training sessions on the management of airway and respiratory circuit occlusions, more emphasis was put on the risk of filter clogging. To prevent liquids from accumulating in the filter, it was decided that the filter should be routinely placed above the lung level or, when this was not possible it should be mounted on the expiratory circuit at a distance from patient's airways. New instructions for use of filters were printed on posters and displayed in all operating rooms.

Comment
This critical incident could be considered as the consequence of the anaesthesiologist's failure to apply basic knowledge. However, similar difficulties have been observed elsewhere. In two cases of mechanical occlusion of the respiratory circuit, the first hypothesis made by anaesthesiologists with regard to the origin of restricted ventilation was bronchospasm. The true cause of the problem was only discovered by disconnecting the patient from the respiratory circuit and obtaining an appropriate oxygenation using a self-inflating bag.

In most cases, the problem is not the individual but the system. Our analysis shows that occlusion was possible because the filter had a hydrophobic membrane and was placed below the patient's head. The ability of the anaesthesiologists to detect airway filter occlusion was limited by the lack of information on the risk associated with the use of this device and by its position under the drapes. The identification of latent failures that are organizational root causes of accidents or critical incidents is, therefore, essential for devising appropriate corrective actions.

At first glance, our strategy, which combines prevention and absorption, could be perceived as convoluted. Compared with the prevailing approach of risk management which, as noted by Cooper, "depends almost solely on the anaesthetist's ability to react instinctively and flawlessly every time a problem arises", this method is much more efficient. Indeed, if $P_o$ is the probability of airway filter occlusion and $P_r$ the probability of not recognizing in time the problem, $P_o \cdot P_r$ will be the probability $P_c$ of the critical incident. As a consequence, any $x$-fold decrease in both $P_o$ and $P_r$ will have a multiplicative effect and result in a $x^2$-fold decrease of $P_c$ whereas a $x$-fold decrease in $P_r$ alone will only cause an equivalent decrease in $P_c$.

Given the usefulness of root-cause analysis with regard to patient safety, it is clear that we should systematically investigate critical incidents and accidents. However, reporting and analysis of such events on a routine basis and setting up appropriate corrective actions will require considerable cultural and organizational changes. Is there any alternative?

Acknowledgement
We are indebted to PALL (Schweiz) AG for providing the posters presenting the filter instructions for use.

References
3 Leape LL. Error in medicine. JAMA 1994; 272: 1851-7
5 Aarhus D, Soreide E, Holst-Larsen H. Mechanical obstruction in the anaesthesia delivery-system mimicking severe bronchospasm. Anaesthesia 1997; 52: 992-4
Methods. In this pilot study we measured cGMP in the saliva of six healthy volunteers and eight patients undergoing general anaesthesia for minor gynaecological procedures. Samples were obtained using a commercially available sampling device and cGMP was determined with an enzyme immunoassay and results expressed as a cGMP per mg protein.

Results. There was no statistically significant variation in salivary cGMP either day-to-day or between time points in healthy volunteers. Analysis of variance of salivary cGMP of patients undergoing general anaesthesia showed that cGMP increased significantly intraoperatively and returned to preoperative levels after surgery ($P=0.03$).

Conclusions. This is the first time that real time in vivo changes in salivary cGMP levels during general anaesthesia in humans have been demonstrated and may allow an alternative technique for measuring depth of anaesthesia in the future.

Br J Anaesth 2002; 89: 635–7

Keywords: anaesthesia, depth; anaesthesia, general; metabolism, second messengers; monitoring, depth of anaesthesia

Accepted for publication: May 25, 2002

Cyclic GMP (cGMP) is thought to play a central role in mediating the effects of anaesthesia. Nitric oxide is a potent stimulant of soluble guanylylcyclase resulting in the production of cGMP, which in turn regulates a variety of cGMP-dependent kinases, ion channels, and phosphodiestersases. There is a reduction of minimum anaesthetic concentration (MAC) of volatile anaesthetic agents in rodents following acute administration of nitric oxide synthase inhibitors. This has been disputed and not been reported in chronic administration and deletion of the type I (neuronal) nitric oxide synthase gene.

cGMP is detectable in saliva, providing an easily accessible sample for measurement during anaesthesia. There are no previous data regarding variation in salivary cGMP in healthy subjects in the absence of anaesthesia, and therefore initial studies assessing any variation were required before undertaking studies in anaesthetized subjects. The aim of this study was to assess whether changes in salivary cGMP occurred during anaesthesia in humans.

Methods and results

Following local ethics approval and written informed consent we collected saliva from six healthy volunteers (25–32 yr) on 5 consecutive days at two time points (10:00 and 15:00 h) using a commercially available collection device, Orasure™ (Altrix Healthcare, Birkenhead, Merseyside, UK). We also collected saliva from eight ASA grade I or II patients (24–36 yr) undergoing minor obstetric procedures, immediately prior to induction, 10 min into the procedure and within 60 min after the operation. The anaesthetic regimen was standardized. All patients received induction of anaesthesia with propofol and maintenance with isoflurane/nitrous oxide in oxygen at 1.3 MAC via a facemask without the use of an airway. None of the patients had any form of pre-medication or received intraoperative opioids.

Saliva samples were frozen in liquid nitrogen immediately after collection and stored at $-80^\circ$C until analysis. For the assay, samples were thawed on ice and microwaved for 8 s to halt enzyme activity. cGMP concentrations were determined using a sensitive enzyme immunoassay kit (R&D Systems Europe, Abingdon, Oxon, UK) as described previously. Protein was measured using Bradford reagent (Sigma-Aldrich, Poole, Dorset, UK) and results were expressed as saliva cGMP pmol (mg protein)$^{-1}$. Data were analysed using Friedman analysis of variance with Wilcoxon signed ranks post hoc testing as appropriate and Bonferroni correction for multiple comparisons as necessary.

There was no statistically significant variation in salivary cGMP either day-to-day or between time points in healthy volunteers. In patients, analysis of variance revealed a statistically significant change in cGMP ($P=0.03$) during anaesthesia and surgery with no change in salivary protein concentration. Post hoc analysis showed that cGMP increased significantly intraoperatively ($P=0.023$) and returned to preoperative levels following surgery (Fig. 1).

Comment

Our data show that concentrations of cGMP in saliva remain constant during normal activity and change during anaesthesia. Confounding variables were reduced to a minimum by choosing a group of patients who were essentially healthy, having minor obstetric surgery—thus all patients were female and of a very narrow age range. In addition, all the operations took place at a similar time of day, with the same anaesthetist, and the duration of the operation was similar (10–15 min). The anaesthetic regimen was standar-
dized, with identical procedures for all patients, no pre-
médication drugs and no opioid usage. Thus, changes in
cGMP are more reliably related to anaesthesia and not other
factors.

Studies in anaesthetized animals have shown decreases in
cGMP within the central nervous system after halothane or
isoflurane anaesthesia. However, in the present study,
salivary cGMP increased during anaesthesia compared with
concentrations immediately pre-induction. This may be
partially explained by nitric oxide synthase activity or
haemoxygenase activity during anaesthesia. Both nitric
oxide, produced by the action of nitric oxide synthase, and
carbon monoxide, the product of haemoxygenase activity,
are potent activators of soluble guanyl cyclase.

The results of this study need to be extended to a larger
study of various anaesthetic techniques to establish whether
this is a common link for a mechanism of anaesthesia in
humans. Also, the possible development of a ‘real time’
cGMP monitor is appealing and may allow an alternative
technique for measuring depth of anaesthesia.

Acknowledgements

We acknowledge financial support from The Royal College of
Anaesthetists, the Association of Anaesthetists of Great Britain and
Ireland and the Chief Scientist Office in Scotland.

References

1. Johns RA, Moscicki JC, DiFazio C. Nitric oxide synthase inhibitor
dose-dependently and reversibly reduces the threshold for
halothane anesthesia. Anesthesiology 1992; 77: 779–84
does not reduce minimum alveolar concentration of halothane in
3. Ichinose F, Huang PL, Zapol W. Effects of targeted neuronal
nitric oxide synthase gene disruption and nitroG-arginine
methylester on the threshold for isoflurane. Anesthesiology
1995; 83: 101–8
on cerebellar cGMP and on motor activity in the mouse. Br J
Anaesth 1983; 55: 250–8
5. Gallely HF, Le Cras AE, Logan SD, Webster NR. Differential
nitric oxide synthase activity, co-factor availability and cGMP
accumulation in the central nervous system during anaesthesia.
monoxide in leukocyte and platelet dynamics in rat mesenteric
during sevoflurane anesthesia. Anesthesiology 2001; 95: 192–9

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002