

Cardiac Toxicity from 3% 2-Chlorprocaine

To the Editor:—We read with interest the case report by Cladis and Litman¹ regarding the intravascular injection of 3% 2-chlorprocaine. The authors are to be congratulated on their ability to postoperatively radiologically document the intravascular placement of the epidural catheter. However, we have concerns with the total dose of 2-chlorprocaine used. The authors state that they injected 4 ml 2-chlorprocaine, 3%, over approximately 30 s. When this dose is calculated on a per-kilogram basis for the 2-month-old, 4-kg child described in the case report, the dose is 30 mg/kg for a total dose of 120 mg.

Neonates and infants up to 6 months of age have approximately half the plasma cholinesterase of older children.² Singler³ suggests a maximum of 7 mg/kg 2-chlorprocaine in infants. Although the rapidity of the cardiac toxicity after administration of the local anesthetic suggests an intravascular injection, the 4 ml 2-chlorprocaine, 3%, seems large enough that it was rapidly absorbed from the epidural space, producing a transient peak blood level and causing the transient cardiovascular effects. Rapidity of development of peak serum concentrations of local anesthetics is known to be related to the site of injection, with intercostal being the fastest, followed by caudal and then epidural.⁴

Because no blood was aspirated from the epidural catheter on two

occasions does not mean that the catheter was not in an epidural vein. It is possible that the catheter migrated into the vein during the case and was found postoperatively.⁵ However, regardless of the catheter placement, we believe that the total dose was too large for the patient.

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In Reply:—Drs. Shroff and Mayhew are concerned that the epidural loading dose of 3% 2-chlorprocaine was too large because plasma cholinesterase concentrations are reduced in neonates and infants.¹ However, the half-life of 2-chlorprocaine is of such short duration that increasing the dose has no significant clinical impact on complications. In our case report, we reported the half-life of chlorprocaine to be 1-4.5 min.² However, others have reported the plasma half-life to be less than 60 s.^{3,4} Plasma chlorprocaine concentrations have been measured in pediatric patients receiving continuous epidural infusions. Former preterm infants undergoing inguinal hernia repair received loading doses of 1 ml/kg 2-chlorprocaine, 3% (30 mg/kg), *via* an indwelling caudally placed epidural catheter and were then given infusions at a minimum rate of 30 mg · kg⁻¹ · h⁻¹.⁵ The mean cumulative dose of 2-chlorprocaine infused over 95 ± 35 min was 84 ± 30 mg · kg⁻¹ · h⁻¹. The plasma chlorprocaine concentrations were 0 mg/ml in four patients and 0.5 mg/ml in one patient, and there was no evidence of neurotoxicity or cardiovascular toxicity.⁵ Suggested loading doses of epidurally administered 2-chlorprocaine in the pediatric regional literature have ranged from 30 to 60 mg/kg.^{3,4}

Based on the above data, the loading dose of 30 mg/kg was clearly

appropriate. However, as we highlighted in our case report, pediatric epidurals should be tested before administration of a loading dose of local anesthetic to minimize the risk of unintentional intravascular injections and subsequent toxicity.

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Postpartum Hemorrhage Is Not the Only Setting for Maternal Myocardial Ischemia

To the Editor:—I read with great interest the article by Karpati *et al.*¹ documenting the high incidence of myocardial ischemia in parturients with significant postpartum hemorrhage. This is the second report that clearly documents the occurrence of myocardial ischemia in this population of young, otherwise healthy women with "normal" coronary arteries. In 2001, Moran *et al.*² used the newly available marker,

myocardial troponin I, to definitively correlate electrocardiogram changes during cesarean section with myocardial ischemia. It is interesting to reflect how much views have changed during the past 15 yr.

In 1990, we published a series regarding the incidence of electrocardiographic changes during cesarean delivery.³ At that time, our hypothesis that parturients could experience ischemia solely on the

basis of an imbalance of myocardial oxygen supply and demand was met with almost universal derision. Numerous other investigators subsequently confirmed a significant incidence of electrocardiographic changes,⁴⁻⁷ but of these, only Mathew *et al.*⁴ conceded that myocardial ischemia might be a possible cause. There was tremendous resistance to the idea that ischemia could be induced in someone with "clean" coronary arteries, despite the fact that in every other setting, such electrocardiogram changes would be considered ischemia until proven otherwise. Almost any other explanation was considered more likely—neurocirculatory asthenia, vasoregulatory asthenia, hyperdynamic heart syndrome, mitral valve prolapse, autonomic system imbalance, cardiac sympathetic block, and epinephrine.^{4,7}

Now, Karpati *et al.*¹ can unabashedly state, "Our study . . . showed that myocardial ischemia was probably related to a significant alteration in the myocardial supply-demand ratio in parturients with otherwise 'normal' coronary arteries . . . myocardial oxygen supply was impaired by lowered arterial blood pressure, whereas increased heart rate resulted in an increased myocardial oxygen demand." Not surprisingly, their findings of decreased blood pressure and increased heart rate mirror the findings in our 1990 series (table 5 in Palmer *et al.*³).

Although it is nice to have our original hypothesis validated after all these years, it also serves to prove the old adage: When you hear hoofbeats (in this case, chest pain, shortness of breath, and electrocardiogram changes), think horses, not zebras.

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High Incidence of Myocardial Ischemia during Postpartum Hemorrhage or Poor Management of Hemorrhagic Shock?

To the Editor:—With interest I read the recent article by Karpati *et al.*¹ in the January issue of *ANESTHESIOLOGY*. I have several questions, mostly regarding the study design, and hope the authors will comment.

It was the defined goal of the study to prospectively evaluate the incidence of myocardial ischemia in women with postpartum bleeding (introduction). In a prospective trial, one would expect to learn about admission criteria, predefined group selection criteria, and outcome measures. This did not seem to be the case in this study. The authors did not mention inclusion or exclusion criteria and, for the most part, seemed to use laboratory data from patient admission as outcome measures. In the Discussion, the authors assert, "myocardial ischemia-induced injury associated with hemorrhagic shock is likely to increase the incidence of [postpartum hemorrhage-associated] cardiac complications." This statement implies that the authors observed cardiac complications. How did the authors define or measure this variable?

The title of this study describes the incidence of ischemia, which implies that the authors identified new cases and the population at risk. The study cohort exhibited severe postpartum hemorrhage. Most subjects were troponin positive or negative at the beginning of the study. There was a good possibility of an admission rate bias (Berkson fallacy).

There were 21 comparisons between troponin-positive and -negative groups, but there was no mention of an adjustment for multiple

comparisons. With reference to the multiple logistic regression used, it is a rule of thumb to have approximately 10 outcomes for every independent variable in the model to achieve adequate power. This would call for a total sample size of at least 210 patients in this study. To illustrate this point, how can the authors assure that being catecholamine dependent, a cell with zero outcomes, is not predictive of ischemia?

The authors should comment on their definition of design, direction (prospective *vs.* cross-sectional), and study factors. They describe a cohort of poorly resuscitated female patients in "severe hemorrhagic shock" with an apparent high prevalence of being cardiac troponin positive. Did the authors find that surprising?

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In Reply:—We thank Drs. Palmer and Frölich for their questions regarding our article recently published in *ANESTHESIOLOGY*.¹ We would like to respond to their questions. Even though this was not a prospective trial but rather a prospective study, in the last paragraph of our introduction, we describe admission criteria for a cohort of women referred to our hospital in severe postpartum hemorrhage. Also defined in this paragraph are our outcome measures (incidence and

outcome of myocardial ischemia and identification of independent risk factors for myocardial ischemia in this subpopulation). Furthermore, we extensively described in the Materials and Methods how these outcome measures were detected (electrocardiogram, cardiac troponin I). Cardiac complications were those described by Arlati *et al.*,² which are likely related to myocardial ischemia.

As usual, univariate analysis was performed before multivariate anal-

ysis. The univariate step allowed a better understanding of the relations between variables and outcomes and allowed to select the variables to introduce in the multivariate model building process (screening process). Indeed, our conclusion was only based on the multivariate analysis. Using multivariate stepwise modeling, the α risk was fixed and appropriately maintained during the procedure. Accordingly, low systolic and diastolic blood pressures and increased heart rate can be considered true independent predictors of myocardial injury in studied patients. In addition, catecholamines were administered exclusively in patients with high cardiac troponin I, implying a strong link between catecholamine administration and myocardial ischemia. As regards the comment on the power, it is not relevant because, as stated in the Conclusion, our study did not rule out other factors that were not identified in our study. However, it is true that the small number of patients implied that we had a reasonable probability only for detecting parameters corresponding to large odds ratio, thus clinically important.

Finally, we would like to reflect on the high prevalence of myocardial ischemia in "poorly resuscitated" women. The mortality as described in the literature is relatively high in this cohort of women, close to 5% in Western countries.³ To date, the study presented by our group¹ is the largest worldwide series of parturients admitted with severe postpartum hemorrhage with hemodynamic follow-up. We are one of the main reference centers for this pathology, catering to 10 million inhabitants in the Paris region in close collaboration with

well-trained interventional radiologists and obstetricians. In a series of more than 400 such patients, the majority of which were transferred from other hospitals, mortality remains less than 2% (mostly amniotic embolisms), likely because we learned to focus, during transport and during early hospital stay, on restoring blood pressure, hemoglobin level, and heart rate while surgical treatment and/or embolization are performed, as rapidly as possible, to stop uterine bleeding and prevent myocardial ischemia.

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Do Alpha Agonists Increase Venous Return?

To the Editor:—I enjoyed reading the review by Gelman and Mushlin¹ of catecholamine actions on the splanchnic vasculature. Nevertheless, I am confused by an unreferenced statement they made regarding the actions of α -agonists on venous return. They state, "Generally, α -agonists increase venous return under normovolemic conditions, but they decrease it when used at high doses or in the presence of severe hypovolemia."

The animal data do not support the statement by Gelman and Mushlin. Yamazaki *et al.*² studied dogs that had received spinal anesthesia and ganglionic blockers (surely analogous to hypovolemia) and found that methoxamine and clonidine increased venous return. Similarly, Supple *et al.*³ found that α_2 -agonists increased the venous return of dogs on constant-flow cardiopulmonary bypass. However, Imai *et al.*⁴ showed that α -agonists decrease venous return and β -agonists increase venous return. Similarly, we found that phenylephrine administered to dogs after spinal anesthesia decreased venous return, whereas isoproterenol and ephedrine increased venous return.⁵ Of note, in our study, the animals underwent splenectomy. The canine splenic capsule contracts with α -agonists, and the canine spleen contains a much larger fraction of total blood volume than the human spleen does.

The human data do not support the statement by Gelman and Mushlin. Bell *et al.*⁶ found that volunteers receiving a 20-min infusion of phenylephrine (20–120 $\mu\text{g}/\text{min}$ —certainly not a "high" dose) showed an increase in splanchnic intravascular volume and a decrease in venous return. Leenen *et al.*⁷ infused epinephrine in healthy subjects with and without β -blockers. Using measured changes in left ventricular end-diastolic dimensions, these authors concluded that selective α -stimulation decreased venous return. Brooker *et al.*⁸ compared phenylephrine and epinephrine in patients with mild hypotension after spinal anesthesia. There was an increase in stroke volume and cardiac output with epinephrine, with no change or a decrease in cardiac output in those receiving phenylephrine. However, in a group of patients receiving a morphine-based anesthetic during constant-flow

cardiopulmonary bypass, Müller-Ruchholtz *et al.*⁹ observed α -agonist-induced increase in venous reservoir volume.

In sum, animal and human studies do not provide convincing evidence that α -agonists generally increase venous return under any condition. Finally, the inappropriate use of α -agonists to increase venous return could have disastrous complications during resuscitation.

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In Reply:—We thank Dr. Butterworth for his attention to our work.¹ He is correct: There is still confusion about the effects of α agonists on venous return. In fact, Dr. Butterworth's letter is confusing. First, he refers to Yamazaki *et al.*,² arguing that hypotension induced by spinal anesthesia and ganglionic blockade in dogs is "analogous to hypovolemia." How could this be true? Clearly, the dogs are normovolemic; the arterial hypotension results mainly from vasodilation and redistribution of blood into the splanchnic vasculature. Hypovolemia, in contrast, empties the splanchnic reservoir. Yamazaki *et al.*² show that α -adrenergic agonists increase venous return, which is exactly what we say in the sentence that Dr. Butterworth quotes from our article. He then refers to Supple *et al.*,³ whose study supports our viewpoint that α -adrenergic agonists can increase venous return. Indeed, the first two references offered by him to refute our position strongly support it.

Dr. Butterworth next cites Imai *et al.*,⁴ noting that α -adrenergic agonists decrease venous return, as is also stated in our article mentioning the same publication. The study by Imai *et al.* shows that methoxamine decreases venous return, but only at high doses. Dr. Butterworth does not mention that in dogs pretreated with a vasodilator, methoxamine increases venous return, ostensibly by reversing vasodilator-induced pooling of blood in the splanchnic vasculature, which again supports our position.

Then, Dr. Butterworth refers to his own study—and misquotes it.⁵ In his letter, he writes, "we found that phenylephrine . . . decreased venous return."⁵ His article, however, states that phenylephrine "had no clear effect on reservoir volume."⁵ Besides, Dr. Butterworth *et al.* studied splenectomized dogs, which are likely to be hypovolemic because of the large blood volume removed with the spleen. They excluded two dogs because of "unexplained metabolic acidosis." If splenectomy caused the hypovolemia, the "unexplained" becomes explicable, *i.e.*, metabolic acidosis from hypoperfusion. After reviewing Dr. Butterworth's data, we understand a source of the confusion. Phenylephrine decreased mean reservoir volume in the highest-dose group but not in the lower-dose groups.⁵ The difference was not statistically significant, in part because of the more variable responses among dogs given high-dose phenylephrine. Ironically, Dr. Butterworth's data support our view that both the dose of α agonist and the degree of hypovolemia determine the net effect of α agonists on venous return.

Dr. Butterworth refers to three more studies^{6–8} to prove that low doses of α -adrenergic agonists decrease venous return. However, in each study, the α agonist increased blood pressure and decreased heart rate, reflecting a baroreflex response. Baroreceptor activation itself dilates splanchnic veins, shifts blood into the splanchnic vasculature, and decreases venous return.^{9,10} The authors of one study⁷ admit that their observation "does not necessarily conflict with the findings that α -receptor stimulation can also result in increased venous return" (page 527). The final reference that Dr. Butterworth cites¹¹ shows that α agonists increase venous reservoir volume, reinforcing our position that α agonists can increase venous return.

References 27 and 33–35 in our original article¹ provide support for our opinion. Many other studies support our position that α agonists can increase venous return^{12–17}; some focus on the matter in dispute. Stokland *et al.*,¹² using a model in which preload was controllable, showed that two thirds of the phenylephrine-induced increase in blood pressure resulted from increased preload, whereas only one third was from increased peripheral vascular resistance. Richer *et al.*¹³ showed that low doses of α agonists increase venous return, whereas high doses decrease it, which directly conflicts with Dr. Butterworth's viewpoint and affirms ours.

The basis for the confusion about α agonists lies in their abilities to constrict splanchnic preportal veins and hepatic resistance veins simultaneously. Constricting the former shifts splanchnic blood to the central circulation; constricting the latter impedes the shift. With high doses of α agonists, the effects on hepatic venous resistance can trap blood within the liver.⁴

Finally, we are happy to note that Dr. Butterworth's letter closes by stressing a key message in our article, namely that "intense vasoconstriction can be detrimental . . . and should not be viewed as a substitute for the immediate replacement of blood volume."¹

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Anesthesia and Multiorgan Protein Remodeling

To the Editor:—I read with particular interest the recent article by Fütterer *et al.*¹ describing both acute and relatively prolonged alteration in the expression of multiple proteins within the brains of rats anesthetized with desflurane. As both the authors and an accompanying editorial² point out, although the functional significance of these observations remains uncertain, the data clearly challenge the common clinical perception that the global effects of volatile anesthetics are effervescent and rapidly reversible.

Although the brain is usually the target organ of clinical anesthesia, other organs are obviously exposed as well, which raises the prospect that persistent subcellular changes may be induced in structures other than the brain. Indeed, previous data indicating that even brief exposure to pentobarbital, propofol, or isoflurane alters immediate-early gene expression in multiple organs of the rat³ suggest that the secondary molecular responses to anesthetics may not be limited to the brain. In this vein, several years ago, we undertook a pilot project to assess whether volatile anesthetics alter expression of proteins regulating excitation-contraction coupling within the heart. Initially proposed as a means to shed light on whether aspects of perioperative management could have influenced results in our clinical study of myocardial remodeling in end-stage human heart failure,⁴ we decided to first examine effects of the prototypical potent volatile agent halothane in a rabbit model. As was previously reported,⁵ ventilation with 1% (0.7 minimum alveolar concentration) halothane in oxygen for 5 h produced a nearly twofold reduction in myocardial expression of the sarcoplasmic endoreticular calcium adenosine triphosphatase type 2a that was associated with a simultaneous time-dependent decrease in left ventricular contractility. In that sarcoplasmic endoreticular calcium adenosine triphosphatase type 2a is a major determinant of both diastolic and systolic function of the heart, molecular remodeling of the protein has been the focus of extensive research in the area of heart failure. In this setting, sarcoplasmic endoreticular calcium adenosine triphosphatase type 2a expression is also decreased, contributing, at least in part, to fundamental abnormalities in myocardial

contraction and relaxation.⁴ Our preliminary observations with halothane and sarcoplasmic endoreticular calcium adenosine triphosphatase type 2a expression lead us to propose the idea that cardiac contractile reserve could be altered postoperatively through a process of “anesthetic-induced myocardial molecular remodeling,” a concept now seemingly supported in principal by the findings of Fütterer *et al.*

As with the elegant work of Fütterer *et al.*, our simple pilot study asked far more questions than it answered; multiple issues related to drug specificity and dose response, mechanisms, duration, and, most importantly, functional significance remain to be sorted out. Nonetheless, the fundamental knowledge that something may be happening within the heart and brain in response to anesthesia that can potentially persist beyond physical presence of the drug is both exciting and intimidating. Only time will tell whether we have entered a truly new era in our understanding of anesthetic pharmacology, but from my perspective, the future looks very intriguing.

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In Reply:—We thank Dr. Heerd for his comments, which support our hypothesis of persisting effects of volatile anesthetics after the end of anesthesia. However, the approaches chosen by Heerd *et al.* and our group were widely divergent.

Heerd *et al.*¹ found changes in the protein expression of the sarcoplasmic endoreticular calcium adenosine triphosphatase subtype 2a in rabbit hearts after 1, 3, and 5 h of halothane anesthesia. This study differs from ours² with respect to animals (rabbits *vs.* rats), volatile anesthetic (halothane *vs.* desflurane), target organ (heart *vs.* brain), and minimum alveolar concentration (0.7 *vs.* 1.0). Another major difference is the killing time, which was immediately after 1, 3, or 5 h of anesthesia in the study of Heerd *et al.*, whereas it was either immediately or 24 or 72 h after 3 h of anesthesia in our study. These different experimental approaches make it difficult to compare both studies directly, although the line of evidence is similar. Interestingly, both findings may be based on a common principle of interaction between drug and protein expression, challenging the current hypothesis of a complete reversibility of the effects of volatile anesthetics.

Because of our strict statistical prerequisites, we cannot exclude that a homologue of sarcoplasmic endoreticular calcium adenosine triphosphatase subtype 2a is also differentially expressed in the brain. Moreover, the technical limits of our approach did not allow us to investigate integral membrane proteins such as sarcoplasmic endoreticular calcium adenosine triphosphatase subtype 2a, because our protocol isolates cytosolic proteins.

Therefore, our current approach follows the line suggested in the editorial by Dr. Hogan.³ Based on our previous exciting findings regarding desflurane anesthesia in the brain, we are currently investigating further volatile anesthetics (*i.e.*, sevoflurane and isoflurane) in different organs (*i.e.*, heart, liver, and kidney) with respect to changes in protein expression profiles of specific tissues.

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Intraservice Time Is Not a Proxy for Operating Room Time

To the Editor:—Dr. Abouleish *et al.*¹ should be commended for their efforts to quantify staffing costs associated with longer-than-average surgical case durations. Identifying these costs and subsequently minimizing their impact may have a salutary financial effect on institutions, such as academic medical centers, where longer case duration is the norm.

In determining “National Average Time” by Current Procedural Terminology procedure, the authors use the intraservice time reported by the Centers for Medicare and Medicaid Services as a proxy for “in-room” time. The Centers for Medicare and Medicaid Services time values are derived from surveys conducted for the American Medical Association-Specialty Society Relative Value Update Committee and the original Harvard Resource-Based Relative Value System studies. In both cases, the intraservice period “includes all ‘skin-to-skin’ work that is a necessary part of the procedure.” Scrubbing, prepping, patient positioning, and waiting are components of the preservice period. Dressing and patient repositioning (*e.g.*, prone to supine) after skin closure is part of the postservice period. All of these activities actually contribute to the total “in-room” time for nearly all surgical procedures.

The authors compared the Centers for Medicare and Medicaid Services intraservice time to the total in-room time obtained from the operating room information systems from the two institutions studied. This calculated time difference is a dependent variable in the additional staffing costs calculated by the authors. Errors in the time data will result in erroneous calculations of staffing costs attributable to longer-than-average duration.

Unfortunately, use of intraservice time as a proxy for operating room time will systematically underestimate national average operating room time because of the exclusion from consideration of all in-room patient time outside of the “skin-to-skin” period. Many procedures, commonly performed in academic medical centers, require time-consuming positioning, skin preparation, and draping, which consume a significant proportion of in-room time. Frequently, anesthesiologists place invasive monitoring devices or insert catheters for postoperative pain management in the operating room. Depending on the practice at the

two academic medical centers studied, these anesthesia interventions may also contribute to in-room time outside of the “skin-to-skin” period.

One other aspect of the methodology also deserves comment. In the Methods section detailing “Surgical Case and Operating Room Data,” the authors note that the surgical Current Procedural Terminology code was obtained from the anesthesia billing database and was the “primary surgical” code for which the anesthesia service was billed. A significant proportion of surgeries involve multiple procedures. Even procedures such as coronary artery bypass grafting or spinal decompression, which would be considered a single surgical intervention to many anesthesiologists, are reported with multiple Current Procedural Terminology codes. By only considering the primary surgical procedure code in determining the intraservice time, the authors have failed to include the intraservice times associated with the Current Procedural Terminology codes also reportable in cases involving multiple procedures. The implication of this choice is a further overstatement of the difference between site-specific and average national time data as defined in the study.

It is our hope that understanding both the definition of a key data element used in this analysis as well as the impact of multiple procedures on total average in-room time will allow the authors to further refine their model, thus resulting in a more accurate and more useful assessment of the impact of longer duration procedures on staffing costs.

Alexander A. Hannenberg, M.D., Norman A. Cohen, M.D.* * Good Samaritan Hospital, Corvallis, Oregon. nacohen@mac.com

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In Reply:—We appreciate the insight provided by Drs. Hannenberg and Cohen into the process used by the Centers for Medicare and Medicaid System to develop the times assigned to each surgical Current Procedural Terminology. Access by Drs. Hannenberg and Cohen, who both have worked with the American Medical Association-Specialty Society Relative Value Update Committee as America Society of Anesthesiologists representatives, clarifies important limitations of our methodology. In our article, we compared Actual In-Room times to “National Average Times” obtained from the Centers for Medicare and Medicaid System database. Because the National Average Times included only skin-to-skin times, whereas we used total in-room times from the contributing institutions, our analysis would systematically overestimate the difference associated with longer surgical times, as suggested by Drs. Hannenberg and Cohen. Unfortunately, the materials provided on the Centers for Medicare and Medicaid System Web site

Table 1. Actual Intraservice Time, Actual In-room Time, and CMS Intraservice Time

	Mean Minutes ± SD
Actual Intraservice	133 ± 114
Actual In-room	146 ± 117
CMS Intraservice	88 ± 69

n = 12,765. Actual Intraservice time is 91% of the Actual In-room time for the academic centers' studies. Intraservice time is defined as “skin-to-skin” time. Comparison of Actual In-room time rather than Actual Intraservice time to the Centers for Medicare and Medicaid (CMS) Intraservice time slightly overstates the differences between these academic centers and the CMS Intraservice time.

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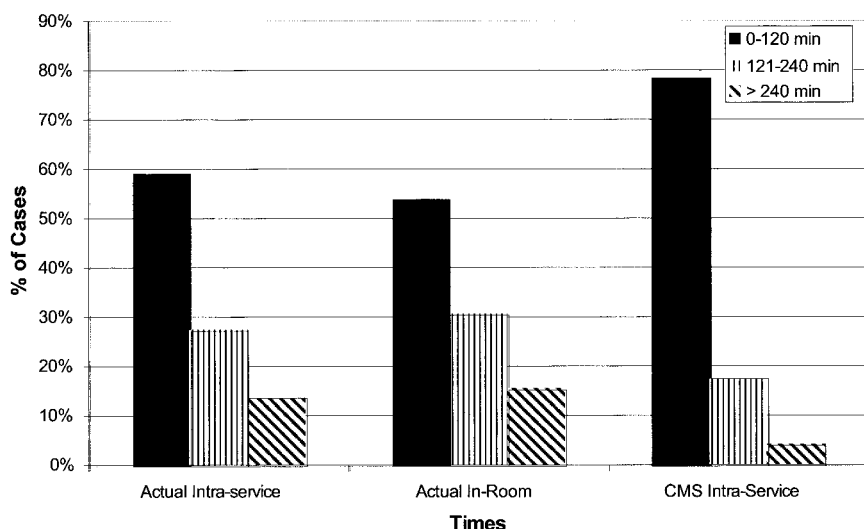


Fig. 1. Distribution of cases by times. The Actual Intraservice and Actual In-Room have similar distributions, with 14–15% of cases with more than 4 h of duration in contrast to 4% of Centers for Medicare and Medicaid (CMS) Intraservice. Intraservice time is defined as “skin-to-skin” time. $n = 12,765$.

with the data^{*} do not specifically define the intraservice times as skin-to-skin.

The obvious question is, “By how much did this analysis overestimate the differences?” To answer this question, we reviewed data from Hospital A comparing case duration (as defined in the study as in-room time) with actual intraservice time (as defined as skin-to-skin time) and Centers for Medicare and Medicaid System National Average Time (also intraservice time). We found that the mean actual intraservice time (133 ± 114 min) represented approximately 91% of the mean actual in-room time (146 ± 117 min) and that the distributions of times were similar (table 1 and fig. 1) Therefore, our systematic error would be approximately 13 min/case.

However, in our study, we set limits to the difference between the actual and average times of 180 and 60 min.¹ As noted in the Discussion of the article, we did this initially to limit the issue of multiple procedures as described by Drs. Hannenberg and Cohen. However, we also believe that use of these limits would reduce the discrepancy due to our use of intraservice time *versus* in-room time for the comparison. Using the 180-min limit, 8% of the cases (1,022 cases) had a duration that was 180 min greater than the National Average Time. With the 60-min limit, 37% of the cases (4,778 cases) had a duration that was 60

min greater than the National Average Time. Therefore, we believe that our cumulative error was less than the apparent 13 min/case.

Unfortunately, the Centers for Medicare and Medicaid System database is one of the only publicly available databases for durations by surgical Current Procedural Terminology. For example, Centers for Medicare and Medicaid System contracted to use a proprietary database to assess the validity of their intraservice times determined by survey information.[†] Therefore, the use of the Centers for Medicare and Medicaid System database has limitations, as we noted in our original discussion of our data. In contrast, the times per anesthesia procedure are actual times billed to Centers for Medicare and Medicaid System and are not based on surveys. These times can be used to evaluate anesthesia times but have limitations in comparing surgical procedures because multiple procedures may be performed even though only one anesthesia code is listed.²

In summary, the purpose of our study was to demonstrate quantification of staffing costs associated with longer surgical durations. We believe that the more precise definition provided by Drs. Hannenberg and Cohen strengthens the value of that demonstration.

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A Word on Hypothermic Preconditioning

To the Editor:—We congratulate Hui-Bih Yuan *et al.*¹ for demonstrating the feasibility of inducing acute preconditioning with mild hypothermia and the adenosine receptors triggering this phenomenon. However, is it truly independent from hypoxia/anoxia, and are two phenomena indeed sharing the same final pathway? Before we can categorically state that hypothermia *per se* is the triggering factor, we must rule in or out the role that bioenergetics might play in activating

adenosine triphosphate-sensitive potassium and adenosine receptors. Having the perfusate oxygenated may not be enough to prove that oxygen was used aerobically to synthesize ~P creatine phosphate by the slice. As pointed out by the authors, although *in vitro* preparations are suited for mechanistic studies, results cannot be extrapolated to *in vivo* conditions; the “protected” time of 20 min of oxygen–glucose deprivation could be far shorter in *in vivo* conditions. Under these

conditions, the anoxia-sensitive blood-brain barrier is broken, and reperfusion is followed by diapedesis, with its consequent deleterious effects of leukocytes on the ischemic neurons. Early (4 h) conventional light microscopy may not discern subtle changes in creatine phosphate or even adenosine triphosphate depletion already jeopardizing viability in a system devoid of leukocytes. It would have been informative if (1) the effluent lactic acid,² glutamate or nitric oxide,^{3,4} lactic dehydrogenase or creatine phosphokinase or (2) the slice creatine phosphate and adenosine triphosphate contents⁵ had been determined before and during preconditioning to assess the role bioenergetics might have had in activating those receptors.

Nevertheless, we credit the authors for further identifying molecular mechanisms involved in neuronal injury and their inhibition by harmless mild hypothermic preconditioning. The fact that in their study the acute hypothermic preconditioning effects lasted for 3–4 h is in accord with the period reported by Benveniste *et al.*³ in which taurine concentrations were increased after ischemia.

The protective mechanisms of taurine, a β amino acid universally present in mammalian tissues, have been attributed to the marked cell membrane effects, nonspecific in nature, acting ubiquitously in the entire body, with the magnitude of such effects depending on the tissue concentration.^{6,7} Taurine is released dose dependently by adenosine in the nonischemic rabbit hippocampus⁸ or during ischemia as part of the naturally protective array of mechanisms triggered by the activation of adenosine triphosphate-sensitive potassium and adenosine receptors in the early stages of ischemia.^{3,6,7} These triggered mechanisms are more or less effective, depending on the subsequent ischemia times, but all aimed at providing protection through different molecular pathways.

We postulate that the mechanistic role the also innocuous taurine may have in preconditioning has been relegated to oblivion but actually might have a role greater than just acute protection. Indeed, taurine used in conjunction with hypothermia potentiated the protective effects of the latter.⁹ Intravenously administered taurine protected the spinal cord of all rabbits ventilated under eucapnic conditions from 60 min of ischemia at 30.6°C, whereas hypothermia at 29.9°C without taurine uniformly failed, and hypothermia at 29.4°C was required to

consistently protect from 60 min of ischemia. These facts also underline the importance of intraschemic temperature and suggest that the beneficial effects of the authors' advocated mild hypothermic preischemic preconditioning are time limited.

We wholeheartedly support the authors' contention of using mild hypothermia to minimize neurologic injury. However, would not it be easier if the same innocuous protection could be readily obtained without having to induce time-consuming hypothermia, or with a lesser degree of hypothermia than that used by the authors, by intravenously administering taurine that would induce hypothermia secondarily? Time constraints might be impractical in the clinical setting.

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In Reply:—We read the letter by Drs. T. A. Miyamoto and K. J. Miyamoto with interest, and we thank them for their interesting discussion of our study. They raised two issues for discussion. First, they wonder whether hypoxia/anoxia is a component of preconditioning stimuli to induce neuroprotective effects that were observed in our study.¹ Hypoxia/anoxia has been reported to produce preconditioning effects on the brain.² However, in our study, the brain slices were kept in a buffer that was gassed with 5% CO₂–95% O₂ during the application of hypothermia. Control slices that were also kept in the oxygenated buffer but without having hypothermic preconditioning were used for comparison. In addition, it is generally accepted that hypothermia reduces cerebral metabolic rate and oxygen requirement. Therefore, we do not expect that brain slices during the application of hypothermia require more oxygen and have worse hypoxia (if it happens) than control slices. Therefore, we believe that the neuroprotective effects that we studied in our article are mainly attributed to hypothermic preconditioning. Of course, we cannot exclude the possibility that hypoxia plays a role in neuronal survival or death in our study. However, we hope that the proper controls performed in our study have isolated the hypothermic preconditioning-induced neuroprotection for us to study.

Drs. T. A. Miyamoto and K. J. Miyamoto then suggest that intravenous application of taurine may be an alternative method for hypo-

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thermic preconditioning to provide neuronal protection against ischemia in clinical practice. This suggestion is interesting and may be practical. However, caution must be executed here because neuroprotection induced by hypothermic preconditioning and taurine are shown only in animal studies,^{1,3} and it is not appropriate to extrapolate these data to humans. Although mild hypothermia that we used in our study is usually safe and easily achievable in clinical practice, more detailed animal studies are needed to show the effectiveness and safety of taurine application for brain ischemia before a clinical trial.⁴ Nevertheless, we should keep our eyes open to any potential neuroprotective agents or methods such as hypothermic preconditioning or taurine application and vigorously test them for potential clinical use.

Very few agents or methods have been shown to be effective and practical against brain ischemia in clinical studies in the field of neuroprotection. However, with studies aimed at the mechanisms of ischemic brain injury and neuroprotective methods, it is hoped that more molecular targets and, therefore, more agents with better selectivity to induce neuroprotection will be identified and tested for clinical use.

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Lack of Tolerance with Propofol in Radiation Therapy Needs Patience

To the Editor:—With the “how will he do that!” anticipation of a child about to see the magician pull the rabbit out of the hat, I read the article by Keidan *et al.*¹ about the absence of tolerance to repeated doses of propofol in children undergoing repeated radiation therapy treatments. Tolerance in this setting has plenty of pharmacologic precedence and reinforces my clinical experience. I finished the article disappointed in the study design and unconvicted of its conclusion.

In their introduction, the authors hypothesize that tolerance should be manifested by a change in depth of sedation, as determined by the Bispectral Index (BIS), to a predetermined, “fixed” dose of propofol administered repeatedly over 6 weeks. Although the hypothesis makes sense, the methods rely on two flawed assumptions, namely that the propofol dose was fixed and that BIS is sufficiently sensitive and reactive to track depth of anesthesia in this clinical scenario. Any available pharmacokinetic modeling program* shows that the bolus plus constant infusion regimen the investigators used does not result in a fixed propofol concentration at the effect site but an ever-changing concentration. Using additional propofol doses at the clinicians’ discretion causes even greater swings in effect site concentrations. Radiation therapy treatments are of short duration and comprise no stimulation beyond airway manipulation, which did not occur in this study. Why did the investigators not titrate the propofol to a predetermined BIS range (40–50) using a target-controlled infusion, *ie*, flip propofol and BIS as the controlled and measured variables, respectively? (Ironically, they mention this reciprocal approach in the first paragraph of the Discussion.) Schmidt *et al.*² and more recently Kreuer *et al.*³ have shown a good correlation between propofol at target-controlled infusion and BIS under steady state conditions. Hoymork *et al.*,⁴ however,

could not confirm this and suggest the reason may be that the correlation may deteriorate during rapid variations and deep levels of anesthesia. BIS nadirs in the 20s and late recovery times around 17 min, with a short context-sensitive half-life agent such as propofol, suggest these patients were deeply anesthetized on induction and thus traversed many planes of anesthesia very rapidly. Titration to a lighter but adequate plane of anesthesia using a target-controlled infusion may place BIS in the linear portion of its relation to the pharmacodynamic effect of propofol at the effect site and will achieve better steady state effect site concentrations. Although BIS has been shown to reflect a concentration–effect relation between propofol and BIS at relatively stable levels, this has not been shown at the enormous variation in dose and BIS levels in this study, thus making the validity of the conclusions questionable.

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* Available at <http://anesthesia.stanford.edu/pkpd>. Accessed June 21, 2004.

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In Reply:—We thank Dr. Overdyk for his comments, which argue that repeated doses of propofol do produce tolerance in children. However, the results of previous work in this field, which were mostly based on clinical criteria alone, are inconclusive.^{1,2} In our study,³ we used the same conventional dose of propofol in all cases and in all the procedures, namely, a fixed dose of 5-mg/kg bolus followed by a continuous infusion of 150 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The option given to the anesthesiologist in charge to administer extra doses of propofol when necessary was rarely used, and the few extra doses that were eventually given were evenly distributed among the 6 weeks of treatment. We did not claim that such a predetermined regimen will result in a “fixed” propofol concentration at the effect site. We did, however, expect that if tolerance had developed during repeated exposures, it would have expressed itself by either a change in Bispectral Index or clinical criteria. We agree with Dr. Overdyk’s suggestion that the use of target-controlled infusion of propofol may have theoretical advantages in conducting such study, although the use of target-controlled infusion in children has not yet been validated. Although it is true that the

Bispectral Index nadirs occurring immediately after the induction of anesthesia were low, they increased rapidly to values of 40–60, as shown in figure 2 in our article. Our results clearly show that in 15 patients, each undergoing a mean of 24 treatments, both the Bispectral Index profiles and all of the clinical criteria did not change and that there was no need to increase the initial conventional propofol dosage.

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Is It in the Episcleral Space or in the Medial Canthal Extraconal Space?

To the Editor:—I was interested to see the article by Nouvellon *et al.*¹ describing their results using the episcleral block technique that was described by Dr. Jacques Ripart. This is an excellent article, but I have a few comments.

In my opinion, the block was not in the episcleral space in the majority of these patients. The authors report that the median depth of needle insertion was 15 mm, with the needle having been inserted posterior to the caruncle. The average eye is approximately 23.5 mm in axial length, which tells us that the tip of the needle was well beyond the equator of the eye (in the frontal plane) in more than half of the patients. With the needle inserted this deeply, I believe that it is anatomically impossible for the needle tip to have remained in the episcleral space. The injections were made into the medial canthal fat-filled space, not into the episcleral space. When the needle depth was only 5–10 mm, it is quite probable that the tip was in the episcleral space. The median volume of anesthetic injected provides further proof of my thesis. When 10 ml anesthetic is injected into the episcleral space, significant and noticeable chemosis occurs 100% of the time, but the authors describe chemosis in only 6 of 2,031 patients.

I am especially worried about the range of needle depth insertion. The deepest reported insertion depth was 35 mm. In my opinion,² a needle longer than 25 mm should never be inserted into this part of the orbit. Even the 25-mm needle should not be inserted to its complete depth, the shoulder of the needle not being allowed to go beyond the

plane of the iris. The reason for this is that the optic canal lies directly at the rear of the medial wall of the orbit. A needle placed aggressively along this wall can reach the optic canal in many patients, resulting in damage to the optic nerve, ophthalmic artery, or both.

Finally, because the majority of injections were made into the medial canthal fat-filled space (in my opinion), why not use a safer route to that space? Husted *et al.*³ described a much safer technique, in which the needle is inserted into the little tunnel that lies between the caruncle and the medial canthus and is advanced parallel and very close to the medial wall. With this technique, there is much less chance of endangering the globe or the medial rectus muscle, and the technique is easy to learn and easy to teach.

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The author has received compensation from coediting a textbook on ophthalmic anesthesia, which is cited in this correspondence.

In Reply:—We thank Dr. Fanning for his interest in our work and for his pertinent comments. We would like to give some responses.

We assume the block we described actually corresponds to a sub-Tenon (episcleral) injection. As we stated in our first article,¹ when we began using this technique, we were convinced that it was another peribulbar approach, similar to the technique of Husted *et al.*² However, after intensive anatomical work,^{3,4} we found that the space of injection was really a sub-Tenon (episcleral) injection rather than a peribulbar (extraconal) or a retrobulbar (intraconal) approach.^{5,6} These anatomical statements are reinforced by the better clinical efficacy of our technique as compared with the peribulbar approach,⁷ which confirms the well-established efficacy of the other approaches of sub-Tenon anesthesia.^{8,9}

Regarding the depth of needle insertion, we agree that it is hazardous to insert a needle into the posterior part of the apex. We advocate not going beyond 15–20 mm to ensure that the needle tip is actually in the sub-Tenon space. In our study, the median depth of needle injection was 15 mm, roughly measured because we used a nongraduated needle. At this depth, we assumed that the injection was in the episcleral space. In our study, the maximum depth of insertion was 35 mm, which is obviously too deep. These blocks (n = 4) were performed at the beginning of the study (all occurred in the first 50 cases).

Sub-Tenon injection frequently produces chemosis. Because the fascial sheath of the eyeball fuses anteriorly with the bulbar conjunctiva, episcleral injection results in subconjunctival infiltration. The occurrence of chemosis is quasi-mandatory in all high-volume sub-Tenon injections, regardless of the route used (needle or blunt canula).⁹ After injection, we

applied an ocular compression using a Honan balloon, which resulted in resorption of the chemosis. In our study, we reported only incidents including persistent chemosis hindering the surgical procedure, not all chemosis observed immediately at the end of injection.

Although it is useful, it is impossible to assume that the technique described by Husted *et al.*² is safer than ours. First, there is a lack of sufficiently powered comparative studies to demonstrate the superiority of one of these techniques in terms of safety. Because of the low incidence of complications such as globe perforation, thousands of patients should be included in such comparative studies. Second, in our technique, we insert the needle tangentially to the sclera, which should prevent perforation. In case of uncontrolled wrong direction of the needle, a point of insertion of the needle located at a greater distance from the globe may result in contact at a 90° angle between the needle and the sclera and may theoretically lead to a perforation more easily than our technique does. Therefore, the main risk factor for perforation is the lack of experience of the physician who performs the block, more than the technique itself.

In conclusion, we are aware that all the techniques requiring a needle insertion into the orbit—including ours—are associated with their own hazards for cataract surgery. If no akinesia is requested, we think that the safest technique is topical anesthesia. If a good akinesia technique is required, sub-Tenon block, regardless of the technique, might be considered because of its efficacy. An effective block may prevent additional injections are thus decrease puncture hazards. Finally, for eye blocks to be efficient and safe, we emphasize the need for anesthesiologists to properly learn and practice them.

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Three Arguments Regarding a Paradigm of General Anesthesia

To the Editor:—I read with interest the article entitled "Consciousness Unbound: Toward a Paradigm of General Anesthesia."¹ The proposal rests on three arguments: (1) There is good evidence that gamma oscillations are implicated in perception (cognitive binding problem) and consciousness; (2) concentrations of general anesthetics sufficient to cause unconsciousness interfere with gamma oscillations; and (3) thus, general anesthetics cause unconsciousness by disrupting gamma oscillations and thus preventing cognitive binding. I would like to offer three comments.

The proposal ignores the alternative, more parsimonious view that gamma oscillations are not necessarily related to higher cognitive processes but are rather simply part of the background activity of the brain, reflecting depolarization of thalamic and cortical neurons,^{2,3} a physiologic condition almost certainly required for consciousness. The background activity view is much less controversial than the cognitive binding proposal and can explain just as well why interference with gamma rhythms leads to unconsciousness. Furthermore, the background activity hypothesis is not incompatible with cognitive binding or other high-level functions that are the subject of much current interest.

The proposal also ignores the possibility that unconsciousness and attenuation or disruption of gamma oscillations are functionally independent effects that both arise from anesthetic action on the brain. Consider the following analogy: When there is pouring rain in London, umbrellas pop up in the streets and car windshield wipers start moving. Would anyone suggest that the two observations are functionally linked?

Finally, I was surprised to see no reference to the early evoked-potentials studies that were the first to demonstrate that general anesthetics attenuate gamma rhythms. Sem-Jacobsen *et al.*⁴ reported in 1956 that thiopental abolishes the electroencephalographic changes

recorded from the posterior sylvian region in response to trains of auditory clicks delivered at rate of approximately 40/s in patients with intracerebral electrodes. Madler and Pöppel⁵ interpreted the anesthetic-induced alteration of the auditory middle latency response as loss of 40-Hz oscillations and suggested that this may explain the disturbance of time perception during general anesthesia. Plourde and Picton⁶ showed that the 40-Hz auditory steady state response provides a reliable measure of anesthetic effect on consciousness. The auditory steady state response may be used to assess the ability of the auditory system to sustain endogenous gamma oscillations.⁷

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In Reply:—I thank Dr. Plourde for his interest in my article, although I disagree with his characterization of my arguments. First, the relation of gamma oscillations and cognitive binding was only one of several potential mechanisms addressed, rather than the singular foundation on which my theory was based. Furthermore, it was not merely gamma activity, but the coherence of gamma activity that was discussed in this context, and it was made explicit that there are data contradicting such coherence as the sole mechanism of information synthesis. Finally, my proposal of general anesthesia as cognitive unbinding was based on evidence of anesthetic effects seen at several different levels of neural

processing (*i.e.*, convergence, assembly, synchrony). For these reasons, the syllogism formulated by Dr. Plourde is flawed.

In terms of the relevance of gamma oscillations, I am unable to reconcile Dr. Plourde's assertion that they are "not necessarily related to higher cognitive processes" and yet ultimately reflect "a physiologic condition almost certainly required for consciousness." The coordinated depolarization of thalamic and cortical neurons could be the foreground rather than the background activity of cognitive neural processes. Indeed, one of the references that Dr. Plourde cites for the "background activity hypothesis" in fact seems to support the alterna-

tive by stating that “the short-scale, discrete synchronization of fast oscillations during waking correlates well with the characteristics of conscious processes in this behavioral state.”¹

As for Dr. Plourde’s assertion that my arguments are undermined by a *post hoc ergo propter hoc* fallacy, I have stated no strict causal relation but rather have offered associated observations. I believe the pursuit of a general theory of anesthesia will necessarily progress from correlation (e.g., general anesthesia is correlated with unbinding) to causation (e.g., general anesthesia causes unbinding) to identity (e.g., general anesthesia is unbinding). Both in the study of anesthesia and consciousness, we are still at the stage of searching for neural correlates, in the hope that they will lead us to a more substantive causal understanding.

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A Sigh Is Not a Sigh, as PEEP Blows By

To the Editor:—The variable ventilation pattern described by Boker *et al.*¹ was certainly thought provoking. Their finding of improved lung function was ascribed to the modulation in tidal volume (using an approximate threefold magnitude change from smallest to largest) despite a constant minute ventilation. They also asserted that they were not just instituting a “sigh” breath, because previous studies showed that “sighs” did not improve lung function.

It seems to me that they were not giving “sigh” breaths but inadvertently using positive end-expiratory pressure. The variable-ventilation computer they used would change the tidal volume to one of 376 prescribed settings, sequentially breath by breath, but by definition, there would be no change in minute ventilation. To do this, the inspiratory and expiratory times of each breath would have to be adjusted to be minute ventilation neutral.

The largest tidal volume used was 14.6 ml/kg and the smallest was 6.4 ml/kg, but the mean was kept at 10 ml/kg. If we take the example of giving a supramaximal breath (14.6 ml/kg) immediately followed by the smallest breath (6.4 ml/kg), we can see that the respiratory rate would have to change from 6.8 breaths/min to 15.6 breaths/min. The total time per breath would decrease from 8.8 s to 3.84 s. The supramaximal expiratory time (assuming an inspiratory:expiratory ratio of 1:2, as stated in the article) should be 5.8 s. However, because the algorithm must shift to the next breath quickly because of the time restraints of the new respiratory rate (15.6 breaths/min), it may only allow 2.56 s of expiratory time (inspiratory:expiratory ratio of 1:2; breath duration of 3.84 s).

Limiting the expiratory time by over 50%, after giving a breath

There is a wealth of literature on the electroencephalographic changes associated with anesthesia, and there were no doubt numerous omissions in my relatively limited article. I very much appreciate those that Dr. Plourde has brought to my attention.

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In Reply:—We thank Dr. Romanoff for his interest in our article. First, we will clarify how the modulation program controls the respiratory cycle. Dr. Romanoff is correct in his understanding that the computer changes tidal volume (V_T) and respiratory rate (RR) according to a file of 376 sequential (not random) settings of normalized rate. The operator sets minute ventilation and RR while in control mode. V_T changes are reciprocal to those of RR as the ventilator functions as a volume divider. Mean V_T (V_{Tm}) is the same as in control mode but has a range of $V_{Tmin} = 0.64V_{Tm}$ and $V_{Tmax} = 1.46V_{Tm}$. The duty cycle of the ventilator (T_I) is fixed while in variable ventilation mode at $T_I:T_E$ (inspiratory time:expiratory time) equal to 1:2. For any given breath within the 376-breath file, the actual respiratory cycle duration = $60/T_T$ with $T_I = 60/T_T/3$ and $T_E = 60/2T_T/3$. Dr. Romanoff’s calculations for the duration of inspiration and expiration for the largest and

volume 146% above the mean, does not allow complete emptying of the alveoli before the next breath, especially in those alveoli with slow time constants. This “stacking” will cause an intrinsic increased end-expiratory pressure or auto-positive end-expiratory pressure. If this is the case, the improvement in oxygenation seen in the study would be due to recruitment and less atelectasis secondary to positive end-expiratory pressure, not to the variability in tidal volume.² The example I used is the most extreme variation in consecutive breaths, but similar changes in the shortening of expiratory time would occur any time the respiratory rate of the subsequent breath was higher than the previous. These changes may even result in an inverse inspiratory:expiratory ratio.

The authors do not mention end-expiratory pressures in their results but may be able to shed some light on this possibility.

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smallest breaths are correct. He errs, however, in the assumption that T_E (or T_I , for that matter) is influenced by subsequent breaths. As the above equation shows, respiratory cycle time for any breath varies only according to V_T , and every breath at that same V_T will have the same T_I and T_E , independent of succeeding or preceding breath size. The “file reading” time for the microprocessor is less than 1 ms as it “reads” the normalized variability file with no discernible effect on duration of either T_I or T_E at any rate.

Could there be an effect of “stacking” leading to “auto-positive end-expiratory pressure” (auto-PEEP) in some of the patients in our study? Certainly this is possible, especially in the case of a series of rapid cycling breaths—when RR is high. However, in this study, the mean RR was set to 10 breaths/min, so the most rapid instantaneous RR was only 14.6 breaths/min. Under the conditions of our experi-

ment, lung function was expected to be abnormal, so it is possible that, as Dr. Romanoff states, there may be alveoli with slow time constants that develop an auto-PEEP effect leading to improved oxygenation. Our protocol did not provide for extrinsic PEEP, and we did not see evidence of auto-PEEP in *post hoc* analysis. Previous work has not demonstrated any auto-PEEP by variable ventilation in animal models.¹ If such an effect is occurring, it is at low levels not associated with increases in mean intrathoracic pressures leading to the deleterious effects on cardiac output and oxygen levels seen with higher levels of extrinsic PEEP.

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Monitoring Direct Thrombin Inhibitors: Time for Standardization

To the Editor:—We congratulate Malherbe *et al.*¹ on their successful management of a complex case requiring urgent cardiac surgery in the presence of acute heparin-induced thrombocytopenia. However, this case serves to illustrate how the irreversibility of direct thrombin inhibitors (DTIs) makes accurate monitoring essential to avoid excessive anticoagulant doses and hemorrhage.

Although hirudin established a role for DTI-based anticoagulation during cardiopulmonary bypass (CPB),² this long-acting agent is being supplanted by the smaller, synthetic DTI agents (argatroban and bivalirudin) with attractive properties including shorter half-lives and less dependence on renal clearance. However, these agents can also have extended pharmacodynamic effects, because CPB can reduce both their hepatic and renal clearance and hypothermia slows the rate of bivalirudin cleavage by thrombin. In addition, given the high plasma concentrations required for conduct of CPB, the duration of residual anticoagulation may be multiple half-lives. This is consistent with the difficulty that the authors described with hemostasis until approximately 3–4 h after stopping an argatroban infusion and our experience with the shorter-acting bivalirudin, despite administering various hemostatic agents.

Our own experience includes a 54-yr-old man with heparin-induced thrombocytopenia presenting for insertion of a left ventricular assist device (Heartmate®; Thoratec Corp., Pleasanton, CA) in the setting of unresponsive cardiogenic shock secondary to idiopathic cardiomyopathy, with acute renal failure and marked hepatic insufficiency. Because of his high titer of heparin-platelet factor 4 antibodies and severe hemodynamic instability, we chose bivalirudin over heparin with prostaglandin infusion despite his renal failure; argatroban was avoided because of hepatic dysfunction. To facilitate the clearance of bivalirudin, we arranged for continuous venovenous hemodialysis and modified ultrafiltration after separation from CPB.

The ecarin clotting time (ECT®; Pharmanetics, Raleigh, NC) is recommended to monitor DTIs³ but was not available, so we monitored anticoagulation with the activated clotting time (ACT) test (maxACT®; Helena Laboratories, Beaumont, TX). Because no guidelines exist for ACT monitoring of DTI during CPB, we calculated an *in vitro* dilution curve that predicted an ACT of approximately 300 s would provide recommended therapeutic drug levels (fig. 1). However, after consideration, we still elected to adopt the more conservative standard target ACT of greater than 400 s during CPB. Even in the setting of hepatic dysfunction, this required high doses (4.5 mg/kg total bolus and 5 mg · kg⁻¹ · h⁻¹), and severe postoperative hemorrhage ensued. The ACT remained above 200 s for more than 4 h after surgery despite continuous venovenous hemodialysis and numerous blood products; bleeding persisted for another 6 h and necessitated re-sternotomy.

Appropriate monitoring of DTI effects remains an unresolved issue, especially because the ECT has limited availability. It is possible that we

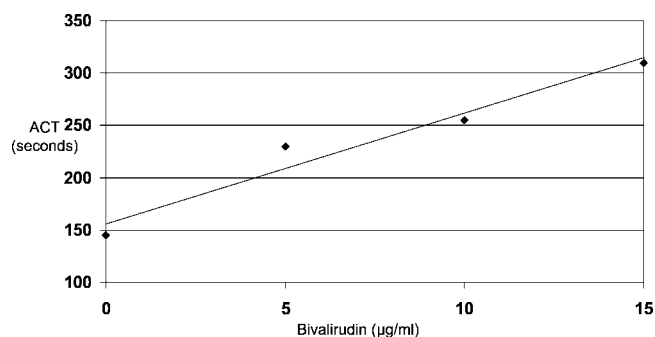


Fig. 1. *In vitro* dilution curve showing the average of duplicate activated clotting time (ACT) values over a 0- to 15-µg/ml range of bivalirudin concentrations. An ACT range of 270–310 s is seen at therapeutic levels (10–15 µg/ml).

and Malherbe *et al.*¹ excessively dosed DTIs to achieve the standard CPB anticoagulation target of an ACT greater than 400 s. As a target value, the safety of 400 s was established for heparin rather than DTI-mediated anticoagulation, using early automated ACT systems with celite blood activation. Compared with ACT systems, the ECT test shows a more linear relation with plasma concentrations of DTIs.⁴ The ECT uses ecarin, a snake venom, to convert prothrombin to meizothrombin, which catalyzes fibrin with resulting clot formation, a reaction sensitive to direct thrombin inhibitors. A target of 400–450 s has been suggested for CPB.⁵ However, 1:1 blood sample dilution with pooled plasma (Pharmanetics) is recommended for ECT monitoring of DTIs because it is dependent on prothrombin levels.⁶ This increased complexity of the ECT test is a practical issue that may limit its application to clinical practice. As part of the care for our patient, we calculated a dose-response curve preoperatively, to assess the effects of bivalirudin on the ACT. Our data (fig. 1) indicate a linear *in vitro* relation between maxACT® and bivalirudin concentration. If this pattern were true among large groups of patients, the standard ACT would rival the ECT test as a more practical way to monitor DTIs. Our data indicated that for our patient, a reduced target ACT range (270–310 s) would have been therapeutic (bivalirudin concentrations of 10–15 µg/ml),⁵ possibly reducing the bleeding complications associated with DTIs. However, it will be essential to establish the relation between each individual DTI and each individual ACT system, because ACT system reproducibility would be crucial with such a narrow therapeutic range, and ACT systems vary in their precision and produce noninterchangeable results.⁷

In summary, it is imperative that the monitoring of DTIs be standardized as the clinical use of these drugs increases. These standards should, ideally, surpass those developed for heparin anticoagulation and be more rigorous than relying on case series.^{2,5} Using biochemical markers of hemostatic activation in addition to clinical endpoints, while encompassing the variability in monitoring technology, provides

The above letter was sent to the authors of the referenced article. The authors did not feel that a response was required. —Michael M. Todd, Editor-in-Chief

us the opportunity to optimize both clinical care and the safety profile of this important group of drugs.

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“Oily” Streak Formation on Aspiration of Cerebrospinal Fluid into Local Anesthetic Solution: Its Significance in the Combined Spinal-Epidural Technique

To the Editor:—The combined spinal-epidural (CSE) technique is performed commonly, either with use of specially designed CSE needles (needle through needle) or with use of separate needles.¹ When normal saline is used for the loss-of-resistance technique to locate and subsequently enlarge the epidural space in preparation for the insertion of an epidural catheter, an unusual problem may occur. We observed that the subsequent identification of subarachnoid space might be misleading because the saline used earlier for localizing the epidural space may flow into the spinal needle before it enters the subarachnoid space and be mistaken for cerebrospinal fluid (CSF). Although various methods, such as testing for glucose, protein, and pH, can be used to distinguish between CSF and saline,^{2,3} immediate confirmation is achieved by noting the temperature of the fluid and by noting the typical “oily” appearance of the CSF as it mixes with local anesthetic (LA) solution while spinal block is being performed. However, we noticed that in a few CSE blocks, the spinal block was not effective despite this oily appearance.

To determine the reliability of the oily appearance as a means of accurately identifying CSF, we aspirated CSF and normal saline separately with 26-gauge spinal needles into glass syringes loaded with either plain or hyperbaric (containing 80 mg/ml dextrose) 0.5% bupivacaine solutions, respectively. We observed that on aspiration into hyperbaric LA solution, CSF and saline both looked oily and were grossly similar in appearance. However, this appearance was not visible with CSF or saline on aspiration into plain LA solution. The identical oily appearance with saline could be the reason for inaccurate placement of hyperbaric 0.5% bupivacaine into the epidural space, thus leading to failure of spinal anesthesia in some of the CSE blocks.

To distinguish between the two, we carefully observed oily patterns produced by CSF and saline. We noticed that CSF produced a clearly visible central and straight streak (the length of the streak was determined by the rate of aspiration, *i.e.*, longer on fast aspiration) that gradually moved upward (fig. 1), whereas normal saline produced a short, hazy, oily pattern that rapidly moved upward without central streak formation (fig. 2) (to highlight the oily appearance, we show CSF and saline stained with a trace of gentian violet in the figures). With the naked eye, these observations were better appreciated from the side view of the glass or transparent plastic syringe. We showed these findings to 20 anesthesiologists in our department, and all of them were able to differentiate between CSF and saline by their different oily patterns.

The typical oily appearance can be explained by the Schlieren effect, a physical phenomenon based on varying refractive indices of a transparent medium.⁴ CSF and normal saline have refractive indices that are different from that of hyperbaric 0.5% bupivacaine solution, which contains dextrose. Hence, any change in the refractive index of hyperbaric LA solution in a glass syringe, as a result of CSF or normal saline aspiration, causes part of the light beam passing through it to be refracted, making this part of the LA solution appear brighter or darker than the rest of the background, thus causing the typical oily appearance. This oily appearance is not well appreciated by the naked eye with plain 0.5% bupivacaine solution because it does not contain dextrose and its refractive index is closer to that of CSF and normal saline.

The formation of a typical central streak with CSF and not after normal saline being aspirated into hyperbaric 0.5% bupivacaine solution can be explained by the different specific gravities of these substances. Normal saline, with a specific gravity of 1.0003, is much lighter than CSF, with specific gravity of 1.00059, which is closer to that of hyperbaric 0.5% bupivacaine (specific gravity 1.0227).^{5,6} Hence, aspiration of saline into hyperbaric LA solution produces an oily haze that immediately floats upward, without central streak formation.

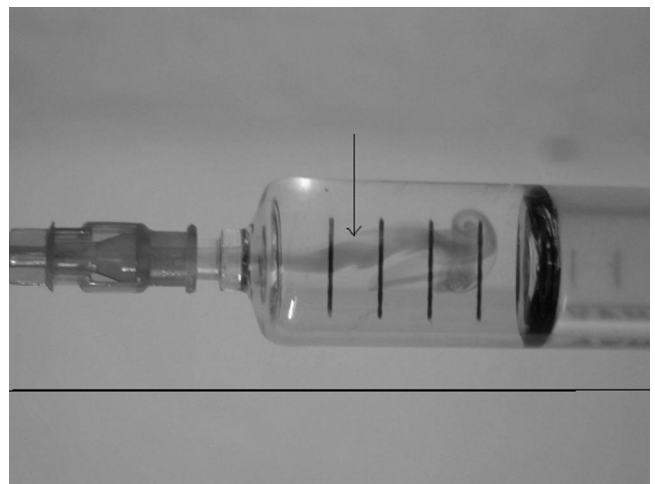


Fig. 1. Central “oily” streak formation on aspiration of cerebrospinal fluid into hyperbaric 0.5% bupivacaine solution.

Support was provided solely from institutional and/or departmental sources.

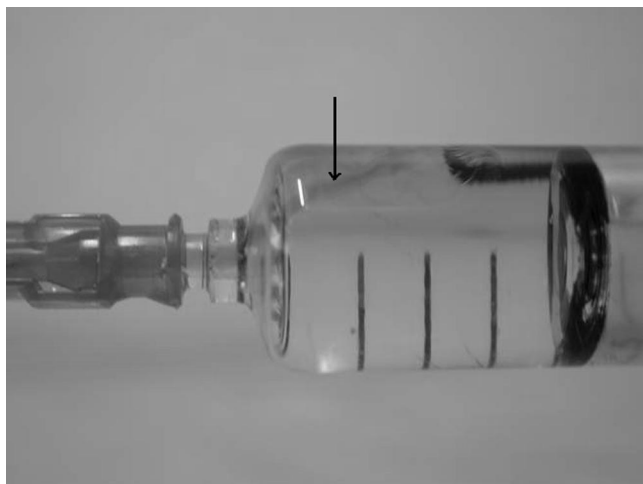


Fig. 2. "Oily" haze floating immediately upward on aspiration of normal saline into hyperbaric 0.5% bupivacaine solution.

In conclusion, both CSF and normal saline produce a typical oily appearance on aspiration into hyperbaric 0.5% bupivacaine solution, and it is important to distinguish between the two by identifying the

characteristic streak pattern of CSF before placing the spinal anesthetic during the CSE technique.

The authors thank Vipul Nanda, M.S., M.Ch. (Assistant Professor, Department of Plastic Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India), for his contribution of photography.

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When Patients Follow Commands

To the Editor:—Recently, a 40-yr-old otherwise healthy man was undergoing a nephroscopy in the prone position under monitored anesthesia care. In the middle of procedure, as the urologist advanced a fiberoptic instrument into the ureter, the patient complained of severe pain. The anesthesiologist proceeded to administer 50 μ g of fentanyl and shortly thereafter instructed the patient to take a deep breath. Moments later, the oxygen saturation dropped from 100% to 95%.

The anesthesiologist again asked the patient to take a deep breath to

which the suffering man responded "I did" in a soft but strained voice. The oxygen saturation continued to drop and the anesthesiologist once again instructed the patient to take a deep breath. By this time the saturation had decreased to 89% and the concerned anesthesiologist told the patient in a loud and commanding tone "take a deep breath." An angry and exasperated patient then exhaled and responded, "I did . . . and I was still holding it!"

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Learning Aid for Geometric Relations of Cardiac Valves

To the Editor:—Although transesophageal echocardiography has been integrated into clinical training of anesthesiology, it is not easy to understand the geometric relations of cardiac valves. We suggest use the hands to memorize the geometric relations of four cardiac valves.

Grip both hands in the position M and T as shown in figure 1. The mitral valve is the most posterior cardiac valve, whereas the tricuspid valve is located anterior and to the right of the mitral valve. These two valves are of similar size. The mitral valve has two leaflets (anterior and posterior), and each leaflet has three scallops, from anterolateral to posteromedial (A1, A2, A3, P1, P2, P3). The tricuspid valve has three cusps (anterior, posterior, and septal).

Move right hand from position T to A as shown in fig. 1. The aortic valve has three cusps (the left coronary cusp, the right coronary cusp, and the noncoronary cusp). The aortic valve is smaller than the mitral

valve and is located anterior and to the right of the mitral valve. It attaches to the mitral valve between the noncoronary cusp and the left coronary cusp. The right coronary cusp is the most anterior cusp of the aortic valve.

Move left hand from position M to P, as shown in fig. 1. The pulmonary valve is located to the left and anterior to the aortic valve. It has three cusps (anterior, right, left). It is attached to the aortic valve between its left and right cusp. These two valves are approximately the same size.

These relations can be useful to remember cardiac valves and each structure for transesophageal echocardiography beginners.

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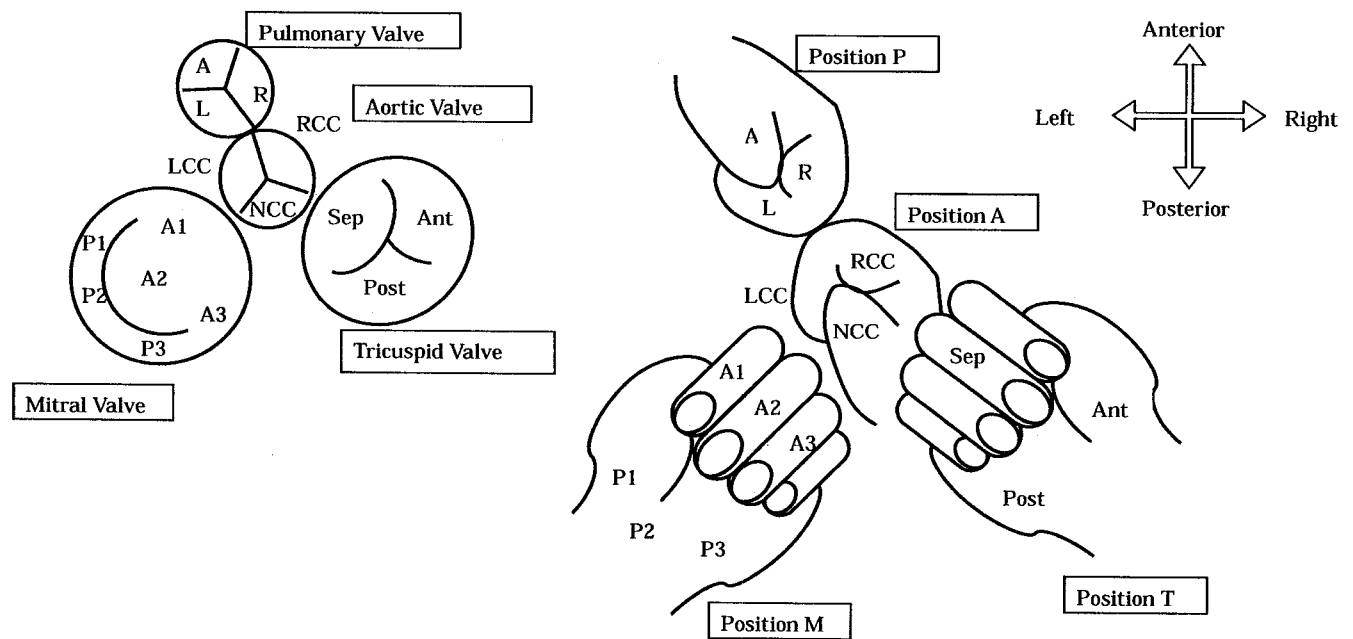


Fig. 1. Schematic drawing of four cardiac valves (anatomic view). *A1, A2, A3*: *A1, A2, A3* = scallops of anterior mitral valve leaflet; *P1, P2, P3*: *P1, P2, P3* = scallops of posterior mitral valve leaflet; *Sep* = septal cusp; *Post* = posterior cusp of the tricuspid valve; *LCC* = left coronary cusp; *RCC* = right coronary cusp; *NCC* = noncoronary cusp of the aortic valve; *A* = anterior cusp; *R* = right cusp of pulmonary valve; *L* = left cusp of pulmonary valve.

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Amateur Dentistry and the Anesthesiologist

To the Editor:— In the last 2 months I have encountered two cases in my personal practice in which objects had been cemented into the mouths of patients using cyanoacrylate cement (“super glue”) to conceal missing teeth and improve cosmetic appearance. In both cases the objects were dislodged during manipulation of a laryngeal mask airway (LMA). Before anesthesia, neither patient admitted to the presence of these objects in response to my direct question “Do you have any removable dental work in your mouth?” Either they did not consider the object removable or vanity or embarrassment kept them from mentioning it.

The first case was a 53-yr-old female presenting for an orthopedic procedure. At the end of an uneventful procedure, the LMA was removed at the appropriate time during emergence. As the LMA was removed, something that did not appear to be secretions was seen to fly from the mouth. A broken-off natural tooth was found on the bed next to the patient’s head. An inspection of the patient’s dentition revealed a gap where the left second upper incisor was missing, but this gap was well healed and there was no remaining root. After the patient was in the postanesthesia care unit, the tooth fragment was presented to the patient’s family. Her sister stated, “Oh, she will be so embarrassed! She has been gluing that in for a year.”

The second case was a 40-yr-old female presenting for a gynecological procedure. After induction, the index finger of my left hand was placed against the inner surface of the upper teeth to aid in opening the mouth as the LMA was inserted. I was dismayed to feel one of the teeth “give” under pressure and become dislodged. On recovery, the “tooth” was found to be a flat, curved fragment of plastic material that the nurses in the room felt was shaped from a white artificial fingernail. From residual glue on the adjacent teeth, it was evident that this had been attached to the short brown remnant of the root of the left second upper incisor and to the sides of the adjacent teeth. This had presented an excellent cosmetic appearance during my cursory evaluation of the patient dentition. Had the LMA been inserted without placing my finger in the mouth, this object could easily have been dislodged without my knowledge. Interestingly, the nurse who had prepared the patient for surgery had been told by the patient that a tooth had been glued in place. This was in response to the same question to which I had earlier received a negative response. Efforts to contact the patient for further information have been unsuccessful.

The occurrence of two such incidents in one practice in so short a time suggests that this practice may not be uncommon and that we should be aware of this possibility. A search of the Internet under “super glue tooth” reveals a number of articles relating to this practice, including specific directions on such dental repair,* an anecdote of a patient gluing a tooth before cesarean delivery,† and a hazardous business opportunity.‡

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* <http://members.cox.net/cosmicrat/t5dental.htm>. Accessed June 11, 2004.

† <http://denturesquest.tripod.com/dentures/background.html>. Accessed June 11, 2004.

‡ <http://www.sparkletoothjewellery.com/>. Accessed June 11, 2004.

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A Novel Maneuver Used to Rule Out Intraarterial Placement of the Introducer Sheath in a Patient with an Ipsilateral Mature Forearm Hemodialysis Fistula

To the Editor:—We present a case of a patient with a mature forearm arteriovenous hemodialysis fistula ipsilateral to the site of insertion of the venous central line before a coronary artery bypass operation.

To differentiate the inadvertent insertion of a venous central line into the carotid artery in a patient with an ipsilateral arteriovenous fistula, we have utilized a novel maneuver that has not been described before.

Since the early description of the percutaneous cannulation of the internal jugular vein in the late 1960s by English *et al.*,¹ the internal jugular vein has become the central vein of choice among anesthesiologists because of its constant anatomy, accessibility intraoperatively, and lower incidence of associated pneumothorax. However, this venous access has been associated with many acute and long-term complications, the most frequent of which is inadvertent puncture of the carotid artery.

Our case is a 66-yr-old woman with a history of severe peripheral vascular and cerebrovascular occlusive disease and end-stage renal disease on hemodialysis *via* a mature left forearm arteriovenous fistula who presented with symptoms of congestive heart failure and respiratory distress. Ejection fraction was 35% with moderate systolic dysfunction. Coronary angiography showed severe multivessel coronary artery disease with diffuse heavy calcification of coronary arteries and aorta. The left anterior descending coronary artery was occluded, the circumflex was small, and the right coronary system was diffusely diseased.

The coronary lesions were not amenable to percutaneous intervention, and the patient was referred for coronary artery bypass grafting. An off-pump coronary artery bypass graft approach was preplanned.

A venous central line insertion was planned for introduction of a pulmonary artery catheter for hemodynamic monitoring. Right internal jugular and right subclavian vein cannulation was not feasible because of significant hematoma provoked during previous attempts of venous central line insertions while in the intensive care unit.

A 9-French introducer (Arrow International, Reading, PA) was placed without difficulty into the left internal jugular vein. Bright blood at high pressure was encountered with that cannulation. To exclude the possibility of arterial puncture, a pressure transducer was connected to the catheter and wave form was displayed on a monitor. The mean pressure was approximately 30 mmHg. A sample of blood, which appeared arterial by gross color inspection, was drawn from that line and submitted for blood gas analysis. The PaO₂ measured 106 mmHg. The PaO₂ in a blood sample obtained from the femoral artery for comparison was 297 mmHg. The possibility of left internal jugular vein puncture with subsequent inadvertent carotid artery cannulation could not be excluded. Another possible source of well oxygenated blood and modestly high pressures obtained from the newly placed line was a high output arteriovenous fistula ipsilateral to the side of the central line, which resulted in significant admixture near the line entry site.

To verify venous cannulation and reject possibility of inadvertent arterial puncture, digital pressure was applied on the venous limb of the arteriovenous fistula. The observation of immediate disappearance of the high pressure wave form from the monitor confirmed a venous-only cannulation.

A 7.5-French pulmonary catheter (Swan-Ganz; Edwards Lifesciences Corp., Irvine, CA) was then placed through the venous introducer

without difficulty. The patient underwent a two-vessel off-pump coronary artery bypass graft operation without complications. She was discharged from hospital on the fourth postoperative day. The internal thoracic artery was not used as one of the bypass grafts because of the risk of a flow steal phenomenon (dialysis access-associated steal syndrome) and potential for venous hypertension in the internal thoracic artery pedicle.²⁻⁴

This resultant phenomenon and consequences of arterialized blood within close proximity to a potential central venous cannulation site should also be considered when selecting the site for the insertion of a central line in patients with a high output upper extremity arteriovenous fistula. Percutaneous cannulation of the internal jugular vein is common practice in surgical patients undergoing open heart procedures. Although is regarded as a safe procedure, a complication rate of 2-13% has been reported.^{1,5-7} The most common complication is inadvertent puncture of the carotid artery with a resultant hematoma.⁸ Simple compression has been reported to provide hemostasis; however, systemic heparinization before cardiopulmonary bypass can result in serious complications.⁹

In the case presented, it is clear that the existence of a high output arteriovenous fistula was the confounding factor in determination of appropriate venous cannulation. The maneuvers employed to rule out an arterial puncture: transduction of the pressure and wave form onto a monitor, comparison of arterial and venous blood sample colors, and blood gas analysis, have been described by different authors.^{10,11}

To our knowledge the description of simple application of digital pressure on the fistula observing simultaneously the disappearance of the pressure wave form from the monitor has not been previously described.

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Detection of Gas Embolism by Bispectral Index and Entropy Monitoring in Two Cases

To the Editor:—Bispectral index (BIS) and entropy measure electroencephalographic voltage between electrodes placed on the forehead. BIS is used to monitor and quantify depth of hypnosis¹ and to guide anesthetic drug administration during general anesthesia.² Entropy assesses loss of consciousness by the quantification of the degree of spatial and temporal integration of cerebral neuronal activity.³ An entropy monitor has been introduced recently; it provides two indices, state entropy and response entropy, that decrease in healthy volunteers receiving propofol with a brief intervening period of wakefulness⁴ and in surgical patients during propofol anesthetic induction.⁵

We report two cases of perioperative gas embolism encountered during laparoscopic surgery while patients were being monitored simultaneously by BIS (Aspect A-2000 XP®, version 3.11; Aspect Medical Systems, Newton, MA) and entropy of electroencephalogram (S/5™ M-Entropy plug-in Module; Datex-Ohmeda Company, Limonest, France).

In our first case, an 83-yr-old man was scheduled for a laparoscopic hemicolectomy under general anesthesia. Target-controlled infusion of propofol and remifentanyl was achieved using a computer-assisted infusion device⁶ while atracurium was administered continuously after a bolus. Standard monitoring was used as was BIS and entropy monitoring. Pneumoperitoneum was achieved with carbon dioxide. The first 90 min of anesthesia and surgery were uneventful. Suddenly, BIS and entropy indices dropped to zero as shown in figure 1. Partial pressure of end-tidal carbon dioxide decreased a few seconds later from 28 mmHg to 19 mmHg and arterial hypotension of 80/45 mmHg was noted (it was previously 149/85 mmHg). The surgeon reported no bleeding. Gas embolism was suspected, and the dramatic change in electroencephalographic-derived indices led to immediate exsufflation and conversion to laparotomy. BIS and entropy remained at low values for approximately 25 min with almost 100% burst suppression even after hemodynamic stability was restored. The colectomy was completed, the anesthetic was discontinued, and the patient awoke. Neurologic examination was performed and was normal. Transesophageal echocardiography performed the day after surgery confirmed a patent foramen ovale.

In our second case, a 46-yr-old woman was scheduled for a laparoscopic cholecystectomy. Anesthesia and monitoring were similar to case 1. Shortly after the onset of carbon dioxide insufflation, partial pressure of end-tidal carbon dioxide suddenly decreased from 32 to 10 mmHg and arterial pressure decreased to less than 60 mmHg. BIS and entropy values decreased to approximately 20 and the burst suppression ratio was 80% within seconds. Laparoscopy showed a tear in the surface of the liver. The pneumoperitoneum was immediately exsufflated, and a laparotomy was performed. BIS and entropy values regained their former values within 5 min, but arterial pressure and partial pressure of end-tidal carbon dioxide remained low for 15 min. Cholecystectomy was performed. Transesophageal echocardiography performed during anesthesia revealed no septal defect. Anesthesia was discontinued at the end of the procedure and the patient awoke. Neurologic examination was normal.

Sudden decreases in BIS have been reported at the onset of clinical deterioration. England was the first to describe the changes in BIS during a hypovolemic cardiac arrest.⁷ An acute decrease in BIS can

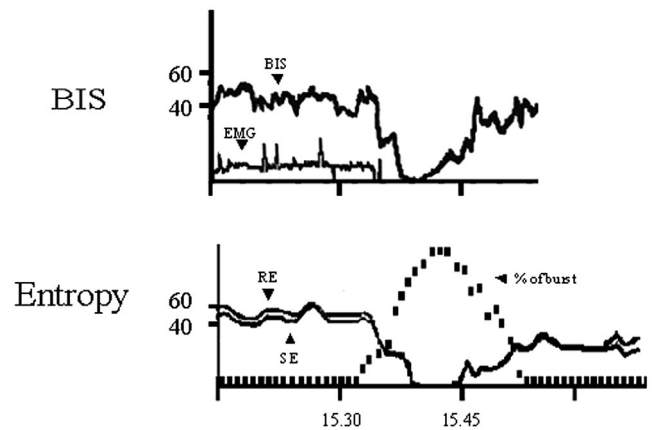


Fig. 1. Drawing from screenshots of Bispectral index (BIS) and entropy monitors during gas embolism (case report 1). *Upper part*, BIS and EMG (electromyographic activity). *Lower part*, response entropy (RE), state entropy (SE), and percentage of burst suppression ratio (% of burst).

reflect cerebral hypoperfusion⁸⁻¹⁰ or cerebral embolization.¹¹ An alternative explanation for an acute decrease in electroencephalographic-derived indices is an increase in plasma concentration of an anesthetic drug, especially propofol, as a result of rapid alteration of its elimination.¹²

Our two cases showed simultaneous acute and profound decrease of BIS and entropy indices that forced the anesthesiologist to react quickly. After verification of good signal quality, the low level of electromyogram, the stability of anesthetic drug concentrations and the absence of acute bleeding, the diagnosis of gas embolism was made; this is a known complication of laparoscopic surgery. Using transesophageal echocardiography, a very sensitive method of detection, Derouin *et al.* reported gas embolism in 11 of 16 patients undergoing laparoscopic cholecystectomy.¹³ The clinical impact of gas embolization can be as serious as cardiac arrest;¹⁴ however, in most instances there are no lasting effects, probably because of the high solubility of carbon dioxide bubbles. Electroencephalographic monitoring modified the surgical and anesthetic management in our two cases. The chronology of events varied between the cases. In the first case, carbon dioxide bubbles reached the brain very rapidly through the patent foramen ovale; BIS and entropy values decreased before any significant changes in other parameters. Other methods of early detection of paradoxical gas embolism have been reported during laparoscopic cholecystectomy; by transesophageal echocardiography¹⁵ and by transcranial Doppler.¹⁶ In our second case, in which a patent foramen ovale was ruled out, the decrease of BIS and entropy was observed after hemodynamic and respiratory parameters changed and was transient, reflecting a decrease in cardiac output as a result of gas embolization.

Finally, anesthesiologists should be aware of the potential for venous gas embolization during routine laparoscopic procedures; BIS or entropy monitoring may play a role in early detection and could complement routine monitoring.

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The M-Entropy plug-in Module S/5™ and electrode sensors were provided without charge from the Datex-Ohmeda Company (Datex-Ohmeda, Limonest, France).

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