The effect of airway anaesthesia on the control of breathing and the sensation of breathlessness in man

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Summary

1. The effect on ventilation of airway anaesthesia, produced by the inhalation of a 5% bupivacaine aerosol (aerodynamic mass median diameter = 4.77 μm), was studied in 12 normal subjects.

2. The dose and distribution of the aerosol were determined from lung scans after the addition to bupivacaine of 99mTc. Bupivacaine labelled in this way was deposited primarily in the central airways. The effectiveness and duration of airway anaesthesia were assessed by the absence of the cough reflex to the inhalation of three breaths of a 5% citric acid aerosol. Airway anaesthesia always lasted more than 20 min.

3. Resting ventilation was measured, by respiratory inductance plethysmography, before and after inhalation of saline and bupivacaine aerosols. The ventilatory response to maximal incremental exercise and, separately, to CO₂ inhalation was studied after the inhalation of saline and bupivacaine aerosols. Breathlessness was quantified by using a visual analogue scale (VAS) during a study and by questioning on its completion.

4. At rest, airway anaesthesia had no effect on mean tidal volume ($V_T$), inspiratory time ($T_i$), expiratory time ($T_e$) or end-tidal $PCO_2$, although the variability of tidal volume was increased. On exercise, slower deeper breathing was produced and breathlessness was reduced. The ventilatory response to CO₂ was increased.

5. The results suggest that stretch receptors in the airways modulate the pattern of breathing in normal man when ventilation is stimulated by exercise; their activation may also be involved in the genesis of the associated breathlessness.

6. A hypothesis in terms of a differential airway/alveolar receptor block, is proposed to explain the exaggerated ventilatory response to CO₂.

Key words: aerosol, airway anaesthesia, control of breathing, dyspnoea, exercise, rest, vagus nerve.

Introduction

Lung inflation within the resting tidal volume range has little effect on ventilation in man [1]. Though volume-related vagal afferent discharge is present at rest [2, 3], vagal blockade has no effect on resting ventilation in anaesthetized or conscious subjects [4, 5]. However, vagal block does reduce the ventilatory response to hypercapnia [6] and diminishes tachypnoea and breathlessness in patients with cardiopulmonary disease [7].

Petit & Delhez [8] reported that local anaesthetic aerosol abolished the tachypnoea and accompanying dyspnoea produced by histamine aerosol inhalation in asthmatics. Further work in animals established that such aerosol was a safe and reversible method of airway receptor blockade [9–11]. In man, airway anaesthesia had no effect on resting ventilation [12, 13] though paradoxically the ventilatory response to hypercapnia increased. Recently this lack of effect on resting ventilation has been disputed [14]. Van Meerhaeghe & Sergyse [15] reported that airway anaesthesia had no effect on the breathing pattern during exercise in normal subjects and in patients with chronic airflow limitation.
The purpose of the present study is to examine the effect of more effective airway anaesthesia than has been previously employed [12] on ventilation at rest, on exercise and during CO₂ rebreathing. Some of the results have been presented in preliminary form [16].

Methods

All studies were performed on healthy volunteers who had given informed consent after full explanation. None of the subjects had a history of asthma or any other atopic condition. Three of the 12 subjects (subjects 3, 4 and 7) were aware of the purpose of the study. The protocol for these studies was approved by the Ethical Committee of Charing Cross Hospital.

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 was nebulized with a DeVilbiss 35B ultrasonic nebulizer (DeVilbiss Health Care Ltd, 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 from a mouthpiece 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 the aerosol produced was available to the subject and that no rebreathing occurred. For the first 5 min subjects breathed the aerosol to a pattern consisting of a 5 s inspiration, a 10 s breath-hold and a 5 s expiration. They were instructed to take deep breaths but were allowed to choose their own depth of breathing. This was followed by 5 min tidal breathing of the aerosol.

Aerosol deposition

In order to determine the dose and distribution of the aerosol in the lung, 11 mCi (4.1 × 10¹¹ Bq) of ⁹⁹ᵐTc⁴⁺ in 0.5 ml of 0.9% (w/v) sodium chloride solution (saline) were added to 5 ml of 5% (w/v) bupivacaine hydrochloride solution. After a 2 min aerosol inhalation, two subjects (3 and 9) were seated in front of a Nuclear Enterprises 8960LF scintillation camera (Edinburgh, U.K.) and posterior scans were recorded on an oscilloscope and stored in a Nodcrest computer (Byfleet, U.K.) for subsequent analysis. Venous blood samples taken 1 min after aerosol inhalation showed similar specific activities to the original solution nebulized. Bupivacaine and technetium were therefore assumed to have been both nebulized and deposited in the lung together.

To derive the lung outline and to provide a calibrating phantom for activity, a lung perfusion scan was obtained for each subject after an intravenous injection of ⁹⁹ᵐTc⁴⁺-labelled macroaggregated albumin. The lung outlines were fitted from the perfusion scans by computer analysis at the count level corresponding to 18% of the maximum number of counts [17] and superimposed on the aerosol scans (Fig. 1). The number of counts in the right lung was measured and, by using the perfusion scan, the activity and therefore the mass of drug deposited in the lung was calculated [18]. The presence of activity in the stomach made a similar measurement for the left lung invalid. The total dose to both lungs was then estimated on the basis of the ratio of counts in each lung from the perfusion scan. By this method, the estimated total dose to the lungs for a 10 min inhalation was 29.3 mg and 26.7 mg for the two subjects.

Assessment of airway anaesthesia

The cough reflex was tested by inhalation of an aerosol of either 5% (w/v) citric acid or saline generated by a Wright's nebulizer (modified from Bickerman & Barach [19]). The aerosols were administered in random order for three breaths.

FIG. 1. Posterior lung scan after inhalation of ⁹⁹ᵐTc-labelled bupivacaine aerosol. The lung outline was derived from the perfusion scan. The aerosol deposited predominantly in the larger airways. Activity due to swallowed aerosol can be seen in the stomach.
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.

**Resting ventilation**

Measurements were made for 5 min before and after inhalation of saline and, later that day, bupivacaine aerosols in five subjects (1, 2, 3, 4 and 5, males, aged 23-54 years). All measurements of ventilation were made on subjects seated comfortably in a chair, blindfolded, wearing sound-proof headphones, in a room separate from the investigators. This ensured a minimum of visual and auditory stimulation. Ventilation ($V_E$) and its subdivisions, tidal volume ($V_T$), respiratory frequency ($f_R$), inspiratory and expiratory time ($T_i$, $T_e$), were measured without using a mouthpiece by respiratory inductance plethysmography (Respirtrace, Ambulatory Monitoring, New York, U.S.A.). Abdominal and rib cage transducer bands were attached and kept in position by an elastic vest. The system was calibrated during quiet breathing on a spirometer in the standing and lying positions [20]. The $V_T$ recorded from the calibrated system was compared with that of a spirometer before each period of resting ventilation was recorded, and the mean difference used to correct the $V_T$ measurement. End-tidal $P_{CO_2}$ was measured at the nose with a Hewlett Packard 47210A capnometer (Hewlett Packard, Wokingham, U.K.). An electrocardiogram (ECG) was recorded from three bipolar chest leads by using a computer assisted system (CASE, Marquette Electronics, Milwaukee, U.S.A.). An electrocardiogram (ECG) was recorded from three bipolar chest leads by using a computer assisted system (CASE, Marquette Electronics, Milwaukee, U.S.A.). An electrocardiogram (ECG) was recorded from three bipolar chest leads by using a computer assisted system (CASE, Marquette Electronics, Milwaukee, U.S.A.). Airflow, volume, end-tidal $P_{CO_2}$ and ECG were recorded on a chart recorder. $T_i$ and $T_e$ were measured for each breath from the airflow record by using the digitizing system described above.

To measure possible central drug effects a series of 16 visual analogue scales (VAS) [21] divided into four categories (mental sedation, physical sedation, tranquillization, other feelings) was completed by each subject before and after each inhalation. In addition, reaction time and vigilance were assessed. A series of 20 vertical or horizontal bars were generated by a microcomputer on a visual display unit in a random manner. Subjects were instructed to respond by depressing either of two keys as quickly and as accurately as possible. The number of correct responses and the time taken for that response, the reaction time, were determined.

Venous blood samples were obtained at 9, 26 and 40 min after the start of aerosol inhalation. Plasma bupivacaine concentrations were determined by gas chromatography (modified from Reynolds & Beckett [22]).

**Bronchial reactivity**

The effect of local anaesthetic aerosol on bronchial reactivity was assessed in two subjects (3 and 5) by using a cumulative methacholine challenge [23]. The dose of methacholine required to produce a 35% fall in the specific airways conductance (PD_{25}) was measured in a body plethysmograph (Fenyves and Gut, Basel, Switzerland) before and after administration of aerosol.

**Exercise**

Exercise tests were performed on a treadmill with variable speed and elevation. The tests consisted of 1 min at rest followed by a 1 min 'warm-up' period of minimum work (1 m.p.h.; 0% slope) after which the work load was increased by a constant amount at 1 min intervals to exhaustion. The workload increment for males was 30 W and for females 25 W. $V_{E}$, $f_R$, $V_T$, oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were measured by an on-line computer assisted pneumotachograph system (Ergostar; Fenyves and Gut, Basel, Switzerland) with subjects breathing on a mouthpiece as described by Reinhard et al. [24]. This produced averages for these variables at 30 s intervals. End-tidal $P_{CO_2}$ was measured at the mouth with a catheter probe connected to a mass spectrometer (MGA 200; Centronics, Croydon, U.K.). An ECG was recorded from three bipolar chest leads by using a computer assisted system (CASE, Marquette Electronics, Milwaukee, U.S.A.). Airflow, volume, end-tidal $P_{CO_2}$ and ECG were recorded on a chart recorder. $T_i$ and $T_e$ were measured for each breath from the airflow record by using the digitizing system described above.

The subjects quantified their sensation of breathlessness during exercise by using a VAS. This consisted of a 10 cm line with 'not at all breathless' marked at one end and 'extremely breathless' at the other. The subjects could control the position of a light along this line by the use of a linear potentiometer. The subjects indicated the onset of breathlessness by using the VAS and, at 30 s intervals thereafter, a VAS response was summoned by the illumination of a small light. Responses were recorded on a chart recorder. The
use of the VAS has been previously described [25].

Eight subjects (1, 2, 3, 4, 5, 6, 7 and 8, six male, two female, aged 23-54 years) performed exercise tests immediately after saline aerosol inhalation and, after a period of rest of approximately 3 h, bupivacaine aerosol inhalation. On completion of each exercise test the cough reflex was tested. It was always present after saline and always absent after bupivacaine inhalation. Plasma bupivacaine levels were measured at the end of exercise in two of these subjects.

To confirm the reproducibility of the response to exercise, six subjects (1, 3, 9, 10, 11 and 12, five male, one female, aged 23-35 years) performed two exercise tests 3 h apart without aerosol inhalation.

In two subjects (3 and 9) exercise tests were performed immediately after intravenous infusion of 20 ml of saline and, 3 h later, 0.25% (w/v) bupivacaine hydrochloride. The bupivacaine (0.75 mg/kg body wt.) was infused over 10-20 min to achieve blood levels comparable with those measured after aerosol inhalation.

Ventilatory response to carbon dioxide

This was tested in four subjects (1, 3, 5 and 6, three male, one female, aged 23-35 years) by a CO₂ rebreathing technique modified from Read [26] in which the end-tidal PO₂ was kept at the normal level of approximately 100 mmHg (13.3 kPa).

Airflow, end-tidal PCO₂, end-tidal PO₂ and VAS for breathlessness were stored on FM tape for subsequent analysis. The response was analysed on a breath-by-breath basis in which Vₜ, Tᵢ and Tₑ were measured for each breath and instantaneous Vₑ calculated. The subjects performed a rebreathe immediately after inhalation of saline aerosol and, after a recovery period of at least 45 min, performed a second rebreathe after bupivacaine inhalation. On completion of each rebreathe the cough reflex was tested. It was always present after saline and always absent after bupivacaine inhalation.

Experimental design

Treatments were tested on the same day to reduce the variability of the respiratory measurements within a subject. The order of the treatments was not randomized as the duration of action of bupivacaine was unknown. Where subjects performed more than one type of study, these were done on separate days.

Statistical analyses

Statistical analyses were performed by using Student's t-test for paired data, variance ratios (F) and two-way analysis of variance as appropriate. The level of significance was taken as P < 0.05 in a two-tailed test.

Results

General effects of aerosol inhalation

After saline inhalation, no subject reported any effect other than a slight salty taste in the mouth. The effects after bupivacaine were similar to, though more intense than, those described by Cross et al. [12]. They included initial irritation of the pharynx followed by profound oropharyngeal anaesthesia, abolition of the ability to swallow and huskiness of the voice. The cough reflex to citric acid was abolished in all subjects for at least 20 min. None of the subjects complained of any reported systemic side effects of bupivacaine. No changes in ECG, heart rate or blood pressure were noted.

Analysis of the VAS for mood and mental state showed no mental sedation or any other central drug effect. Neither the vigilance nor reaction time of any subject was affected.

The mean plasma concentrations of bupivacaine at rest for the five subjects 9, 16 and 40 min after the start of aerosol inhalation were 1.072 (SD 0.197), 0.910 (SD 0.166) and 0.796 (SD 0.184) µg/ml respectively. No concentration exceeded 1.4 µg/ml. In two subjects plasma bupivacaine concentrations at the end of exercise were 1.02 and 1.54 µg/ml.

Resting ventilation

Resting ventilation was measured for periods of 5 min before and after inhalation of saline and bupivacaine aerosols in five subjects. The number of breaths recorded in each period varied and ranged from 40 to 74 breaths. Vₜ, Tᵢ and Tₑ were measured for each breath and the results are shown in Table 1.

Analysis of variance was used to compare the mean values of these variables for 40 breaths from each subject before and after saline and bupivacaine aerosols. There was no significant difference between the means for Vₜ (P > 0.5), Tᵢ (P > 0.7) or Tₑ (P > 0.6).

The degree of variability in Vₜ, Tᵢ and Tₑ was determined from the ratio of the variances of the samples before and after each aerosol by using an F table. The variability in Vₜ was unchanged in all five subjects after saline aerosol but was increased
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(P < 0.05) in four subjects after bupivacaine aerosol. Neither saline nor bupivacaine aerosols had any consistent effect on the variability of $T_i$ or $T_e$.

End-tidal $P_{CO_2}$ was averaged over each 5 min period. This did not change after saline ($P > 0.2$) or bupivacaine ($P > 0.2$) aerosol (paired t-test).

**Bronchial reactivity**

The $PD_{50}$ values for methacholine challenge in two subjects were 27.2 μmol and 13.5 μmol before, and 34.9 μmol and 20.6 μmol after bupivacaine aerosol. These values are within the normal range for this laboratory (> 6.3 μmol; [23]) and showed no increase in bronchial reactivity.

**Exercise**

Eight subjects were studied. There were no differences in the ability to exercise after saline as compared with bupivacaine aerosol: maximal workload [saline: mean 191 (sd 52.3) W; bupivacaine: mean 195 (sd 52.4) W; $P > 0.3$], maximal $\dot{V}_{O_2}$ [saline: mean 2780 (sd 604) ml/min; bupivacaine: mean 2780 (sd 796) ml/min], and maximal $\dot{V}_{CO_2}$ [saline: mean 3460 (sd 725) ml/min; bupivacaine: mean 3530 (sd 915) ml/min; $P > 0.5$].

The effects on the pattern of breathing are shown for one subject in Fig. 2. For each of the subjects, each of the variables $f_R$, $V_T$, $V_E$ and end-tidal $P_{CO_2}$ was compared over matched 30 s intervals during exercise by using a paired t-test. In six subjects, $f_R$ fell with airway anaesthesia, while in seven $V_T$ increased. The slower deeper breathing pattern resulted in overall $V_E$ increasing in five subjects, while end-tidal $P_{CO_2}$, reflecting alveolar ventilation, fell in six out of eight subjects. These changes were significant ($P < 0.01$).

The relationship between $V_T$, $T_i$ and $T_e$ during the control exercise test after saline aerosol, showed considerable variability between subjects. No subject showed a range of $V_T$ where $T_i$ was constant. Fig. 3 shows the relationship for the same subject as in Fig. 2. Analysis of variance on pooled data from all the subjects showed that $T_i$ and $T_e$ decreased during exercise ($P < 0.001$) although the decrease in $T_e$ was greater. No clear break-points in the $V_T/T_i$ and $V_T/T_e$ relationships were seen in any subject.

Similar decreases in $T_i$ and $T_e$ were seen after airway anaesthesia ($P < 0.001$). The relationships between $V_T/T_i$ and $V_T/T_e$ were altered: for a given $V_T$, $T_i$ and $T_e$ were increased (Fig. 3).

The data from the eight subjects have been pooled for the last 5 min of exercise for each of

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>$V_T$ (ml)</th>
<th>$T_i$ (s)</th>
<th>$T_e$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>328 ± 85</td>
<td>573 ± 102</td>
<td>670 ± 74</td>
</tr>
<tr>
<td>2</td>
<td>508 ± 144</td>
<td>759 ± 125</td>
<td>874 ± 78</td>
</tr>
<tr>
<td>3</td>
<td>439 ± 68</td>
<td>581 ± 32</td>
<td>690 ± 12</td>
</tr>
<tr>
<td>4</td>
<td>1033 ± 143</td>
<td>739 ± 137</td>
<td>877 ± 72</td>
</tr>
<tr>
<td>5</td>
<td>543 ± 82</td>
<td>463 ± 78</td>
<td>561 ± 77</td>
</tr>
</tbody>
</table>

Values are means ± SD for 5 min periods.
The effect of saline and bupivacaine aerosol inhalations on the ventilatory response to maximal incremental exercise in one subject is shown in Fig. 2. Exercise (EX) is preceded by a rest (R) and a warm-up (W) period. Airway anaesthesia produced slower, deeper breathing with an increase in ventilation and a decrease in end-tidal Pco₂; V̇O₂ was unchanged.

The variables and compared after saline and bupivacaine aerosol by using analysis of variance (Fig. 4). After bupivacaine, fR decreased (mean difference 9.2%, P < 0.05) and V̇T increased (mean difference 18.3%, P < 0.001). V̇E was increased (mean difference 7.7%) but this just failed to reach significance (P > 0.05) while end-tidal PCO₂ decreased (mean difference 6.0%, P < 0.05). V̇O₂ and heart rate were unchanged (P > 0.5, P > 0.2). When the variables were compared over the first 5½ min of exercise the results were similar: fR decreased (mean difference 10.8%, P < 0.05), V̇T increased (mean difference 16.7%, P < 0.01), V̇E increased (mean difference 5.0%, P > 0.1) and end-tidal PCO₂ decreased (mean difference 4.7%, P < 0.05).

To determine whether this change in the pattern of breathing on exercise was related to a change in physiological dead space (V̇D), this was calculated for the eight subjects after aerosol inhalation by using the Bohr equation [27] with CO₂ as the reference gas. Since the end-tidal PCO₂ in all subjects exhibited an end-expiratory plateau, the end-tidal PCO₂ was taken to equal mean alveolar PCO₂. The mixed expired PCO₂ was calculated from V̇CO₂ and V̇E. There was no significant difference (P > 0.3) between the calculated V̇D after saline inhalation [mean 162 (SD 66) ml] and that after bupivacaine inhalation [mean 186 (SD 69) ml] before the start of exercise.

As a control for these studies, two exercise tests were performed on six subjects without aerosol inhalation. The data were analysed as above. There was no difference between the two exercise tests for V̇T (P > 0.1), V̇E (P > 0.05) and end-tidal PCO₂ (P > 0.05), whilst fR was increased
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Airway anaesthesia produced slower, deeper breathing with a decrease in end-tidal \( PCO_2 \) and an increase in ventilation towards the end of exercise; \( VO_2 \) was unchanged. (mean difference 5.8%, \( P = 0.04 \)) on repeat exercise.

Two subjects performed exercise tests immediately after saline and bupivacaine intravenous infusions. The bupivacaine infusion resulted in plasma bupivacaine concentrations of 0.57 and 1.22 \( \mu g/ml \) at the start of exercise and 0.55 and 0.57 \( \mu g/ml \) at the end of exercise. For each subject, each variable was compared over matched 30 s intervals during exercise by using a paired \( t \)-test as described above. Intravenous bupivacaine infusion had no effect on breathing.

**Sensation of breathlessness on exercise**

Seven subjects, when questioned at the end of exercise, reported feeling less breathless after bupivacaine. By using the VAS, four subjects indicated the onset of breathlessness at a higher \( V_E \); the mean \( V_E \) at threshold VAS was 43.2 (SD 20.7) litres/min after saline and 49.9 (SD 31.8) litres/min after bupivacaine. This difference was not significant (\( P > 0.1 \)). In addition, five subjects indicated lower VAS scores for equivalent levels of ventilation after the onset of breathlessness.

No differences in breathlessness were reported or indicated by the six subjects performing exercise 3 h apart without aerosol inhalation, nor by the two subjects performing exercise after intravenous infusion of bupivacaine.

**Ventilatory response to \( CO_2 \)**

The response to normoxic rebreathing was studied in four subjects after saline inhalation and then, after complete recovery, bupivacaine inhalation. The duration of rebreathing and the maximal level of end-tidal \( PCO_2 \) achieved was similar in these three subjects, whilst in a fourth it was lower after bupivacaine. \( V_E \) was plotted against corresponding values of end-tidal \( PCO_2 \), and a linear regression analysis performed. The results are shown in Table 2. In all subjects the sensitivity to \( CO_2 \) (\( V_E/\text{end-tidal } PCO_2 \) slope) was increased by airway anaesthesia, though the intercept of the relationship was unchanged. The relationships between \( V_E/V_T \), \( V_T/T_1 \) and \( V_T/T_e \) were unchanged by airway anaesthesia in three subjects. In one subject the slope of the \( V_E/V_T \) relationship was decreased such that \( V_T \) was greater for a given \( V_E \) in this subject. For a given \( V_T \) both \( T_1 \) and \( T_e \) were increased. No relationship was seen between the slopes of \( V_E/\text{end-tidal } PCO_2 \) and \( V_E/V_T \) as suggested by Hey et al. [28].

**Sensation of breathlessness during rebreathing**

When questioned at the end of rebreathing three of the subjects reported feeling breathless
TABLE 2. Effect of saline and bupivacaine aerosol inhalation on the ventilatory response to CO₂

The slopes, intercepts and correlation coefficients are from linear regression analyses on the relationship between VE and end-tidal PCO₂.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Post saline</th>
<th>Post bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (1 min⁻¹ mmHg⁻¹)</td>
<td>CO₂ intercept (mmHg)</td>
</tr>
<tr>
<td>1</td>
<td>3.31</td>
<td>46.16</td>
</tr>
<tr>
<td>3</td>
<td>3.56</td>
<td>42.59</td>
</tr>
<tr>
<td>5</td>
<td>7.11</td>
<td>49.56</td>
</tr>
<tr>
<td>6</td>
<td>2.83</td>
<td>36.67</td>
</tr>
</tbody>
</table>

after saline and bupivacaine inhalations. One of these was distressed by rebreathing after bupivacaine and tolerated a lower maximal end-tidal PCO₂, but did not report feeling more breathless. Of the other two subjects, one felt more breathless, while in the other breathlessness was unaffected by bupivacaine. However, by using the VAS these three subjects all indicated the onset of breathlessness at a higher VE (25.5, 9.5, 19.7 litres/min after saline inhalation and 34.4, 18.6, 23.2 litres/min after bupivacaine inhalation). The VAS scores for equivalent levels of VE after the onset of breathlessness were similar.

Discussion

The present study employed a technique of aerosol generation that resulted in more effective airway anaesthesia than had been previously employed [12]. The cough reflex was abolished for at least 20 min, more profound oropharyngeal anaesthesia was achieved, yet the method was safe and reliable and no subject reported effects other than those due directly to the local anaesthetic on the airway itself. Moreover, the plasma bupivacaine concentrations were similar to those reported by Cross et al. [12], and well below any published toxic level [29, 30]. The longer duration of effective anaesthesia allowed adequate time to study either resting ventilation or the ventilatory response to maximal incremental exercise.

The use of ⁹⁹ᵐTc-labelled bupivacaine aerosol enabled the dose of drug delivered to the lung and its distribution to be determined. The deposition of the aerosol was predominantly in the larger airways, as would be predicted from its aerodynamic mass median diameter [31]. It is in these airways where the majority of the slowly adapting stretch receptors are believed to lie [32]; these receptors probably mediate the inhibitory Hering-Breuer inflation reflex.

Resting ventilation was studied by respiratory inductance plethysmography because of evidence that the use of a mouthpiece and noseclip affects the breathing pattern of conscious subjects [33]. In addition, subjects were seated comfortably in an isolated room and deprived of auditory and visual stimulation; such stimuli have been shown to have significant effects on ventilation [34].

Airway anaesthesia had no effect on the mean levels of VT, T₁ and Tₚ studied in this way. These results are in agreement with previous findings [12, 13] and with the effects of vagal block in man [4, 5], but are in contrast to those of Savoy et al. [14]. These workers demonstrated a decrease in respiratory frequency and an increase in VT and T₁ after lignocaine aerosol inhalation. In that study subjects were not isolated from the investigators nor deprived of auditory or visual stimuli; average minute ventilation using a mouthpiece and noseclip before aerosol inhalation was 8.0 litres/min as opposed to 6.1 litres/min in the present study; in addition the effectiveness and duration of airway anaesthesia to 4% lignocaine was not established. Airway anaesthesia in the present study did, however, increase the variability in VT. This finding has not previously been reported in man [12-14], but has been reported with vagal blockade in the awake dog [35]. It is possible that, in man, both the state of resting wakefulness and the use of entirely non-invasive techniques for measuring ventilation are prerequisites for the demonstration that airway stretch receptors minimize breath-by-breath fluctuations in depth; these conditions were fulfilled in the present study.

On exercise, airway anaesthesia produced slower, deeper breathing. The control studies of exercise tests without aerosol inhalation and those after intravenous saline and bupivacaine infusions showed that this effect is due directly to airway anaesthesia itself: it is not a result of the experimental protocol, nor is it due to the systemic effects of the drug or to changes in the physiological dead space. These results are in contrast
to those reported by Van Meerhaeghe & Segysels [15]; these authors found no changes in $V_E$, $V_T$ or $f_R$ during exercise after lignocaine aerosol inhalation compared with the control response in normal subjects and in patients with chronic air flow limitation. Uncertainty as to the duration and effectiveness of airway anaesthesia used in their study must exist, as a 2% lignocaine aerosol was employed and the gag reflex alone (mechanical irritation of the pharynx) was used to test anaesthesia only immediately after the aerosol was inhaled.

The results of the present study are evidence that, when tidal volume is increased by a reflex drive such as exercise, stretch receptor activity does limit inspiration as originally described in animals by Hering & Breuer [36]. Previous work [1, 4] has demonstrated the presence of the inflation reflex in man at inflation volumes greater than 1 litre above the functional residual capacity. Block of the inflation reflex was not formally tested in our study, the effectiveness of airway anaesthesia being assessed by the absence of the cough reflex mediated by receptors located in the surface epithelium. However, a 5% bupivacaine aerosol has been shown to block the inflation reflex in animals [10] and to partially block this reflex in anaesthetized man [12].

The relationships found between $V_T$, $T_i$ and $T_e$ in the control exercise tests contrast with the results of previous findings in non-steady-state exercise [37] and steady-state exercise [38]; these relationships were unaltered by airway anaesthesia. The present study therefore lends no support, in man, to the model of the organization of breathing proposed by Clark & von Euler [39].

The lower end-tidal $P_{CO_2}$ for a similar $CO_2$ production during exercise must imply that alveolar ventilation was greater after bupivacaine aerosol. The control system with removal of stretch receptor input appears to accept a lower $P_{CO_2}$. This effect is similar to that described in anaesthetized dogs where vagotomy increased alveolar ventilation and decreased arterial $P_{CO_2}$ [40].

Although some discrepancy existed between reported sensation and that indicated by VAS, breathlessness did appear less after bupivacaine inhalation. This effect was not apparent with either intravenous drug infusion or repeat exercise. The difference was evident even though the $V_E$ and $V_T$ for a given work load increased, lower VAS scores being recorded for equivalent levels of $V_E$. The central deposition of the aerosol together with the present findings, suggests a role for airway receptors in the genesis of breathlessness in these subjects.

The exaggerated ventilatory response to $CO_2$ breathing is similar to that reported by Cross et al. [12], also using airway anaesthesia. It is in contrast to the results of Guz et al. [5] and Guz & Widdicombe [6], who showed a reduced ventilatory response to $CO_2$ after combined glossopharyngeal and vagal nerve block, primarily due to lack of increase in respiratory frequency. The present results seem analogous to those of Phillipson et al. [41], who found in conscious dogs that cooling the vagi to 4-8°C increased the ventilatory response to $CO_2$ while abolishing the inflation reflex. Further cooling of the vagi to 0.4°C resulted in a decrease in the response to $CO_2$, abolishing the frequency effect. The interpretation was that the initial cooling removed the inhibitory influences of stretch receptor activity while further cooling removed the excitatory influence of smaller fibres. Afferent activity in pulmonary C-fibres, with endings located at alveolar level, has recently been shown to mediate the increase in respiratory frequency during hypercapnia in rabbits [42]. The pattern of aerosol deposition in the present study would produce a differential effect on pulmonary receptors, leaving intact those located at alveolar level while abolishing inhibitory stretch receptor activity.

The enhancement of an established pulmonary alveolar C-fibre reflex (the ventilatory response to phenyl diguanide), has been previously demonstrated in rabbits after the inhalation of a 5% bupivacaine aerosol that blocked the inflation reflex [9]. If such alveolar receptors exist in man and have similar reflex effects, the exaggerated ventilatory response to $CO_2$ inhalation could be explained on the basis of a differential receptor block.

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