evidence that vagal afferent activity is responsible for the abnormal ventilatory response to exercise in patients with interstitial lung disease. The perception of breathlessness in these patients was not diminished by anaesthesia of the airway.

Key words: aerosol, airway anaesthesia, control of breathing, dyspnoea, exercise, interstitial lung disease.

Abbreviation: VAS, visual analogue scale.

INTRODUCTION

Patients with diffuse interstitial lung disease characteristically exhibit abnormal increases in minute ventilation and breathing frequency accompanied by an exaggerated sensation of breathlessness at rest or on exercise [1–3]. Since these changes are not mediated by alterations in arterial blood gases [1, 4], it has been suggested that they may be due to increased vagal afferent activity from the lung [1, 2, 5]. Evidence from animal studies has demonstrated the importance of pulmonary vagal afferent fibres in the genesis of tachypnoea in lung inflammation [6]. A study of experimental pneumonitis in dogs [7] showed that vagal blockade could abolish excessive ventilation and breathing frequency on exercise and improve exercise tolerance.

Guz et al. [8] have studied the effect of vagal blockade, with and without concomitant glossopharyngeal nerve block, in five patients with lung infiltrations at rest. This resulted in a reduction in respiratory frequency in four of their subjects and in some relief of breathlessness in two. However, Savoy et al. [9] failed to detect an effect of airway anaesthesia, produced by inhalation of local anaesthetic aerosol, on the pattern of breathing in patients with fibrotic lung disease at rest.

We have studied the effect of local airway anaesthesia in patients with interstitial lung disease on exercise when the hyperpnoea and breathlessness experienced by these patients is particularly apparent.

METHODS

Subjects

The study was performed on six male subjects with interstitial lung disease, each of whom gave written consent after a full explanation of the nature of the study but not its purpose. The protocol of the study was approved by the Ethical Committee of Charing Cross Hospital.
Details of the subjects are given in Table 1. No subject had evidence of chest infection or was in respiratory failure at the time of study. All subjects had chest radiographs with widespread bilateral shadowing characteristic of interstitial lung disease and showed a reduction in lung volumes or a defect in gas transfer in the absence of airflow obstruction on pulmonary function tests. Subjects 1 and 2 had a positive Kveim test for sarcoidosis and a liver biopsy documenting a granulomatous hepatitis. Subject 3 had a clinical course consistent with cryptogenic fibrosing alveolitis. In subjects 4, 5 and 6 the diagnoses were confirmed by open lung biopsy.

Throughout the course of the study subjects 1 and 2 were taking prednisolone (Deltacortril Enteric, Pfizer) 30 mg and 10 mg orally respectively as a single morning dose, while subject 5 regularly received mianserin (Bolvidon, Organon) 30 mg and temazepam (Normison, Wyeth) 10 mg orally nightly. None of the other subjects was taking any medication.

**Aerosol generation and administration**

A 5 ml aqueous solution of either 5% (w/v) bupivacaine hydrochloride (Marcain, Duncan Flockhart) or 0.9% (w/v) sodium chloride (saline) was nebulized with a DeVilbiss 35B ultrasonic nebulizer (DeVilbiss Health Care Ltd, Feltham, Middlesex, U.K.). This produced an aerosol with an aerodynamic mass median diameter of 4.77 μm (Malvern laser particle size analyser). Subjects breathed the aerosol through a system incorporating inspiratory and expiratory one-way valves. Aerosol was continuously generated in the nebulizer, but flow of aerosol to the subject occurred only on inspiration. This system ensured that all aerosol produced was available to the subject and that no rebreathing occurred. Subjects breathed the aerosol for 10 min; they were instructed to take slow, deep breaths.

**Assessment of airway anaesthesia**

The cough reflex was tested by inhalation of an aerosol of either 5% (w/v) citric acid or 0.9% (w/v) sodium chloride (saline) generated by a Wright's nebulizer (modified from Bickerman & Barach [11]). The aerosols were administered in random order for three breaths. The subjects were unaware of the order of administration. The cough reflex was considered present if a subject coughed on any of three breaths of citric acid aerosol and absent if no cough occurred. No subject coughed on inhalation of saline.

**Exercise**

Exercise tests were performed on an electronically braked cycle ergometer (Lode, Groningen, Holland). The tests consisted of 1 min at rest followed by a 4 min "warm-up" period of minimum work (5 W) after which the work load was increased in 15 W increments at 1 min intervals to maximum exercise. Ventilation ($V_{E}$), respiratory frequency ($f_R$), tidal volume ($V_T$), oxygen consumption ($\dot{V}_{O_2}$)
and carbon dioxide production ($V_{CO_2}$) were measured by using an on-line computer-assisted pneumotachograph system (Ergostar; Fenyes and Gut, Basel, Switzerland) with subjects breathing on a mouthpiece as described by Reinhard et al. [12]. This produced averages for these variables at 30 s intervals. End-tidal $PCO_2$ ($PETCO_2$) was measured at the mouth with a catheter probe connected to a mass spectrometer (MOA 200; Centronics, Croydon, U.K.). Arterial oxygen saturation ($Sao_2$) was measured continuously with an ear oximeter (Hewlett-Packard, Wokingham, U.K.). An electrocardiogram was recorded from three bipolar chest leads by using a computer-assisted system (CASE; Marquette Electronics, Milwaukee, U.S.A.). Airflow, volume, $PETCO_2$, $Sao_2$ and electrocardiogram were recorded on a chart recorder.

The subjects quantified their sensation of breathlessness every 30 s from the beginning of the exercise using a visual analogue scale (VAS). The VAS consisted of a 10 cm line with the words 'not at all breathless' marked at one end and 'extremely breathless' at the other. Subjects could control the position of a light along this line by the use of a linear potentiometer. Responses were recorded on a chart recorder. All subjects understood that it was their sensation of breathlessness specifically which they were to record. The measurement of breathlessness by this technique has previously been described in detail [13]. In addition at the end of each exercise test subjects were questioned about their breathlessness.

**Design of the study**

Each patient performed an exercise test at the same time of day on each of 3 days. The first test was used to familiarize the patient with the procedure, to practise them in the use of the VAS for breathlessness and to assess the degree of arterial oxygen desaturation on exercise. During the two subsequent tests the $Sao_2$ was kept at 95% or above by adding oxygen to the inspired air if required.

On the second and third days each patient performed an exercise test immediately after inhalation of saline or bupivacaine aerosol. Five patients were given saline on day 2 and bupivacaine on day 3. In the other patient the order was reversed. The cough reflex was tested before the administration of bupivacaine aerosol and on completion of the subsequent exercise test. A venous blood sample was then taken for the determination of plasma bupivacaine by gas chromatography (modified from Reynolds & Beckett [14]).

**Statistical methods**

Values are given as means ± SD. Statistical analysis was performed by using Student’s t-test for paired data and two-way analysis of variance. The level of significance was taken as $P<0.05$ in a two-tailed test.

**RESULTS**

No subject reported any effect after saline aerosol inhalation. The effects after bupivacaine were similar to those we have previously described in normal subjects [15] including profound oropharyngeal anaesthesia and impairment of the ability to swallow. None of the subjects noted wheeze or reported any other side effect of the drug. The cough reflex to citric acid aerosol was present in all subjects before bupivacaine inhalation. It was completely abolished in five of the six subjects at the end of the exercise test after bupivacaine inhalation. The other subject coughed on the last of three breaths of citric acid after bupivacaine; after saline he coughed on the first breath of citric acid. The mean plasma bupivacaine concentration for five of the subjects at the end of the exercise test after local anaesthetic was 1.18 ± 0.43 µg/ml.

**Ventilatory response**

All subjects showed a fall in $Sao_2$ during exercise on the familiarization day. Consequently, in all subsequent tests, supplementary oxygen was given to keep the $Sao_2$ at 95% or greater throughout the period of exercise. In subject six this was not achieved for the last half-minute of exercise after saline when $Sao_2$ fell to 90%. The addition of varying amounts of oxygen to the inspiratory airflow throughout each exercise test made the measurements of $V_{O_2}$ invalid.

There were no differences in the ability to exercise after bupivacaine as compared with saline aerosol: maximum workload (saline: mean 88 ± 40 W; bupivacaine: mean 80 ± 32 W; $P>0.2$), maximum $V_{CO_2}$ (saline: mean 1.31 ± 0.63 litres/min; bupivacaine: 1.17 ± 0.47 litres/min; $P>0.1$), maximum heart rate (saline: mean 124 ± 19 beats/min; bupivacaine: 121 ± 17 beats/min; $P<0.3$).

To examine the effect of bupivacaine compared with saline aerosol on the incremental response to exercise a two-way analysis of variance was performed. Since this approach requires an equal number of data points in each group the response could be analysed only up to the maximum duration of exercise achieved by all subjects (6.5 min). The results are shown in Fig. 1. After bupivacaine there was no significant difference in $f_R$ ($P>0.7$), $V_T$ ($P>0.15$), $V_E$ ($P>0.6$), $PETCO_2$ ($P>0.15$) or $V_{CO_2}$ ($P>0.6$). Although the changes were not statistically significant, there was an increase in $V_T$ (mean difference 9.1%) and a decrease in $PETCO_2$ (mean difference 5.4%).

Since this analysis does not examine data at maximum exercise, for most of the subjects an additional approach was used: values for each of the above variables were compared at the maximum workload that was achieved by a subject after both saline and bupivacaine aerosols. No difference was seen using a paired t-test after bupivacaine aerosol in $f_R$ (saline: mean 47.9 ± 14.0 breaths/min; bupivacaine: mean 49.3 ± 11.2 breaths/min; $P>0.6$), $V_T$ (saline: mean 1336 ± 573 ml; bupivacaine: mean 1282 ± 515 ml; $P>0.4$), $V_E$ (saline: mean 59.1 ± 18.2 litres/min; bupivacaine: mean 58.6 ± 12.4 litres/min; $P>0.7$), $PETCO_2$ (saline: mean 30.0 ± 9.5 mmHg; bupivacaine: mean 28.4 ± 8.0 mmHg; $P>0.1$) or $V_{CO_2}$ (saline: mean 1.20 ± 0.53 litres/min; bupivacaine: mean 1.16 ± 0.48 litres/min; $P>0.5$).
workload achieved by that subject after both saline and bupivacaine aerosols. The values after saline for subjects 1–6 were: 60.8, 30.4, 41.4, 67.1, 73.7 and 51.7 (mean 54.1 ± 16.2). The respective values after bupivacaine were: 63.4, 33.5, 40.9, 72.8, 76.4 and 52.6 (mean 56.7 ± 17.5). This increase in $V_{E}/V_{CO_2}$ after bupivacaine was statistically significant ($P < 0.05$).

To determine whether there was a relationship between the degree of hyperventilation and the reduction in lung volume, linear regression was performed on the relationship between $V_{E}/V_{CO_2}$ and total lung capacity as a percentage of the predicted normal value; no significant correlation was found ($r = -0.14$). A similar analysis showed no correlation between $V_{E}/V_{CO_2}$ and the carbon monoxide transfer coefficient as a percentage of the predicted normal value ($r = -0.69$). Those subjects (1, 4 and 5) with reductions in both lung volumes and gas transfer showed the greatest hyperventilation at the end of exercise (highest $V_{E}/V_{CO_2}$), while the two subjects (2 and 3) with reductions solely in lung volumes showed the least hyperventilation. Subject 6, exhibiting a reduction in gas transfer alone, showed an intermediate degree of hyperventilation.

A linear correlation was seen after saline aerosol between the maximum $V_{E}$ achieved on exercise and the vital capacity ($r = 0.91 ; P < 0.02$). After bupivacaine the correlation between these just failed to reach statistical significance ($r = 0.79 ; 0.1 > P > 0.05$).

**Breathlessness**

When questioned at the end of exercise, patients 2, 5 and 6 reported feeling more breathless after bupivacaine, patient 3 felt less breathless, and patients 1 and 4 noticed no difference. Using the VAS, patients 3 and 6 indicated breathlessness *ab initio* at rest and throughout the exercise test after both saline and bupivacaine aerosols, patient 4 indicated breathlessness *ab initio* after saline but not bupivacaine, and patients 1, 2 and 5 did not indicate breathlessness at rest but became breathless during exercise on both occasions (Fig. 2). These last three patients indicated the onset of their breathlessness at a lower $V_{E}$ after bupivacaine (saline: 28.6, 45.0, 37.8 litres/min; bupivacaine: 17.6, 15.8, 20.2 litres/min). Using analysis of variance, there was a 28.5% increase in the mean VAS scores after bupivacaine compared with those after saline for the first 6.5 min of exercise, although this failed to reach statistical significance ($P > 0.2$). At the maximum workload that was achieved by a subject after both saline and bupivacaine aerosols, no difference was seen in the VAS scores using a paired $t$-test (saline: mean 70.7 ± 28.1 mm; bupivacaine: mean 88.2 ± 13.7 mm; $P > 0.2$).

To relate breathlessness to $V_{E}$ rather than workload, VAS scores in each subject were compared after saline and bupivacaine aerosols at the highest $V_{E}$ achieved by all subjects (40 litres/min); there was no significant difference after bupivacaine (saline: mean 51.0 ± 25.6 mm; bupivacaine: mean 65.3 ± 20.0 mm; $P > 0.4$). To compare the degree of breathlessness at the end of exercise after saline and bupivacaine aerosols, the VAS scores, at the
maximum values for $V_e$ which could be matched within 2 litres/min between the two runs, were examined. The VAS scores at matched maximum $V_e$ were not significantly different after bupivacaine (saline: mean 75.7 ± 23.5; bupivacaine: mean 86.2 ± 14.3; $P > 0.3$).

**DISCUSSION**

The results of the present study provide no evidence that the exaggerated ventilatory response on exercise or the accompanying sensation of breathlessness in patients with interstitial lung disease is the result of altered airway receptor activity. The design of the study, by maintaining normal $SaO_2$ throughout exercise, removed any variation in the hypoxic drive to breathe which might otherwise have made the results difficult to interpret.

The purpose of this study was to test whether the tachypnoea and increased breathlessness seen in these patients on exercise was due to increased vagal activity from lung receptors; if this was so we may expect aerosol anaesthesia to decrease the $f_R$ and sensation of breathlessness. No decrease was found in either; indeed there was a small but statistically insignificant increase in VAS for breathlessness. For this increase to be statistically significant it can be calculated that approximately 75 subjects would be required for study [17]. The number of patients studied in the present investigation was limited as we required subjects who became tachypnoeic and breathless on exercise yet could perform sufficient exercise to allow a useful amount of data to be collected for analysis.

Previous work in animals has established that inhalation of a local anaesthetic aerosol provides an effective blockade of pulmonary afferent reflexes [18–20]. In man, bupivacaine aerosol abolishes the cough reflex and in anaesthetized subjects impairs the Hering–Breuer inflation reflex [19]. In normal subjects it produces slower deeper breathing during exercise [15] and abolishes the burning sensation in the chest produced by central intravenous injection of capsaicin believed to be mediated by unmyelinated fibres originating from the pulmonary vascular bed [21]. In the present study we were only able to establish blockade of the cough reflex, and are therefore unable to exclude the possibility that the lack of effect of the bupivacaine aerosol is due to remaining activity in some vagal afferent fibres. Residual activity in vagal afferent fibres could account for the difference in results between application of local anaesthetic to the vagus nerves [8] and inhalation of local anaesthetic aerosol [9] in patients with interstitial lung disease at rest.

Another interesting possibility that could account for our negative results is the observation of Cotes et al. [22] that in early 'active' interstitial lung disease, characterized by infiltration with inflammatory cells, respiratory rate can be increased disproportionately to the reduction in $V_e$. In this phase of the disease it was proposed that the breathing pattern is determined by lung receptors being involved in the inflammatory process whereas the breathing pattern associated with the fibrosis of later disease was solely an adaptation to altered lung mechanics. It is therefore possible that local anaesthetic aerosol had no effect on the pattern of breathing in our subjects since all but one (subject 6) had longstanding restrictive lung disease.

It has been argued that, since a given pattern of breathing is adopted in order to minimize respiratory muscle force [23] and work [24], patients with interstitial lung disease when exercising minimize the peak intensity of force development (smaller $V_T$) and the duration of force development (increased $f_R$) [25]. This raises the question whether the changes in the pattern of breathing can occur without the need to involve vagal airway reflexes. The nature of the receptors involved in optimizing the breathing pattern is a matter of speculation but could include
intercostal muscles spindles [26] or receptors in the chest wall or diaphragm. They are unlikely to be located in the airways, since the detection and scaling of elastic loads in normal subjects (used as a model for the decreased elastance of interstitial lung disease) is unaffected by airway anaesthesia [27, 28]. Whatever receptors are involved, the abolition of a tachypnoeic response to elastic loads by general anaesthesia [29, 30] suggests consciousness is involved in the control of breathing in such situations. Recent experiments in patients with interstitial lung disease have shown that, during stage 4 sleep, $V_T$ is unchanged from wakefulness while $f_R$ falls, indicating that consciousness is involved in the wakeful tachypnoea of these patients [31]. This suggests that the pattern of breathing seen in our patients on exercise may be a conscious adaptation to minimize a sensation of discomfort arising from receptors located in the chest wall and/or diaphragm consequent on the altered mechanical properties of the lung.

The patients studied in the present investigation varied considerably in the extent of the reduction in their lung volume and gas transfer. Those subjects showing reductions in both of these indices showed the greatest hyperventilation on exercise ($V/\dot{V}CO_2$), and those exhibiting a reduction in lung volume alone showed the least. The small number of subjects studied makes it difficult to be certain about the relative importance of these measurements in determining the degree of hyperventilation found in these patients. Further, it has recently been shown [32] that patients with interstitial lung disease have a marked increase in physiological dead space which may account for their hyperventilation. We did not feel that the arterial cannulae required for the accurate calculation of physiological dead space in these patients to be justified.

Paintal [33] has proposed that juxtapulmonary capillary receptors are an important source of dyspnoeic sensation from the lung. The results of Guz et al. [8] have been used as support for this belief since they document that combined vagal and glossopharyngeal nerve blockade or block of the exposed vagus nerves alone reduces breathlessness in patients with lung infiltrations at rest. However, analysis of their study reveals that two of their patients were not breathless before vagal blockade and another was unable to comment on any change in her sensation; one of the remaining two patients reported the abolition of a tight feeling in his chest after vagal blockade and the other 'ceased to feel her breathing'. These results cannot, therefore, be used as firm evidence that vagal afferent discharge from the lung is important in the sensation of breathlessness. Our results do not demonstrate that breathlessness is reduced after airway anaesthesia; indeed there is a suggestion that it may be increased.

Recent experiments in patients with severe chronic airflow obstruction have shown breathlessness to be greatly reduced when hyperventilation was voluntary rather than reflexly driven, although the lung mechanics in these two situations were similar [34]. In exercising normal subjects who were suddenly made hypoxic, breathlessness increased before ventilation [35]. These results together suggest that breathlessness is not simply awareness of increased ventilation or sensing of afferent information from peripheral receptors (e.g. muscle spindles) but is perceived centrally in situations where a reflexly increased drive to breathe causes motor respiratory activity [36]. It is possible in the present study that some remaining afferent information from the lung, normally exerting a negative feedback on breathing during exercise [15], is removed by the local anaesthetic aerosol. This may be seen centrally as a reflexly increased drive to breathe and result in increased motor respiratory activity. Although this may not be expressed as a significant change in the breathing pattern, due to a decreased lung compliance and a need to minimize the work of breathing, it could be expressed as an increase in breathlessness.

In conclusion our results provide no evidence that vagal afferent activity is responsible for the abnormal ventilatory response to exercise or the accompanying sensation of breathlessness in patients with interstitial lung disease.

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REFERENCES

Airway anaesthesia and pulmonary fibrosis


