The effect of anaesthesia of the airway in dog and man: a study of respiratory reflexes, sensations and lung mechanics

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Summary
1. The effect of breathing an anaesthetic aerosol of 5% bupivacaine hydrochloride has been assessed in dog and man.
2. In the dog, the cough reflex was abolished and the Hering–Breuer inflation reflex severely impaired or abolished; breathing became slower and deeper; no pathological changes were found in the lungs of these dogs.
3. In man, no untoward effects resulted from a 10 min period of aerosol inhalation; there were no systematic effects on airway resistance or lung volumes and the cough reflex in response to either tactile or chemical (citric acid aerosol) stimulation was invariably abolished. The Hering–Breuer inflation reflex was impaired, but this was not associated with any change in resting ventilation. The $\dot{V}_{\text{E}}/\text{CO}_2$ response was enhanced after aerosol anaesthesia; subjects felt an exaggerated dyspnoea. The aerosol anaesthesia abolished the afferent pathway of a reflexly elicited bronchoconstriction in one subject. There was no effect on the ability to hold the breath, or on the quality of the associated sensation.
4. Control aerosols of sodium chloride solution or phosphate buffer produced no effects. Control experiments with intravenous infusions of bupivacaine proved that none of the effects could have been produced by systemic effects of the absorbed anaesthetic.
5. Plasma concentrations of bupivacaine in man did not exceed a recognized toxic level. The experiments demonstrate a safe reversible anaesthesia of the airways in man lasting for a period of 10–20 min.

Key words: aerosol, airway, anaesthesia, bupivacaine, lung mechanics.

Introduction
The physiological effects of anaesthesia of the airways in the rabbit have been studied by Jain, Trenchard, Reynolds, Noble & Guz (1973) and more recently in the rabbit and dog by Dain, Boushey & Gold (1975). The motive for this experimental approach has been interest in the role of pulmonary vagal afferent mechanisms in respiratory reflexes and sensation in man. Petit & Delhez (1970) have already reported the use of an inhaled aerosol of 20% lignocaine in patients with asthma; these authors did not study which areas of the lung were anaesthetized and what reflexes were affected.

The purpose of the present study has been to assess whether the nature and degree of blockade of airway receptors obtainable in the rabbit, could also be obtained in man. To do this, it was thought necessary first to study a mammal larger than the rabbit to establish whether the greater airway surface could be anaesthetized safely and reversibly.

Methods
Studies in dogs
Eleven dogs (18–35 kg) were used. All surgical
procedures were performed under 1.0-1.5% halothane in N₂O/O₂ (50:50). Before any observations were made, eight of the eleven dogs were anaesthetized with chloralose (Merck, 40 mg/kg); in the remaining three dogs, anaesthesia was maintained with a 1.0-1.5% halothane in O₂ mixture only. Either an endotracheal tube or a tracheal cannula was inserted and connected in series with a pneumotachograph (Fleish no. 1). A polyvinyl catheter was introduced into the common carotid artery. Both cervical vagus nerves were prepared for section later in the experiment. Oxygen was added to the inspired air to maintain the arterial Pa₂>19.95 kPa (150 mmHg) and thus minimize chemoreceptor stimulation. ECG, airflow, tidal volume, airway pressure, carotid arterial pressure, PaO₂ and PaCO₂ were measured as described by Guz & Trenchard (1971). Rectal temperature was monitored and kept between 37°C and 38°C. Powdered anaesthetic was dissolved in water to make solutions of 20% lignocaine and 5% bupivacaine hydrochloride. The aerosol generated in a Wright nebulizer (particle size 5-19 µm) was administered in the same manner as that previously described for rabbits (Jain et al., 1973), except that aerosol inflations generating 5-15 cmH₂O airway pressure were used. Lignocaine aerosol was generated at room temperature and administered to one dog, whereas bupivacaine aerosol was generated at 53°C and administered to ten dogs.

Lignocaine and bupivacaine concentrations in plasma were measured by a modification of the method of Reynolds & Beckett (1968) using gas chromatography, on samples of arterial blood taken at various times during and after the administration of the aerosol.

Two reflex responses were investigated. First, cough was studied by inserting a fine polythene probe into the trachea as far as its bifurcation, to produce tactile stimulation of the epithelial lining. Secondly, stretch-receptor function was tested by eliciting the apnoeic response to lung inflation over a range of constant pressure inflations from a pressurized bag. Both responses were tested before and immediately after the administration of anaesthetic aerosol. The animals were usually allowed to recover for at least 30 min before the responses were again tested. The cervical vagi were then cut and the observations repeated.

Before the study could be extended to man under general anaesthesia (for examination of the Hering-Breuer inflation reflex) it was first necessary to modify the method of local anaesthetic administration. An aerosol of bupivacaine was generated by passing a mixture of 1.0-1.6% halothane in O₂ from a specially designed fluothane vaporizer (Hunter & Bush, 1971) at a pressure of 414 kPa (60 lb/in²) to the Wright nebulizer. In this way the aerosol could be administered to the dog (or patient) while a steady state of general anaesthesia was maintained. Examination of the physical characteristics of such an aerosol showed that while the mean weight of bupivacaine dispersed as aerosol/min was the same (3.2 mg/litre of O₂) as found in the standard technique, the frequency distribution of the size of the particles showed a slight shift to the right. This aerosol was given to three dogs and the pharmacological effects and the plasma concentrations of bupivacaine were assessed as described above. All three animals were allowed to recover from this experimental procedure and examined over a period of 1 week for evidence of cough, fever or general ill-health. These animals were then killed and the lungs and airways were examined both macroscopically and microscopically.

Studies in conscious man

Studies were performed only on subjects who had given consent after full explanation. Sanction for these studies was also given by the Ethical Committee of Charing Cross Hospital. Two groups of subjects were studied: healthy volunteers and patients with a permanent tracheostomy after laryngectomy for neoplasms of the larynx.

Administration of aerosols and infusions of bupivacaine. (i) Bupivacaine aerosol. The aerosol was generated from a solution of 5% bupivacaine in the same manner as that described for dogs, except that two nebulizers were used, connected in parallel. Subjects breathed the aerosol through a mouthpiece or a tracheostomy tube, attached to the vertical limb of a T tube; the aerosol was passed through the horizontal limb of the T tube at a flow rate of 32 l/min. This high flow rate prevented the rebreathing of expired air. Subjects were trained to inhale the aerosol for 5 s, hold their breath for a further 10 s and then exhale to functional residual capacity (FRC) over the next 5 s. The cycle was then immediately repeated so that a respiratory frequency of 3 breaths/min resulted; the subject was allowed to choose his own depth of breath. This 'held-inspiratory' pattern was employed for the first 5 min of aerosol administration, and was followed by 5 min of eupnoic breathing. Electro-
cardiogram, arterial pressure (by sphygmomanometry) and heart rate were monitored throughout the aerosol administration. In preliminary studies, peripheral venous blood samples were taken at intervals during and after aerosol administration, for an estimation of plasma bupivacaine by gas chromatography (see above). Venous rather than arterial blood was sampled, primarily for ethical reasons. In addition, it has been established in man that, during intravenous infusion of bupivacaine at a constant rate, the drug is taken up by limb musculature at a fairly constant rate so that the arteriovenous concentration ratio varies only between 1.3 and 1.4 (Reynolds, 1970).

(ii) Non-anaesthetic aerosols. A 5% solution of bupivacaine-hydrochloride in water has an osmolality of 307.5 mosmol/kgH₂O, and a pH of 5.4. Control experiments were therefore performed with solutions of sodium chloride (saline; 300 mosmol/kgH₂O) or phosphate buffer, pH 5.4. Aerosols of these solutions were administered in exactly the same manner as for the anaesthetic experiments including heating the aerosol generator and inflowing O₂ to 53°C.

(iii) Intravenous bupivacaine. An intravenous infusion of a 0.25% solution of bupivacaine hydrochloride (0.75 mg/kg body weight) was given over a period of 10 min to achieve plasma concentrations of the drug comparable with those obtained with aerosol inhalation.

Experimental procedures. Each experimental procedure was performed before and within 10 min of the termination of aerosol inhalation or anaesthetic infusion. Some of the procedures, e.g. testing of cough reflex, were repeatedly performed until the results had returned to the control state.

(i) Cough reflex. This was tested by chemical stimulation in all subjects, and also by tactile stimulation in the tracheostomized subjects. An aerosol was generated with a Wright nebulizer, from a solution of citric acid (100 g/l). Subjects breathed from a stream of this aerosol, or from an aerosol of saline generated in the same way, without knowing the order of administration. A maximum of five normal inspirations of the aerosol was permitted. This method of testing the cough reflex was essentially that described by Bickerman & Barach (1954).

Sterile tracheal suction catheters were inserted through the tracheostomy to elicit cough with a tactile stimulus. The length of catheter that it was necessary to insert, before provoking cough, was noted.

(ii) Resting ventilation. The breathing pattern was recorded for 1 min before, and then again for 1 min soon after, an aerosol inhalation or bupivacaine infusion. In the laryngectomized subjects, a low-dead-space (17 ml), low-resistance, unidirectional valve was attached to the tracheostomy tube, and a timed collection of expired air was made. A mouth-piece was not used for the mouth-breathing subjects, since these subjects had not been trained for respiratory studies, and because some concern exists about the effect of a mouthpiece on the measured respiratory parameters (Gilbert, Auchincloss, Brodsky & Boden, 1972); tidal volume was therefore not measured in this group. In both groups of subjects, respiratory frequency and end-tidal Pco₂ (PET,CO₂) were obtained from the recorded output of an infra-red CO₂ analyser (Uras 4, Hartmann and Braun). To achieve this, expired air was continuously sampled from the dead space of the valve used for the laryngectomized patients, or with a small tube loosely resting between the teeth in mouth-breathing subjects.

(iii) Lung volumes and airway resistance. To determine whether the inhalation of an aerosol of bupivacaine had any deleterious effect on the lung, airway resistance (Rₐ,w) and lung volumes (FRC,¹) residual volume, vital capacity and inspiratory capacity) were measured by standard plethysmographic techniques (Dubois, Botelho & Comroe, 1956) and spirometry. Specific airway conductance (sGₐ,w) was calculated as the reciprocal of the airway resistance per unit of panting thoracic gas volume (TGV); this minimized the effect of changing TGV on measurements of airway calibre.

(iv) Ability to hold the breath. The ability to hold the breath and the associated sensations were tested at FRC before and after the inhalation of bupivacaine aerosol in some of the laryngectomized and mouth-breathing subjects. The tracheostomy tube of the laryngectomized patients was connected with a short, flexible, soft-rubber tube to the low-dead-space unidirectional breathing valve, through which the subject first breathed 100% O₂ for 2 min. On command, the subjects obstructed the flexible rubber connection with a clamp, and held it there until breaking point was reached. Mouth-breathing subjects also breathed 100% O₂ for 2 min through an unidirectional breathing valve; these subjects were able to hold their breath at FRC on command by

¹ Abbreviations: FRC, functional residual capacity; TGV, thoracic gas volume.
closing the glottis. $\text{PET}_{\text{CO}_2}$ was recorded before and immediately after the termination of breath-holding, which was made with an expiratory effort rather than with the more usual inspiration. The duration of breath-holding was noted; suitable encouragement was given to prolong the time of breath-holding to a maximum.

(v) Ventilatory response to carbon dioxide. (a) Response to rebreathing. The method used was that of Read (1967), and these studies were confined to the mouth-breathers. Subjects rebreathed from a thin-walled rubber bag containing 6 l of $\text{O}_2/\text{CO}_2$ (93:7). Ventilation was recorded by enclosing the rebreathing bag in a 25 l glass bottle connected to a wedge spirometer (Medox); the output of the latter was recorded on a Cambridge oscillographic recorder. Continuous records of $\text{CO}_2$ concentration were obtained with the infrared CO$_2$ analyser by sampling gas near the mouthpiece; the sensitivity of the record was of the order of 0-067 kPa (0-5 mmHg)/mm deflection. Before commencing rebreathing, the subject breathed air for 2 min to obtain a stable ventilatory pattern. The subject was allowed to continue rebreathing until breathlessness became intolerable. After complete recovery, bupivacaine aerosol was administered as described above. Immediately after this, the rebreathing procedure was repeated. (b) Response to a single constant $\text{CO}_2$ concentration. The breath by breath ventilatory response to the inhalation of $\text{O}_2/\text{CO}_2$ (95:5) was recorded for 5-15 min in two subjects with a modification of the spirometric system used for the rebreathing manoeuvre.

(vi) Bronchial response to irritation of the airway surface. The inhalation of an aerosol generated (with a Wright nebulizer) from a solution of citric acid (200 g/l) was used to irritate the airways (Simonsson, Jacobs & Nadel, 1967). Subjects sat in a body plethysmograph and repeated measurements of $R_w$ and TGV were made until reproducible control values were established. The subjects then inhaled the irritant aerosol for five breaths through a port in the body plethysmograph; it was possible to do so without contaminating the inside of the plethysmograph with the irritant aerosol. Within 10 s of concluding the administration of the citric acid, serial measurements of $R_w$ and TGV were made over the next 3-4 min. Although eleven apparently healthy subjects were tested, a reproducible bronchoconstriction was found in only one subject. The effect of a prior administration of an aerosol of bupivacaine on this bronchoconstrictor response to an airway irritant could then only be examined in this one subject (A.S.). On a separate occasion, control values for $R_w$ and TGV were established after the anaesthetic inhalation, and the effect of the citric acid inhalation was then determined. To establish the role of parasympathetic efferent pathways in the bronchoconstrictor response to citric acid, 2 mg of atropine was given intravenously to subject A.S. on a separate occasion, and the effect of the inhalation of the citric acid aerosol then recorded.

Studies in anaesthetized man

Hering–Breuer inflation reflex. Five volunteer patients undergoing minor leg surgery were selected for this study. The entire procedure was fully explained, and their consent was freely given; the study was approved by the Ethical Committee of Charing Cross Hospital.

The administration of a local anaesthetic aerosol, while general anaesthesia was maintained by inhalation, and the incorporation of a means of testing the apnoeic response to lung inflation, was a complex problem. The bupivacaine aerosol was generated, as described above for the dog, under halothane anaesthesia; the halothane concentration used was 1·8% in $\text{O}_2$. The anaesthetic mixture (with or without bupivacaine aerosol) was administered to the patient via an endotracheal tube. Atropine (0·6 mg) was given intravenously before the start of the study. $\text{PET}_{\text{CO}_2}$ was continuously measured by sampling gas from the endotracheal tube and analysed with the infrared $\text{CO}_2$ analyser. As the performance of the analyser was adversely affected by bupivacaine aerosol, expired gases were first passed through a drying 'trap' of magnesium perchlorate; the aerosol particles were also trapped. ECG and heart rate were continuously monitored. Ventilation was monitored with a pneumotachograph (Fleish no. 1), in series with the endotracheal tube, connected to a differential pressure gauge (Pye Ether UP-1). Airway pressure was measured with a Statham strain gauge (PM5). A suitable arrangement of valves enabled the anaesthetic gas mixture to be diverted away from the patient while the inflation reflex was tested by connecting the airway to a pressurized bag. A series of inflation pressures (and hence inflation volumes) were used to record the apnoeic response to lung inflation (Widdicombe, 1964; Guz, Noble, Trenchard, Cochrane & Makey, 1964).

After a steady state of general anaesthesia had been
established, the control inflation pressure/apnoeic response curve was established. The local anaesthetic aerosol was then administered with a positive pressure held-inspiration pattern at a rate of 3 breaths/min for 10 min. The depth of breath was adjusted to minimize any change in \( P_{ETCO_2} \). Immediately after, when a steady state of ventilation was recorded, the inflation pressure/apnoeic response curve was again determined.

Cough reflex. The presence of the cough reflex before and after the administration of the anaesthetic aerosol was tested by a tactile stimulus from a fine catheter passed through the endotracheal tube.

Statistical methods

The Wilcoxon matched-pairs signed-rank test was used (Siegal, 1956; Wilcoxon & Wilcox, 1964). The level of significance has been taken as \( P<0.05 \) in a two-tailed test.

Results

Dogs

Inflations of local anaesthetic aerosol were given until the apnoeic response to lung inflation was either abolished or severely reduced; this required between thirty and seventy-five inflations in the eleven dogs studied. The \( PaO_2 \), \( PaCO_2 \), systemic arterial pressure and heart rate did not show any consistent changes. The concentrations of bupivacaine in the plasma immediately after the administration of the aerosol were between 1.3 and 2.56 \( \mu g/ml \), and that of lignocaine in a single experiment was 3.21 \( \mu g/ml \). No evidence of drug toxicity, e.g. convulsions, was detected in any of the experiments.

Cough reflex. Before administration of anaesthetic aerosol, the cough reflex could be elicited in six of the eleven dogs; this reflex was always blocked after the aerosol and did not recover for at least 20–30 min.

Hering–Breuer inflation reflex. The strength of the inflation reflex was assessed from the relationship between volume and inhibitory ratio (duration of apnoea divided by the average duration of five preceding cycles; Widdicombe, 1964). Abolition of the inflation reflex is characterized by an inhibitory ratio of 1 over the entire range of inflation volumes, which extended up to 2–3 litres above FRC. Such complete abolition of the reflex was found in only two of the dogs given bupivacaine aerosol. These were the two dogs receiving the aerosol through a tracheal cannula. In all the remaining dogs receiving either of the aerosols through an endotracheal tube, the reflex was inhibited to various degrees, i.e. the inhibitory ratio was reduced at any given inflation volume. The strength of the inflation reflex began to return to control values within 10 min of the end of aerosol administration. The degree and duration of block was comparable in those animals given the aerosol with halothane.

Pattern of breathing. The effects of an anaesthetic aerosol on the frequency of breathing \( f \), tidal volume \( V_T \), inspiratory time \( t_i \) and expiratory time \( t_e \) are shown in Table 1. At a time when the inflation reflex was completely blocked or impaired, \( V_T \) was increased and \( f \) was reduced, primarily as a result of a lengthening of \( t_i \); there was no consistent change in \( t_e \). Vagotomy performed in five dogs caused a further slowing and deepening of breathing, even when the inflation reflex was completely blocked.

Findings in dogs allowed to recover. No evidence of fever, cough, general ill-health, or radiological change in the lungs, could be demonstrated in the three dogs (no. 9, no. 11 and no. 12) allowed to recover after the administration of the bupivacaine aerosol/halothane mixture. Both macroscopic and microscopic appearances of the lungs were normal.

Man

General effects of aerosol breathing. The aerosol always tasted bitter until the oropharyngeal mucosa was anaesthetized. After the first minute, the subject experienced a sense of irritation in the pharynx; there was no such feeling in the retrosternal area. As the pharyngeal mucosa became anaesthetized after 4–5 min, the sense of irritation disappeared. The pharyngeal discomfort, which could result in cough, was minimized by the ‘held-inspiratory’ pattern of breathing as compared with a normal pattern of breathing. Towards the end of the 10 min aerosol inhalation period, the ability to swallow became impaired, though never abolished. At the termination of aerosol breathing, all subjects felt a profound anaesthesia of the tongue and oropharynx, and huskiness of the voice. A repeated comment by some subjects was that they did not know how deeply they were breathing. On occasion, they added that inspiration felt more difficult, whereas expiration felt normal. None of the subjects complained of headache, dizziness, paraesthesiae or drowsiness. There were no
TABLE I. Effect of airway anaesthesia on resting ventilation in dogs

L, Lignocaine; B, bupivacaine. Effect on inflation reflex is indicated as: ++++, complete block; ++, severe reduction; +, moderate reduction. Control values represent the average of the pre-aerosol and the recovery values. \( f \), frequency of respiration; \( V_T \), tidal volume; \( t_i \), inspiratory time; \( t_e \), expiratory time. N.D., Not done.

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>No. of aerosol inflations</th>
<th>Effect on inflation reflex</th>
<th>( f ) (min(^{-1}))</th>
<th>( V_T ) (ml)</th>
<th>( t_i ) (s)</th>
<th>( t_e ) (s)</th>
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<tr>
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<td>++</td>
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<td>+++</td>
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<td>N.D.</td>
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<td>30</td>
<td>20</td>
<td>15</td>
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adverse effects on the ECG, heart rate or arterial pressure either during or after aerosol administration. All the manifestations of the local anaesthesia disappeared within 30–50 min. With recovery, subjects usually experienced a cold sensation in the chest on inspiration, and a tickling sensation in the pharynx.

The plasma concentrations of bupivacaine were estimated at intervals on fourteen occasions in twelve subjects. The results are shown in Fig. 1. The concentration of bupivacaine in the plasma rose steadily and reached peak values at or shortly after the termination of aerosol inhalation; subsequently the concentration declined. No concentrations exceeded 1.6 µg/ml.

Cough reflex. (a) Chemical stimulation. In preliminary studies the ability to elicit cough, by inhaling an aerosol of citric acid (100 g/l), was tested in nine subjects. Seven of these responded with a cough after one or two inhalations and the remaining two coughed after the third inhalation. The cough response was always accompanied by a raw sensation in the lower anterior neck and upper anterior chest. The inhalation of saline aerosol did not result in cough or any unpleasant sensation.

The effect of the bupivacaine aerosol on this cough response was tested in ten mouth-breathing subjects and six laryngectomized subjects. The citric acid (100 g/l) aerosol now failed to produce cough or any associated raw sensation, even after five or six inhalations had been given. Recovery of the reflex and the sensation occurred within 8–20 min.

(b) Tactile stimulation. Cough provoked by the mechanical stimulus of the suction catheter was studied in ten tracheostomized subjects and three intubated patients under general anaesthesia, in whom the Hering–Breuer inflation reflex was studied (see below). Before breathing the bupivacaine aerosol, cough could be elicited particularly after 13–15 cm length of the catheter had been introduced; the tip then lay approximately at the tracheal bifurcation. After aerosol breathing, however, the tip of the catheter could be advanced generally up to 22–30 cm until it became impacted in one of the airways without generation of cough. Introduction of the catheter into the airway of the laryngectomized patients before airway anaesthesia, caused a sense of tickling felt retrosternally; after aerosol administration the patients felt nothing. The cough reflex and the tickling sensation returned within 8–20 min pari passu with the return of the response to chemical stimulation. In the anaesthetized patients, the cough reflex took 30–40 min to recover. In two subjects the cough reflex remained intact after infusion of bupivacaine intravenously.
Resting ventilation. Nine mouth-breathing, four tracheostomized and three intubated subjects were studied on one or more occasions. Detailed results can be found in Clinical Science and Molecular Medicine Table 76/1 deposited with the Librarian, the Royal Society of Medicine (1 Wimpole Street, London W1M 8AE), from whom copies can be obtained on request. Data for each individual have been compared before and after the anaesthetic; there was no obvious difference in the behaviour of any of the groups. On this basis, the results have been pooled for a statistical analysis. Bupivacaine aerosol did not cause any significant change in resting f (P > 0.1) or in Vt (P > 0.1). In most instances, a small fall in PET,CO₂ was found after the anaesthetic aerosol, but in some instances there were small rises; however, the difference in the values of PET,CO₂ before and after the aerosol just failed to reach the level of significance (0.05 < P < 0.1). There were only five observations in the control aerosol group, but the changes in f and PET,CO₂ were not significant (P > 0.1 in both cases).

Effect of bupivacaine aerosol on lung volumes and airway resistance. The results of inhaling bupivacaine aerosol in seven subjects on FRC, expiratory reserve volume, inspiratory capacity and vital capacity, are shown in Fig. 2(a). There was no consistent change. The results of measurements of Rₐₙ and sGₛₐₙ for these subjects are shown in Figs. 2(b) and 2(c). There was no consistent change after aerosol inhalation, despite any subjective feelings suggesting an increase in inspiratory resistance, and this was substantiated by lack of any divergence between inspiratory and expiratory resistances.

![Graphs](image-url)

**Fig. 2.** Effect of bupivacaine aerosol inhalation on (a) lung volumes (ml), (b) airway resistance (kPa l⁻¹ s⁻¹) and (c) specific airway conductance (s⁻¹ kPa⁻¹). ●, Expiratory reserve volume; ▲, inspiratory capacity; ○, vital capacity; △, functional residual capacity. Note that there is no consistent change in any variable after bupivacaine. The lines of identity are shown.
Effect of anaesthesia of airway

Fig. 3. Ventilatory response to CO₂ rebreathing before (●) and after (▲) inhalation of bupivacaine aerosol. Minute ventilation (Ve) is plotted against end-tidal CO₂. (a) Response of one individual (D.B.); (b) response obtained after averaging linear slopes drawn visually from the points of rise to points of peak response for each of nine studies. Horizontal and vertical bars represent ±1 SE about the mean value. After anaesthetic inhalation the slope is increased; the end-tidal CO₂ at peak ventilation is significantly lower after bupivacaine than before.

Fig. 4. Ventilatory response to CO₂ rebreathing before (●) and after (▲) inhalation of bupivacaine aerosol. Frequency (f) is plotted against end-tidal CO₂. (a) Response of one individual (D.B.); response obtained after averaging linear slopes drawn visually from the points of rise to the points of peak response for each of nine studies. Horizontal and vertical bars represent ±1 SE. After anaesthetic inhalation the slope is increased.
448 Brenda A. Cross et al.

**Ability to hold the breath.** There was no consistent effect of aerosol anaesthesia of the airway on the breath-holding time or quality or intensity of the associated sensations in the chest. The $\text{PET,CO}_2$ immediately before breath-holding was comparable before and after the inhalation of local anaesthetic. Complete relief of the sensation was achieved with the first breath after breath-holding, on both occasions.

**Ventilatory response to CO₂.** (a) Response to rebreathing. Eight subjects were studied, one of these on two occasions. All felt that dyspnoea was exaggerated during rebreathing with airway anaesthesia. As a result of this, the duration of rebreathing was shortened and the tolerable $\text{PET,CO}_2$ was lower than before anaesthesia.

Minute ventilation ($\dot{V}_E$), $V_T$ and $f$ were averaged in relation to incremental rises of 0.067 kPa (0.5 mmHg) $\text{PET,CO}_2$. Both $\dot{V}_E$ and $f$ were then plotted against the corresponding values of $\text{PET,CO}_2$, and typical examples are shown in Fig. 3(a) and Fig. 4(a) respectively. For each subject, linear slopes for $\dot{V}_E/\text{PET,CO}_2$ and $f/\text{PET,CO}_2$ were drawn visually from the points of rise of $\dot{V}_E$ and $f$ respectively to the points of their peak responses. The initial apparent 'dog leg' of the response curve was ignored. Detailed results for each subject have been deposited as *Clinical Science and Molecular Medicine* Tables 76/2 and 76/3 with the Librarian, the Royal Society of Medicine, and the group mean data are shown in Fig. 3(b) and Fig. 4(b). All individual values of the $\dot{V}_E/\text{PET,CO}_2$ slope were increased with airway anaesthesia; the increase in mean slope was significant at $P<0.01$. The mean value of $\dot{V}_E$ at the peak of the response was significantly increased by airway anaesthesia ($0.05>P>0.02$) and this peak $\dot{V}_E$ occurred at a significantly lower mean value of $\text{PET,CO}_2$ ($P<0.01$). In eight of the nine studies, the slope of the $f/\text{PET,CO}_2$ relation was greater during anaesthesia; the increase in mean slope was 'significant' ($0.05>P>0.02$). In seven of the nine studies, $V_T$ at any given $\text{PET,CO}_2$ was greater during anaesthesia. The relationship between $\dot{V}_E$ and $V_T$ was unchanged with airway anaesthesia in six out of the nine studies; in two subjects $V_T$ was slightly greater at any given $\dot{V}_E$, and in one it was lower.

![Fig. 5. Ventilatory response to CO₂ rebreathing before (○) and after (▲) inhalation of aerosols of either saline or phosphate buffer (pH 5.4). Ventilation ($\dot{V}_E$) is plotted against end-tidal CO₂. (a) Response of one individual before and after inhaling phosphate buffer; (b) response obtained by averaging linear slopes drawn visually between points of rise and points of peak response for each of five studies. Horizontal and vertical bars represent ± 1 se. Note that a non-anaesthetic aerosol has no effect on the ventilatory response to CO₂.](image-url)
Effect of anaesthesia of airway

Fig. 6. Subject S.J. Ventilatory response to CO₂ inhalation before (○), just after intravenous infusion of bupivacaine (△) and again 10 min later (●). Note that the systemic blood concentrations of anaesthetic after infusion (1.0–1.3 pg/ml of plasma) do not influence the response.

$t_i$ and $t_e$ shortened together to produce an increase in respiratory frequency during rebreathing; this remained true with anaesthesia of the airway.

The effect of control aerosols on the response to rebreathing was studied in three subjects with saline aerosol and in two with phosphate buffer aerosol. The results are shown in Figs. 5(a) and 5(b). There were no significant changes in any parameter.

Intravenous infusions of bupivacaine in two subjects, resulting in plasma concentrations of 1–1.3 μg/ml, had no effect on the ventilatory response to rebreathing (Fig. 6). No abnormal subjective effects were reported by the subjects.

(b) Response to a single constant CO₂ concentration. Two subjects breathed O₂/CO₂ (95:5) for periods of 5–15 min. At any given time beyond the first 0.5 min of CO₂ inhalation, $V_e$ was greater after airway anaesthesia than before. In one subject (A.H., Fig. 7), the response was principally in $f$, and the $V_T$ response changed little. In the other subject (K.W.), the response was predominantly in $V_T$ with minimal changes in $f$. There was little difference between the rate of rise of $P_{ET,CO₂}$ during the initial 0.5–1 min; subsequently the steady-state value for $P_{ET,CO₂}$ was lower with airway anaesthesia owing to the increased $V_e$.

Bronchial response to irritation of the airway surface. Airway anaesthesia diminished the bronchoconstrictor response to the inhalation of an aerosol generated from a solution of citric acid (200 g/l), in the one subject studied (A.S., Fig. 8). The four control responses to the citric acid aerosol were established in separate days; a response was always present, but its magnitude varied. After airway anaesthesia an average $sG_{aw}$ 1.6 s⁻¹ kPa⁻¹ (0.16 s⁻¹ cmH₂O⁻¹) was recorded and this was comparable with the mean range of 1.6–1.8 s⁻¹ kPa⁻¹ (0.16–0.18 s⁻¹ cmH₂O⁻¹) found on other days in the absence of anaesthesia; the citric acid aerosol produced no apparent bronchoconstriction, and no associated raw sensation or cough resulted from its inhalation. The bronchoconstriction described in subject A.S. was absent, after intravenous injection of 2 mg of atropine, when the $sG_{aw}$ had risen to 3 s⁻¹ kPa⁻¹ (0.3 s⁻¹ cmH₂O⁻¹); the raw sensation was felt to be even more pronounced.

Hering-Breuer inflation reflex. In one of the five studies performed on patients under general anaesthesia the Hering-Breuer inflation reflex was unaffected by the experimental procedure (Fig. 9a). It was noted that the feed-tube of the Wright nebulizer was blocked, and the volume of bupivacaine solution was unaltered; this implied that no anaesthetic had been released as aerosol. This study provided a 'double-blind' control, as the patient had received the same pattern of lung inflations with a halothane/O₂ mixture alone.

In the remaining four studies, the administration of the bupivacaine aerosol impaired the inflation reflex to various degrees (Fig. 9b). There was no obvious change in the volume inflated for a given airway pressure as the result of the aerosol anaesthesia. Inhalation of bupivacaine aerosol had no effect on $f$ or $V_T$ (see the section on 'Resting ventilation', above).
Fig. 7. Subject A.H. Effect on ventilation of breathing O₂/CO₂ (95: 5) before (○) and after (●) the inhalation of an aerosol of bupivacaine. Tidal volume (V₅), frequency (f) and minute ventilation (Vₑ) are plotted against time. In the lower graph end-tidal CO₂ is also plotted against time, before (---) and after (----) aerosol. Arrows on the abscissa indicate points of onset and termination of CO₂ breathing. Note that the rate of rise of ventilation as well as ventilation in the 'apparent' steady state is greater after the anaesthetic than before. The response is predominantly due to an increase in frequency.

Fig. 8. Inhibitory effect of the inhalation of bupivacaine aerosol in one subject (A.S.) on the bronchoconstrictive response to five breaths of an aerosol of citric acid (200 g/l). Specific airway conductance is plotted against time. Points at zero time represent the average of at least five measurements before citric acid inhalation; subsequent points are individual measurements recorded at times from exposure to the 'irritant'. The response obtained after bupivacaine aerosol inhalation is represented by ●—●. The reproducibility of the response without anaesthesia, recorded on 4 different days, is represented by the remaining traces.
Effect of anaesthesia of airway

Discussion

The results demonstrate that in both dog and man it is possible reliably and safely to produce a reversible, short-term anaesthesia of the airway. The control experiments performed show that the results seen are due to the anaesthetic properties of the aerosol particles and not to their acidity, nor to the resultant plasma concentrations of the drug. The sense of pharyngeal irritation experienced during the initial administration of the aerosol in conscious mouth-breathing subjects was the only significant problem found.

The abolition of sensation and reflexes arising from the stimulation of receptors on the airway surface was the most constant feature of the block produced. Abolition of the responses to the inhalation of a citric acid aerosol proved to be a simple reproducible indication of airway surface anaesthesia.

The inability to block the inflation reflex completely in both dog and man when an endotracheal tube was used may perhaps be explained by the fact that there is a length of at least 7 cm around the balloon and the tip of the endotracheal tube, which would not receive any aerosol. This area, containing stretch receptors (Widdicombe, 1964), would be subject to
distorting lengthening forces during the testing of an inflation reflex. The isolated trachea of the dog at this site may be distended to elicit a reflex apnoeic response (Hammouda & Wilson, 1938). If this is the reason for failure to achieve a complete block of the inflation reflex, then inflation of the aerosol by mouth would be more likely to produce a more complete stretch receptor/fibre block. An alternative explanation may be that not all stretch receptor/fibres affected are completely blocked. Support for this view has been obtained in the cat by Jain (1975), using an exactly similar method of aerosol anaesthetic administration. The discharge from single pulmonary vagal stretch receptors was recorded. Of the thirty-five fibres studied, thirty-four were affected by the anaesthetic, but only twenty of these became completely silent; the rest were partially blocked.

The failure of bupivacaine aerosol to produce any consistent bronchodilatation in man suggested that parasympathetic bronchomotor fibres remained unaffected, i.e. there was no atropine-like effect. Additional evidence for the integrity of the parasympathetic bronchomotor pathway was obtained in the rabbit (Jain et al., 1973). Bitensky, Chambers, Chayen, Cross, Guz, Jain & Johnstone (1975) demonstrated with radioautographic techniques that an aerosol of tritiated bupivacaine does not penetrate the bronchial smooth muscle of the rabbit in a nerve-blocking concentration. Dain, Boushey & Gold (1974) agreed that a bupivacaine aerosol had no affect on bronchomotor fibres in the dog, but more recently these authors have reversed their opinion (Dain et al., 1975).

The studies on reflex bronchoconstriction were unsatisfactory in that reproducible responses to an airway irritant were in general unobtainable in normal subjects. The most reproducible bronchomotor responses to the inhalation of a citric acid aerosol have only been described in patients with asthma, none of whom had a normal airway resistance at the time of study (Simonsson et al., 1967). Nevertheless, the results obtained in the one subject, A.S., do suggest that the aerosol anaesthetic will block the afferent limb of a reflexly elicited bronchoconstriction. It should be noted that the irritant was being given to airways whose diameter had been unaffected by airway anaesthesia. The response was also blocked by prior administration of atropine and this suggests that the response seen was a reflexly elicited bronchoconstriction.

With airway anaesthesia, man, unlike dog or rabbit, showed no evidence of the typical slow deep breathing characteristic of vagotomY (Hering & Breuer, 1868). There is no direct proof, from the studies in conscious man, that the inflation reflex was blocked at the time when measurements were made of the resting breathing pattern after aerosol anaesthesia. Nevertheless, in subjects under general anaesthesia in whom the aerosol was given in the same way, such proof of impairment of the inflation reflex was obtained, and again slow breathing did not develop. These results in man, both conscious and under general anaesthesia, are entirely in keeping with previous findings, using vagus nerve block alone under general anaesthesia (Guz et al., 1964) and a combined glossopharyngeal and vagus nerve block in the conscious state (Guz, Noble, Widdicombe, Trenchard, Mushin & Makey, 1966a).

The results of the present study are surprising in that a selective sensory airway block in man, involving large myelinated stretch fibres as well as the small myelinated fibres from the intra-epithelial receptors, caused an exaggerated response to inhalation of CO₂. These observations apparently stand out in sharp contrast to those of Guz, Noble, Widdicombe, Trenchard & Mushin (1966b) and Guz & Widdicombe (1970). These authors have shown that after a bilateral block of the cranial nerves IX and X in man, the ventilatory response to inhaled CO₂ is reduced, primarily owing to a failure of f to rise; at any given $\dot{V}_E$, $V_T$ was greater and f was less. Important differences between the studies of Guz et al. and the present study are: (a) a complete block of all vagal myelinated fibres compared with only a partial block of such fibres in the present study; (b) a block of the J receptor/fibre system from the alveolar level (Paintal, 1970), compared with their presumably normal function in the present study; (c) block of cranial nerve IX compared with its normal function in the present study.

The ventilatory sensitivity to inhaled CO₂ has never been assessed in man with a complete bilateral vagal nerve block alone. However, a brief report on what was probably a partial block of both vagus nerves was made by Nakada, Nitta, Kawakami, Arakaki, Chiba, Egawa, Okaniwa & Ohkuda (1973), who used the direct application of procaine (5 g/l) to the cervical vagus. These authors documented the abolition to the inflation reflex, together with a striking enhancement of the ventilatory response to inhaled CO₂ due primarily to an exaggerated response of $V_T$; f did not change. Although details of
this study are incomplete, the findings nevertheless bear some resemblance to those of the present study.

Enhanced CO₂ sensitivity has also been reported in the dog whose cervical vagi were cooled (Phillipson, Fishman, Hickey & Nadel, 1973). These authors used conscious animals and cooled the vagi to 4–8°C to abolish the Hering–Breuer inflation reflex. At this time the ventilatory response to rebreathing a mixture of O₂/CO₂ (93:7) was enhanced, although it is not clear from the data whether there was an increase in slope as well as a shift to the left of the response curve. Further cooling of the vagi to 0–4°C resulted in a depression of the \( \dot{V}_E/\text{CO}_2 \) response curve with abolition of any increase in \( f \). These authors interpreted their experiments as indicating that stretch-receptor blockade removed an inhibitory influence from the \( \dot{V}_E/\text{CO}_2 \) response curve; blockade of smaller fibres at lower temperatures removed an excitatory influence on the response curve, and this was postulated as coming from airway surface receptors. In the present study in man, the airway surface receptors are blocked, but the stretch receptor/fibre system may be blocked to the same degree as that resulting from the vagal cooling in dogs to 4–8°C.

The concept of a vagally mediated inhibition to the \( \dot{V}_E/\text{CO}_2 \) response has been supported by studies in the cat (Borison & McCarthy, 1973; Purves & Ponte, 1975). The results of stimulating the larynx of the cat with CO₂ (Boushey & Richardson, 1973) have indicated a possible site from which an inhibitory influence on the \( \dot{V}_E/\text{CO}_2 \) response could arise.

The present study would appear to exclude a role for vagal airway receptors in the genesis of the sensation of breath-holding. The results are in sharp contrast to the marked prolongation of breath-holding time and abolition of the associated sensation after a bilateral block of cranial nerves IX and X under hyperoxic conditions (Guz et al., 1966a). These authors have made this type of observation with block of the vagus nerve alone in only one patient with lung infiltrations due to sarcoidosis. Although the maximum breath-holding time was not measured, the severe breath-holding sensation present in the chest within 3 s of the onset of breath-holding was totally abolished. It may be that any vagal drive to breathe that develops with breath-holding may originate from the type J receptors at alveolar level, and these receptors would not be affected by the aerosol of bupivacaine (Jain, 1975). Some of the drive to breathe originates from arterial chemoreceptors (Davidson, Whipp, Wasserman, Koyal & Lugliani, 1974).

This study describes the safety, duration, reversibility and nature of the airway anaesthesia that can be produced in the normal subject by inhaling an aerosol of bupivacaine under standard conditions. The results obtained resemble those found in the dog and are compatible with previous work in the cat and rabbit. A physiological background is therefore now available for the extension of these studies to man with diseased lungs. The method of anaesthesia appears to be free of hazard, at least in the normal subject. However, it is necessary to add a warning; two patients with bronchial asthma given bupivacaine aerosol at a time when their airway resistance was in the normal range developed severe asthma. This experience should preclude the use of such an aerosol in a physiological laboratory ill-equipped to deal with a clinical emergency.

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