MEASUREMENT OF THE SENSITIVITY OF UPPER AIRWAY REFLEXES

J. A. LANGTON, P. J. MURPHY, P. BARKER, A. KEY AND G. SMITH

SUMMARY
We describe a method for measurement of the sensitivity of upper airway reflexes. The technique is based upon delivery of an irritant chemical stimulus (dilute concentrations of ammonia vapour) to the upper airway. The technique is non-invasive and uses equipment which is portable, allowing measurements to be made in the clinical environment. (Br. J. Anaesth. 1993; 70: 126-130)

KEY WORDS

During induction of anaesthesia, heightened upper airway reflexes may lead to laryngospasm and airway obstruction, and during recovery from anaesthesia, rapid return of laryngeal and upper airway reflexes is important to protect the lower airway from aspiration. Laryngeal competence may be reduced after tracheal intubation [1-4] and may contribute to atelectasis and respiratory failure [2], especially in the elderly.

In early work, Hoglund and Michaelsson [5] attempted to measure the reactivity of the upper airway using small concentrations of ammonia vapour; 10 years later, Pontoppidan and Beecher [6] used a similar technique, but in both these studies, the concentration of ammonia vapour inhaled by the subject was not known accurately, and their results were variable and unreliable.

The aim of our study was to develop a method which would measure the sensitivity of upper airway reflexes reliably. We have modified a previously described method, and designed new portable equipment that allows measurements to be made in the clinical environment. The reliability of this technique was evaluated in normal volunteers.

SUBJECTS AND METHODS
Measurement system
Small concentrations of ammonia vapour were used as an irritant chemical stimulus. The subject’s upper airway was exposed to single intermittent breaths containing a small concentration of ammonia and, by measurement of the inspiratory flow pattern, a measure of the sensitivity of the subject’s upper airway reflexes was made. This was expressed as the threshold concentration, that is the smallest concentration of ammonia required to elicit a reflex response.

The system is shown diagrammatically in figure 1. A small concentration of ammonia vapour in air was produced in the ammonia limb of the breathing system by mixing air from an air pump flowing at 10 litre min⁻¹ with an adjustable flow of ammonia in nitrogen. The ammonia was delivered via a flow-meter from a calibrated cylinder containing 3% ammonia in nitrogen. The breathing system was calibrated to deliver accurate concentrations of ammonia vapour in the range 0-3500 p.p.m. The gas mixture flowed via a reservoir bag and clear plastic tubing around the system, as indicated in the figure by the arrows.

A pneumatic two-way balloon valve (V) allowed the subject to breathe room air via limb B: on switching the pneumatic valve, the subject took a single breath from the ammonia in air limb A. The two-way pneumatic balloon valve (Hans Rudolph) was controlled by the investigator and allowed the mixture to be directed to the subject for one breath, or to pass around the system to a specially constructed absorber without the subject being aware of the change. The balloon valve had a low compliance and an inflation time of 45-60 ms and deflation time of 60-75 ms.

The switching device, pneumotachograph head and mouthpiece were supported by an adjustable arm and held at a height convenient to the subject’s mouth with the subject in either the sitting or the supine position. A Gould pneumotachograph recorded inspiratory flow pattern onto a Gould 2022 chart recorder. The subject breathed through a close fitting mouthpiece, whilst wearing a noseclip, via one-way valves, and exhaled to atmosphere. Subjects wore dark goggles and listened to music via a pair of headphones so that they were unaware of the switching of the pneumatic valve.

The absorber contained crystals of sodium benzoate absorbed onto silica gel matrix. Ammonia...
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Absorber
Air pump
Pneumotachograph
One-way valve
Mouthpiece
Switching mechanism
2-litre reservoir bag

Fig. 1. Diagram of the equipment used to measure the sensitivity of upper airway reflexes. A = Ammonia-air limb; B = room air limb; V = balloon valve.

<table>
<thead>
<tr>
<th>Flowmeter setting</th>
<th>Measured flow (ml min⁻¹)</th>
<th>Final [NH₃] (p.p.m.)</th>
<th>Time to 95% final [NH₃] (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>73.1 (9.1)†</td>
<td>76 (12.3)‡</td>
<td>105</td>
</tr>
<tr>
<td>100</td>
<td>155.1 (1.02)</td>
<td>251 (12.6)</td>
<td>105</td>
</tr>
<tr>
<td>200</td>
<td>195.6 (0.85)</td>
<td>524 (33.7)</td>
<td>70</td>
</tr>
<tr>
<td>300</td>
<td>241.3 (0.54)</td>
<td>878 (17.8)</td>
<td>70</td>
</tr>
<tr>
<td>400</td>
<td>332.8 (0.88)</td>
<td>1140 (18.8)</td>
<td>70</td>
</tr>
<tr>
<td>500</td>
<td>427.1 (0.2)</td>
<td>1620 (61.5)</td>
<td>70</td>
</tr>
<tr>
<td>600</td>
<td>539.5 (2.95)</td>
<td>1970 (52.1)</td>
<td>70</td>
</tr>
<tr>
<td>700</td>
<td>635.5 (1.35)</td>
<td>2360 (60.4)</td>
<td>70</td>
</tr>
<tr>
<td>800</td>
<td>749.3 (0.63)</td>
<td>2790 (56.6)</td>
<td>70</td>
</tr>
<tr>
<td>900</td>
<td>863.7 (0.83)</td>
<td>3160 (142.2)</td>
<td>70</td>
</tr>
<tr>
<td>1000</td>
<td>964.6 (3.11)</td>
<td>3550 (170.2)</td>
<td>70</td>
</tr>
</tbody>
</table>

The time for the ammonia concentration to decrease to zero after the ammonia–nitrogen flow was stopped was less than 2 min at all flow rates.

**Ammonia-air.** Small concentrations of ammonia in air were measured using a Bruel and Kjaer multigas analyser type 1302. The measurement principle used in this gas analyser is based on the photo acoustic infra-red detection method. The selectivity of the multigas analyser is determined by the optical filters installed. By studying the absorption spectra of gases to be monitored, the relevant optical filter is installed and the analyser zero calibrated and then span calibrated using the known certified ammonia concentration.

The Bruel and Kjaer multigas analyser was calibrated by the manufacturers to measure ammonia to a concentration of 10 p.p.m. (0.001 %). The filter used was type 0976 with a centre wavelength 10.6 μm.

Initially, zero readings were obtained using a gas known not to contain ammonia vapour. The multigas analyser was then span calibrated using the certified gas concentration of 3.12 % ammonia–nitrogen supplied by the British Oxygen Company. The breathing system was then calibrated in several stages. Measurements of the concentration of ammonia–air were made in the ammonia–air limb opposite the pneumatic switching valve (V).

The time to produce a reading and the concentration of ammonia in the circuit were measured. The air flow was set at 10 litre min⁻¹, the ammonia–nitrogen flow was started at 50 ml min⁻¹ and record-
measurements made repeatedly on one day compared with measurements made on separate days.

The calibration was performed at flows of ammonia–nitrogen 50 and 100 ml min⁻¹ and then at increasing flow rates of ammonia–nitrogen in 100-ml increments up to a maximum of 1000 ml min⁻¹.

**Volunteer studies**

After obtaining Ethics Committee approval and informed written consent, we studied 10 healthy, non-smoking volunteers (8 male; ages 29–35 yr, weights 72–85 kg). The subjects were not taking any medication, were asked to refrain from drinking alcohol from noon the previous day, and were starved for 6 h before the study. We excluded subjects who were known asthmatics, and volunteers who were suffering from, or had a history of an upper respiratory tract infection within the previous 1 month.

Measurements of upper airway reactivity were made using the system described above.

The subject rested on a couch, wearing blackened goggles and listened to continuous loud music via a pair of headphones. A noseclip was applied and the subject was allowed to breathe through the mouthpiece via the one-way valve. The pneumatic switching valve was operated by the investigator at the end of expiration, so that the subject took one inspiratory breath from the ammonia limb.

The concentration of ammonia–air was increased in a stepwise manner in the ammonia limb (A), starting at the smallest concentration of ammonia. The threshold level of response to the ammonia stimulus was determined by the occurrence of a glottic stop, defined as a rapid decrease in the inspiratory flow, the flow decreasing by at least 25% of the peak inspiratory flow, followed by a swift recovery, the whole event lasting less than 0.5 s. An example of a glottic stop is shown in figure 2.

Each subject was investigated every 30 min for 4 h, and on six different days at least 1 week apart, in order to determine the reliability and repeatability of our measurements. In some subjects, we also presented the ammonia concentrations in a random order.

The deadspace of the equipment was calculated by measuring the volume of water required to fill it (48 ml).

RESULTS

**Volunteers**

The concentrations of ammonia vapour required to produce a glottic stop in each of the 10 volunteers are shown in table II.

The mean threshold of sensitivity of the upper airway was in the range of concentrations of ammonia 363–642 p.p.m. Statistical analysis (Mann-Whitney-U test) showed no significant differences between the measurements made repeatedly on one day compared with measurements made on separate days.

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**Table II. Threshold concentration of ammonia required to cause a glottic stop in 10 subjects (mean (median) (interquartile range))**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Different days (n = 6)</th>
<th>Same day (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>642 (524) [524-878]</td>
<td>465 (524) [376-524]</td>
</tr>
<tr>
<td>B</td>
<td>642 (524) [524-878]</td>
<td>499 (524) [524-674]</td>
</tr>
<tr>
<td>C</td>
<td>387 (387) [251-524]</td>
<td>363 (289) [251-524]</td>
</tr>
<tr>
<td>D</td>
<td>380 (387) [251-524]</td>
<td>471 (524) [327-524]</td>
</tr>
<tr>
<td>E</td>
<td>504 (524) [455-600]</td>
<td>435 (425) [327-524]</td>
</tr>
<tr>
<td>F</td>
<td>537 (524) [455-612]</td>
<td>544 (524) [524-674]</td>
</tr>
<tr>
<td>G</td>
<td>573 (524) [524-870]</td>
<td>440 (327) [327-524]</td>
</tr>
<tr>
<td>H</td>
<td>490 (524) [524-674]</td>
<td>536 (524) [524-600]</td>
</tr>
<tr>
<td>I</td>
<td>549 (524) [524-600]</td>
<td>536 (524) [524-543]</td>
</tr>
<tr>
<td>J</td>
<td>596 (524) [524-699]</td>
<td>627 (524) [524-678]</td>
</tr>
</tbody>
</table>

We found that, when the ammonia stimulus was presented in a random order rather than in an ascending challenge, the thresholds were the same, but the subjects found this to be considerably more unpleasant. Therefore this was performed in only five subjects.

DISCUSSION

Laryngeal reflexes are evoked by chemical or mechanical stimuli via receptors thought to be located in the hypopharynx and larynx [7]. Afferent pathways travel in both the parasympathetic and sympathetic nervous system and the motor response is temporary closure of the vocal cords [8]. In 1870, Kratschmer [9] demonstrated that mechanical and chemical irritation of the laryngeal and nasal mucosa caused reflex glottic closure and this reflex is now termed the Kratschmer reflex.

Hoglund and Michaelsson [5] described a technique for eliciting the Kratschmer reflex in humans. This involved injecting dilute ammonia vapour into the subject’s breathing system using multiple gas
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syringes, each filled with a different concentration of ammonia vapour. This chemical stimulus produced temporary closure of the glottis and inhibition of inspiration, sensed by a pneumograph around the subject’s waist. The concentration of ammonia required to produce this reflex was 800–1600 p.p.m. Pontoppidan and Beecher [6] investigated the effects of ageing on laryngeal reflexes, using a similar method. Ventilation was monitored with a wet spirometer, but their system contained a considerable deadspace (approximately 300 ml). The results indicated a decrease in protective laryngeal reflexes with increasing age. In 1971, Hinkle and Tantum [7] used a multiple syringe technique with a large deadspace to investigate the effects of codeine phosphate on laryngeal reflexes, and in 1980 Duckett and Hirsh [10] investigated glottic competence in a small number of postoperative patients, and found increased thresholds in all patients who had undergone tracheal intubation.

In 1987, Groves, Rees and Rosen [11] studied the effect of i.v. Diazemuls and lormetazepam on laryngeal reflexes in volunteers. After Diazemuls 15 mg i.v., the ammonia thresholds were increased by 200 % and remained increased for more than 4 h. All of the studies described above suffered from several problems leading to inaccuracy. The final concentration of ammonia reaching the subject’s larynx was not known accurately because of large deadspaces [6]. It may also have been affected by streaming or channelling of gas flow through the breathing system; the subjects may therefore have had warning of the imminent arrival of ammonia because the gas was not presented as a bolus. An early prototype of our equipment contained a large deadspace (300 ml), and that was associated with large scatter of results in individual subjects who volunteered that they could sense that the next breath contained ammonia. In further development of our equipment, we have reduced the deadspace volume to 48 ml, with marked improvement in the reproducibility of the results obtained.

The use of pre-prepared syringes and lack of an absorber in these early methods also made them unsuitable for use in the clinical environment.

The mechanism of the glottic stop is not known. Inhalation of irritant vapour stimulates chemoreceptors and rapidly adapting irritant receptors thought to be located in and around the entrance to the larynx. In work by Szereda-Przestaszewska and Widdicombe in cats [12], it was found that the response to insufflation of ammonia vapour across the larynx was virtually abolished by sectioning the superior laryngeal nerve. This provides some evidence for an upper airway site for the afferent limb of this reflex. In earlier work, Widdicombe [13] had observed that mechanical or chemical irritation of the laryngeal mucosa caused laryngeal adduction, even if the stimulus was too weak to cause coughing. It is thought that chemical irritation of the upper airway causes rapid movement of the vocal cords across the inspiratory air flow [7], with interruption to inspiration. With greater inhaled concentrations of irritant vapour, a cough is elicited. A repeatable observation in our subjects was that the glottic stop response occurred at concentrations of ammonia vapour smaller than those required to elicit a cough response.

Previous workers [7], using x-rays to image the movements of the vocal cords, demonstrated that the vocal cords adduct across the inspiratory air flow during a glottic stop, and concluded that this adduction of the vocal cords was the cause of the decrease in the inspiratory air flow. Several of our volunteers spontaneously reported a feeling of sudden involuntary closure in the throat when a glottic stop occurred. Using an ultrasound technique to image the vocal cords [14], we have recorded the movements of the vocal cords during a glottic stop: the cords were seen to adduct rapidly and then abduct, coinciding with the appearance of a glottic stop on the inspiratory flow trace.

In summary, we have described a method of measuring the threshold response of the upper airway to an ammonia stimulus. The subjects found that the technique was acceptable and not unpleasant. Measurements in young, non-smoking volunteers showed a mean threshold of response at ammonia 363–642 p.p.m. There were no significant differences in the mean threshold values recorded on the same day or on separate days.

ACKNOWLEDGEMENTS

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REFERENCES

