Upper airway reflexes and Anaesthesia

A Thesis submitted to the University of Leicester for the degree of Doctor of Medicine.

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Contents

Summary

In this thesis I describe the importance of upper airway reflexes to anaesthesia and discuss the anatomy and physiology relating to normal upper airway function and protective airway reflexes.
The measurement of upper airway reflexes has not previously been fully investigated in humans and I describe the background to the measurement of the sensitivity of upper airway reflexes and outline a technique to measure the sensitivity of upper airway reflexes. Using this technique I have explored the changes in the sensitivity of upper airway reflexes that occur due to ageing and following administration of drugs. Smokers are known to have an increased incidence of coughing and laryngospasm on induction of anaesthesia. The effect of cigarette smoking and the changes in the sensitivity of upper airway reflexes which occur on stopping smoking were investigated. Benzodiazepines are commonly used for premedication and intravenously to produce sedation, the effects of these drugs on the sensitivity of upper airway reflexes was examined as well as the effect of the reversal agent flumazenil. Patients who have consumed ethyl alcohol may readily aspirate gastric contents with fatal consequences. The effect of ethyl alcohol on the sensitivity of upper airway reflexes is measured and the relevance to anaesthetists providing emergency anaesthesia is discussed. The inhalation of nitrous oxide and oxygen mixtures is frequently used for analgesic purposes in groups of patients known to have full stomachs and who are at risk from aspiration of gastric contents. I have studied the effects of nitrous oxide and oxygen mixtures on upper airway reflexes. The final chapter of this thesis uses a fibre-optic method of measuring the movements of the vocal cords on induction of anaesthesia, to examine the actions of two commonly used anaesthetic induction agents on the sensitivity of upper airway reflexes.

Publications

Parts of this thesis have already been presented to meetings and published as abstracts and as full papers as detailed below, these full papers are included in chapter 12.

Abstracts

1. **Langton J.A., Wilson I., Barker P., Smith G.**
Preliminary observations of vocal cord movements following induction of anaesthesia with thiopentone or propofol. **Br J Anaesth** 1990;65:4:582P-583P.

2. **Langton J.A., Murphy P., Barker P., Smith G.**
A portable method to assess upper airway reactivity. **Br J Anaesth** 1991;67;5:648P-649P.

3. **Murphy P., Langton J.A., Barker P., Smith G.**
An investigation of the effect of oral diazepam on upper airway reactivity.**Br J Anaesth** 1991;67;5:660P-661P.

4. **Erskine R., Murphy P., Langton J.A.**
The effect of age on the sensitivity of upper airway reflexes.**Br J Anaesth** 1992;69:5:538P-539P.

5. **Erskine R.J., Murphy P.J., Langton J.A.**
The effect of stopping smoking on upper airway reflexes. **Br J Anaesth** 1993;70:4:478P.

6. **Murphy P., Erskine R., Rabey P., Langton J.A.**
The effect of Entonox on the sensitivity of upper airway reflexes. **Obstetric Anaesthetists Association.** Sept 1992.

7. **Erskine R., Murphy P., Langton J.A.**
Measurement of the sensitivity of upper airway reflexes.
Royal Society of Medicine Breathing Club 1992.

8. **Erskine R., Murphy P., Langton J.A., Smith G.**
Upper airway reactivity in smokers and non-smokers.
Abstract 197, **World Congress of Anaesthesiologists**
The Hague June 1992.

Full Publications

1. **Barker P., Langton J.A., Wilson I.G., Smith G.**
Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol.
Br J Anaesth 1992;**69**:23-25.

2. **Langton J.A.,Murphy P.,Barker P., Key A.,Smith G.**
Measurement of the sensitivity of upper airway reflexes.
Br J Anaesth 1993;**70**:126-130.

3. **Murphy P., Langton J.A., Barker P., Smith G.**
The effect of oral diazepam on the sensitivity of upper airway reflexes.**Br J Anaesth** 1993;**70**:131-134.

4. **Erskine R.J., Murphy P.J., Langton J.A., Smith G.**
Effect of age on the sensitivity of upper airway reflexes.
Br J Anaesth 1993;**70**:574-575.

5. **Murphy P., Erskine R., Langton J.A.**
The effects of intravenous Diazemuls, midazolam and flumazenil on the sensitivity of upper airway reflexes. **Anaesthesia** 1993 (in press).

6. **Erskine R., Murphy P., Langton J.A.**
The effects of ethyl alcohol on the sensitivity of upper airway reflexes. **Alcohol and Alcoholism** 1993 (in press).

7. **Langton J.A., Erskine R., Murphy P.**
The effect of chronic cigarette smoking and stopping smoking, on the sensitivity of upper airway reflexes. **Br J Anaesth** (submitted).

8. **Langton J.A., Murphy P., Erskine R.**
The effects of entonox on the sensitivity of upper airway reflexes. (in preparation).

Declaration

This thesis was written and composed by myself and all books and papers quoted in this thesis were consulted by me personally. This work has not been submitted for a degree of another university.

This research was conducted while I was a lecturer (Honorary Senior Registrar) in the *University Department of Anaesthesia* at the Leicester Royal Infirmary between 1989 - 1992.

The idea for this research was my own and I was assisted technically by Mr Andrew Key, Medical Physics technician in the University Department of Anaesthesia.

Several junior anaesthetists were seconded by the Head of department to gain research experience under my supervision. These individuals are listed in the publications described on pages 6-8. In all instances they worked directly under my supervision and according to an experimental protocol which I designed and implemented.

Leicestershire District Ethics Committee approval was obtained for all this work, which was carried out at Leicester Royal Infirmary and at Leicester General Hospital.

Statistical analysis was performed using SPSS for Windows Release 5.0.1.

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List of abbreviations

ANOVA	Analysis of variance
ART	Auditory reaction time
ASA	American Society of Anesthesiologists classification
atm	atmospheric pressure
AUC	Area under the curve
CC	Closing capacity
Cl	Chloride
cm	centimetre
CNS	Central nervous system
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyheamoglobin
CXR	Chest x-ray
FEV1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
GTN	Glyceryl Trinitrate
Hb	Haemoglobin
Hct	Haematocrit
hr	hour
Kg	Kilogram
LOS	Lower oesophageal sphincter pressure
MANOVA	Multiple analysis of variance
mcg	microgram
MCV	Mean corpuscular volume
mg	milligram
min	minute
ml	millilitre
msec	millisecond
N_2O	Nitrous oxide
NH_3	Ammonia
NH_3TR	Threshold concentration of ammonia vapour
O_2	Oxygen
$P(A\text{-}a)O_2$	Alveolar arterial partial pressure difference of oxygen

$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
ppm	Parts per million
RBC	Red blood cell count
SaO_2	Haemoglobin saturation
SD	Standard deviation
sec	second
SEM	Standard error of the mean
$t_{1/2}$	Half life
TLC	Total lung capacity
UARS	Upper airway reflex sensitivity
VC	Vital capacity
WBC	White blood cell count
yr	year

CHAPTER 1

The importance of the larynx and upper airway reflexes to anaesthesia

(i) Upper airway reflexes and anaesthesia.

(ii) The consequences of laryngospasm in the peri-operative period.

(iii) Anaesthetic agents and their effects on the reactivity of the upper airway.

(iv) The function of the larynx in the peri-operative period.

(i) Upper airway reflexes and anaesthesia

Upper airway reflexes are of considerable importance to anaesthetists. Laryngospasm and coughing impair the smooth administration of anaesthesia and when severe may be life threatening and pose a serious danger to patients. After anaesthesia and surgery the larynx plays a primary role in protection of the lungs from aspiration of foreign material. Impairment of airway reflexes may lead to serious complications, including airway obstruction and hypoxaemia. Aspiration of foreign material into the respiratory tract predisposes to the development of post-operative chest infection, aspiration pneumonia and lung abcesses.

Maintenance of a clear unobstructed upper airway during anaesthesia and rapid return of normal laryngeal reflexes after the end of general anaesthesia form two of the most fundamental principles of anaesthetic practice. A clear airway allows safe ventilation and oxygenation of the patient, and a means by which the desired level of anaesthesia may be rapidly altered.

The sensitivity of the upper airway reflexes are important during induction of anaesthesia. Heightened upper airway reflexes at this time may lead to the development of life threatening laryngospasm.

After anaesthesia the rapid return of laryngeal reflexes are vital to allow protection of the lower airway from secretions, blood and gastric contents. Rex (1970) stated that laryngeal spasm is potentially the most frequent source of respiratory obstruction during general anaesthesia in man. Guedel (1951) concluded that the two mechanisms which contribute to the occurrence of laryngeal spasm during clinical anaesthesia are : first direct irritation of the vocal cords, occurring when there is a sudden increase in

concentration of irritant anaesthetic vapour in the face mask, and second traction on abdominal and pelvic viscera.

The literature contains many reports of the inhalation of irritant vapours producing laryngeal spasm, interruptions of respiratory rhythm, coughing or bronchospasm in both man and animals (Allen 1929, Comroe 1965, Harrison 1962, Rex 1966). Laryngeal spasm has been reported during general anaesthesia in all species of domestic animals, the condition occurs frequently in cats, particularly when they are subjected to high concentrations of ether or when there is excessive mucus, saliva or blood in contact with the larynx. Harrison (1962) proposed that anaesthetic agents sensitise the receptors, and this may explain why some anaesthetic vapours and intravenous agents appear to stimulate laryngospasm easily.

(ii) The consequences of laryngospasm in the peri-operative period.

Laryngospasm is a common and potentially dangerous complication of general anaesthesia. The complication is not uncommon and indeed is potentially life threatening (Olsson & Hallen 1984). Poor risk patients are especially vulnerable to hypoxia. The avoidance of factors that may contribute to laryngospasm is of prime importance. Laryngospasm may be defined as occlusion of the glottis by the action of the intrinsic laryngeal muscles. In general, laryngospasm is considered to be present when inflation of the lungs is hindered or made impossible by unwanted muscular action of the larynx. The laryngeal muscles are striated in nature. The most important muscles involved in the production of laryngospasm are the lateral cricoarytenoid and thyroarytenoid (adductors of the glottis) and the cricothyroid (a tensor of the vocal cords). During laryngeal spasm in man, either the true vocal cords alone or the true and false cords become apposed in the midline and close the glottis. Laryngospasm is essentially a protective reflex to prevent foreign material reaching the tracheobronchial tree and lungs.

In 1949 the Association of Anaesthetists of Great Britain and Ireland initiated a project encouraging the reporting of anaesthetic deaths. This study by Edwards, Morton and colleagues (1956) showed that 50 deaths of 1,000 were due to respiratory obstruction. In a more recent study (Olsson & Hallen 1984) investigated the incidence of laryngospasm during 156,064 general anaesthetics. In this study the risk of developing laryngeal spasm was quantified in everyday anaesthetic practice. They found that the overall incidence in all patient groups was 8.7 / 1000 patients, which indicates that a thorough knowledge of this complication is necessary in clinical practice. The incidence of laryngospasm was high in children aged

between 0 - 9 years. Other authors have emphasised the increased risk of laryngospasm which children possess during anaesthesia, Bergman (1972) postulated that laryngospasm may be one of the causative factors in the sudden infant death syndrome. They found a peak incidence in the age group 1-3 months. Sasaki (1979) studying neurophysiological development in puppies, found that laryngeal adductor hyperexcitability was present between 50 - 75 days of post-natal life. He concluded that this finding was of importance in the search for aetiological factors in the sudden infant death syndrome. Taylor and colleagues (1976) reported similar findings in studies of monkeys and baboons.

Olsson & Hallen (1984) reported that the incidence of laryngospasm in the age group 1-3 months was 27.6 / 1000, that is more than three times the incidence in the other age groups (8.6 / 1000). Pre - anaesthetic conditions which are thought to be risk factors for developing bronchospasm may also be associated with a high incidence of laryngospasm. The incidence was increased in patients with a history of asthma and respiratory tract infection. When children with a respiratory tract infection were anaesthetised, the incidence of laryngospasm was highest at 95.8 / 1000. The incidence of laryngospasm has been found to be high during inhalation anaesthesia 17.6 / 1000. This may be explained by the irritant effect of gases upon the airways. In a cross sectional study of complications of inhalation anaesthesia (Lew 1991) found that the overall incidence of laryngospasm was 12 / 1000 cases but that patients receiving isoflurane had a much higher incidence of 29 / 1000.

(iii) Anaesthetic agents and their effects on the reactivity of the upper airway.

Inhalation agents

Clinically the respiratory tract is hypersensitive to stimuli arising during light anaesthesia. Harrison (1962) studied the effects of different anaesthetic agents on the response to respiratory tract irritation. He concluded that the duration of hypersensitivity after a constant stimulus varied; in particular, the effects after anaesthesia using thiopentone or cyclopropane were marked with long periods of coughing, and laryngospasm. This study was conducted with only 5 patients in each group and it is difficult to see how the depth of anaesthesia was controlled following induction with the different agents. It was suggested that the afferent and efferent pathways from the larynx via the vagus were not depressed significantly by general anaesthesia.

The respiratory tract certainly seems to be hypersensitive to stimuli occurring during light anaesthesia, and this is borne out by the clinical experience of most anaesthetists. Harrison (1962) commented on the fact that there have not been any studies on the threshold response of the upper airway to stimulation during light anaesthesia. A further study by Harrison & Vanik (1963) showed that the administration of very large doses of atropine had little effect on laryngeal reflexes in cats.

In 1963 Harrison and colleagues (1963) studied the sensitivity of the respiratory tract during anaesthesia in the cat. The animals were sedated and ether was used as the irritant stimulus. They found little alteration in the threshold response to irritation during N_2O or cyclopropane anaesthesia. There was a progressive decrease in sensitivity during

halothane and trichloroethylene anaesthesia and they concluded that they could not find any evidence for the postulated increase in upper airway reactivity during light anaesthesia.

Rex (1966,1970) studied laryngospasm in the cat induced by volatile anaesthetic agents. With the object of defining the sites of stimulation of the upper respiratory tract which may contribute to laryngospasm. He used the decerebrate feline preparation for most of his studies although some cats were studied during chlorolase anaesthesia.
After decerebration, the activity of the diaphragm and laryngeal muscles was measured electrophysiologically. He found that inhalation of ether, halothane or methoxyflurane via a face mask produced laryngospasm. The concentrations used were quite high, notably ether 10 - 20%, halothane 6 - 8%. Direct spraying of the laryngeal structures with inhalation agents produced laryngospasm. Ether was a potent stimulus to laryngospasm leading to greater discharge from the cricothyroid and causing more disturbance of respiratory rhythm than saline. In these experiments halothane had even more pronounced effects.
When ether or halothane were administered directly into the distal trachea they caused laryngospasm and interruption of the regular rhythmic contractions of the diaphragm.
Methoxyflurane had no effect when administered directly into the trachea, although when given by face mask, it stimulated laryngospasm.
Ether was studied in greater detail than the two other agents. When a segment of trachea with its nerve and blood supply intact was isolated, the passage of ether vapour through this isolated segment stimulated laryngospasm and apnoea. In conclusion he discussed the possible causes for the increase in excitability, but he did not establish threshold concentrations for a response.

In more clinically based studies, Kinston (1986) compared the use of halothane with isoflurane in paediatric day case anaesthesia. Isoflurane has a low blood / gas solubility coefficient of 1.4, compared with 2.3 for halothane, and in theory this should be associated with more rapid induction of and recovery from anaesthesia. However, there was a shorter induction time with halothane and no difference in recovery times. In the isoflurane group, 25% of patients showed evidence of increased airway irritability, as defined by coughing, breath holding and laryngospasm. It was concluded that isoflurane had no advantages over halothane, in terms of inhalation induction of anaesthesia.

In a study of respiratory complications and hypoxic episodes during inhalation induction of anaesthesia with isoflurane in children Warde and colleagues (1991), found that inhalation of 4% isoflurane in O_2 from the start of induction produced significantly shorter induction times and less respiratory complications and a higher SaO_2 than isoflurane in 60% N_2O in oxygen or incrementally increasing the isoflurane concentration. They suggested that the reduction in airway complications is less a function of pungency but one of a shortening the second stage of anaesthesia.

In another recent study, Coleman and colleagues (1991) found that children who underwent inhalation induction of anaesthesia using isoflurane with the addition of CO_2 5%, resulted in a more rapid induction and a significantly reduced incidence of airway related problems.

Desflurane a new inhalation anaesthetic has been found by Hemelrijck and colleagues (1991) to be associated with a high incidence of upper airway irritation. This agent was noted to have airway irritant properties with breath holding, coughing and laryngospasm occurring in 39% of patients when desflurane was used for inhalation induction of anaesthesia.

In summary, upper airway reflexes are of great importance to anaesthetists, laryngospasm and coughing impair the smooth administration of anaesthesia and may be life threatening. After anaesthesia and surgery the larynx and upper airway reflexes play a crucial role in protecting the lungs from the aspiration of foreign material.

The incidence of laryngospasm in daily anaesthetic practice was identified by Olsson and Hallen (1984) as 8.7 / 1000. A much higher incidence being found in children, particularly infants. Children with a history of a recent upper respiratory tract infection were noted to have an especially high incidence of laryngospasm. Neurophysiological studies in dogs have identified a period of laryngeal adductor neuronal hyperexcitability occurring between 50 - 75 days of post natal life.

Differing anaesthetic agents have been found to be associated with widely different incidence of laryngospasm and upper airway complications. Lew and colleagues (1991) found that the incidence of laryngospasm was high during inhalation anaesthesia, with isoflurane having the highest incidence. The upper respiratory tract is hypersensitive to stimuli occurring during light anaesthesia. It has been hypothesised that some anaesthetic agents sensitise the airway, although there have not been any investigations to measure the threshold response of the upper airway during anaesthesia. Clinical studies have found that the irritant properties of isoflurane impede smooth inhalation induction with this agent, despite favourable physical characteristics which should produce a more rapid induction of anaesthesia.

The new agent desflurane has also been shown to possess airway irritant properties which may limit its application to anaesthetic practice, especially for inhalation induction of anaesthesia in children.

Intravenous agents

Thiopentone

Thiopentone was first administered for induction of anaesthesia on March 8th 1934 by Ralph M.Waters, at the University of Wisconsin in Madison U.S.A. In 1937 Burstein reported his experiments on the effect of some short acting barbiturates on the patency of the glottis. These experiments were conducted on normal cats using various barbituric acid derivatives including the thio-barbiturate, thiopentone (pentothal). In each case a 2% aqueous solution was injected intravenously at a constant rate of 1 mg sec^{-1}.

It was noticed that most of the animals would cough, sneeze or hiccup considerably during the course of anaesthesia. Inspection of the glottis showed adduction of the vocal cords, and in cases where there was no spontaneous coughing then inspection of the glottis showed hyperactive adducted vocal cords and lifting the epiglottis would elicit complete closure of the glottis.

Further work was performed to examine the nature of this reflex. Burstein (1938) found that the administration of atropine in large doses (3-5mg kg^{-1}), would lead to relaxation of the vocal cords and he concluded that closure of the glottis following intravenous administration of short acting barbiturates was probably mediated via the parasympathetic nervous system.

After the introduction of thiopentone into human anaesthetic practice several reports of laryngeal spasm as a complication of thiopentone anaesthesia began to appear (Samson 1947, Heard 1944, Ruth and colleagues 1939).

The paper by Ruth and colleagues (1939) entitled *" Pentothal sodium is its growing popularity justified "* comprised an audit of five years use of the drug and a review of the literature relating to more than 20,000 administrations of thiopentone.They highlighted the occurrence of temporary closure of the glottis and the hyperactive state of the laryngeal reflex after induction of anaesthesia with thiopentone.

In the article by Horita & Dille (1955), it was concluded that the laryngospasm and apparent hypersensitivity of the upper airway reported during the administration of thiopentone occurs early, when the reflex mechanism is hypersensitive.

The response of the respiratory tract to stimulation during anaesthesia with different anaesthetic agents was investigated by Harrison (1962). Marked differences were found in the duration of laryngeal spasm, coughing and breath holding with different agents. They concluded that their results supported the clinical impression that for a given stimulus the duration of response was longest with cyclopropane followed by thiopentone, and halothane least likely to cause upper airway problems. The reason for these differences is unknown. Possible mechanisms for the increase in sensitivity may be that peripheral afferent nerve endings are more sensitive to stimuli. It is noteworthy that there have not been any studies of the changes in threshold of the laryngeal reflexes during light anaesthesia. A second possible site proposed by Harrison to explain the increased sensitivity may be mediated by the pathway between the afferent vagal nucleus of the solitary tract and the efferent vagal nucleus ambiguus.

Propofol

Propofol is a relatively new intravenous induction agent, which has a novel chemical structure. Propofol (di-isopropyl phenol) was introduced into clinical practice in 1977. Since its introduction, there have been several reports of lack of excitatory upper airway effects associated with the use of the drug for induction of anaesthesia.

Kay and Stephenson (1980) compared althesin for induction of anaesthesia with propofol and noted that coughing occurred in 50% of the patients who received althesin but in only two of those who received propofol.

Mackenzie and Grant (1985) performed a comparative study of thiopentone, methohexitone and propofol for induction of anaesthesia in day cases. They found a surprisingly high percentage (35%) of patients in the thiopentone group had respiratory excitatory problems on induction of anaesthesia, in contrast induction of anaesthesia was smooth in all patients in the propofol group. They also made the point that a consistent feature of induction of anaesthesia with propofol was the toleration of an oral airway by the patient, which made possible a short period of manual ventilation via face mask.

It was noted by DeGrood (1985) that during induction of anaesthesia with propofol the vocal cords seemed to be abducted and tracheal intubation was possible using propofol alone. They also commented that in contrast, after thiopentone induction, the vocal cords in >50% of subjects seemed to be closed or only half open and that attempts to intubate the patients often led to further adduction of the vocal cords and coughing.

Keaveny and Knell (1988) described the intubation of the trachea of 20 patients using an induction dose of propofol without the use of muscle relaxants and found that propofol 2.5mg kg^{-1} allowed easy laryngoscopy and intubation in 19 out of 20 patients.

McKeating and colleagues (1988) studied 158 patients who were randomly allocated to receive an induction dose of thiopentone or propofol. They concluded that visualisation of the vocal cords by standard laryngoscopy was possible more often after propofol than thiopentone and pharyngeal and laryngeal reactivity seemed to be depressed more frequently following propofol.

In an interesting study by Szneke (1989) it was demonstrated that oral airways were tolerated more easily after induction with propofol compared with a standard thiopentone induction; manifestations of airway irritability such as coughing and laryngospasm were significantly less in the propofol group.

A recent study by Brown (1991) compared conditions for laryngeal mask insertion following either thiopentone or propofol. After laryngeal mask insertion there was a higher incidence of gagging and coughing with thiopentone than with propofol, and the authors concluded that propofol was more effective in providing satisfactory conditions for insertion of the laryngeal mask airway.

In summary there is evidence that thiopentone produces an increase in the reactivity of the upper airway leading to upper airway problems on induction of anaesthesia. The exact mechanism for this effect is not known. The intravenous induction agent propofol has been reported to be associated with a much lower incidence of upper airway problems on induction of anaesthesia. It is possible to intubate the trachea using propofol alone, oral airways are more readily tolerated and insertion of the laryngeal mask is easier when propofol is used for induction of

anaesthesia. This clinical evidence points to the fact that these two induction agents have a fundamentally different action on the sensitivity of the upper airway reflexes on induction of anaesthesia.

(iv) The function of the larynx in the peri-operative period.

Introduction

The mammalian larynx serves three principle functions, respiratory, protective and phonatory. The respiratory function of the larynx is manifest by rhythmic vocal cord abduction produced by contraction of the posterior cricoarytenoid muscles under control of the medullary inspiratory centre. The protective function of the larynx provides sphincteric closure of the glottis in order to prevent intrusion of foreign substances into the lower respiratory tract. This primary function of the larynx is based on a dominant and stable reflex producing glottic closure by contraction of all other intrinsic laryngeal muscles, but predominantly by rapid contraction of the thyroarytenoideus muscle in response to stimulation of the superior laryngeal nerve.

Laryngeal closure also plays a vital role in the production of an effective cough, permitting clearance of secretions from the lower respiratory passages. Associated with the protective function of the larynx is the production of laryngospasm. A relatively late development of laryngeal function is phonation, which is vital to communication.
The larynx and its function has an important place in anaesthetic practice. Apart from laryngoscopy and the daily procedure of tracheal intubation, the larynx is important in the post-operative period in protecting the lungs from aspiration of gastric contents.
In the period after surgery, patients may still be under the influence of opioids or volatile anaesthetic agents and therefore the risk of gastro-

oesophageal reflux is increased in comparison with healthy non-medicated subjects (Blitt and colleagues 1970).

Regurgitation and aspiration

Regurgitation of acid gastric contents and subsequent pulmonary aspiration remain a major cause of morbidity and mortality in clinical anaesthesia. Olsson & Hallen (1986) found an incidence of aspiration during the perioperative period of 4.7 / 10,000 anaesthetics. The patients most often affected were children and the elderly. In 83% of cases there was more than one pre-operative factor which correlated with increased risk of aspiration, including emergency operation, upper abdominal surgery and a history of delayed gastric emptying. In 29 cases there was a history indicating an increased risk of regurgitation for example, the presence of a nasogastric tube, oesophageal disease or pregnancy.

The main barrier preventing reflux of oesophageal contents into the pharynx is the upper oesophageal sphincter, formed by the cricopharyngeus muscle. The cricopharyngeus muscle is innervated by the vagus nerve and tone decreases during swallowing.

In disease states such as poliomyelitis or upper motor neurone disease, the muscle is relaxed if damage has occurred to the nucleus ambiguus, and consequently aspiration may be more likely.

Reflux from the stomach into the oesophagus is prevented by several mechanisms. The oblique angle at which the oesophagus enters the fundus of the stomach is thought to create a flap valve mechanism. The crura of the diaphragm may act as a pinchcock mechanism. It is generally accepted that the major factor in preventing gastrooesophageal reflux in man is the lower oesophageal sphincter.

Lower Oesophageal Sphincter

In man the lower oesophageal sphincter (LOS) is 2-5 cm long and moves upwards with inspiration and downwards with expiration. It maintains a resting pressure greater than gastric. The sphincter relaxes on swallowing to allow the passage of food into the stomach. The resting tone of the LOS is thought to be an intrinsic property of the muscle (Goyal and Rattan 1976). There are three layers of muscle in the oesophagus, an outer longitudinal layer, an inner circular and the muscularis mucosa. The sphincter characteristics are thought to be within the circular layer. The nerve supply to the sphincter is derived from the autonomic nervous system. The parasympathetic nerve supply is by filaments of the vagus nerve. The sympathetic supply arises from T6 - T10; the precise role of these fibres is not certain.

Factors affecting regurgitation

The main mechanism preventing regurgitation is the barrier pressure (the difference between gastric pressure and the pressure exerted by the lower oesophageal sphincter).

1. Benzodiazepines

A small significant decrease in barrier pressure persisted for 45-75 min after ingestion of 10 mg diazepam (Cotton and Smith 1981). They noted that there was considerable individual variation in the response to diazepam with respect to drowsiness and LOS tone. Rubin and colleagues (1982) demonstrated that the barrier pressure decreased significantly 7 min after intravenous injection of 10 mg diazepam. It would seem that

diazepam is associated with decreases in barrier pressure and this response may lead to an increased risk of regurgitation.

2. Inhalation agents

Sehhati and colleagues (1980) studied the effects of halothane and enflurane in combination with nitrous oxide on the LOS. Inhalation of 66% nitrous oxide caused a highly significant decrease in barrier pressure after 2 min. When halothane or enflurane 2% was added to the inspired gas mixture, there was a further decrease in barrier pressure.

3. Atropine

Because of pharmacokinetic factors, intramuscular atropine in a standard clinical dose has relatively little effect on the LOS (Fell & Cotton 1982); but it was found to largely antagonise the effects of subsequent doses of metoclopramide, a drug known to increase the barrier pressure. Intravenous atropine 0.6mg has been shown to consistently decrease lower oesophageal sphincter pressure in man and animals (Skinner and Camp 1968, Laitinen 1978). The effects of atropine are evident 3 min after intravenous injection with a significant decrease in barrier pressure after 5 min. Thereafter, this decrease is sustained for at least 40 min (Cotton and Smith 1981).

4. Beta-blockers

Vater and colleagues (1982) studied the effects of beta-blockers on LOS pressures. It was found that these drugs caused an elevation of the barrier pressure.

5. Pregnancy

The generally held view is that the altered hormone pattern during pregnancy causes a decrease in the tone of the LOS permitting reflux to occur more readily. Van Theil and Wald (1981) performed serial measurements of LOS pressure and gastric secretions throughout pregnancy. It was found that LOS pressure reached the lowest point at 36 weeks gestation. It was suggested that the increase in plasma progesterone concentrations alone or in combination with oestrogens are responsible for these changes.

Aspiration

The classic study by Mendelson (1946) showed the importance of acidity in determining the extent of pulmonary damage when he described the clinical course of 66 patients who had aspirated during labour and delivery. He showed that instillation of acid gastric juice into the lungs of rabbits produced a reaction similar to that following 0.1 N HCl. However if the pH of the gastric juice was neutralised, there was only minimal reaction. Teabeault (1952) extended this work and showed that in the rabbit the critical pH below which severe lung damage occurred was 2.4. Bannister & Sattilaro (1962) suggested a critical pH of 2.5 for humans. In addition to pH, the volume of the gastric aspirate is also critical for the production of widespread pulmonary damage, this has not been determined directly in man but in the monkey the critical volume was found to be 0.4 ml kg^{-1} this corresponds to a value of 25 ml in the human adult (Roberts & Shirley 1974).

There have been many studies of the volume and pH of gastric contents present in patients in various circumstances.

In pregnant patients at term presenting for emergency surgery, it was shown that 55% had a gastric volume greater than 40 ml and that 42.3 % of these patients possessed a gastric pH lower than 2.5 (Taylor & Pryse-Davies 1966). 46% of patients presenting for general surgical emergencies, had a gastric pH below 2.5 and 32% had gastric volumes greater than 40 ml (Hester & Heath 1977).

In patients prepared for elective surgery, 53% had a gastric pH of less than 2.5 and 31% of patients had total gastric volumes greater than 40 ml (Hester & Heath 1977). In outpatients the mean gastric volume was 70 ml, with a mean pH of 1.8 and 25% of the patients studied had gastric volumes in excess of 90 ml (Ong & Palahniuk 1978). In obese patients, 88% had gastric volumes greater than 25 ml and 86% had a gastric pH below 2.5 (Vaughan & Bauer 1975).

In unpremedicated children, only 7.4% of patients had a gastric pH greater than 2.5 and the mean gastric volume of 0.6 ml kg^{-1} (Salem & Wong 1976). These findings were confirmed by Goudsouzian and colleagues (1981) who demonstrated that 100% of children presenting for elective surgery had a gastric juice pH below 2.5 and that 64% of these had gastric volumes in excess of 0.4 ml Kg^{-1}.

Incidence of aspiration

Cotton and Smith (1984) stated that regurgitation and subsequent aspiration of gastric contents remain a major cause of morbidity and mortality in clinical anaesthesia. Morgan (1980) observed that pulmonary aspiration of gastric contents remains one of the commonest causes of death directly related to anaesthesia. Hunter & Moir (1983), commenting on the Report on Confidential Enquiries into Maternal Deaths in England and Wales 1976-78, called attention to the fact that 23 deaths of 40 were caused by inhalation of gastric contents. Lunn and colleagues (1983) noted that 6 of 112 deaths that were partly or entirely due to anaesthesia were attributable to aspiration of vomit.

However there have been few reports on deaths due to aspiration in which the total number of anaesthetics was indicated. Data on the incidence of

non-fatal aspiration during anaesthesia are scarce, but in general the incidence of aspiration is low.

The incidence of aspiration during anaesthesia has been studied experimentally. Using an indicator dye technique, Culver and colleagues (1951) found that 16.3% of 300 unselected patients aspirated during general surgery. Blitt and colleagues (1970) studied 900 randomly selected, non emergency cases involving more modern techniques of anaesthesia and found an incidence of aspiration of 0.7%. These studies showed that gastric fluid could be regurgitated and traced in the trachea but this is not synonymous with inhalation of gastric contents during anaesthesia.

Mortality associated with vomiting and regurgitation

Regurgitation and subsequent aspiration of gastric contents remain a major cause of morbidity and mortality in clinical anaesthesia (Cotton & Smith 1984). The overall mortality from aspiration has changed little over the past 20 years in the UK (Edwards 1956, Lunn & Mushin 1982). In every published study on deaths attributable to anaesthesia there have been reports of fatalities resulting from vomiting or regurgitation and subsequent aspiration (Harrison 1978, Hovi-Viander 1980). The occurrence of regurgitation has been estimated at 14 - 26% using older techniques of anaesthesia with ether, cyclopropane and uncuffed tracheal tubes (Culver and colleagues 1951, Berson & Adriani 1954); of these 7-16% had evidence of aspiration as judged by the appearance of tracer dye in the trachea at laryngoscopy and bronchoscopy. Using modern anaesthetic techniques and the same methodology it was shown (Blitt & Gutman 1970) that the frequency of regurgitation had decreased to 7.8% and of this number 8.6% of patients had aspirated. Olsson (1986) showed that the

incidence of aspiration was 1:2000 anaesthetics, whilst the mortality due to aspiration occurring during anaesthesia was 5%.

Laryngeal function in the peri-operative period

Tomlin & Howarth (1968) studied postoperative atelectasis and laryngeal competence. They investigated 56 patients recovering from body surface surgery under general anaesthesia. The anaesthetic techniques and premedication were not standardised. The patients had a chest x-ray pre-operatively, then when the patient had apparently recovered fully from the effects of general anaesthesia (within 2hr of the conclusion of surgery), they were asked to swallow 10ml of contrast medium. Of the 56 patients studied, 12 developed post-operative atelectasis radiologically and 6 of these also inhaled small quantities of the contrast medium. No other patients inhaled. This study failed to identify any particular anaesthetic technique with post-operative inhalation of dye, but does indicate that in at least half the patients who developed x-ray changes in the chest in the post-operative period this complication was probably caused by an incompetent larynx.

It is well known that during anaesthesia the larynx is incompetent and coloured dye placed on the back of the tongue may be readily aspirated into the trachea. However the data of Tomlin and Howarth (1968) showed that the disturbance of laryngeal reflexes may persist for at least 2hr following anaesthesia. Healy and Vickers (1971) studied the incidence of aspiration of dye placed on the back of the tongue in patients under going sedation for dental procedures using 0.2mg kg^{-1} diazepam. They found that out of 19 patients studied 8 aspirated at the time of maximal sedation following intravenous diazepam. They concluded that although patients

sedated in this way are apparently conscious and able to communicate verbally, it is clear that for a period of 5-10 min they are at risk from aspiration of foreign material into the trachea during the act of swallowing. In an interesting study, Siedlecki & Borowicz (1974), examined 30 adult patients after they had fully regained consciousness following anaesthesia and tracheal intubation. The subjects were asked to swallow 20ml of contrast medium, and chest x-rays were taken for signs of aspiration. The results showed that in the group of patients whose trachea was intubated without the use of topical lignocaine the frequency of aspiration of dye into the trachea was 25%, and in patients whose trachea was intubated with the aid of topical lignocaine that the incidence of aspiration was 30%. In operations lasting about 100 min they found that the incidence of aspiration was 66%. Taylor and Towey (1971) found that the competence of the laryngeal closure reflex was depressed in patients receiving ketamine anaesthesia.

Aspiration of gastric contents is a recognised hazard in post-operative patients whose laryngeal reflexes are inhibited by sedatives or residual effects of general anaesthetic agents. Burgess and colleagues (1979) observed that there was relatively little data on laryngeal function in post-operative patients who are awake and alert. Gardner (1958) reported aspiration of radio opaque dye given orally by 10 of 94 alert ambulatory patients 2 - 4 days post operatively. Tomlin & Howarth (1968), challenged awake patients with dye 2hr or more after anaesthesia of 60 min duration and found aspiration in 9 of 41 patients whose trachea had been intubated. Using a similar dye test 15 min after tracheal extubation Davis & Cullen (1974), found that aspiration of dye occurred in 9 of 26 alert post-operative patients whose trachea had been intubated for 12 -18 hr. Burgess & Cooper (1979), studied patients who had undergone tracheal intubation

for 8 - 28 hr after cardiac surgical procedures. Following a standard anaesthetic and post-operative sedation regimen the patient's trachea was extubated and the patient was then asked to swallow 10ml of radio opaque dye. Patients in group 1 were given the dye immediately after tracheal extubation, in group 2, 4hr following extubation and in group 3, 8 hr following extubation. A chest x-ray was taken within 30 min of dye administration. The results showed that 33% of patients in group 1 aspirated dye, none of these patients coughed upon swallowing the dye, 20% aspirated in group 2, and 5% in group 3. The potential for aspiration upon attempted swallowing immediately after anaesthesia has been documented by others. In previous studies, the incompetence of the larynx may have been due to laryngeal depression by residual inhalation anaesthetic rather than due to the tracheal tube. Davis & Cullen (1974), studied patients who had the trachea extubated 12 - 18 hr after anaesthesia and clinically had recovered completely from any effect of the inhalation agent. They sought to determine if a tracheal tube had a detrimental effect on laryngeal function and they reported aspiration of dye in 35% of alert patients when challenged within 15 min of tracheal extubation. In the study by Burgess & Cooper (1979) all the patients had recovered from the effects of the inhalation anaesthetic which had been discontinued a mean of 11.8hr previously. Aspiration decreased as the time elapsed after tracheal extubation increased. Burgess & Cooper (1979), did not find that an increased period of tracheal intubation led to an increased risk of aspiration. This was thought to be due to the fact that the detrimental effects of intubation occur during the first few hrs, or that it occurs in susceptible patients. The mechanism of laryngeal incompetence after tracheal extubation may be due to either sensory or mechanical impairment of laryngeal function. The absence of any cough in all the patients who aspirated dye is evidence that the sensory ability of the larynx

is impaired. Evidence in support of this theory was provided by Aucott & Prinsley (1989), who reported two patients who had undergone emergency tracheal intubation and were later found to have signs of supraglottic anaesthesia, thought to be due to neuropraxia of the internal branch of the superior laryngeal nerve, presumably as a result of trauma related to intubation.

Laryngeal closure and coughing is a complex muscular event. Coughing consists of an initial laryngeal opening, followed by closure of both the glottis and supraglottic structures, the structures then open and air is forced through the larynx, causing the epiglottis to move (Von Leden & Isshiki 1965). When the laryngeal muscles are activated by stimulation of the internal branch of the superior laryngeal nerve this results in more forceful closure than when stimulation occurs via the recurrent laryngeal nerve (Murakami & Kirchner 1972).

Duckett and Hirsh (1980), studied 23 patients in the post-operative period using an ammonia stimulus technique. Measurements were made before surgery and repeated post-operatively in 11 patients 24 hr after surgery. They concluded that tracheal intubation was responsible for a significant reduction in the competence of the glottic reflex.

In summary, upper airway reflexes play an integral role in clinical anaesthetic practice and an understanding of the factors which influence the sensitivity of upper airway reflexes will lead to an improvement in the anaesthetic management of patients. The sensitivity of upper airway reflexes are important during induction of anaesthesia, with heightened upper airway reflexes leading to the development of laryngospasm. Following anaesthesia the rapid return of laryngeal reflexes is vital to protect the lower airway from aspiration. Investigation of the function of the larynx in the post-operative period has demonstrated that laryngeal function is impaired for a number of hours after tracheal intubation which may predispose patients to aspiration of gastric contents. The cause of this impairment of laryngeal function has not been fully elucidated, and further work is required to examine the factors which impair upper airway reflexes and laryngeal function in the post-operative period.

Anaesthetic agents have been shown to have different actions on the upper airway. Some of the newer inhalation agents are particularly irritant. Intravenous agents seem to have different actions, thiopentone has been reported to cause upper airway problems on induction of anaesthesia which are thought to be due to heightening of upper airway reflexes. In contrast propofol is notable due to the lack of upper airway problems reported after its use for induction of anaesthesia. There have been reports of the use of propofol alone for tracheal intubation (McKeating and colleagues 1988). Oral airways are more easily tolerated after propofol is used for induction of anaesthesia, and conditions for the insertion of a laryngeal mask are more favourable after propofol (Brown 1991).

CHAPTER 2

Upper airway structure and function

i) Anatomy of the upper airway

Mouth

The mouth extends from the lips anteriorly to the palatoglossal folds posteriorly. The anterior two-thirds of the tongue forms the floor of the mouth, and the hard and soft palates constitute its roof. The tongue is the largest organ in the mouth, is composed of intrinsic and extrinsic muscles and fills most of the oral cavity.

The tongue plays a major role in maintaining an open airway. The extrinsic muscles of the tongue originate from structures above and below it and insert into it. Contraction of the extrinsic muscles of the tongue is important during deglutation, swallowing and speech as well as for maintenance of an open airway. The mucous membrane of the tongue connects the tongue laterally to the pharyngeal wall and posteriorly to the epiglottis through the glossoepiglottic folds.

The nose

The nose extends from its external openings (external nares), through the nasal cavity and its posterior openings (chonae), into the nasopharynx. The hard palate consists the floor of the nose and separates the nasal cavity from the mouth. The nasal cavity is divided into two chambers by the nasal septum, which constitutes their medial wall. The lateral wall has three boney projections termed turbinates or conchae. The inferior turbinate is the longest and broadest; the superior turbinate is the smallest. The area below each turbinate is called a meatus, into which the paranasal sinus open. A single paranasal sinus opening exists in each of the superior and inferior meati; the middle meatus receives all other paranasal sinus openings.

The sensory nerve supply of the nasal mucosa is derived from the first (ophthalmic) and second (maxillary) divisions of the trigeminal nerve. The sympathetic innervation is derived from the superior cervical ganglion. Any increase in sympathetic activity results in vascular spasm and shrinkage of the mucous membrane. General anaesthesia depresses nervous system activity, including sympathetic activity, therefore causing vasodilatation and engorgement of the mucous membrane. This increases the incidence of nasal bleeding during nasotracheal intubation.

The pharynx

The pharynx is 12 - 15 cm long and extends from the base of the skull to the level of the cricoid cartilage, where it becomes continuous with the oesophagus. The pharyngeal muscles include the superior, middle and inferior constrictors. During swallowing, these muscles contract and push the bolus of food downward. The lower part of the inferior constrictor muscle originates from the cricoid cartilage and is called cricopharyngeus muscle. This acts as a sphincter at the entrance of the oesophagus. The cricopharyngeus muscle is considered to be the last barrier to regurgitation of gastric contents; however with the onset of anaesthesia the muscle loses its tone, and any fluid in the oesophagus may enter the oropharynx, increasing the chance of aspiration. The pharynx communicates anteriorly with the nasal cavity (nasopharynx) the oral cavity (oropharynx), and the larynx (hypopharynx or laryngopharynx).

Nasopharynx

The nasopharynx is bounded superiorly by the base of the skull, inferiorly by the soft palate, posteriorly by the body of the 1st cervical vertebra, and anteriorly by the nasal chonae and nasal septum. The opening of the Eustachian tube lies in the lateral wall of the nasopharynx below the inferior turbinate. The normal soft tissue prominence surrounding the entrance of the Eustachian tube is termed the torus tubarius. Lateral to the torus tubarius is the fossa of Rosenmuller or pharyngeal recess. The adenoids or nasopharyngeal tonsils lie in the mucous membrane of the posterior wall of the nasopharynx.

Oropharynx

The oropharynx is bounded superiorly by the soft palate, anteriorly by the posterior third of the tongue, inferiorly by the epiglottis, and posteriorly by the bodies of the 2nd and 3rd cervical vertebrae. On the lateral wall of the oropharynx is the tonsillar fossa with its anterior (palatoglossal) and posterior (palatopharyngeal) folds. The oropharyngeal walls are not rigid and are subject to collapse if a negative transmural pressure develops.

Hypopharynx

The hypopharynx lies at the level of the 4th to the 6th cervical vertebrae, between the superior border of the epiglottis and the inferior border of the cricoid cartilage. The pyriform fossae or sinuses constitute the lowest part of the hypopharynx and lie lateral to the larynx. The sensory innervation of the mucous membrane of the nasopharynx is derived from the maxillary nerve and that of the oropharynx from the glossopharyngeal nerve. The mucous membrane near the entrance of the larynx is innervated by the internal branch of the vagus nerve.

The Larynx

The larynx is an organ of phonation, an air passage and a sphincteric mechanism. It extends from the root of the tongue to the trachea. It is covered anteriorly by the skin, the fasciae and the depressor muscles of the hyoid bone. Above it opens into the laryngeal part of the pharynx, and below it is continuous with the trachea. In the adult male it is situated opposite the third, fourth, fifth and sixth cervical vertebrae. It occupies a higher position in the child and adult female.

The average measurements in the European adult are:

	Males	Females
Length	44mm	36mm
Transverse diameter	43mm	41mm
A-P diameter	36mm	26mm

The framework of the larynx is formed by cartilages which are connected by ligaments and membranes. The internal lining is a mucous membrane that is continuous above and behind with that of the pharynx and below with that of the trachea.

Cartilages of the Larynx

The larynx is composed of several cartilages, the thyroid, cricoid and epiglottis in addition the paired arytenoid, cuneiform and corniculate cartilages.

The thyroid cartilage is the largest cartilage of the larynx, it consists of two laminae the anterior borders of which are fused to form a subcutaneous projection the laryngeal prominence. Above, the laminae are separated by a V-shaped notch; this is termed the superior thyroid notch. The anterior border is fused with that of the opposite lamina forming an angle of about 90° in men and about 120° in women. In men the greater projection of the laryngeal prominence, the greater length of the vocal fold and the resultant deeper pitch of the voice are all associated with the smaller size of the thyroid angle.

The cricoid cartilage is smaller but thicker and stronger than the thyroid cartilage. It has the shape of a signet ring and comprises a posterior lamina and a narrow anterior arch. The lamina of the cricoid cartilage is deep and broad, it measures vertically between 2-3cm, the arch is narrow anteriorly measuring vertically 5-7mm. The inferior border of the cricoid cartilage is horizontal and connected with the highest ring of the trachea by the cricotracheal ligament. The superior border runs obliquely upwards and backwards. It gives attachment to the cricothyroid ligament.

The arytenoid cartilages, these are pyramidal and have three surfaces, a base and an apex. The anterior angle or vocal process is pointed it projects horizontally forwards and is attached to the vocal ligament.

The cartilage of the epiglottis is a thin leaf-like lamella of elastic fibrocartilage, which projects obliquely backwards behind the tongue and body of the hyoid bone in front of the entrance to the larynx. The upper part of the anterior surface of the epiglottis is free, and covered with mucous membrane, which is reflected on to the pharyngeal part of the tongue and onto the lateral part of the pharynx.

Muscles of the Larynx

These may be classified into two groups, the extrinsic group and the intrinsic group.

The extrinsic muscles

The sternothyroid and thyrohyoid muscles act as a unit which has actions very similar to the sternohyoid muscle, except that the thyroid cartilage and hyoid bone are pulled down in addition.
Acting alone the thyrohyoid approximates the thyroid cartilage to the hyoid bone. This pulls the larynx up under the base of the tongue and brings the arytenoid cartilages under the cover of the epiglottis. It is therefore largely responsible for closing the laryngeal orifice and is of great importance in preventing food from entering the larynx during swallowing. Acting on its own the sternothyroid pulls the thyroid cartilage away from the hyoid bone so opening the laryngeal orifice. In forced inspiration the muscle contracts to help raise the sternum and to keep the laryngeal orifice fully open.
The pharyngeal constrictor muscles contract involuntarily during swallowing. This contraction takes place sequentially from above downward, and propels the bolus of food onward into the oesophagus.

The intrinsic muscles

These can be grouped functionally as follows:

The muscles of the laryngeal inlet :

The oblique arytenoids and their extension into the aryepiglottic folds, the aryepiglottic muscles. Contraction of these muscles brings the aryepiglottic folds together and pulls the arytenoid cartilages towards the epiglottis, thus helping to close the laryngeal inlet. Muscle fibres running from the thyroid cartilage into the epiglottis, the thyroeppigloticcus tend to widen the inlet of the larynx.

The muscle groups that open and close the glottis :

Adductors : The lateral cricoarytenoid muscles, attached to the muscular processes of the arytenoid cartilages, rotate the arytenoid cartilages medially, swing the vocal processes inward and approximate the vocal folds.

Abductors : The abductors of the vocal cords are the posterior cricoarytenoid muscles.

Tensors : The main tensors are the cricothyroid muscles

Relaxers : The main relaxers of the vocal cords are the two thyroarytenoid muscles.

The cavity of the Larynx

This extends from the laryngeal inlet to the level of the lower border of the cricoid cartilage, where it communicates with the cavity of the trachea. It is divided into three parts by an upper and lower pair of folds of mucous membrane which project from the sides of the cavity into its interior. The upper pair are the vestibular folds and the fissure between them is termed the rima vestibuli. The lower pair are concerned with the production of the voice, and are therefore termed the vocal folds, the fissure between them is called the rima glottidis.

The inlet of the larynx is the aperture through which the laryngeal cavity opens into the pharynx. The plane is directed backwards and upwards. The vestibule of the larynx is the part between the laryngeal inlet and the level of the vestibular folds; it is wide above and narrow below. Its anterior wall is much longer than its posterior wall. The vestibular folds are two thick, pink folds of mucous membrane each enclosing a narrow band of fibrous tissue. The vocal folds are two sharp white folds of mucous membrane which stretch from the middle of the angle of the thyroid cartilage to the vocal processes of the arytenoid cartilages. They are concerned with the production of the voice. The stratified squamous epithelium which covers the vocal folds is closely bound down to the underlying vocal ligament.

Laryngeal mucous membrane

The laryngeal mucous membrane is continuous above with that of the mouth and pharynx, below with that of the trachea. It is loosely attached to the anterior surface of the epiglottis, and to the adjacent tissues in the valleculae. It covers the aryepiglottic folds, which limit the inlet of the larynx. It lines the cavity of the larynx. On the anterior surface and the upper half of the posterior surface, of the epiglottis, the upper part of the aryepiglottic folds, and the vocal folds the epithelium of the mucous membrane is of the stratified squamous type. The remainder of the laryngeal mucous membrane is covered by ciliated columnar epithelium.

Upper airway physiology

Reflexes and receptors of the upper respiratory tract

Introduction

The literature on reflexes from the upper respiratory tract goes back more than 100 years, the paper by Kratschmer (1870), being one of the early foundations of this work.

On superficial inspection the reflex appears to be quite simple. Stimulation of irritant receptors in the upper respiratory tract causes a reflex motor response. The receptors of the respiratory tract include slowly adapting stretch receptors that are responsible for the Hering-Breuer reflex and rapidly adapting "irritant" receptors which can be activated by light touch, chemical stimuli and cold air (Widdicombe 1982). The afferent signals travel via the vagus nerve, the superior laryngeal branch carries afferents from the supra laryngeal area. These afferents pass to a central reflex site which is located in the medulla. Efferent impulses then travel via the vagus to the laryngeal muscles and by appropriate nerves to other respiratory muscles, diaphragm, intercostal and abdominal muscles.

A simple reflex consists of a nervous receptor, afferent pathway, central synapses, motor pathway, and effector organ. In the upper airway few stimuli even if limited to a single anatomical site, activate a single type of nervous receptor, the central integrations are tortuous and there may be many motor pathways. For upper respiratory tract reflexes it is probably correct to say that no nervous end organ has been identified histologically and convincingly linked to a nervous reflex. This is in striking contrast to the lower respiratory tract.

Little is known about the central nervous circuits involved in the reflexes from the upper respiratory tract again in sharp contrast to the lower airways. There have been many studies of the effects of electrical stimulation of nerves from the upper respiratory tract and of responses either in brain stem neurones or in the motor nerves to respiratory muscles. However little is known about the central nervous circuits involved in such reflexes again in contrast to the Hering-Breuer inflation reflex from the lungs. The studies on the electrical stimulation of the upper respiratory tract give important information about whether nerves such as the superior laryngeal nerve contain fibres that excite or inhibit the diaphragm, about reflex latencies and about those areas of the brain stem that can be affected by afferent inputs. The mapping of neuronal circuits of the respiratory complex in the brain stem is incomplete, even when considering the genesis of the respiratory rhythm, the way in which afferent pathways from the upper respiratory tract interact with this complex has not been defined.

Reflexes from the nose

Receptors and afferent nerves

The structure of nasal afferent end organs has not been elucidated in detail. There are a few descriptions of non-myelinated nerves under and within the mucosal epithelium. Cauna and Hinderer (1969), have shown that in humans the nerves stain for acetylcholinesterase and under the electron microscope show many mitochondria and some vesicles, an appearance consistent with an afferent role, which has been established by postganglionic degeneration experiments in the rat by Grote and colleagues (1975). Histological studies of the nasal mucosa have not identified any specialised receptor structures (Cauna 1982, Christensen 1934, Graziadei 1971). Hensel and colleagues (1974) found warm and cold receptors in the skin of the anterior nose in the cat and Zotterman (1959), has shown that the vibrissae and skin of the nares are a sensitive reflexogenic area. Recent studies have demonstrated the presence of substance P in nerves in and under the nasal epithelium (Lundblad 1984). These fibres are probably the same as those that stain for acetylcholinesterase and they can be destroyed by afferent denervation or by capsaicin (Uddman and colleagues 1983).

Reflexes from the nose have been extensively studied and have been reviewed by Angell-James and Daly (1969) and Widdicombe (1981). Nasal irritation more commonly causes apnoea than the sneeze under experimental conditions. The apnoeic reflex is part of the complex diving response (Elsner and Gooden 1983). The physiological stimulus is water applied to the face or into the nose. Apnoea can be induced by odours or irritants and by water sensed as an irritant in the nose. The response has

been identified in all mammalian and terrestrial vertebrate species that have been studied including birds. Associated with the apnoea are cardiovascular changes and complete laryngeal closure occurs as part of the diving response (Banting and colleagues 1938) and is presumably beneficial in preventing water entering the lungs. The receptors that initiate the apnoeic reflex have not been identified but probably include the bare nerve endings in the nasal mucosa. The fact that the reflex can be caused by intranasal odours, irritants and cold water and even by facial wetting is strong evidence against a single modality of receptor. As similar responses can be obtained from the larynx it follows that many different inputs can activate the central nervous integrators of the diving response.

The same nasal irritant stimuli that mimic the diving response also close the larynx (Szereda-Przestaszewska & Widdicombe 1973) by the same nervous pathways.

A wide variety of chemical and mechanical stimuli applied to the nasal mucosa can cause sneezing. Chemical mediators such as histamine can also cause sneezing. Local application of capsaicin which depletes substance P containing nerves of their neuropeptide, can prevent the sneeze due to inhaled irritants, the nonmyelinated nerves containing substance P may be the receptors for the sneeze (Lundblad 1984).

Irritants and odours in the nose can cause sniffing, sniffing directs airflow towards the olfactory mucosa.

Positive pressure in the nose and nasopharynx can stimulate breathing in man and experimental animals and negative pressure has the opposite effect. Nasal irritation can cause bronchoconstriction or bronchodilatation by two afferent pathways. Nasal irritation also constricts the larynx transiently during the sneeze and also during the apnoea of the diving response. This is a sensitive and separate reflex if the stimuli are weak.

Pharynx and nasopharynx

Receptors and afferent nerves

The nasopharynx is the site of origin of powerful reflexes with motor actions including diaphragmatic contractions and hypertension. Nerve fibres that could be part of this reflex have been identified in the squamous epithelium of the nasopharynx. Nonmyelinated branches of nerve terminals occur under the squamous cell epithelium of the nasopharynx (Fillenz and Widdicombe 1971). Single fibre recordings show two types of receptor: rapidly adapting (Nail and colleagues 1969) and more slowly adapting receptors (Hwang and colleagues 1984), these more slowly adapting receptors respond to mainly mechanical stimuli, especially distension and collapse.

Recordings from single myelinated fibres in the glossopharyngeal nerve show that they can be localised to receptors in the nasopharyngeal epithelium sensitive to mechanical stimuli touch and distending pressures, but have been shown to be insensitive to chemical irritants (Nail and colleagues 1969).

Swallowing can be elicited from the posterior pharyngeal wall and surrounding areas by mechanical and chemical stimuli (Miller 1982). Swallowing is associated with an inhibition of breathing and closure of the larynx.

Reflexes from the larynx

Histologically nerve fibres thought to be sensory are found in almost all areas of the laryngeal mucosa and deeper structures.
Various types of nerve ending have been identified in and beneath the laryngeal epithelium (Fillenez & Widdicombe 1971, Korpas & Tomori 1979). Some are specialised structures resembling taste buds or small encapsulated terminals (Boggs & Bartlett 1982, Bradley & Cheal 1980, Feindel 1956, Koizumi 1953, Hatakeyama 1960, & Wyke & Kirchner 1978). The most frequent appearance is of free nerve endings in the mucosa and submucosa, with myelinated or non-myelinated fibres (Boggs & Bartlett 1982, Feindel 1956, Fillenz & Widdicombe 1971, Hatakeyama 1960, Wyke & Kirchner 1978, Van Michel 1963). The densest region for the free nerve plexus is in the posterior supraglottic region and this sends its fibres in the superior laryngeal nerve. The infraglottic area has fewer corpuscular endings and its afferent fibres pass into the recurrent laryngeal nerve. There are species differences in laryngeal receptor histology. There are relatively few electron-microscope studies of nervous end organs in the laryngeal region (Jeffery & Korpas 1978, Lewis & Prentice 1980).
Laryngeal afferent neurones with receptive fields in the epiglottis can be activated by a range of stimuli, but mechanical stimuli are the most effective, particularly light touch that moves over several receptive fields (Sweazey & Bradley 1989). The sensory units are thought to consist of free nerve endings that lie between the mucosal cells of the airway epithelium (Sato & Koyano 1987).

These fibres have been shown to respond accurately up to high frequencies (Davis & Nail 1987). Laryngeal receptors also respond to cooling and the presence of water (Jammes & Nail 1983, Sampson & Eyzaguirre 1964). The response to fluids is discriminatory, with isotonic sodium chloride showing little stimulation, but solutions which are iso-osmolar but free of chloride ions are potent stimuli for laryngeal mucosal receptors (Boggs & Bartlett 1982).

Collections of sensory receptors are found over the arytenoid cartilages and also on the laryngeal aspect of the epiglottis (Storey 1968). Afferent impulses from rapidly adapting receptors in structures such as the epiglottis are transmitted via the superior laryngeal nerve in small diameter myelinated fibres group III, A delta or B sensory fibres. The recurrent laryngeal nerve also carries sensory fibres (Hirose 1961), these are mainly from rapidly adapting receptors that are activated by light touch. These receptors are found in large numbers on the anterior and posterior extremities of the inferior surface of the vocal cords. Stimulation of these receptors results in vocal cord movement (Suzuki & Kirchner 1969). These afferent fibres in the laryngeal nerves project centrally to the nucleus tractus solitarius, particularly the caudal and posterior parts (Sweazney & Bradley 1989).

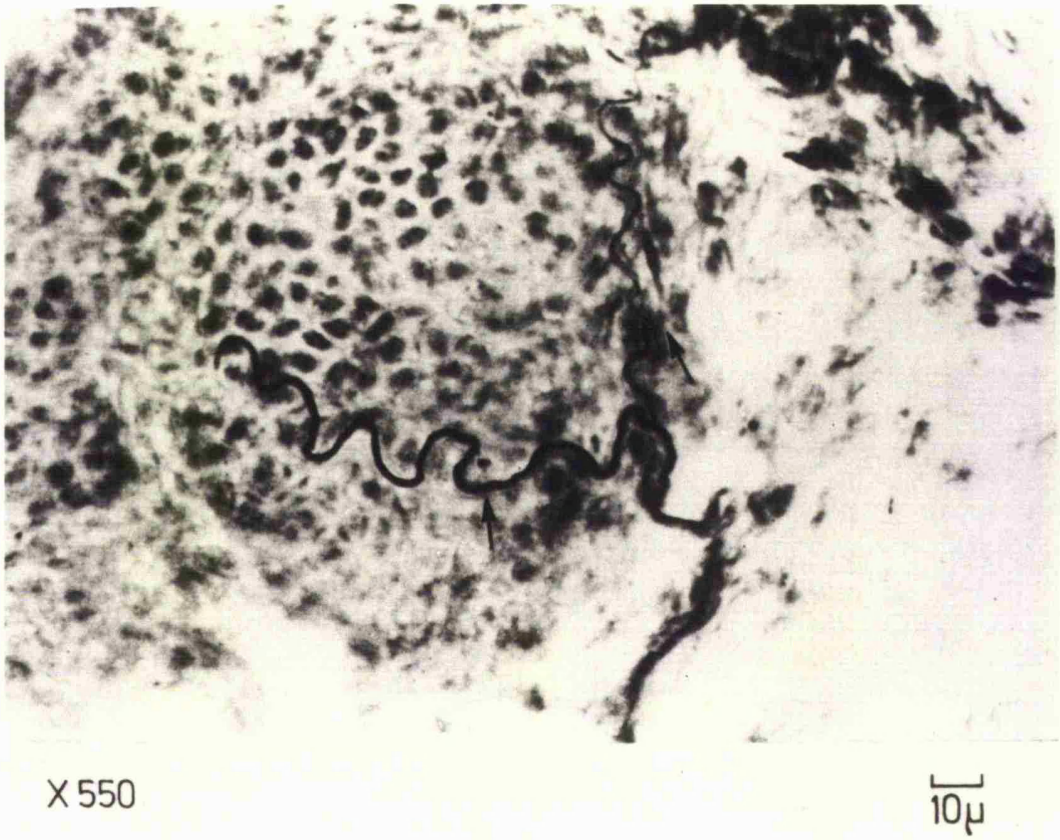


Figure 2.1 Frozen section, with Schofield's silver stain, of cat epipharyngeal region showing nerve fibres ramifying amongst epithelial cells. (Reproduced with permission from Fillenz and Widdicombe Handbook of Sensory Physiology, Berlin: Springer-Verlag 1971, vol 3; 81-112.)

Afferent fibre recordings

Early studies concerned with the response to mechanical stimulation identified two types of receptor. The slowly adapting receptor with tonic resting discharge, and the rapidly adapting receptors that are especially sensitive to chemical stimulants. Boushey & Richardson (1974) classified these as type 1 (rapidly adapting) and type 2 (slowly adapting). Other classifications have been produced, Storey (1968) identified five groups.

i) Proprioceptive located deep in laryngeal tissue and related to muscles and joints.
ii) Pressure receptors.
iii) Tactile receptors found very superficial in the mucosa.
iv) Water receptors, activated by distilled water.
v) Hybrid units.

Pressure receptors - These are the commonest receptors studied, they respond with a slowly adapting discharge to distension and collapse of the larynx (Mathew and colleagues 1982, Sant'Ambrogio 1983, Hwang 1984). They have been studied in the rat, lamb, dog, cat and rabbit and it is obvious that there are clear species differences.

Drive receptors - These receptors depend upon upper airway skeletal muscle contraction (Sant'Ambrogio 1983). These receptors adapt rapidly to a maintained mechanical stimulus and normally show inspiratory modulation.

Cold / Flow receptors - In the dog 15% of the laryngeal mechanoreceptors responded to inspiratory, but not expiratory flow. Subsequent studies have shown that these endings respond to *cold* air flow.

Irritant-sensitive endings - A wide variety of irritant gases and aerosols have been shown to stimulate laryngeal receptors as studied by single fibre recordings from the superior laryngeal nerve (Andrew 1956, Boushey & Richardson 1974, Widdicombe 1981). Stimuli include ammonia, sulphur dioxide, cigarette smoke, 10 - 30% carbon dioxide, and mechanical deformation. These receptors were classified as type 1 by Boushey & Richardson (1974), and were rapidly adapting, with an irregular discharge and an off response to maintained mechanical deformation. Some of the pressure receptors also respond to irritant gases such as ammonia.

Chemosensitive endings - Early studies have shown that water in the larynx stimulates laryngeal receptors with afferent fibres in the superior laryngeal nerve of cats and rabbits (Boushey & Richardson 1974, Shingai 1977 & 1979, Storey 1968, Storey & Johnson 1975). Many of these receptors are also mechanosensitive, with a rapidly adapting response. Boggs and Bartlett (1982), showed that in puppies the receptors responded primarily to a deficiency in anions, particularly Cl ions.

Respiratory reflexes.

The main respiratory response to stimulation of the laryngeal structures are apnoea, coughing and expiratory efforts (Bosma & Showacre 1976, Korpas & Tomori 1979, Pressman & Keleman 1955, Widdicombe 1964 , 1977, & 1981, Wyke & Kirchner 1978).
Sullivan & Murphy (1978), studied the stimulation of the larynx in awake and sleeping dogs with a tracheostomy by applying water or inflating a small balloon in the larynx. With the same stimulus and presumably exciting the same afferent end organs they obtained either swallowing, apnoea coughing or expiratory efforts. However the type of response obtained was strongly influenced by wakefulness or sleep pattern. Stronger stimuli were required to produce arousal and coughing during rapid eye movement sleep than during slow wave sleep.
In human adults inhalation of aerosols of water or of solutions low in concentrations of Cl ions causes coughing, these solutions do not cause reflex bronchoconstriction unless the osmolarity is abnormal suggesting that the two reflexes may have different origins and afferent pathways (Eschenbacher & Boushey 1984). Although it is difficult to establish that the larynx is the site of these responses in humans, it is the most plausible origin in view of its sensitivity for cough and the fact that aerosols should be impacted there and because the cough can be inhibited by local anaesthetics restricted to the pharynx and larynx (Higenbottam 1984).
New-born infants do not respond by cough when the larynx is touched during tracheal intubation and the laryngeal cough reflex only appears at approximately 35 weeks after birth. There are quite large species differences in the sensitivity of the cough reflex.

Expiration reflex

Mechanical stimuli to the vocal cords do not cause coughing but instead produce a transient expiratory effort called the expiration reflex. The function of this reflex is to prevent entry of foreign material into the lower respiratory tract. This has been extensively studied by Korpas and colleagues (Ivanco & Korpas 1954, Korpas 1972, Korpas & Tomori 1979). The expiration reflex consists of a sudden brief expiratory effort when the vocal cords are touched, consisting of an expiratory effort without preceding inspiration. It can interrupt any phase of breathing, its site of origin is specifically the vocal folds. It is more resistant to general anaesthesia and to antitussive drugs than is cough and is present in new-born animals before the cough reflex develops (Korpas & Tomori 1979). The role of the reflex is to prevent aspiration of material that touches the vocal folds, when a preliminary inspiratory effort of a cough might draw material into the lower airways, thus the reflex may be important in preventing conditions such as aspiration pneumonia.
It is not possible to be certain which nervous receptors in the laryngeal wall are responsible for respiratory reflexes described, nor is it clear which afferent pathways studied by single fibre recording are involved.

Hypertension and vagal bradycardia are the primary cardiovascular reflexes elicited from the laryngeal mucosa (Tomori & Widdicombe 1969). Cardiac arrythmias may occur as may bronchoconstriction mediated by an atropine sensitive vagal reflex. The receptors and afferent nerves for these reflexes are unknown.

Laryngeal response

Mechanical or chemical irritation of the laryngeal mucosa causes laryngeal adduction (SzeredaPrzestaszewska & Widdicombe 1971) even if the stimulus is too weak to cause coughing or apnoea (Suzuki & Sasaki 1976, 1977). The response is prevented by section of either the superior laryngeal nerves (afferent) or the recurrent laryngeal nerves (motor) (SzeredaPrzestaszewska & Widdicombe 1971). It is associated with increased activity in the thyroarytenoid muscle (adductor) and in expiratory motor fibres in the recurrent laryngeal nerve. The laryngeal reflex has been seen in adult cats, dogs and humans. Puppies seem to lack the adductor reflex, and it appears in an exaggerated form between 50-70 days after birth (Sasaki & Suzuki 1976).

Responses from the tracheobronchial tree and lungs

There are three main groups of lung receptors, the slowly-adapting stretch receptors, the rapidly adapting irritant stretch receptors and the C-fibre receptors. Each group is distributed throughout the tracheobronchial tree and the C fibre receptors are also found within the alveolar walls. There is indirect evidence to suggest that the rapidly adapting irritant receptors have some branches close to the lumen of the airways, and are concentrated at points of airway branching (Widdicombe 1954,1981). Histologically the only nerves seen that could correspond are the intra-epithelial free nerve fibres (Das & Jeffery 1978) that connect to myelinated nerve fibres with central connections. Degeneration experiments have shown that they are sensory (Das & Jeffery 1979). However, histologically only single nerves are found and as yet the whole nerve complex has not been unravelled. Physiological studies suggest that

the single receptor may ramify not only in the epithelium but also deep into airway muscle (Fisher 1964, Sant' Ambrogio 1978). C fibres have not been definitely identified except possibly at the alveolar level (Coleridge 1984) here they are non-myelinated.

Rapidly-adapting irritant stretch receptors

Since their first detailed description by Knowlton and Larrabee (1946), these receptors have been extensively studied. They respond to inflation and deflation of the airways and lungs with rapidly adapting irregular discharges often with a prominent on-off response (Widdicombe 1954). They occur throughout the trachea and larger bronchi with concentrations at points of branching. Those in the lungs are less rapidly adapting than those in the trachea. They are distinct from slowly adapting receptors, not only in their response to mechanical stimuli but also the fact that they are sensitive to many inhaled irritants. They are also sensitive to many inhaled dusts suggesting that they may be superficial in the mucosa. Irritant receptors in the lung and upper airway are distinct from pulmonary stretch receptors and specific deflation receptors, they have action currents and conduction velocities typical of small myelinated fibres. These receptors have an irregular discharge pattern unrelated to the respiratory phase. They are consistently stimulated by irritant gases and vapours.

Histologically their physiological properties are identical to those of irritant (cough) receptors these have been localised in the epithelium of the trachea and extrapulmonary bronchi (Widdicombe 1954). As these receptors are rapidly adapting their discharge depends not only on the size but also on the rate of change of mechanical or chemical stimuli.

These receptors have been studied and their response to inhaled irritants such as ammonia, ether, sulphur dioxide, and cigarette smoke has been recorded. The sensitivity and uniformity of response varies. In general the receptors are excited with maintained responses showing little adaptation (Mills 1969,1970, Sellick and Widdicombe 1971). The discharge and sensitivity of the receptors are increased in a number of pathological conditions. In general the irritant receptors are polymodal and respond to physiological and pathological changes. C-fibres normally have little tonic discharge, but are activated by large inflations in dogs, however the main stimulus to the receptor seem to be endogenous mediators such as bradykinin, Prostaglandin E, 5-hydroxytryptamine, acetylcholine and histamine.

The epithelial site of these receptors and their responses to intraluminal stimuli indicate that they cause cough (from the carina and large bronchi) and hypernoea (from the smaller bronchi) (Mills 1970, Widdicombe 1981). The irritant receptors are also thought to cause other reflex changes associated with coughing namely bronchoconstriction, laryngospasm and mucus secretion.
Recent work (Nishino and colleagues 1993) studying the action potentials from the cut end of superior laryngeal nerves in dogs, has shown that when inhalation anaesthetic agents are administered halothane proved to be the most effective in producing an inhibitory effect from receptors in the upper airway.

Receptors

Intraepithelial vagal sensory receptors are found within the paracellular spaces between epithelial cells, these are sensitive to both mechanical and chemical stimuli. These afferent receptors are found within the paracellular spaces to a level just below the tight junctions. They have a role in protection of the airway, when harmful alterations to the airway epithelium occur for example mechanical pressure or changes in the chemical composition of the airway epithelial lining fluid (Higenbottam 1984).

Airway epithelium is leaky and water and small molecular weight solutes, such as urea, potassium and sodium can permeate passively between epithelial cells. Air passages are covered in a liquid consisting of two elements. Airway surface liquid bathes the cilia and is 4-6 micrometers deep above which is the mucus which is propelled by the beating cilia. Ciliary beat frequency is dependant on the luminal concentration of Cl ion. A reduction in the luminal concentration of NaCl below 80 mmol results in a reduction in ciliary beat frequency.

In evolutionary terms the earliest mechanism to protect the lungs was laryngeal closure and apnoea (Negus 1949). The upper airways are endowed with extensive intra-epithelial sensory nerves. There are

abundant unmyelinated intraepithelial nerve fibres throughout the laryngeal mucosa of kittens, lambs, monkeys, puppies and human infants. The presence of water or several other fluids in the larynx has been shown to cause the apnoeic response in young animals. This apnoeic response is lost as the animal matures but the laryngeal receptors are still able to respond to low Cl ion solutions. Other protective reflex responses develop as the animal matures. There are receptors within the laryngeal epithelium capable of responding to a reduction of Cl ion below 75 mmol L^{-1}.
It appears therefore that a sensitive upper airway mechanism exists which will in most subjects respond to changes in Cl ion concentration by inducing a cough (Higenbottam 1984). This mechanism may have value in life for protecting the lungs from wide excursions in ionic composition of the airway epithelium.

Physiology of the Larynx

The larynx serves three important functions.
In order of priority : (1) Protective
(2) Respiratory
(3) Phonatory

In primitive fish the larynx functioned as a simple sphincter to protect the lower airway from the intrusion of water and other foreign matter. To further enhance flow requirements through the laryngeal aperture certain amphibians, such as the Mexican axolotl, phylogenetically acquired lateral laryngeal cartilages. These cartilages formed bars on either side of the glottis into which the dilator muscles inserted. To augment the mechanical advantage of these muscles, higher vertebrates acquired a

cartilaginous ring between the glottis and the trachea from which dilator muscles could originate. When viewed from a phylogenetic viewpoint therefore the primary function of the larynx is sphincteric, protecting the lower airway from intrusion of liquids and food. Its secondary function was determined by the sequential phylogenetic acquisition of the cricoarytenoid complex, which facilitates its role in respiration, governed by active muscular dilation of the laryngeal aperture.

The third function of the larynx, phonation, is a late phylogenetic development.

The basic functions of the larynx are derived from a complicated interrelation of diverse polysynaptic brainstem reflexes. At one end of the spectrum is protective function which is entirely reflexive and involuntary, and at the other are the respiratory and phonatory functions that may be initiated voluntarily and are under conscious control.

Neurophysiology of protective function

The protective function of the larynx may be viewed neurophysiologically by examining the glottic closure reflex. This is a simple reflex producing laryngeal closure during swallowing. By stimulating the superior laryngeal nerve, the threshold of this adductor reflex is 0.5v and has a latency of 25ms indicating that this is a polysynaptic brainstem reflex. Humans however do not have a crossed adductor reflex, that is to say, stimulation of one superior laryngeal nerve does not produce simultaneous action potentials in the contra lateral adductor muscles. In healthy subjects the sphincteric closure of the upper

airway produced by bilateral superior laryngeal nerve stimulation results in protective adduction of three muscular tiers. The highest level of closure occurs at the aryepiglottic folds, which contain the superior most division of the thyroarytenoid muscle. With reflex contraction of these fibres the aryepiglottic folds approximate to cover the superior inlet of the larynx. The second tier of protection occurs at the level of the false cords, consisting of bilateral folds that form the roof of the laryngeal ventricles. Laterally, along each fold are fibres of the thyroarytenoid muscle that are capable of bringing the folds together in a reflex response to superior laryngeal nerve stimulation.

The third tier of protection occurs at the level of the true cords, these are shelf-like with slightly upturned borders, the inferior division of the thyroarytenoid muscle forms the bulk of each cord producing the potential for strong reflex protective closure. In conjunction with the passive valvular effect caused by the upturned borders of the cord margin, the true cords represent the most important of the three barriers to aspiration. Other sensory stimuli are capable of eliciting the glottic closure reflex. For example, stimulation of all the major cranial afferent nerves produces strong adductor responses. The susceptibility of this reflex response to such diverse sensory elicitation is unique and emphasises its primitive role in respiratory protection of the organism from a wide variety of potentially noxious influences. Conversely, physiological exaggeration of the glottic closure reflex, laryngospasm, may be counterproductive. It consists of prolonged glottic closure in response to intense glottic or supraglottic stimulation. Usually strong closure is maintained well beyond the cessation of mucosal irritation. From neurophysiological analysis, laryngeal spasm consists of prolonged tonic adductor spike activity in the recurrent laryngeal nerve. Characteristically this spike activity has no precise temporal relationship to the initiating stimulus. The sensitivity of adductor

motor neurones is depressed by hypoventilation, and hypoxia. Also in hypoxic states post synaptic recovery lags behind pre-synaptic recovery, producing a net depressive effect on all reflex neural activity. Superior laryngeal nerve stimulation, apart from the variety of excitatory adductor responses that it produces also exerts an inhibitory effect on the medullary inspiratory neurones. Not only does laryngeal abductor activity cease, but phrenic nerve activity is also inhibited, resulting in various degrees of reflex apnoea.

Physiology of laryngospasm

The protective function of the larynx is based on a dominant and stable reflex, producing glottic closure by contraction of all other intrinsic laryngeal muscles but principally involving thyroarytenious function.
In a study by Suzuki & Sasaki (1976) they examined the initiation of glottic closure reflex using cats. They concluded from their data that the glottic closure reflex is polysynaptic with a latency varying between 10 - 50 msec. In further work (1977) they examined the effects of other stimuli in producing reflex laryngeal adduction. Stimulation of major cranial afferents produced a strong adductor response and also a strong response was seen following stimulation of the vagus and splanchnic nerves. The responses in the recurrent laryngeal nerve produced by single shock stimulation of the superior laryngeal nerve is a well known reflex of low threshold and brief latency. It has been described by numerous investigators as a primitive, dominant and stable reflex providing the primary basis for protective laryngeal closure. However, single shock stimulation of distant somatosensory nerves such as the radial and sciatic

nerves produces weaker recurrent laryngeal nerve response and with a longer latency.
Stimulation of special sensory nerves (acoustic, optic and chorda tympani nerves) produces moderate recurrent laryngeal nerve evoked response of brief latency.
The characteristics of each afferent system known to affect laryngeal adduction can be summarised. The superior laryngeal nerve, when subjected to repetitive stimulation produces the least attenuation in its evoked adductor responses. The vagus, splanchnic and trigeminal nerves follow in order of increasing attenuation. Furthermore somatic sensory (radial nerve) stimulation produces more attenuation than special sensory (optic nerve) stimulation.
Therefore the stimulation of major cranial afferents (superior laryngeal nerve, vagus nerve and trigeminal nerves) or splanchnic nerve in the abdomen may produce strong glottic closure affecting both protective and phonatory laryngeal function. However, comparable stimulation of special sensory and distant spinal somato-sensory nerves produces rapidly attenuated evoked adductor responses.

In neurophysiological terms laryngeal spasm appears as an exaggerated closure produced specifically by superior laryngeal nerve stimulation alone (Sukuki & Sasaki 1977). In this respect it is a more discriminating response than the glottic closure reflex which is capable of production by a variety of afferent stimuli. Laryngeal spasm characteristically consists of prolonged tonic adductor spike activity, which often bears no precisely reproducible temporal relationship to the initiating stimulus. Some investigators claim that laryngospasm bears certain similarities to a focal seizure initiated by a local sensory aberration. From a clinical perspective laryngospasm produces strong closure which is maintained well beyond

the cessation of mucosal irritation. Prolonged obstructive apnoea caused by laryngeal spasm may therefore produce death by acute hypoxia and hypercapnea. Neurophysiologically the glottic closure reflex is distinct from laryngeal spasm. The distinction is twofold, firstly laryngeal spasm is composed of heavy after discharge activity which may be elicited only by repetitive supra threshold stimulation of superior laryngeal nerve but not by single shock excitation. Further distinction is based on the observation that superior laryngeal nerve seems to be the only potential mediator of intense after discharge activity in the thyroarytenoid muscle. The rapid attenuation of primary evoked thyroarytenoid muscle responses and obvious paucity of thyroarytenoid after discharges when other than superior laryngeal nerve is repetitively stimulated appears to support this theory. Work by Ikari & Sasaki (1980) examined the activity of adductor neurones during the respiratory cycle. They found that the threshold of the laryngeal adductor neurone varied sinusoidally with spontaneous respiration, laryngeal closure occurring much more readily during the expiratory phase than during the inspiratory phase of spontaneous respiration. They also concluded that CO_2 has an effect on laryngeal adductor neuronal activity. Their data showed that CO_2 decreased the reactivity of the adductor neurones and that the threshold of adductor neurones varied quantitatively as a linear function of arterial CO_2. At higher levels of $paCO_2$ the adductor neurones are less active. Furthermore prolonged laryngeal closure or laryngospasm, is more likely to occur in hypocapniec states and is inhibited by hypercapnia. Hypoxia also clearly diminishes the excitability of the adductor neurones such that laryngospasm is inhibited. So to summarise; laryngospasm is facilitated by expiratory phase, decreased arterial $paCO_2$, increased arterial paO_2 and negative intrathoracic pressure.

These data would support a fail safe mechanism by which asphyxia (acute hypercarbia and hypoxia) prevents glottic closure or sustained laryngospasm therefore in the healthy adult laryngospasm represents a self limiting threat to life in the presence of normal cardiopulmonary reserve, as hypercapnia and hypoxia accumulate the laryngospasm is automatically broken. But in the incapacitated patient with poor cardiopulmonary reserve, laryngospasm may represent a serious threat to life. Exactly how these control mechanisms are affected by the presence of anaesthetic agents is not known. In infants the laryngeal adductor reflexes are already hyperexcitable due to normal patterns of neurologic development.

There is much evidence in the literature that in the majority of neurones in the mammalian central nervous system a rise in $PaCO_2$ is accompanied by hyperpolarisation indicating a reduction in the excitability of these neurones.

The imbalance between excitatory and inhibitory neurones affecting laryngeal reflexes, has been proposed by Sasaki (1979) to explain the tendency of infants to develop life threatening laryngospasm. They studied the superior laryngeal and recurrent laryngeal nerves of the beagle pup, with respect to their postnatal myelination and nerve conduction velocity. The distribution of superior laryngeal nerve and recurrent laryngeal nerve myelinated fibres stabilises at 50 days. At birth the conduction velocities of the superior laryngeal nerve and recurrent laryngeal nerve were predictably low measuring 5.2 m sec^{-1} and 1.5 m sec^{-1} respectively however conduction velocity rapidly increased achieving a maximum of 70 m sec^{-1} in adulthood. The physiological activity of laryngeal motor neurones located in the nucleus ambiguus depends upon the net excitatory and inhibitory input. If there is differential maturation of excitatory influences as compared to inhibitory influences then a state of imbalance

may exist. This may explain an age related imbalance of neurological mechanisms which could produce abnormally exaggerated laryngeal closure response, producing a period of maximum risk at a time distant from birth but prior to the completion of neurological maturation. They concluded from their observations that in beagle pups there appeared to be a transient state of laryngeal hyperexcitability occurring between 50 - 75 days of post-natal life. During this period of brain stem development the adductors nucleus appeared to be especially sensitive to afferent stimuli resulting in summated action potentials suggestive of laryngeal spasm. These action potentials contained sustained spike activity identical to the laryngospastic response of adult dogs.

Inhalation of irritant gases and vapours

Among gases and vapours those that are usually classed as irritants are substances that would normally be regarded as corrosive. They injure surface tissues. The effects of different irritants vary, these differences depend in part on the solubilities. Irritants can be subdivided into primary and secondary irritants. Primary irritants are those which have little or no systemic toxic effects in addition to surface irritation, this is particularly true at high concentrations. Primary irritants exert no systemic effects because the products formed by them on tissues of the respiratory tract are non-toxic after absorption and also because their irritant effects are so violent as to obscure any systemic toxic action. For example the inhalation of the primary irritant hydrochloric acid gas leads to the formation of sodium chloride, which is non-toxic. Alarie (1973) extended the classifications of airborne chemicals capable of stimulating nerve endings in the respiratory tract.

1. Sensory irritant : This is a substance that when inhaled via the nose, stimulates nerve endings, and evokes a burning sensation of the nasal passages and inhibit respiration. It will also induce coughing by laryngeal stimulation.

2. Pulmonary irritant : This is a substance that when inhaled stimulates sensory receptors within the lung and increases respiratory rate with a decreasing tidal volume resulting in rapid, shallow breathing.

3. Bronchoconstrictor agents.

4. Respiratory irritants.

Mechanisms of irritation

Sensation evoked by inhaled irritants varies greatly (Douglas 1981). Ammonia is odorous in concentrations (3500 micrograms m^{-3}) far lower than those that cause unpleasant sensations. Gases such as hydrogen chloride "irritate" at threshold detection levels of 7200 micrograms m^{-3}. The distinction between smell and irritation may depend on the interaction between olfactory and trigeminal (irritation) pathways.

Chemical sensibility seems to be more concentrated in the respiratory mucosa than in the skin. The sense of chemical irritation has been distinguished from pain on several counts, although if the concentration of an inhaled irritant is high enough, pain results.

Sheldon (1909) and Parker (1922), showed that cocaine could block noxious responses to mechanical stimulation, while those to chemical irritants persisted. Depletion of substance P from nocioceptive afferent nerves by the use of capsaicin, blocks the chemical irritant responses while leaving those to mechanical stimuli intact. However these types of experiment probably only show that more than one afferent pathway is involved in responses to noxious stimuli. Many of the afferent mechanisms underlying sensation from inhaled irritants are also involved in sensation associated with respiratory disease. Some irritants that cause these sensations may initially be restricted to the airway epithelium and only exert surface actions, but disease processes may extend deeper into tissue. Both types of condition may involve release of mediators and cellular breakdown products that could diffuse into deeper tissues.

There are various hypotheses to explain the mechanism of irritation, all of them concentrate on reactivity with proteins. Early work by Peters (1963), and Dixon (1946) implicated the ability to react with SH groups in proteins as the basis of the mechanism of irritation. Chemical groups which interact

with SH groups include chemicals with a positive halogen, known as thiol alkylating agents and chemicals containing an ethylenic double bond.

CHAPTER 3

Background to the thesis

Introduction

In this chapter I shall outline the background to the thesis. I will discuss the historical development of methods to measure the sensitivity of upper airway reflexes and the problems associated with the technique. I shall also discuss the chemistry and toxicology of ammonia vapour.

i) Historical development of methods to measure the sensitivity of upper airway reflexes.

The origins of the development of a method to measure the reactivity of the larynx began with the work by Kratschmer 1870. In a series of animal experiments, he isolated the larynx of dogs and passed tobacco smoke across the larynx or into the bronchi. By direct vision through the tracheostomy, he observed that puffing smoke or other irritant vapours into the nose or onto the vocal cords resulted in closure of the glottis for as long as the irritant was present.

Hoglund and Michaelsson (1950) described a method for determining the cough threshold and reported some preliminary experiments on the effect of codeine on the cough threshold. The method that Hoglund and Michaelsson used was suggested by Professor E. Barany. They described a technique which involved eliciting minimal cough response by the sudden introduction of small amounts of ammonia vapour into the airways of the subject during inspiration. The threshold response was sudden closure of the glottis and momentary inhibition of inspiration. They commented that if the normal subject breathes through his mouth, this threshold response usually occurs at lower ammonia concentrations than can be perceived by taste, and that subliminal ammonia doses are not detectable. The ammonia was stored in the liquid state in a gas cylinder. A 2% mixture was obtained by diluting the gas with air in a rubber balloon. Further dilution to the desired concentration for experimental purposes was achieved by using a 100ml glass syringe, the syringe being oiled with glycerol. The subject breathed via a valve the inspiratory part of which was connected to a metal tube, 100cm in length and with a diameter of 2.2cm. Within this metal tube was placed a narrow rubber tube of 90cm length. One end of the rubber tube lay 10cm from the valve and the other at the open orifice of the metal tube. The ammonia mixture was injected through the rubber tube at the end of expiration. The cough response (if any) occurred at the next inspiration. They deliberately kept the noise level in the room high so that the sound of the injection was not heard by the subject.

The decision as to whether a threshold level had been reached was made with the aid of a pneumograph attached around the subjects waist and connected to a Marey capsule carrying a pointer.

The course of a typical experiment was as follows :
The subject sat comfortably, breathing through the valve. They instructed the subject to breathe deeply and slowly, to shut his eyes and not to breathe through his nose. By varying the concentration of ammonia vapour in steps of 20%, using in all 10-15 injections of various amounts of ammonia at least two steps below and above the threshold level. They reported that frequent injections of air were interspersed between ammonia injections. After establishing the normal threshold, codeine phosphate was administered orally in four dosages. Five observations were made with 10mg, seven with 20 mg, six with 30 mg. One subject was given 30mg, 15mg, 15mg, 30mg on different occasions at intervals of a couple of days. Complete studies were made on 17 subjects most of whom were medical students. They reported that the cough threshold increased at 15-30 minutes following administration of codeine orally. The height and duration of this effect increased with the amount administered. The peak effect was reached after about 90 minutes, returning to the normal level after 80-160 minutes.
They reported that no harmful effects were observed attributable to the inhalation of ammonia vapour.

Gravenstein & Devloo (1954), working in the Anaesthesia Laboratory, Harvard Medical School, Massachusetts General Hospital, published further work on the effects of antitussive agents on experimental cough and pathological cough in man. They used the method that had previously been described (Hoglund & Michaelsson 1950). In addition during preliminary studies they also investigated several different vapours and smoke, in various dilutions in air or oxygen. Ammonia vapour, sulphur dioxide, tobacco smoke, pine needle smoke, beech leaf smoke and tear gas were used.

After many preliminary experiments they concluded that the method employing inhalation of ammonia vapour deserved further study.
They made efforts to eliminate errors and sources of inaccuracy that they felt existed in the previous work of Hoglund & Michaelsson (1950). They stated that they did not rely solely upon the subjects' judgement alone as to whether or not a threshold level had been obtained. They recorded a threshold level only if the mechanical record showed a stop in the subjects breathing pattern. They discussed potential areas of inaccuracy in the previous work, and they felt that the storage of the ammonia vapour in a rubber container for *long* periods of time (weeks at a time) may have led to inaccuracies in previous work. They used a chemical assay to ensure accuracy of the concentration of ammonia vapour. A metabolic spirometer was used as a pneumograph. The valve next to the mouthpiece directed the expired air to atmosphere. The ammonia containing gas was deposited into a tube that was installed parallel to the inspiratory breathing tube. For their experiments the subject lay on a bed and his nose was closed using a clamp. When respiration was regular the air inlet was closed and the ammonia containing gas was deposited at the blind end of the gas tube. The arrangement was such that during expiration the switch could be turned without the subject being aware of it and with the next breath all the ammonia containing gas reached the subject.

During this study they investigated the effects on cough threshold of various drugs including codeine, diamorphine, morphine, in 17 volunteers but the results were not clear. They claimed that the threshold measurements were reasonably reproducible although they did not produce any data on the reproducibility of their measurements and failed to reproduce the previously reported findings of Hoglund and Michaelsson (1950).
They discuss a number of possible explanations for these differences, including the lack of a placebo for comparison in the earlier study also the ammonia mixture was stored in a rubber container which may have led to inaccuracies in the concentration of ammonia produced. In this publication they also described an alternative technique of eliciting a cough using citric acid mist.

In 1960 Pontoppidan and Beecher examined airway reflexes with advancing age and published data in a paper entitled *"Progressive loss of protective reflexes in the airway with the advance of age"*. They based their method on that previously described (Hoglund & Michaelsson 1950). They described the threshold response as indicated by a sudden closure of the glottis and a momentary check in inspiration. This was described as a brief catch in the breathing. This effect was visible and the breathing was recorded on to a pneumograph and the catch was shown as a small notch in the inspiratory slope. They also commented that stimulation above the threshold level produced coughing. They chose to use a 1.6% concentration of ammonia. The subject's respirations were recorded by a modified metabolic spirometer. The spirometer was modified in the following way; the inlet was closed and a wide tube led from the outlet to a cylindrical mouthpiece. The expired air was directed out into the atmosphere via a one-way valve. On the other side of this valve the tube

from the spirometer contained a cylindrical reservoir with a volume of 175ml. At one end of this reservoir was a small sidearm with a threeway stopcock for the introduction of the ammonia containing gas. The authors stated that the concentration of ammonia reaching the subject was *not actually known* but was assumed to be proportional to the amount of ammonia injected into the sidearm of the reservoir. During the experimental measurements, the subject sat in a chair and a nose clip was applied they state as a further precaution the subject was asked to keep his eyes closed during the experiment. During expiration they deposited an amount of ammonia containing gas into the reservoir, and with the subject's next breath he inhaled this mixture.

They tested 103 healthy male subjects of age range 15 - 84 yrs. They found an increase in the median threshold to ammonia inhalation with increasing age, signifying a reduction in the sensitivity of upper airway reflexes in the elderly age group. The sensitivity to the inhalation of ammonia gas decreased considerably but they also found that ageing was accompanied also by increased variability of the measurement. They retested several of the volunteers some weeks and months following the original measurements and the results showed that the thresholds were consistent and reproducible. These workers were not able to draw any conclusions about the effects of smoking on the irritability of airways as the number of non-smokers was too small. The conclusions of this interesting study were that this apparent decrease in the airway reactivity in the later years of life may explain the increased frequency of silent tracheal aspiration in the elderly; and this may be part of the reason why bronchopneumonia is so common in this age group. They also warned of the hazard of further depression of the airway reflexes by the injudicious use of depressant drugs in the elderly.

In 1971 Hinkle and Tantum described a technique for measuring the reactivity of the glottis. The aim of this study was to identify the site of afferent stimulation of this reflex. They used an ammonia stimulus to the upper airway and they studied the effects of the application of local anaesthesia to the upper airway on the threshold responses. An 9 litre Collins spirometer was connected by rubber tubing to the inspiratory port of an Ambu-Hesse valve. At the junction of the valve and the corrugated tubing they inserted the tip of a narrow bore catheter. To the other end of this catheter they attached a 50ml syringe containing various concentrations of ammonia in air mixture. A 2% ammonia in air mixture was contained within a gas cylinder and aliquots of this gas mixture were diluted with room air to produce varying concentrations of ammonia gas. The subject breathed via a mouthpiece with a nose clip applied, after recording a regular respiratory pattern on the spirometer a bolus of 50ml of the ammonia in air mixture was injected into the inspiratory tubing, to be incorporated into the next inspiratory breath.

Normal threshold responses were measured and the upper airway was then anaesthetised using 4% lignocaine. The hypopharynx and superior laryngeal nerve were anaesthetised. This was judged to have been successfully accomplished by voice changes and the fact that the subjects had difficulty handling their own secretions. The ammonia thresholds were then repeated. Also the tests were repeated after administration of 150mg lignocaine given intravenously over 20 min. The movements of the vocal cords were recorded using X-rays during testing. The application of local anaesthesia to the upper airway led to the threshold concentrations to ammonia being considerably increased. They concluded that reflex closure of the glottis is initiated by the inhalation of ammonia vapour and this is mediated by afferent receptors located in the upper airway in the hypopharynx and larynx.

Depression of laryngeal reflexes was investigated by Rosen & Harrison (1963) in a clinical study of 80 patients. The stimulus was applied to the larynx whilst the patient was anaesthetised with halothane and nitrous oxide in oxygen. During induction of anaesthesia, four different methods were used to apply local anaesthetic to the larynx. The stimulus applied was flexion of the head after 20 min of spontaneously breathing anaesthesia. The responses were judged by observing the tidal volume and observing the contraction of the abdominal muscles. The conclusions from this study were that halothane and nitrous oxide in the concentrations used depress the laryngeal reflexes.

Claeys and Lockhart (1973), studied the effects of translaryngeal block and thiopentone on glottic competence. They used the chemical stimulus technique with ammonia vapour and performed translaryngeal block on ten subjects using 2ml of 4% lignocaine injected into the trachea percutaneously through the cricothyroid membrane. Another group of ten volunteers had 2 ml of thiopentone administered intravenously but it is not clear from this paper what strength of thiopentone solution was used. The ammonia threshold increased significantly after translaryngeal block, suggesting that the glottis was unprotected. Interestingly they found that a small dose of thiopentone did not have any significant effect on the ammonia thresholds.

In 1980 Duckett and Hirsh, reported investigations with 2% ammonia vapour into glottic competence in 23 post-operative patients aged 21 - 70 yrs, 19 were scheduled for major thoracic or abdominal surgery, requiring tracheal intubation and four patients scheduled for surgery that would not require tracheal intubation. The patients were investigated 24 hr post

extubation. Unfortunately only eight of the patients whose trachea had been intubated were followed up, but all of these patients showed an increase in threshold to ammonia inhalation compared to their pre-operative value.
They commented that the pre-operative ammonia thresholds showed considerable variation and speculated that this may have been due to age, smoking habits or other chronic medication that the patients were receiving. Their findings in the post-operative period were thought to be consistent with other studies indicating that the sensory function of the larynx is obtunded and that this alteration to normal function persists for at least 24 hr post-extubation in patients who have undergone tracheal intubation for surgery.

The effects of benzodiazepines on laryngeal reflexes was investigated by Groves & Rees (1987) using ammonia vapour. The breathing system contained an injection port 200ml proximal to the mouthpiece. Through this port 50 ml air boluses were injected containing various concentrations of ammonia vapour. The boluses were stored prior to injection in a battery of 50ml ground glass syringes, which had been produced by drawing in various amounts of 1.6% ammonia gas from a gas bag and diluted with air. Amounts of ammonia sufficient to elicit the laryngeal reflex cause a brief, temporary closure of the vocal cords (the "glottic stop"), this was seen as a brief step on the inspiratory flow trace of the spirometer. Four groups of volunteers were studied, three groups given lormetazepam at differing rates of intravenous injection and the fourth group were given 15 mg Diazemuls over 15 sec intravenously. Laryngeal reactivity and psychomotor function tests were performed before drug administration to establish baseline data. After drug administration, laryngeal reactivity was measured at 15 min intervals for 90 min and then

at 30 min intervals for a further 150 min. This study produced some interesting results. The sensitivity of laryngeal reflexes were found to be depressed for over four hours after 15mg Diazemuls intravenously. They also claimed that the different benzodiazepines used in this study produced differing degrees of depression of the laryngeal reflex and suggested that this was due to receptor multiplicity as lormetazepam was found to produce much less depression of laryngeal reflexes for equivalent degrees of sedation.

There are several problems with all of these previous studies, and the older methods of measuring the sensitivity of upper airway reflexes : -

1. All of these previous methods rely on the preparation of pre-prepared syringes. This is not really practical in the design of portable equipment. It is also quite time consuming.

2. The previously described systems all had large dead space volumes which may have led to inaccuracies and errors as the actual concentration of ammonia vapour inhaled by the subject was not known and it may have been dependant on inspiratory air flow and also may have been affected by streaming and channelling in the circuit.

3. Previous workers did not assess the reliability and repeatability of results from the various pieces of equipment.

4. The lack of portability has limited the collection of data in the clinical environment.

ii) NH_3 vapour : chemistry and toxicology

Physical Properties

Ammonia is a colourless alkaline gas, less dense than air with characteristic pungent odour. It is easily liquefied by pressure and is available in compressed liquid form in steel containers. The commercial grade contains about 99.5% ammonia. Ammonia is involved in the nitrogen metabolism of plants and animals and is present in small amounts in nature from the decomposition of organic matter.

Molecular weight = 17.03
Melting point = -77.7°C
Boiling point = -33.3°C
Density = 0.77 at 0°C
Vapour pressure 10 atm at 25.7°C
Vapour density 0.59 at 25°C
Odour threshold = 5 - 53 ppm.

Ammonia is very soluble in water. Ammonia is also soluble in methanol, ethanol, diethyl ether, chloroform and other organic solvents.

Manufacture

Ammonia is normally manufactured by modification of the Haber-Bosch process which involves reaction of hydrogen and nitrogen under a pressure of 200 - 1,000 atm and at a temperature of about 600°C in the presence of an iron catalyst.

Uses

Ammonia in solution (ammonia water, ammonium hydroxide) in varying concentrations is used in a variety of products such as cleaning agents, and aromatic spirits. Ammonia solutions are sometimes used as fertilisers. Anhydrous ammonia gas, liquefied under pressure, is also applied directly to the soil or mixed with irrigation water as a fertiliser. Liquid ammonia is used as an industrial refrigerant.
Ammonia is used in the manufacture of explosives, synthetic fibres, plastics, synthetic resins, pesticides and dyestuffs. Ammonia is also used in the textile, leather pulp and paper processing, petroleum technology, metal ore extraction, photography and reprographics.

Biological hazards

Ammonia gas has an odour threshold of 5 parts per million (ppm) in air. The principal hazard of using ammonia is acute exposure to very high concentrations as a result of valve failure and leakages. Vapour inhalation is irritant to the upper respiratory tract; levels in excess of 100 ppm are reported to cause pain in the throat, cough and difficulty in breathing. At levels of continuous inhalation of > 1700 ppm coughing becomes severe with copious watery sputum. With exposure to > 5,000 ppm, pulmonary oedema and asphyxia occur rapidly with fatal consequences. The most dangerous consequence of exposure to high concentrations of ammonia gas is pulmonary oedema often appearing 6 or more hours after exposure. Ingestion of ammonia solutions produces effects similar to other corrosive alkalis, notably corrosive oesophagitis and gastritis, later gastric, duodenal and jejunal stenosis may result. The eye is able to tolerate higher concentrations of ammonia gas than the respiratory tract but a splash of anhydrous liquid ammonia solution can severely injure the eyes and produce first and second degree burns to the skin. Ammonium hydroxide has a greater tendency than other alkalis to penetrate the cornea and damage it and deeper structures within the eye, such as the iris and lens. The resulting uveitis may lead to iris atrophy and cataract formation, both lesions occurring only late in the course of the illness.
Experimental evidence by Weatherby (1952), indicated no significant cumulative effects of chronic ammonia exposure. He investigated the effects of chronic exposure of 12 guinea pigs to ammonia vapour, six were used as controls. Animals were exposed to ammonia for 6 hours per day, 5 days per week in a chamber concentration of 170 ppm (range 140 - 200 ppm). At intervals of 6 weeks 4 experimental and 2 control animals

were killed and examined for evidence of systemic toxicity. The animals showed no abnormalities which could be attributed to ammonia for 6 - 12 weeks. After 18 weeks the animals were seen to have mild changes in the spleen, kidneys and adrenal glands.

In the absence of metabolic disease, the human body has a high capacity to buffer ammonia base, generating the ammonium ion which is subsequently used in the synthesis of urea.

Recommended U.K. exposure limits for ammonia are 35 ppm for short term (10 min) exposure and 25 ppm for long term exposure (8 hrs).

Handling and storage

Ammonia should be stored in a cool, well ventilated store preferably outside or detached storage away from sources of ignition and other chemicals. Cylinders should be protected from direct sunlight. Tank cylinders and valves should be of iron or steel as ammonia does not attack these metals.

CHAPTER 4

Methodology

Introduction

In this chapter I shall discuss the development of the methods used in this thesis.

i) Development and description of the method used to measure the sensitivity of upper airway reflexes.

ii) Development of the method to measure the movements of the vocal cords on induction of anaesthesia.

I will also discuss the problems that I encountered during this time and the solutions that were found. I will describe the calibration of the equipment and the validation data in normal volunteers.

i) Development and description of the method used to measure the sensitivity of upper airway reflexes.

The previous chapter outlined the background to the measurement of the sensitivity of upper airway reflexes. Previous work in this area has suffered from several limitations:

1. The reliance on pre-prepared syringes. This is not practical in terms of preparation and portability for use in portable equipment.

2. Previous equipment contained large dead space volumes, which may have led to inaccuracies and errors being introduced into the measurement system.

3. There is not any data from previous work on the reliability and repeatability of the results that were obtained.

4. Previous methods were not portable.

I aimed to develop equipment that was safe, portable and relatively easy to use. Furthermore it was necessary to measure accurately the concentration of ammonia vapour produced within the system, and to produce data on the reliability and repeatability of measurements made using this equipment on normal volunteers.

I began developing this equipment in late 1989, initially constructing a laboratory based system. The first problem to be overcome was the supply of a known concentration of NH_3. Early work with ammonia solutions and Boyles bottles were unsuccessful and we decided to approach the British Oxygen Company and requested a 3% NH_3 / N_2 gas composition in a cylinder. This cylinder required a stainless steel reducing valve, to prevent the risk of leaks and occupational exposure to ammonia vapour.

We assembled a system to deliver the Air / NH_3 mixture using an air pump to provide an air flow of 10 litres / min, regulated via an O_2 flowmeter block. The gas flow was calibrated using a dry gas meter. The NH_3 / N_2 gas flow was regulated by means of a cyclopropane Rotameter, calibrated using a bubble flow meter. The delivery circuit was initially constructed from black corrugated anaesthetic tubing but as this was found to be heavy and cumbersome it was changed to clear plastic tubing. A 2 litre anaesthetic reservoir bag was incorporated into the system to allow for maximal inspiratory flows.

A switching valve was used to allow the subject to take one breath from the Air / NH_3 circuit . Initially we used a manual gas tap, but this was found to be inefficient and too bulky as the movements of the valve pulling on the gas tubing alerted the subject to the switching of gas flows.

We directed our efforts therefore towards developing a switching device which fulfilled the requirements of the system, notably it should be of low internal volume, have a silent, vibration free action and be controlled by the investigator from a distance. Early prototypes were constructed from a plastic Y-connector, into each limb of the Y-connector were inserted

balloons constructed from the cut off fingers of surgical gloves. These balloons were sealed around manometer tubing to make them air tight.
The next task was to construct a mechanism which allowed inflation of one balloon simultaneous with the deflation of the other. The switching mechanism had to comply with several requirements : the operation of the switching mechanism should be silent, and it should not transmit vibrations that could be detected by the subject. The solution was to link two syringes in such a manner that as one syringe was emptied, the other filled. This double syringe assembly was mounted on the anaesthetic machine. This assembly performed acceptably well, apart from that when the syringes were moved to inflate or deflate the balloons, this caused a slight movement of the machine which could be detected by the subject via the mouthpiece. The solution to this problem was to mount the double syringe assembly separately on a metal pole.
The inflation / deflation cycle for the balloons was controlled by a double syringe mechanism, connected by manometer tubing. Problems continued due to leakage, the balloons bursting and non-luer lock connections on the syringes. These were overcome by using angiography syringes with luer lock connections and replacing the ends of surgical gloves with urinary catheters.
Eventually I was able to purchase a commercially produced switching device (Hans Rudolph). This is a pneumatically controlled switching device which is operated using a hand held controller by the investigator.

The original pneumotachograph head used had a large dead space (250 ml). This was not initially perceived as a problem because this compared favourably with other work (Groves & Rees 1977). During further development of this equipment it became obvious that the dead space was crucial to the success of this method.

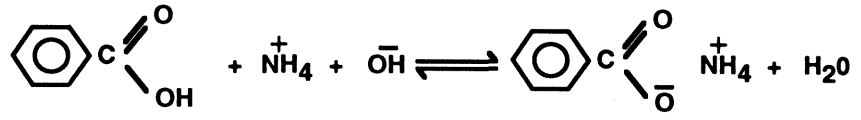
The existence of a large dead space meant that the subject was able to sense that the end of one breath contained a small quantity of NH_3 vapour and therefore knew that the next breath would contain the rest of the ammonia stimulus. Thus the subject was able to adapt the inspiratory flow pattern during the next breath in the knowledge that it would contain ammonia vapour. Also, at this time during development the subject was not blinded as to when the next NH_3 breath was coming. He was told to start breathing knowing that sooner or later a breath containing NH_3 would be presented. These factors affected the accuracy of the results considerably. I therefore radically changed the design of the system.

The dead space from the balloon valve to the subject was reduced to only 48ml by removing unwanted connectors, using small volume mouthpieces and changing to a much smaller pneumotachograph head. The subject was also instructed to breathe continuously through the mouthpiece whilst wearing headphones listening to music and wearing blackened goggles. This effectively blinded the subject to the activities in the laboratory. These changes resulted in considerable improvement in the results obtained.

The next requirement was to design an effective absorption system. This was vital to avoid polluting the atmosphere with noxious ammonia vapour if the system was to be used in the clinical situation.
The method that we designed utilised benzoic acid absorbed onto large mesh silica-gel matrix. This provided a large surface area for the chemical reaction. The reactions involved are shown in Figure 4.1.

The Chemical Reactions involved in the absorber are:

1. $NH_3 + H_2O \rightleftharpoons \overset{+}{N}H_4 + \overline{O}H$

2. 

The preparation of the crystals involves benzoic acid being absorbed onto large mesh silica gel matrix. This provides a large surface area and also promotes the reaction by binding.

Figure 4.1 The chemical reactions involved in the absorber.

This is in effect a buffer system, both reactions being reversible. The benzoic acid shifts reaction 1 to the right by removing OH ions. No water is consumed in the reaction but it must be present.
Benzoic acid is relatively non-volatile, stable and cheap and not known to be toxic. The crystals were coated with an indicator neutral red which changed to orange, when they were exhausted.
The absorber canister was attached to the end of the circuit.

Description of the technique

Low concentrations of ammonia vapour are used in this technique as an irritant chemical stimulus. The subject's upper airway is exposed to single intermittent breaths containing a low concentration of ammonia, and by measuring the inspiratory flow pattern a measure of the sensitivity of the subject's upper airway reflexes is made. This is expressed as the threshold concentration, that is the lowest concentration of NH_3 required to elicit the reflex response (NH_3TR).

The system is shown diagrammatically in figure 4.2, a low concentration of ammonia vapour in air is produced in the ammonia limb of the breathing system by mixing air from an air pump flowing at 10 litres / minute with an adjustable flow of NH_3 in Nitrogen. The NH_3 is delivered via a flowmeter from a calibrated cylinder containing 3% NH_3 in N_2. The breathing system was calibrated to deliver accurate concentrations of ammonia vapour in the range 0 - 3500 ppm. The gas mixture flows via a reservoir bag and clear plastic tubing it passes around the system as indicted by the arrows (figure 4.2).

A pneumatic two way balloon valve (V) allows the subject to breathe room air via limb (B). On switching the pneumatic valve, the subject takes a single breath from the ammonia in air limb (A). The two way pneumatic balloon valve (Hans Rudolph) is controlled by the investigator and allows the mixture to be directed to the subject for one breath, or pass around the system to the specially constructed absorber without the subject being aware of the change. The balloon valve has a low compliance and an inflation time of 45 - 60 msec and deflation time of between 60 - 75 msec. The switching device and the pneumotachograph head and mouthpiece are supported by an adjustable arm and held at a convenient height to the

subject's mouth with the subject in either the sitting or supine position (figures 4.3 & 4.4). A Gould pneumotachograph records inspiratory flow pattern onto a Gould 2022 chart recorder. The subject breathes through a close fitting mouth piece whilst wearing a nose clip, via one way valves and exhales to atmosphere. Subjects wear dark goggles and listen to music via a pair of headphones so that they are unaware of the switching of the pneumatic valve (figure 4.4).

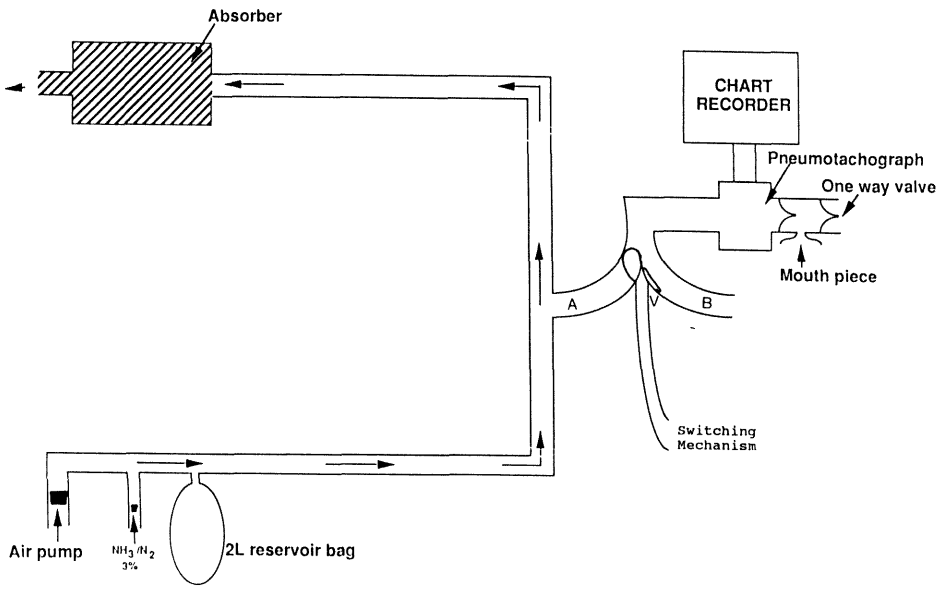


Figure 4.2 Diagram of the equipment used to measure the sensitivity of upper airway reflexes. (V) represents the balloon valve, (A) the NH_3 / Air limb, and (B) the room air limb.

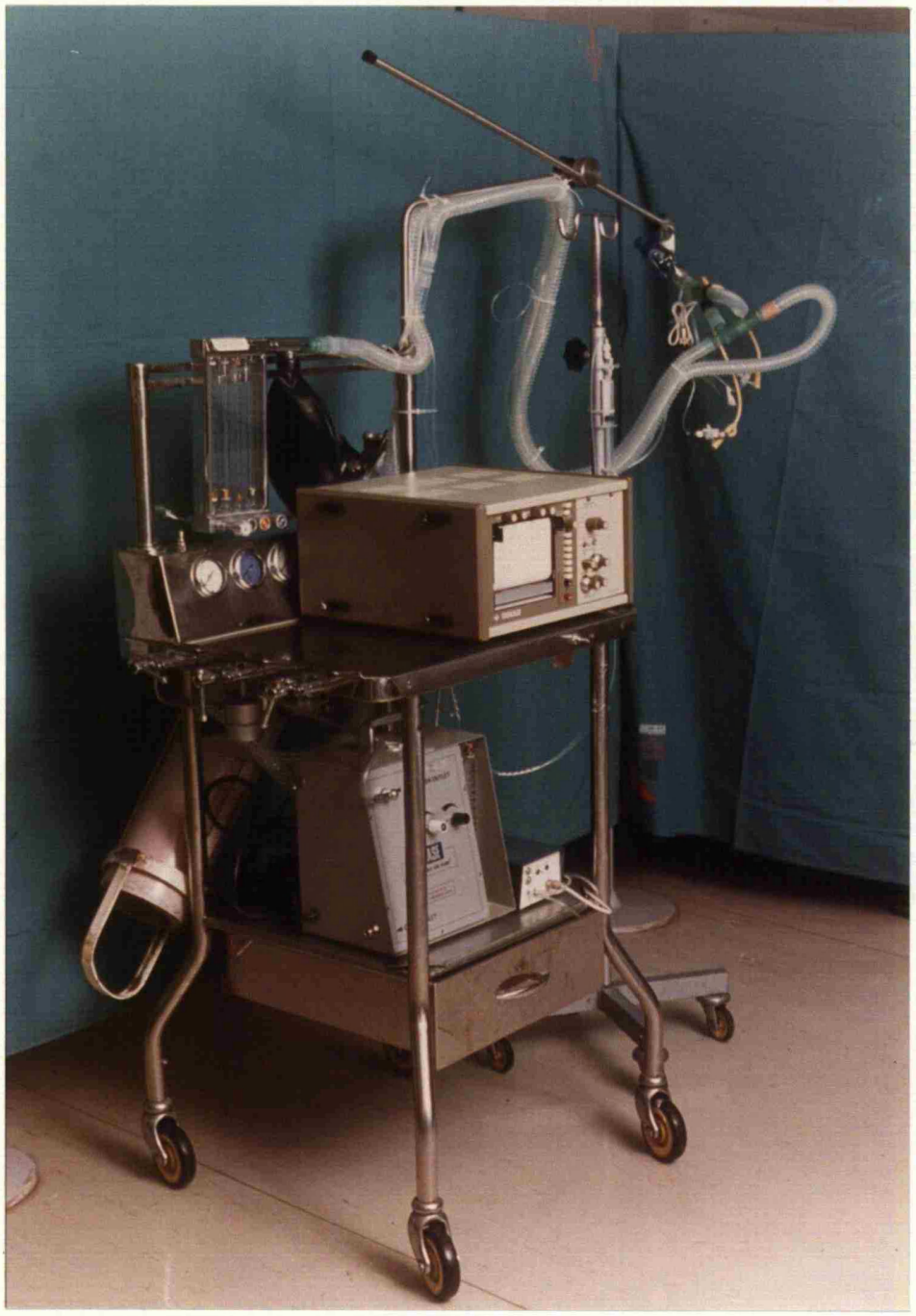


Figure 4.3 Photograph of the system used to measure the sensitivity of upper airway reflexes

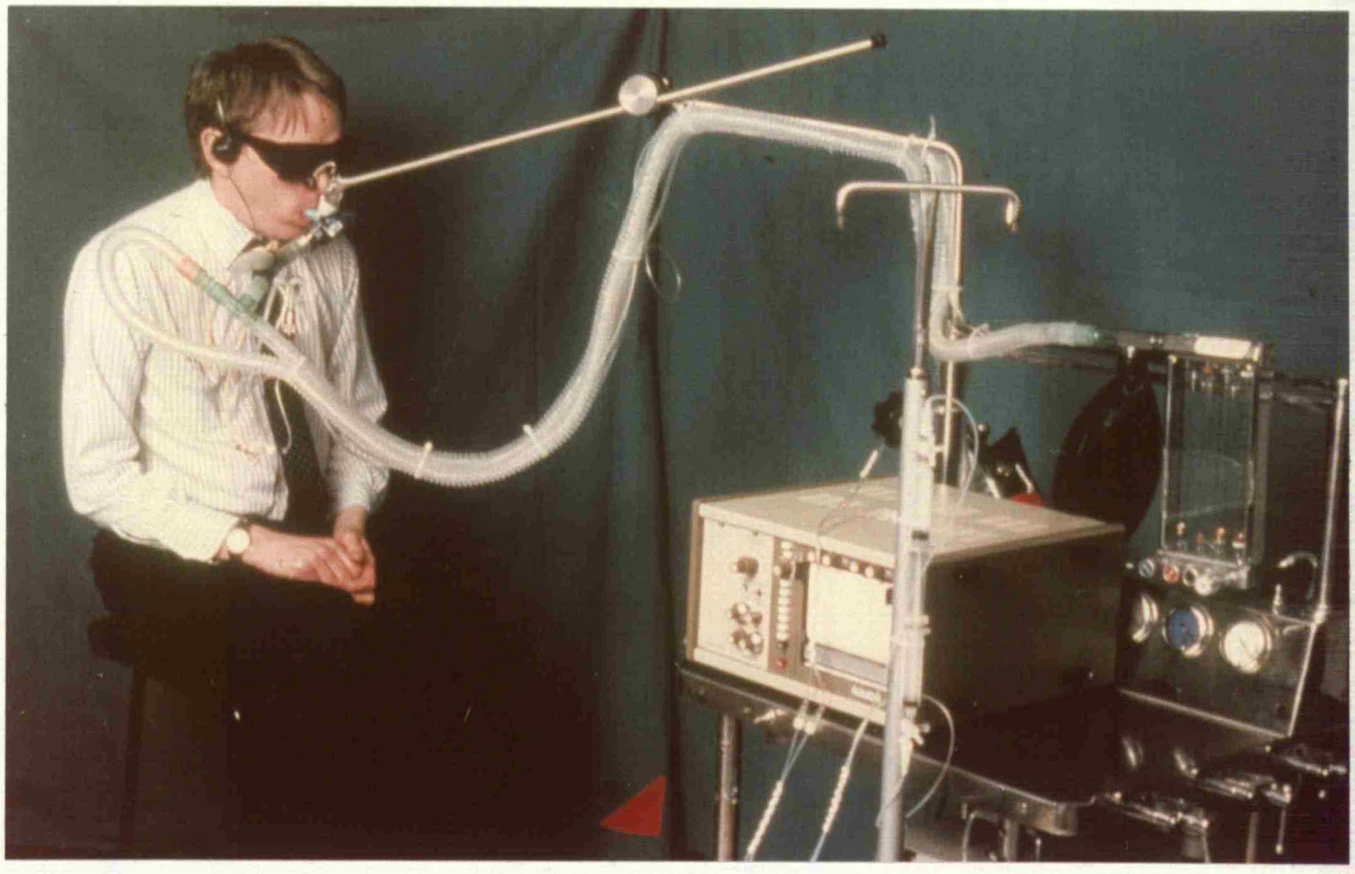


Figure 4.4 A subject breathing on the equipment used to measure the sensitivity of upper airway reflexes.

Method

The subject rests wearing blackened goggles and listening to music via a pair of headphones. A nose clip is applied and the subject is allowed to breathe through a mouthpiece via a one-way valve, the inspiratory flow being measured using a Gould pneumotachograph and recorded on a chart recorder.The balloon valve is operated by the investigator so that the subject takes one inspiration from the NH_3 / Air circuit.

A glottic stop (figure 4.5) was 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 0.5sec".*

The concentration of NH_3 is increased in regular steps until the concentration is reached to produce a glottic stop.

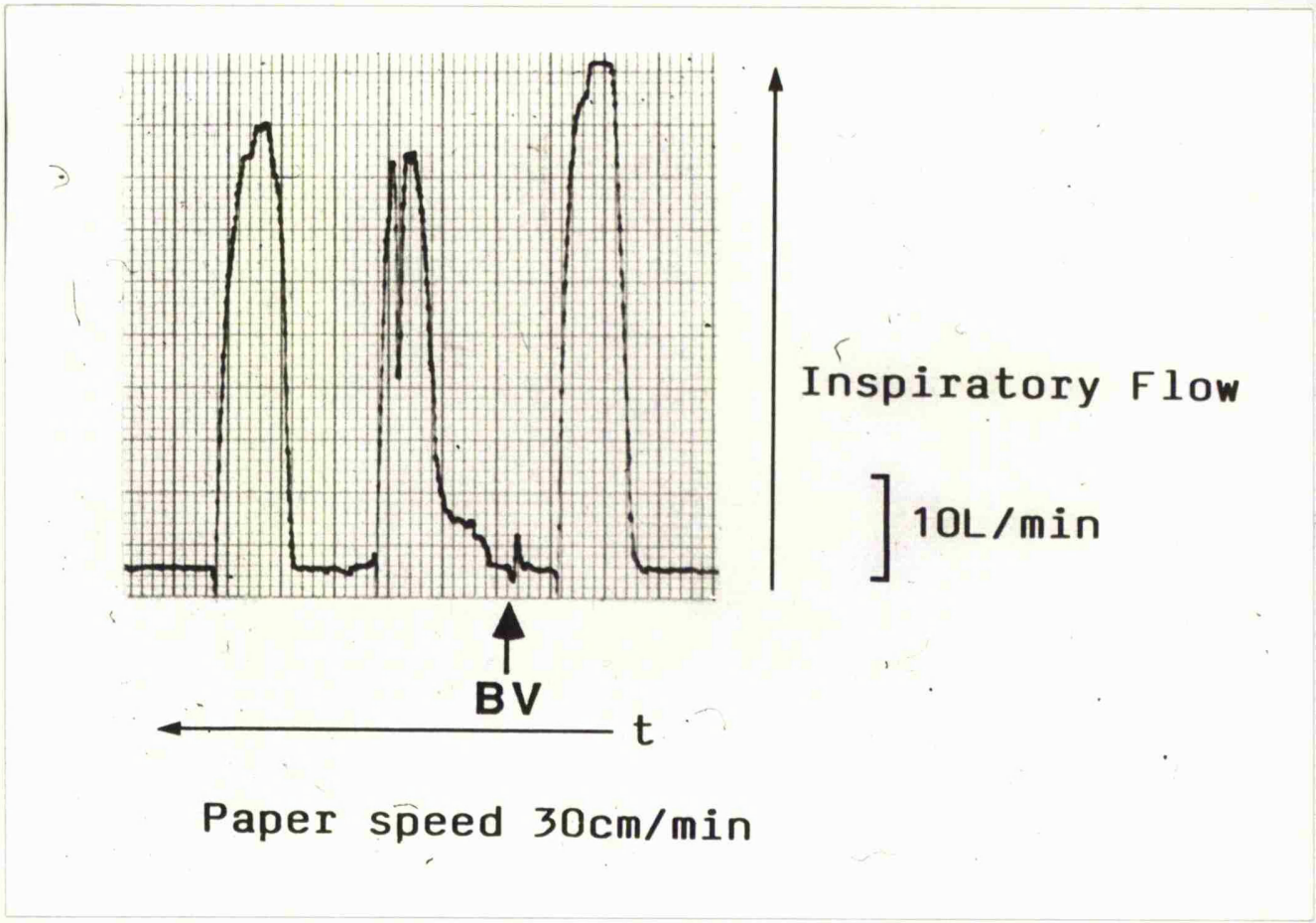


Figure 4.5 An example of a glottic stop recording. BV = Switching of the balloon valve, allowing the subject to take one breath from the ammonia-air limb. Paper speed 30 cm min^{-1}; calibration bar = 10 litre min^{-1}.

Calibration of the equipment

The accurate measurement of low concentrations of NH_3 in air proved to be a difficult problem. Mass spectrometry was attempted but due to band overlap and equipment failure this was not successful. Gas chromatography and chemical methods were tried but again were not successful.

Eventually we used a Bruel and Kjaer multigas monitor type 1302. This is an industrial gas monitor, having a large number of applications in the chemical industry for the monitoring of environmental pollution.

The measurement principle is based on the photo acoustic infrared detection method. This piece of equipment was set up and calibrated by the Bruel and Kjaer company to measure NH_3 to a concentration of 10 ppm (0.001%) NH_3. The selectivity of the multigas monitor 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 monitor is zero calibrated and then span calibrated using the known certified NH_3 concentration from the British Oxygen Company.

Principle involved in the photo acoustic method of gas analysis.

The Bruel and Kjaer multi-gas monitor type 1302 is a microprocessor controlled gas analyser the measurement principle is based on the photo acoustic infra-red detection method. This means that the gas analyser can be used to measure almost any gas which absorbs infra-red light. Depending on the gas to be analysed appropriate optical filters are installed. The reliability of measurement results from regular self tests and the ability of the analyser to compensate any measurement for temperature fluctuations, water vapour interference and interference from other gases that are present.

Selectivity

The selectivity of the multi-gas analyser is determined by the optical filters installed in the filter carousel. By studying the absorption spectra of the gases to be monitored the most appropriate filter is chosen.
The filter for ammonia measurements is the 0976 with a centre wave length of 10.6 micrometers. This produces a detection limit of 0.15 ppm at 25^{o}C at 1 atm.
Water vapour which is nearly always present in ambient air absorbs infra-red light at nearly all wavelengths so that irrespective of which optical filter is being used, water vapour will contribute to the total acoustic signal in the analysis cell. The higher the concentration of water vapour in the cell the more it contributes to the measured signal. However a special optical filter is permanently installed in the filter carousel which allows the water vapour contribution to be measured separately during each measurement cycle, and therefore the gas analyser is able to compensate for the interference produced by water vapour.

Measurement Cycle

Details of the measurement cycle are shown in figure 4.6.

1. The pump draws air from the sampling point through two air filters to flush out the "old" air in the measurement system and replace it with the "new" sample of air.

2. The "new" air sample is hermetically sealed in the analysis cell by closing the inlet and outlet valves.

3. Light from an infra-red source is reflected off a mirror, passed through a mechanical chopper, which pulsates it, and then through one of the optical filters in the filter carousel.

4. The light transmitted by the optical filter is absorbed selectively by the gas being monitored, causing the temperature of the gas to increase. The temperature of the gas increases and decreases because the light is pulsating , and this causes an equivalent increase and decrease of the pressure of the gas (acoustic signal) in the closed cell.

5. Two microphones mounted in the cell wall measure this pressure wave, which is directly proportional to the concentration of the monitored gas present in the cell.

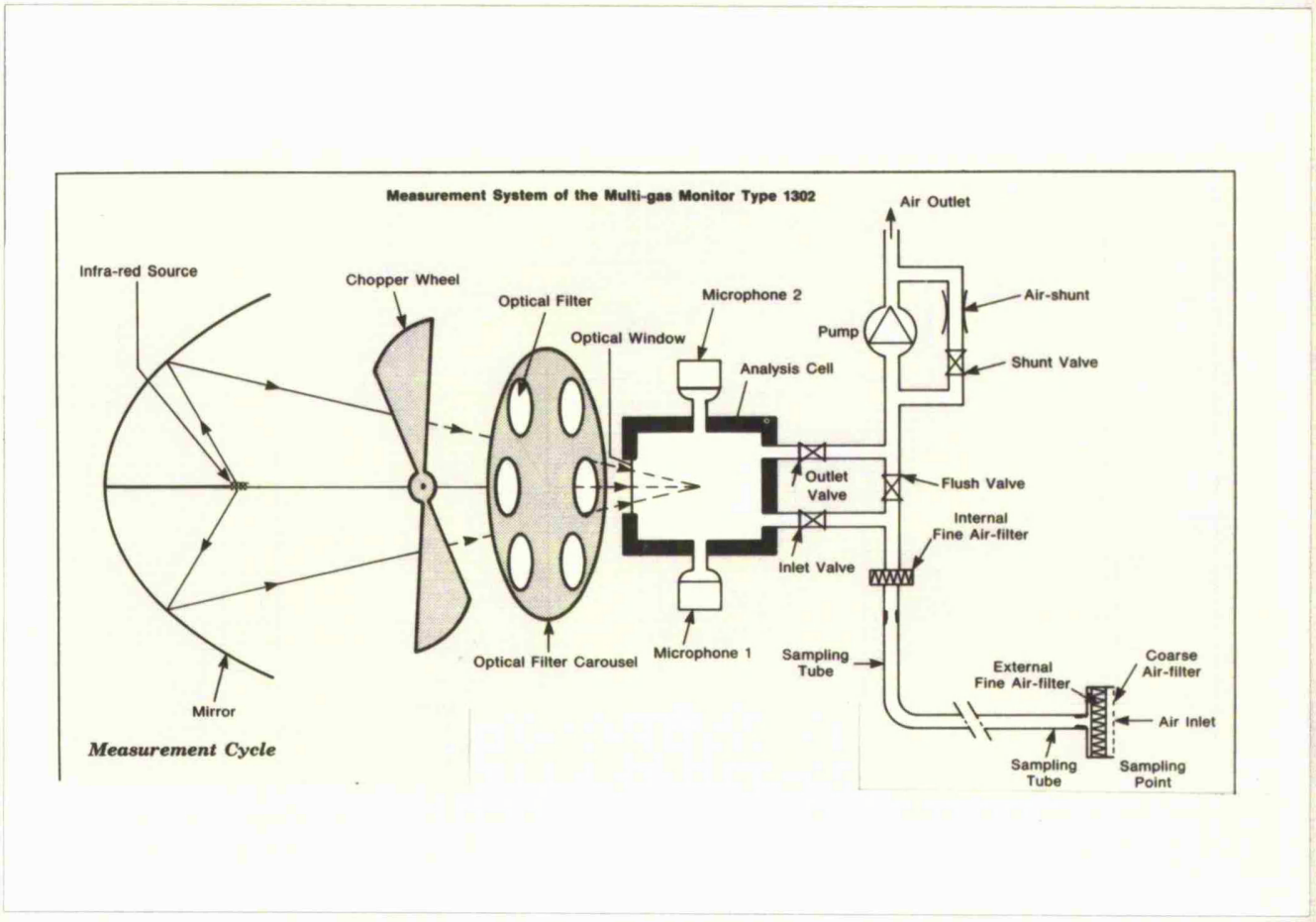


Figure 4.6 Diagram of the measurement principle used in the Bruel & Kjaer Multigas analyser type 1302.

Calibration of the circuit.

Gas flows (flowmeter calibration)

Air Flow

Air flow via the oxygen flowmeter was calibrated using a dry gas meter. With the flowmeter set at 10 litres / min, the total measured flow over a 30 min period was 324.9 litres (10.83 litres / min).

NH_3 / N_2 flow

These results are shown below in Table 4.1, the flow of the 3.18% NH_3 / N_2 mixture via the cyclopropane flowmeter was measured using a bubble flowmeter.

Table 4.1

Flowmeter calibration

Air flowing via O_2 rotameter

Set flow (litres / min)	Actual flow (litres / min)
10	10.83

3.18 % NH_3 / N_2 via cyclopropane rotameter

Set flow (ml / min)	Actual flow (ml / min)
50	73.1
100	155.1
200	195.6
250	216.4
300	241.3
350	278.6
400	332.8
450	377.6
500	427.1
550	481.3
600	539.5
650	594.1
700	635.5
750	688.5
800	749.3
850	810.7
900	863.7
950	921.3
1000	964.6

NH_3 concentration produced within the NH_3 / Air limb

Initially zero readings were checked using gas known to contain no ammonia vapour. The multigas analyser was then span calibrated using the certified gas concentration of 3.18% NH_3 / N_2 supplied by B.O.C.

The circuit was then calibrated in a number of stages.

The time to produce a reading and the concentration of NH_3 was measured in the circuit opposite to the switching valve. The air flow was maintained at 10 litres / min and the NH_3 / N_2 flow was started at 50 ml / min the bag was squeezed twice and the measurements of NH_3 concentration were recorded. Ten measurements by the multigas analyser were made over 3 - 4 min. Then the NH_3 / N_2 flow ceased and the time for the reading to fall to zero was noted. The bag was squeezed twice during this phase and the zero reading was always achieved within 2 min. This testing sequence was repeated at NH_3 / Air flow rates between 100ml - 1000ml. Measurements were made in different parts of the circuit and found not to vary.
The concentration of NH_3 produced in the system varied between 76 - 3550 ppm NH_3 at the differing flow rates. The time required to achieve 95% of the final concentration was 105 sec at the lower flow meter settings of 50 and 100ml. At higher flows the time to reach 95% of the final concentration was 70 seconds.
The data is shown in Table 4.2 and summarised in Table 4.3.

TABLE 4.2

NH_3 concentration produced in NH_3 / Air limb

Calibration data

Air flow set at 10 litres / min

NH_3 / Air rotameter	**NH_3 ppm**	**% NH_3**
50ml / min	160	0.01
	129	0.0129
	82	0.0082
	114	0.0114
	113	0.0113
	78	0.0078
	85	0.0085
	86	0.0086
	77	0.0077
	52	0.0052
Mean	**76**	**0.0076**
SD	**12.3**	
100ml / min	236	0.0236
	260	0.026
	248	0.0248
	233	0.0233
	217	0.0217
	247	0.0247
	257	0.0257
	252	0.0252
	244	0.0244
	257	0.0257
Mean	**251**	**0.0251**
SD	**12.6**	
150ml /min	280	0.028
	345	0.0345
	326	0.0326
	298	0.0298
	327	0.0327
	354	0.0354
	367	0.0367
	327	0.0327
	314	0.0314
	335	0.0335
Mean	**327**	**0.0327**
SD	**25.68**	

Table 4.2 (ctd)

NH_3 / Air rotameter	**NH_3 ppm**	**% NH_3**
200ml / min	475	0.0475
	569	0.0569
	493	0.0493
	516	0.0516
	543	0.0543
	534	0.0534
	406	0.0406
	541	0.0541
	509	0.0509
	630	0.0630
Mean	**524**	**0.0524**
SD	**33.7**	
250ml /min	577	0.0577
	614	0.0614
	637	0.0637
	589	0.0589
	610	0.0610
	579	0.0579
	598	0.0598
	596	0.0596
	590	0.0590
	610	0.061
Mean	**600**	**0.06**
SD	**18.18**	
300ml / min	916	0.0916
	887	0.0887
	897	0.0897
	860	0.086
	886	0.0886
	885	0.0885
	884	0.0884
	847	0.0847
	889	0.0889
	887	0.0887
Mean	**878**	**0.0878**
SD	**17.8**	
400ml / min	1180	0.118
	1170	0.117
	1160	0.116
	1160	0.116
	1150	0.115
	1150	0.115
	1160	0.116
	1110	0.111
	1130	0.113
	1150	0.115
Mean	**1140**	**0.114**
SD	**18.8**	

Table 4.2 (ctd)

NH_3 / Air rotameter	**NH_3 ppm**	**% NH_3**
500ml / min	1790	0.179
	1630	0.163
	1580	0.158
	1710	0.171
	1590	0.159
	1610	0.161
	1590	0.159
	1630	0.163
	1620	0.162
	1660	0.166
Mean	**1620**	**0.162**
SD	**61.5**	
600ml / min	2030	0.203
	2010	0.201
	1980	0.198
	1880	0.188
	1950	0.195
	1880	0.188
	2030	0.203
	1990	0.199
	1940	0.194
	1990	0.199
Mean	**1970**	**0.197**
SD	**52.1**	
700ml / min	2250	0.225
	2420	0.242
	2450	0.245
	2410	0.241
	2300	0.23
	2330	0.233
	2310	0.231
	2410	0.241
	2380	0.238
	2340	0.234
Mean	**2360**	**0.236**
SD	**60.4**	
800 ml / min	2790	0.279
	2950	0.295
	2750	0.275
	2790	0.279
	2820	0.282
	2770	0.277
	2780	0.278
	2810	0.281
	2840	0.284
	2740	0.274
Mean	**2790**	**0.279**
SD	**56.6**	

Table 4.2 (ctd)

NH_3 / Air rotameter	**NH_3 ppm**	**% NH_3**
900 ml / min	3560	0.365
	3120	0.312
	3090	0.309
	3200	0.32
	3080	0.308
	3140	0.314
	3270	0.327
	3020	0.302
	3210	0.321
	3180	0.318
Mean	**3160**	**0.316**
SD	**142.2**	
1000ml / min	2990	0.299
	3350	0.335
	3390	0.339
	3530	0.353
	3470	0.347
	3560	0.356
	3540	0.354
	3510	0.351
	3590	0.359
	3570	0.357
Mean	**3550**	**0.355**
SD	**170.2**	

Table 4.3

Summary of calibration data

Rotameter setting	Measured flow ml / min mean (SEM)	Final [NH_3] ppm mean (SD)	t (sec) 95% final [NH_3]
50	73.1 (9.1)	76 (12.3)	105
100	155.1 (1.02)	251 (12.6)	105
150	174.3 (1.4)	327 (25.7)	70
200	195.6 (0.85)	524 (33.7)	70
250	216.4 (0.9)	600 (18.2)	70
300	241.3 (0.54)	878 (17.8)	70
400	332.8 (0.88)	1140 (18.8)	70
500	427.1 (0.2)	1620 (61.5)	70
600	539.5 (2.95)	1970 (52.1)	70
700	635.5 (1.35)	2360 (60.4)	70
800	749.3 (0.63)	2790 (56.6)	70
900	863.7 (0.83)	3160 (142.2)	70
1000	964.6 (3.11)	3550 (170.2)	70

Absorber function and room air pollution measurements

Measurements were made at the exit point from the absorber, for five minutes at each NH_3 / Air flow rate with the concentration of NH_3 (ppm) being measured every minute.
The air flow was set at 10 litres / min for all measurements.

NH_3 / N_2 flow (ml / min)	NH_3 (ppm)
zero	0.69
	0.69
	0.55
	0.55
	0.61
300 ml / min	1.18
	0.81
	1.24
	1.13
	0.95
1000 ml / min	1.76
	0.79
	1.06
	0.98
	1.57

Room air measurements were made for five minutes following this

Time (min)	NH_3 ppm (room air)
1	1.36
2	1.54
3	1.42
4	1.49
5	1.52

Reproducibility volunteer studies

Following Ethics Committee approval and informed written consent, we studied ten healthy non-smoking volunteers (8 male) age 29 - 35 yr, weight 72 - 85 Kg. The subjects were not taking any medication, and they were asked to refrain from drinking alcohol from noon the previous day, and were starved for 6hr before 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 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 nose clip 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 NH_3 limb.
The concentration of NH_3 / Air was increased in a stepwise manner in the NH_3 limb (A), starting at the lowest concentration of NH_3. The threshold level of response to the NH_3 stimulus was determined by the occurrence of a glottic stop.

We defined a glottic stop 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 0.5sec*".

The concentration of NH_3 was increased in regular steps, until a concentration was reached that produced a glottic stop.

Measurements were made on each subject every 30 min for 4 hr, (a total of eight measurements) and also single measurements on six different days at least one week apart, to determine the reliability and repeatability of our measurements.

Results

The concentrations of ammonia vapour required to produce a glottic stop in each of the ten volunteers are shown in the Table 4.4 and the data is summarised in Table 4.5 as mean, median and inter-quartile range.

Table 4.4

Volunteer data of NH_3 threshold response (NH_3TR) on different days and on the same day

Subjects A - J

Subject A	**Different days**	**Same day**
	878	524
	524	327
	524	524
	524	524
	878	524
	524	524
	-	251
	-	524
Mean	**642**	**465**
Median	**524**	**524**
IQR	**524-878**	**376-524**
Mann-Whitney p = 0.0625		

Subject B	**Different days**	**Same day**
	524	524
	878	524
	524	524
	878	524
	524	524
	524	524
	-	327
	-	524
Mean	**642**	**499**
Median	**524**	**524**
IQR	**524-878**	**524-674**
Mann-Whitney p = 0.0872		

Subject C	**Different days**	**Same day**
	524	251
	524	251
	251	524
	251	524
	524	524
	251	251
	-	251
	-	327
Mean	**387**	**363**
Median	**387**	**289**
IQR	**251-524**	**251-524**
Mann Whitney p = 0.8852		

Table 4.4 (ctd)

Subject D	**Different days**	**Same day**
	524	327
	524	327
	251	524
	251	600
	524	524
	251	524
Mean	**380**	**471**
Median	**387**	**524**
IQR	**251-524**	**327-524**
Mann-Whiney p = 0.2268		

Subject E	**Different days**	**Same day**
	524	524
	600	327
	251	327
	524	327
	524	600
	600	524
	-	524
	-	327
Mean	**504**	**435**
Median	**524**	**425**
IQR	**455-600**	**327-524**
Mann Whitney p = 0.3387		

Subject F	**Different days**	**Same day**
	524	524
	251	524
	878	524
	524	524
	524	**878**
	524	524
	-	524
	-	327
Mean	**537**	**544**
Median	**524**	**524**
IQR	**455-612**	**524-674**
Mann Whitney p = 1.00		

Table 4.4 (ctd)

Subject G	**Different days**	**Same day**
	524	524
	524	327
	524	327
	524	524
	878	524
	524	327
	-	878
Mean	**583**	**490**
Median	**524**	**327**
IQR	**524-612**	**327-524**
Mann-Whitney p = 0.2177		

Subject H	**Different days**	**Same day**
	524	524
	524	524
	524	524
	524	600
	524	524
	327	524
Mean	**495**	**536**
Median	**524**	**524**
IQR	**524-674**	**524-600**
Mann Whitney p = 0.2116		

Subject I	**Different days**	**Same day**
	600	524
	524	524
	524	524
	600	524
	524	524
	524	600
Mean	**549**	**536**
Median	**524**	**524**
IQR	**524-600**	**524-543**
Mann Whitney p = 0.5948		

Subject J	**Different days**	**Same day**
	524	524
	524	1140
	878	524
	600	524
	524	524
	524	524
Mean	**596**	**627**
Median	**524**	**524**
IQR	**524-699**	**524-678**
Mann Whitney p = 0.7526		

Table 4.5

Summary of threshold (NH_3TR) ppm required to cause a glottic stop in ten subjects mean (median) (interquartile range).

Subject	Different days	Same day
A	642 (524) (524-878)	465 (524) (376-524)
B	642 (524) (524-878)	499 (524) (524-674)
C	387 (387) (251-524)	363 (289) (251-524)
D	380 (387) (251-524)	471 (524) (327-524)
E	504 (524) (455-600)	435 (425) (327-524)
F	537 (524) (455-612)	544 (524) (524-674)
G	583 (524) (524-612)	490 (327) (327-524)
H	495 (524) (524-674)	536 (524) (524-600)
I	549 (524) (524-600)	536 (524) (524-543)
J	596 (524) (524-699)	627 (524) (524-678)

Statistical analysis

The mean threshold level of sensitivity of the upper airway varied between 363 ppm and 642 ppm NH_3. The data was analysed using analysis of variance, measurements made repeatedly on one day were analysed using Kruskal-Wallis one-way ANOVA, no significant differences between subjects was found. Measurements made on separate days was analysed using Kruskal-Wallis one-way ANOVA and no significant differences between subjects was found. Measurements made on the same day and on different days were analysed using Friedman two-way ANOVA and no significant differences were found.

Statistical analysis using Mann-Whitney U tests, showed no significant differences between the measurements made on one subject repeatedly on one day compared with measurements made on separate days.

We found that when the NH_3 stimulus was presented in a random order instead of as an ascending challenge the threshold levels were the same, but the subjects found this to be considerably more unpleasant; thus this was performed in only five subjects.

Acknowledgement

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Measurement of the sensitivity of upper airway reflexes. **Br.J.Anaesth** 1993;70:126-130.

ii) Development of the method to measure the movements of the vocal cords on induction of anaesthesia

To record the movements of the vocal cords on induction of anaesthesia, we used an Olympus LF1 fibre-optic scope with a Panasonic video camera CCD GL110 AE that fitted to the eyepiece of the scope via an Olympus adapter type AK-2C. Video images were recorded on Sony Umatic tape using a Sony Umatic video recorder type 5630.

Early pilot studies indicated the need for careful preparation of the nasal mucosa, to prevent trauma and to minimise the discomfort to the patient. We soon discovered that the use of a drying agent was necessary to prevent accumulation of secretions obscuring the view through the fibre-optic scope. In early work we used benzocaine lozenges to anaesthetise the posterior pharyngeal wall and to aid the passage of the scope but we found these to be ineffective and subsequently we administered glycopyronium intramuscularly 1 hour prior to the investigation. On arrival of the patient in the anaesthetic room we sprayed the nasal mucosa with 4% lignocaine spray, we found that it was important not to be hurried in preparation of the nasal mucosa and that it was helpful to pass a size 7.0 nasopharyngeal airway through the nasal passage before introducing the fibre-optic scope. We usually chose the right nostril if possible as this was found to be easier to visualise the vocal cords from.

We adapted an oxygen mask to allow the patient to receive oxygen whilst the scope was manipulated through the nasal passages. When the vocal cords were visualised easily anaesthesia was induced. It helped considerably if an assistant supported the patient's chin as he was anaesthetised and maintained the head in the extended position.

Following induction of anaesthesia the movements of the vocal cords were recorded on to video tape for 60 seconds.

The video recordings of the movements of the vocal cords were analysed by a blinded observer, using video equipment with high quality freeze frame facilities. This was performed at the university audio-visual laboratory. The video tape was played back and at regular time intervals measurements of the angle between the vocal cords was made using a goniometer.

Discussion

Laryngeal reflexes are evoked by chemical or mechanical stimuli via receptors thought to be located in the hypopharynx and larynx (Hinkle & Tantum 1971). Afferent pathways travel in both the parasympathetic and sympathetic nervous system and the motor response is temporary closure of the vocal cords (Pontoppidan & Beecher 1960). In 1870 Kratschmer 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 (1950), 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 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 placed around the subjects waist. The concentration of ammonia required to produce this reflex was 800 - 1600 ppm NH_3. Pontoppidan and Beecher (1960), investigated the effects of ageing on laryngeal reflexes, using a similar method. Respiration was monitored with a wet spirometer, but their system contained a considerable dead space (approx. 300ml). The results indicated a decrease in protective laryngeal reflexes with increasing age. Hinkle and Tantum (1971), used a multiple syringe technique with a large dead space to investigate the effects of codeine phosphate on laryngeal reflexes, and Duckett and Hirsh (1980), investigated glottic competence in a small number of post-operative patients, and found increased thresholds in all patients who had undergone tracheal intubation.

Groves and Rees (1987), studied the effect of intravenous Diazemuls and lormetazepam on laryngeal reflexes in volunteers. After Diazemuls 15mg

intravenously the NH_3 thresholds were increased by 200%, and remained elevated for over 4hr.

All of the above studies suffered from several problems leading to inaccuracy. The final concentration of NH_3 reaching the subject's larynx was not known accurately because of large dead spaces. It may also have been affected by streaming or channelling of gas flow through the breathing system; the subjects might 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 dead space (300ml), and 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 the dead space volume was reduced to 48ml 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.

Ammonia vapour is known to stimulate irritant and pressure receptors within the upper airway (Widdicombe 1986, Boushey & Richardson 1974). The reflex response to this stimulation is glottic closure and a brief stop in inspiration at low levels of stimulation. Higher levels of stimulation result in a laryngeal cough; a cough without preceding inspiratory effort (Widdicombe 1977). Evidence to support the theory that these reflex responses to inhaled ammonia arise from stimulation of upper airway receptors is provided in a previous study by Hinckle & Tantum (1971). They anaesthetised the upper airway and superior laryngeal nerves of volunteers with topical lignocaine as judged by voice changes and an inability to handle secretions, and they showed an eight fold rise in the threshold concentration of ammonia required to produce glottic closure.

From these results it is clear that this reflex is mediated via upper airway receptors. In work by Szereda-Przestaszewska & Widdicombe (1973) it was found in cats, that the response to insufflation of NH_3 vapour across the larynx was virtually abolished by the sectioning of the superior laryngeal nerve. This provides further evidence in support of an upper airway site for the afferent limb of this reflex.

In all our studies we found that glottic closure in response to inhaled ammonia occurs early during inspiration. This implies, not only rapidly responding receptors and a simple reflex arc, but also that the receptors must sense the ammonia stimulus early and therefore it is probable that they are situated within the upper airway.

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 previous work by Boushey & Richardson (1974), it was 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, with interruption to inspiration. At higher levels of irritant vapour inhalation a cough is elicited. A repeatable observation in our subjects was that the glottic stop response occurred at lower concentrations of NH_3 vapour than were required to elicit a cough response.

Several of our volunteers spontaneously reported a feeling of sudden involuntary closure in the throat when a glottic stop occurred.

In this chapter I have described the method of measuring the threshold response of the upper airway using an NH_3 stimulus. The subjects found that the technique was acceptable and not unpleasant. Measurements in young non-smoking volunteers showed a mean threshold level of response

of 363 - 642 ppm NH_3. There were no significant differences in the mean threshold levels recorded on the same day or on separate days.
A technique has also been described for measuring movements of the vocal cords on induction of anaesthesia.

CHAPTER 5

Study 5.1

The effect of age on the sensitivity of upper airway reflexes.

Introduction

Reflex activity is thought to diminish with advancing age. Laryngeal reflexes in the elderly appear to be less active both during induction of anaesthesia and in the post-operative period in the recovery room and on the surgical wards, when compared with younger patients. This suggests that protection of the airway may be impaired in the elderly group (Davenport 1983).

The protective reflex of the larynx is evoked by stimulation of receptors thought to be located in the hypopharynx and larynx. At concentrations of irritant vapour below that required to produce a cough, the response is glottic closure, and a brief pause in inspiration (Widdicombe 1977). The upper airway is sensitive to both chemical and mechanical stimuli, the former being both quantifiable and reproducible (Langton, Murphy & Barker 1993).

Using equipment and the technique that I have described in the previous chapter, we measured the sensitivity of the upper airway in differing age groups.

Previous workers (Pontoppidan & Beecher 1960) found a six fold increase in the concentration of inhaled ammonia vapour required to produce a reflex stop in inspiration from the second to the eighth and ninth decades. However the study population contained a large proportion of

smokers and our early work (Erskine, Murphy & Langton 1992) indicated that smokers have considerably more sensitive upper airway reflexes compared with non-smokers. The aim of this study was to measure the threshold level of sensitivity of the upper airway (NH_3TR) in non-smokers over a broad age range in order to assess the effect of age alone on upper airway reflex sensitivity.

Method

Following Ethics Committee approval and written informed consent, we studied 102 healthy, non-smoking subjects, evenly distributed over the age range 17 - 96yr. The majority (85) were pre-operative elective surgical patients, the remainder being members of this department, nursing staff and nine patients from geriatric wards.
We excluded subjects with mental or neurological impairment, chronic bronchitis and asthma, a history of upper respiratory tract infection in the last month, and anybody taking sedative medication. Two subjects had smoked in the past, one stopped 25 years previously, the other stopped 4 weeks before the measurement.

Measurements were made either in our laboratory or on the ward using the same portable equipment. A single measure of NH_3TR was made, using the method described in Chapter 4.

Table 5.1

NH_3TR (ppm) age and medication of subjects.

Subject	Age	Sex	Medication	NH_3TR (ppm)
A	79	m	-	1140
B	75	m	-	1140
C	68	m	Warfarin,digoxin captopril, frusemide	1140
D	79	m	bendrofluazide	1140
E	66	m	Atenolol,diltiazem,GTN	878
F	81	m	aspirin	1970
G	70	m	-	878
H	83	m	frusemide	1140
I	78	m	paracetamol	1140
J	66	m	paracetamol, Migraleve	878
K	79	m	frusemide	1620
L	75	m	bendrofluazide	1140
M	51	m	-	878
N	68	f	-	878
O	73	m	-	1140
P	71	m	-	1140
Q	73	m	oxypentifylline Frumil	878
R	82	m	GTN	1620
S	84	f	Warfarin, digoxin aspirin	1620
T	82	m	coproxamol	1970
U	55	m	-	878
V	40	m	-	878
W	61	m	-	878
X	46	m	-	600
Y	52	f	-	600
Z	46	f	-	878
AA	42	m	-	600
AB	83	f	frusemide	1620
AC	52	m	indomethicin	1140
AD	80	f	Frumil	1970
AE	60	m	aminophylline	2360
AF	50	f	-	524
AG	37	m	-	251
AH	48	m	-	524
AI	33	m	-	524
AJ	93	f	Warfarin,digoxin captopril,Frumil	1970
AK	92	f	frusemide,amiloride captopril	1970
AL	92	f	thiazide	1620
AM	89	m	Frumil	2360
AN	64	f	iron	878
AO	63	f	cefuroxime	1140

Table 5.1 (ctd)

Subject	Age	Sex	Medication	NH_3TR
AP	62	f	-	1140
AQ	57	m	-	1140
AR	55	f	Migraleve	878
AS	54	f	iron, paracetamol	1140
AT	39	m	-	878
AU	30	m	-	251
AV	31	m	-	327
AW	30	m	-	524
AX	31	f	-	327
AY	33	m	-	524
AZ	33	m	-	524
BA	34	m	-	524
BB	28	m	-	524
BC	26	m	-	524
BD	36	m	-	878
BE	30	m	-	878
BF	26	m	-	1140
BG	31	m	-	600
BH	29	m	-	524
BI	34	m	-	600
BJ	33	m	Ventolin	524
BK	36	m	Ventolin	1140
BL	27	f	-	524
BM	47	m	-	878
BN	55	m	-	878
BO	42	f	-	600
BP	19	f	-	524
BQ	93	f	Brufen,Frumil	1970
BR	21	f	-	600
BS	89	f	Frumil	1970
BT	94	f	Frumil	1970
BU	59	f	paracetamol	1140
BV	42	m	-	1140
BW	84	m	isosorbide	1620
BX	67	f	Librium,allopurinol	1140
BY	43	f	-	878
BZ	20	m	-	327
CA	46	m	-	1140
CB	17	f	-	524
CC	23	f	-	524
CD	23	m	-	600
CE	21	f	-	600
CF	96	m	Brufen,paracetamol	1970
CG	91	f	frusemide,amiloride	1970
CH	92	f	frusemide,slow K	1795
CI	93	f	paracetamol	1620
CJ	95	m	Frumil	1620
CK	90	m	paracetamol	1620
CL	75	f	frusemide	878
CM	86	m	nifedipine,GTN	1620
CN	92	m	paracetamol	1795
CO	85	m	-	1620
CP	79	f	-	878

Table 5.1 (ctd)

Subject	Age	Sex	Medication	NH_3TR
CQ	27	f	-	327
CR	21	f	-	524
CS	23	f	-	600
CT	49	m	-	524
CU	59	f	-	600
CV	54	m	-	1140
CW	65	f	Voltarol	1140
CX	62	f	-	1140
CY	69	m	-	1620

Results

NH_3TR (ppm) was plotted against age (yr) for each subject (fig 5.1). It can be clearly seen that there was an increase in NH_3TR with advancing age. The correlation coefficient was calculated as +0.85 indicating a strong positive correlation between age and NH_3TR. The mean NH_3TR for the age group 21-30 yr (n=14) was 571 ppm (SEM 41.5), compared with a value of 1791 ppm (SEM 52) for the age group aged 86-95 yr (n=14).

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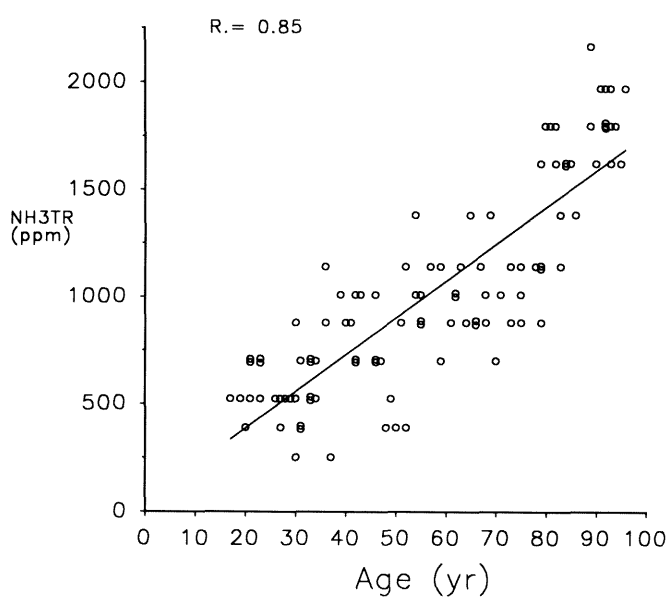

Figure 5.1 Relationship between NH_3TR (ppm) and age (yr).

Discussion

Reflex activity is thought to diminish with advancing age. Laryngeal reflexes in the elderly appear to be less active both during induction of anaesthesia and in the recovery room compared with the younger patient. This suggests that protection of the airway may be impaired throughout the perioperative period in the elderly group (Davenport 1983). The elderly are known to lose peripheral reflexes, but this may be of no clinical significance. However, a reduction in the sensitivity of upper airway reflexes associated with age may well be important, particularly following anaesthesia and sedation, when full airway protection may be delayed with a consequent increased risk of aspiration.

Pontoppidan and Beecher (1960) carried out a similar study using ammonia vapour. They studied 103 subjects aged 15-84yr and found that the threshold increased more than six fold from the second to the eighth and ninth decades; and that the inter subject variability in sensitivity increased with age. However there are several areas in their methodology and study population that may have led to inaccuracies.

Firstly, the breathing system used contained a large canister into which the ammonia vapour was injected. This could have allowed streaming to occur, and, depending upon inspiratory flow and the timing of inspiration, the concentration of ammonia reaching the subject may have been quite variable. Also, depending upon the tidal volume and inspiratory flow rate of the subject, the stimulus may have been presented to the upper airway at differing times during the respiratory cycle. They stated that the actual concentration of inhaled ammonia was unknown but was assumed to be directly proportional to the absolute amount of ammonia employed. Furthermore seven subjects failed to respond to the maximum delivered

stimulus of 50ml of ammonia, which is also suggestive of marked variability in the stimulus.

Secondly a metabolic spirometer was used to record the change in inspiratory flow and this is likely to have been insensitive to subtle changes in air flow.

Finally their population contained a high proportion of smokers (85%), varying from 33% in the 70-79 yr group to 83% in the 50-59 yr group. They found no consistent influence of smoking on upper airway reflex sensitivity but, we have found that subjects who regularly smoke greater than 15 cigarettes per day have a significantly lower NH_3TR than an equivalent group of non-smokers of the same age (Erskine & Murphy 1992) indicating that smokers have more sensitive upper airway reflexes than non-smokers. Therefore we excluded smokers in our study.

In general the results of the investigation into the sensitivity of the upper airway with advancing age support Pontoppidan and Beecher's work, showing an increase in NH_3TR with increasing age. However, the mean NH_3TR increased only threefold from the third to the ninth decades, half of that found in the previous study. We also found no increase in inter subject variability of response with age and in general our data were more tightly clustered in each age group.

These factors, including the lack of difference between smokers and non-smokers in the original study may be explained by the design of the ammonia delivery apparatus.

The cause of this increased reflex threshold in the elderly is unknown. The irritant receptors in the upper airway are thought to consist of free nerve endings ramifying among epithelial cells and have been classified as type 1 rapidly adapting receptors, however no nervous end organ has been specifically identified histologically. Increasing age is associated with a reduction in the population of nerve endings and combined with the

thickening that occurs in the mucosa of the upper airway reducing penetration of noxious chemicals, this may lead to an apparent increase in stimulation threshold. A decrease in amplitude of electrical potentials in pulmonary afferent vagal fibres with age, possibly due to degenerative changes in sensory neurones of the Nodose (Vagal) ganglion, has been described suggesting a primary alteration in the receptors and afferent nerve fibres (Brizzee & Ordy 1979) and a similar mechanism may affect fibres from the superior laryngeal nerve. In a study by Rosenberg (1989), age related changes in the internal branch of the rat superior laryngeal nerve were investigated. Female Wistar rats of differing age ranges, young (3-5 months), old (25 months) and very old (29-30 months) were studied using electron microscopic morphometric techniques. Total fibre counts, fibre populations (size categories), and mean fibre size for myelinated and unmyelinated fibres did not change with age. Qualitative changes were consistent with segmental demyelination and axonal degeneration in the older animals. There was also a significant age-related increase in the volume fraction of adexonal Schwann cell cytoplasm. Ultrastructural correlates of intracellular support and axonal transport showed a significant decrease in the numerical density of neurofilaments in the older animals. There was also a significant increase in the volume fraction of the intrafascicular extracellular space indicating a late, age related change in the extracellular environment. These changes could lead to decreased conduction velocity or complete fibre dysfunction. A number of these changes resembled those of aged human peripheral nerves already examined. In addition, a 37% decrease in fibres of nerve trunks may be expected in a 75yr old man when compared with a 30yr old. Demyelination associated with age may also contribute.

In general it seems likely that the effect that we have observed is the result of a combination of features of the ageing process on the nervous system, both peripheral and central.

It is not possible to directly infer from our results that a progressively greater NH_3TR associated with the advance of age, equates directly with increased risk of aspiration. However, the increased reflex stimulus threshold we have demonstrated may be a contributory factor in the elderly and emphasises the need for increased vigilance for the return of upper airway reflexes following further depression by anaesthetic agents.

A reduction in the sensitivity of upper airway reflexes associated with increasing age may well be important particularly following anaesthesia and sedation, when full airway protection may be delayed with a consequent increased risk of aspiration.

Overall our results support previous work, and we have shown an increase in NH_3TR with increasing age. This may be due to the effect of ageing on the nervous system both peripherally and centrally.

CHAPTER 6

Smoking and Anaesthesia

Smoking is an important cause of peri-operative morbidity (Warner & Offord 1989, Pearce & Jones 1984). Post-operative pulmonary complications occur up to six times more frequently in smokers than in non-smokers (Morton 1944) and smokers carry a 70% greater risk of coronary artery disease (Beckers & Camu 1991). In anaesthetic practice upper airway problems such as coughing, laryngospasm on induction of anaesthesia and bronchospasm following tracheal intubation are thought to be far more common in smokers as are problems with the airway following tracheal extubation and recovery from anaesthesia (Conroy 1969). Also during recovery from anaesthesia smokers are at increased risk of hypoxaemia (Tait & Kyff 1990).

Cigarette smoke contains over 4000 identified substances (Holbrook 1987) with a wide range of effects on the cardiovascular, respiratory, gastrointestinal, renal, haemostatic, and immune systems and on drug metabolism and patient mood. Between 80% and 90% of cigarette smoke is gaseous consisting mainly of nitrogen, oxygen and carbon dioxide, the remainder is particulate. Carbon monoxide (CO) and nicotine are the major toxic ingredients while a number of elements are ciliotoxic, irritant and carcinogenic.

Some of the effects of smoking are chronic and irreversible. There is evidence, however, to show that a significant improvement in some of the adverse pathophysiological effects can be achieved by even a short period of pre-operative abstinence.

The effects of smoking on the cardiovascular system

Cigarette smokers are more likely to die post-operatively from ischaemic heart disease than non-smokers (Goldman & Caldera 1977). Vodinh & Bonnet (1989) found that 38% of vascular surgical patients who had an intraoperative cardiac complication, 80% were current or ex-smokers. Although existing atheromatous changes are unlikely to be affected by pre-operative abstinence, the adverse effects of carbon monoxide and nicotine are particularly amenable to pre-operative abstinence.

Carbon monoxide

Carbon monoxide (CO) is present in cigarette smoke at a concentration of about 400 ppm. The affinity of CO for haemoglobin (Hb) is 200 times that of O_2 and smokers have carboxyhaemoglobin (COHb) concentrations of between 5-15% compared with 0.3-1.6% in the non-smoking population (Cole 1981, Sillett & Wilson 1978). In contrast environmental pollution is of little importance, policemen on traffic duty having mean COHb concentrations of only 1.9% (Castelden & Cole 1974). COHb concentrations vary amongst smokers being dependent upon cigarette type, frequency and method of smoking; however concentrations remain fairly constant in individuals throughout the day (Castelden & Cole 1974). COHb half-life ($t_{1/2}$) is dependent on pulmonary ventilation and is thus longer at night and shorter during strenuous exercise. Smokers retiring to bed with a mean COHb of 8% wake with a mean of 3.7% still significantly greater than a non-smoker (Castleden & Cole 1974).

Carbon monoxide has two important effects: firstly to decrease the amount of Hb available to bind O_2 and a left shift of the oxyhaemoglobin dissociation curve (Ellenhorn & Arceloux 1988). The combined effect is to decrease O_2 availability to tissues. Also carbon monoxide binds with cytochrome oxidase and myoglobin and inactivates mitochondrial enzymes in cardiac muscle resulting in reduced intracellular O_2 transport and usage and a negative inotropic effect. The chronic tissue hypoxia results in a compensatory increase in red cell mass, improving O_2 content but only at the expense of increased plasma viscosity. These effects have greater significance in the smoker with coronary artery disease. Advice for the period of pre-operative abstinence should take into account the variation in the $t_{1/2}$ of COHb under differing conditions. Thus during the day a period of 12hr will result in a decrease of COHb to normal in most smokers and they should be advised not to smoke the evening prior to a morning operation.

Nicotine

Nicotine is an alkaloid, with ganglion stimulating and inhibitory effects. It is also a co-carcinogen. Its overall effects on the cardiovascular system are stimulant resulting from the release of catecholamines from the adrenal medulla and a direct effect on the carotid body, aortic chemoreceptors and autonomic ganglia. The net results are an increase in heart rate, systolic and diastolic blood pressure and peripheral vascular resistance. The increased myocardial contractility results in increased myocardial oxygen consumption which is combined with an increase in myocardial excitability and coronary vascular resistance. This combination of factors leads to a reduced myocardial oxygen supply / demand ratio. Nicotine may also exacerbate the myocardial cell damage which occurs

during a period of ischaemia by increasing intracellular calcium concentrations (Anderson & Belani 1990). Plasma nicotine concentrations reach 15-50 ng /ml in smokers (Ellenhorn & Arceloux 1988) the $t_{1/2}$ of nicotine is 30-60 min and the pressor response usually settles within 20-30 minutes of the last cigarette. It is metabolised in the liver and lungs to the inactive compounds nicotine-N-oxide and cotinine the latter being found in urine samples of smokers for up to 7days after the last cigarette thus providing a useful marker of abstinence.

Respiratory effects

In addition to its effects on oxygen transport and delivery, cigarette smoke has a number of direct effects upon the airway. The result of this is a post-operative pulmonary complication rate of over 50% following coronary artery bypass grafting (Warner & Offord 1989), 53% following abdominal aortic aneursym surgery and 37% following all abdominal surgery (Vodinh & Bonnett 1989), although criteria for diagnosis vary between studies. It is clear, however that smokers have an increased risk (up to six fold) of developing severe post-operative pulmonary complications than do non-smokers (Morton 1944).

Long term heavy smoking commonly causes chronic obstructive airways disease with consequent emphysema, pulmonary hypertension and right heart failure.

Even in the absence of these chronic complications, smoking increases peri-operative pulmonary morbidity by mucus hypersecretion, impaired tracheobronchial clearance and small airway narrowing. The larynx is also adversely affected by chronic smoke exposure.

Mucus secretion and impaired tracheobronchial clearance

Cigarette smoke is directly irritant to both the upper and lower airway causing morphological changes in the epithelium and an increase in mucus production. A number of components of cigarette smoke are also ciliotoxic (Beckers & Camu 1991).

The mucin composition of mucus in smokers and non-smokers is different (Kollerstrom & Lord 1977), hyperviscosity and alterations in elasticity affect the interaction of mucus with cilia thus impairing the clearance of particulate matter (Shih & Litt 1977). In vitro studies have shown tobacco induced ciliostasis in rats, calves and human epithelial scrapings, and in vivo studies in cats have confirmed these findings using a "physiological" smoking method, ie. concentrations of smoke similar to those in the human smoker's trachea. Measurement of tracheobronchial clearance rates, representing this interaction between cilia and mucus, have shown varying results. Cramner & Philipson (1973) found smokers to have slower tracheobronchial clearance rates than non-smokers with a significant improvement only after 3 months of abstinence. Goodman & Yergin (1978), showed markedly reduced rates even in young asymptomatic smokers without evidence of small airways disease and some still had reduced velocities after 7 months abstinence. Some smokers claim a transient increase in sputum production in the few days after stopping smoking possibly because of recovery of ciliary function, others report difficulty clearing sputum and this may represent a loss of the irritant effect of smoke on the airway combined with increased sputum tenacity.

It is thought that ciliary activity starts to recover after 4-6 days of abstinence. The clinical effect may not be apparent until more than a week of abstinence and further improvement may be expected for a period of

several months. The sputum volume may take 2-6 weeks to return to normal.

Small airway narrowing

An increase in non-specific bronchial reactivity in smokers is well known to anaesthetists and has been confirmed by histamine challenge (Gerrard & Cockcroft 1980). Smokers without symptoms of respiratory disease and with normal gross spirometry (FEV_1/FVC) may yet have significant small airways disease with an associated increase rate of post-operative pulmonary complications (Pearce & Jones 1984). Tockman (Pearce & Jones 1984) showed no difference in total lung capacity (TLC) and vital capacity (VC) between age matched smokers and non-smokers, but significant differences in closing capacity (CC), slope of the phase III of the single breath nitrogen test, FEV_1/FVC, RV/TLC and CO diffusing capacity. In a study of young smokers after 6 weeks abstinence, 60% had significant improvements in inspiratory reserve volume, functional residual capacity and maximum ventilatory volume, there being no improvement after only 3 weeks. Buist & Sexton (1976), performed spirometry, measured closing volume and the slope of phase III of the single breath nitrogen test, in smokers attending a cessation clinic before and at 1, 3, 6, 12 months after stopping smoking. After 1 month the slope of the nitrogen test had changed significantly and by 6 months a significant improvement in CV/VC and CC/TLC had also occurred, respiratory symptoms also improving dramatically. Chodoff (Pearce & Jones 1984) showed no improvement in small airway function after only 1 week of abstinence. Martin (Pearce & Jones 1984) showed an improvement in 8 of 12 people 2 months after stopping smoking. Other factors may affect small airways closure in smokers and Hoeppner & Cooper (1974), suggested that

changes in the CC of smokers may reflect a loss of elastic lung recoil and not only intrinsic small airway pathology. Smoke exposure may cause increased synthesis and release of elastase enzymes from alveolar macrophages. Superoxide anions, hydroxyl radicals and hydrogen peroxide released by macrophages to kill micro-organisms may also damage the lung. Cigarette smoke is known to disrupt the epithelial lining of the lung causing an increase in pulmonary epithelial permeability as measured by Technetium-99m labelled diethylene triamine penta acetate even in asymptomatic smokers (Pearce & Jones 1984). The reason for this may be a change in shape of the epithelial cells from a many cornered shape to a less closely fitting rounded form. This returns to normal over about 7 days following cessation. This loss of epithelial integrity may also occur in viral infections and by allowing irritants to penetrate the epithelium more easily could explain the increase in bronchial and laryngeal reactivity associated with smoking and upper respiratory tract infections.

The overall effect on post-operative pulmonary morbidity

Many factors combine to increase the incidence of pulmonary complications after general anaesthesia. Complications in the recovery period include a significantly greater likelihood of hypoxia probably due to a combination of reduced FRC and increased CC, giving an increased $P(A\text{-}a)O_2$, in the presence of increased COHb (Tait & Kyff 1990). Later in the post-operative course smokers are also more likely to develop pulmonary complications.

Different studies have used varying definitions of post-operative pulmonary complications. Mitchell & Garrahy (1982), used purulent sputum alone, Vodinh & Bonnett (1989), used purulent sputum, atelectasis, pleural effusion and the need for a period of ventilation of more

than 12 hr and less than 48 hr as minor complications and at least two of these, greater than 48 hr ventilation, and the occurrence of pneumonitis as criteria for a major complication. Warner & Offord (1989), chose six factors that necessitated more definitive therapy than was standard in that unit, and, in their study of 200 coronary artery bypass patients showed that patients who had stopped smoking pre-operatively for 8 weeks or less had a pulmonary complication rate almost 4 times that of those who had stopped smoking for greater than 8 weeks (57.1% vs 14.5%). Those stopping for a period for a period of 6 months or more had rates similar to those who had never smoked (11.1% vs 11.9%). Mitchell & Garrahy (1982), found that smokers who stopped more than 8 weeks before operation had a 25% incidence of purulent sputum post-operatively whereas a period of abstinence of less than 8 weeks gave a rate of 50%. They concluded that mucus hypersecretion is the most important factor contributing to post-operative pulmonary morbidity.
The apparent disadvantages to the respiratory system of stopping smoking pre-operatively are a worsening of existing asthma and a reported increase in difficulty clearing sputum over the first few days.

So to summarise it appears that the minimum period of abstinence required to see an improvement in small airway function is 4 weeks and that improvements in function may continue for up to 6 months. A period of at least 8 weeks results in a significant reduction in pulmonary morbidity both in cardiac and general surgical patients. There is no experimental evidence to suggest a significant worsening of chest symptoms or increase in pulmonary complication rate following short term abstinence when compared to those who did not stop.

Haematological system

Cigarette smoke affects many haematological parameters as well as the haemostatic system itself. Smokers have an increased haemoglobin concentration (Hb), haematocrit (Hct), red cell count (RBC), mean corpuscular volume (MCV), and white cell count (WBC). Bain & Rothwell (1992), measured haematological parameters in smokers before and for 13 days after stopping smoking. There were significant reductions in Hb, RBC, Hct, WBC, and lymphocyte count within 24 hr of stopping smoking. The platelet count was significantly less by day 3. In another study the values of all parameters except MCV, basophil, eosinophil and monocyte counts were significantly less two weeks after cessation when compared with two weeks before. Significant concentrations of COHb combined with chronic lung disease with tissue hypoxia stimulates erythropoiesis increasing Hb, RBC and PCV. However the speed with which changes occur after starting and stopping smoking suggest either a direct effect of CO, possibly by increasing capillary permeability, or an effect of nicotine increasing venous tone leading to reduced plasma volume and relative polycythemia.

Increased blood viscosity, fibrinogen concentration, platelet count and enhanced platelet reactivity probably all contribute to the thrombotic tendency and greater risk of cardiovascular disease seen in smokers.

Immune system

Some components of cigarette smoke impair the immune response. The white cell count is increased and Bain & Rothwell 1992, suggested that, because this persists in those who have not smoked for many years, it may be due to chronic tissue damage. The lymphocytosis seen is mainly due to an increase in T-cells. The alteration of lymphocyte numbers and an imbalance between T-cell subsets may contribute to the smoker's increased risk of infection and neoplasia.

Gastrointestinal system

It has been suggested that smoking reduces the oesphageal barrier pressure with possible increase in the risk of reflux and thus regurgitation and aspiration of gastric contents. Adelhoj & Petring (1987), have shown no difference in gastric pH or volume of gastric aspirate after tracheal intubation or just prior to extubation between non-smokers, smokers abstaining the night before surgery and in an earlier study acute smokers. The effect of smoking upon the kidney is minimal; there is dilutional hyponatreamia due to stimulation of antidiuretic hormone secretion.

Drug metabolism

Tobacco smoking induces liver microsomal enzymes and the metabolism of a number of drugs is altered in smokers (Beckers & Camu 1991). Most sedative drugs are needed in greater doses to achieve the same effect in smokers and although smoking increases the pain threshold acutely, post-operative analgesic requirements may be expected to be

increased in smokers due to a combination of increased metabolism and anxiety due to withdrawal. Age lessens the effect of smoking upon drug metabolism probably reflecting a reduced capacity for enzyme induction. A period of abstinence of 6-8 weeks may be required to abolish the enzyme induction due to smoking.

Study 6.1

The effect of cigarette smoking on the sensitivity of upper airway reflexes and the changes that occur on stopping smoking for 24 hr.

Introduction and background

Smokers are well known to present problems to anaesthetists. They are more likely than non-smokers to suffer laryngospasm and coughing on induction of anaesthesia (Conroy 1969). They are up to 6 times more likely to develop post-operative complications such as chest infections (Morton 1944). The aim of this study was to assess upper airway reflex sensitivity in a group of healthy non-smokers and a group of healthy cigarette smokers. In the group of smokers we also assessed the effect on upper airway reflex sensitivity of abstaining from cigarette smoking for 24hr.

Upper airway reactivity was assessed using a chemical stimulus technique, using the method described in chapter 4.

Method

Following Ethical Committee approval and informed consent, studies were performed on 40 healthy subjects (12 female) aged 17 - 40yr, twenty were regular cigarette smokers smoking at least 20 cigarettes per day, and twenty were non-smokers. Each subject attended the laboratory and a measurement of the NH_3 threshold concentration (NH_3TR) was made. A venous blood sample was taken from the smokers for measurement of carboxyhaemoglobin levels (COHb %). The smokers were then asked to abstain from smoking for 24hr. Twenty four hours later the smokers had NH_3TR thresholds repeated and a further blood sample was taken.

Results

Table 6.1

Summary of NH_3 threshold levels (NH_3TR) (ppm) and COHb concentration (%) mean (SEM). In a group of smokers before and after 24 hr abstention, and in a group of non-smokers.

Group	Threshold level (NH3TR) ppm	COHb (%)
NON-SMOKERS	683.9 (59.0)	(not measured)
SMOKERS	264.1 (27.3)	6.58 (0.60)
SMOKERS (AFTER 24 hr ABSTINENCE)	262.8 (37.5)	1.53 (0.31)

Table 6.2 NH_3TR (ppm) and COHb% data for smokers before and after stopping smoking for 24hr, and in a group of non-smokers.

Subject	*NH3TR Day 1*	*COHb Day 1*	*NH3TR Day 2*	*COHb Day 2*
A	524	8.2	524	0.1
B	327	13.3	327	0.4
C	524	2.8	251	0.7
D	251	3.8	327	1.0
E	251	7.4	327	0.6
F	251	4.7	327	0.7
G	251	8.3	76	1.7
H	251	6.0	251	0.9
I	327	8.3	524	0.3
J	251	10.1	76	0.6
K	76	7.1	76	5.2
L	251	8.9	251	4.3
M	327	7.6	76	1.9
N	251	3.8	251	1.7
O	251	4.7	600	1.3
P	251	3.9	76	1.7
Q	76	4.8	327	1.6
R	76	5.1	76	1.1
S	251	6.3	251	3.2
Mean	**264.1**	**6.58**	**262.8**	**1.53**
SEM	**27.3**	**0.60**	**37.5**	**0.31**

Subject	*NH3TR non-smokers*
T	251
U	878
V	251
W	524
X	600
Y	524
Z	878
AA	524
AB	524
AC	1140
AD	878
AE	600
AF	878
AG	878
AH	1140
AI	600
AJ	524
AK	878
AL	524
Mean	**683.9**
SEM	**59.0**

Results

Complete sets of data were collected from 19 subjects in each group. The mean (SEM) NH_3TR of normal non-smokers was 683.9 (59.0) and that of smokers was 264.1 (27.3), after stopping smoking for 24hrs was 262.8 (37.5). On stopping smoking for 24hrs the mean (SEM) COHb level in the smokers fell from 6.58% (0.6) to 1.53% (0.31) COHb, confirming that the subjects had stopped smoking.

Statistical analysis

The COHb data was analysed using a paired t-test and this revealed a highly significant ($p<0.0001$) reduction in COHb levels.
The NH_3TR data was analysed using the Wilcoxon matched pairs signed ranks test. The NH_3TR values in the smoking group before and after stopping smoking were not significantly different ($p=0.96$). This indicates that the NH_3TR levels did not change following a period of 24hrs abstinence from smoking.
The NH_3TR data from the smoking group before stopping smoking and following stopping smoking, was highly significantly different ($p=0.0005$ & $p=0.0008$) from the non-smoking group. This indicates that smokers have more reactive upper airways than non-smokers.

This data is shown graphically in Figure 6.1.

In conclusion, smokers have more sensitive upper airways than non-smokers when measured using the ammonia stimulus technique. A period of abstinence from smoking of 24 hrs produces a significant fall in COHb levels, but the sensitivity of upper airway reflexes does not change, with smokers still having more sensitive upper airways than non-smokers.

Acknowledgement

Some of the data in this study 6.1 has been published in abstract form:

Erskine R., Murphy P., Langton J.A., Smith G.
Upper airway reactivity in smokers and non-smokers. Abstract 197
World Congress of Anaesthesiologists. The Hague June 1992.

part of this data has been included in a paper that has been submitted for publication :

Langton J.A., Erskine R., Murphy P. The effect of chronic cigarette smoking and stopping smoking, on the sensitivity of upper airway reflexes.
Br J Anaesth.

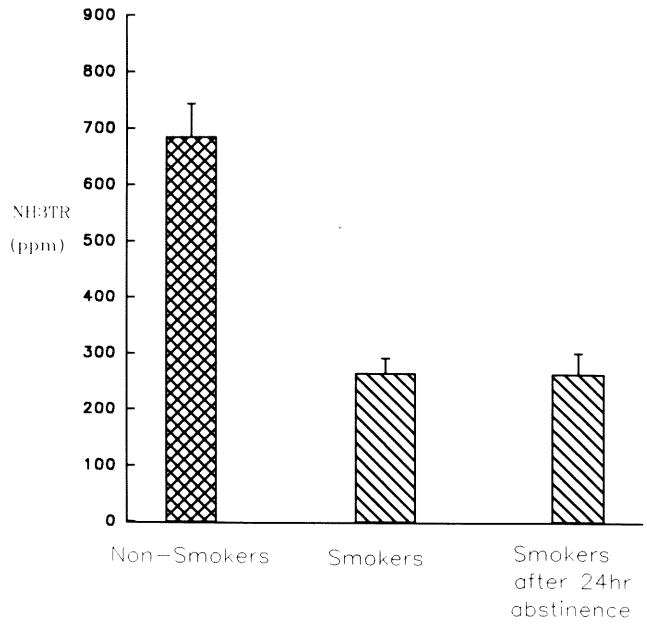

Figure 6.1 NH_3TR (ppm) mean (SEM) in smokers and non-smokers, and also showing smokers following 24 hr abstention from smoking.

Study 6.2

The effect on the sensitivity of upper airway reflexes of stopping smoking for 25 days.

Background and introduction

In the previous study 6.1, we found that the sensitivity of the upper airway of smokers who abstain from smoking for 24 hrs remained significantly higher than non-smokers. Therefore the next step in this investigation was to examine the changes in the sensitivity of the upper airway reflexes that may occur when subjects stop smoking for a longer period of 25 days.

Method

Following Ethical Committee approval and written informed consent, we recruited 25 subjects who regularly smoked 15 or more cigarettes daily. The baseline NH_3TR was measured in each subject using the previously described technique, we measured end tidal COHb concentration (%) using a Bedfont EC50 Smokerlyser breath carboxyhaemoglobin meter, this uses a sealed electrochemical sensor and the response time is less than 30 seconds. This battery-operated, hand-held device has been demonstrated to give an accurate indication of carboxyhaemoglobin concentrations (COHb%) over the range of values encountered in human beings (Jarvis and colleagues 1986). This was used in preference to blood sampling to improve the compliance of volunteers.

Thirteen subjects agreed to stop smoking, the remainder to carry on. Over the next 25 days repeated measurements of NH_3TR and COHb % were made at regular intervals.

Eight subjects (4 male), mean age 31.5 yr, range 23-51 yr managed to stop smoking completely for the period of the study, whilst eight others (3 male), mean age 33.8 yr, range 23-48 yr, continued to smoke and acted as the control group. Nine subjects failed to complete the study.

Results

Table 6.3 Details of subjects who stopped smoking for 25 days, the effect on NH_3TR (ppm) and COHb %.

	Age	*Sex*	*Med^n*	*Cigs*	*Day 0 COHb*	*Day 0 NH3TR*
Subject A	28yr	Female	-	20/day	4.8	251
Subject B	23yr	Male	-	20/day	2.4	327
Subject C	28yr	Male	-	30/day	3.3	251
Subject D	51yr	Male	-	25/day	5.4	524
Subject E	46yr	Female	-	15/day	3.6	524
Subject F	32yr	Female	-	20/day	5.1	524
Subject G	48yr	Female	-	40/day	3.9	327
Subject H	25yr	Male	-	20/day	4.5	327

	Day 2 COHb	***Day 2 NH3TR***	***Day 3 COHb***	***Day 3 NH3TR***
Subject A	0.6	524	-	-
Subject B	0.7	251	-	-
Subject C	0.5	251	-	-
Subject D	-	-	2.0	1140
Subject E	1.6	524	-	-
Subject F	0.3	524	-	-
Subject G	0.9	251	-	-
Subject H	0.6	524	-	-

	Day 4 COHb	***Day 4 NH3TR***	***Day 5 COHb***	***Day 5 NH3TR***
Subject A	-	-	0.4	524
Subject B	-	-	0.9	524
Subject C	0.9	878	-	-
Subject D	-	-	-	-
Subject E	0.4	1140	-	-
Subject F	-	-	-	-
Subject G	0.9	878	-	-
Subject H	-	-	0.2	1140

	Day 6 COHb	***Day 6 NH3TR***	***Day 7 COHb***	***Day 7 NH3TR***
Subject A	-	-	-	-
Subject B	-	-	0.8	1140
Subject C	0.9	1140	-	-
Subject D	1.1	1620	-	-
Subject E	-	-	2.0	1620
Subject F	0.8	878	-	-
Subject G	-	-	0.5	1620
Subject H	-	-	-	-

Table 6.3 (ctd)

	Day 8 COHb	*Day 8 NH3TR*	*Day 9 COHb*	*Day 9 NH3TR*
Subject A	-	-	0.6	878
Subject B	-	-	-	-
Subject C	0.5	1140	-	-
Subject D	-	-	-	-
Subject E	-	-	-	-
Subject F	-	-	1.4	1140
Subject G	-	-	-	-
Subject H	0.4	1140	-	-

	Day 10 COHb	*Day 10 NH3TR*	*Day 11 COHb*	*Day 11 NH3TR*
Subject A	-	-	-	-
Subject B	0.4	1140	-	-
Subject C	-	-	-	-
Subject D	-	-	1.9	1140
Subject E	1.0	1620	-	-
Subject F	-	-	0.5	1140
Subject G	1.1	1140	-	-
Subject H	-	-	-	-

	Day 12 COHb	*Day 12 NH3TR*	*Day 13 COHb*	*Day 13 NH3TR*
Subject A	0.5	1140	-	-
Subject B	-	-	-	-
Subject C	0.8	1620	-	-
Subject D	-	-	1.3	1140
Subject E	-	-	-	-
Subject F	-	-	-	-
Subject G	-	-	-	-
Subject H	0.6	1140	-	-

	Day 14 COHb	*Day 14 NH3TR*	*Day 15 COHb*	*Day 15 NH3TR*
Subject A	0.4	1140	-	-
Subject B	0.9	1140	-	-
Subject C	-	-	-	-
Subject D	-	-	-	-
Subject E	0.4	1620	-	-
Subject F	-	-	0.8	1620
Subject G	1.0	1620	-	-
Subject H	-	-	-	-

	Day 16 COHb	*Day 16 NH3TR*	*Day 17 COHb*	*Day 17 NH3TR*
Subject A	0.6	878	-	-
Subject B	-	-	0.8	1140
Subject C	0.8	1620	-	-
Subject D	1.4	1620	-	-
Subject E	-	-	-	-
Subject F	-	-	-	-
Subject G	-	-	-	-
Subject H	0.5	1140	-	-

Table 6.3 (ctd)

	Day 18 COHb	*Day 18 NH3TR*	*Day 19 COHb*	*Day 19 NH3TR*
Subject A	-	-	0.4	878
Subject B	-	-	-	-
Subject C	-	-	1.3	1620
Subject D	-	-	-	-
Subject E	0.6	1620	-	-
Subject F	0.6	1140	-	-
Subject G	-	-	1.0	1620
Subject H	0.8	1140	-	-

	Day 20 COHb	*Day 20 NH3TR*	*Day 21 COHb*	*Day 21 NH3TR*
Subject A	-	-	-	-
Subject B	0.4	1140	-	-
Subject C	-	-	-	-
Subject D	1.4	1620	-	-
Subject E	-	-	0.6	1620
Subject F	-	-	-	-
Subject G	-	-	-	-
Subject H	-	-	-	-

	Day 22 COHb	*Day 22 NH3TR*	*Day 23 COHb*	*Day 23 NH3TR*
Subject A	-	-	0.6	878
Subject B	-	-	0.4	1140
Subject C	1.2	1620	-	-
Subject D	-	-	-	-
Subject E	-	-	-	-
Subject F	0.4	1140	-	-
Subject G	-	-	1.1	1140
Subject H	0.2	1140	-	-

	Day 24 COHb	*Day 24 NH3TR*	*Day 25 COHb*	*Day 25 NH3TR*
Subject A	-	-	0.4	1140
Subject B	-	-	-	-
Subject C	-	-	-	-
Subject D	1.2	1620	-	-
Subject E	-	-	-	-
Subject F	-	-	-	-
Subject G	-	-	-	-
Subject H	-	-	-	-

Results

Table 6.4 Details of subjects who continued smoking for 25 days, the effects on NH_3TR (ppm) and COHb %.

	Age	*sex*	*Medn*	*cigs*	*Day 0 COHb*	*Day 0 NH3TR*
Subject I	40	Female	-	20/day	3.8	327
Subject J	53	Male	-	20/day	4.3	76
Subject K	23	Female	-	15/day	2.9	327
Subject L	28	Female	-	20/day	4.2	251
Subject M	25	Male	-	20/day	3.8	327
Subject N	31	Female	-	20/day	5.5	76
Subject O	22	Female	-	15/day	5.1	327
Subject P	26	Male	-	20/day	3.6	524

	Day 1 COHb	*Day 1 NH3TR*	*Day 2 COHb*	*Day 2 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	4.9	76
Subject K	2.4	327	-	-
Subject L	-	-	5.1	251
Subject M	-	-	4.0	524
Subject N	-	-	-	-
Subject O	-	-	-	-
Subject P	-	-	-	-

	Day 3 COHb	*Day 3 NH3TR*	*Day 4 COHb*	*Day 4 NH3tr*
Subject I	2.5	327	-	-
Subject J	-	-	4.5	76
Subject K	3.1	327	-	-
Subject L	-	-	-	-
Subject M	-	-	-	-
Subject N	5.5	251	-	-
Subject O	4.9	251	-	-
Subject P	5.1	524	-	-

	Day 5	*COHb*	*Day 5 NH3TR*	*Day 6 COHb*	*Day 6 NH3TR*
Subject I		-	-	-	-
Subject J		-	-	-	-
Subject K		-	-	2.4	251
Subject L		-	-	5.2	251
Subject M		2.9	524	-	-
Subject N		-	-	4.8	327
Subject O		-	-	3.7	327
Subject P		-	-	2.9	327

Table 6.4 (ctd)	*Day 7 COHb*	*Day 7 NH3TR*	*Day 8 COHb*	*Day 8 NH3TR*
Subject I	1.6	327	-	-
Subject J	-	-	5.3	76
Subject K	-	-	-	-
Subject L	-	-	-	-
Subject M	-	-	-	-
Subject N	3.6	327	-	-
Subject O	-	-	-	-
Subject P	-	-	-	-

	Day 9 COHb	*Day 9 NH3TR*	*Day 10 COHb*	*Day 10 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	3.5	251
Subject K	2.5	327	-	-
Subject L	-	-	4.9	251
Subject M	2.9	524	-	-
Subject N	-	-	3.6	251
Subject O	-	-	4.8	327
Subject P	3.2	524	-	-

	Day 11 COHb	*Day 11 NH3TR*	*Day 12 COHb*	*Day 12 NH3TR*
Subject I	2.4	327	-	-
Subject J	-	-	-	-
Subject K	-	-	1.5	327
Subject L	-	-	-	-
Subject M	-	-	-	-
Subject N	-	-	-	-
Subject O	-	-	-	-
Subject P	-	-	5.0	327

	Day 13 COHb	*Day 13 NH3TR*	*Day 14 COHb*	*Day 14 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	-	-
Subject K	-	-	-	-
Subject L	4.8	327	-	-
Subject M	-	-	4.5	327
Subject N	-	-	-	-
Subject O	-	-	-	-
Subject P	-	-	-	-

	Day 15 COHb	*Day 15 NH3TR*	*Day 16 COHb*	*Day 16 NH3TR*
Subject I	2.8	524	-	-
Subject J	3.3	251	-	-
Subject K	3.0	251	-	-
Subject L	-	-	3.0	251
Subject M	-	-	-	-
Subject N	3.7	76	-	-
Subject O	3.8	327	-	-
Subject P	5.3	524	-	-

Table 6.4 (ctd)	*Day 17 COHb*	*Day 17 NH3TR*	*Day 18COHb*	*Day 18 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	-	-
Subject K	-	-	-	-
Subject L	-	-	-	-
Subject M	-	-	-	-
Subject N	2.2	251	-	-
Subject O	-	-	3.6	327
Subject P	-	-	4.9	327

	Day 19 COHb	*Day 19 NH3TR*	*Day 20 COHb*	*Day 20 NH3TR*
Subject I	3.5	327	-	-
Subject J	-	-	3.3	76
Subject K	3.6	327	-	-
Subject L	3.3	251	-	-
Subject M	-	-	-	-
Subject N	-	-	-	-
Subject O	-	-	-	-
Subject P	-	-	-	-

	Day 21 COHb	*Day 21 NH3TR*	*Day 22 COHb*	*Day 22 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	-	-
Subject K	-	-	-	-
Subject L	-	-	-	-
Subject M	2.3	327	-	-
Subject N	4.8	251	-	-
Subject O	-	-	3.6	524
Subject P	5.3	327	-	-

	Day 23 COHb	*Day 23 NH3TR*	*Day 24 COHb*	*Day 24 NH3TR*
Subject I	-	-	-	-
Subject J	-	-	3.8	327
Subject K	-	-	3.5	76
Subject L	5.5	251	-	-
Subject M	-	-	-	-
Subject N	-	-	-	-
Subject O	-	-	-	-
Subject P	-	-	4.1	327

	Day 25 COHb	*Day 25 NH3TR*
Subject I	-	-
Subject J	-	-
Subject K	3.0	251
Subject L	-	-
Subject M	-	-
Subject N	-	-
Subject O	-	-
Subject P	-	-

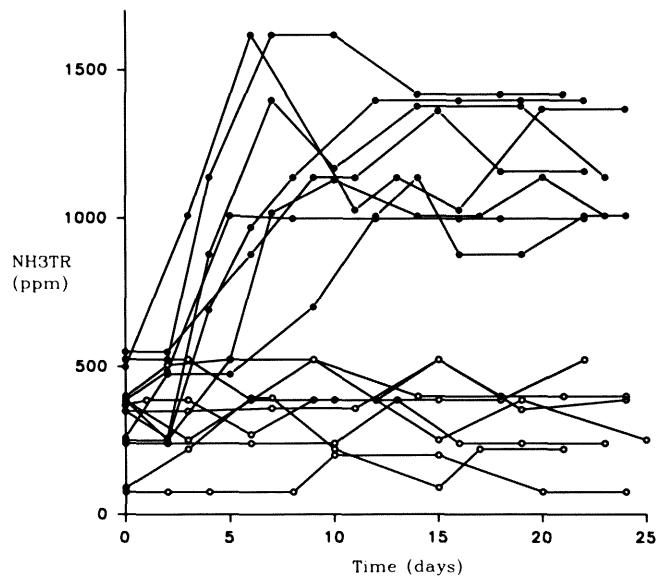

Figure 6.2 Relationship between NH_3TR (ppm) and time (days)

- ● - smokers who stopped smoking
- o - smokers who continued to smoke

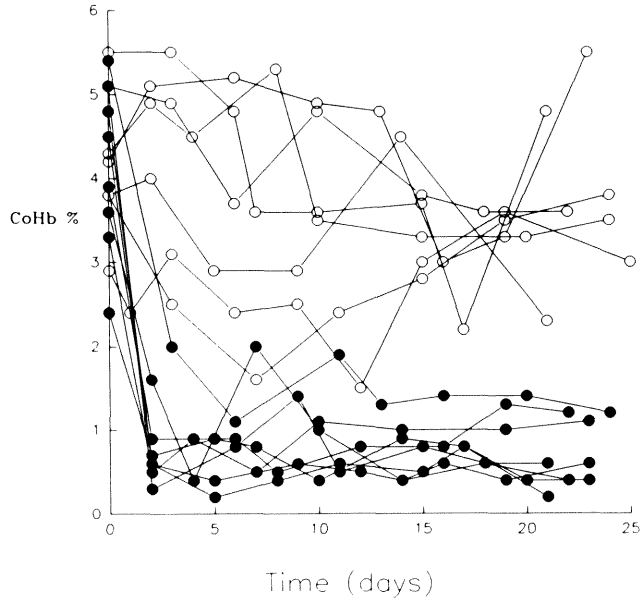

Figure 6.3 Relationship between carboxyhaemoglobin levels (COHb %) and time (days). ● - smokers who stopped smoking
○ - smokers who continued to smoke.

Sixteen smokers (8 female) were investigated over a period of 25 days. Regular measurements of NH_3TR and COHb% were made when practical every 48 hrs. The data is displayed in Tables 6.3 & 6.4 and is summarised in Figures 6.2 & 6.3.

Initially the mean (SEM) NH_3TR of the group who continued to smoke were 279.4 (52.2) and the COHb levels were 4.15% (0.29). In the group who were to stop smoking the mean (SEM) NH_3TR were 381.9 (43.1) and COHb levels were 4.12% (0.36). Statistical analysis revealed no significant difference between these measurements confirming that they come from the same population of smokers. The group who continued to smoke showed little change in the NH_3TR or COHb levels throughout the 25 day study period.

In the group who stopped smoking, the first change that was observed was a fall in COHb levels. This occurred, as expected within 24 hrs of stopping smoking. These levels remained low as a marker of continued abstinence from smoking. The NH_3TR levels did not change for 2-3 days, after this time we observed that NH_3TR levels began to increase and had risen in all subjects between 7 - 10 days. This implies a decrease in the sensitivity of upper airway reflexes over the period of 7 - 10 days after stopping smoking. For the rest of the study period the subjects who stopped smoking displayed raised NH_3TR levels, and quite clearly by the end of the study had formed a separate population from the subjects who continued to smoke.

Statistical analysis

The NH_3TR and COHb % of the two groups were analysed using the Wilcoxon matched pairs signed rank test and a paired t-test and were found not to be significantly different at the start of the study.

The NH_3TR of the subjects in group 2 (who continued to smoke) showed only minor variations over the period of study, with no obvious peaks or troughs, whereas the subjects in group 1 (all of whom stopped smoking) showed an increase in NH_3TR. This increase occurred over the period from the second to the fourteenth day. The mean area under the curve (AUC) for group 1 was calculated as 23,319 p.p.m.days (SEM 1144) compared with 7915.4 p.p.m.days (SEM 915) for group 2. There was a highly significant difference between the area under the curves of the two groups ($p=<0.0001$).

Discussion

In this chapter, we have investigated the effect of cigarette smoking on upper airway reflexes. We undertook two studies, in the first (study 6.1) the effect of chronic cigarette smoking on the sensitivity of upper airway reflexes and the effect of stopping smoking for 24 hrs was studied. In the second investigation (study 6.2) we measured the changes that occur on stopping smoking for 25 days and explored the relevance of this to clinical anaesthesia.

Clinically anaesthetists are aware of the potential problems that smokers present during anaesthesia and surgery. These problems can be divided into peri and post-operative complications. On induction of anaesthesia smokers are known to cough, have a tendency to be intolerant to inhalation anaesthetic agents, particularly the newer more irritant inhalation agents for example isoflurane. Smokers may also develop laryngospasm very readily both on induction of anaesthesia and during the recovery period. In the post-operative period the combination of many factors increase the incidence of pulmonary complications in smokers after a general anaesthetic. Various studies have defined post-operative pulmonary complications in a different manner. All of these studies have indicated that smokers have an increased incidence of post-operative chest infections and it appears that a minimum period of abstinence required to produce an improvement in small airways function is 4 weeks and that improvements in function may continue for up to 6 months. A period of abstinence of at least 8 weeks results in a significant reduction in pulmonary morbidity both in cardiac and general surgical patients. Bronchial hyperreactivity has been studied by Gerrard & Cockcroft (1980), using a histamine inhalation test they found that smokers showed

non-specific bronchial hyperreactivity. The mechanism of this increased non-specific bronchial reactivity is uncertain. Histamine probably induces bronchoconstriction by either stimulating irritant receptors in the epithelium, or by a direct action on the smooth muscle of the airway. Using recordings from action potentials from single nerve fibres in rabbits Sellicke & Widdicombe (1971), were able to show an increase in discharge frequency with cigarette smoke reflecting irritant receptor activity and was similar to that induced by both histamine and carbon dust. The acute effect of cigarette smoke on laryngeal receptors was investigated by Lee & Sant'Ambrogio (1987), in dogs. The inhalation of cigarette smoke had a profound effect on laryngeal afferent activity as recorded from the whole superior laryngeal nerve. Single fibre recording showed the presence of laryngeal receptors (laryngeal irritant receptors) that are stimulated by smoke. The activity of these receptors increased markedly within the first few seconds following smoke exposure.
The epithelium lining the surfaces of the upper and lower airways provide a protective barrier against inhaled material. The histological changes in the airways of cigarette smokers are similar to those produced in animal models, and consist of varying degrees of denudation of the ciliated epithelium, an increase in the number of goblet cells and squamous metaplasia (Wanner 1977, Regland and colleagues 1976). The junctions between epithelial cells provide a protective barrier, the fact that cigarette smoke can disrupt this barrier was first shown in animal experiments in which the tracer horse radish peroxidase broke through the airway epithelial junctions at all levels of the airways after guinea pigs were exposed to cigarette smoke (Simani & Inoue 1974). Using diethylene triamine penta acetate (99m TcDTPA) increases in pulmonary epithelial permeability have been found in asymptomatic smokers (Mason & Uszler 1983). This change is steadily reversible on stopping smoking, although

about 7 days is necessary for the airway permeability to return towards normal. It has been suggested that leaks develop around the corners of epithelial cells (Walker & Mackenzie 1982). This study found that the upper lobes of the lungs were more permeable, other work has suggested that permeability is greatest just prior to the appearance of mitosis. This means that permeability would be increased maximally at the time of maximum DNA synthesis by the dividing cells. It is possible that the changes in permeability produced by smoking might enhance the penetration of substances through the epithelial layer. Epithelial damage has been proposed by Empey & Laitinen (1976) as a mechanism by which upper respiratory tract infection produces bronchial hyperreactivity, epithelial disruption exposing the rapidly adapting airway receptors to inhaled irritants. Viral infection causes acute mucosal oedema followed by shedding of epithelial cells (Crofton 1969), bronchial reactivity being increased for up to 7 weeks after viral infection (Empey and colleagues 1976). In addition to this, acute smoke exposure is known to increase tracheal mucosal permeability in guinea pigs which also demonstrated increased airway responsiveness to inhaled histamine (Burns and colleagues 1987).

This epithelial disruption in smokers might permit greater chemical exposure of the irritants to the sub epithelial irritant receptors.

Walker & Mackenzie (1982), suggested that the leaks develop at the corners where epithelial cells meet rather than along their lateral surfaces. Stopping smoking might allow the epithelium to repair and regenerate so that the disrupted barrier would have a chance to recover.

Recent evidence suggests that chronic cigarette smokers have depressed production of salivary epidermal growth factor, a factor known to stimulate epithelial proliferation, protect mucosa against acute injury and to heal gastric and duodenal ulcers (Jones and colleagues 1992).

In studies of experimental damage to airways Golden and colleagues (1978) concluded that ozone exposure damages airway epithelium and thereby sensitises bronchial irritant receptors.

Although there is quite a large amount of experimental data relating to lower airway function and hyper-reactivity in smokers, there has not been any work investigating the sensitivity of the upper airway in smokers. As discussed above smokers have a higher incidence of post-operative chest infections following major surgery, and a period of pre-operative abstinence is advised. The length of time required to reduce the incidence of upper airway complications, during anaesthesia is not known.

We have demonstrated in these studies that smokers have more sensitive upper airways, as measured by a significantly lower NH_3 concentration (ppm), required to elicit the reflex glottic stop. Stopping smoking for 24hrs has no effect on this threshold level, the smokers remaining hypersensitive. The carboxyheamoglobin levels were as expected elevated in the smokers and COHb is a useful marker to follow abstention from smoking.

The cessation of smoking for 25 days has demonstrated there is a change in the sensitivity of the upper airway in smokers who manage to stop smoking. Smokers who stop smoking demonstrated a gradual reduction in the sensitivity of upper airway reflexes, over a period of 7 - 10 days. Previous work has demonstrated reversible changes in epithelial permeability which has also been found to return to normal over a 7 day period. The increase in epithelial permeability in smokers may be part of the mechanism by which smokers have increased sensitivity of the upper airway. It is also possible that the receptors and nerve fibres in the upper airway in smokers undergo chronic changes. I believe that this would be a fruitful area for future work.

There is a paradox in that smokers, who chronically inhale irritant gases, should have a more sensitive upper airway. The explanation for this is that

smoking is a learnt pattern of behaviour, designed to achieve nicotine absorption without irritating the airway. Non-smokers who smoke for the first time will often cough and choke. Rodenstein and Stanescu (1985) found that regular cigarette smokers developed a technique of sucking smoke into their mouth with the tongue closed against the soft palate following which they inhaled through both their nose and mouth thereby diluting the inhaled smoke. In another study Higenbottam and colleagues (1980) found that whereas all smokers tested were able to inhale smoke into their lungs during "normal" smoking, only 60% were able to tolerate inhaling undiluted cigarette smoke directly through the cigarette into their lungs. The pause that smokers take between sucking smoke into their mouth and inhaling it, diluted with nasal air, allows a reduction in its temperature as well as allowing some particulate and chemical irritants to be deposited in the oral cavity (Higgenbottam and colleagues 1980).
The smoker is also aware of when the irritant stimulus is to be presented to the upper airway, this is in sharp contrast to the situation on induction of anaesthesia, where the patient is anaesthetised and therefore unaware of when the irritant vapour is being inhaled. This is similar to the situation during our experiments, as the subject is unaware of activity in the laboratory and is unaware of when the irritant stimulus is to be presented, effectively removing higher influences from this reflex. This is in keeping with the behaviour of smokers on induction of anaesthesia who suffer episodes of coughing and laryngospasm much more frequently than non-smokers.

In conclusion, using the ammonia stimulus technique to measure the sensitivity of the upper airway we have found that in normal subjects and in subjects who smoke cigarettes, the measurement of upper airway reflex sensitivity is reproducible and practical to perform. From these two studies it can be concluded that smokers have more sensitive upper airway reflexes, and that abstinence from smoking for 24 hr produced no change in the sensitivity of upper airway reflexes. The increased sensitivity of the upper airway in smokers may be due to increased epithelial permeability which allows greater penetration of irritants through the epithelial layer, and exposure to the subepithelial irritant receptors. If smokers manage to stop smoking for 7 - 10 days then the sensitivity of their upper airway reflexes reduces and they seem to settle at a level of sensitivity somewhat less sensitive than normals. Therefore in clinical terms, to see any benefit from cessation of smoking to improve airway complications on induction of anaesthesia a period of abstinence of at least 7 days is required.

CHAPTER 7

The effects of benzodiazepines on the sensitivity upper airway reflexes.

We studied the effect of benzodiazepines on the sensitivity of upper airway reflexes, in two separate studies. In study 7.1, we investigated the effect of oral diazepam, and in study 7.2, we investigated the effect of intravenous Diazemuls, midazolam and the specific benzodiazepine reversal agent flumazenil on the sensitivity of upper airway reflexes.

Study 7.1. The effect of oral diazepam on the sensitivity of upper airway reflexes

Introduction

Receptors known to respond to chemical irritants are found in the epithelial and sub-epithelial layers of the larynx and pharynx (Boushey & Richardson 1974). Afferents from these fibres travel mainly in the superior laryngeal nerve and synapse in the brain stem. In adult humans the main responses to irritant receptor stimulation are glottic closure and a brief stop in inspiration (Widdicombe 1977). At higher levels of stimulation the reflex response produced is termed the expiration reflex or laryngeal cough (a short expiratory effort without preceding inspiration) (Korpas 1972).

Upper airway reflex activity is important, having implications for both airway protection and upper airway complications during anaesthesia (i.e.

laryngospasm, coughing). Previous work has shown that subjects given Diazemuls 15mg intravenously had a 300% decrease in the sensitivity of upper airway reflexes, which persisted for at least 4hr after the administration of the drug (Groves & Rees 1987). The apparent longevity of this reflex depression compared with the short lived clinical effects of a single dose of intravenous Diazemuls has major implications as it suggests that a patient may be at increased risk of aspiration despite appearing to have recovered from the acute sedative effects. The aims of this study were to assess the effect of a premedicant dose of oral diazepam on upper airway reflexes and to investigate the time course of this effect especially in relation to changes in the level of sedation.

Method

In a double-blind cross over study we investigated 10 healthy, non-smoking, male volunteers (age 25-35yr) who were currently not taking any medication. The study was approved by the local Ethics Committee and all subjects gave written informed consent. The subjects abstained from alcohol from noon the previous day and had a light breakfast on the day of the study. Exclusions included any subject developing an upper respiratory tract infection within 1 month prior to the study or during the study period and anyone with a past medical history of atopy.

All subjects were allocated randomly to receive diazepam 20mg orally on one occasion, and placebo on another. The investigators and subjects were blinded to the identity of which medication was to be taken by a system of coded envelopes (the code being broken only at the end of the study). Baseline measurements of upper airway reflex sensitivity (UARS) and reaction time to an auditory stimulus (ART) were measured. The subjects then took the medication which they had been randomised to receive on

that occasion. Measurements of UARS and ART were then made every 30 min for the next 4hr. This procedure was repeated at least one week later the subject taking the alternative medication.

Upper airway reflex sensitivity was measured using the method described in Chapter 4.

Measurement of Auditory Reaction Time

Using an electronic timer, we recorded the time taken for the subject to press a trigger in response to an auditory stimulus (bleep) administered via headphones. The stimulus occurred at random time intervals. At the end of each 30 min period 10 recordings of auditory reaction time were taken and the mean value recorded. Each subject was allowed ample practice time before commencing the study in order to eliminate practice effects.

Data were analysed statistically using multiple analysis of variance and paired t-tests and significance was taken at the $p = 0.05$ level.

Results

Table 7.1

Auditory reaction time (msec) and NH_3TR (ppm) of subjects receiving placebo or diazepam 20 mg

Auditory Reaction times mean (msec)

Placebo

	t=0	*t=30*	*t=60*	*t=90*	*t=120*	*t=150*	*t=180*	*t=210*	*t=240*
Subject A	168	172	163	179	170	175	171	174	183
Subject B	167	173	186	168	175	176	173	174	180
Subject C	157	166	168	156	178	179	177	179	186
Subject D	135	141	140	136	130	136	137	140	137
Subject E	146	140	135	145	135	133	132	141	142
Subject F	200	192	197	184	228	204	207	208	216
Subject G	136	131	141	150	140	143	139	136	135
Subject H	176	168	152	171	178	157	172	175	188
Subject I	145	142	140	147	143	143	151	145	149
Subject J	168	172	176	180	167	188	162	170	170
Mean	**159.8**	**159.7**	**159.8**	**161.6**	**164.4**	**163.4**	**162.1**	**164.2**	**168.6**
SEM	**6.38**	**6.24**	**6.85**	**5.36**	**9.23**	**7.7**	**7.25**	**7.28**	**8.49**

Diazepam 20mg orally

	t=0	*t=30*	*t=60*	*t=90*	*t=120*	*t=150*	*t=180*	*t=210*	*t=240*
Subject A	192	213	224	209	227	216	200	169	170
Subject B	169	210	177	194	181	205	180	173	179
Subject C	160	186	157	158	170	238	155	152	150
Subject D	143	186	185	182	184	182	198	164	168
Subject E	137	168	149	173	167	151	126	135	152
Subject F	221	250	279	370	275	201	205	213	210
Subject G	158	171	173	190	215	165	177	174	162
Subject H	179	190	192	179	172	178	151	184	193
Subject I	154	152	179	237	284	217	200	194	143
Subject J	139	157	152	159	142	143	135	140	145
Mean	**165.2**	**188.3**	**186.7**	**205.1**	**201.7**	**189.6**	**172.7**	**169.8**	**167.2**
SEM	**8.31**	**9.37**	**12.4**	**19.8**	**15**	**9.78**	**9.21**	**7.55**	**6.89**

NH_3TR (ppm)

placebo

	t=0	*t=30*	*t=60*	*t=90*	*t=120*	*t=150*	*t=180*	*t=210*	*t=240*
Subject A	524	524	327	327	327	327	327	524	327
Subject B	524	327	251	327	327	251	251	327	327
Subject C	251	251	251	251	327	327	251	251	327
Subject D	524	878	878	600	878	878	878	327	524
Subject E	251	251	251	251	251	251	251	251	327
Subject F	524	878	327	327	327	327	251	327	327
Subject G	878	878	878	878	878	878	327	524	878
Subject H	878	524	600	600	524	600	600	600	524
Subject I	524	327	327	327	327	524	327	524	524
Subject J	524	327	524	524	600	524	524	327	524
Mean	**540.2**	**516.5**	**461.4**	**441.2**	**476.6**	**488.7**	**398.7**	**398.2**	**460.9**
SEM	**66.4**	**84.4**	**78.7**	**64.3**	**74.7**	**75.2**	**65.7**	**41.1**	**55.7**

Table 7.1 (ctd)

Diazepam 20 mg orally

	t=0	t=30	t=60	t=90	t=120	t=150	t=180	t=210	t=240
Subject A	327	1140	600	600	600	524	327	327	251
Subject B	524	878	878	1620	1140	1140	878	524	327
Subject C	524	1140	1620	1140	2360	1140	2360	878	1620
Subject D	878	1620	2790	878	1620	524	524	524	524
Subject E	524	251	1140	524	1140	878	251	251	251
Subject F	524	878	1620	1620	1620	1140	878	600	327
Subject G	524	878	524	1140	878	878	878	600	327
Subject H	524	878	878	878	878	878	524	524	524
Subject I	524	524	1620	1620	1620	1620	1620	524	524
Subject J	524	878	524	524	600	600	524	524	600
Mean	**538**	**907**	**1219**	**1054**	**1266**	**932**	**876**	**527.6**	**537**
SEM	**42.4**	**115**	**225**	**142**	**176**	**108**	**206**	**52.7**	**129**

All ten subjects successfully completed the study. After oral diazepam 20mg, mean ammonia threshold values increased from a baseline of 538 ppm to a peak of 1266 ppm at 120 mins and had decreased to 537 ppm by 240 mins. Significant increases in the ammonia threshold levels occurred between 30 - 150 mins. After the placebo there was no significant change in ammonia threshold (figure 7.1).

After diazepam, the mean auditory reaction times increased from a baseline of 165 msec to a peak of 205 msec at 90 mins and had decreased to 167 msec by 240 mins. After placebo no significant change in auditory reaction times was seen (figure 7.2).

Acknowledgement

The data included in this study 7.1 has been published in:

Murphy P., Langton J.A., Barker P., Smith G.
The effect of oral diazepam on the sensitivity of upper airway reflexes.
Br. J. Anaesth 1993;**70**:131-134.

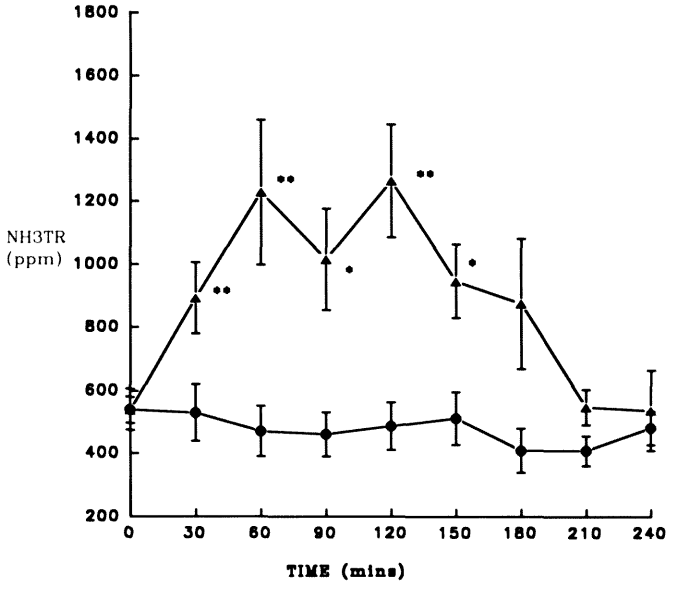

Figure 7.1 Relationship between NH_3TR (ppm) mean (SEM) and time (min) after oral diazepam 20mg (▲) or placebo (●).

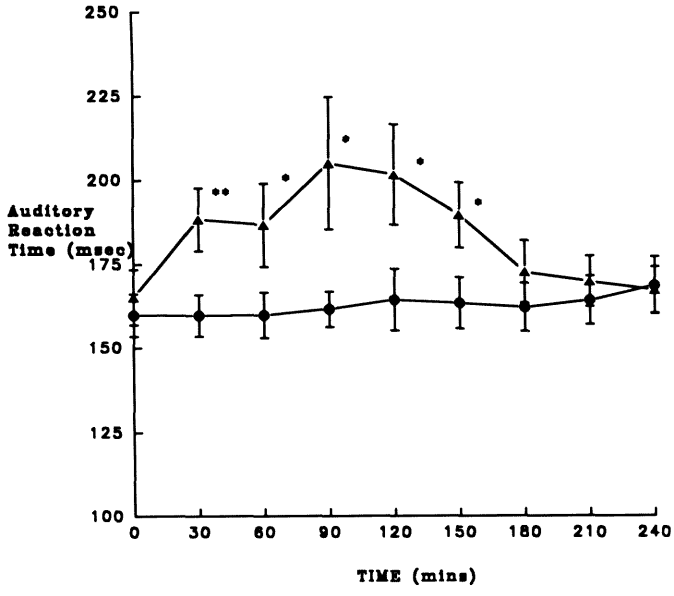

Figure 7.2 Relationship between auditory reaction time (msec) mean (SEM) and time (min) following oral diazepam 20mg (▲) or placebo (●).

In this study 7.1 we have used ART as a measure of sedation in order to identify the time course of the sedative effect of oral diazepam. The results demonstrate that after an oral dose of 20mg diazepam, significant depression of upper airway reflex sensitivity occurred at 30, 60, and 150 min, but that by 210 min upper airway reflex sensitivity had returned to baseline values. We have not found any evidence of depression of upper airway reflex sensitivity beyond the period of the sedative effect as measured by the auditory reaction time. After placebo there was no significant change in upper airway reflex sensitivity.

Study 7.2 :The effect of intravenous Diazemuls, midazolam and flumazenil on the sensitivity of upper airway reflexes.

Introduction and Background

Intravenous benzodiazepines are used extensively in medicine to produce short term sedation and anxiolysis, to facilitate procedures such as endoscopy and minor surgical procedures (Whitwam 1990).
However these drugs may produce depression of the sensitivity of upper airway reflexes (Groves & Rees 1987), this may reduce patients ability to protect their lower airway from aspiration of noxious material.
A number of these procedures are performed on a day case basis and the time course of drug effects are of importance.
Previous work investigating upper airway reflex sensitivity and intravenous benzodiazepines (Groves & Rees 1987), concluded that following 15 mg Diazemuls intravenously, subjects had a 300% decrease in the sensitivity of upper airway reflexes, which persisted for 4 hr following administration of the drug. This has important clinical

implications as it implies that the patients' ability to protect the lower airway may be impaired for up to 4 hr following a single intravenous dose of diazepam.
In the previous study 7.1, we have shown that following oral administration of diazepam 20 mg maximal depression of the sensitivity of the upper airway reflexes occurred between 60 - 120 min, reflex sensitivity having returned to baseline values within 4 hr.

The aim of this study was to observe the effects of intravenous benzodiazepines, and the specific benzodiazepine reversal agent flumazenil, on the sensitivity of upper airway reflexes and to examine the time course of these effects.

Method

Following Ethical Committee approval and informed written consent we studied 8 healthy non-smoking male volunteers (aged 25-35yr) who were not receiving any medication and had no significant past medical history, including atopy.
The subjects abstained from alcohol from noon the previous day and were starved for 6 hours prior to the study period. We excluded any subject who developed an upper respiratory tract infection either during or immediately prior to the study period.
The design of the study was double blind, all subjects were randomly allocated to receive each of the 4 study regimens outlined in Table 7.2 with an interval of at least one week between each study regimen.

Table 7.2

Details of study regimens.

Group	Sedation	Reversal at 10 min
(1) Placebo (n=6)	Saline	Saline
(2) Diazemuls (n=6)	Diazemuls 0.2mg kg^{-1}	Saline
(3) Midazolam (n=6)	Midazolam 0.07mg kg^{-1}	Saline
(4) Midazolam + Flumazenil (n=6)	Midazolam 0.07mg kg^{-1}	Flumazenil 300mcg

Following randomisation a 20g cannula was inserted into a small vein on the dorsum of the left hand and was flushed with heparinised saline. Baseline measurements of upper airway reflex sensitivity (UARS) and reaction time to an auditory stimulus (ART) were then measured, using methods previously described. Throughout the study period the subject was continuously monitored using an ECG and pulse oximeter.
At time T=0 mins the subject was given the intravenous sedation according to the randomisation protocol, this was administered over 30 seconds. Measurements of UARS and ART were then made at 5 and 10 mins. Following the 10 min measurements the appropriate reversal for each study regimen was given. Further measurements of UARS and ART were then made at 15, 20, 30, 40, 50, and 60 mins. Both the subject and the investigator assessing UARS and ART were unaware of which treatment regimen was being administered. All drug administration was performed by a second investigator. Two investigators were present throughout each study period and full resuscitation equipment was available. On completion of the study the subjects were advised not to work or drive a motor vehicle during the 24 hr period following the study, and the subjects were driven home by one of the investigators.

Statistical analysis

Data were analysed as follows: For each subject graphical plots of NH_3TR and ART were made against time for each of the four groups. The area beneath each of these curves (AUC) was calculated. Groups were compared by applying the Wilcoxon signed rank test to the AUC's. Significance was taken at the $p = 0.05$ level.

Results

Table 7.3

Auditory reaction times (msec) and NH_3TR (ppm) results for all groups

Auditory Reaction times (msec)

Diazemuls group

Placebo (saline + saline)

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	200	168	218	220	213	203	187	208	211
Subject B	154	144	153	140	156	147	133	162	137
Subject C	184	173	177	185	191	183	173	191	166
Subject D	180	169	172	165	182	179	178	172	174
Subject E	188	188	178	186	180	187	197	191	190
Subject F	130	121	127	131	125	125	120	129	124
Mean	**172.7**	**160.5**	**170.8**	**171.2**	**174.5**	**170.7**	**164.7**	**175.5**	**167.0**
SEM	**10.6**	**9.8**	**12.3**	**13.4**	**12.4**	**11.8**	**12.6**	**11.4**	**13.3**

Diazemuls + Saline reversal

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	223	260	223	226	202	224	226	223	224
Subject B	163	225	189	163	174	169	165	157	149
Subject C	186	289	274	206	194	218	206	193	222
Subject D	200	360	365	374	310	255	167	180	189
Subject E	212	304	268	309	262	242	234	243	219
Subject F	157	239	239	224	241	252	219	164	173
Mean	**190.2**	**279.5**	**259.7**	**250.3**	**230.5**	**226.7**	**202.8**	**193.3**	**196**
SEM	**10.8**	**20.1**	**24.6**	**31.4**	**20.6**	**13.0**	**12.2**	**13.8**	**12.6**

Table 7.3 (ctd)

Auditory Reaction times (msec)

Midazolam group

Placebo (saline + saline)

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	154	144	153	149	155	146	132	161	136
Subject B	180	169	172	165	182	179	178	172	173
Subject C	188	188	178	176	170	187	197	190	189
Subject D	130	121	128	131	125	125	120	129	124
Subject E	122	133	168	158	152	154	155	152	129
Subject F	167	173	168	169	181	167	179	180	166
Mean	**156.8**	**154.7**	**161.2**	**158**	**160.8**	**159.7**	**160.2**	**164.0**	**152.8**
SEM	**10.8**	**10.6**	**7.4**	**6.6**	**8.8**	**9.3**	**12.2**	**8.9**	**10.9**

Midazolam + Saline reversal

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	134	222	233	236	345	179	144	169	177
Subject B	192	900	650	796	882	444	245	182	175
Subject C	172	1520	876	982	861	426	307	253	193
Subject D	145	513	430	440	343	402	210	187	160
Subject E	132	617	583	585	648	502	253	194	160
Subject F	188	2001	1728	1968	632	615	251	217	211
Mean	**160.5**	**962**	**750.0**	**834.5**	**618.5**	**428.0**	**235.0**	**200.3**	**179.0**
SEM	**11.0**	**275**	**214.5**	**250.6**	**96.6**	**58.7**	**22.2**	**12.4**	**8.1**

Midazolam + Flumazenil reversal

			*Flumazenil						
	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	134	516	419	146	160	153	136	150	145
Subject B	192	681	693	214	220	199	169	156	180
Subject C	159	710	758	227	189	199	196	176	166
Subject D	157	487	533	200	201	188	168	139	155
Subject E	143	2807	1917	245	335	412	445	337	237
Subject F	170	703	1126	246	189	212	323	180	216
Mean	**159.2**	**984**	**907.7**	**213**	**215.2**	**227.2**	**239.5**	**189.7**	**183.2**
SEM	**8.4**	**367**	**224.7**	**15.2**	**25.2**	**37.9**	**49.0**	**30.1**	**14.8**

Table 7.3 (ctd)

NH_3TR Results

Diazemuls group

Placebo (saline + saline)

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	600	878	878	878	878	878	1140	878	1140
Subject B	251	327	327	327	524	524	251	251	251
Subject C	524	251	251	251	524	524	524	251	251
Subject D	251	251	251	251	251	251	251	251	251
Subject E	600	524	600	600	600	878	600	878	878
Subject F	524	524	600	600	524	524	600	524	524
Mean	**458.3**	**459.2**	**484.5**	**484.5**	**550.2**	**596.5**	**561.0**	**505.5**	**549.2**
SEM	**67.0**	**98.0**	**102.5**	**102.5**	**82.0**	**99.0**	**133.1**	**125.5**	**155.4**

Diazemuls + Saline reversal

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	600	1620	878	600	524	524	524	524	600
Subject B	251	2360	2360	2360	1970	1620	1140	878	878
Subject C	327	1140	1620	1620	1620	1140	878	524	878
Subject D	251	3160	2360	1620	1140	878	524	327	251
Subject E	878	2360	1140	1620	1620	1970	878	1140	878
Subject F	878	2360	1970	1970	1620	1620	1140	878	878
Mean	**531**	**2167**	**1721.3**	**1631.7**	**1415.7**	**1292.0**	**847.3**	**711.8**	**727**
SEM	**122**	**286**	**254.1**	**238.7**	**208.5**	**220.5**	**112.8**	**123.5**	**106**

Table 7.3 (ctd)

NH_3TR Results

Midazolam group

Placebo (saline + saline)

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	600	524	524	524	524	878	524	524	524
Subject B	251	327	327	327	524	327	327	524	327
Subject C	524	251	251	327	327	524	327	524	327
Subject D	878	600	600	327	327	524	524	600	600
Subject E	327	327	524	524	327	524	600	524	327
Subject F	524	524	524	327	524	327	327	524	327
Mean	**517.3**	**425.5**	**458.3**	**392.7**	**425.5**	**517.3**	**438.2**	**536.7**	**405.3**
SEM	**90.2**	**57.7**	**55.8**	**41.5**	**44.1**	**82.2**	**51.0**	**12.7**	**50.5**

Midazolam + saline reversal

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	327	2360	2360	1970	600	600	878	878	524
Subject B	251	1620	1620	1620	1140	1140	1140	1140	878
Subject C	524	2360	2360	1140	1140	700	878	878	1140
Subject D	327	3160	2360	1970	878	600	524	878	878
Subject E	878	1970	878	1140	1620	524	600	524	600
Subject F	878	2360	1140	1140	878	600	524	327	524
Mean	**531**	**2305**	**1786**	**1497**	**1042.7**	**694.0**	**757**	**803.7**	**757**
SEM	**116**	**210**	**274**	**168**	**141.7**	**92.1**	**102**	**97.7**	**102**

Midazolam + Flumazenil reversal

*Flumazenil

	t=0	*t=5*	*t=10*	*t=15*	*t=20*	*t=30*	*t=40*	*t=50*	*t=60*
Subject A	327	2360	2360	878	600	251	251	327	327
Subject B	251	1620	1140	600	524	524	600	524	327
Subject C	524	2360	3160	600	524	524	600	327	327
Subject D	524	3160	1620	524	878	524	524	524	524
Subject E	878	1970	1970	524	600	524	524	878	524
Subject F	600	1620	1620	878	600	524	878	524	524
Mean	**562**	**2182**	**1978.3**	**667.3**	**621.0**	**478.5**	**562.8**	**517.3**	**425.6**
SEM	**73.2**	**238**	**288.8**	**68.1**	**53.6**	**45.5**	**82.1**	**82.2**	**107.9**

Results

The subjects were aged 26-35 yr, and weighed mean (SD) 78.7 Kg (6.8)
The mean (SD) dose of drugs used was 15.4mg (1.9) Diazemuls and 5.4 mg (0.6) midazolam.
We have included data from six subjects, and the results of the NH_3TR and ART measurements are shown in Figures 7.3 and Figure 7.4, data are expressed as mean and SEM.

An increase in ammonia thresholds (NH_3TR) was seen following both midazolam and Diazemuls (Figure 7.3). Following placebo there was no change in either NH_3TR or ART.
Following midazolam (0.07mg Kg^{-1}) mean (SEM) ammonia thresholds (NH_3TR) increased from a baseline value of 531ppm (116) to a peak of 2305ppm (210) at 5mins. The mean ammonia thresholds then gradually decreased to 757ppm (102) at 60min.
Following Diazemuls (0.2mg Kg^{-1}) mean (SEM) NH_3TR values increased from a baseline value of 531ppm (122) to a peak of 2167ppm (286) at 5mins. The mean threshold values then gradually decreased to 727ppm (106) at 60min.
When compared to placebo the increase in NH_3TR values following both Diazemuls and midazolam was significant ($p= 0.05$).
In the midazolam and flumazenil group mean (SEM) NH_3TR values increased from a baseline of 562ppm (73.2) to a peak of 2182ppm (238) at 5 mins. Following administration of flumazenil 300 micrograms, NH_3TR values decreased to 667ppm (68) and remained lower than the midazolam group, reaching 425ppm (107) at 60mins. Statistical analysis revealed a

significant difference between the midazolam and midazolam/flumazenil groups in relation to NH_3TR.

The Auditory reaction time (ART) msec for all groups are displayed in figure 7.4, data are expressed as mean and SEM.
In the diazemuls group mean (SEM) ART values increased to a maximum 279msec (20) at 5mins returning to 196 (12) by 60mins.
Following midazolam ART values rose to 962msec (275), returning to 179msec (8.1) at 60 min.
In the midazolam / flumazenil group ART values peaked at 984msec (367) prior to the administration of flumazenil. Following the administration of flumazenil ART values decreased immediately towards baseline values, reaching 213msec (15.2) at 15 mins.
When compared to placebo the increase in ART values following both Diazemuls and midazolam was shown to be statistically significant. However statistical analysis of AUC data did not reveal a significant difference between ART values for the midazolam and midazolam / flumazenil groups.

Acknowledgement

Some of the data from this study 7.2 has been accepted for publication in:

Murphy P., Erskine R., Langton J.A.
The effect of intravenous diazepam, midazolam and flumazenil on the sensitivity of upper airway reflexes.**Anaesthesia** 1994

Other data included in study 7.2 has not been published.

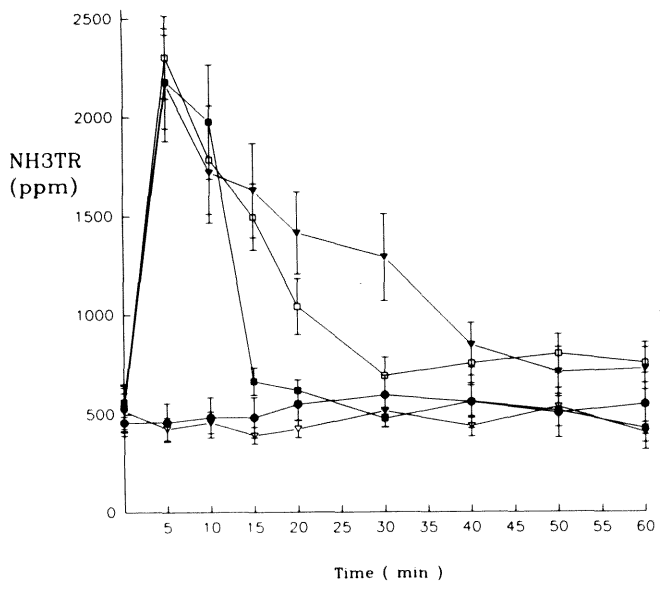

Figure 7.3 Relationship between NH_3TR (ppm) mean (SEM) and time (min).

- ● - Diazemuls placebo
- ∇ - midazolam placebo
- ▼ - Diazemuls 0.2mg kg^{-1}
- □ - midazolam 0.07mg kg^{-1}
- ■ - midazolam 0.07 mg kg^{-1} + flumazenil 300 micrograms at T=10 (min).

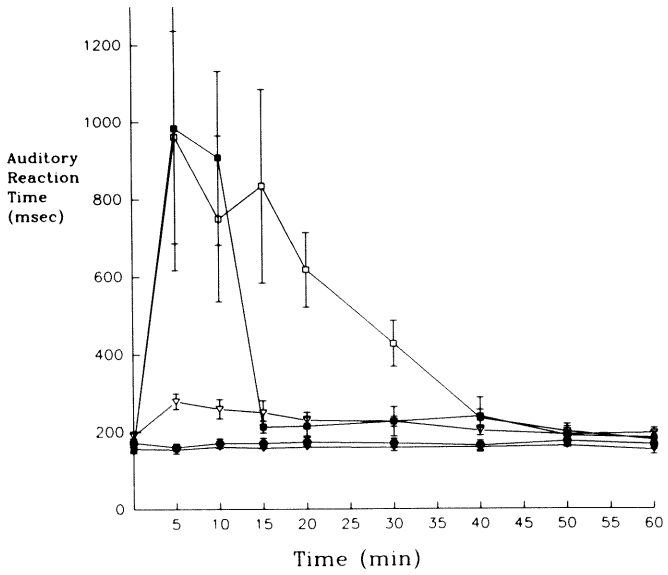

Figure 7.4 Relationship between auditory reaction time (msec) mean (SEM) and time (min).

- ● - Diazemuls placebo
- ▼ - midazolam placebo
- ▽ - Diazemuls 0.2mg kg^{-1}
- □ - midazolam 0.07mg kg^{-1}
- ■ - midazolam 0.07mg kg^{-1} + flumazenil 300 micrograms at T=10 (min).

Discussion

Upper airway reflex activity is important, having implications for both airway protection and upper airway complications during anaesthesia (i.e. laryngospasm, coughing). Previous work has shown that subjects given Diazemuls 15mg intravenously had a 300% decrease in the sensitivity of upper airway reflexes, which persisted for at least 4hr after the administration of the drug (Groves & Rees 1987). The apparent longevity of this reflex depression compared with the short lived clinical effects of a single dose of intravenous Diazemuls has major implications as it suggests that a patient may be at increased risk of aspiration despite appearing to have recovered from the acute sedative effects.

The first drug that we investigated in study 7.1, was the commonly used premedicant oral diazepam. The aims of this study were to assess the effect of a premedicant dose of oral diazepam on upper airway reflexes and to investigate the time course of this effect especially in relation to changes in the level of sedation.

Simple auditory reaction times have been used before to assess recovery after diazepam (Gale 1976). In this study we used ART as a measure of sedation in order to identify the time course of the sedative effect of oral diazepam.

We found that, after oral diazepam 20mg, significant depression of UARS occurred at 30, 60 and 150 min post-dose but after 210 mins UARS returned to baseline values. This change followed a similar time course as the changes in ART. Thus we can infer that, for oral diazepam, there was no prolonged depression of UARS beyond the period of the sedative effect as measured by the ART.

After placebo there was no significant change in UARS. These data concur with the results in chapter 4, where it was shown that there was not any tachyphylaxis to the ammonia stimulus.

The laryngeal closure reflex is thought to be a brainstem reflex affected by many factors (Ikari & Sasaki 1980), including central inhibitory influences (Sasaki 1979). It is probable that diazepam produces depression of upper airway reflexes by facilitating inhibitory neurotransmitter activity, although whether this occurs via general depression of CNS activity or via more specific inhibitory pathways is unclear.

The timing of the changes in UARS can be explained in relation to the pharmacokinetics of oral diazepam. The mean plasma first phase half life of a single oral dose has been found to be 5.08 hr (Smith & Dekirmenjian 1976) with the peak effect occurring at 60 mins (Hillerstad & Hansen 1974, Vickers & Schnieden 1984). There was a considerable increase in inter-subject variability in ammonia threshold values after oral diazepam. It is well known that there is marked inter-individual variability in the time taken to reach peak diazepam plasma concentrations after an oral dose. After oral diazepam 0.3mg kg^{-1} peak plasma concentrations have been shown to occur within an hour in more than 80% of subjects and to have decreased to 30-60% of maximum values within 6hr in most subjects. However in some individuals peak plasma concentration may not occur until 6hr after an oral dose (Smith & Dekirmenjian 1976).

It is possible that some of the variability may be secondary to changes in inspiratory flow after diazepam. Studies using citric acid aerosols to induce cough found that lower inspiratory flows were associated with a greater cough stimulus, probably because of increased laryngeal deposition (Barros & Zammattio 1990). Although an ammonia stimulus differs markedly from a citric acid aerosol, it is possible that changes in inspiratory flow may affect the rate of change of ammonia stimulus at the

laryngeal receptors. Whilst we used recordings from the pneumotachograph to identify a glottic stop, we did not accurately measure inspiratory flow rates. However previous work has shown that diazepam 0.15mg kg^{-1} intravenously appeared to cause slight, but not significant, depression of mean inspiratory flow rates (Berggren & Eriksson 1987). It is thus unlikely that any changes in inspiratory flow after oral diazepam would have had a major effect on our measurement of UARS but they may have added to the variability.
The larynx contains cold receptors and some chemosensitive nerve endings which may not be stimulated by ammonia (Widdicombe 1986). We cannot be certain that all reflexes evoked by stimulation of laryngeal receptors are depressed to the same extent by diazepam. However the irritant receptors which respond to ammonia also respond to ether (Widdicombe 1977) and are most probably implicated in laryngeal reflexes induced by other anaesthetic agents.

My conclusions from study 7.1, are that following oral diazepam there is a significant reduction in the sensitivity of upper airway reflexes between 30 -150 mins after a 20 mg oral dose in healthy young men. In a patient not at risk from regurgitation this depression of upper airway reflexes may be beneficial in reducing airway complications during induction of anaesthesia. However in patients deemed to be at risk from regurgitation, any depression of upper airway reflexes is undesirable. In chapter 5, we demonstrated that upper airway reflex sensitivity decreases with age special care should be taken when using this drug in elderly patients.

In study 7.2, we have shown that following intravenous Diazemuls (0.2mg kg^{-1}) maximal depression of UARS occurred within 10min of drug administration and that after 60min UARS has returned almost to baseline

values. This is consistent with known pharmacokinetic and clinical data. Pharmacokinetic data for a single dose of intravenous Diazemuls indicates peak plasma concentrations occur within minutes followed by a rapid decrease in plasma concentration as redistribution of the drug takes place (Smith & Dekirmenjian 1976).

Following intravenous midazolam maximal UARS depression occurred within 10 min of drug administration. Peak levels of UARS depression were quantitatively similar to those following Diazemuls showing a greater than fourfold increase in NH_3TR, however there is a significant difference in ART values following each drug indicating that different levels of sedation occurred. The administration of midazolam produced increases in ART that were much greater than those seen following Diazemuls. This is of importance as this provides evidence that the change in NH_3TR is not directly linked with the level of sedation, because if this was the case then we would have expected a much greater change in NH_3TR after midazolam than after Diazemuls.

The ability to protect the airway relies on many factors. It is interesting to note that previous workers, using an oral lipiodol challenge technique, have shown that laryngeal competence was impaired for only 5-10mins following intravenous Diazemuls 0.2mg kg^{-1} (Healy & Vickers 1971). They demonstrated that in the 10 min period following administration of diazepam 10 of 27 patients aspirated dye into their lungs.

Because of this previous work we felt it was particularly important to make several measurements of UARS during the 15 min period following drug administration since it is during this period that previous work has shown subjects to be at risk of aspiration.

This study has produced different results from earlier work (Groves & Rees 1987), the explanation for this may be that our apparatus had a low

dead space which ensured that the ammonia stimulus was presented as a bolus to the upper airway receptors. Also by using a specially designed breathing system we were able to produce an ammonia stimulus of known concentration, without the need for specially prepared syringes filled with ammonia vapour, thus reducing the inaccuracies.

As with oral diazepam following intravenous administration of each benzodiazepine, there was an increase in the inter individual variability of NH_3TR values. This may have many causes. Certainly there is variability in drug distribution characteristics between individuals and, drug induced changes in inspiratory flow patterns may increase variability by altering the way in which the ammonia stimulus is presented to upper airway receptors (Barros & Zammattio 1990).
Due to the time constraints imposed by making measurements in 5 minute intervals it was necessary to increase the size of the stepwise increments of ammonia in air concentrations, this may have contributed to the increase in variability of the measurement that were seen after drug administration, and may have decreased the accuracy of our results. Because of the findings in study 5.1, showing an decrease in upper airway reflex sensitivity with increasing age, and studies 6.1 & 6.2, where smokers were found to have far more sensitive upper airways we attempted to reduce variability by avoiding subjects who smoked and employing subjects from a narrow age range.

Following placebo there was no change in UARS. This is consistent with our previous work and suggests minimal tachyphylaxis to the ammonia stimulus during the study period.

Following intravenous midazolam maximal UARS depression occurred within 10mins of drug administration. Peak levels of UARS depression were quantitatively similar to those following diazemuls, however there was a significant difference in ART values following each drug.
We attempted to use equipotent doses of the two benzodiazepines. Previous reports of equipotency (Whitwam 1990, Reves & Fragen 1985) revealed that an intravenous dose of midazolam 0.07mg/Kg produced greater sedation and amnesia than 0.15mg kg^{-1} diazepam. Therefore we used a slightly larger dose of diazemuls (0.2mg kg^{-1}). Despite this we discovered that these two doses of benzodiazepines produced quite noticeably different degrees of sedation as is clearly seen in the ART data. Therefore we cannot say with any certainty that we used equipotent doses.
Despite the shorter distribution half life of midazolam compared with diazepam (Amrein & Hetzel 1991) we observed no significant difference in UARS depression between the two drugs. The time course of the UARS depression following midazolam is in keeping with previous data regarding the longevity of its other clinical effects (Pearson & McCloy 1990).
Reversal of midazolam with flumazenil (300micrograms) appeared to result in a significant improvement in ART scores.
However, because of the large inter-individual variability in ART values following midazolam administration statistical analysis of AUC data failed to show a significant difference.
A similar lowering of NH_3TR values was significant and suggests that flumazenil reversed the depression of UARS induced by midazolam.
Benzodiazepines are in widespread use for sedation of patients undergoing short diagnostic procedures (Amrein & Hetzel 1991), as many of these patients will be managed as day cases the rapid return of upper airway reflexes is desirable. These results suggest that, in these

circumstances, flumazenil, as well as reversing the sedative effects of benzodiazepines, may enhance the return of upper airway reflex activity.

In conclusion, we have shown that UARS depression following intravenous midazolam or Diazemuls is maximal within 10 min of drug administration and returns towards normal values within 60 min. This is in keeping with known pharmacokinetic and clinical data for these drugs. We have found that the specific benzodiazepine reversal agent flumazenil will reverse this depression. In contrast to other workers, we have found that airway reflexes are unlikely to remain depressed for 4 hr following a single intravenous dose of Diazemuls. Disagreement with previous work is probably a result of the improvements we have made to the measurement system. It is hoped that further work will give rise to useful data regarding the state of UARS during various sedation techniques.

CHAPTER 8

Study 8.1

The effect of ethyl alcohol on the sensitivity of upper airway reflexes.

Introduction

Intoxication with ethyl alcohol is thought to predispose to the risk of aspiration of foreign material into the lungs. In early work by Nungester and Klepser (1938), it was shown in rats, that the closure of the glottis was impaired following the administration of ethyl alcohol. It has been hypothesised that ethyl alcohol may impair the mechanisms involved in protecting the lungs from foreign material (Berkowitz & Reichel 1973). Chronic alcoholics are known to have a high incidence of acute pulmonary infections such as pneumococcal pneumonia and aspiration pneumonia (Tilloston & Lerner 1966, Schweppe & Knowles 1961). However the precise mechanism and the degree by which ethyl alcohol impairs the glottic closure reflex in humans is not known (Berkowitz & Reichel 1973).

There has not been any previous work investigating the sensitivity of upper airway reflexes following the administration of ethyl alcohol.

The effects of ethyl alcohol on the human larynx are particularly relevant to anaesthetists. We are frequently asked to anaesthetise patients, who, whilst intoxicated with ethyl alcohol, have sustained injuries requiring emergency surgery. In this situation anaesthetic agents may further depress the reactivity of the upper airway. It is important for anaesthetists therefore, to be aware of the time course and nature of any effect that ethyl alcohol may have on the sensitivity of reflexes in the upper airway.

The aim of this study was to investigate the sensitivity of upper airway reflexes in normal volunteers following ingestion of moderate quantities of ethyl alcohol. To record the effect on upper airway reflex sensitivity and to measure the duration of any effect seen.

We used the technique that I have previously described in chapter 4, to measure the upper airway reflex sensitivity (UARS), utilising low concentrations of ammonia vapour as a stimulus to the upper airway.

Methods

The study was approved by the Ethics Committee and all subjects gave written informed consent. In a double - blind, cross over study we studied 10 healthy, non-smoking, male volunteers aged 25-35yr, weight 75-90 Kg who were currently not receiving any medication. Subjects abstained from alcohol from noon the previous day and had a light breakfast on the morning of the study all subjects were investigated at 11am. Exclusions included any subject developing an upper respiratory tract infection one month before or at any time during the study. Subjects with a history of atopy were also excluded.

Subjects were allocated randomly by coded envelope to receive either plain 150ml orange juice or 150ml orange juice containing five units of vodka. The drink was prepared by a second investigator. The content of the drink being unknown to both the investigator and subject. Each subject was studied on two occasions at least one week apart.

Baseline measurements of upper airway reflex sensitivity (UARS), auditory reaction time (ART), and breath alcohol concentration were performed before the subject was given the drink. Upper airway reflex sensitivity was measured using low concentrations of dilute ammonia vapour.

Measurements of auditory reaction time (ART) were made using an electronic timer. We recorded the time taken for the subject to press a trigger in response to an auditory stimulus (bleep) administered via headphones. The bleeps occurred at random intervals. For each measurement 10 recordings of ART were made and the mean value recorded.

A measurement of breath alcohol concentration was made using Drager Alcotest 7410. This device measures breath alcohol concentration using an electrochemical method. This method has a repeat analysis time of 20 seconds, with a maximum measuring error of +/- 0.005mg/100ml at concentrations below 100mg / 100ml and at above 100mg / 100ml +/- 5mg / 100ml. The Drager 7410 alcometer was calibrated by the manufacturers and requires calibrating at six monthly intervals, with a long term maximum drift of 1.6% per month. The Drager 7410 alcometer uses a conversion factor to derive the blood alcohol concentration from the breath sample.

Measurements of breath alcohol concentration were made using the alcometer three times every 15 minutes for three hours. Measurements of auditory reaction time and UARS were then made every 30 minutes for three hours.

At the conclusion of the study subjects who had received alcohol were then advised not to drive or to operate machinery for 24 hrs.

Results

Table 8.1

Auditory reaction time (msec), NH_3TR (ppm) and blood alcohol levels (mg/100ml)

Auditory Reaction times (msec)

Placebo

	T=0	*T=30*	*T=60*	*T=90*	*T=120*	*T=150*	*T=180*
Subject A	168	172	176	180	167	188	162
Subject B	145	142	140	147	143	143	151
Subject C	196	175	175	186	195	185	190
Subject D	203	210	201	196	210	214	207
Subject E	147	146	129	130	134	142	151
Subject F	155	201	212	150	193	173	181
Subject G	136	135	127	135	133	173	144
Subject H	159	176	174	169	177	176	165
Subject I	146	159	162	163	167	153	142
Subject J	194	201	191	187	175	181	190
Mean	**164.9**	**171.7**	**168.7**	**164.3**	**169.4**	**172.8**	**168.3**
SEM	**7.7**	**8.3**	**9.3**	**7.3**	**8.3**	**7.0**	**7.1**

Alcohol

	T=0	*T=30*	*T=60*	*T=90*	*T=120*	*T=150*	*T=180*
Subject A	168	144	139	148	153	150	144
Subject B	156	181	188	174	178	158	150
Subject C	207	255	243	214	215	204	191
Subject D	184	238	270	217	222	201	196
Subject E	140	167	179	144	151	133	141
Subject F	125	169	163	139	177	165	138
Subject G	144	186	178	179	186	168	165
Subject H	159	191	169	182	166	167	167
Subject I	177	205	210	241	248	202	196
Subject J	172	175	183	160	196	174	172
Mean	**163.2**	**191.1**	**192.2**	**179.8**	**189.2**	**172.2**	**166.0**
SEM	**7.5**	**10.6**	**12.3**	**10.9**	**9.9**	**7.5**	**7.2**

Table 8.1 (ctd)

NH_3TR (ppm)

Placebo

	T=0	*T=30*	*T=60*	*T=90*	*T=120*	*T=150*	*T=180*
Subject A	524	327	524	524	600	524	524
Subject B	524	600	327	524	327	524	327
Subject C	251	251	251	251	251	251	251
Subject D	700	878	878	1620	1140	1140	1140
Subject E	524	524	524	524	251	524	524
Subject F	878	524	600	251	600	524	878
Subject G	251	251	251	524	251	251	251
Subject H	878	600	524	600	600	878	600
Subject I	524	878	251	600	251	524	251
Subject J	600	327	251	251	524	524	524
Mean	**555.4**	**516.0**	**438.1**	**566.9**	**479.5**	**614.4**	**527.0**
SEM	**66.8**	**73.7**	**66.2**	**125.5**	**89.1**	**124.5**	**92.7**

Alcohol

	T=0	*T=30*	*T=60*	*T=90*	*T=120*	*T=150*	*T=180*
Subject A	878	878	600	600	878	600	600
Subject B	600	878	524	600	600	524	600
Subject C	524	524	1140	1140	524	878	878
Subject D	327	524	327	327	327	327	327
Subject E	878	878	1140	600	600	327	524
Subject F	524	327	251	251	1140	878	524
Subject G	251	600	878	1140	327	251	251
Subject H	251	524	251	251	251	327	251
Subject I	878	1620	1140	1140	1140	600	1140
Subject J	251	251	76	76	76	76	76
Mean	**536.2**	**700.4**	**632.7**	**612.5**	**586.3**	**478.8**	**517.1**
SEM	**84.5**	**124.1**	**130.8**	**127.6**	**115.9**	**83.9**	**100.3**

Table 8.1 (ctd)

Blood Alcohol levels (mg/100ml)

	T=0	*T=15*	*T=30*	*T=45*	*T=60*	*T=75*	*T=90*	*T=105*	*T=120*
Subject A	0	38	42	43	48	42	46	38	41
Subject B	0	50	62	72	59	54	45	34	25
Subject C	0	106	115	116	95	88	64	64	58
Subject D	0	47	81	69	61	51	47	42	38
Subject E	0	44	76	63	80	75	68	63	60
Subject F	0	55	105	109	85	74	65	62	54
Subject G	0	77	77	91	91	92	89	79	74
Subject H	0	49	71	85	64	62	60	54	52
Subject I	0	39	68	81	78	82	86	-	91
Subject J	0	72	71	58	53	44	43	40	39
Mean	**0**	**57.7**	**76.8**	**78.7**	**71.4**	**66.4**	**61.3**	**52.9**	**53.2**
SEM	**0**	**6.7**	**6.5**	**7.1**	**5.2**	**5.8**	**5.3**	**5.1**	**6.1**

	T=135	*T=150*	*T=165*	*T=180*	*T=195*
Subject A	35	30	31	30	-
Subject B	19	-	-	-	-
Subject C	53	44	-	43	-
Subject D	30	25	17	-	-
Subject E	50	47	-	-	-
Subject F	-	-	-	-	-
Subject G	73	72	61	55	-
Subject H	-	40	-	30	-
Subject I -	88	-	89	-	
Subject J	37	37	28	31	25
Mean	**42.4**	**47.9**	**34.3**	**46.3**	**25.0**
SEM	**6.7**	**7.6**	**9.4**	**9.4**	**-**

The threshold response to ammonia vapour (NH_3TR) and auditory reaction time (ART) are displayed in Figures 8.1 & 8.2. The maximum increase in the ART occurred at 60 min with a value of 192msec. The NH_3TR increased to a maximum value of 700 ppm, 30 min following ingestion of ethyl alcohol.

The blood alcohol concentrations produced are shown in Figure 8.3. The maximum mean blood alcohol concentration was 78.7 mg / 100ml (SEM 10.3), this occurred at 45min following ingestion.

The data was analysed using ANOVA and when compared to placebo data neither the ART nor the NH_3TR reached significance at the $p = 0.05$ level.

Acknowledgement

The data in this chapter has been accepted for publication in:

Erskine R., Murphy P., Langton J.A. The effect of ethyl alcohol on the sensitivity of upper airway reflexes. **Alcohol and Alcoholism** 1993.

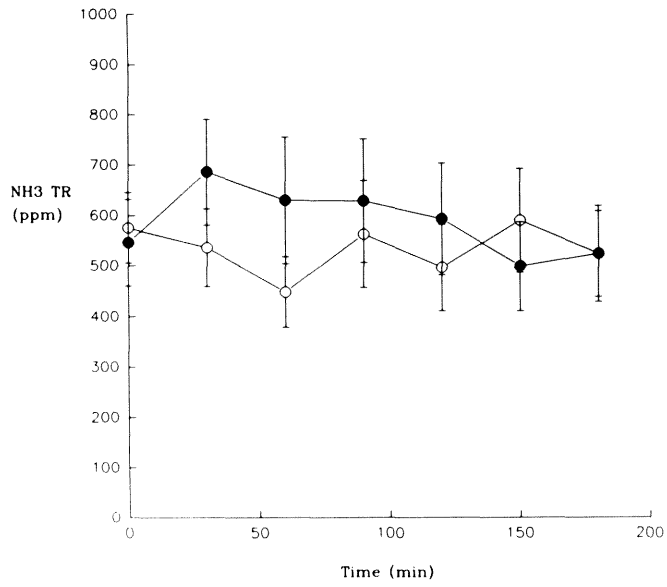

Figure 8.1 Relationship between NH_3TR (ppm) mean (SEM) and time (min) after ethyl alcohol (●) or placebo (○).

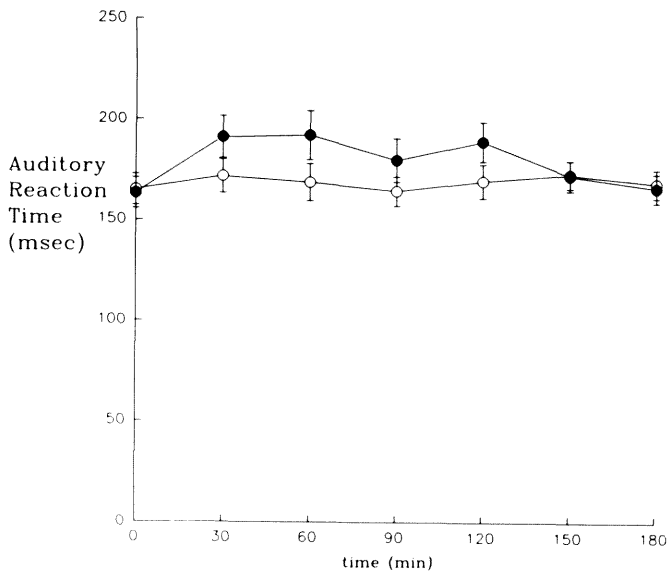

Figure 8.2 Relationship between auditory reaction time (msec) mean (SEM) and time (min) after ethyl alcohol (●) or placebo (○).

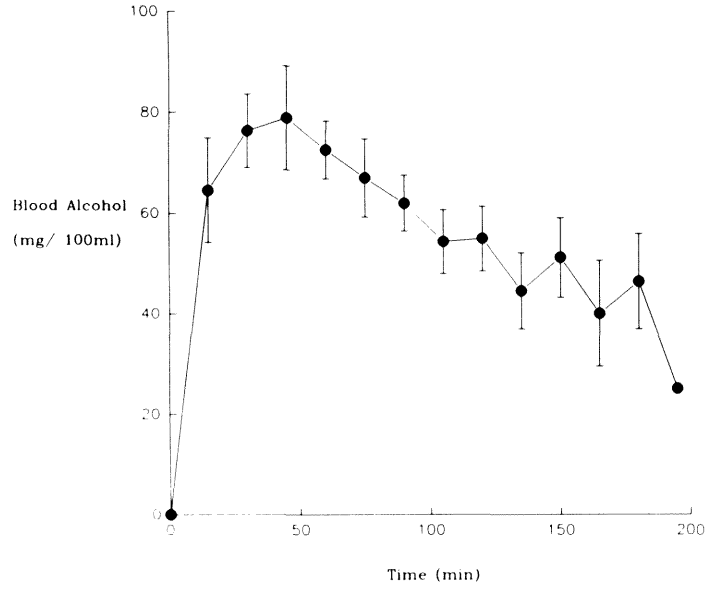

Figure 8.3 Blood alcohol levels (mg/100ml) mean (SEM) and time (min).

Discussion

Anaesthetists are commonly asked to anaesthetise patients who have consumed large quantities of ethyl alcohol and have subsequently injured themselves and require emergency surgery. This presents a number of hazards including the risk of the patient having a full stomach and being at risk of aspiration of gastric contents into the lungs. The degree by which ethyl alcohol depresses the sensitivity of upper airway reflexes has not been investigated.

Several studies have been conducted to examine the distribution and elimination of ethyl alcohol. It is now known that ethyl alcohol follows Michaelis-Menten kinetics, that is to say that the rate of metabolism is proportional to the blood alcohol concentration up to a maximum rate (Holdford 1987). However if the blood alcohol concentration is above the level at which the maximum rate of metabolism occurs then metabolism continues at a constant rate. Alcohol is unusual in that typical blood concentrations are above the maximum rate of metabolism, therefore much of its metabolism continues at zero-order and only the later stages of elimination, when the blood concentrations are relatively low, does the rate of metabolism become dependent on blood levels. Blood alcohol concentrations in individuals are dependent on a variety of factors including sex, weight, body build, previous exposure to alcohol any concurrent drugs (Saunders & Paton 1981, Frezza 1990) time of day and smoking (Holdford 1987). It is therefore very difficult to achieve a predictable concentration in the blood after administration of a standard dose. Wilkinson & Sedman (1976), administered 720ml of 8% v/v ethanol to 6 healthy male volunteers. This produced peak blood alcohol concentrations ranging from 63 mg/ 100ml to 84 mg/ 100ml. Rangno & Kreeft (1981), administered a variety of intravenous and oral doses of

alcohol to 8 healthy male volunteers. They administered 0.375, 0.5 and 0.75g Kg^{-1} alcohol in normal saline diluted to 5 or 10g alcohol / 100ml over 30 minutes. Wide inter-individual variation in blood levels were found after a standard dose, despite the fact that both of these studies accounted for sex, time of day and previous alcohol intake.

In this study 8.1, we have found that following a standard oral dose of five units of alcohol (50g), the blood alcohol concentrations that subjects achieved were quite variable. The maximum mean blood alcohol levels were 78.9mg / 100ml with a range of between 43mg / 100ml to 116mg / 100ml. These findings are consistent with the previously reported work when standard amounts of alcohol were given to volunteers.

We were not able to demonstrate any significant depression of upper airway reflex sensitivity when tested using an ammonia stimulus. However, the blood alcohol levels produced were modest, with some individuals' blood alcohol levels remaining below the legally permitted level for driving. When individual subject data was analysed we found two subjects who both had blood alcohol concentrations in excess of 110mg/100ml. These subjects showed increases in the NH_3TR from the normal level of between for non-smokers of 400-500ppm, to values in excess of 1000ppm. This represents a significant depression of upper airway reflexes similar to that we have described in the previous chapter occurring after the administration of 0.2mg Kg^{-1} Diazemuls intravenously. The time course of the effect of ethyl alcohol on upper airway reflexes was maximum at 30 min following ingestion and declined steadily, returning to baseline at 150 min.
It would appear that to produce significant depression of the sensitivity of upper airway reflexes, greater blood alcohol levels would be required.

It must be borne in mind that we only investigated the effects of ethyl alcohol on upper airway reflexes in healthy male volunteers. The effects in females or in the elderly population may be different. In study 5.1 we have described the progressive depression of upper airway reflexes that occurs with increasing age. Ethyl alcohol may have further additive effects in the elderly.

It is thought that the protective function of the larynx may be impaired in the post-operative period (Tomlin & Howarth 1968), especially following tracheal intubation when due to disruption of the laryngeal mechanoreceptors and sensory receptors the larynx may be functionally incompetent for a number of hours (Burgess & Cooper 1979). In the post-operative period the additive effects of ethyl alcohol on the function of the larynx must be considered.

We conclude from this study 8.1, that following the oral administration of five units of ethyl alcohol (50g) to normal healthy male volunteers, the sensitivity of upper airway reflexes was not significantly depressed when measured using an ammonia stimulus technique. Following this standard dose of oral ethyl alcohol, we found quite a wide range of blood alcohol levels, some individuals who developed high blood alcohol levels did exhibit quite large changes in their NH_3TR.

It is possible that the effects of ethyl alcohol on the sensitivity of upper airway reflexes may be additive to the depressant effects produced by anaesthetic agents and the disruption of laryngeal function which is known to occur following tracheal intubation. The combination of all these factors should be considered when general anaesthesia is required for a patient who has consumed considerable amounts of ethyl alcohol.

The blood levels that were produced were modest, with some individuals' blood alcohol level remaining below the legally permitted level for driving.

In conclusion five units of ethyl alcohol, given to healthy male volunteers does not produce significant depression of upper airway reflex sensitivity as measured using an ammonia stimulus technique.

CHAPTER 9

The effect of breathing Entonox on the sensitivity of upper airway reflexes.

Introduction

Nitrous oxide is commonly used in medicine for its sedative and analgesic properties. It is used widely in obstetric practice to produce analgesia, other common areas of use are in the emergency situation either in the field or in the accident and emergency department to produce short term analgesia. Nitrous oxide is also used in dental practice to produce sedation and analgesia to allow removal of teeth. In many of these situations the patients may have a full stomach and be at risk of regurgitation and subsequent aspiration. The aim of this investigation was to assess the effect of breathing 50% nitrous oxide in oxygen on the sensitivity of upper airway reflexes.

Using the method that we have previously described in chapter 4, the sensitivity of upper airway reflexes were measured using a low concentration of ammonia vapour to assess the reactivity of the upper airway.

Method

In a single blind, cross-over study 10 healthy non-smoking male volunteers aged 25-35yr were studied. Exclusions included a history of a recent upper respiratory chest infection within the previous month and atopy and asthma.

Baseline measurements of ammonia threshold (NH_3TR) were made and auditory reaction time (ART) was measured using response to an auditory stimulus delivered via headphones.
The volunteers were then allocated randomly to receive either oxygen (50%) enriched air or N_2O (50%) in O_2 via a mouth piece. The nasal airway was occluded with a nasal clip. The subjects breathed the gas mixture for 30 min and were then allowed to breath room air.
Measurements of NH_3TR and ART were made at 5, 10, 20, 30 and 40 min.
Two weeks later the subject attended the laboratory again and the experiment was repeated using the alternative gas mixture.

Results

Table 9.1

Auditory reaction time (msec) and NH_3TR (ppm) after breathing placebo (Air + O_2) or 50% N_2O in O_2.

Auditory Reaction Time (msec)

Placebo (Air + O_2)

	T=0	*T=5*	*T=10*	*T=20*	*T=30*	*T=40*	*T=50*
Subject A	174	154	167	173	162	151	160
Subject B	124	152	118	121	136	160	152
Subject C	184	160	209	146	176	156	140
Subject D	196	181	191	192	173	164	152
Subject E	231	210	218	234	275	219	200
Subject F	154	160	172	168	161	180	172
Subject G	163	158	161	167	152	178	143
Subject H	141	147	151	157	134	141	140
Subject I	154	156	178	163	180	131	158
Subject J	168	159	171	154	146	167	159
Mean	**168.9**	**163.7**	**173.6**	**167.5**	**169.5**	**164.7**	**157.6**
SEM	**9.5**	**5.9**	**9.0**	**9.4**	**12.8**	**7.7**	**5.7**

N_2O / O_2

	T=0	*T=5*	*T=10*	*T=20*	*T=30*	* Air *T=40*	*T=50*
Subject A	161	246	352	369	327	192	180
Subject B	188	220	307	334	358	244	198
Subject C	121	220	307	334	358	244	198
Subject D	122	167	279	281	290	125	130
Subject E	167	234	365	365	289	160	173
Subject F	180	220	281	348	497	228	193
Subject G	170	221	270	340	258	211	192
Subject H	143	328	346	391	413	222	163
Subject I	189	217	327	500	745	482	201
Subject J	164	213	210	217	343	190	172
Mean	**160.5**	**228.6**	**304.4**	**347.9**	**387.8**	**229.8**	**180.0**
SEM	**7.8**	**12.8**	**14.7**	**23.0**	**45.2**	**30.4**	**6.9**

NH3TR (ppm)

Placebo (Air +O_2)

	T=0	T=5	T=10	T=20	T=30	T=40	T=50
Subject A	327	251	251	327	251	251	251
Subject B	524	524	327	524	327	327	327
Subject C	327	251	251	524	327	327	327
Subject D	524	524	327	524	524	327	327
Subject E	327	327	524	327	524	327	327
Subject F	600	524	600	524	600	524	524
Subject G	600	600	524	327	600	524	600
Subject H	600	878	878	600	878	600	878
Subject I	327	524	327	327	251	251	327
Subject J	600	878	600	524	524	600	600
Mean	**475.6**	**528.1**	**460.9**	**452.8**	**480.6**	**405.8**	**448.8**
SEM	**41.5**	**70.3**	**63.5**	**35.0**	**61.9**	**44.2**	**62.3**

N_2O/O_2

	T=0	T=5	T=10	T=20	T=30	T=40	T=50
Subject A	327	1620	1620	1620	1620	1140	524
Subject B	524	1140	1140	2360	1970	878	878
Subject C	327	1140	1620	1970	1620	878	524
Subject D	524	1620	1970	2790	1970	878	524
Subject E	327	1140	1970	2790	1970	878	327
Subject F	524	1140	1620	1620	1140	878	600
Subject G	524	878	1620	1620	1620	1140	524
Subject H	600	878	1140	1620	1620	1140	524
Subject I	327	878	1970	1970	1620	1620	878
Subject J	600	1140	1970	1970	1620	1620	878
Mean	**460.4**	**1157.4**	**1664.0**	**2033.0**	**1677.0**	**1105.0**	**618.1**
SEM	**37.5**	**85.9**	**101.7**	**147.1**	**79.3**	**93.8**	**60.7**

Statistical analysis

The Auditory reaction time data was analysed using Friedman two-way ANOVA. The values following the inhalation of 50% oxygen enriched air did not reach significance ($p=0.26$). However following inhalation of 50% N_2O in oxygen the increase in ART was highly significant ($p < 0.001$). Analysis at separate time points using Wilcoxon matched pairs signed ranks test revealed significant increases at all time points.

The analysis of NH_3TR data using Freidman two-way ANOVA revealed no significant change following breathing of 50% O_2 in air ($p=0.46$). However following breathing 50% N_2O in O_2 a highly significant change in NH_3TR was found ($p<0.001$). Analysis at separate time points using Wilcoxon matched pairs signed ranks test revealed significant increases at all time points.
The NH_3TR showed a significant rise within 5 min of exposure to N_2O in O_2, this increased to a peak value mean 2033 (147) at 20 min. Following cessation of exposure to N_2O in O_2 at 30 min the NH_3TR fell back towards normal at 50 min but again did not reach basal levels before the end of the experiment (Figure 9.1).

The results show that the Auditory reaction time did not change during the inhalation of oxygen 50% enriched air. On breathing the mixture of N_2O in O_2 the auditory reaction time started to rise reaching a peak at 30 min mean 387 (45.2) msec. At 30 min when the inhalation of N_2O in O_2 ceased the ART fell back towards normal but did not fully return to basal levels before the end of the investigation (Figure 9.2).

Table 9.2

Summary of auditory reaction time (msec) and NH_3TR (ppm) after breathing placebo (Air + O_2) or 50% N_2O in O_2.

Auditory Reaction times (msec)
mean (SEM)

Time	Placebo ART	N_2O ART
T0	168.9 (9.5)	160.5 (7.8)
T5	163.7 (5.9)	228.6 (12.8)
T10	173.6 (9.0)	304.4 (14.7)
T20	167.5 (9.4)	347.9 (23.0)
T30	169.5 (12.8)	387.8 (45.2)
T40	164.7 (7.7)	229.8 (30.4)
T50	157.6 (5.7)	180.0 (6.9)

NH_3TR (ppm) mean (SEM)

Time	Placebo NH_3TR	N_2O NH_3TR
T0	475.6 (41.5)	460.4 (37.5)
T5	528.1 (70.3)	1157.4 (85.9)
T10	460.9 (63.5)	1664.0 (101.7)
T20	452.8 (35.0)	2033 (147.1)
T30	480.6 (61.9)	1677.0 (79.3)
T40	405.8 (44.2)	1105.0 (93.8)
T50	448.8 (62.3)	618.1 (60.7)

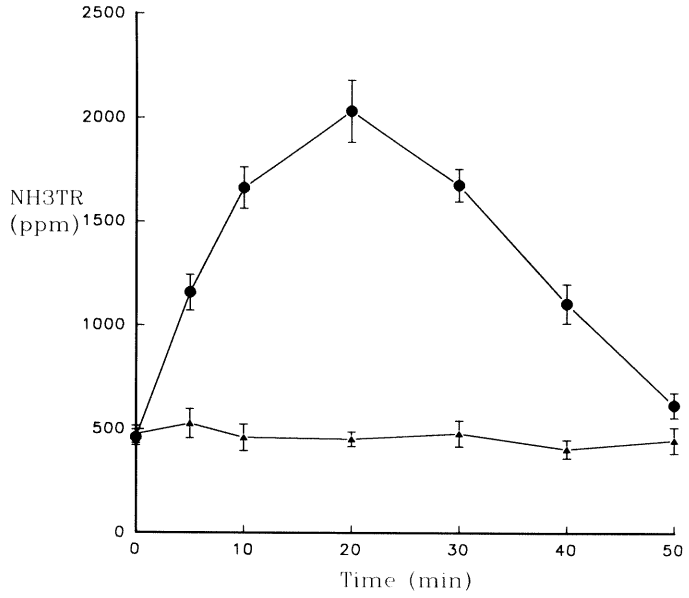

Figure 9.1 Relationship between NH_3TR (ppm) mean (SEM) and time (min) after inhalation of either placebo (Air $+O_2$) (▲) or 50% N_2O in O_2 (●).

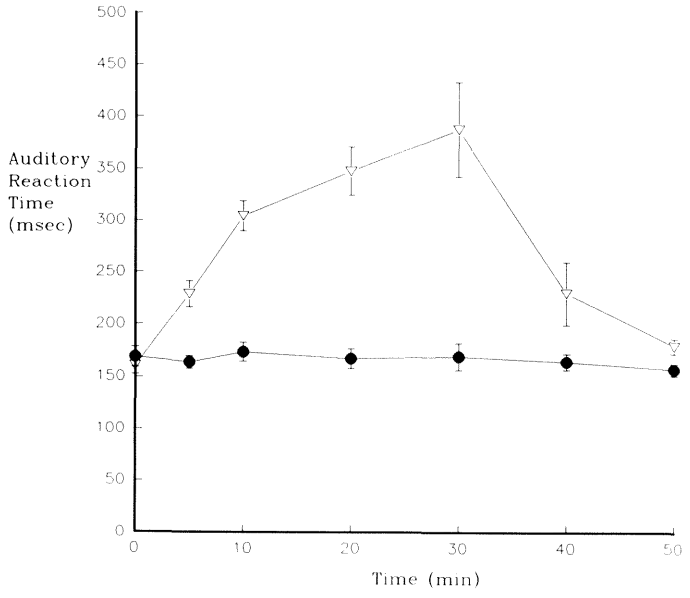

Figure 9.2 Relationship between auditory reaction time (msec) mean (SEM) and time (min) after inhalation of either placebo (Air + O_2) (●) or 50% N_2O in O_2 (▽).

Discussion

In this study 9.1, we measured the sensitivity of upper airway reflexes during inhalation of 50% N_2O in O_2 in normal healthy male volunteers. These results are of importance because 50% N_2O in O_2 (Entonox) is routinely administered for its analgesic properties by midwives during labour, and by paramedics treating trauma victims before they reach hospital. These groups of patients are well known to be at risk of regurgitation and aspiration of gastric contents, our results indicate that prolonged inhalation of Entonox places these patients at risk.

The results show that there is significant depression of upper airway reflexes that occurs following inhalation of the mixture of 50% N_2O in O_2. The maximum effect was reached after breathing the gas mixture for 20 min, at which point the NH_3TR had increased to a mean value of 2033 ppm. The effect of the gas mixture on auditory reaction time showed a peak effect occurring at 30 min with the ART reaching a peak of 387 msec.

The laryngeal closure reflex and N_2O / O_2 mixtures was investigated by Cleaton-Jones (1976). He investigated 14 subjects aged 22-29 yr and each subject was asked to breathe 50% N_2O / O_2. After 5 min, 10ml of a radio-opaque dye (Dionosil - a suspension of propyliodone) was placed on the back of the tongue with a syringe and then swallowed. He found that none of his subjects aspirated any of the dye into their lungs.

This is very interesting as our data indicates that the NH_3TR at 5 min will not have reached the peak effect with a mean threshold of 1157 (85). This would tend to indicate that the depression of upper airway reflexes at 5 min with a NH_3TR of approx. 1000 ppm is not sufficient to allow aspiration of the dye into the lungs of healthy normal male subjects.

Further work by Rubin (1977), investigated laryngeal competence during relative analgesia with 50% N_2O in O_2 . In this study 10 healthy normal adult volunteers inhaled the gas mixture for a longer period of 10 min before the radio-opaque dye was placed on the back of the tongue. This time a number of the subjects did aspirate the dye. This concurs with our results because at 10 min the NH_3TR will have increased considerably to a mean value of 1664 (101) ppm. It would seem that for there to be a significant risk of aspiration occurring the NH_3TR would need to reach values in excess of 1500 ppm or show an increase from baseline values of 300%.

Roberts and Wignall (1982), measured the efficacy of the laryngeal reflex during oxygen-nitrous oxide sedation in children aged 4 - 18yr. The technique used in this study was different from the previous two studies. The induction procedure was as follows: the mixture dial was set to 100% oxygen and the patient was settled in the dental chair. The nasal mask was positioned and the patient encouraged to breathe gently through the nose. The flow of oxygen was increased gradually until it matched the patients tidal volume. At this point the administration of 10% N_2O commenced, this was held at this concentration for 60 sec and then increased up to 20% and if necessary up to 30%. Patients were studied in the supine position. Before the start of drilling, a quantity of propyliodone was deposited onto the tongue, sufficient to cause swallowing. This was repeated halfway through the operative procedure. The total amount of dye swallowed was in excess of 10ml. Immediately after treatment was completed a lateral x-ray of the larynx and throat was obtained and later a chest x-ray was taken in the radiology department.

They did not find any evidence of aspiration of radio-opaque dye. However, there are a number of important differences between this study and the previous work. Firstly this investigation was conducted in children,

and the concentration of N_2O in O_2 used was lower at 30%. The chest x-ray was also taken later in the radiology department and not immediately following exposure.

Using a different technique the depression of the swallowing reflex during sedation and / or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen was investigated by Nishino (1987). Swallowing results in reflex closure of the glottis and has an obvious protective value against the aspiration of foreign material into the respiratory tract. The protective pharyngeal and laryngeal reflexes, including the swallowing reflex are depressed by deep general anaesthesia. They examined the changes in the activity of the swallowing reflex during sedation produced by the inhalation of 50% nitrous oxide in oxygen. Their results supported the hypothesis that pharyngeal protective reflexes might be obtunded during nitrous oxide-oxygen sedation. and provides additional evidence of incompetence of upper airway function during sedation. In this regard inhalation of radio-opaque dye may occur during sedation or light anaesthesia and is due in part to depression of the swallowing reflex.

The swallowing of radio opaque dye has been used in a number of studies to show that the laryngeal closure reflex is depressed during conventional anaesthesia, Brock-Utne (1976), found evidence of aspiration of radio opaque dye in eight patients undergoing neurolept anaesthesia for carotid angiography and concluded that neurolept analgesia should be accompanied by tracheal intubation with a cuffed tube to protect the airway.

In conclusion, we have investigated the effect that breathing 50% N_2O in O_2 has upon the sensitivity of upper airway reflexes. The results indicated that there is a depression of upper airway reflexes associated with the inhalation of a 50% mixture of N_2O in O_2. The effect was seen after 5 min and reached a peak after breathing the gas mixture for 20 minutes. There were also significant effects on the auditory reaction time which were maximal after 30 min. Both the NH_3TR and the auditory reaction time decreased following cessation of breathing the mixture, but did not return back to baseline levels before the end of the study.

It is important therefore, that it is appreciated that the administration of Entonox for analgesic purposes, if continued for prolonged periods, that is, in excess of 10 minutes, then depression of the sensitivity of upper airway reflexes will be produced. This may expose a high risk group of patients to the risk of aspiration.

CHAPTER 10

Study 10.1

Vocal cord movements on induction of anaesthesia using either thiopentone or propofol.

Introduction

Propofol has become used widely for intravenous induction of anaesthesia and is associated with ease of maintenance of the airway and early toleration of a Guedel airway (McKenzie & Grant 1985). Intubation of the trachea may also be accomplished easily under anaesthesia with propofol alone (Keaveny & Knell 1988). This evidence indicates that propofol may have different actions upon the upper airway, and upper airway reflexes than thiopentone.

This study was designed to observe the movements of the vocal cords after induction of anaesthesia with propofol or thiopentone.

Method

After Ethics Committee approval and informed patient consent had been obtained, we studied 30 patients (23 male), ASA 1 and 2 aged 20-78 years undergoing dental surgery. Patients were excluded from the study if they had a history of hiatus hernia, symptoms of regurgitation, obesity, laryngeal pathology, nasal obstruction, or coagulation disorders.

All patients were premedicated with temazepam 10-20 mg orally and as it was found in preliminary studies that it was necessary to prevent secretions obscuring the view through the fibrescope, glycopyrronium 0.3 mg intramuscularly was given 1 hour before anaesthesia. On arrival in the anaesthetic room monitoring was commenced using pulse oximetry and ECG and a 16g cannula was inserted into a forearm vein.

The nasal mucosa was anaesthetised with 4% lignocaine spray (maximum dose of 150 mg) and a 6mm nasopharyngeal airway was introduced. Preoxygenation was commenced for 5 minutes via a specially adapted face mask.

After preoxygenation, a fibrescope (Olympus LF1) was passed via the nasopharyngeal airway into the pharynx until a clear view of the larynx was obtained. A video camera (Panasonic CCD GL110 AE with Olympus AK-2C adapter) was attached to the eyepiece of the fibrescope and colour video recordings of the vocal cord movements were made on to a videocassette recorder (Sony Umatic VO 5630). Events were recorded on the soundtrack simultaneously with the video recordings.

Patients were allocated randomly to receive either propofol 2.2 mg kg^{-1} or thiopentone 3.6 mg kg^{-1} for induction of anaesthesia (Grounds & Moore 1986). Before induction of anaesthesia the patients were asked to hold a 20 ml syringe between the thumb and forefinger; induction of anaesthesia

was judged to have occurred when the subject had dropped the syringe (Cummings & Dixon 1984).

After 20 seconds of recording the induction agent was administered over 20 seconds. Video recordings were continued for 60 seconds after induction of anaesthesia had occurred, as judged by the subject dropping the syringe. During the video recording of the larynx, we attempted to ensure that the position of the laryngoscope remained constant. At the end of this time the fibre optic laryngoscope was removed and anaesthesia continued for the operative procedure.

The video recordings were played back on a video recorder with a freeze frame facility and measurements were made by a blinded observer. The anterior angle between the vocal cords was measured using a goniometer while the video frame was frozen. Measurements were made with the subjects awake, at the time of dropping the syringe and every five seconds for the first minute after induction. Data were analysed statistically using multiple analysis of variance for repeated measures to identify a difference between the two groups and by Student's t test to identify the times at which the difference occurred. Chi - squared test was used to compare the sex ratio of the two groups and Fisher's exact test to compare the incidence of complete glottic closure.

Results

Table 10.1

Angle between the vocal cords (degrees) before, and for 60 seconds after induction of anaesthesia with propofol or thiopentone.

Angle between vocal cords (degrees).

Propofol

Subject	*Awake*	*Syringe drop*	*T5*	*T10*	*T15*	*T20*	*T25*	*T30*	*T35*	*T40*
A	35	30	30	20	20	20	20	20	20	20
B	50	50	50	35	35	35	40	50	50	50
C	30	40	40	40	40	40	40	40	40	40
D	53	51	60	49	67	60	56	36	34	26
E	68	-	55	59	55	-	49	75	44	35
F	30	24	35	31	31	20	24	28	20	20
G	65	60	55	45	45	55	40	50	45	40
H	45	45	30	50	40	50	50	50	40	50
I	45	45	45	40	40	40	30	30	30	30
J	60	30	30	30	30	30	40	40	30	40
K	40	40	20	30	20	0	0	0	0	0
L	55	50	50	50	40	30	30	35	30	30
M	30	20	20	20	20	25	20	10	25	20
N	70	50	50	60	40	50	50	40	40	40
Number	**14**	**13**	**14**	**14**	**14**	**12**	**14**	**14**	**14**	**14**
Mean	**48.2**	**41.1**	**40.7**	**39.9**	**37.4**	**35**	**34.2**	**36**	**32**	**31.5**
SD	**14.1**	**11.9**	**13.2**	**12.9**	**13.3**	**16.7**	**15.2**	**18.6**	**13.0**	**13.6**

Subject	*T45*	*T50*	*T55*	*T60*
A	20	30	30	30
B	50	50	50	50
C	40	40	40	40
D	25	23	23	24
E	38	41	34	34
F	-	-	-	-
G	35	40	40	-
H	40	40	40	40
I	40	40	40	40
J	40	40	40	40
K	40	20	40	40
L	30	30	30	30
M	10	20	15	20
N	50	60	70	70
Number	**13**	**13**	**13**	**12**
Mean	**35.2**	**36.4**	**37.8**	**38.1**
SD	**11.4**	**11.6**	**13.1**	**13.0**

Table 10.1 (ctd)

Thiopentone

Subject	*Awake*	*Syringe drop*	*T5*	*T10*	*T15*	*T20*	*T25*	*T30*	*T35*	*T40*
O	50	10	10	10	10	10	10	20	20	20
P	35	30	20	20	20	20	10	10	10	10
Q	55	30	25	25	20	20	20	20	20	20
R	40	-	-	40	40	20	20	40	40	40
S	50	0	0	0	0	0	0	0	0	0
T	50	50	40	40	50	50	50	50	50	50
U	55	35	20	20	10	10	10	10	10	10
V	45	45	10	10	10	10	15	20	20	20
W	60	40	40	40	40	30	30	30	30	30
X	50	40	20	30	20	30	30	20	20	30
Y	30	30	21	26	0	0	0	0	0	0
Z	60	28	0	0	0	0	0	0	0	0
AA	74	77	73	77	75	74	0	0	0	0
AB	60	50	40	30	30	30	20	20	20	20
Number	**14**	**13**	**13**	**14**	**14**	**14**	**14**	**14**	**14**	**14**
Mean	**51**	**35.8**	**24.5**	**26.2**	**23.2**	**21.7**	**15.3**	**17.1**	**17.1**	**17.9**
SD	**11.3**	**18.9**	**19.9**	**19.9**	**21.8**	**20.7**	**14.5**	**15.4**	**15.4**	**15.7**

Subject	*T45*	*T50*	*T55*	*T60*
O	20	20	20	30
P	10	10	10	10
Q	20	20	20	20
R	40	30	30	30
S	0	0	0	0
T	40	50	50	50
U	10	10	10	10
V	30	30	30	30
W	30	30	30	30
X	30	30	30	30
Y	0	29	23	-
Z	0	0	0	0
AA	0	0	0	0
AB	20	30	30	30
Number	**14**	**14**	**14**	**13**
Mean	**17.9**	**20.6**	**20.2**	**20.8**
SD	**14.8**	**14.9**	**14.7**	**15.5**

Two patients (one from each group) were excluded from analysis as they were unable to tolerate insertion of an airway or the fibrescope.

In all patients arterial oxygen saturation exceeded 90% throughout the study period.

The groups were comparable in age, weight, and sex (Table 10.2).

Table 10.2.

Patient data, duration of apnoea, minimum arterial oxygen saturation and incidence of complete glottic closure after induction of anaesthesia. (mean (SD) [range]). * P<0.05 between groups.

	Thiopentone	**Propofol**
n	14	14
Sex (M/F)	11/3	12/2
Age (yr)	45 (23-68)	39 (20-78)
Weight (kg)	75.4 (12.6)	68.5 (9.4)
Duration of apnoea	20.5 (21.9)	38.0 (11.6)*
(sec)	[0-60]	[20-60]
Glottic closure (No.)	4	1
Minimum SpO_2 (%)	93.6 (2.4)	97.7 (1.2)
	[92-100]	[96-100]

The mean induction dose of thiopentone was 332 mg (SD 106) and the mean induction dose of propofol was 170 mg (SD 29.6). There was no statistical difference in the pre-induction vocal cord angle between the two groups (Figure 10.1).

The angle between the vocal cords decreased in both groups after induction of anaesthesia. The decrease in angle was significant in the thiopentone group (MANOVA $p= 0.009$) , and also in the propofol group (MANOVA $p < 0.001$). However, the decrease in angle was significantly greater in the former group (MANOVA $p= 0.008$). In the thiopentone group the decrease in angle was significantly greater at times induction plus 5 seconds 10 s, 15 s, 25 s and 35 s ($p< 0.05$), at 30 s, 50 s, and 60 s ($p<0.01$) and at 45s, and 55s ($p<0.005$). There were no significant differences between the groups at syringe drop or at 20 seconds post syringe drop.

Acknowledgement

The data in this study 10.1 has been published in:

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Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol. **Br.J.Anaesth** 1992;69:23-25.

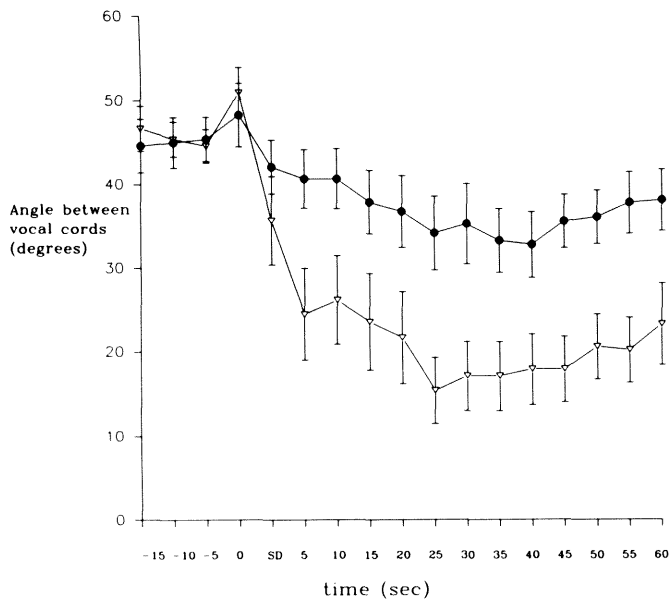

Figure 10.1 Graph showing the angle between the vocal cords (degrees) mean (SD) before and during induction of anaesthesia with propofol (●) or thiopentone (∇).

Discussion

In this chapter, I have described a study that we undertook to measure the movements of the vocal cords on induction of anaesthesia with either thiopentone or propofol. This study was undertaken because there is clinical evidence of a fundamentally different nature of action on the upper airway of these two commonly used anaesthetic induction agents.

The results indicate that the vocal cords are adducted to a greater extent after induction of anaesthesia with thiopentone than with propofol. The mechanism underlying this difference may include a greater depressant effect of propofol on airway reflexes, heightening of airway reflexes by thiopentone or possible neuromuscular blocking actions of propofol. However, available evidence suggests that the first two mechanisms are the most likely.

In studies by Burnstein (1937), on the effects of short acting barbiturates on the patency of the glottis, it was found that most of the animals studied would cough, sneeze or hiccup during the course of anaesthesia. Inspection of the glottis revealed adduction of the vocal cords. Burnstein also found that in cases where there was not any spontaneous coughing then inspection of the glottis showed hyperactive adducted vocal cords, and lifting the epiglottis would elicit complete closure of the vocal cords. After the introduction of thiopentone into human anaesthetic practice in 1934, a number of reports of laryngeal spasm as a complication of thiopentone anaesthesia began to appear (Ruth & Tovell 1939). In this paper Ruth reviewed the first five years of the use of thiopentone and highlighted the occurrence of temporary closure of the glottis and the hyperactive state of the laryngeal reflex following induction of anaesthesia using thiopentone.

Brown and colleagues (1991), compared propofol with thiopentone for insertion of a laryngeal mask, and found that propofol was more effective in producing satisfactory conditions for the insertion of the laryngeal mask and there was a lower incidence of gagging on the airway after insertion.

Evidence for depression of upper airway reflexes by propofol was provided by Mackenzie and Grant (1985), who commented on the ease of insertion of a Guedel airway after induction of anaesthesia with propofol. Szneke (1989), also found that an oral airway could be inserted earlier after induction of anaesthesia with propofol than with thiopentone. Keaveny and Knell (1988), found that in 19 of 20 patients in whom anaesthesia was induced with propofol 2.5 mg kg^{-1} had satisfactory conditions for tracheal intubation, although 7 coughed on tracheal intubation. There is little evidence for any muscle relaxant effects of propofol, Jacques & Gold (1990) found that propofol possessed poor muscle relaxant properties.
Syringe drop (Cummins & Dixon 1984) was used to assess induction of anaesthesia as the eyelash reflex is difficult to assess in the presence of involuntary movements such as those occurring during induction with propofol; this also avoids the repeated stimulation of testing the eyelash reflex.

The mechanism underlying this different effect of these two induction agents may include a greater depressant effect of propofol on airway reflexes or heightening of airway reflexes by thiopentone.

In conclusion we have found that the vocal cords remained abducted after induction of anaesthesia with propofol 2.2 $mgkg^{-1}$ but after induction with thiopentone 3.6 $mgkg^{-1}$ the vocal cords tended to adduct. I believe that the likely explanation for this is that propofol produces greater depressant actions on upper airway reflexes, and this may explain the low incidence of laryngospasm that has been reported after induction of anaesthesia with propofol (Sanderson & Blades 1988). It may also explain why many anaesthetists find the airway much easier to manage following induction of anaesthesia with propofol.

CHAPTER 11

Conclusions & clinical recommendations.

Upper airway reflexes play an important role in anaesthesia, and understanding the factors which influence their activity and sensitivity is clinically important. The maintenance of a clear unobstructed upper airway and the return of normal laryngeal reflexes following the end of general anaesthesia form two of the most fundamental principles of anaesthesia. The sensitivity of upper airway reflexes are important during induction of anaesthesia, as heightened upper airway reflexes at this time may lead to the development of life threatening laryngospasm. In chapter one, I described the consequences of laryngospasm in the peri-operative period. The incidence of this complication in routine anaesthetic practice has been found to be 8.7 / 1000 patients, but the risk increases when considering anaesthesia in children. The highest incidence occurs in children aged between 1 - 3 months, with a sharp rise in the incidence if the child has an upper respiratory tract infection.

Laryngospasm is a serious complication of general anaesthesia, when considering anaesthesia for infants the anaesthetist should be prepared for an increased incidence and this becomes even higher if the child has an upper respiratory tract infection, and for this reason anaesthesia and surgery should be delayed until the child has recovered. However the mechanism by which upper respiratory tract infections increase the excitability of the airway is not known. Also it is not known for how long the upper airway reflexes remain hyperexcitable following an upper respiratory tract infection. This would be a very interesting area for future

investigation, which would help anaesthetists decide when the risks are reduced for children to undergo anaesthesia.

The use of inhalation anaesthetic agents is associated with laryngospasm and this is explained by the irritant effect of these agents on the upper airway. Isoflurane has been found to have the highest incidence when compared with other agents. It has also been shown that the newer agent desflurane is associated with a high incidence of laryngospasm when used for inhalation induction of anaesthesia (Hemelrijck 1991). Sevoflurane is soon to be introduced as a new inhalation anaesthetic agent in the United Kingdom. One of the advantages proposed by the manufacturers for sevoflurane is its lack of airway irritability, and smooth induction characteristics especially in children. Why this agent is less irritant than other new agents such as desflurane and isoflurane has yet to be fully investigated.

In the post-operative period normal laryngeal reflexes are vital to protect the lungs from contamination with gastric contents or blood and saliva. There are a number of factors which affect the lower oesophageal sphincter pressure and I have reviewed these in chapter 1. The larynx and upper airway reflexes are clearly impaired in the post-operative period and aspiration of gastric contents is a recognised hazard for post-operative patients whose laryngeal reflexes are impaired.

In chapter two, I have outlined the current state of knowledge regarding reflexes and receptors of the upper respiratory tract. It is interesting that in the upper airway that a nervous end organ has not been identified histologically, and that little is known about the central nervous circuits involved in the reflexes from the upper respiratory tract.

Histologically nerve fibres that are thought to be sensory are found in almost all areas of the laryngeal mucosa and deeper structures.

The most frequent appearance is of free nerve endings in the mucosa and submucosa, with myelinated or non-myelinated fibres. The densest collection of nerve fibres are found in the posterior supraglottic area sending fibres in the superior laryngeal nerve. The rapidly adapting receptors are especially sensitive to chemical stimulants, such as ammonia vapour.

The measurement of the sensitivity of upper airway reflexes dates back to 1950 with some of the early work using ammonia as a stimulus to investigate the upper airway, as I have explained in chapter 3, there were considerable problems with previously described systems which were contributing to the inaccuracy of the measurements obtained. The system described in chapter 4, overcomes many of the problems that existed with previous methods. Data on the concentration of ammonia vapour produced within the circuit has been obtained, so that the exact concentration of ammonia vapour that is used to stimulate the upper airway is known. We have produced data in normal volunteers on the repeatability and reliability of this measurement for the measurement of the sensitivity of upper airway reflexes. This has not been done in any of the previous work in this area. We have also designed an efficient absorber system that allows this system to be used safely in the clinical area.

In chapter five we found a close relationship between increasing age of patients and an increase in NH_3TR, which means that elderly patients have less sensitive upper airway reflexes than younger patients, elderly patients may therefore be at increased risk of aspiration. After anaesthesia the effect of residual anaesthetic agents and disruption of laryngeal sensory and mechanical function following tracheal intubation, will also increase the risk of aspiration in this vulnerable group of patients and increased vigilance and meticulous clinical management is required in these patients if silent aspiration is to be avoided.

Smoking is still, unfortunately, a frequent habit of many patients presenting for anaesthesia and surgery, despite the well known risks to health. In chapter six we have outlined many of the known deleterious effects of smoking on the human body and I have described the known effects of smoking on peri-operative morbidity and mortality. In study 6.1, smokers were found to have significantly more sensitive upper airway reflexes than non-smokers and the sensitivity of these reflexes did not change on stopping smoking for 24 hr. This means that for patients admitted to hospital pre-operatively on the day before surgery, stopping smoking the day before anaesthesia will not reduce the sensitivity of their upper airway reflexes. There will be some improvement in carboxyhaemoglobin levels which will improve oxygen carriage if smokers stop smoking the day prior to anaesthesia. The half life of carboxyhaemoglobin depends on pulmonary ventilation and is therefore longer at night and so maximum benefit in terms of reduction in carboxyhaemoglobin levels will be achieved by stopping smoking earlier in the day. In study 6.2 we have demonstrated that for smokers to reduce the sensitivity of upper airway reflexes, smoking should be stopped between 7 - 10 days pre-operatively. To prevent the increase in pulmonary morbidity, with chest infections and impaired gas exchange then smoking should cease at least six weeks pre-operatively. It is therefore vital that patients are advised strongly in the out-patient department when they are seen by the surgeon to stop smoking. Stopping smoking 7 - 10 days pre-operatively should reduce the incidence of airway problems during anaesthesia. This would be a useful area for future work. The other area which deserves further investigation is the mechanism by which smoking causes hypersensitivity of upper airway reflexes and how the change which we have measured on stopping smoking is mediated. It may be that on stopping smoking there is recovery in the generalised leakiness of epithelium that has been measured in

smokers, and therefore receptors are less likely to be stimulated by irritants in the airway.

Or it is possible that smoking itself produces a change in the receptors of the upper airway, which on withdrawal of the smoke recover.

It would be of interest to measure the time course of change in sensitivity of upper airway reflexes, on starting smoking again following a period of abstention.

Oral benzodiazepines are commonly prescribed as premedication prior to anaesthesia. Our results from study 7.1 indicate that diazepam produces depression of the sensitivity of upper airway reflexes that returns to baseline values by 210 min. We did not find any evidence of depression of upper airway reflex sensitivity beyond the period of the sedative effect. This depression of upper airway reflexes may be beneficial in reducing airway complications during induction of anaesthesia. In the second study 7.2, on the effect of intravenous benzodiazepines, Diazemuls and midazolam on the sensitivity of upper airway reflexes was investigated. The only previous study in the literature in this area indicated that upper airway reflexes remain depressed for at least 4 hr following a single intravenous dose of diazepam. This has clinical implications as these agents are commonly used to produce sedation and amnesia in patients undergoing procedures as day cases. If upper airway reflexes remain depressed for longer than the sedative effects of these drugs then their use in day case procedures should be questioned. We have found that the maximal depression of upper airway reflexes occurs within 10 min of drug administration and that by 60 min the sensitivity of upper airway reflexes have returned to normal. We also discovered that the specific benzodiazepine reversal agent flumazenil will reverse the depression of upper airway reflexes. Therefore we can conclude that airway reflexes do not remain depressed for prolonged periods of time following a single

intravenous dose of Diazemuls or midazolam. As the depression of upper airway reflexes does not last longer than the sedative effects, existing procedures for monitoring recovery from sedative techniques will be satisfactory to manage patients safely.

The sensitivity of upper airway reflexes following ethyl alcohol has not been previously investigated. Patients who are intoxicated with alcohol are known to be at risk from aspiration, the degree of depression of upper airway reflexes induced by ethyl alcohol and how this may interact with anaesthesia is unknown. We can state that following the dose of ethyl alcohol used in our investigation that upper airway reflexes were not significantly depressed. Therefore to produce significant depression of airway reflexes, that will place a patient at risk of aspiration of gastric contents will require higher blood alcohol levels than those used in our study. If upper airway reflexes were depressed by higher blood levels of ethyl alcohol, then how this depression interacts with other anaesthetic and sedative agents would be an interesting area for future study.

We discovered that the inhalation of a 50% mixture of N_2O / O_2 (Entonox) produces depression of upper airway reflexes that reaches a peak after breathing this gas mixture for 20 min. This depression of the sensitivity of upper airway reflexes returned towards normal baseline values on breathing room air. These results are important because Entonox is routinely administered for its analgesic properties by midwives attending women during labour, and by paramedics treating trauma victims before they reach hospital. Both of these groups of patients are well known to be at risk of regurgitation and aspiration of gastric contents. The results indicate that prolonged inhalation of Entonox, places these patients at risk from aspiration. This concurs with other studies that have been conducted on the aspiration of dye into the respiratory tract following the inhalation

of Entonox. Short periods of inhalation have been found not to be associated with risk of aspiration, whereas prolonged inhalation resulted in aspiration of dye into the respiratory tract. This concurs well with our findings that indicate at 5 min the sensitivity of airway reflexes are not depressed sufficiently to allow aspiration of dye into the respiratory tract. However the depression of the sensitivity of upper airway reflexes that occurs on longer exposure results in greater depression of the sensitivity of upper airway reflexes and may lead to aspiration in some patients. It is important therefore that it is appreciated that the administration of Entonox for analgesic purposes, if continued for prolonged periods produces depression of the sensitivity of upper airway reflexes that exposes a high risk group of patients to the risk of aspiration.

Propofol is used widely for induction of anaesthesia and a number of papers have highlighted the ease of management of the upper airway following induction of anaesthesia with propofol.
We have demonstrated that the vocal cords tend to abduct following induction of anaesthesia with propofol, whereas following induction of anaesthesia with thiopentone the vocal cords tend to adduct across the airway, making inflation of the patients lungs and airway management more difficult.
Manipulation of the upper airway, for example the insertion of oropharyngeal airways and laryngeal mask airways, have been found to be much easier following the use of propofol for induction of anaesthesia.
I believe that the explanation for this is that propofol produces a greater depressant effect on upper airway reflexes, whereas thiopentone may cause the upper airway to become hyperexcitable. This may explain the lower incidence of laryngospasm after induction of anaesthesia with propofol. This is an interesting hypothesis and requires further work to

examine the different effects that intravenous induction agents have on the sensitivity of upper airway reflexes. The mechanism for this action is not known, but it is a favourable action that if possible new intravenous induction agents should possess.

This thesis has explored the sensitivity of upper airway reflexes in humans. I have described a technique for the measurement of the sensitivity of upper airway reflexes and described a method for measurement of the movements of the vocal cords on induction of anaesthesia.
I have described a number of changes that occur in the sensitivity of upper airway reflexes due to normal physiological processes such as ageing and also changes that occur due to smoking of cigarettes. These studies have important clinical implications for anaesthetists involved in the safe perioperative management of patients.
I have examined the effects of some commonly used drugs on the sensitivity of upper airway reflexes, this has revealed interesting and clinically useful information.

There is great scope for further work in this field as there remain many gaps in our knowledge, especially relating to the normal and abnormal physiological processes of the upper airway. This work would include further identification of the receptors in the upper airway and how these receptors respond and adapt during physiological and pathological changes.

CHAPTER 12

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British Journal of Anaesthesia 1993; 70: 126–130

ORIGINAL ARTICLES

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

Airway. Measurement techniques: airway reflexes.

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 flowmeter 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

This article is accompanied by Editorial I.

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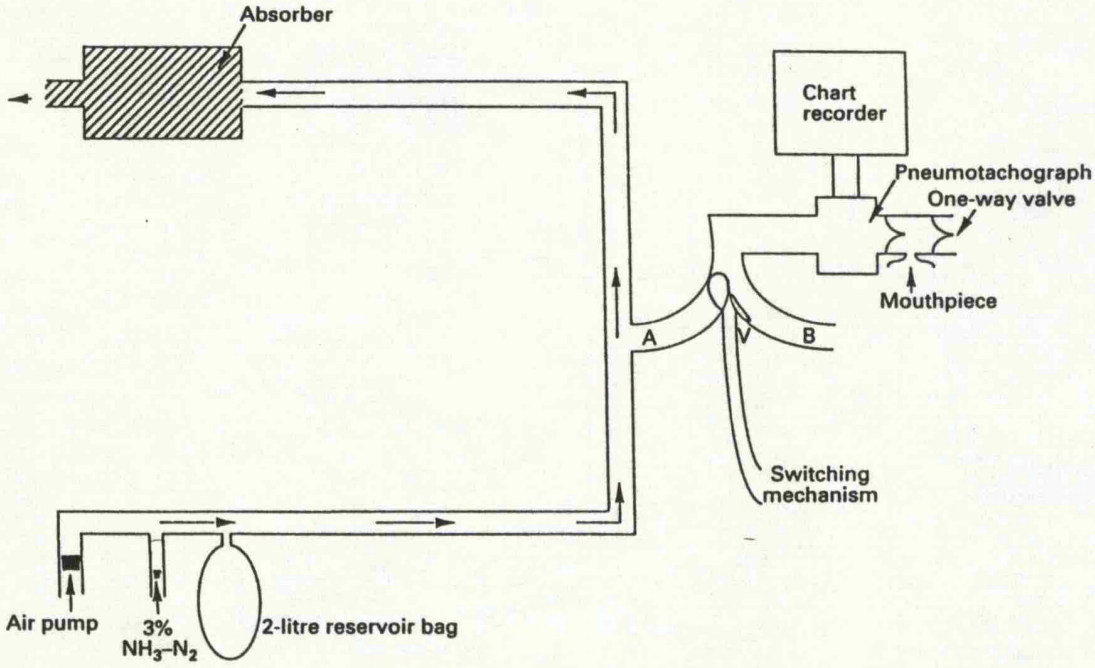

FIG. 1. Diagram of the equipment used to measure the sensitivity of upper airway reflexes. A = Ammonia–air limb; B = room air limb; V = balloon valve.

TABLE I. *Calibration data* (*mean* († *SEM*; ‡ *SD*))

Flowmeter setting	Measured flow (ml min^{-1})	Final [NH_3] (p.p.m.)	Time to 95% final [NH_3] (s)
50	73.1 (9.1)†	76 (12.3)‡	105
100	155.1 (1.02)	251 (12.6)	105
200	195.6 (0.85)	524 (33.7)	70
300	241.3 (0.54)	878 (17.8)	70
400	332.8 (0.88)	1140 (18.8)	70
500	427.1 (0.2)	1620 (61.5)	70
600	539.5 (2.95)	1970 (52.1)	70
700	635.5 (1.35)	2360 (60.4)	70
800	749.3 (0.63)	2790 (56.6)	70
900	863.7 (0.83)	3160 (142.2)	70
1000	964.6 (3.11)	3550 (170.2)	70

vapour in the carrier gas was removed by reaction with the crystals to produce ammonium benzoate and water. The crystals contained a marker dye which changed colour when the crystals were exhausted.

Calibration

Air. The air flow through the oxygen flowmeter was calibrated using a dry gas meter. With the flowmeter set at 10 litre min^{-1}, the total measured flow over a 30-min period was 324.9 litre (10.83 litre min^{-1}).

Ammonia–nitrogen. The flow of the 3% ammonia–nitrogen mixture via the cyclopropane flowmeter was measured using a bubble flowmeter (table I). The final ammonia concentration (p.p.m.), and the time (s) required for the concentration of ammonia to reach 95% of the final concentration were also recorded (table I). The concentration of ammonia produced in the system varied in the range 76–3550 p.p.m. at the differing flow rates. The time required to achieve 95% of the final concentration was 105 s at the slower flow meter settings of 50 and 100 ml; at faster flows, the time to reach 95% of the final concentration was 70 s.

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-

ings of ammonia concentration were started. Ten measurements were made over a period of 3–4 min. Then the ammonia–nitrogen flow was stopped and the time for the reading to decrease to zero was noted.

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 (eight 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.

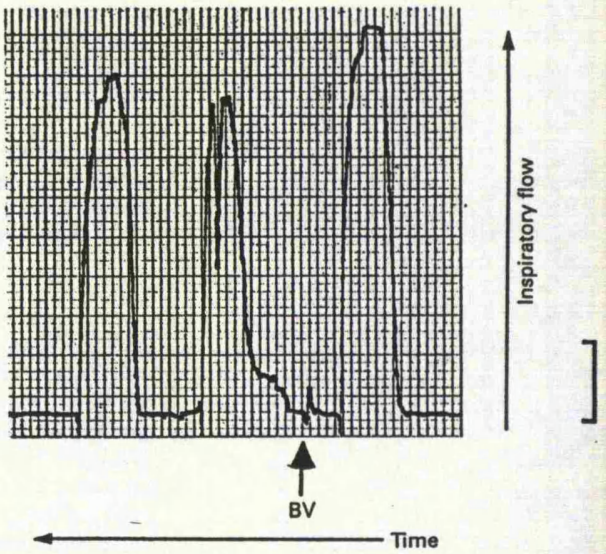

FIG. 2. An example of a glottic stop recording. BV = Switching of the balloon valve, allowing the subject to take one breath from the ammonia–air limb. Paper speed 30 cm min^{-1}; calibration bar = 10 litre min^{-1}.

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

Subject	Threshold concn (p.p.m.)	
	Different days ($n = 6$)	Same day ($n = 8$)
A	642 (524) [524–878]	465 (524) [376–524]
B	642 (524) [524–878]	499 (524) [524–674]
C	387 (387) [251–524]	363 (289) [251–524]
D	380 (387) [251–524]	471 (524) [327–524]
E	504 (524) [455–600]	435 (425) [327–524]
F	537 (524) [455–612]	544 (524) [524–674]
G	573 (524) [524–870]	440 (327) [327–524]
H	495 (524) [524–674]	536 (524) [524–600]
I	549 (524) [524–600]	536 (524) [524–543]
J	596 (524) [524–699]	627 (524) [524–678]

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

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.

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SHORT COMMUNICATIONS

EFFECT OF AGE ON THE SENSITIVITY OF UPPER AIRWAY REFLEXES

R. J. ERSKINE, P. J. MURPHY, J. A. LANGTON AND G. SMITH

SUMMARY

We have recorded the threshold concentration of inhaled ammonia vapour required to elicit reflex glottic closure (NH_3TR) in 102 healthy, non-smoking volunteers (39 female) aged 17–96 yr in order to assess the effect of age upon upper airway reflex sensitivity. A single measurement of sensitivity was made in each subject using a system delivering small concentrations of ammonia vapour for single intermittent breaths to the upper airway and recording glottic closure using an inspiratory pneumotachograph. We found a strong positive correlation between age and NH_3TR, indicating a decrease in upper airway reflex sensitivity with increasing age. (Br. J. Anaesth. 1993; **70**: 574–575)

KEY WORDS

Age factors. Airway: reflex sensitivity.

Reflex activity is thought to diminish with advancing age. Laryngeal reflexes in the elderly appear to be less active, both during induction of anaesthesia and in the recovery room, compared with the younger patient—suggesting that protection of the airway may be impaired in the elderly [1].

The protective reflex of the larynx is evoked by stimulation of receptors thought to be located in the hypopharynx and larynx. With concentrations of irritant vapour smaller than that required to produce cough, the response is glottic closure, and a brief pause in inspiration. The upper airway is sensitive to both chemical and mechanical stimuli, the former being both quantifiable and reproducible [2].

Using equipment described previously [2], we have measured the threshold concentration of ammonia vapour (NH_3TR) required to stimulate reflex glottic closure in patients. Previous workers [3] found a six-fold increase in the concentration of inhaled ammonia vapour required to produce a reflex stop in inspiration in patients between the second and eighth and ninth decades. However, that study population contained a large proportion of smokers and our early work [4] has shown that smokers have considerably more sensitive upper airway reflexes than non-smokers.

The aim of this study was to measure NH_3TR in non-smokers over a broad age range in order to assess the effect of age alone on upper airway reflex sensitivity.

METHODS AND RESULTS

After obtaining Ethics Committee approval and informed subject consent, we studied 102 healthy, non-smoking subjects aged 17–96 yr. The majority (85) were preoperative elective surgical patients, the remainder being members of our department, nursing staff and nine patients from geriatric wards. We excluded those with mental or neurological impairment, chronic bronchitis and asthma, a history of upper respiratory tract infection in the past month, and those receiving sedative medication. Two subjects had smoked in the past: one stopped 25 yr previously, the other stopped 4 weeks before the study.

Measurements were made either in our laboratory or on the ward, using the same portable equipment. A single measurement of NH_3TR was made in each subject, using the method described previously [2]. We have found that no significant difference exists between repeated measures made on the same day and on separate days in the same individual [2].

NH_3TR was plotted against age for each subject (fig. 1); there was an increase in NH_3TR with advancing age. The correlation coefficient was calculated as $+0.85$, indicating a strong positive correlation between age and NH_3TR.

Mean NH_3TR for the age group 21–30 yr ($n = 14$) was 571 (SEM 41.5) p.p.m., compared with a value of 1791 (52) p.p.m. for the group aged 86–95 yr ($n = 14$).

COMMENT

Whilst loss of peripheral reflexes in the elderly may be of little anaesthetic significance, the reduction in the sensitivity of upper airway reflexes associated with age may be important, particularly after anaesthesia or sedation, when full airway protection may be delayed, with a consequent increased risk of aspiration [1].

In 1960, Pontoppidan and Beecher carried out a similar study using ammonia vapour [3]. They

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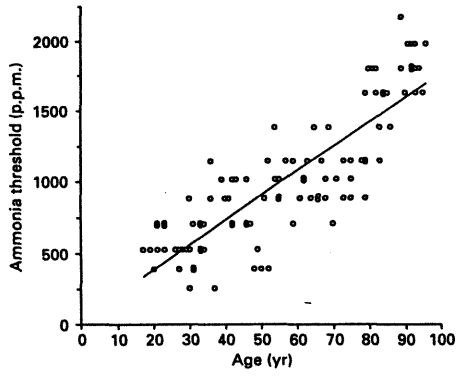

FIG. 1. Correlation between age and ammonia threshold. Regression equation: $y = 17.1x + 43.4$; correlation coefficient: +0.85.

assessed 103 subjects aged 15–84 yr and found that the threshold increased more than six-fold from the second to the eighth and ninth decades, and that the between-subject variability in sensitivity increased with age. However, we have identified several factors that may have produced inaccuracies.

First, their breathing system contained a large canister into which the ammonia vapour was injected. This could have allowed streaming to occur and, depending upon inspiratory flow and the timing of inspiration, could have produced a variable concentration of ammonia. Also, depending upon the tidal volume and inspiratory flow rate of the subject, the stimulus may have been presented to the upper airway at differing times during the ventilatory cycle. The authors stated that the actual concentration of inhaled ammonia was unknown, but was assumed to be directly proportional to the absolute amount of ammonia used. Furthermore, seven subjects failed to respond to the maximum delivered stimulus of ammonia. Second, they used a metabolic spirometer to record the change in inspiratory flow, and not a pneumotachograph. Finally, their population contained a high proportion of smokers (85%), although this varied between 33% in the 70–79 yr group and 83% in the 50–59 yr group, but they could find no consistent influence of smoking upon airway irritability. In contrast, we have found that those subjects who regularly smoke more than 15 cigarettes per day have a significantly smaller NH_3TR than non-smokers of the same age [4], indicating that smokers have more sensitive upper airway reflexes. Therefore, in this study we have excluded smokers.

In essence, our results support Pontoppidan and Beecher's work, indicating an increase in NH_3TR with increasing age, but we found the mean NH_3TR increased only three-fold from the third to the ninth and tenth decades—a change which was only 50% of that of their study. In addition, we found no increase in between subject variability in NH_3TR with age and, in general, our results were more tightly clustered in each age group. These differences between the earlier study and ours, in particular regarding distinction between smokers and non-smokers, may be explained by the improved design of our system, which delivers a more constant, known concentration of ammonia vapour [2].

The cause of this increased threshold in the elderly is unknown. The irritant receptors in the upper airway are thought to consist of free nerve endings ramifying among epithelial cells; they have been classified as type 1, rapidly adapting receptors, although no nervous end-organ has been identified histologically. Increasing age is associated with a reduction in the population of nerve endings and this, combined with the thickening that occurs in the mucosa of the upper airway thus reducing penetration of noxious chemicals, may lead to an increase in stimulation threshold. A decrease in amplitude of electrical potentials in pulmonary afferent vagal fibres with age (possibly caused by degenerative changes in sensory neurones of the Nodose (Vagal) ganglion) has been described in humans [5]. A similar mechanism may affect fibres from the superior laryngeal nerve. A histological study of age-related changes in the rat superior laryngeal nerve has demonstrated segmental demyelination and axonal degeneration in the elderly group and other ultrastructural changes associated with complete fibre dysfunction [6]. Several of these changes resemble those seen in aged human peripheral nerves, in which a decrease in fibre numbers is also a significant feature [5].

It is not possible to infer directly from our results that a progressively greater NH_3TR associated with advancing age implies a loss of protective reflexes and consequent increased risk of aspiration. However, the increased reflex stimulus threshold in the elderly may be a contributory factor, and emphasizes the need for increased vigilance during recovery from anaesthesia or sedation.

ACKNOWLEDGEMENTS

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EFFECT OF ORAL DIAZEPAM ON THE SENSITIVITY OF UPPER AIRWAY REFLEXES†

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

SUMMARY

In a double-blind, cross-over study, we have investigated the effect of oral diazepam 20 mg and placebo on the sensitivity of upper airway reflexes in 10 male volunteers (aged 25–35 yr). Upper airway reflex sensitivity (UARS) was assessed using small concentrations of ammonia vapour as a stimulus to upper airway receptors. A threshold concentration of ammonia, at which reflex glottic closure occurred in response to the ammonia stimulus, was used as a measure of UARS. With diazepam, there was significant depression of UARS from 30 to 150 min after administration. (Br. J. Anaesth. 1993; 70: 131–134)

KEY WORDS

Hypnotics, benzodiazepines: diazepam. Measurement techniques: airway reflexes.

Receptors known to respond to chemical irritants are found in the epithelial and sub-epithelial layers of the larynx and pharynx [1]. Afferents from these fibres travel mainly in the superior laryngeal nerve and synapse in the brain stem. In adult humans, the main responses to irritant receptor stimulation are glottic closure and a brief stop in inspiration [2]. At higher levels of stimulation the reflex response produced is termed the expiration reflex or laryngeal cough (a short expiratory effort without preceding inspiration) [3].

Upper airway reflex activity is important, with implications for both airway protection and upper airway complications during anaesthesia (laryngospasm, coughing). Previous work has shown that subjects given Diazemuls 15 mg i.v. had a 200% decrease in the sensitivity of upper airway reflexes, which persisted for at least 4 h after administration of the drug [4]. The apparent longevity of this reflex depression compared with the short-lived clinical effects of a single dose of i.v. Diazemuls has major implications, as it suggests that a patient may be at increased risk of aspiration despite appearing recovered from acute sedative effects. The aims of this study were to assess the effect of a premedicant dose of oral diazepam on upper airway reflexes and to investigate the time course of this effect.

SUBJECTS AND METHODS

In a double-blind, cross-over study, we have investigated 10 healthy, non-smoking, male volunteers (aged 25–35 yr) who were currently taking no medications. The subjects abstained from alcohol from noon the previous day and had a light breakfast on the day of the study. Exclusions included any subject developing an upper respiratory tract infection within 1 month before or during the study and those with a history of atopy.

Subjects were allocated randomly to receive diazepam 20 mg orally on one occasion, and placebo on another. The investigators and subjects were blinded to the identity of the medication by a system of coded envelopes (the code being broken only at the end of the study).

Baseline measurements of upper airway reflex sensitivity (UARS) and reaction time to an auditory stimulus (ART) were measured, after which subjects ingested the medication. Subsequently, measurements of UARS and ART were made every 30 min for the next 4 h.

At least 1 week later this procedure was repeated, the subject taking the alternative medication.

All subjects were advised not to work or drive a motor vehicle for 24 h after each medication.

Assessment of UARS using small concentrations of ammonia vapour as a chemical stimulus has been described [5–7]. We have recently modified the original technique to produce a more reliable system [8]. UARS was assessed with this new system, as described in the accompanying paper [9].

ART was measured using an electronic timer. We recorded the time taken for the subject to press a trigger in response to an auditory stimulus (bleep) administered via headphones. The bleeps occurred at random intervals. At the end of each 30-min interval, 10 recordings of auditory reaction time were taken and the mean value recorded. Each subject was allowed ample practice time before commencing the study, in order to eliminate practice effects.

Data were analysed using multiple analysis of variance and paired t tests; significance was taken at $P = 0.05$.

After diazepam, paired ART and ammonia threshold values, for each individual at each time-point,

This article is accompanied by Editorial I.

P. J. MURPHY, F.R.C.ANAES.; J. A. LANGTON, F.R.C.ANAES.; P. BARKER, F.R.C.ANAES.; G. SMITH, B.SC., M.D., F.R.C.ANAES.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: August 9, 1992.

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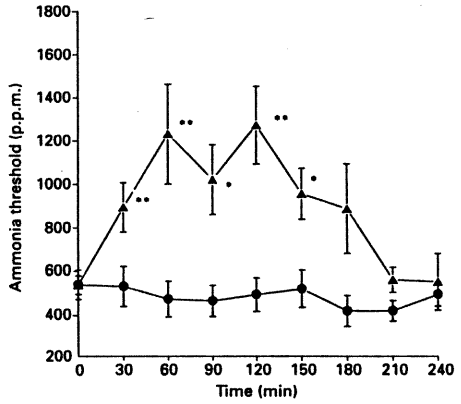

FIG. 1. Relationship between ammonia threshold (mean, SEM) and time. ▲ = Oral diazepam; ● = placebo. *$P < 0.05$; **$P < 0.01$ between groups.

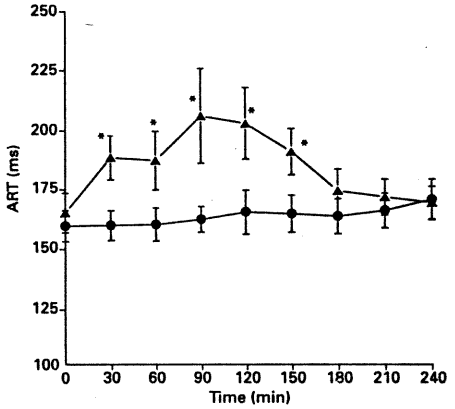

FIG. 2. Relationship between auditory reaction time (ART (mean, SEM) and time. ▲ = Oral diazepam; ● = placebo. *$P <$ 0.05 between groups.

were plotted against each other. Correlation of these variables was tested using the Spearman Rank Correlation Coefficient.

RESULTS

All 10 subjects successfully completed the study. After oral diazepam 20 mg, mean ammonia threshold values increased from a baseline of 538 p.p.m. to a peak of 1266 p.p.m. at 120 min and had decreased to 537 p.p.m. by 240 min. Significant increases in the ammonia threshold concentrations occurred between 30 and 150 min. After placebo there was no significant change in ammonia threshold (fig. 1).

After diazepam, mean ART increased from a baseline of 165 ms to a peak of 205 ms at 90 min and had decreased to 167 ms by 240 min. After placebo, there was no significant change in ART (fig. 2).

Correlation testing of paired ART and ammonia threshold values following diazepam gave an RS value of < 0.2.

DISCUSSION

Ammonia vapour stimulates sensitive nerve endings situated in the laryngeal epithelium and some laryngeal pressure receptors [10]. At a threshold of stimulation, a reflex response occurs which results in glottic closure and a brief pause in inspiration. We have used this ammonia threshold as a measure of upper airway reflex sensitivity.

Simple auditory reaction times have been used before to assess recovery after diazepam [11]. In this study we used ART as a measure of sedation in order to identify the time course of the major sedative effect of oral diazepam.

We have found that, after oral diazepam 20 mg, significant depression of UARS occurred between 30 and 150 min, but within 210 min UARS had returned to baseline values. This change followed a similar time course as changes in ART. However, after diazepam, there was no correlation between individual ART and ammonia threshold values. This lack of correlation may be attributable to several factors. For example, in many individuals the peak effect on ART occurred earlier or later than the peak effect on ammonia threshold. Also, some subjects exhibiting a marked increase in ammonia threshold had only small changes in ART, raising the possibility that measurement of ART may itself lead to increased arousal and in some individuals produce falsely decreased ART values.

After placebo there was no significant change in UARS. These data suggest that there appeared to be little tachyphylaxis to the ammonia stimulus during the period of the study.

The timing of the changes in UARS is explained easily in relation to the pharmacokinetics of oral diazepam. Studies have shown that the mean plasma first-phase half-life of a single oral dose is 5.08 h [12], with the peak effect occurring at 60 min [13, 14]. Although we cannot compare our study directly with one in which i.v. Diazemuls was used, there does appear to be a discrepancy between our results and those of the previous study [4] which demonstrated prolonged depression of UARS with maximal reflex suppression still present at 4 h after Diazemuls 15 mg i.v. Pharmacokinetic data for a single dose of i.v . Diazemuls indicate peak plasma concentrations are achieved within minutes, followed by a rapid decrease in plasma concentrations as redistribution of the drug takes place [13]. Thus one would expect i.v. Diazemuls to have a more transient effect than a similar dose of oral diazepam. This is supported by previous work which suggests that laryngeal competence is impaired for only 5–15 min after i.v. Diazemuls [15].

The answer to this discrepancy may lie in part in the improvement of UARS measurement provided by our new technique. Early work in our department,

using a prototype, showed that a large deadspace between the mouthpiece and the switching mechanism resulted in poor reproducibility and an increase in intra-individual variability of UARS measurement. It would appear that a large deadspace alters the presentation of the ammonia stimulus to the laryngeal receptors, presumably by allowing greater mixing of the ammonia stimulus with deadspace gas, such that the rate of increase in the ammonia concentration at the receptor is reduced. As the receptors which respond to the ammonia stimulus are thought to be rapidly adapting [10], it is possible that such changes may result in altered receptor activity. In the previous study, workers used a system with an apparent deadspace of 200 ml. The deadspace in our new system is 48 ml [8].

There was considerable increase in intersubject variability of ammonia threshold values after oral diazepam. It is well known that there is some inter-individual variability in the time taken to reach peak diazepam plasma concentrations after an oral dose. After oral diazepam 0.3 mg kg^{-1}, peak plasma concentrations have been shown to occur within 1 h in more than 80% of subjects and to have decreased to 30–60% of maximum values within 6 h in most subjects. However, in some individuals peak plasma concentrations may not occur until 6 h after an oral dose [12].

It is possible also that some of the variability may be secondary to changes in inspiratory flow after diazepam. Studies using citric acid aerosols to induce cough found that slower inspiratory flows were associated with a greater cough stimulus, probably because of increased laryngeal deposition [16]. Although a stimulus technique using ammonia vapour differs from one using a citric acid aerosol, it is possible that changes in inspiratory flow may affect the rate of change of the ammonia stimulus at the laryngeal receptors. Although we used recordings from the pneumotachograph to identify glottic stops, we did not measure inspiratory flow rates accurately. However, previous work has shown that diazepam 0.15 mg kg^{-1} i.v. appears to cause slight, but not significant, depression of mean inspiratory flow rates [17]. It is unlikely, therefore, that any changes in inspiratory flow after oral diazepam would have had a major effect on our measurement of UARS, but they may have added to the variability.

Because the larynx also contains cold receptors and some chemosensitive nerve endings which may not be stimulated by ammonia [10], we cannot be certain that all reflexes evoked by stimulation of laryngeal receptors are depressed to the same extent by diazepam. However, the irritant receptors which respond to ammonia also respond to ether [2] and are most probably implicated in laryngeal reflexes induced by other anaesthetic agents.

The laryngeal closure reflex is thought to be a brainstem reflex and many factors [18], including central inhibitory influences [19], have been shown to affect it. It is probable that diazepam produces suppression of upper airway reflexes by facilitating inhibitory neurotransmitter activity, although it is not clear if this occurs via general depression of CNS activity or via more specific inhibitory pathways.

We conclude that oral diazepam 20 mg resulted in a significant reduction in the sensitivity of upper airway reflexes, as measured by our technique, from 30 to 150 min in healthy young men. This implies that, to depress upper airway reflexes and thus reduce airway complications during induction of anaesthesia, oral diazepam should be administered in the period from 30 min to 2 h before induction. As previous work has shown that upper airway reflex sensitivity decreases with age [20], special care should be taken when using this drug with elderly patients as further depression of upper airway reflexes may be undesirable.

ACKNOWLEDGEMENTS

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MOVEMENTS OF THE VOCAL CORDS ON INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR PROPOFOL

P. BARKER, J. A. LANGTON, I. G. WILSON AND G. SMITH

SUMMARY

Using a fibreoptic laryngoscope, we have recorded on video tape the movements of the vocal cords after induction of anaesthesia with either propofol or thiopentone. The angle formed by the vocal cords decreased after induction of anaesthesia in both groups. This reduction in angle was significantly greater in the thiopentone group. The vocal cords closed completely in four patients in the thiopentone group and one patient in the propofol group. This difference may be explained by greater depression of laryngeal reflexes by propofol and this may account for the lower incidence of laryngospasm after induction of anaesthesia with propofol in comparison with thiopentone.

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Intubation: tracheal.

Propofol has become widely used for i.v. induction of anaesthesia and is associated with ease of maintenance of the airway and early toleration of a Guedel airway [1]. Intubation of the trachea may also be accomplished easily under anaesthesia with propofol alone [2].

This study was designed to observe the movements of the vocal cords after induction of anaesthesia with propofol or thiopentone.

PATIENTS AND METHODS

After Ethics Committee approval and informed consent had been obtained, we studied 30 patients (23 male), ASA I and II, aged 20–78 yr undergoing dental surgery. Patients were excluded from the study if they had a history of hiatus hernia, symptoms of regurgitation, obesity, laryngeal pathology, nasal obstruction or coagulation disorders.

All patients were premedicated with temazepam 10–20 mg orally and glycopyrronium 0.3 mg i.m. 1 h before anaesthesia. On arrival of the patient in the anaesthetic room, monitoring was commenced using pulse oximetry and ECG and a 16-gauge cannula was inserted into a forearm vein.

The nasal mucosa was anaesthetized with 10% lignocaine (maximum dose of 150 mg) and a 6-mm nasopharyngeal airway was introduced. Preoxygenation was commenced for 5 min via a specially adapted face mask.

After preoxygenation, a fibrescope (Olympus LF1) was passed via the nasopharyngeal airway into the pharynx until a clear view of the larynx was obtained. A video camera (Panasonic CCD GL110 AE with Olympus AK-2C adaptor) was attached to the eyepiece of the fibrescope and colour video recordings of the vocal cord movements were made on to a videocassette recorder (Sony Umatic VO 5630). Events were recorded on the soundtrack simultaneously with the video recordings.

Patients were allocated randomly to receive either propofol 2.5 mg kg^{-1} or thiopentone 4.4 mg kg^{-1} for induction of anaesthesia [1, 3–5]. Before induction of anaesthesia the patients were given a 20-ml syringe to hold between the thumb and forefinger; induction of anaesthesia was judged to have occurred when the subject had dropped the syringe [6].

After 20 s of recording, the induction agent was administered over 20 s. Video recordings were continued for 60 s after induction of anaesthesia, as judged by the subject dropping the syringe. During the video recording of the larynx, we attempted to ensure that the position of the laryngoscope remained constant. At the end of this time the fibreoptic laryngoscope was removed and anaesthesia continued conventionally for the operative procedure.

The video recordings were played back on a video recorder with a freeze frame facility and a blinded observer made measurements of the anterior angle between the vocal cords, using a goniometer with the frame frozen. Measurements were made with the subjects awake, at the time of dropping the syringe and every 5 s for the first 1 min after induction.

Data were analysed statistically using multivariate analysis of variance for repeated measures to identify a difference between the two groups and by Student's t test to identify the times at which the difference occurred (SPSS PC+ version 3.0). Chi-square test was used to compare the sex ratio of the two groups and Fisher's exact test to compare the incidence of complete glottic closure. Wilcoxon rank sum test was used to compare the minimum arterial oxygen saturation and duration of apnoea, as these data were not normally distributed.

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TABLE I. *Patient data, duration of apnoea, minimum arterial oxygen saturation and incidence of complete glottic closure after induction of anaesthesia (mean (SD) [range]). * P < 0.05 between groups*

	Thiopentone	Propofol
n	14	14
Sex (M/F)	11/3	12/2
Age (yr)	45 [23–68]	39 [20–78]
Weight (kg)	75.4 (12.6)	68.5 (9.4)
Duration of apnoea (s)	20.5 (21.9) [0–60]	38.0 (11.6)* [20–60]
Glottic closure (No.)	4	1
Minimum Sp_{O_2} (%)	93.6 (2.4) [92–100]	97.7 (1.2) [96–100]

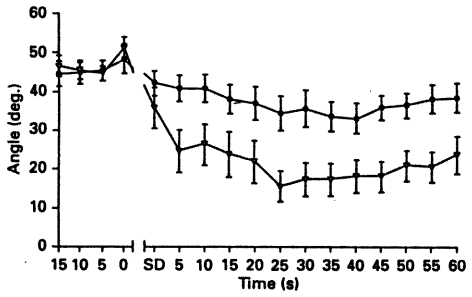

FIG. 1. Angle between vocal cords after induction of anaesthesia with propofol or thiopentone (mean, SEM). Time 0 = start of injection of thiopentone (▽) or propofol (●); SD = syringe drop.

RESULTS

Two patients (one from each group) were excluded from analysis as they were unable to tolerate insertion of an airway or the fibrescope. The groups were comparable in age, weight and sex (table I).

The mean induction dose of thiopentone was 332 (SD 106) mg and the mean induction dose of propofol was 170 (29.6) mg. There was no statistical difference in the pre-induction vocal cord angle between the two groups (fig. 1).

The angle between the vocal cords decreased in both groups after induction of anaesthesia. The decrease in angle was significant in the thipentone group (MANOVA $P = 0.009$) and in the propofol group (MANOVA $P < 0.001$). However, the decrease in angle was significantly greater in the former group (MANOVA $P = 0.008$). In the thipentone group, the decrease in angle was significantly greater at the following times after induction: 5 s, 10 s, 15 s, 25 s and 35 s ($P < 0.05$); 30 s, 45 s, 50 s, 55 s and 60 s ($P < 0.01$). There were no significant differences between the groups at syringe drop or at 20 s after syringe drop.

DISCUSSION

This study has shown that the vocal cords were adducted to a greater extent after induction of anaesthesia with thiopentone than with propofol. The mechanism underlying this difference may include a greater depressant effect of propofol on airway reflexes, heightening of airway reflexes by thiopentone or possible neuromuscular blocking actions of propofol. However, available evidence suggests that the first mechanism is the most likely.

Evidence for depression of upper airway reflexes by propofol was provided by Mackenzie and Grant [1], who commented on the ease of insertion of a Guedel airway after induction with propofol induction, and by Szneke [7] who found that an oral airway could be inserted earlier after induction of anaesthesia with propofol than with thiopentone.

Keaveny and Knell [2] found that 19 of 20 patients in whom anaesthesia was induced with propofol 2.5 mg kg^{-1} had satisfactory conditions for tracheal intubation, although seven coughed on tracheal intubation. Mulholland and Carlisle [8] intubated the trachea of 22 of 30 patients after induction of anaesthesia with propofol 2.5 mg kg^{-1}.

There is little evidence for any neuromuscular blocking effects of propofol. Jacques and colleagues [9] found that propofol possessed poor neuromuscular blocking properties and could not recommend its use as a post-induction intubating agent.

In studies by Burnstein [10] on the effects of short acting barbiturates on the patency of the glottis, it was found that most of the animals studied would cough, sneeze or hiccup during the course of anaesthesia. Inspection of the glottis revealed adduction of the vocal cords. Burnstein also found, in cases where there was no spontaneous coughing, that inspection of the glottis showed hyperactive adducted vocal cords and lifting the epiglottis elicited complete closure of the vocal cords. After the introduction of thiopentone into human anaesthetic practice in 1934, several reports of laryngeal spasm as a complication of thiopentone anaesthesia began to appear [10]. In 1939, Ruth and colleagues [11] reviewed the first 5 years of the use of thiopentone and highlighted the occurrence of temporary closure of the glottis and the hyperactive state of the laryngeal reflex after induction of anaesthesia using thiopentone.

In a recent study, Brown, Patel and Ellis [12] compared propofol with thiopentone for laryngeal mask insertion and found that the former was more effective in producing satisfactory conditions for insertion of the mask and there was a lower incidence of gagging after insertion.

In this study we found that 28 of the 30 patients examined were able to tolerate the procedure; in all patients, arterial oxygen saturation exceeded 90% throughout the study. Patients were premedicated with an antisialagogue, as it was found in preliminary studies that it was necessary to prevent secretions obscuring the view through the fibrescope.

Syringe drop [6] was used to assess induction of anaesthesia, as the eyelash reflex is difficult to assess in the presence of involuntary movements such as those occurring during induction with propofol; this also avoids repeated stimulation of testing the eyelash reflex.

In summary, we found that the vocal cords adducted after induction of anaesthesia with propofol 2.5 mg kg^{-1} or with thiopentone 4.4 mg kg^{-1}. The vocal cords adducted to a greater extent after

induction of anaesthesia with thiopentone than with propofol. It is likely that this was caused by greater depressant effects of propofol on upper airway reflexes, and this may explain the low incidence of laryngospasm after induction of anaesthesia with propofol [13].

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