Sensitivity of upper airway reflexes in cigarette smokers: effect of abstinence

R. J. Erskine, P. J. Murphy and J. A. Langton

Summary

In two studies we have compared the upper airway reflex sensitivity (UARS) of chronic cigarette smokers with that of non-smokers and also the effect of different periods of abstinence on UARS in the smoking groups. UARS was measured by recording the threshold concentration of dilute ammonia vapour required to stimulate reflex glottic closure. The first study compared UARS in 20 non-smokers with 20 smokers, followed by another measurement in the smoking group after 24 h of abstinence. In study two, we measured UARS repeatedly over a period of 3-4 weeks in 16 smokers, half of whom had stopped smoking on day 0. Chronic cigarette smokers were found to have significantly greater UARS compared with non-smokers; the sensitivity was unaltered after 24 h of abstinence but was found to reduce over several days, the change commencing between 24 and 48 h, with most achieving a consistent change within 10 days. (Br. J. Anaesth. 1994; 73: 298-302)

Key words

Measurement techniques, airway reflexes. Airway, reflexes.

Smoking is an important cause of perioperative morbidity [1]. During both induction and recovery from anaesthesia and during airway instrumentation, smokers appear to be more likely than non-smokers to suffer laryngospasm and episodes of airway obstruction leading to a reduction in oxygen saturation. While it has been shown that smokers demonstrate bronchial hyper-reactivity after chemical and mechanical stimulation of the airway, the sensitivity of upper airway reflexes associated with chronic smoking has not been studied previously.

During development of a method to measure upper airway reflex sensitivity (UARS), using inhaled ammonia vapour to stimulate reflex glottic closure, we noticed that the smokers tested appeared to react to much lower concentrations of ammonia vapour than non-smokers of a similar age [2]. The clinical impression of most anaesthetists is that smokers have more irritable upper airways than non-smokers but the cause and timing of this irritability in relation to preoperative abstinence from smoking is not known.

The aims of this study were two-fold; first, to compare the threshold concentration of ammonia vapour (NH₃TR) required to stimulate reflex glottic closure in smokers and non-smokers and, in the smoking group, to repeat the measurements after 24 h to assess the effect of a typical period of "preoperative" abstinence; and second, to determine the effect of a longer period of abstinence from smoking on UARS.

Subjects and methods

STUDY 1

After obtaining Ethics Committee approval and informed subject consent, we studied 40 healthy volunteers. They were allocated to two equal groups; group NS (seven female), mean age 28.8 (range 17-38) yr, were non-smokers, and group S (six female), mean age 26.4 (19-40) yr, regularly smoked 15 or more cigarettes per day. The subjects were not receiving any other medication. Exclusion criteria included chronic bronchitis and asthma and a history of upper respiratory tract infection in the previous month.

A single measurement of UARS was made using a method described previously [2]. This involved the subject inhaling single intermittent breaths of ammonia vapour of increasing concentration until reflex glottic closure occurred, signifying the NH₃TR [2]. The investigator was unaware of the smoking habits of the subject and the subjects were unaware of the level of ammonia in each breath. On the same occasion, venous blood was obtained to measure blood carboxyhaemoglobin concentration. The smokers were then asked to abstain from smoking and to take no medication, including alcohol and nicotine, for a period of 24 h. Subsequently, they returned to the laboratory and the second measurements of NH₃TR and carboxyhaemoglobin concentration were made.

Data were analysed using paired (to compare group S before and after abstention) and unpaired (to compare group S and group NS) t tests; significance was taken at P < 0.05.

R. J. Erskine*, FRCA, P. J. Murphy, FRCA, J. A. Langton, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: March 28, 1994.

*Address for correspondence: Department of Anaesthesia, Derbyshire Royal Infirmary, Derby DE1 2QY.
STUDY 2
The results from the first study prompted us to measure UARS in a group of smokers who had been asked to stop smoking and to compare them with a group of persistent smokers over a longer time scale.

After obtaining Ethics Committee approval and informed subject consent, we recruited 25 subjects who regularly smoked 15 or more cigarettes per day. Baseline NH₃ TR was measured in each subject using the technique described previously [2] and end-tidal carbon monoxide concentration was measured using the Bedfont EC50 Smokerlyser to avoid the need for repeated blood sampling (in order to increase compliance). This battery-operated, hand-held device incorporates an electrochemical sensor and has been shown to give an accurate indication of carboxyhaemoglobin concentrations over the range of values encountered in humans [3]. Following this, 13 subjects (group 1) agreed to stop smoking while the remaining 12 (group 2) carried on smoking. Over the next 3–4 weeks, we made repeated measures of NH₃ TR and end-tidal carbon monoxide.

Data were analysed by comparison of the mean area under the curves of the smoking and abstaining groups after NH₃ TR had been plotted against time. The means were compared using an unpaired t test.

Results
STUDY 1
All 40 subjects successfully completed the study. Mean venous carboxyhaemoglobin concentration in the smoking group decreased significantly at 24 h from 6.76% (SEM 0.6%) to 0.95% (0.16%), confirming their abstinence from smoking (fig. 1). Baseline mean NH₃ TR for the smokers was 270 (29.9) ppm compared with 713 (62.5) ppm for the non-smokers. The difference in NH₃ TR between the two groups was highly significant (P < 0.001), indicating that the smokers had a far more sensitive upper airway than the non-smokers. After 24 h of abstinence the NH₃ TR value of the smokers was 261.9 (41.3) ppm, showing no significant change from the first measurement (P = 0.86) and demonstrating no change in UARS after only 24 h without cigarettes (fig. 2).

STUDY 2
We were able to make repeat measurements of NH₃ TR and carboxyhaemoglobin concentration in 16 subjects. Eight subjects in group 1 (four male), mean age 31.5 (23–51) yr, managed to stop smoking completely for the period of study while eight others in group 2 (three male), mean age 33.8 (23–48) yr, continued to smoke and acted as the control group. The other nine subjects were excluded from the study because they failed to attend for further measurements because of illness or lack of interest.

The end-tidal carbon monoxide concentration of those in group 1 decreased rapidly to the normal range for non-smokers demonstrating their compliance; group 2 remained within the usual range for smokers (fig. 3). NH₃ TR was plotted against time for each individual in group 1 (fig. 4) and group 2 (fig. 5). The NH₃ TR of the subjects in group 2 showed only minor variations over the period of study, with no obvious peaks or troughs, whereas all subjects in group 1 showed an increase in NH₃ TR.
This change commenced at 24–48 h and continued until the majority reached a consistent plateau by 10 days of abstinence (fig. 4). The final NH$_3$TR values achieved by all except one of those who stopped smoking in group 1 were at least 1000 ppm, this being at the higher end of the range for those of a similar age who have never smoked. The mean area under the curve (AUC) for group 1 was calculated as 23319 (1144) ppm.days compared with 7915.4 (915) ppm.days for group 2. There was a highly significant difference between the AUC values of the two groups ($P < 0.0001$). We compared the final NH$_3$TR values of group 1 with those of group 2 using the Wilcoxon matched-pairs signed rank test and found them to be significantly different ($P = 0.012$).

These results support our findings from study 1 and our clinical impression that smokers have more sensitive upper airway reflexes. The evidence from group 1 demonstrated that there was a change in this increased sensitivity when smoking stopped.

**Discussion**

A previous study using an ammonia stimulus on the change in sensitivity of protective upper airway reflexes with increasing age found no consistent effect of smoking on the irritability of the upper airway [4]. Unfortunately, the subjects studied were mostly smokers, preventing comparison with non-smokers. In addition, we have outlined previously several possible inaccuracies in their method of assessment [5].

Although there have been studies of the acute reflex response of the upper and lower airways to stimulation of the laryngeal region and lungs with cigarette smoke [6–9], the exact mechanism of the increased UARS caused by chronic cigarette smoke exposure demonstrated here is not clear. The mechanisms may include the acute pharmacological effect of tobacco smoke on irritant receptors and chronic changes in the characteristics of the airway epithelium allowing greater exposure of subepithelial irritant receptors to chemical stimuli.

The first mechanism seems unlikely because the acute pharmacological effect of nicotine or any other of the 4000 or more compounds found in cigarette smoke would be expected to have terminated after 24 h of abstinence, a finding contrary to the results of both our studies.

Evidence for the second mechanism is stronger. Several studies have suggested that damage to or loss of the epithelial lining of the airway is an important factor in increased airway responsiveness and that the airway epithelium plays an important role in restricting access of inhaled solutes to subepithelial structures [10, 11]. Chronic cigarette smokers develop inflammation, metaplasia and dysplasia of laryngeal epithelium [12, 13], which may disrupt its integrity. Furthermore, recent evidence suggests that chronic smokers have depressed production of salivary epidermal growth factor, which is known to stimulate epithelial proliferation, protect mucosa against acute injury and heal gastric and duodenal ulcers [14]. The only evidence available for epithelial injury or inflammation as a cause of increased airway sensitivity has come from studies on tracheal and bronchial mucosa. Some clues may be provided by work on the effect on lower airway reflexes of damaging airway epithelium mechanically or chemically. Golden, Nadel and Boushey concluded that ozone exposure damages airway epithelium and...
thereby sensitizes bronchial irritant receptors [15]. Another study suggested that the mechanism for bronchial hyper-reactivity after viral upper respiratory tract infection was increased exposure of intra-epithelial sensory receptors to inhaled irritants [16]. Viral infection causes acute mucosal oedema followed by shedding of epithelial cells [17], bronchial reactivity being increased subsequently for up to 7 weeks [16]. Other workers agree that epithelial loss and damage may be extensive with similar changes to those caused by ozone and this probably accounts for increased bronchial reflex sensitivity after infection [15, 18-20]. In addition, acute smoke exposure in guineapigs is known to increase tracheal mucosal permeability with increased airway responsiveness to inhaled histamine [21]. We postulate that a similar mechanism may affect the airway lining in the chronic smoker.

The time taken for the increased UARS to improve in our subjects and the evidence cited above support the theory that epithelial disruption and inflammation caused by chronic cigarette smoke exposure is the most likely mechanism for the increased UARS.

The results from group 1 show that the final NH$_3$TR values achieved lie at the top end of the range expected for those who have never smoked. We are unsure if this represents a rebound phenomenon and if the NH$_3$TR, if measured for a longer period, increases or decreases further. This also raises the question of a possible increase in susceptibility to chest infection during this period. However, this range of NH$_3$TR is found in many normal patients aged 35-70 yr [5].

Most anaesthetists would agree that chronic smokers are more likely to suffer upper airway "events" such as laryngospasm and cough, particularly on induction of anaesthesia. We are unaware of a study that has formally demonstrated this but we believe that the increased UARS in chronic smokers supports this view, particularly as ether is known to act on the same irritant receptors as ammonia [22].

There is a paradox in that smokers are able to inhale irritant cigarette smoke without developing laryngeal spasm although they have increased UARS and they demonstrate increased upper airway irritability on induction of anaesthesia. The explanation is that cigarette smoking is a learned technique, designed to achieve nicotine absorption without irritating the airway. Rodenstein and Stanescu found that regular cigarette smokers developed a technique of sucking smoke into the mouth with the tongue closed against the soft palate following which they inhaled through both nose and mouth thereby diluting the inhaled smoke [23]. In another study, Higenbottam, Feyeraband and Clark found that whereas all the smokers tested were able to inhale smoke into their lungs during "normal" smoking, only 60% were able to tolerate inhaling "neat" smoke directly through the cigarette into the lungs. The pause that smokers take between sucking smoke into their mouth and inhaling it, diluted with nasal air, causes a reduction in temperature, allowing some particulate and chemical irritants to be deposited in the oral cavity [6].

We conclude that smokers have increased UARS and that a period of abstinence from smoking of at least 48 h and, in the majority, possibly up to 10 days, may be required to allow this to improve. This may provide anaesthetists with a guideline as to how long to advise patients to stop smoking before operation in order to reduce the risk of upper airway hyper-irritability and allow smooth and safe administration of inhalation anaesthetics.

Acknowledgements

This study was supported by grants from the Trent Regional Health Authority and the Association of Anaesthetists of Great Britain and Ireland.

References


