

Vascular Thrombosis Associated with Aprotinin and Deep Hypothermic Circulatory Arrest: Where Are We in 2006?

To the Editor:—I read with great interest the recent report by Shore-Lesserson and Reich¹ detailing diffuse venous thromboembolism in the setting of aprotinin and adult deep hypothermic circulatory arrest. To my knowledge, this is the first reported case of venous thrombosis associated with aprotinin and adult deep hypothermic circulatory arrest in the era of adequate heparinization, as defined by standard-of-care activated clotting time and heparin levels. This case report adds to the recent reports of arterial thrombosis (both pulmonary and systemic) associated with aprotinin in adult cardiac surgery with or without deep hypothermic circulatory arrest.^{2–4}

Therefore, significant life-threatening thrombosis is possible throughout the cardiovascular system during complex cardiac surgery in the setting of aprotinin, despite standard-of-care heparinization. It seems to be uncommon, as evidenced by randomized controlled trials.⁵

Conceptually, perioperative vascular thrombosis could cause mortality in the intraoperative or postoperative period. The case reports describe intraoperative death in this scenario.^{1–4} The possibility of death and/or serious morbidity in the postoperative period from vascular thrombosis associated with aprotinin has recently been raised.^{6,7}

Massive vascular thrombosis associated with aprotinin in complex cardiac surgery is rare, but real and catastrophic. The common factor in all the case reports is the onset during or shortly after heparin reversal with protamine, heralded by hemodynamic collapse and ventricular failure.^{1–5} There may or may not be an identified prothrombotic risk factor including factor V Leiden.¹ Clearly, there is a net prothrombotic effect achieved during or after heparin reversal, triggering disseminated major acute intravascular thrombus. On the basis of the existing reports, further clarification of the mechanism is conjecture. However, it is also clear that this phenomenon is not only possible with aprotinin but also with aminocaproic acid.^{4,8}

In complex cardiac surgery, pharmacologic dampening of fibrinolysis reduces allogeneic transfusion and mediastinal reexploration for bleeding, an independent predictor for perioperative mortality.⁹ There is, however, a small but important risk of catastrophic cardiovascular thrombosis in the setting of antifibrinolytic exposure, despite standard-of-care anticoagulation with heparin (monitored by activated clotting time and/or heparin level).

How do we balance these risks? Should the criteria for heparin-based anticoagulation be refined? If so, how and based on what evidence? What about the role of possible concomitant antithrombin deficiency?¹⁰ Should patients be screened for underlying procoagulant conditions such as factor V Leiden?^{1,8,11} How are all of these considerations modified in the presence of direct thrombin inhibitors, given their arrival as alternatives to heparin for clinical anticoagulation and suppressive effects on thrombin generation?^{12–14} What is the clinical significance of aprotinin's effect on protein C activity?¹⁵

These case reports together ask many important questions. There is an imperative for further data, not only an international registry but

also further clinical trials, to balance the benefits and risks of antifibrinolytics in complex cardiac surgery with cardiopulmonary bypass. The BART study (*blood conservation using antifibrinolytics: a randomized trial in a cardiac surgery population*)* is an important step in this direction.

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* International standard randomized controlled trial number register (ISRCTN). ISRCTN No. 15166455. Available at: www.controlled-trials.com. Accessed November 20, 2006.

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Thrombosis after Hypothermic Circulatory Arrest for Cardiovascular Surgery, Antifibrinolytic Drugs, and Thrombophilia

To the Editor:—We read with great interest the report of Shore-Lesserson and Reich¹ regarding a fatal case of venous thromboembolism during cardiac surgery with hypothermic circulatory arrest associated with the use of aprotinin in a patient diagnosed, with postmortem analysis, as a carrier of factor V Leiden. The same authors had previously described two fatal cases of intraoperative thrombosis in patients undergoing the same surgical procedure and treated with ϵ -aminocaproic acid: One of the two patients was a postmortem-diagnosed carrier of the factor V Leiden mutation.² Because of the occurrence over a 3-yr period of four fatal thrombotic events in cardiovascular patients operated on with hypothermic circulatory arrest and treated with antifibrinolytic drugs, the authors of these reports are now screening for the factor V Leiden mutation all patients scheduled to undergo elective surgical procedures requiring hypothermic circulatory arrest to avoid the use of antifibrinolytic drugs in patients who are carriers of the mutation.

It has been proposed to classify the major hereditary prothrombotic conditions in two major groups, including hereditary deficiencies of natural anticoagulants and hereditary disorders associated with increased function of coagulation factors.³ The factor V Leiden mutation, which renders activated factor V resistant to proteolysis by activated protein C, belongs to the second group of inherited prothrombotic conditions and is frequently observed in white but not in Asian or African people.⁴ Whereas many subjects with deficiency of natural anticoagulants experience venous thromboembolism before the age of 60 yr, only a minority of factor V Leiden carriers will ever develop thromboembolic events.³ If factor V Leiden plays a contributory role in the development of intraoperative thrombosis in patients undergoing cardiac surgery with hypothermic circulatory arrest and receiving antifibrinolytic drugs, then patients with deficiency of natural anticoagulants should be at even greater risk, also given the effect of hemodilution. In addition, screening for the prothrombin G20210A mutation should also be recommended, because the associated hyperprothrombinemia has been shown to inhibit plasma fibrinolysis through a thrombin activatable fibrinolysis inhibitor-mediated mechanism.⁵ On a cost-benefit basis, screening of the general population for thrombophilia defects is ineffective, and it is currently a matter of debate whether such screening should be performed even in patients with venous thromboembolic events.⁶ In the absence of evidence-based data, caution against screening for factor V Leiden patients undergoing cardiovascular surgery with hypothermic circulatory arrest has already been suggested.⁷ Before depriving patients at high risk for bleeding of the

proven antihemorrhagic effect of antifibrinolytic drugs,^{8–10} we suggest the institution of an international registry of severe thrombotic complications occurring during cardiac surgery to study the prevalence and the possible causes of this surely underestimated phenomenon. If thrombophilia plays an important role, one would expect history of thromboembolism to be associated with an increased occurrence of this devastating complication of cardiac surgery.

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In Reply:—We are pleased to respond to the comments that address our case report “A Case of Severe Diffuse Venous Thromboembolism Associated with Aprotinin and Hypothermic Circulatory Arrest in a Cardiac Surgical Patient with Factor V Leiden.”¹ We agree with Dr. Augoustides that thrombosis after cardiac surgery is a rare event, yet often fatal. When it is reported, it is temporally related to the reversal of heparin with protamine, presumably because the anticoagulant effect of heparin therapy is being neutralized and thus any “protective” effect from thrombosis is removed. Dr. Augoustides’ suggestion that this may be the first report of venous thrombosis in association with

antifibrinolytic therapy is true with respect to the published literature; however, we know this complication to be dramatically underreported. Furthermore, it remains to be proven that thrombosis of the pulmonary artery is truly “arterial” pathology. Often, this complication is the result of venous thromboembolic phenomena that present as pulmonary thromboembolism.

The sheer volume of cardiac surgical procedures that are performed using antifibrinolytic therapeutic agents where no occult thrombosis occurs, further affirms the hypothesis put forth. That is, when life-threatening thrombosis occurs in association with cardiac surgery and

antifibrinolytic therapy, there should be some other hypercoagulable predisposition responsible for tipping the balance in favor of thrombosis. This delicate balance between bleeding and thrombosis is steadied by procoagulant factors, anticoagulant factors, fibrinolysis, and platelet-related factors. Many of these previously undiagnosed adverse thrombotic outcomes are now prospectively being identified as heparin-induced thrombocytopenia type 2, as a result of better diagnostic techniques.² This addresses Dr. Augoustides' question regarding the use of direct thrombin inhibitors. We would agree that better suppression of thrombin formation coupled with the avoidance of heparin would reduce the occurrence of many of these adverse thrombotic events.³ The suggestion for an international registry for reporting of thrombotic events is commendable and would be supported by us. An international registry for deep hypothermia and circulatory arrest is also currently under investigation.

We also embrace the comments of Dr. Casati *et al.* in that they have also suggested a registry for the reporting of adverse thrombotic events. However, we do continue to support the screening of elective deep hypothermia and circulatory arrest patients in our institution. This represents a very small subset of cardiac surgical patients at any institution.⁴ The cost is therefore not prohibitive, and the accuracy of testing is extremely high. Both the factor V Leiden mutation and the prothrombin mutation G20210A occur with a prevalence of 1–8% in the European population and are even less prevalent in Asian and African-American persons. Therefore, the number of patients identified as positive will be small. Donahue *et al.*⁵ have shown that patients with factor V Leiden can undergo cardiopulmonary bypass safely even with the use of antifibrinolytic drugs. In fact, these patients have less bleeding and may not need the benefit of antifibrinolytic agents, irrespective of the safety of this practice.⁵ Therefore, the question arises: Is a patient with a genetic predisposition to hypercoagulability one that would be considered to benefit from the use of antifibrinolytic agents?

Dr. Casati *et al.* suggest that patients with a deficiency of anticoagulant activity would be at greater risk than those with an excess of procoagulant activity due to hemodilution. We do not necessarily agree with this conclusion and think that it is difficult to conjecture which groups of patients would be at highest risk for thrombosis. The

hemostasis system is rich with feedback mechanisms and protective pathways that act as fail-safe mechanisms to ensure normal clotting. When a patient has excess thrombotic activity, it is the fibrinolysis system that acts to restore the balance. If fibrinolysis is inhibited, coagulation can proceed unchecked.^{6,7} However, a patient with deficient fibrinolysis (such as PAI-1 excess or the prothrombin mutation G20210A) already has ineffective fibrinolysis and thus relies on other functional anticoagulant pathways that are not pharmacologically inhibited to restore the balance. In cardiac surgical patients where the perturbations of the hemostasis system are extreme, we support that patients with a history of hypercoagulability should be screened so that appropriate hematologic management can be instituted.

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Association of High Tidal Volume with Postpneumonectomy Failure

To the Editor:—I read with interest the article titled “Intraoperative Tidal Volume as a Risk Factor for Respiratory Failure after Pneumonectomy” by Fernández-Pérez *et al.*¹ This is an important article because the traditional approach to one-lung ventilation has been to deliver 10–12 ml/kg tidal volume.² As the authors pointed out, two previous studies reported that high intraoperative airway pressures during one-lung ventilation were associated with postoperative acute lung injury.^{3,4} The study by Fernández-Pérez *et al.*¹ showed that larger tidal volumes were associated with a higher risk of postoperative respiratory failure. However, the largest tidal volume recorded on the chart was used in the analysis. This would most likely have been during two-lung ventilation, even if the tidal volume had been reduced during one-lung ventilation. If the tidal volume is not adjusted when initiating one-lung ventilation, the airway pressure will increase due to reduced compliance. It is possible that the ventilator will not deliver the full tidal volume, and then the largest recorded tidal volume would be the two-lung tidal volume. Data were missing in more than 20% of the cases in this study, but it may still have been useful to examine what data were available, because this is the critical time period, and apparently there still would have been more than 100 cases to analyze. It would be important to follow up this study with either a prospective,

randomized study using different tidal volumes during one-lung ventilation or even a retrospective study in which the tidal volumes can be definitely correlated with one-lung ventilation.

The authors stated that their most interesting finding was the association of both large tidal volume and greater fluid administration with postoperative respiratory failure. This makes sense in that the larger fluid administration can lead to pulmonary edema, once there is a capillary leak from a ventilator-induced injury. The authors hypothesized that the larger tidal volumes might have led to hypotension, which “forced” the anesthesiologists to administer more fluid. Although it is possible that resulting hypotension could have been treated with fluid, an alternative would have been infusion of a vasoconstrictor, such as phenylephrine. A more likely possibility is simply that the anesthesiologist who does not limit the tidal volumes or airway pressures during one-lung ventilation is less likely to be vigilant in limiting fluid administration. I do not understand, based on their data, how the authors concluded that even brief exposure to such ventilator settings could cause the postoperative complications.

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In Reply:—We thank Dr. Neustein for his comments and appreciate the opportunity to reply.

We agree with Dr. Neustein that the absence of reliable data on airway pressures and tidal volumes during one-lung ventilation is a major limitation of our study. Indeed, we are currently undertaking a prospective cohort study in patients at high risk for postoperative pulmonary complications such as those undergoing lung resection to evaluate the cumulative exposure to potentially harmful intraoperative ventilator settings. This study includes a precise calculation of exposure during one-lung ventilation.

Our study design did not allow us to determine the mechanism of the observed interaction between the intraoperative tidal volume and fluid administration.¹

A definitive trial to prove that intraoperative mechanical ventilation *per se* causes acute lung injury in humans would be difficult to design. Short-term large tidal volume mechanical ventilation during anesthesia has been associated with worsening pulmonary inflammatory response in experimental animal models.^{2,3} Despite some controversies, corresponding human data support the hypothesis that even brief exposure to high-tidal-volume ventilation influences the inflammatory and coagulation response in the lung.^{4–6} In our study, postoperative respiratory failure in the group of patients receiving larger tidal volume was observed during surgery as short as 244 min (25% interquartile range). Although optimal ventilator settings in patients undergoing pneumonectomy are yet to be determined, we believe that to maximize patient safety, routine use of very large tidal volumes (> 10 ml/kg predicted body weight) during two- and in particular during one-lung ventilation is potentially harmful and should be avoided.^{7–9}

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Therapy in Postpuncture Meningitis

To the Editor:—We read with great interest the comprehensive overview by Baer¹ regarding post-dural puncture (bacterial) meningitis (PDPM). However, some questions can be raised regarding treatment recommendations for patients with PDPM.

The recommendation for empiric treatment that is made in this article follows Infectious Diseases Society of America guidelines for *Streptococcus pneumoniae* meningitis.² In these guidelines, use of vancomycin plus the third-generation cephalosporins ceftriaxone or cefotaxime is recommended with the addition of ampicillin in patients older than 50 yr.² Of the 179 reviewed cases in this article, indeed,

almost half had meningitis due to viridans streptococci; however, relatively high rates of *Staphylococcus aureus* (9 patients, 5%), *Pseudomonas aeruginosa* (8 patients, 4%), and *Enterococcus faecalis* (3 patients, 2%) were also found.¹ This specific distribution of species stresses that PDPM should be regarded as a specific category of patients that most resembles the “standard” category of patients with recent neurosurgery.^{3,4} In this category, recent guidelines recommend vancomycin plus ceftazidime. Ceftazidime, and not ceftriaxone or cefotaxime, has shown efficacy in several studies of patients with *Pseudomonas* meningitis.^{2,5} Alternatively, one can use cefepime, which also has greater *in vitro* activity than the third-generation cephalosporins.^{2,5}

In addition, Baer recommends the use of adjunctive dexamethasone in patients with PDPM.¹ In a recent European randomized clinical trial, adjunctive dexamethasone therapy reduced mortality from 15% to 7%.⁶ Of the total of 301 included patients in this trial, 9 (3%) had meningitis

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due to viridans streptococci, and were partly described previously.⁷ One of the 5 patients included in the placebo group died, *versus* 1 of the 4 in the dexamethasone group. Both patients died of *S. milleri* meningitis; others had meningitis due to *S. salivarius* (n = 4), *S. sanguis* (n = 2), and *S. oralis* (n = 1) (van de Beek, unpublished, October 2006). In a recent quantitative review of the effect of adjunctive dexamethasone in adults with community-acquired bacterial meningitis that included the results of five clinical trials, treatment with dexamethasone was associated with a significant reduction in mortality and neurologic sequelae.⁸ On basis of these data, dexamethasone is advised for patients with suspected or proven community-acquired bacterial meningitis and should be continued for 4 days, regardless of microbial cause.³ However, PDPM has a different pathophysiology, and cerebrospinal fluid cultures yielded specific distribution of causative species, as compared with patients with community-acquired bacterial meningitis.^{1,9} Therefore, adjunctive dexamethasone is not recommended in the subgroup of patients with PDPM.

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Think about Room Air

To the Editor:—I read the articles “Post-Dural Puncture Bacterial Meningitis”¹ and “Incidence of Epidural Hematoma, Infection, Neurologic Injury in Obstetric Patients with Epidural Analgesia/Anesthesia”² and the editorial “Gloved and Masked—Will Gowns Be Next? The Role of Asepsis during Neuraxial Instrumentation”³ in the August 2006 issue of ANESTHESIOLOGY. They are very informative with many excellent areas of discussion. However, it seems to me that there is one glaringly large area that was missed in all three articles. The issue is the source of contamination of the epidural space. It makes me shudder to see anesthesiologists inject room air, which may have a droplet from any of a dozen people's noses who have been in the room in the past hour! Many residents, not sure of the feel, will then inject several more milliliters. Then they wonder why they have a spotty block! But that is another issue. In my opinion, injecting air should have been clearly condemned, but it was not even mentioned. Three of the four deaths presented had multiple epidural attempts, at least some with inexperienced personnel. How many cubic centimeters of air were injected? Maybe the source of infection results from the combination of air plus a dural puncture. Was there an epidural attempt before the obstetric spinal case? The only thing that should be injected into the epidural space is sterile liquid that is filtered for glass. Preferring the feel of the air is not enough reason to use air for the loss-of-resistance technique. Are there any other reasons that are backed up with data for using air?

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Gloved and Masked—Will Gowns Be Next? Let the Data (Not Logic) Decide This Issue

To the Editor:—The editorial “Gloved and Masked—Will Gowns Be Next?” by Hepner¹ is both interesting and disconcerting. The main reason surgeons resist neuraxial anesthesia is because “It takes too long!” For this reason, it is frightening to see the rubric “Will gowns be next?” Demanding that anesthesiologists wear gowns to perform neuraxial anesthesia will, in my opinion, be the death knell for spinal

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Rather than go through the inconvenience of learning the feel of the saline method, those practitioners continue to subject the patient to the risk of infection. This ban should include the hanging drop method. Although less air is entrained, why allow any? It seems clear that the data show that room air has contaminated droplets and that injecting them into the epidural space is unnecessary and of greater risk than using saline. Of even more concern is how many other issues are out there, easily discovered, if we only followed up with our patients and accurately measured outcomes as we are morally obligated to, but rarely, do.

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and epidural anesthesia. Locating and donning a gown for these procedures will obviously not make doing them less time-consuming. More importantly, is it even necessary?

Despite outcome data demonstrating a 1:10,000 to 1:50,000 risk of post-dural puncture meningitis, Dr. Hepner bases his recommendations for using gowns during neuraxial anesthesia on logic: “we must

institute uniform sterile safety practices that have been proven, or seem by common logic to be prudent, and continue to study techniques used in other arenas [infection owing to central venous catheters (CVCs)] to determine their utility."¹ That is, if gowns and full barriers are better for CVC insertions, it is logical that they are also good for neuraxial anesthesia.

In the study showing that full-barrier precautions (sterile gloves, long-sleeved sterile gown, mask, cap, and large sterile sheet drape) reduced the incidence of CVC-related bloodstream infection compared with standard precautions (sterile gloves and small drape), the incidences of infection were 4 of 176 patients (2.3%, full-barrier precautions) and 12 of 167 patients (7.2%, standard precautions).² The extrapolated CVC infection rate is 227:10,000 for full barrier and 718:10,000 for standard barrier.

If the neuraxial anesthesia infection rates were the same as for CVC insertions, no one would argue against the use of neuraxial full-barrier precautions. However, infections associated with neuraxial anesthesia (assuming 1:10,000 with standard precautions) are 718 times less than the infection rate for CVC placement. Why do we need to look to the CVC data, which clearly are irrelevant to neuraxial infections, and why do we need to depend on logic when we have valid neuraxial outcome data? If a 1:10,000 infection risk for lumbar puncture is unacceptable, what risk is acceptable? How much better can we do with full-barrier precautions and at what cost? How will we know whether full-barrier precautions are better? Based on the data, one could argue that full barriers for neuraxial anesthesia are an illogical solution to a non-problem.

I have done many spinals and epidurals during 25 yr of practice. Fortunately, none have caused an infection. However, my numbers are not close to approaching 10,000. It is encouraging to learn from Baer's data³ that the odds that I will have an infection are exceedingly low. I wear gloves and a cap when doing neuraxial anesthesia. Although I have not routinely done so, I will wash my hands before putting on sterile gloves because that will apparently easily and conveniently further lessen any risk. On the other hand, I am resisting the donning of a gown until there is more than "logic" to justify it. Doing so will only jeopardize neuraxial anesthesia by making it take longer than it already does.

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Parturients Expect Safe and Clean Regional Anesthesia

To the Editor:—The largest single group of patients receiving central blockades worldwide is undoubtedly parturients. Fortunately, serious complications are rare, as pointed out in two recent studies published in *ANESTHESIOLOGY*.^{1,2}

Ruppen *et al.* found six epidural hematomas and justly considered these numbers inadequate to produce a robust estimate of event rates. Because of their study design, several cases reported in the literature are excluded from the statistical calculation performed in the meta-analysis. For example, the Closed Claims project included three spinal hematomas in obstetric patients.³ Many other excluded cases occurred in patients with impaired coagulation due to preeclampsia or large blood loss, conditions that might predispose even to a spontaneous spinal hematoma.^{4–6} Nonetheless, despite frequent bloody taps and thrombocytopenia, spinal hematoma is rare in obstetric patients.^{7,8} The compliant spinal canal in a young individual permits the introduction of volumes that may cause severe symptoms and permanent damage in an older person with a stenotic spinal canal.

However, a healthy parturient receiving epidural blockade for pain relief might overnight turn into a patient with severe coagulopathy. The calculated low risk then no longer applies to this patient. Such was the case with one patient in our study⁹: After delivery, the epidural catheter was removed before transferring the patient to the intensive care unit for treatment of the syndrome of hemolysis, elevated liver enzymes, and low platelets, and the subsequent spinal hematoma was diagnosed with delay. The perception of low incidence in the healthy parturient contributes to underestimation of risk when she becomes affected by coagulopathy.

Whereas patient characteristics seem to influence development and outcome after some severe complications, such as spinal hematoma and epidural abscess, no predisposing conditions are found for iatrogenic meningitis. Purulent meningitis will develop in any patient, however healthy, if bacteria are introduced into the spinal fluid, devoid

of any immunologic defense. Dr. Baer's comprehensive review of post-dural puncture meningitis (PDPM) includes reports of three tragic and unnecessary deaths in previously healthy obstetric patients. These cases could reflect a higher incidence of PDPM due to lower hygienic standards in the obstetric setting, lower diagnostic preparedness, or higher motivation to report these cases. Finally, the parturient could be at higher risk of developing PDPM. The reason being that α -hemolytic streptococci are normally part of the flora in the genitourinary tract and fluids containing these bacteria obviously will cover the lower backs of many parturients. As a consequence, faulty skin disinfection before performing a central blockade in the parturient could be more hazardous than in the average surgical patient.

The author and the editorial comment both address the incidence of PDPM.¹⁰ Important as this may seem, we would like to quote a recent editorial by Prof. Reynolds: "there can be no such thing as a 'true incidence' of an infective complication, . . . , as its occurrence will vary with the number of risk factors both in local clinical practice and among the patient population."¹¹

We agree with Dr. Baer that these three mortalities, the increasing antimicrobial resistance of viridans streptococci, and oropharyngeal presence of more invasive pathogens should be sufficient for every anesthetist to adopt truly aseptic technique whenever performing a central blockade.

Analyzing literally every aspect of PDPM, the author does, however, leave one question unanswered: Why do physicians have such an aversion to facemasks? The editorial comment proposes the remedy, advocating shift in culture, guided by responsible leadership and compelling guidelines. To this we can only totally agree. We would also like to add a further question: Shouldn't all cases of PDPM be subject to epidemiologic evaluation and thorough scrutiny of the hygienic standard in the departments where PDPM has occurred? The polymerase chain reaction is no longer exclusive and expensive, and clarifying the

pathogenetic pathway in cases of PDPM certainly deserves our attention. After lumbar puncture, the failure of bacterial growth is not uncommon, neither in community-acquired meningitis nor in PDPM. In our series of 29 cases, culture was positive in 12 cases, and 11 of these were α -hemolytic streptococci (not 28 as quoted by Baer).⁹ Immediate incubation of cerebrospinal fluid in medium for anaerobic blood culture might favor growth.

Dr. Baer makes the assumption that hundreds of cases with PDPM have gone unreported and unrecognized. This assumption is strengthened by the fact that viridans streptococci are low-grade pathogens that may cause subtle symptoms. In our study, only 14 of 29 patients presented classic symptoms of meningitis.⁹ In several of the remaining cases, correct diagnosis of PDPM was reached only because of a high level of suspicion. Worldwide, many cases of PDPM have probably unintentionally been cured by antibiotic treatment intended for some other infection. In view of the numerous reports of PDPM published, it would seem awkward primarily to propose the diagnosis of aseptic meningitis before excluding an infectious origin when presented with a similar case.

One pitfall in the diagnosis of PDPM in the obstetric patient is the anticipation of severe headache after accidental dural puncture. When signs of meningeal irritation such as photophobia or vomiting are present, these might be accompanying symptoms of severe post-dural puncture headache, but the suspicion of PDPM should arise. The combination of headache and infection in a patient recently subject to central blockade should be a warning signal.

As with spinal hematoma and epidural abscess, the symptoms of PDPM often appear after discharge from hospital, and the care of the patient is the responsibility of a physician not necessarily familiar with anesthetic procedures. It is our duty as anesthesiologists to inform colleagues in other specialties regarding the signs and symptoms of these potentially extremely dangerous complications. An information leaflet distributed among general practitioners regarding post-dural puncture headache has been shown to improve their knowledge of this complication.¹² Similarly, information regarding the rarer, but potentially more serious complications might be of great value.

We should be grateful for the significant contribution offered by Dr. Baer.

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In Reply:—I thank Drs. Edsall, Dr. Lambert, and Drs. Moen, Dahlgren, and Irestedt for their interest on this controversial topic, and for their insightful comments and questions. Their remarks clearly show the hurdles to overcome in developing evidence-based guidelines for strict aseptic technique during neuraxial instrumentation in anesthesia practice.

Dr. Edsall raises a question that is often debated and quite controversial: Is the loss of resistance to saline superior to that to air? Although many complications, including pneumocephalus, nerve root compression, subcutaneous emphysema, venous air embolism, incomplete analgesia, and paresthesias, have been attributed to the loss of resistance to air,¹ there is no mention in the anesthesia literature regarding air as a source of contamination in the epidural space. I would argue that there is a significantly higher chance of contamination from the large volume of air over the tray than the small amount injected with the syringe. The only way to prevent the epidural tray from being exposed to air is to do the procedure in a vacuum. Furthermore, epidural abscess has only been demonstrated to occur as a result of skin bacteria passing through a needle track, contaminated syringes, or local anesthetics, or hematogenous spread from another source.²

Dr. Edsall correctly points out that there are many reports of spotty or incomplete blocks when using air instead of saline.^{3,4} Beilin *et al.*⁴ demonstrated that more parturients in the air group had incomplete

analgesia and higher visual analog pain scores requiring additional local anesthetic when compared with those in the saline group. A survey in the United Kingdom demonstrated that use of loss of resistance to saline has progressively increased among obstetric anesthesiologists from just over 50% in 1998 to 74% in 2003.⁵ Interestingly, another United Kingdom survey demonstrated that although almost 60% of respondents first learned to identify the epidural space with loss of resistance to air, nearly a quarter have changed to loss of resistance to saline.⁶ I must admit that I, trained using intermittent loss of resistance to air, have been reluctant to change to saline for fear of having increased complications. However, given the abundance of data supporting the use of the loss of resistance to saline and the lack of complications when switching from one technique to the other,⁶ I am strongly considering a change in my practice.

Dr. Lambert seems to have misinterpreted my comments and, furthermore, feels that a 1:10,000 risk of post-dural puncture meningitis is acceptable. As noted in my editorial⁷ and the comments of Drs. Moen, Dahlgren, and Irestedt, Baer's statistics suggest that many cases of post-dural puncture meningitis are unreported and unrecognized, suggesting that the actual US rate is higher than reported.⁸ In addition, as discussed by Dr. Moen in his letter and eloquently stated by Dr. Reynolds,⁹ risk varies with both clinical practice and patient population. Causes of complications are multifactorial and include the performance of neuraxial techniques by trainees who may not be able to

maintain sterility as well as experienced anesthesiologists. These techniques in parturients may be higher risk for infective complications if a laboring patient has skin contamination with amniotic fluid, blood, or other body secretions. Finally, laboring rooms are less likely to provide aseptic conditions when compared with operating rooms.

Even if we assume that the US rate is 1:10,000, why is the provision of general anesthesia to American Society of Anesthesiologists physical status I or II patients nearly 100-fold safer than that of spinal anesthesia? A 1:10,000 risk is neither an ultrasafe system (1:1,000,000) nor a high-reliability organization (1:100,000) but rather a system that is in need of immediate improvement.¹⁰ I am not necessarily advocating that sterile gowns be used. However, adoption of uniform sterile safety guidelines and continued study of the efficacy of these techniques is important. After all, many of the recently drafted American Society of Regional Anesthesia guidelines on aseptic techniques during neuraxial anesthesia^{11,12} were extrapolated from the medical and surgical literature, and clearly state that a specific outcome cannot be guaranteed.

To clarify the sentence that Dr. Lambert and other readers may have found unclear: "we must institute uniform sterile safety practices that have been proven [hand washing], or seem by common logic to be prudent [facemasks], and continue to study techniques used in other arenas [gowns for central venous catheters] to determine their utility." Evidence has implicated upper mouth commensals in cases of post-dural puncture meningitis. Experience informs us that practitioners talk and sometimes sneeze or cough during a procedure. Because infection control data suggest that the use of facemasks will diminish spread of infectious organisms from droplets, it would also seem prudent to wear a facemask when performing this procedure. I never implied that it is logical that gowns should be used for neuraxial instrumentation. In fact, to quote, "Although Baer states that all aspects of sterile technique are part of the 'standard-of-care defense,' there [are] no data that support the use of sterile gowns during the performance of neuraxial techniques." I assume that Dr. Lambert wears a mask when doing neuraxial techniques. I am hopeful that he does agree that wearing a mask is a speedy and painless solution to a problem, post-dural puncture meningitis, whose morbidity and mortality dwarf the inconvenience of the mask.

The comments of Drs. Edsall, Moen, Dahlgren, and Irestedt regarding postoperative outcomes measures and root cause analysis deserve a closer look. The American Society of Anesthesiologists* clearly states that anesthesia care is a continuum and that it should be documented as such. The postanesthesia care is more than the stay in the postanesthesia care unit and should include a postanesthesia visit. Although other healthcare providers may inform us of major anesthetic-related complications, we will discover our own complications most quickly and thoroughly only by routine institution of postoperative visits. I completely agree with Drs. Moen, Dahlgren, and Irestedt's recommendation that all patients with evidence of post-dural puncture meningitis be evaluated for the contributing factors including aseptic standard. Educating our medical, surgical, and obstetric colleagues regarding potential complications related to anesthetic practice is a worthy endeavor.

* Available at: <http://www.asahq.org/publicationsAndServices/standards/21.pdf>. Accessed November 17, 2006.

† Available at: <http://www.asahq.org/publicationsAndServices/infectioncontrol.pdf>. Accessed November 17, 2006.

There are two points that, although not related to any of these letters, I would like to raise. The first one has to do with a typographical error in my editorial related to the American Society of Anesthesiologists Task Force on Infection Control.[†] I inadvertently wrote "maximal sterile barrier precautions during central venous catheter infection" rather than "central venous catheter insertion." The second point has to do with the recently published guidelines for aseptic techniques during regional anesthesia.¹² I wrote that although a chlorhexidine solution has a faster and stronger bactericidal effect than povidone iodine, the consensus stopped short of recommending an alcohol-based chlorhexidine antiseptic solution for skin disinfection before neuraxial techniques (electronic personal communication, Joseph M. Neal, M.D., Staff Anesthesiologist, Virginia Mason Medical Center, Seattle, Washington, and Editor-in-Chief, *Regional Anesthesia and Pain Medicine*, April 2006). However, it seems that in the final revision of the guidelines, the decision was made to encourage the use of an alcohol-based chlorhexidine solution as the antiseptic of choice before regional techniques.¹² The expert panel felt strongly that although the US Food and Drug Administration has not approved chlorhexidine before lumbar puncture, it has a significant advantage over povidone iodine because of its onset, efficacy, and potency (verbal personal communication, James R. Hebl, M.D., Assistant Professor, Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota, November 2006). Upon contacting the Food and Drug Administration, the panel found that the lack of approval was not because of toxicity but because of lack of scientific data. Interestingly, povidone iodine is also not approved for lumbar puncture. Finally, it is important to mention that the guidelines conclude that there are insufficient data regarding the routine use of surgical gowns before performing a regional technique.¹²

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In Reply:—I welcome the letters in response to two articles^{1,2} and the editorial³ in the August 2006 issue of ANESTHESIOLOGY regarding aspects of infectious complications of neuraxial instrumentation.

van de Beek and de Gans discuss important information related to the treatment of post-dural puncture meningitis (PDPM). They recommend that ceftazidime or cefepime be substituted for the empiric third-generation cephalosporin recommendation in my review.¹ The former drugs have been found to have greater *in vitro* activity against *Pseudomonas aeruginosa*. (However, their reference 5⁴ does not mention either *P. aeruginosa* or cefepime.)

Their admonition against adjunctive steroids in PDPM needs further clarification. Korinek *et al.*⁵ (van de Beek and de Gans' reference 3) studied 6,243 consecutive craniotomies to evaluate the effect of preoperative antibiotic prophylaxis on the incidence of postoperative meningitis. They found 50% reduction in incision infections (skin, bone) but no reduction in meningitis for the group that received prophylaxis. van de Beek and de Gans give as the reason for withholding adjunctive dexamethasone in PDPM, that PDPM resembles postcraniotomy meningitis more than it resembles community-acquired meningitis. Postcraniotomy meningitis is clearly different from community-acquired meningitis. Adjunctive dexamethasone *would* be inappropriate in the presence of a wound infection. But PDPM may have more in common with the community-acquired type than it has with the neurosurgical type. Should not PDPM be considered as a distinguished subset? Each of the three types of meningitis has a different spectrum of causative organisms, but the high incidence of viridans streptococci in the PDPM group (a primarily upper respiratory, mouth, and skin commensal) makes it more like the community-acquired (*Streptococcus pneumoniae*, *N. meningitidis*) than the neurosurgical type (staphylococci [skin commensals] and enterococci). In addition, the complication of the concomitant surgical wound is absent in PDPM. Therefore, would not the desirable antiinflammatory effect of dexamethasone be the same in postpuncture meningitis as in community-acquired meningitis (other things being equal, *e.g.*, no other infected foci)?

van de Beek and de Gans' reference 7,⁶ covering meningitis due to viridans streptococci, reports seven cases of meningitis due to viridans streptococci—three of which are termed iatrogenic. Two patients had undergone thermocoagulation of the gasserian ganglion, and one had endoscopic sclerotherapy for esophageal varices. These three cases suggest meningitis of the post-dural puncture type (albeit inadvertent). It is not clear whether van de Beek's unpublished cases of meningitis due to viridans streptococci are community-acquired, neurosurgical, or post-dural puncture in type. Two other cases described in van de Beek and de Gans' reference 7⁶ died of *S. milleri* meningitis. The underlying cause for these cases of meningitis is not given, but the mechanism of death in each case⁶ is given as brain herniation accompanied by cerebral edema. Whether adjunctive dexamethasone is appropriate for treatment in puncture-type meningitis needs further study.

I thank Dr. Edsall for drawing attention to the practice, by some, of injection of air into the epidural space as a possible source of infection.

Dr. Lambert's letter is puzzling. Science is the wedding of logic and observation. Dr. Lambert's readiness to jettison logic is perverse. He is encouraged that statistics show "... that the odds that I will have an

infection are exceedingly low." However, the data reflect incidence expected when the anesthesiologist washes his or her hands. Lambert admits that he has "... not routinely done so ..." but he wants credit for sterile gloves and cap. No mention of a mask. May we conclude that he does not "routinely" wear one? He states, "If the neuraxial anesthesia infection rates were the same as for [central venous catheter] insertions, no one would argue against the use of neuraxial full-barrier precautions." (Isn't it logical to surmise that if all anesthesiologists were as cavalier about sterile technique, the infection incidence might approach that of inserting a central venous catheter?) He then implies that because the incidence rate of central venous catheter infection is much higher than that for dural puncture, that makes applying the central venous catheter precautions "illogical" because a 1:10,000 infection rate is a "nonproblem." (It is a serious problem for that unlucky 1 in 10,000.) He asks, "... what risk is acceptable?" The answer is that (in the case of prevention of PDPM) the acceptable risk is the lowest possible under conditions of meticulous attention to sterile technique. The idea that there must be a cost-benefit analysis for every intervention, no matter how trivial, is impractical. Why does Dr. Lambert wear a cap and gloves while invading a patient's nervous system? Where are the data, and where is the logic?

Drs. Moen, Dahlgren, and Irestedt point out an error in the article text,¹ stating that in their series, 28 cases (instead of 11 cases) of PDPM were culture positive for α -hemolytic streptococci. (Table 1 and Table 4 have the correct value.) They ask, "Why do physicians have such an aversion to facemasks?" (Perhaps the situation is analogous to the reaction to automobile seat belts and bike helmets when they were first introduced.) They opine that the unnecessary deaths could reflect, among other things, "... lower diagnostic preparedness." Not only does this serious complication often go unrecognized, but in several of the case reports, the existence of PDPM is denied and attributed to other causes.

The absence of inclusion of PDPM in the US Practice Guidelines⁷ for the management of bacterial meningitis is inexplicable, as is the Centers for Disease Control and Prevention's exclusion of PDPM as a nosocomial disease. Perhaps forums such as this one will reduce the incidence, as well as heighten awareness, of this preventable disease.

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David C. Wartier, M.D., Ph.D., served as Handling Editor for this exchange. Dr. Ruppen was asked to provide a reply to the two letters regarding his Review Article but did not feel that a response was required.

Can Precise Data Improve a Nonprecise Anesthetic?

To the Editor:—The article by Heller *et al.*¹ was informative and adds precision to the effect of temperature on the baricity of local anesthetics. They provide interesting new data on the temperature at which local anesthetics used for spinal anesthesia are isobaric (the “isobaric temperature”). Clearly, the next question is, what is the clinical relevance of this added precision? The authors themselves state, “Whether this concept in fact improves patient safety in terms of hemodynamic stability or even allows dose reductions of local anesthetics must be confirmed in further clinical studies.”

In 1989, Beardsworth and I published a simple study comparing the injection of 3 ml plain 0.5% bupivacaine at room temperature to an identical solution adjusted to 37°C (very close to but not precisely within the limits [34.3°–35.8°C] of the so-called isobaric temperature).² The injection was performed with the patients in the lateral decubitus position, and they were then immediately turned to the supine horizontal position. For the same reasons indicated by Heller *et al.*, we hypothesized that increasing the temperature of the bupivacaine would make it more isobaric and limit its spread. We found no difference in the extent of pinprick analgesia. However, the 37°C solution produced a more prolonged block, which we suggested was due to a decrease in pKa associated with the increased temperature.

Beardsworth’s study compared but one dose of bupivacaine and one position after its injection. Other doses and patient positions will likely produce different results.

Heller’s and Beardsworth’s studies beg the question as to whether it is possible (with the exception of using a very hyperbaric solution for

saddle or thoracic levels of block) to precisely control the level of spinal anesthesia. Although the temperature effect on the baricity of local anesthetics used for spinal anesthesia reported by Heller has achieved this pinnacle of precision, this effect will have to overcome the manifold factors that control the level of spinal anesthesia³ to significantly impact clinical practice. Whether this can be accomplished will only be determined through clinical trials that will undoubtedly derive from Heller’s publication. However, after 25 yr of studying, practicing, and watching spinal anesthesia, I suspect that the precise control of the level of spinal anesthesia will require more than simply adjusting the temperature of the injected local anesthetic.

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In Reply:—We thank Dr. Lambert for his comments, which add interesting aspects to the discussion.

The difficulties of controlling local anesthetic (LA) spread during “isobaric” subarachnoid block in daily practice are well-known. As Dr. Lambert states, there is a manifold of influencing factors whereof several are unknown to the practitioner before LA injection (*e.g.*, lumbosacral cerebrospinal fluid volume).

Former studies have confirmed that pharmacokinetic action of cold and warm LA is quite different in the subarachnoid space^{1–5} in terms of faster onset and higher maximum level of sensory block when using the warmed solution. Moreover, prolonged analgesia was reported by Dr. Lambert.⁶

After equilibration of the injected LA to cerebrospinal fluid (body) temperature, with the exception of articaine and mepivacaine, all commercially available LA solutions will behave hypobarically. This means that LA after injection at room temperature will initially descend and, after passing the isogravimetric point, ascend. This is supported by the fact that by keeping the patient in a sitting position during and after administration of warmed LA, a higher maximum level of sensory blockade is obtained.^{3–5} Shortening the period of sitting or puncturing in the lateral decubitus position masks the hypobaric effect of warmed LA.² This may, likewise, be illustrated by Dr. Lambert’s study,⁶ where no difference in maximum level of sensory blockade was found in patients punctured in the lateral decubitus position and then immediately turned to the supine horizontal position. The clinical impact of positioning during “isobaric” subarachnoid block is further supported by the effect of (un)intended late posture change.^{7,8} Further, cerebrospinal fluid density is lower in women.⁹ Therefore, the absolute effect of warming LA on individual baricity must be considered smaller in

females than in males at a given body temperature and may bias the results.⁶

From the available data, we conclude that the sitting position during puncture is a prerequisite for obtaining clinical impact of the hypobaricity concept of warmed LA solutions in terms of higher maximum level of sensory blockade, and a smaller variability of the number of blocked segments. Whether those observations are clinically transferable into lower doses of warmed LA in the sitting position must be evaluated in forthcoming trials.

With regard to puncturing in the lateral decubitus position, another point of view deserves discussion. Because the sensory nerves derive from the dorsal horn of the spinal cord and the roots are located posteriorly, in the supine position hypobaric (37°C) LA will ascend ventrally apart from these target structures and may even have less analgesic effect. In this regard, it would have been of particular interest if in his work⁶ Dr. Lambert observed differences between anterior or posterior nerve roots. Because motor neurons and sudomotor output derive from the anterior roots, in their setting the usual difference of two segments between sensory and (suo)motor block may have been lost in the hypobaric (37°C) group. This hypothesis is supported by data in a comparable setting (lateral decubitus puncture) from Higuchi *et al.*,¹⁰ who found a trend to correlation between motor block onset and cerebrospinal fluid density—not, however, between time to peak sensory block level and cerebrospinal fluid density.

The discussion on pKa values of LA in conjunction with subarachnoid block, as already addressed elsewhere,^{6,11} should not be overemphasized. LAs gain body temperature within 2 min¹² when injected at room temperature, and pKa values are then equilibrated with those LAs injected at 37°C. Therefore, the decreased pKa values of LAs

injected at 37°C⁶ are comparatively effective for 2 min and may account for earlier onset of blockade but not, however, for the prolonged LA effects more than 2 h later.

Taken together, the discussed effects carry uncertainty for daily practice but may, besides others, explain the high interindividual ranges in maximum level of sensory blockade reported in many studies using "isobaric" solutions. *In vitro* studies and modeling as performed in our work¹¹ always observe and depict a limited part of reality. They never allow conclusions on the reality itself; rather, they may be hypothesis generating or may improve existing hypotheses, which then must be verified (or falsified) in reality. The problems associated with the complex physiology of subarachnoid block may not be solved with simple physics. The intention of our study was to identify isobaric temperatures and, thus, make the course of LA within the subarachnoid space more predictable to improve the *nonprecise anesthetic*.

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Use of Vasopressin Bolus and Infusion to Treat Catecholamine-resistant Hypotension during Pheochromocytoma Resection

To the Editor:—In a recent review of vasopressin, it was stated that there were only two reported cases using bolus vasopressin (10–20 U) to restore blood pressure after pheochromocytoma resection.¹ This letter documents another rare case, using a lower dose of bolus vasopressin, for treatment of catecholamine-resistant hypotension after pheochromocytoma resection.

A 54-yr-old man (height, 180 cm; weight, 84 kg) underwent laparoscopic right adrenalectomy for treatment of pheochromocytoma. Preoperative medications included phenoxybenzamine, metoprolol, ramipril, and atorvastatin. Preinduction blood pressure was 129/74 mmHg, and heart rate was 57 beats/min. During manipulation of the adrenal gland, the patient developed hypertension, which was treated with sodium nitroprusside (up to 10 ml/h of 200 µg/ml) and esmolol (up to 5 ml/h of 10 mg/ml) infusions. After resection and discontinuation of the nitroprusside and esmolol, the patient developed hypotension. A norepinephrine infusion of 24 µg/min was only able to increase the patient's systolic blood pressure to the low to mid 80s. Two 0.4-U vasopressin boluses were administered, which increased the systolic blood pressure to 120 mmHg. The patient was started on a 4-U/h infusion of vasopressin resulting in maintenance of a systolic blood pressure at 110 mmHg while permitting a decrease in the norepinephrine infusion rate. Both infusions were continued throughout the rest of the surgery and were weaned several hours postoperatively. The patient did well and was discharged home on postoperative day 2.

There are now three previous reports of bolus vasopressin being used to treat hypotension after adrenal resection for pheochromocytoma.^{2–4} Repeated bolus doses of 10–20 U followed by an infusion were required to treat hypotension after pheochromocytoma resection.² In another adult patient, an infusion of vasopressin required 20 min to achieve improvement in blood pressure during pheochromocytoma resection complicated by a large blood loss.³ In an 11-yr-old

patient, a 5-U bolus followed by an infusion was successful in treating postresection hypotension.⁴

Although vasopressin infusions have been used in a variety of other situations, there are limited data to guide bolus dosing. Others report lower doses of vasopressin bolus. A 2-U bolus dose was used to treat anaphylactic shock.⁵ As in this case, two 0.4-U boluses successfully treated hypotension secondary to both bowel retraction in patients having abdominal aortic resection repair and postreperfusion syndrome during liver transplantation.^{6,7} Terlipressin (a vasopressin precursor) in doses of 1 or 2 mg successfully treated hypotension secondary to induction of anesthesia in patients chronically treated with renin-angiotensin system inhibitors.⁸ Additional well-controlled studies must be conducted to establish the indications, safety, and efficacy of bolus vasopressin for rapid correction of hypotension, particularly catecholamine-resistant hypotension.

This patient adds to the small number of reported cases that suggest vasopressin can be safely and effectively used to treat postadrenalectomy catecholamine-resistant hypotension in patients with pheochromocytoma. Although vasopressin is a vasoconstrictor and it is not surprising that it can treat hypotension, there may be a specific need for vasopressin in some pheochromocytoma patients. First, vasopressin is effective in the presence of residual α -adrenergic blockade and down-regulation of those receptors. Second, in some patients with pheochromocytoma, there is an oversecretion of vasopressin, which may contribute to the induced hypertension.^{9,10} It is possible that chronic oversecretion of vasopressin leads to a down-regulation of vasopressin receptors, thus contributing to the postresection hypotension. Whether preoperative determination of vasopressin over secretion will affect management is an open question. Catecholamines are also known to inhibit vasopressin release.¹¹ It has been proposed that chronic inhibition by catecholamines may down-regulate neurohypophyseal vasopressin synthesis, thereby preventing the acute high release of vasopressin during a hypotensive episode.² Last, the use of

vasopressin can reduce the catecholamine dose, thus allowing one to avoid their undesirable side effects such as increased myocardial oxygen consumption and ventricular arrhythmias.

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Impact of Terlipressin on Hepatosplanchnic Perfusion: “Only the Dose Makes a Thing Not a Poison” (Paracelsus)

To the Editor:—With great interest, we read the comprehensive and well-written review article of Drs. Treschan and Peters¹ providing a thorough overview of the physiology and therapeutic indications of arginine vasopressin and its synthetic analogs. Nevertheless, we believe that the impact of the long-acting vasopressin analog terlipressin on hepatosplanchnic perfusion in the treatment of sepsis-related arterial hypotension has not been discussed appropriately. The authors conclude that “terlipressin is a potent intestinal vasoconstrictor, and evidence suggests decreased intestinal perfusion with terlipressin infusion.”¹ First, we wish to rectify that the cited study of Westphal *et al.*² investigated the effects of arginine vasopressin on gut mucosal microcirculation in septic rats, and not of terlipressin (as wrongly cited by Drs. Treschan and Peters¹). Second, the effects of terlipressin on splanchnic perfusion are dependent on two important aspects, which the authors of the current review article did not refer to: (1) the role of aggressive fluid resuscitation and (2) the dose itself. In this context, Asfar *et al.*³ reported that terlipressin even improved ileal microcirculation in fluid-challenged endotoxic rats. In contrast, in non-fluid-challenged rats, terlipressin infusion contributed to detrimental effects within the intestinal macrocirculation and microcirculation. In addition, the impact of terlipressin on intestinal perfusion seems to be dependent on the drug dosage and application form. Again, Asfar *et al.*⁴ demonstrated that a goal-directed continuous low-dose infusion of terlipressin not only reversed the hypotensive-hyperdynamic circulation in porcine endotoxemia but also decreased global systemic oxygen consumption without compromising splanchnic metabolism and organ func-

tion. In summary, the current literature, also limited in extent, supports the view that low-dose terlipressin in conjunction with aggressive fluid challenge is a promising adjunct in our therapeutic repertoire for the treatment of systemic arterial hypotension resulting from distributive shock.⁵

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In Reply:—We appreciate the comments of Dr. Roth regarding the use of vasopressin to restore blood pressure after pheochromocytoma resection. This case certainly adds an interesting experience to the few published cases discussed in our recent review.¹

The use of a very small vasopressin bolus dose (0.4 U) is a reasonable approach to evaluate the patient's reaction toward the drug. Dr. Roth used a vasopressin infusion (4 U/h \approx 0.07 U/min) for blood pressure

maintenance. This dose is consistent with the recommendations for continuous vasopressin infusion when used as an adjunct vasopressor in septic shock (1–4 U/h \approx 0.01–0.07 U/min).²

Use of vasopressin during pheochromocytoma resection has been described in a few patients with very different preoperative conditions (well-controlled blood pressure *vs.* hypertensive spells^{3,4}), treated with different anesthetic regimens (intraoperative use of thoracic epidural *vs.* general anesthesia only^{3,4}), and intraoperative complications (e.g., severe blood loss⁴). Therefore, data are not comparable, and it is much too early to provide treatment recommendations. Undoubtedly, the

David C. Warltier, M.D., Ph.D., served as Handling Editor for this exchange.

role of the vasopressin system is of greatest interest in patients with pheochromocytoma and stresses the importance of the vasopressin system as an important backup system for blood pressure control.¹ We agree with Dr. Roth that some patients may have a specific need for treatment with exogenous vasopressin, due to down-regulation and/or preoperative pharmacologic blockade of adrenoceptors, down-regulation of vasopressin receptors, and/or "inadequately low" vasopressin release during acute hypotension. Further studies are needed to address these issues.

We thank Drs. Lange, van Aken, and Westphal for their comments on the impact of the long-acting vasopressin analog terlipressin on hepatosplanchnic perfusion. Westphal *et al.*⁵ investigated the effects of arginine vasopressin on gut mucosal microcirculation in septic rats. In fact, their study provides evidence for severe abnormalities in mucosal blood flow after vasopressin infusion, adding to a number of studies that showed jeopardized splanchnic microcirculation due to vasopressin agonist activity at intestinal V1 receptors. In addition, both agents, arginine vasopressin and the specific vasopressin V1 agonist terlipressin, have been shown to significantly reduce the oxygen content of the gastric mucosa, suggesting malperfusion of the intestinal mucosa.^{6,7} Furthermore, Westphal *et al.*⁸ themselves summarized similar results as "data suggest that, in sepsis, vasopressin and terlipressin infusion may decrease gastrointestinal mucosal blood flow." In our recent review,¹ we concluded that "terlipressin is a potent intestinal vasoconstrictor, and evidence suggests decreased intestinal perfusion with terlipressin infusion."

We agree with Dr. Lange *et al.* that this conclusion can be discussed further by taking into account also the role of fluid management and the dose itself. Asfar *et al.*⁹ used studies in animals to investigate the influence of terlipressin on splanchnic perfusion, and results obtained in pigs show that a continuous low-dose infusion of terlipressin (5–15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) does not have detrimental effects on hepatosplanchnic perfusion, oxygen exchange, and metabolism. However, to our knowledge, this regimen has not been used in clinical trials in humans. Rather, terlipressin is usually administered in intravenous boluses of 1–2 mg. Bolus doses have been used by Asfar *et al.*¹⁰ in their study on endotoxic rats. The bolus of 6 $\mu\text{g}/\text{kg}$ used in this study, however, is only 25–50% of the dose reported to be used in humans, and lower boluses have not been studied in clinical trials with humans so far. Even with their low bolus doses, Asfar *et al.* found a high mortality in endotoxic animals treated with terlipressin alone. Only when terlipressin was administered after adequate fluid resuscitation, ileal microcirculation improved, as expected. Therefore, these latter results sup-

port the importance of early and aggressive fluid resuscitation in sepsis¹¹ and also warrant further research on dosing of terlipressin in sepsis. However, until these results are available, terlipressin can not be recommended for routine use in septic patients because of its potentially detrimental intestinal vasoconstrictor activities. That is, what dose it takes to make this drug not a poison is unsettled.

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GlideScope® Intubation Assisted by Fiberoptic Scope

To the Editor:—The difficult airway continues to challenge anesthesiologists. Recently, the development of laryngoscopes that have video cameras built in has led to some improvement in visualization of airway anatomy. One such device is the GlideScope®¹ (Saturn Biomedical Systems, Burnaby, British Columbia, Canada). It is equipped with a patent antifogging system that, together with a design that tends to keep the camera free of blood and secretions, has made visualization of airway structures better. However, despite better glottic visualization, on some occasions the endotracheal tube may still be difficult to pass into the larynx.

We recently provided general anesthesia to an obese female patient, aged 32 yr, weighing 142 kg, with a Mallampati class 4 airway. The patient had a short neck with a hyomental space of three finger-breadths. We chose to use the GlideScope® to facilitate the intubation. Although the camera revealed a class II view (only a portion of the vocal cords were visualized), it was impossible to maneuver the endotracheal tube into the

laryngeal opening even using the stylet supplied by the manufacturer of the GlideScope®. We then removed the stylet while leaving the endotracheal tube tip still visible in the GlideScope® monitor. We threaded a fiberoptic scope through the endotracheal tube until its tip also became visible on the GlideScope® monitor. Then, by using the thumb lever on the fiberoptic scope to control the tip, we managed to pass the fiberoptic scope through the vocal cords into the trachea and then pass the tube over the scope. In essence, the fiberoptic endoscope provides a "controllable stylet" to facilitate entry into the airway.

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Optimizing GlideScope® Laryngoscopy: An *In Vitro* Study on an Airway Model

To the Editor:—The GlideScope® Videolaryngoscope^{1*} (GVL; Diagnostic Ultrasound Corporation, Bothell, WA, and Saturn Biomedical Systems Inc., Burnaby, British Columbia, Canada) has a video camera incorporated in the undersurface of its curved plastic blade, providing a detailed airway image on an integrated monitor. The shape of the GVL partially resembles the shape of the standard Macintosh laryngoscope (fig. 1A). However, a 60° upward angulation of the distal half of the blade allows for an easy visualization of the larynx, which is often better than that of a rigid laryngoscopy.² Despite better laryngoscopic view with the GVL, intubation using a Macintosh laryngoscope was significantly faster.² In addition, in one series of 728 patients, the intubation failure rate of the GVL was 3.7% despite the ability to obtain grade 1 or 2 views most of the time.³⁻⁵ The paradox that the GVL provided better glottic visualization but not easy intubation may have been caused by patient-related factors, insufficient skills of intubators, and/or limitations of the device. Intubation with the GVL is limited by a sole reliance on the video image, because a line-of-sight view is nonexistent. We wondered whether this special design of the GVL might actually hinder accomplishment of intubation as a central purpose of the device.

Three steps are necessary for a successful intubation with the GVL: laryngoscope insertion and glottic visualization, delivery of the stylet-ended endotracheal tube (s-ETT) in front of the GVL camera, and guidance of the disengaged endotracheal tube (d-ETT) through the glottis and into the trachea. As described in the operator's manual, the GVL is inserted down the midline of the tongue and can be used as either a curved blade (Macintosh style) or a straight blade (Miller style). We noticed that some novice intubators actually lever the laryngoscope and halt its advancement as soon as they obtain a glottic view, which can ensue before the tip of the laryngoscope reaches the vallecula. Others insert the GVL too quickly and too deeply and obtain either a close glottic view or an esophageal view. Retracting the GVL from the esophagus provides a close glottic view. The operators' manual states, "maximum laryngeal exposure may not facilitate intubation."¹ This is contrary to usual attempts made by intubators to obtain the best laryngoscopic view possible. We postulated that such attempts might actually render the passage of the ETT more difficult or impossible, and we explored these observations in an airway model.

We used a Laerdal airway anatomical model 252 500 on which to simulate GlideScope® laryngoscopy and tracheal intubation (figs. 1B and C). The GVL was slowly advanced down the midline of the model's tongue. The advancement was ceased at three locations: At location 1, the blade tip was at the tip of the epiglottis; at location 2, the blade tip was within the vallecula; and at location 3, the laryngoscope was behind (posterior to) the epiglottis (figs. 2A-C, main panels). The initial position of the laryngoscope at each location was adjusted to give a view of only the arytenoids, grade 2b laryngoscopic view⁵ (figs. 2A-C, accessory panels in the upper right corner). After performance of tracheal intubation with this initial laryngoscopic view, the GVL position was modified twice at each location. The laryngoscope was lifted first, and the trachea was intubated. The laryngoscope was then levered, with the distal end pointing up, and the trachea was intubated.

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* Additional instructions available at: <http://www.virox.com/protocols/pdf/ManufacturersGlideScopeManual.pdf>. Accessed November 5, 2006.

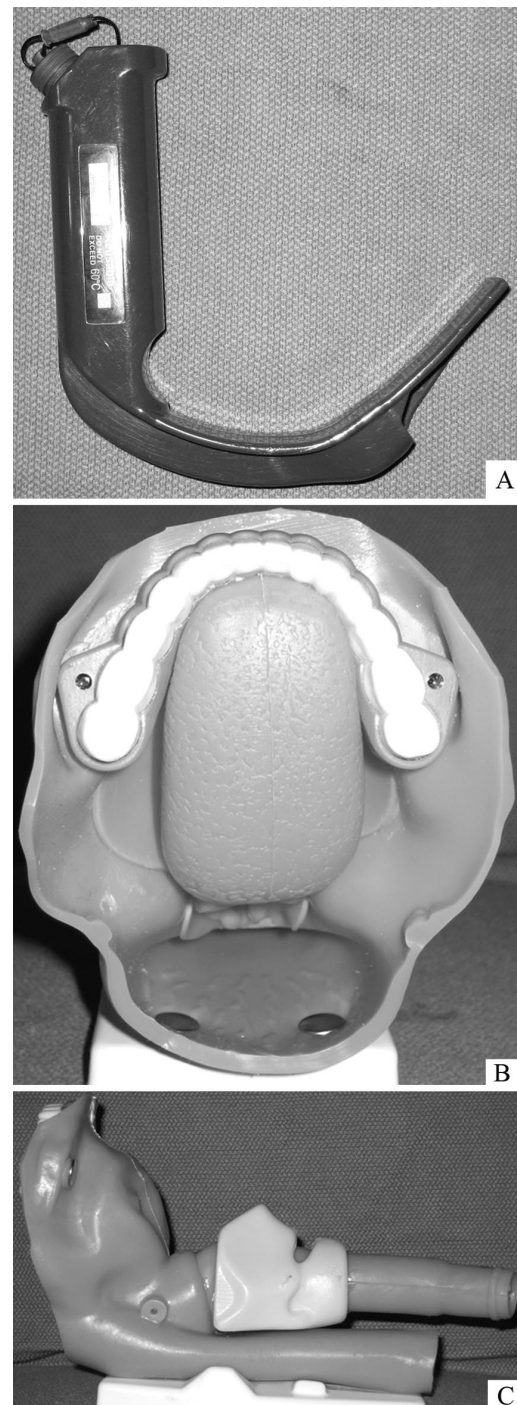


Fig. 1. (A) A standard GlideScope® Videolaryngoscope (Diagnostic Ultrasound Corporation, Bothell, WA, and Saturn Biomedical Systems Ind., Burnaby, British Columbia, Canada) with a visible bulge of the camera that is embedded in the distal half of the GlideScope® Videolaryngoscope blade. The tip of the GlideScope® Videolaryngoscope blade extends above the camera axis. (B) View of the oropharynx and the glottis of a plastic Laerdal airway anatomical model 252 500 (Laerdal Medical LTD, Orpington, Kent, United Kingdom). (C) Side view of the larynx and the trachea of the same model.

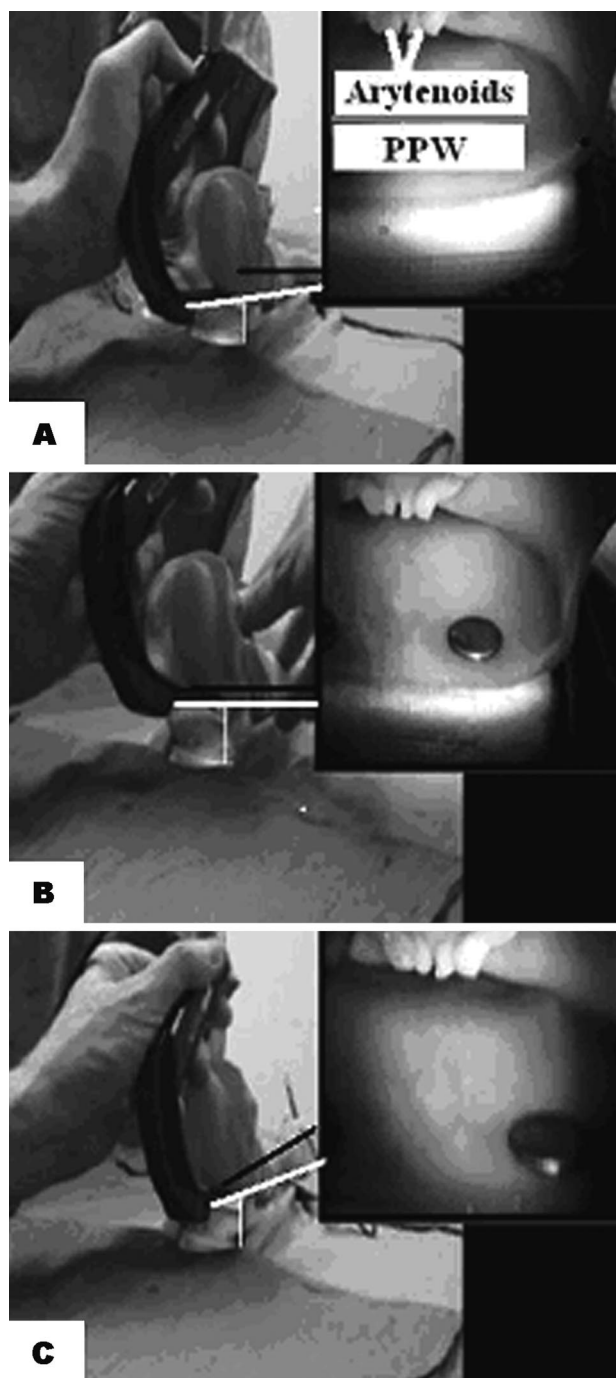


Fig. 2. The tip of the GlideScope® Videolaryngoscope blade was placed at three airway locations. (A) Location 1: The tip of the GlideScope® Videolaryngoscope is at the tip of the epiglottis. (B) Location 2: The tip is in the vallecula. (C) Location 3: The tip is behind (posterior to) the epiglottis. The initial position of the laryngoscope at each location was adjusted to give a view of only the arytenoids (accessory panels in the *upper right corner*); notice a close-up view of the glottis in C. The GlideScope® Videolaryngoscope camera axis (*white horizontal line*) is almost fully aligned with the laryngotracheal axis (*black line*) at all three locations. PPW = posterior pharyngeal wall.

The same course of action was followed at locations 1, 2 (figs. 3A and B), and 3. We performed the whole process of nine intubations twice: the first time using a recommended 60° stylet angle¹ and the second time using a 90° stylet angle.⁶ A lubricated 5.5-mm s-ETT was used to

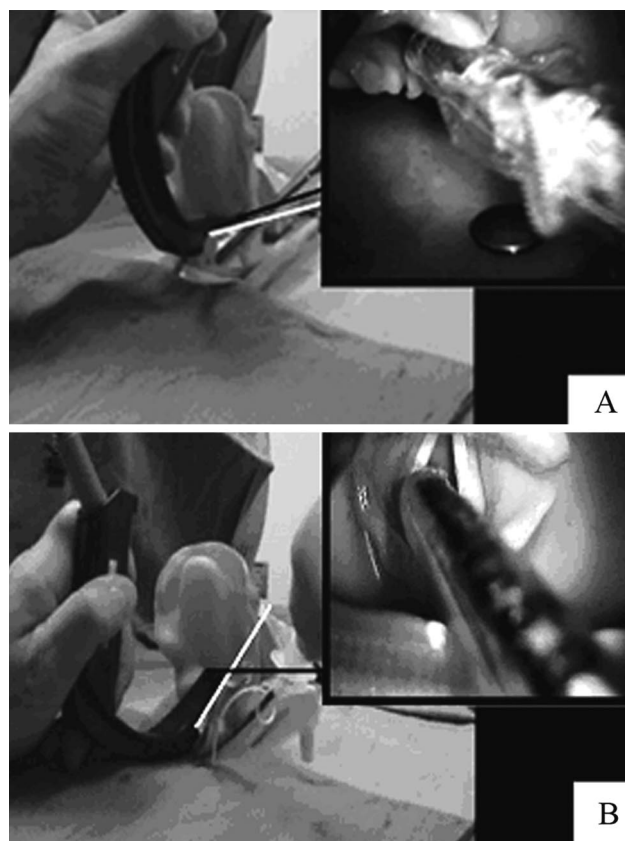


Fig. 3. The GlideScope® Videolaryngoscope blade is at location 2 (vallecular position). (A) The laryngoscope was gently lifted, providing adequate room for endotracheal tube (ETT) insertion and advancement. Camera axis and the laryngotracheal axis are aligned. (B) The laryngoscope was levered, resulting in extreme reduction of the oropharyngeal space and immediate glottic space for ETT insertion and advancement. There is a severe misalignment of the camera axis and the tracheal axes. Advancement of the disengaged ETT into the trachea is difficult because of an unfavorable angle of impact of the ETT tip and the anterior tracheal wall. Twisting the styletless ETT in a corkscrew manner is used to advance the ETT into the trachea.

minimize adhesion between the ETT and the model structures. The ETT was loaded on a malleable stylet with the ETT bevel facing to the left for all intubations. The intubator's hands maneuvering the laryngoscope and the s-ETT were recorded using a camcorder, while the passage of the d-ETT through the glottis was captured from the GVL video output (figs. 2 and 3, main panels and accessory panels, respectively). These two videos were synchronized and processed using video editing software (Adobe Premiere Pro 1.5; Adobe Systems Inc., San Jose, CA). Two compiled videos were then reviewed simultaneously.

Because of softness of the tongue, lifting the laryngoscope at location 1 misdirected the camera axis from the arytenoids toward the vallecula, shifting the view from grade 2b to grade 3. Gentle lifting of the GVL at locations 2 and 3 enhanced the laryngoscopic view from grade 2b to grade 2a. Levering the GVL pointed the camera axis upward as to provide visualization of the anterior portion of the glottis (fig. 3B). During this phase, the intubator purposefully avoided lifting the laryngoscope to avoid lifting the glottic structures. Extreme levering of the laryngoscope provided a grade 1 view at locations 1 and 2. The position of the camera close up to the glottis prevented visualization of the most anterior glottic portion at location 3. Insertion of the s-ETT and advancement of the d-ETT was easier and quicker at location 2 than at locations 1 and 3. Advancement of the d-ETT was easier and

time to intubation was shorter using the 60° stylet angle than the 90° stylet angle.

The GVL gently lifted within the vallecula provided a grade 2a laryngoscopic view and yielded the smoothest and quickest intubation using the 60° stylet angle. Adequate room for delivery of the s-ETT, optimal alignment of the camera axis with the laryngotracheal axis, and decreased impact of the d-ETT tip with the anterior tracheal wall are the most probable explanations (fig. 3A). The Miller-style placement of the GVL resulted in a close glottic view but reduced the space between the GVL camera and the glottis for the s-ETT insertion. We recommend the Miller-style use of the GVL only if the best laryngoscopic view with the Macintosh style is a grade 3 view. Levering the GVL shifts the proximal end of the laryngoscope down and brings more bulk of the GVL blade into the oropharynx. That will severely reduce the space available to pass the ETT, especially if intubators attempt to pass the s-ETT underneath the scope. Levering the GVL also produces upward orientation of the camera portion of the blade such that the d-ETT that is passed alongside the blade easily gets hung up on the anterior commissure or cricoid or tracheal cartilages (fig. 3B). In either case, although the view is improved, accessing the laryngeal inlet and advancing the tube may be more complicated, resulting in failed intubations.

In conclusion, several considerations support our suggestion that maneuvers necessary to achieve a grade 1 laryngoscopic view may render intubation with the GVL more difficult. We believe that a grade 2a view with the blade lifted within the vallecula is preferable for intubation with this device. It provides the adequate space in the oropharynx and in the immediate glottic area for the s-ETT insertion as well as optimal alignment of the camera axis with the laryngotracheal axis for ETT advancement.

The use of an open airway model does not, of course, completely model the challenges of tracheal intubation in patients. However, the

use of the open model allowed us to visibly demonstrate both good and bad laryngoscopic maneuvers and their corresponding glottic views. We hope that this letter may bring forth more understanding to GVL users about proper laryngoscopic and intubating maneuvers and may guide them to more intubation success with the device.

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