Oxygenation criteria—a plea for more information

Sir,—We were interested to read the editorial by Peek and Firmin1 arguing for the greater use of extracorporeal membrane oxygenation (ECMO) in the management of severe acute lung injury. Their results in Leicester seem impressive (although apparently unpublished elsewhere) and the authors issue a challenge to other units to match their 34% hospital survival rate in a similar group of patients. Unfortunately, however, they do not give enough information to allow this.

Values are given for the mean Murray score2 and \( P_{Aa}/P_{Aa} \) ratio in their group of 50, but more is needed if this category of patients is to be defined accurately and reproducibly. While a mean \( P_{Aa}/P_{Aa} \) ratio of 8.7 provides an approximate indication of the problems with oxygen transfer in these patients, the picture is incomplete. First, it would be helpful to know how long the problems persisted at this level before extracorporeal support was started; was it one or more hours or was the mean calculated from the single worst value for each patient and so based in each case on a single blood-gas result? Second, apart from the Murray score which includes positive end-expiratory pressure (PEEP) as one component, we are given little clue as to mean airway pressure at this time, despite the fact that this is accepted as being a major determinant of arterial oxygenation.3

As long ago as the 1970s the importance of at least some reference to airway pressure was recognized and the American ECMO study entry criteria reflected this by referring to specific levels of PEEP together with defined requirements for \( P_{Aa} \) and \( P_{Aa} \).4 At the time, this was reasonable in that PEEP was the only commonly used means of increasing mean airway pressure. It is, of course, still used extensively and is one of the components of the Murray score. However, today, particularly in the most severe forms of acute lung injury, the extensive use of inverse ratio ventilation to maximize mean airway pressure means that its relationship to the level of PEEP is less predictable. It would be helpful, therefore, if future descriptions of severity of lung injury in patients undergoing ventilation could include data on the mean airway pressure being used.

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Lateral positioning for regional analgesia during labour

Sir,—The letter by Richardson and Wissler1 described several cases of labouring women who had extradural test doses while in the sitting position. They were placed in the left lateral recumbent position only after development of high spinal block. The sitting position may cause problems both in the spread of drug in the subarachnoid space, as highlighted by the authors, and also in the cardiovascular consequences of regional block.

Richardson, Lee and Wissler’s initial report2 suggested that cephalad spread in these cases may have been more extensive than would have been expected if patients were in the lateral position. Hamilton and Cohen also discussed extensive cephalad spread of isobaric solution while sitting as a factor in cases of high sensory block3 or respiratory depression4 after intrathecal sufentanil analgesia. Various “isobaric” solutions are hypobaric both in vivo5 and in vitro6.

Richardson and Wissler changed their local anaesthetic test dose from lignocaine 45 mg to bupivacaine 5 mg. Bupivacaine is theoretically safer if a high block results because of its greater sensory-motor differential than lignocaine. However, the dose of bupivacaine (0.25% solution 2 ml) may not be adequate. Stacey and colleagues7 used bupivacaine 5 mg to produce spinal analgesia in labour. Although sym pathetic block was usually present 5 min after this dose, analgesia was present in only two-thirds of patients and moderate to severe motor block did not develop in one-third of women. Furthermore, the deadspace of the extradural catheter and filter, if used, may vary from 0.25 to 1 ml. Therefore, only 2.5–4.375 mg of bupivacaine may enter the spinal canal. A large number of false negative test doses are to be expected.

The answer would seem to be to use a larger dose of bupivacaine, but manage the woman in the lateral position so that the effects of baricity alter lateral rather than cephalad spread.6 Position also has major effects on venous return. Sitting is associated with orthostatic stress on the circulation which may be combined with inferior vena caval compression during late pregnancy.5,9 Greene and Brull10 stressed the importance of a slight head-down tilt during spinal anaesthesia for this reason. Maintaining labouring women sitting after administration of isobaric spinal solutions or extradural test doses may result in greater hypotension than if they were lateral; this is exacerbated if the block is subsequently unexpectedly high.

The position in which the woman is managed for the first dose and thereafter usually follows on from the position chosen for insertion of the regional block. Vincent and Chestnut1 found no overall difference in comfort if women curled up sitting and then lateral as for regional block, but in those who expressed a preference slimmer women preferred the lateral position and larger women preferred sitting. I ask women who request regional analgesia during labour which position they think will be most comfortable for insertion of the block; the majority indicate the lateral position rather than sitting. This is to be expected in our population with a low mean body mass index.9 As far as the operator is concerned, anaesthetists who prefer to perform extradurals with the woman sitting find it harder if she is positioned laterally. The converse is not the case: if they prefer the lateral position for insertion, it is equally easy to place extradural catheters with the woman in either position.11 Trainees should be encouraged to use the lateral position for regional block during labour, because there are occasions when this may be indicated clinically.12 I believe the lateral position to be optimal for administration of

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spinal or potentially spinal drugs, not only for the woman’s comfort, but also in terms of safety. If the sitting position is deemed necessary for insertion of the block, consideration should be given to repositioning the woman into the lateral position, immediately (for intended spinal anaesthesia using isobaric solutions) or before an extradural test dose.

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Sir,—We appreciate Dr Kinsella’s interest in our letter. He and other authors continue to refer to non-glucose-containing anaesthetics as “isobaric solutions”. We have shown that glucose-free local anaesthetics, opioids and combinations, commonly used for intrathecal administration for analgesia in labour, are hypobaric relative to the cerebrospinal fluid. We and others have observed positional effects on the extent of block in labouring parturients which are likely to be attributable to the hypobaricity of the intrathecal injectate. Although the clinical significance of hypobaricity and patient positioning as factors contributing to the extent of block remains to be fully elucidated, these solutions should no longer be referred to as isobaric.

In 1981, Moore and Batra described the simultaneous injection of lignocaine and adrenaline as a test to detect occult i.v. or intrathecal placement of the extradural catheter. Although they reported only on the predictive value of the i.v. component (adrenaline) in non-pregnant patients, their test dose rapidly gained acceptance for use in parturients. For years, investigators have focused on the safety, sensitivity and specificity of the i.v. component (adrenaline). Although the intrathecal component has received attention recently, we are unaware of any study that has evaluated the safety or predictive value of the intrathecal component of an extradural test dose in labouring parturients. Despite this, there is much published opinion on the correct test dose for intrathecal catheter detection in this population. The cases reported by us and others serve to suggest that the local anaesthetic component (lignocaine 45 mg) described by Moore and Batra (and still used by many today) is excessive in the labouring parturient. This is not surprising, as relatively minuscule doses of intrathecal bupivacaine (with or without adrenaline) produce rapid and profound analgesia in labour. The current use of dilute anaesthetic solutions for extradural analgesia in labour has effectively eliminated the risk of systemic toxicity from the initial therapeutic dose, and has rightly focused our attention on the possibility of accidental high spinal block in the parturient.

Dr Kinsella suggests that the sensitivity of a 2-ml test dose containing bupivacaine 5 mg and adrenaline 15 µg in labouring parturients may be unacceptably low. Stacey and colleagues administered the same dose of hypobaric bupivacaine (5 mg in 2 ml) to labouring parturients in the left lateral position (parturients were not moved after intrathecal injection). The authors reported detectable sensory analgesic levels and “substantial pain relief” in all 30 parturients. The extent of analgesic block varied considerably, probably attributable to inadequate cephalad spread of the hypobaric solution administered in the lateral position. Subsequent to publication of our letter, we have detected two intrathecal catheters using the bupivacaine-adrenaline test dose. In both cases, sensory analgesia was detected promptly and seated parturients were moved to the lateral position; neither experienced significant changes in haemodynamic state and both had immediate and complete analgesia. Sensory blocks were dense and easily demonstrated and motor block was restricted to the lower extremities. The dramatic and rapid sensory and analgesic effects observed in both cases indicate to us that false negative intrathecal tests are very unlikely; we have not observed any thus far. However, in the event of a false negative test, the ensuing fractionated administration of the therapeutic dose (typically including fentanyl and a total of bupivacaine 12.5–20 mg) with the parturient positioned laterally further safeguards against the potentially catastrophic complications of high spinal block. We shall continue to use this testing method until further studies become available.

Some investigators recommend extradural test doses containing amounts of bupivacaine known to rapidly produce high levels of sensory and motor anaesthesia adequate for Caesarean section. We have never advocated such practice as there have been no studies on the safety of intrathecal injection of hypobaric bupivacaine doses in labouring parturients who receive smaller amounts of i.v. prehydration. Although large intrathecal doses of bupivacaine produce dramatic effects, we believe that careful questioning and examination by the experienced anaesthetist at the time of administration of the test dose are preferable to induction of extensive and profound subarachnoid block in the labour room.

The clinical significance of positional effects on the haemodynamic state of the parturient has not been determined, and may or may not be influenced by foeto–maternal health. Today, it is not uncommon for healthy parturients to assume the upright position after administration of intrathecal and extradural local anaesthetics. We do not routinely dictate patient position during extradural catheter placement, but rather allow the parturient to chose the position most comfortable to her. We agree with Dr Kinsella’s comments on development of skill in performing regional anaesthesia in parturients positioned laterally. Such practice undoubtedly contributes to success in performing spinal anaesthesia for many emergency Caesarean sections which would otherwise be performed under general anaesthesia.

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### Interactions between mivacurium and prilocaine

Sir,—In their study of mivacurium supplementation of i.v. regional anaesthesia with prilocaine in volunteers, Torrance, Lewer and Galletly noted that the duration of action of mivacurium was prolonged significantly beyond that which was expected, and that the incidence of systemic effects from prilocaine after tourniquet release was much increased when mivacurium was also given.1 The authors did not provide any explanation for these phenomena and I would offer the following.

In common with all amide local anaesthetics (hence dibucaine number) prilocaine is a potent inhibitor of plasma cholinesterase.2 Thus metabolism of mivacurium by plasma cholinesterase would be inhibited and its effects exaggerated. Until now, I have always thought of this as a theoretical, rather than a clinically relevant, interaction, but it is clearly important for mivacurium. I wonder if the increased incidence of systemic effects of prilocaine after tourniquet release can be explained by some of the observations made during the study. Urticarial wheals were noted in two of the five volunteers who received mivacurium and prilocaine, and the authors concluded that the former produced an increase in vascular permeability. I would suggest that this might allow prilocaine to diffuse more rapidly into the blood from the tissues of the forearm after tourniquet release and so produce a more rapid increase in plasma concentration to a higher peak. Evidence of systemic effects would thus be more likely.

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### Effects of volume on spinal anaesthesia with 0.25% hyperbaric bupivacaine

Sir,—Chung and colleagues1 reported their clinical results on spinal anaesthesia with hyperbaric bupivacaine. Three groups (1, 2 and 3) of term parturients received 0.25% bupivacaine 3.2–3.6 ml (8–9 mg), 3.6–4.0 ml (9–10 mg) and 4.0–4.4 ml (10–11 mg) in 5% glucose, respectively. They found that cephalad spread of sensory analgesia was increased significantly with an increase in volume, and the onset time of sensory analgesia to T6 was significantly faster in group 3 than in group 1. The mean maximal level of analgesia in group 3 (T2–3) was significantly higher than that in groups 1 and 2 (T4–5 in each). They concluded that a large volume in itself may influence the spread of local anaesthetic in cerebrospinal fluid (CSF) and final block, especially in the narrow subarachnoid space of term parturients. Our clinical investigations with isobaric and hyperbaric amylcocaine in parturients (King HK, Wood L, Khan AK. Spinal anaesthesia for Caesarean section: isobaric vs hyperbaric solution, unpublished data) and isobaric amylcocaine in non-pregnant patients2 produced similar results indicating that the volume of local anaesthetic is the most immediate significant factor affecting the extent of spread because of simple “bulk displacement” or area of contact; that is the greater the volume, the more extensive is the spread.

An anaesthetic solution administered into the subarachnoid space is diluted by CSF and absorbed by the neural tissues during spread. A hyperbaric solution has a density greater than that of CSF. When the patient is in the horizontal supine position, the subarachnoid space is inclined downward from the lumbar lordosis, towards the low-lying parts, in both caudad and cephalad directions, and the hyperbaric solution reaches the lowest points in both directions unless its baricity is decreased to CSF during the process. Additionally, we may surmise that when the drug concentration has reached its minimal pharmacologically active concentration, no clinical analgesia can be detected even if the solution spreads further. Moreover, sacral pooling of hyperbaric solution reduces the mass (effective dose, amount undetectable) of local anaesthetic that spreads cephalad and subsequently affects the results observed.

Chung and colleagues1 used the same 0.25% hyperbaric bupivacaine solution. As increasing the volume of local anaesthetic solution implies an increase in drug dose, the results obtained may also have been affected by the dose of drug.3 With multiple factors such as drug volume, dose and baricity/position effects, the claim that the results obtained in this study were caused by drug volume alone is not justifiable.

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### Converting pH and H+ to pKa

Sir,—Further to the letter by Burden and McQuillan4 on converting pH and H+, I was taught the following trick nearly 30 yr ago by Professor Roy Simpson. Between pH 8.0 at 10 nmol litre−1 hydrogen ion concentration and pH 7.0 at 100 nmol litre−1, simply double or halve the hydrogen ion concentration for each 0.5 pH unit (table 1).

<table>
<thead>
<tr>
<th>pH</th>
<th>8.0</th>
<th>7.9</th>
<th>7.7</th>
<th>7.6</th>
<th>7.4</th>
<th>7.3</th>
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<tr>
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<td>10</td>
<td>12.5</td>
<td>20</td>
<td>25</td>
<td>40</td>
<td>50</td>
<td>80</td>
<td>100</td>
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</tbody>
</table>
This method is easy to remember and a good demonstration of a logarithmic progression for juniors to learn.

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“Renal” dopamine
Sir,—We read with interest the recent study1 and editorial2 regarding the use of low-dose, “renal” dopamine. The study by Girbes and colleagues appeared to provide further evidence that the effects in question result from an increase in cardiac output. The editorial by McCrory and Cunningham concluded that the effects produced by a fixed rate infusion of dopamine in a critically ill patient.

First, in a study by Zaritsky and colleagues3 on dopamine pharmacokinetics in critically ill infants and children, the authors concluded “substantial interindividual variation was observed in steady state dopamine clearance, . . . plasma dopamine could not be predicted accurately from the infusion rate”. Different texts quote varying dose ranges for the renal–inotropic–vasoconstrictor effects of dopamine and this arouses suspicion. This study showed that with such pharmacodynamic variation it is impossible to predict the effects produced by a fixed rate infusion of dopamine in a critically ill patient.

Second, a study by Duke, Briedis and Weaver4 compared low-dose dopamine with low-dose dobutamine. They studied 18 intensive care patients, each receiving, in random order, dopamine, dobutamine and placebo. They found a higher incidence of side effects with dopamine (tachycardia, hypertension, hypovolaemia and worsened PaO2/FiO2 ratio). The study found that while dopamine produced significant diuresis with no change in creatinine clearance, dobutamine produced significant improvement in creatinine clearance without diuresis. Taken together these studies undermine the cosy rationale of “renal” dopamine. The pharmacodynamic case to justify infusion rate vs effects in intensive care is untenable. Dopamine appears to act as a diuretic but with side effects including those related to catecholamines. Dobutamine may not produce the gratifying increase in urine output but appears to produce improvement in renal function with less side effects. An increasing number of intensive care units are abandoning the uncritical use of dopamine and adopting a more scientific rationale for haemodynamic management. The recent study and editorial add to this evidence.

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Sir,—Inglis and Hilditch refer to two important topics. First, they state that it is impossible to predict the effect of a given dose of dopamine because of the pharmacodynamic variation of dopamine. In our recently published study,1 we also measured plasma dopamine concentrations by HPLC, as described in the article (table 1). In another yet unpublished study in seven healthy volunteers, dopamine at a rate of 4 μg·kg⁻¹·min⁻¹ was given during simultaneous infusion with different doses of noradrenaline while measuring systemic and renal haemodynamics. It is clear from the data that interindividual differences are substantial, which under- scores the pharmacodynamic variation.

However, another important feature of dopamine should be mentioned, that is the different sensitivity and effects in different patient groups (and individuals). Our group and others have reported on these different effects of dopamine (agonists) with respect to renal haemodynamic state and plasma noradrenaline concentrations. In patients with a glomerular filtration rate (GFR) < 50 ml 1.73 m⁻², dopamine was unable to increase GFR or renal blood flow.7 The effect on renal haemodynamics in patients with congestive heart failure is, in contrast, more pronounced than in healthy volunteers. The same is true for the DA2 receptor stimulation related suppression of noradrenaline release from the presynaptic terminal of sympathetic nerves.8 Furthermore, it has been shown, or at least been shown highly likely, that the response to DA2 receptor stimulation is geneti- cally determined.16 With respect to the second remark by Inglis and Hilditch, we agree that it becomes more and more clear that the renal haemodynamic effects result mainly from the systemic haemodynamic effects of dopamine. We disagree however with their conclusion that dobutamine produces less side effects, based on a single study. Furthermore, the cited study by Duke, Briedis and Weaver7 mentioned tachycardia and hypertension in four and three of 18 patients as a side effect of dobutamine, respectively. An important flaw of this study, in our view, is the introduction of carry-over effects of dobutamine because of the sequential design. We agree however, that the uncritical use of dopamine (as a “renal” dose) should be abandoned, but the same holds true for dobutamine. Low-dose dopamine is probably a useful drug in the initial treatment of (severe) congestive heart failure and will remain useful in the initial treatment of hypotensive patients, in whom the diagnosis is not yet established.8

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<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Dopamine dose (μg kg⁻¹ min⁻¹)</th>
<th>Plasma dopamine (nmol litre⁻¹)</th>
<th>Patients</th>
<th>Healthy volunteers</th>
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</thead>
<tbody>
<tr>
<td>t1</td>
<td>0</td>
<td>5.0 (2.7–11.3)</td>
<td>nd</td>
<td>nd</td>
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<tr>
<td>t2</td>
<td>2</td>
<td>297 (75–337)</td>
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<td>t3</td>
<td>4</td>
<td>410 (110–683)</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>t4</td>
<td>8</td>
<td>413 (268–589)</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

Table 1 Plasma concentrations of dopamine in patients (n=7) after infrarenal aortic surgery and in healthy volunteers (n=7) during simultaneous infusion with different doses of noradrenaline. Each time indicates 1 h of infusion. Plasma dopamine concentrations are represented as medians (interquartile range). nd = not detectable.


