CORRESPONDENCE

Ventilatory response to carbon dioxide

Sir,—Saito and colleagues examined the influences of administration of morphine and lignocaine in the extradural space on the ventilatory response to carbon dioxide in female patients [1]. One of their observations was that ventilatory carbon dioxide sensitivity decreased significantly after morphine.

Saito and co-workers used a modification of Read’s rebreathing method to obtain the ventilatory response to carbon dioxide [2]. Read introduced his method in 1967 which consists of rebreathing from a small rebreathing bag (4–6 litre) filled with 7% carbon dioxide in oxygen. The modification by Saito and colleagues was the use of a 10-litre rebreathing bag. Features that are observed when rebreathing is carried out in this way are [3–5]: end-tidal \( P_{\text{CO}_2} \) (\( P_{\text{CO}_2}^{\prime} \)) increases in a step-wise manner and rebreathing is initiated at a \( P_{\text{CO}_2} \) value close to that of mixed venous blood; rapid equilibrium is established between the \( P_{\text{CO}_2}^{\prime} \) of end-tidal, mixed venous and arterial blood, the gas in the rebreathing bag, and presumably also brain tissue \( P_{\text{CO}_2} \), all increase with the same rate of increase; ventilation (\( V_e \)) increases linearly in time and the \( V_e - P_{\text{CO}_2} \) rebreathing line is linear; the rate of increase in \( P_{\text{CO}_2} \) is independent of the ventilatory response; Read observed in an initial study in three subjects that the slopes of the \( V_e - P_{\text{CO}_2} \) responses obtained from rebreathing and a steady-state method were not different.

Read’s method allows acquisition of carbon dioxide sensitivity with minimal discomfort to the subject within a short period of time. Despite its popularity, there are several misconceptions regarding Read’s rebreathing technique, especially when considering the effects of drugs on ventilatory control. Several recent studies have shown that carbon dioxide sensitivity from rebreathing exceeds steady-state carbon dioxide sensitivity by a factor of 2 [6–8]. The larger carbon dioxide sensitivity obtained from Read’s method is explained by the increase in brain blood flow on increasing arterial \( P_{\text{CO}_2} \), resulting in a decreased cerebral venous to arterial gradient at steady-state (see [6]). Abolishing the mixed venous–arterial \( P_{\text{CO}_2} \) gradient to zero is insufficient to reduce brain tissue–arterial \( P_{\text{CO}_2} \) sufficiently close to zero. The mixed venous to arterial \( P_{\text{CO}_2} \) gradient is approximately 0.8 kPa in humans, while the jugular venous to arterial \( P_{\text{CO}_2} \) gradient is 1.5–2.0 kPa [9]. In contrast with the steady-state method, the measured carbon dioxide sensitivity from Read’s rebreathing method depends on the magnitude of the initial step increase in \( P_{\text{CO}_2} \) at the start of rebreathing and, to a lesser extent, on the subsequent rate of increase in \( P_{\text{CO}_2} \) in time [9]. The larger the initial step increase in \( P_{\text{CO}_2} \), the larger the measured carbon dioxide sensitivity. This is important when considering the effects of drugs that affect ventilatory control such as morphine. Ventilatory depression and the subsequent increase in \( P_{\text{CO}_2} \) changes (i.e. decreases) the magnitude of the initial step increase in \( P_{\text{CO}_2} \) at the start of rebreathing and consequently decreases the slope of the \( V_e - P_{\text{CO}_2} \) response curve. This decrease may then reflect the change in initial conditions and not a drug effect on chemoreceptors, respiratory integration centres or the link between brainstem and respiratory movements.

However, an effect at these sites cannot be excluded. Read’s rebreathing method yields results that are difficult and sometimes impossible to interpret. Bourke and Warley [8] showed this elegantly in a study comparing the steady-state method and Read’s rebreathing method during i.v. administration of morphine. Morphine caused a decrease in the rebreathing carbon dioxide response slope, while the steady-state carbon dioxide response slope was shifted to higher \( P_{\text{CO}_2} \) levels without any change in slope. They concluded that this parallel shift is specific to drugs acting on opioid receptors. Changes in overall and brain metabolism, steady-state brain blood flow and brain blood flow reactivity to carbon dioxide affect the rebreathing carbon dioxide response slope differently from the steady-state carbon dioxide response slope [9]. For example, drugs that reduce brain metabolism and steady-state brain blood flow cause a reduction in the rebreathing carbon dioxide response compared with the steady-state carbon dioxide response slope [9].

It is possible that the decrease in the \( V_e - P_{\text{CO}_2} \) response slope after extradural morphine in the study of Saito and co-workers [1] is related to the above mentioned items.

In summary, we plead for the use of the steady-state method instead of Read’s rebreathing method to study the effects of drugs on ventilatory control.

A. DAHAN
B. BERKENBOSCH
Departments of Anaesthesiology and Physiology
Leiden University Hospital
Leiden, The Netherlands


Sir,—We recognize the expertise of Drs Dahan and Berkenbosch in the field of ventilatory control and thank them for their valuable comments. We agree that Read’s rebreathing technique (RB) is associated with the ventilation depression induced by various factors other than the central chemoreceptors and that the steady-state (SS) technique is suited to examine the effects of drugs on ventilatory control. However, the SS method did not fit in with our study design. The aim of our study was to investigate if extradural administration of lignocaine increased the risk of ventilatory depression induced by extradural morphine, which had been well established [1]. In contrast with morphine, transient effects of extradural lignocaine require a more strict study design regarding its baseline and use of a method that can be performed easily. While a measurement with RB can be completed within 6 min, SS takes more than 20 min to perform. Indeed, most previous studies examining the effect of extradural lignocaine have measured the ventilatory response 20–30 min after administration of local anaesthetic using RB [2]. One might argue that we could have used SS if a continuous infusion had been taken. However, on ethical grounds we could not take a longer time before surgery.

In interpreting our results, we should consider that the parallel shift of the carbon dioxide response curve without the decrease in slope in the SS method is specific to drugs acting on opioid receptors [3]. However, we believe that we can compare the ventilatory effects of extradural morphine and the combination of morphine and lignocaine, and conclude that extradural co-administration of lignocaine does not increase the risk of respiratory depression associated with morphine because the two groups include the same modulatory factors, as pointed out by Drs Dahan and Berkenbosch.
It is undeniable that we should choose the best technique available to obtain reliable that are not contaminated by other undesirable factors in a scientific study. However, it is as important to use a technique that is practicable in a study using real patients.

Y. SATO
S. SAKURA
Y. KOSAKA
Department of Anaesthetics
Shinmei Medical University
Izumo City, Japan


3. Bourke DL, Warley A. The steady-state and rebreathing system was less efficient [3] and although more modern machines (using a fresh gas flow of 8 litre min⁻¹) showed that the Bain system was less efficient [3] and although more modern machines can deliver much higher flows, I have seen many trainees believing they are preoxygenating the lungs of patients with 6–8 litre min⁻¹ of oxygen via the Bain system. The face mask seal is clearly important, but other factors need to be addressed if we are to improve the application of this vital technique.

4. Sir,—It is clearly correct to say “it is reasonable to suppose” that a leak impairs preoxygenation. Our aim was to quantify the leak, not to embark on a wide ranging investigation of preoxygenation. In the light of this, the variations from normal practice are less important and were introduced after a pilot study to improve reproducibility.

5. Thus, although our study did not wholly reflect current UK clinical practice, we believe that we have quantified the magnitude of leaks with a sub-optimal mask fit and shown that they are appreciable.

6. The other questions, such as use of the “Everseal” masks or larger reservoir bags, clearly merit investigation in the future, but are not central to our work.

P. McCowan
Department of Anaesthesia
Royal London Hospital
London
A. Skinner
Department of Anaesthesia
Whiston Hospital, Merseyside


4. Sir,—We read with interest the review article by Mushambi, Halligan and Williamson on recent developments in the pathophysiology and management of pre-eclampsia [1]. However, there was no mention of the possible role of serotonin which we believe may be important.

5. We suggest that serotonin, released from platelet aggregates, stimulates 5-HT; receptors causing generalized vasospasm and subsequent endothelial damage. Platelets could be attracted by embolic trophoblastic fragments which have been found in increased amounts in the venous circulation of women with pregnancy-induced hypertension compared with non-hypertensive controls [2, 3]. This role of serotonin is supported by Fähr and colleagues [4] who demonstrated increased concentrations of the serotonin metabolite 5-hydroxyindole acetate (5-HIAA) in the urine of pre-eclamptic patients. In addition, ketanserin, a 5-HT₃ receptor blocker, has been used successfully in the treatment of pre-eclampsia [5, 6]. Clearly, the role of 5-HT₃ receptor blockers...
in the management of pre-eclampsia and eclampsia requires further study.

N. M. GAJRAJ
C. HUTTER
Department of Anaesthesia
City Hospital
Nottingham


Cost of volatile agents

Sir,—In 1992, Dion published a formula by which the cost of volatile agent use could be calculated [1], I have recently had cause to use this for newer agents and UK prices. Colleagues may find it of use when dealing with their pharmacies, etc. The cost is calculated by:

\[ \text{Cost} = \frac{\text{PFMTc}}{d^2} \]

where \( P \) = agent concentration (%), \( F \) = fresh gas flow (litre min\(^{-1}\)), \( T \) = time (min), \( M \) = molecular weight, \( C \) = price of the agent (£ ml\(^{-1}\)) and \( d \) = density of liquid agent (g ml\(^{-1}\)).

Using values taken from Dion, the British National Formulary [2] and the manufacturers, I have calculated that at a fresh gas flow of 1 litre min\(^{-1}\) for 1 h, the costs, in pounds sterling, at different concentrations are those shown in table 1.

<table>
<thead>
<tr>
<th>Agent</th>
<th>1 MAC</th>
<th>1% (adult in 100 % O(_2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>£0.172 (£0.148</td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>£0.428 (£0.812</td>
<td></td>
</tr>
<tr>
<td>Isoflurane</td>
<td>£1.193 (£1.431</td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>£1.445 (£3.189</td>
<td></td>
</tr>
<tr>
<td>Desflurane</td>
<td>£0.551 (£3.306</td>
<td></td>
</tr>
</tbody>
</table>

Alternatively “gas induction” using 8 % sevoflurane at a fresh gas flow of 6 litre min\(^{-1}\) for 1 min costs £1.16p.

R. N. FOSTER
Department of Anaesthesia
Hope Hospital
Salford

Effect of transdermal hyoscine on nausea and vomiting

Sir,—I read with interest the recent article by Honkavaara on the effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia [1].

It was interesting, although not surprising, that the incidence of intra- and postoperative nausea and vomiting was lower in the treatment group (receiving prophylactic transdermal hyoscine) than in the placebo group, who received no prophylactic antiemetic treatment, as the antiemetic properties of hyoscine are already well known and documented [2, 3].

Honkavaara makes the assumption that the reduction in nausea and vomiting in the hyoscine group, in relation to motion sickness, may result from specific inhibition of the postsynaptic potential in the neurones of the vestibular nuclei. This may well be so, but one fact appears to have been overlooked in the design of the study. The two groups received preoperative oxycodone and intra-operative fentanyl, both of which have emetic side effects. The placebo group therefore received potentially emetic drugs without prophylactic antiemetic treatment. This would influence the incidence of nausea and vomiting in its own right, and the assumption that the reduction in nausea and vomiting in the hyoscine group was caused by reduced stimulation of the vestibular apparatus cannot be validated. One can only speculate on how the results would have been affected if another group had been included, receiving prophylactic antiemetic therapy known not to be as effective as hyoscine in motion sickness, such as metoclopramide.

R. N. FOSTER
Department of Anaesthesia
Hope Hospital
Salford


Sir,—I agree with Dr Foster that one of the causes of multifactorial postoperative nausea and vomiting (PONV) after middle ear surgery might be the emetic effect of the opioids used. However, I would hesitate to ascribe significance to opioids in this type of surgery causing physical stimuli to the inner ear. The amount of opioids used (oxycodone or fentanyl) did not predict PONV in middle ear surgery as assayed by logistic regression analysis [1, 2].

In patients undergoing middle ear surgery, the noise from the drilling and suctioning exceeds 107 dB(A) in the mastoid cavity and furthermore, low frequency vibrations caused by the slowly rotating cutting burr can lead to a Tullio-phenomenon-like state [2]. In the Tullio phenomenon, sound pressure induces electrical potentials equivalent to cochlear microphonics from different receptors of the vestibular labyrinth leading to vestibular stimulation [3]. Patients with chronic otitis media or cholesterol otorrhea are more susceptible to the Tullio phenomenon than healthy controls [3].

Dr Foster suggests that another group receiving metoclopramide should be included in the design of the study. This seems to be unjustified on the following grounds. Even though several studies support the efficacy of metoclopramide in PONV, there is at least an equal number of reports which do not confirm this result. Rowbotham concluded in his review [4] that i.v. administration of metoclopramide at induction appeared to be ineffective against PONV.

Thus the results presented in this letter and in earlier reports [1, 2] suggest that physical stimuli resulting in vestibular dysfunction are the main cause of the emetic episodes associated with ear surgery. The contributing effect of opioids on PONV, possibly sensitizing the vestibular system, is unclear, but it should be of

I. BARKER
Department of Anaesthesia
Sheffield Children's Hospital NHS Trust
Sheffield


Sir,—I agree with Dr Foster that one of the causes of multifactorial postoperative nausea and vomiting (PONV) after middle ear surgery might be the emetic effect of the opioids used. However, I would hesitate to ascribe significance to opioids in this type of surgery causing physical stimuli to the inner ear. The amount of opioids used (oxycodone or fentanyl) did not predict PONV in middle ear surgery as assayed by logistic regression analysis [1, 2].

In patients undergoing middle ear surgery, the noise from the drilling and suctioning exceeds 107 dB(A) in the mastoid cavity and furthermore, low frequency vibrations caused by the slowly rotating cutting burr can lead to a Tullio-phenomenon-like state [2]. In the Tullio phenomenon, sound pressure induces electrical potentials equivalent to cochlear microphonics from different receptors of the vestibular labyrinth leading to vestibular stimulation [3]. Patients with chronic otitis media or cholesterol otorrhea are more susceptible to the Tullio phenomenon than healthy controls [3].

Dr Foster suggests that another group receiving metoclopramide should be included in the design of the study. This seems to be unjustified on the following grounds. Even though several studies support the efficacy of metoclopramide in PONV, there is at least an equal number of reports which do not confirm this result. Rowbotham concluded in his review [4] that i.v. administration of metoclopramide at induction appeared to be ineffective against PONV.

Such the results presented in this letter and in earlier reports [1, 2] suggest that physical stimuli resulting in vestibular dysfunction are the main cause of the emetic episodes associated with ear surgery. The contributing effect of opioids on PONV, possibly sensitizing the vestibular system, is unclear, but it should be of

I. BARKER
Department of Anaesthesia
Sheffield Children’s Hospital NHS Trust
Sheffield

equal intensity in both the placebo and hyoscine groups because of the same amount of opioid received by both groups.

P. HONKAVAARA
Otolararyngological Hospital
University Central Hospital
Helsinki, Finland


Gastric tonometry

Sir,—In a recent letter [1], Dr Fiddian-Green stated that an article written by us [2] was deficient and misleading. In support of his allegations Dr Fiddian Green cited three letters [3–5]. None of these letters was written by him at the time, and none found our article either “deficient” or “misleading”. Our article clearly states that the purpose was to “...investigate the association between pH, and other measures of metabolic acidosis...” by examining correlations between measurements. The numbers of patients involved were too small to make statements concerning any predictive effect, and no such claims were made. All three letters erroneously implied that this was the purpose of our study. Also, the letters suggested that there might be some patients in whom measurement of “intramucosal” pH might provide additional information. We made the same point, stating that we are unable to “...exclude the possibility that there are some patients with selective splanchnic ischaemia not reflected by systemic acidosis...”. This hardly represents deficiency or an attempt to mislead.

Dr Fiddian-Green [1] went on to describe two studies [6, 7] which showed results contradictory to ours. He stated that these studies were more definitive, but did not mention others which disagreed with aspects of their results. Maynard and colleagues [6] showed that intramucosal pH was a better predictor of outcome than base deficit. However, continued data collection from the same institution, recording the same variables, has not confirmed the original findings. A retrospective analysis of a clinical database of 214 patients admitted to intensive care [8] showed that by 12 h after admission, base deficit was significantly different between survivors and non-survivors. This difference was found only for intramucosal pH at 24 h. Furthermore, analysis of ROC curves showed that discrimination by intramucosal pH was no greater at any time than measurement of base deficit. The authors concluded that “the routine measurement of [intramucosal] pH in clinical practice does not contribute additional information about likely outcome over and above that available from the simultaneous measurement of base excess and arterial pH”.

In the careful study of Gutierrez and colleagues [7], three data points were collected for 21 patients, while investigating the effect of dobutamine on intramucosal pH. They did not specifically study the correlation between the variables, but the data showed that an increase in the mean value of intramucosal pH after infusion of dobutamine was not accompanied by an increase in the mean value for base deficit. Interestingly, a more recent study [9] on the effects of dobutamine on intramucosal pH has shown contrasting results, although the results of blood-gas analysis were not given. In this study dobutamine reduced intramucosal pH, particularly in patients who already had low intramucosal pH and low cardiac output. While the two carefully conducted studies quoted by Dr Fiddian-Green [6, 7] clearly suggested results different from our own, it is unclear as to which of these studies is the more “definitive”.

O. BOYD
R. M. GROUNDS
Department of Anaesthesia
St George’s Hospital
London


Measurement of competence

Sir,—Ellis’s editorial [1], using the stimulus of Kestin’s application of cusum analysis in the assessment of training [2], had me nodding in agreement until the concluding paragraph: “A quantitative approach to education is overdue. In the past there has been too much reliance on examinations as the only guide to the acquisition of knowledge.” (My italics.) Training is not education; skills are not knowledge [3]. McManus listed the differentiating characteristics. For a course intended to educate, competency is not easy to assess, nor is the content of the course readily definable in any core curriculum. Training can be taught by restrictive methods, without insight, and the content of the course is readily put into compartments and tested in parts.

Before we go further down the road of syllabuses and structured training, we should stop to ask if we are training or educating.

N. W. GOODMAN
University Department of Anaesthesia
Southmead Hospital
Bristol

