Intraoperative gut hypoperfusion may be a risk factor for postoperative nausea and vomiting

Sir,—We read with interest the article on nausea and vomiting after cardiac surgery by Grebenik and Allman.1 There are two issues which we believe are important but were not discussed by the authors.

Gut mucosal hypoperfusion is common after cardiac surgery and may be another factor that explains the high associated incidence of postoperative nausea and vomiting.2 Animal studies have shown that damage to the gut is accompanied by an increase in 5-HT₁ in gut mucosa.3 Radioligand binding studies demonstrated the presence of large number of 5-HT₁ receptors on vagal terminals that innervate the intestinal mucosa and on the same vagal afferent nerves located in the brain stem vomiting centre.3 Furthermore, it has been demonstrated recently that plasma volume expansion during cardiac surgery is associated with maintenance of gut perfusion and reduction in postoperative morbidity, including persistent nausea and vomiting.4

The authors mentioned that “if the patients did not meet the criteria for tracheal extubation and required sedation to tolerate intubation and ventilation, an infusion of propofol 1–4 mg kg⁻¹ h⁻¹ was commenced until another trial of spontaneous breathing was performed at the discretion of the nursing staff”. Propofol is an antiemetic in its own right. Numerous studies have shown that propofol as a primary agent for maintenance of anaesthesia was associated with a lower incidence of postoperative nausea and vomiting.5,6 When used in this manner, it is more efficacious than ondansetron 4 mg.7 We have defined plasma concentrations of propofol for effective treatment of PONV as 405 ng ml⁻¹ (95% confidence interval 280–530 ng ml⁻¹).8 Data from computer simulation using the pharmacokinetic variables of Gepts and colleagues9 demonstrated that infusion of propofol 1–4 mg kg⁻¹ h⁻¹ for sedation, as used by the authors, produces plasma propofol concentrations in the effective range for treatment of nausea and vomiting for up to 180 min after termination of infusion (fig. 1). However, they did not provide information on the number of patients treated with propofol and the duration and dose of propofol used in each group, which may affect the overall results.

Hence it is important to specify the details of propofol administration in studies that investigate the incidence of PONV.

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Figure 1 Simulated plasma decay of propofol concentrations after 2-, 4-, 6- and 8-h infusions.

Ethanol monitoring during hysteroscopy

Sir,—The complications of endometrial resection were reviewed by Williamson and Mushambi in an editorial in the September issue of British Journal of Anaesthesia.1 The importance of fluid absorption in this context is emphasized by the fact that several fatal cases of the “female TUR syndrome” have occurred.2 In their article, the authors did not recommend the ethanol method for monitoring fluid absorption because they could not account for the sex-related differences in breath ethanol and serum sodium responses to fluid absorption that were described by me in a recent review article.3 I have stated that the ethanol response to fluid absorption is 10% greater in middle-aged women undergoing endometrial resection than in elderly men undergoing transurethral resection of the prostate. This difference is easy to account for as most women are of a smaller size than men. The authors’ distrust,
Correspondence

however, was probably elicited by my suggestion that the serum sodium response to fluid absorption is 40% greater in females than in males. The magnitude of this difference can be illustrated by assuming that 1000 ml of irrigating fluid containing 1.5% glycine with 1% ethanol is absorbed by a male and a female. My nomograms suggest the reduction in serum sodium concentrations would amount to 8 mmol litre\(^{-1}\) in males and 11 mmol litre\(^{-1}\) in females.\(^4\) Is this difference reasonable? Yes, I think so. The amount of extracellular water in the extracellular space, which is the distribution volume for sodium, has been reported to be 200 ml/kg body weight in males and 150 ml/kg body weight in women.\(^5\) Based on these data, the difference that I have reported is what would be expected.

I admit that in the original study of fluid absorption by myself and Olsson there were too few in number to allow construction of a nomogram.\(^6\) However, as stated in my review article, the published nomogram was also based on a series of additional patients (up to a total of 70) who actually absorbed irrigating fluid. One of the additional cases has been described to show the elegance with which the ethanol method works.\(^7\)

The “fluid deficit” is suggested in this editorial to be the best indicator of fluid absorption during hysteroscopy. This implies routine use of volumetric fluid balance. However, many factors need to be controlled to make routine use of this method accurate.\(^4\) To my knowledge, its sensitivity has never been tested. Poor correlations between key variables which should all reflect fluid absorption are usually reported in studies where the method seems to have been used on a routine basis. My group has had difficulty obtaining useful data with it during prostatectomy.\(^8\) The fluid deficit needs to be compared with more precise methods of measuring fluid absorption before I would recommend it as a standard method. As far as ethanol monitoring is concerned, several such studies have been conducted and its accuracy and precision are well known.

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ACE inhibitors and renal protection

Sir,—I read with interest the article by Licker and co-workers\(^1\) and agree that angiotensin converting enzyme (ACE) inhibitors, may be of some value in renal protection during surgery. In a previous study we found that aortic cross-clamping-induced haemodynamic changes were less marked in enalapril-treated patients compared with controls,\(^2\) in agreement with the study of Licker and colleagues. However, regarding renal perfusion, we established that effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were not maintained at baseline levels during aortic cross-clamping in enalapril-treated patients, although ERPF and GFR were good before clamping.\(^2\) Licker and colleagues established that ACE inhibitors were effective in improving renal perfusion during aortic abdominal surgery and this seems to refute our own conclusions. In fact, these differences may be explained easily.

Their renal haemodynamic studies showed that aortic cross-clamping induced a significant decrease in ERPF in controls only (approximately −21%). However, although this decrease in ERPF in enalapril-treated patients was not statistically significant (approximately −14%), the renal blood flow:cardiac output ratio decreased significantly only in enalapril-treated patients (−25%); this strongly suggests that blood flow was redistributed away from the kidney during clamping. Moreover, although not statistically significant, the mean increase in renal vascular resistance and mean decrease in GFR during aortic cross-clamping (+43% and −20%, respectively) were not less relevant than the decrease in ERPF in controls. The data may have been confusing therefore because the threshold of statistical significance was not reached because of the small number of patients studied. Moreover, patients had different pathologies, notably both aortic aneurysm and atherosclerotic occlusive disease.

In my opinion, Licker and colleagues cannot assert that, in contrast with calcium antagonists,\(^2\) ACE inhibitors prevent the renal vasoconstrictive effect of infrarenal aortic abdominal cross-clamping. Nevertheless, I agree that ACE inhibitors may boost renal perfusion before and after aortic clamping.

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Sir,—We thank Dr Colson for his comments. We acknowledge that the small sample size of the study precludes firm conclusions concerning the haemodynamic changes induced by renin-angiotensin system block. The numbers of patients whose before we can recommend it for routine use during TCER. There is no doubt that, despite its limitations, volumetric fluid balance is still the most commonly used method of assessing fluid absorption during TCER. We agree with Professor Hahn that ethanol monitoring is a non-invasive, easy and accurate method of assessing fluid absorption during TURP. Hopefully in the near future this will also be applicable to its use during TCER.

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renal data were evaluated were nine and 11 for the saline and enalapril groups, respectively. At P<0.05 this number of patients was sufficient to detect a significant decrease in ERPF from a mean value of 472 to 371 ml min⁻¹ after aortic cross-clamping in the saline group whereas the (ns) changes observed in the enalapril group (from 582 to 499 ml min⁻¹) may represent a type II error. If we assume similar ERPF values in larger groups (n=69), “true differences” would have been reached for (within and between) group comparisons while maintaining a power of 0.90 (β=0.10); such data would confirm lesser impairment of renal haemodynamic state after pretreatment with enalapril.

During aortic cross-clamping, the renal blood flow/cardiac output ratio (RBF:CO) decreased by 25% in enalapril-treated patients and this was attributed entirely to a decrease in RBF as there was no change in CO. In contrast, proportional changes in RBF and CO were observed in saline-treated patients resulting in an unchanged RBF:CO ratio. Activation of unblocked vasopres-
sor support systems (such as arginine vasopressin and the sympa-
thetic nervous system) in response to aortic clamping could be
implicated in the renal vasoconstruction in the two groups. In
addition, the systemic haemodynamic pattern suggested that
enalapril-induced vasodilatation was effective in renal and
distal support systems (such as arginine vasopressin and the sympathetic nervous system) in response to aortic clamping could be implicated in the renal vasoconstruction in the two groups. In addition, the systemic haemodynamic pattern suggested that enalapril-induced vasodilatation was effective in renal and extrarenal vascular tissues; these data agree with experimental data supporting the notion that the splanchic vascular bed is more sensitive to the vasoconstrictor effects of sympathetic stimulation and angiotensin II.¹²

The beneficial renal haemodynamic effects of enalapril were demonstrated clearly in the present study as: (1) the RBF:CO ratio increased before aortic cross-clamping as a result of a greater increase in RBF compared with CO, (2) during aortic clamping, ERPF was reduced to a lesser extent; (3) a greater glomerular filtration rate (GFR) was maintained; GFR and ERPF were strongly associated (r=0.65 in the enalapril group) after aortic clamping, implying that approximately 40% of the observed changes in GFR could be explained by haemodynamic variability. Taken together, our preliminary data suggest lesser impairment of renal perfusion and function during aortic abdominal surgery after enalapril pretreatment.

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Possible mechanism to explain increased coagulability of blood after haemodilution

Sir,—We read with interest the discussion ensuing from the article by Ruttmann, James and Viljoen on hypercoagulability of blood after administration of i.v. crystalloids. Farmery and Kong¹ suggested that anticoagulant factors are strongly associated (r=0.65 in the enalapril group) after aortic clamping, implying that approximately 40% of the observed changes in GFR could be explained by haemodynamic variability. Taken together, our preliminary data suggest lesser impairment of renal perfusion and function during aortic abdominal surgery after enalapril pretreatment.

2. Farmery AD, Kong A. Hypercoagulability induced by crystal-

Sir,—We thank Fletcher and Heard for their comment on our article. The argument they make that anticoagulant factors are diluted to the same degree as procoagulant factors is valid, and has been suggested previously by Monkhouse,¹ who suggested that haemodilution may disturb the ratio of thrombin to antithrombin III. An imbalance between the two may predispose to a procoagulant effect. Subsequent in vivo data, which are currently under consideration for publication, suggest that antithrombin III is decreased to a greater extent after haemodilu-
tion than could be explained by haemodilution alone, the infer-
ence being that the act of haemodilution per se, had induced the conversion of prothrombin to thrombin with subsequent thrombin–antithrombin III interaction. The suggestion by Fletcher and Heard that this effect may have a teleological basis is particularly elegant, as it could explain the reason for its occurrence.

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Regional anaesthesia in moyamoya disease

Sir,—We have read the article of Ngan Kee and Gomersall on extradural anaesthesia for Caesarean section in a patient with moyamoya disease.¹ We wish to describe our own experience with extradural anaesthesia for Caesarean section in a patient with moyamoya disease.¹

A 34-yr-old woman suffered intraventricular bleeding in her 24th week of pregnancy, requiring intensive care and mechanical ventilation for 8 days. During this period the only unusual problem was development of pneumonia. She recovered without any sequelae and moyamoya disease was diagnosed by arteriography. The patient remained healthy for the remainder of the pregnancy and in the 38th week an elective Caesarean section was planned. Preoperative investigations were normal, including anti-cardiolipin antibody concentrations. After a preload of 1000 ml of lactated Ringer’s solution, a left radial artery cannula and central venous catheter (via the antecubital fossa) were inserted under local anaesthesia. Analysis of arterial blood was carried out at 15-min intervals. Anaesthesia was perforated with 0.5% spinal bupivacaine 15 mg and fentanyl 50 µg at L2–3, using a 25-gauge Whitacre needle, and 28% oxygen was given by face mask. The level of sensory analgesia to pinprick was T3. Total intraopera-
tive fluid given was 1500 ml of mild lactated Ringer’s solution.

There were no changes in heart rate, direct arterial pressure or temperature, apart from transient hypotension (80% of preoper-
active value) treated with ephedrine 15 mg i.v. A healthy 3250-g male baby was delivered with Apgar scores of 8 (1 min) and 9 (5 min).

After surgery the patient remained in the PACU for 6 h and was discharged uneventfully without any change in her neurological status. There were no other problems in the subsequent 3 months.

Several cases have been reported of patients with moyamoya

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Converting pH and $H^+$: a “rule of thumb”

Sir,—Many centres have changed to the use of hydrogen ion concentration ($H^+$) rather than the traditional pH when dealing with acid–base problems. Converting $H^+$ to pH of vice versa is very simple when tables are available. We propose a straightforward method for conversion when they are not.

We have observed that, between pH values of 7.10 and 7.60, the sum of the hydrogen ion concentration (in nmol litre$^{-1}$) and the numerical value of the two digits after the pH decimal point is relatively fixed around 83, the mean of these sums in this pH range (table 1).

<table>
<thead>
<tr>
<th>pH</th>
<th>$H^+$</th>
<th>$H^+$ + 2</th>
<th>$H^+$ + 3</th>
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<th>$H^+$ + 5</th>
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<td>7.10</td>
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<td>107</td>
<td>114</td>
<td>121</td>
<td>128</td>
<td>135</td>
<td>142</td>
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<tr>
<td>7.20</td>
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<td>114</td>
<td>121</td>
<td>128</td>
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<tr>
<td>7.30</td>
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<td>7.40</td>
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<td>7.50</td>
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<td>114</td>
<td>121</td>
<td>128</td>
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<td>142</td>
</tr>
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To convert pH from $H^+$, the numerical value of the two digits after the pH decimal point is calculated by subtracting $H^+$ from 83. For example, if $H^+$ is 70.6 nmol litre$^{-1}$, the estimated value of pH would be (7.83–70.8), or 7.12. The actual pH value at this hydrogen ion concentration is 7.15.

To convert $H^+$ from pH, the numerical value of the two digits after the pH decimal point is subtracted from 83. Therefore, if pH is 7.50, the estimated value of $H^+$ would be 83–50, or 33 nmol litre$^{-1}$. The actual hydrogen ion concentration at this pH is 31.6 nmol litre$^{-1}$.

The errors are small and clinically inconsequential for conversions performed between pH values of 7.10 and 7.60. We feel that our simple “rule of thumb” will be useful to doctors dealing regularly with clinical situations in which acid–base disturbances are a feature.

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Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation

Sir,—We read the article of Mallick, Smith and Bodenham with interest and wish to make a few comments. In their study, although the use of local anaesthetic solution reduced the need for sedation in patients who underwent ventilation, it also suppressed the cough reflex. Patients appeared to be less bothered by pulmonary suctioning. The technique may be safe if used for short periods but our concern is that, if used over a longer period it may increase the risk of pulmonary infection.

Mucociliary clearance is an important mechanism of pulmonary defence. Effective mucociliary clearance depends on proper coordination of the cilia and their coordinated beating. 4Corssen and Allen1 studied ciliary function in tracheobronchial epithelium obtained with a punch biopsy and found that lignocaine caused a dose-related but reversible effect on ciliary activity. At low doses ciliary beating was stimulated and as the dose increased the cilia stopped beating. In contrast, amethocaine and chlohexidine caused irreversible stoppage of ciliary activity. It is clear that topical anaesthesia may cause areas of ciliary dysfunction and could predispose to airway colonization and pneumonia. The effects of long-term local anaesthesia on ciliary motility have not been studied.

We believe that further studies are needed to evaluate the effect of local anaesthetics on respiratory epithelium. Our suggestion is to compare the effect of local anaesthetics on mucociliary clearance using either a dye or a radio-opaque contrast as a marker. If the use of topical anaesthesia is found to be safe, then reduced requirements for sedatives may prove beneficial and may reduce the morbidity and mortality of patients undergoing artificial ventilation.

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Anticholinesterases and subsequent duration of block of suxamethonium

Sir,—I read with interest the article by Fleming and colleagues on the effects of anticholinesterases on subsequent duration of block with suxamethonium. The clinical observations are clear and in accord with conventional wisdom.

The authors have however fallen into a common trap with regard to their interpretation of the cholinesterase activity values. Their pooled data are in accord with those of Viby-Mogensen,2 who they referenced, in that over the clinical range the correlation between measured activity and duration of suxamethonium block is poor. In this study, a correlation can be shown clearly only in the presence of extremely low levels of measured activity. Another part of the problem is that the substrate used is not that used clinically (suxamethonium) but a thiocholine derivative, and that the correlation between different assay techniques and suxamethonium sensitivity is less than ideal.3

In addition, although not stated by the authors, such measurements of cholinesterase activity involve a large dilution of the plasma sample; this varies between laboratories but is usually 30–300-fold dilution into the reaction mixture. For cholinesterase inhibitors with prolonged covalent binding such as neostigmine, any inhibition produced would be likely to persist over a short period of dilution. Neostigmine concentrations decrease rapidly in vivo to approximately $6 \times 10^{-7}$ mol litre$^{-1}$.4 This concentration is associated with approximately 50% inhibition of cholinesterase activity (unpublished personal data, see fig. 1) and accords with the authors observations. Other less tightly bound agents such as edrophonium5 would be expected to be associated after such dilution with a lower inhibition than might be predicted from plasma concentrations at the time of sampling. The assumption that enzyme inhibition measured after dilution ex vivo accurately reflects in vivo conditions is a common but erroneous one.

Figure 1 Effects of neostigmine on plasma cholinesterase catalysis. Data are means of repeated measures of plasma from a normal individual. The assay is a modification of that of Ellman and colleagues.6


Sir,—We thank Dr Graham for his interest in our work and appreciate the opportunity to respond to his comments. Although we beg to differ as to whether the interpretation of our results constitutes “falling into a common trap”, we feel his letter highlights some limits of our studies and emphasizes aspects of this work which could benefit from further discussion. We agree that although Viby-Mogensen described the most commonly referenced relationship between measured activity of plasma cholinesterase and the duration of action of suxamethonium,1 when cholinesterase activity is in the normal clinical range, the slope of this graph is indeed shallow. The hyperbolic relationship he plots is largely determined by values outside the normal range. Although the sensitivity of the plasma cholinesterase activity assay for detection of less active variants of the enzyme may be improved slightly by the use of alternative substrates as described by Evans and Wroe,2 their study focuses on the detection of less active variants of the plasma cholinesterase enzyme, not on the characteristics of normal enzyme which has been exposed to a cholinesterase inhibitor. It is the effects of the mechanism of inhibition which we believe deserve emphasis.

As non-competitive inhibitors which react to form a carbamoylated cholinesterase enzyme, neostigmine and pyridostigmine are unlikely to be affected by assay techniques which include a dilutional step. In contrast, edrophonium, as a competitive inhibitor, may be profoundly affected. This may explain the contrast between studies which demonstrate minimal inhibition of plasma cholinesterase activity by edrophonium3 while the metabolism of other substrates (e.g. mivacurium) is inhibited.4

For non-competitive inhibitors, dilutional effects on enzyme activity measurements should be at best, minimal, and at worst, comparable. There is no evidence that the substrate used for the assay should have a differential sensitivity for these chemically related inhibitors. In our studies, pyridostigmine produced profound inhibition of plasma cholinesterase (79% of baseline) compared with neostigmine (48% of baseline). In contrast, the duration of action of suxamethonium increased only 35% after pyridostigmine compared with 78% after neostigmine. Despite the limitations of the enzyme activity assay, we believe this contrast provides the strongest evidence that this is a much more complex drug interaction than previously realized.

1. Viby-Mogensen J. Correlation of succinylcholine duration of


I. v. anaesthetics and binding to calcium channels

Sir,—The article by Hirota and Lambert demonstrating an interaction between a variety of i.v. agents and the dihydropyridine binding site on L-type voltage-sensitive Ca2+ channels is an interesting addition to the bewildering literature on mechanisms of anaesthesia.

The concept that i.v. anaesthetic agents may reduce neurotransmitter release via diminished influx of calcium ions is attractive as calcium influx is the common trigger for neurotransmitter release in invertebrates and vertebrates.

The authors hypothesize that i.v. anaesthetics may act via inhibition of calcium influx through L-type channels. Although their discussion may appear convincing, there are reservations with this hypothesis.

First, L-type channels do not seem to be crucial to stimulus–secretion coupling in the majority of vertebrate preparation studied as this coupling is generally insensitive to dihydropyridine antagonists. If the likely target for anaesthetics is transient calcium channels, then the significance of L-type calcium channel inhibition for anaesthesia may be minimal. Interestingly, other calcium channels, for example P and N channels, have been implicated in neurotransmitter release in vertebrate neurones.

Second, the authors, therefore, observing non-specific actions of anaesthetic agents rather than actions which underlie anaesthesia? Stereoselective differences in anaesthetic effects are seen at the receptor level for isoflurane on the GABA_A receptor. Hypnosis may also be Stereoselective.

Although it is perhaps too early to say if stereoselectivity may be a marker for actions that are relevant to the mechanism of anaesthesia, it is worthy of note that the anaesthetic effects of isoflurane on L-type calcium channels do not demonstrate stereoselectivity.

Third, the overwhelming fact remains that traditional dihydropyridine antagonists have minimal action as anaesthetics in the conventional sense, even if the blood–brain barrier is crossed.

I believe that these considerations significantly weaken the case for inhibition of calcium influx in L-type channels being an important mechanism of action of i.v. anaesthetic agents.

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5. Stanley EF, Atralchi AH. Calcium currents recorded from a vertebrate presynaptic nerve terminal are resistant to the dihydropyridine nifedipine. Proceedings of the National Academy of Sciences USA 1990; 87: 9683–9687.


7. Moody EJ, Harris BD, Skolnick P. Stereoscopic actions of the inhalation anaesthetic isoflurane showing that L channels (VSCC) have a role to play in anaesthesia but we are equally not convinced that they do not. We feel that it is premature to exclude this important class of ion channels as anaesthetic target sites and hoped that this is what our article and a recent editorial conveyed. We agree that the literature is bewildering but as Dr Wilkinson points out, inhibition of VSCC and hence neurotransmission is an attractive site for anaesthetic action.

Before we respond to his detailed comments We wish to state clearly our position. We are not totally convinced that voltage-sensitive Ca2+ channels (VSCC) have a role to play in anaesthesia but we are equally not convinced that they do not. We feel that it is premature to exclude this important class of ion channels as anaesthetic target sites and hoped that this is what our article and a recent editorial conveyed. We agree that the literature is bewildering but as Dr Wilkinson points out, inhibition of VSCC and hence neurotransmission is an attractive site for anaesthetic action.

2. Hirning LD, Fox AP, McCleskey EW, Olivera BM, Thayer SA, Mill er RJ, Tsien RW. Dominant role of N-type Ca^2+ channels in rat cerebrocortical membranes.


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