Correspondence

Proportional and continuous NO delivery systems

Editor,—We read the report of Hiesmayr and colleagues, which evaluated the Pulmonox-mini delivery system. As the manufacturer of the Pulmonox-mini system, we realize it is important to examine different systems to highlight differences in performance. Because of the doubtful results of this report, we saw an urgent need to evaluate our Pulmonox-mini system under the conditions described in the study of Hiesmayr and colleagues. Unfortunately, we found great differences in relation to their results.

We rebuilt the experimental set-up, shown in their Figure 1, using the same ventilator set-up and the same breathing circuit material, with the same dimensions and distances as described, to guarantee the same conditions. As shown in Figure 1 for pressure-controlled ventilation (PCV) and Figure 2 for volume-controlled ventilation (VCV), we did not find the large variations in nitric oxide (NO) concentrations reported by Hiesmayr and colleagues. The NO values measured in our experiment with three different Pulmonox-mini systems ranged from 4.8 to 5 ppm with a set concentration of NO 5 ppm measured at site E (near the Y-piece, according to Hiesmayr and colleagues).

For analysis of NO, we used a superfast CLD instrument (CLD 77 advance medical, ECO PHYSICS, Düren/Switzerland) with a t90 value of 0.1 s! The reasons for the large differences between our measurements and those of Hiesmayr and colleagues could be different use of CLD technology. We used a CLD system with a declared response time of 0.1 s, whereas Hiesmayr and colleagues used an instrument with a response time of 3 s. It is not true that Hiesmayr and colleagues were provided with a Pulmonox-mini system for test reasons. Furthermore, to our knowledge, neither Dr Hiesmayr nor any of the authors has been officially trained in the use of the Pulmonox-mini system. Also, Hiesmayr and colleagues did not use the appropriate flow interface. Therefore, the comparison between the two PGIS systems was invalid because one system was directly interfaced to the ventilator but the Pulmonox-mini system was not, even though a direct flow interface was available and recommended for this experiment.

Furthermore, Hiesmayr and colleagues used the numerical simulation of the flow model formulae designed for smooth tubes and not the ones for corrugated tubes as supplied by LABOREX and cited by Hiesmayr and colleagues.

We think that the validity of the study of Hiesmayr and colleagues would have been strengthened if accurate experimental design and calculations had been used.

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Editor,—Schofnagl and Krebs contend that they could not detect the large variations in nitric oxide (NO) concentrations that we measured in our study using the Pulmonox-mini system. They showed that at site E, corresponding to the Y-piece, an ultra-fast NO analyser traced variations in NO concentrations within a single breath. In their recordings, the NO mixture had a peak to trough amplitude of approximately 8% in both pressure-controlled and volume-controlled modes. They presented data only for the smallest tidal volume...
(300 ml) used in our study, for one ventilatory frequency (20 bpm) at one single site. At this site, we found that the NO–N₂ mixture with the respiratory gases was maximal, regardless of the system used.

In our study, we reported that at the settings chosen by Schöfnagl and Krebs, measured NO concentrations were 10.97–11.64 ppm for a target NO concentration of 10 ppm during volume-controlled ventilation, and 7.93–9.78 ppm during pressure-controlled ventilation. These data are the extreme values over the three ventilatory frequencies investigated in our study. When we restricted the data to a ventilatory frequency of 20 bpm, NO concentrations varied between 11.21 and 11.5 ppm during volume-controlled ventilation and between 9.40 and 9.78 ppm during pressure-controlled ventilation. Thus rather than invalidating our data, Schöfnagl and Krebs provide strong support for it as they showed larger variations than we did during a single experimental condition using a fast response NO analyser. They also found systematic under-dosing during pressure-controlled ventilation, as we did. Measurements during their unique experimental setting were almost identical to the prediction of our model that true NO concentrations vary regardless of the system used.

Schofnagl and Krebs, measured NO concentrations were 10.97–11.64 ppm for a target NO concentration of 10 ppm during volume-controlled ventilation, and 7.93–9.78 ppm during pressure-controlled ventilation. These data are the extreme values over the three ventilatory frequencies investigated in our study. When we restricted the data to a ventilatory frequency of 20 bpm, NO concentrations varied between 11.21 and 11.5 ppm during volume-controlled ventilation and between 9.40 and 9.78 ppm during pressure-controlled ventilation. Thus rather than invalidating our data, Schöfnagl and Krebs provide strong support for it as they showed larger variations than we did during a single experimental condition using a fast response NO analyser. They also found systematic under-dosing during pressure-controlled ventilation, as we did. Measurements during their unique experimental setting were almost identical to the prediction of our model that true NO concentrations vary between 9.2 and 10.6 ppm at site E (see Fig. 4 in our article). Nevertheless, Schofnagl and Krebs claim that they found large differences between their measurements and our investigation. Unfortunately, they do not provide evidence for this from measurements at the five sampling sites with varying tidal volumes and ventilatory frequencies.

It is correct that the provider of the Pulmonox-mini for our investigation was not directly Messer Griesheim, but their distributor for clinical use, Mediscus, Austria. The Pulmonox-mini is leased to users by the Mediscus Company on behalf of Messer Griesheim, because they can provide 24-h support. Thus we have to apologize that we did not state the name of the distributor in our article. With respect to lack of expertise in using the Pulmonox-mini, we wish to make two points. Each user of the Pulmonox-mini is given training before use. This is routine in this hospital and takes a maximum of 60 min. The reason for these short training requirements is that the Pulmonox-mini is user-friendly. We added the NO–N₂ mixture at the same site for all three devices studied and not near the Y-piece, as proposed by the manufacturer. This was the only modification of the recommendations of Messer Griesheim and has been stated clearly in the methods.

Schofnagl and Krebs raise a more important issue when stating that a direct flow interface would have been recommended for our type of experiments. However, we used the Pulmonox-mini as it is recommended for routine care in patients. As any other direct interface with a ventilator is not routinely available, we suggest that it would have been helpful if Schofnagl and Krebs had provided data proving the better performance with the use of a direct flow interface. If such large differences in performance occur depending on the flow pick-up used, then clear advice should be given in the instruction manual of the Pulmonox-mini system. But in the clinical setting, it is not practical to exchange the flow pick-up when the setting of the ventilator is changed. From a practical point of view, the use of the Pulmonox-mini with a single flow pick-up independent of the type of ventilator is one of its advantages.

Finally, Schofnagl and Krebs question the validity of our numerical simulation because we did not adapt it for use with corrugated tubes. We considered this point to be of minor importance because the velocity at the tubing wall is equal to zero. We agree that corrugated tubes may modify mixing to a certain extent. We tried to account for this fact by using a fractional exchange ratio between contiguous volume elements empirically derived from data obtained during experiments with corrugated tubes.

In summary, we believe that the validity and strength of our study cannot be questioned based on the data provided by Schofnagl and Krebs. We would be grateful if they could provide us with data on the 24 experimental conditions we have studied, because such data may allow us to refine our model.

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Consciousness and molecular mechanisms of anaesthesia

Editor,—The search for specific receptor sites of action of anaesthetic agents, as elegantly described by Lees,¹ is noble work but ill-focused. Molecular biologists would do well to collaborate with cognitive scientists in order to more fully understand what we are trying to achieve with our anaesthetics. If we define abolition of consciousness as our end-point, then what is consciousness, and why do we have it?

Most of the incisive thinking in this difficult field comes from philosophers of neuroscience and the most accessible ‘hard’ argument is expounded by Dennett.² He argues that consciousness is a slippery concept to pin down because it is the product of all other brain activity at a given time. Consciousness is not a specific sensory modality and is certainly not a simple design programme for survival brought about as a result of natural selection. One might view consciousness as a delightful accident.

If we try to make sense of consciousness using scientific reductionism, the brain is best seen as an algorithmically ordered parallel processor which we can compartmentalize according to specific functions. Consciousness is the sum total of each and every one of these functions but also encapsulates the irreducible concepts of self-awareness or reflectivity (not only am I aware, I am aware that I am aware) and sentience (awareness of the philosophical qualia or irreducible essence of a particular state of being).
Using these arguments, we can see that abolition of consciousness must involve activity at multiple receptor sites, indeed at each and every receptor site responsible for brain activity. Anaesthetics by definition must therefore be non-specific agents, as reasoned by Lees, and specific target therapy can only give us clues as to the relative importance of each receptor in overall brain activity.

Theories of consciousness are conceptually difficult, but in that abolition of consciousness is the stuff of our everyday working lives, it is surprising that these theories have not as yet found their way into our college examination syllabus. It is more surprising that they are not required reading for basic scientists working in the field of anaesthetic action.

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Editor,—First, thanks to your readership for their response to my original article: I have been inundated with requests for reprints from the international anaesthesiology/neuroscience community. I would like to briefly respond to the points made in Dr Collins’ response on the cellular basis of consciousness itself. I agree with the general thrust of the letter but as Dr Collins points out, in common with many cellular and molecular physiologists I am probably ill-equipped to contribute forcefully to a debate on these issues because of a lack of awareness of holistic models of consciousness in humans. I wholeheartedly agree that a greater dialogue should be established between cognitive scientists and cellular neurobiologists/pharmacologists, if only for the sake of mutual awareness of how the component parts may contribute to the whole. I think that the reductionists have a distinct advantage in that their models and discrete circuitry or defined receptors are much more accessible to experimental manipulation and therefore validation of theory. Hence the flurry of papers on anaesthetics and ion channels in high profile outlets such as Science and Nature, which have recently ‘exposed’ novel actions for both nitrous oxide and xenon. With the increasing availability of non-invasive brain scanning in human volunteers, the cognitive neuroscientists should increasingly be in a position to move away from ‘hard’ (but philosophical) ‘arguments’ into the realms of hard experimental data on the proposed diffuse neural basis for reflectivity and sentence.

Although my editorial emphasized the relative lack of selectivity of anaesthetic action, I believe that Dr Collins’ extension of this observation is extreme and rather naive. He states that ‘abolition of consciousness must involve activity at multiple receptor sites, indeed at each and every receptor site responsible for brain activity’. All of us who study neuronal signalling know that most molecules expressed in the cell’s phenotype are crucial for either development, procreation, physiological homeostasis or apoptosis, but that disruption of small subsets of these (or in many cases a single target molecule) is sufficient to disrupt, absolutely, the firing properties of the cells. With increasing awareness of synaptic plasticity, the cognitive capacity of the 10^{12} neurones of the brain has moved on from the binary principles of cells simply being ‘on’ or ‘off’ by analogy with modern day computers. However, at a superficial level this simplistic argument is sufficient to explain fixed behavioural activity/repertoires in many simplistic but defined neural circuits. Let us take respiration as a defined behavioural end-point. We can disrupt this by removing activity in the respiratory motor neurone using a variety of pharmacological strategies. An overdose of barbiturate does this effectively but the net effect is probably caused by interaction with diverse targets in the CNS and possibly PNS/end-plate receptors. In contrast, botulinum toxin, tetrodotoxin, curare, organophosphates and even cyanide can, in an exquisitely selective manner, disrupt a single target molecule with the same consequence for the respiratory muscles: if they do not fire rhythmic action potentials we do not breathe. In other words, liganding of a single molecular target with a drug or toxin is often sufficient to completely alter the firing pattern in target cells (hyper-excitation or axonal silence) and hence the circuit. There are many examples of inherited diseases where neural proteins are mutated, non-functional or even completely absent which lead to demonstrable pathology but none, to my knowledge, completely disrupts consciousness in an analogous manner to anaesthetics.

I, personally, am very receptive to the idea of greater awareness of conceptual theories of consciousness, particularly if the proponents of these can concurrently overview experimental strategies for their validation.

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Intubating conditions after propofol and remifentanil

Editor,—We were interested in the article by Grant and colleagues who assessed intubation using propofol and remifentanil. One of the most important conclusions of the study was that the decrease in arterial pressure was not regarded as clinically significant in the three groups (their definition was a decrease in mean arterial pressure of more than 20%).

Nevertheless, two patients in group III were given ephedrine because the decrease in arterial pressure was more than 25%. Therefore, they cannot conclude that induction was clinically safe. Also, we would be interested to know the
Correspondence

exact time after intubation when mean arterial pressure was measured, and its value 5 or 10 min after intubation, when catecholamine release may have caused it to increase.

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Editor,—We are grateful for the opportunity to respond. The first point made was that we cannot conclude that this induction technique was clinically safe. We would disagree with this and use the evidence that none of our subjects was adversely affected clinically by the temporary decrease in arterial pressure. The second point was the exact timing after intubation of our measurement of arterial pressure. This was performed 60 s after intubation and was recorded at this time in an effort to show the maximum demonstrable decrease in arterial pressure. As one would expect from the pharmacokinetics of remifentanil, 5 or 10 min after intubation, arterial pressure had returned to baseline.

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Mental nerve neuropraxia associated with tracheal intubation using an RAE tube

Editor,—Nerve injury is a well documented occurrence in anaesthesia. In a review of more than 1500 anaesthesia-related malpractice claims, 15% were for nerve injury, of which ulnar nerve (34%), brachial plexus (23%) and lumbosacral nerve root (16%) injuries constituted the majority. Cranial nerve damage caused by orotracheal airway management is uncommon (<1% for individual nerves), although cases of bilateral vocal cord paralysis, recurrent laryngeal nerve palsy, lingual nerve and hypoglossal nerve injury have been attributed to tracheal intubation and the use of the laryngeal mask.

We report a case of mental nerve neuropraxia associated with the use of an RAE tracheal tube.

A healthy 28-yr-old Saudi male (weight 98 kg, height 179 cm) with bilateral keratoconus was undergoing left eye epikeratoplasty under general anaesthesia. Premedication comprised hydroxyzine 100 mg and cimetidine 200 mg orally. Anaesthesia was induced with a bolus dose of fentanyl 1.5 μg kg⁻¹ and propofol 200 mg, and his trachea was intubated with a size 8.0 cuffed oral tracheal tube (Mallinckrodt RAE, Ireland) after neuromuscular block with atracurium 0.5 mg kg⁻¹. As is common practice in our institution, a tightly folded surgical gauze swab (approximately 3×3 cm) was placed as padding between the RAE tube and the patient’s chin to avoid pressure-related damage to the skin. Anaesthesia was maintained with 1% isoflurane and 65% nitrous oxide in oxygen. At the end of the procedure, lasting 1 h 55 min, his trachea was extubated uneventfully.

On the second day after operation, the patient complained of numbness of the lower lip and chin. Examination revealed sensory loss restricted predominantly to the distribution of the left mental nerve without intra- or extra-oral signs of trauma. No subjective improvement occurred over the next 2 days, much to the patient’s distress. On day 5 after operation, the patient admitted to partial return of sensation and was discharged with reassurance that there should be complete recovery.

To our knowledge, mental nerve neuropraxia after tracheal intubation using an RAE tube has not been described previously. In our case, it seems likely that pressure on the tracheal tube was transmitted via the surgical gauze padding, either because of external pressure from the surgical assistant or from excessively firm taping of the tube to the patient’s chin, resulting in injury to the nerve as it emerged from the mental foramen.
Correspondence

mental foramen. Although not clear from the anaesthetic notes, it is possible that the tube was secured to the left of the mid-line, hence the pattern of sensory loss (Fig. 1). It is now our practice to ensure that the RAE tracheal tube is secured exclusively in the mid-line.

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3 Nagai K, Sakuramoto C, Goto F. Unilateral hypoglossal nerve paralysis following the use of a laryngeal mask airway. Anaesthesia 1994; 49: 603–4

Hazards of laparoscopic surgery

Editor,—I feel it is appropriate, given the increase in laparoscopic surgery, to note one of the often overlooked hazards of this technique. During a recent laparoscopic cholecystectomy, I noticed an intense smell of burning, only to see a small plume of smoke rising from the tip of the laparoscope light source (Dyonics Halogen, Smith and Nephew Medical Ltd, Hull, UK) which had temporarily been laid on the drapes. The heat at the distal end of this halogen light is clearly sufficient to ignite flammable materials in close proximity to it. This particular light source was autoclavable and had not been in contact with flammable sterilizing solutions. The resulting damage is shown in Figure 1.

Fortunately, there was no harm to patient or staff, but the potential for thermal injury during laparoscopy should not be forgotten. The role of the anaesthetist in the prevention of fires and explosions in theatre is clearly as relevant today as it was 30 yr ago.

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Ropivacaine and bupivacaine for analgesia in labour

Editor,—We read with interest the recent meta-analysis of trials comparing ropivacaine and bupivacaine for analgesia in labour by Writer and colleagues.1 We must express concern with some of the methods the authors used, and in particular must question the claim of superior neonatal outcome.

All six studies in the meta-analysis compared 0.25% concentrations of the two local anaesthetics given either by bolus or continuous infusion. Whereas all of these studies found analgesia to be equivalent between the groups, and in vitro data notwithstanding, there is recent evidence that epidural ropivacaine is substantially less potent than epidural bupivacaine.2 Therefore, the comparison between the drugs may not have compared functionally equivalent doses.

Analysis of infants using the neonatal neurologic and adaptive capacity score (NACS) <35 is particularly disconcerting. First, the creators of this measure themselves argue that the number 35 was ‘arbitrarily chosen’ and would require ‘further experience with large numbers of infants’ to validate it.3 To our knowledge, we still await such validation. An editorial accompanying the publication of the NACS criticized specifically the summed score and the number 35 as being statistically inappropriate measures of neonatal neuropsychiatric status.4

Second, Writer and colleagues used a stratified Mantel–Haenszel chi-square test to compare NACS <35 between the ropivacaine and bupivacaine groups. The stratification means that various strata of study, site and parity were analysed separately, then combined to yield the final P value. However, had all the data from the meta-analysis been from a single, large, randomized trial, the difference in NACS would not have been apparent (chi-square = 3.598, df=1, continuity-corrected P=0.1025). This would seem to imply that some subgroup of patients (i.e. stratum) demonstrated a much larger difference between groups than others. Which one(s) was it, and how do the authors explain the difference?

Third, the authors performed multiple pairwise comparisons between NACS scores and subscores and claimed a significance of P<0.05 for each. As the active tone and capacity scores are subsets of the total NACS, these cannot be viewed as independent measurements and some correction for multiple comparisons is required. Furthermore, the 2-h and 24-h tests should be treated as part of a repeated-measures analysis, as they are likely to be correlated.

Finally, the authors’ explanation for the difference in NACS at 24 h but not at 2 h is difficult to reconcile with

Fig 1 Damage to the drapes caused by the laparoscope light source.
other data comparing these drugs. For example, Datta and colleagues gave 150 mg (approximately 50% more than the mean dose in the six studies of Writer and colleagues) of either epidural bupivacaine or ropivacaine to women undergoing elective Caesarean section and found no abnormal NACS at 2 or 24 h. Surely a difference in clearance of these drugs would have been at least as apparent with larger doses as it was with the lower doses spread over several hours in the present study?

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4 Tronick E. A critique of the neonatal neurologic and adaptive capacity score (NACS). Anesthesiology 1982; 56: 338–9  

Editor,—Thank you for the opportunity to reply to the points raised by Drs Segal and Bader. They question if the concentrations of ropivacaine and bupivacaine used in our study were ‘functionally equivalent’. Our article described the results of six phase III studies, undertaken in five separate countries, before the approved release of ropivacaine. The development of a protocol, and decision on the appropriate concentrations of drug, therefore antedated by several years the debate surrounding the relative potencies of these local anaesthetics. The use of identical drug concentrations (2.5 mg ml−1) was validated by in vitro studies, for example that of Bader and colleagues, which demonstrated comparable sensory block between ropivacaine and bupivacaine in the isolated rabbit vagus nerve model. We are aware of recent abstracts which suggested a ropivacaine:bupivacaine potency ratio approximating 0.6, based on measurement of the minimum local analgesic concentration (MLAC) in labouring women. Neither study took account of changing cervical dilatation, and the increasing pain as labour progressed. Capogna and colleagues demonstrated that the MLAC for bupivacaine varied from 0.048% at 2 cm to 0.14% at 5 cm dilatation. If we extrapolate from these data, and assume a potency ratio of 0.6, the 0.25% ropivacaine concentration would appear to be appropriate for women in late labour. However, we recognize that this concentration of bupivacaine may be greater than required. We suggest that further studies of the MLAC in labour should be conducted at the full range of cervical dilatation, before advocating different ropivacaine, or bupivacaine, concentrations in the name of ‘equivalence’.  

Segal and Bader cavil at our choice of NACS <35 as an index of neonatal drug effect. The early criticism of NACS notwithstanding, we respectfully suggest that this assessment has convincingly replaced its progenitors, the Brazelton scoring system and the ENNS, in the 16 yr since its introduction. As NACS was designed to detect drug effects, and to differentiate them from birth trauma and perinatal asphyxia, we considered it the appropriate neonatal evaluation tool in this local anaesthetic study. The continued use of NACS in many published studies might suggest that the ‘further experience with large numbers of infants’, which its authors sought, has now been gained. In common with Segal and Bader, we know of no study which has validated or refuted the choice of 35 as a ‘threshold’ value. Amiel-Tison and colleagues considered scores of 34 or below ‘low enough to detect babies with possible problems, yet not so low as to mislead us into mislabelling an inordinate number of vigorous babies as depressed’. Therefore, we consider the use of NACS <35 justifiable in this prospective evaluation, and we believe the significant differences observed at 24 ± 2 h between ‘ropivacaine neonates’ and those whose mothers received bupivacaine, merited publication.

With respect to our statistical analysis, there was no single stratum that showed large differences; on the contrary, the results in most strata were in the same direction, although the differences were too small to be significant. The fact that an unstratified analysis yields a result with a larger, and in this case non-significant P value, does not surprise us. The main reason for stratifying is to compare results in more homogeneous patient subgroups in order to reduce the variability and then combine the results from these different strata into an overall result. In an unstratified approach, as suggested by Segal and Bader, ignoring possible confounding factors can give misleading results. The chosen stratification variables were decided upon during the planning stage of this meta-analysis before the individual studies were completed.

All tests were performed marginally at a significance level of P<0.05. A simple multiplicity correction would, for example, be the Bonferroni–Holm method. However, as the different tests on NACS are highly correlated, the Bonferroni–Holm method would give too conservative P values. In fact, if the correlation between the variables tested was 1 there would be no need for a multiplicity correction. P values for differences in total NACS at 24 h (P=0.0001), the subscores for active tone (P=0.009) and adaptive capacity
(P=0.006), together with the significant result for NACS <35, provided evidence of a difference in NACS scores between ropivacaine and bupivacaine, 24 h after delivery.

We did not provide an ‘explanation’ for the observed difference in NACS at 24 h. Rather, we hypothesized that bupivacaine, by virtue of its greater lipid solubility, persisted in the neonatal neural tissues for a longer period than ropivacaine, and we offered some experimental support for our hypothesis.\(^8\) Segal and Bader refer to the work of Datta and colleagues,\(^9\) who found no difference in NACS at 2 and 24 h in the neonates of mothers who received ropivacaine or bupivacaine 150 mg for Caesarean section. Although the mean dose of local anaesthetic that our subjects received was approximately 100 mg, the recipients were exposed for a longer time (median >5 h) and we wonder if this might have enabled comparatively greater bupivacaine uptake in the neonatal lipid tissues.

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