To the Editor.—I read with great interest the recently published article by Nakahata et al. 1 Propofol Restores Brain Microvascular Function Impaired by High Glucose via the Decrease in Oxidative Stress. 2 In this study, the authors observed that propofol, at potentially clinically relevant concentrations, dose-dependently attenuated or abolished rat brain microvascular dysfunction induced by high glucose, and that the protection of propofol, similar to that of the superoxide dismutase mimetic Tempol, is attributable to its inhibition of superoxide production induced by high glucose. Further, the authors found that nicotinamide adenine dinucleotide phosphate oxidase, but not xanthine oxidase, is the major source of superoxide production in the brain microvascular arteriolar wall after high glucose stimulation. 3 This is an interesting finding because nicotinamide adenine dinucleotide phosphate oxidase has also been reported as a major source of superoxide production in the diabetic heart 4 that is complicated by hypertrophic cardiomyopathy in the rat. 5 Therefore, theoretically, propofol may provide protection against oxidative injury of the diabetic heart through superoxide scavenging.

I congratulate Nakahata et al. for the interesting and detailed results about the role of superoxide scavenging in propofol restoration of microvascular function impaired by high glucose.

However, I think that the study design of Nakahata et al. 1 should be debated. Oxidative stress results from an imbalance between the formation and neutralization of pro-oxidants (such as superoxide and hydrogen peroxide). Pathologic processes (such as high glucose or diabetes) disrupt this balance by increasing the formation of prooxidants in proportion to the available antioxidants (such as the intracellular antioxidant enzymes: superoxide dismutase and glutathione peroxidase) and subsequently results in oxidative injury (oxidative stress). Therefore, a more suitable title for the study of Nakahata et al. 1 would be “Propofol Restores Brain Microvascular Function Impaired by High Glucose via the Decrease in Superoxide Production.” Given that parameters that reflect oxidative damages were not measured in the study.

High glucose has been shown to decrease intracellular levels of glutathione, 3 a potent endogenous antioxidant that converts hydrogen peroxide (H2O2) to water (H2O) catalyzed by glutathione peroxidase (i.e., 2GSH + H2O2 → GSSG + 2H2O, where GSSG represents glutathione disulfide). Acute high glucose 3 as well as chronic hyperglycemia 3 can significantly increase the production of tumor necrosis factor (TNF-α) in humans. TNF-α in turn has been shown to cause significant human vascular endothelial cell apoptotic death, accompanied by more profound decreases in intracellular glutathione peroxidase activity (approximately 50% reduction vs. control) than in superoxide dismutase activity (approximately 30% reduction vs. control). 7 As such, a small dose of hydrogen peroxide can significantly augment TNF-α cellular toxicity, which can be attenuated by treatment with propofol. 3 Propofol has been shown to attenuate hydrogen peroxide–induced myocardial dysfunction in rats. 8 Of interest, we recently found that TNF-α (at 40 ng/ml) caused more profound increases in intracellular hydrogen peroxide (approximately 20-fold) than in superoxide (approximately 16-fold) in cultured human umbilical vein endothelial cells as measured by dihydroethidium and dichlorofluorescein fluorescence staining, respectively, and that abolishment of the increase of hydrogen peroxide but not the superoxide overproduction prevented TNF-α cellular toxicity (Fang Wang, M.D., M.Sc., Zhengyuan Xia, M.D., Ph.D., Jingping Quyang, M.D., Wuhan, Hubei, China, unpublished observation, April 2007).

I am surprised that hydrogen peroxide production was not measured in the study of Nakahata et al. 1 Furthermore, I propose that attenuation of hydrogen peroxide–mediated oxidative injury could be the major mechanism by which propofol restores brain microvascular function impaired by high glucose.

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(Submitted for publication May 15, 2008.)

In Reply.—We appreciate Dr. Xia’s comments regarding our article. 1 As far as we understand, the comments can be summarized into two issues, including why we did not adopt the term “superoxide production” in the title of our article and why we focused our study on levels of superoxide, but not hydrogen peroxide, induced by the high concentration of glucose. We agree with Dr. Xia’s concern that oxidative stress results from an imbalance between the formation and the neutralization of oxidants. This is why we mentioned in the title of our article that propofol confers a decrease in oxidative stress, but not superoxide production, because we did not find definite evidence to support whether the effect of propofol on levels of superoxide in the rat brain slice is due to the inhibitory effect of this intravenous anesthetic on the formation or the neutralization of superoxide. Whether short- or long-term, exposure to high glucose reportedly increases superoxide levels within human tissues including vascular smooth muscle cells. 2–5 Considering these previous results, we conducted our study to evaluate the involvement of superoxide in the malformation of cerebral microvessels induced by high glucose. 6 It is also crucial to note that chronic hyperglycemia predisposes to exaggerated
inflammatory response and leukocyte dysfunction corresponding with superoxide production induced by nicotinamide adenine dinucleotide phosphate oxidase. Therefore, it seems difficult to draw the conclusion that hydrogen peroxide solely contributes to all inflammatory processes induced by hyperglycemia and/or diabetes mellitus.

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In Reply: —I greatly thank Drs. Downing and Baysinger for raising an important issue, my mistranslation of the Mallampati classification in my Editorial view for the noticeable article by Kodali et al. I totally agree with Drs. Downing and Baysinger that accurate knowledge and proper translation of the historical backgrounds of development of the anesthesia practice are important. Mallampati considered and hypothesized that the size of the base of the tongue is an important factor for determining the degree of difficulty during direct laryngoscopy. Mallampati et al. prospectively tested and proved the clinical usefulness of a simple grading system of the relative tongue size into three classes by beautifully demonstrating its significant association with the laryngeal view during direct laryngoscopy in 210 adult patients. After the milestone article was published in 1985, Samsoon and Young recalled 13 patients with failed intubation who were anesthetized during 1982–1985 at their institute and performed the airway assessment proposed by Mallampati et al. They noticed that even the soft palate was not visible in 12 of the 13 patients with failed intubation, and created the class 4 for these patients by modifying the original Mallampati classification.

For reasons of historical accuracy and because of the fundamental differences between them, a clear distinction between the 3/3 Mallampati score and the 4/4 Samsoon-Young score is necessary. As Drs. Downing and Baysinger indicated in their letter, confusion was introduced after the article was published by Samsoon and Young, although, needless to say, they significantly contributed to the improvement of preoperative airway assessment. Most likely, careless reading of the articles resulted in the confusion of “modified” Mallampati score currently used by many clinicians and researchers. The number of airway classes is not the only difference between the airway classification systems. Very few careful readers may recognize that the anatomical landmarks used for definitions of the airway classes and order of concealment of the structures by the tongue base significantly differ between them. Mallampati et al. defined three classes according to three anatomical landmarks seen as follows: class 1, faucial pillars, soft palate, and uvula; class 2, faucial pillars and soft palate; and class 3, soft palate. Samsoon and Young defined four classes according to four structures seen as follows: class 1, soft palate, fauces, uvula, and pillars; class 2, soft palate, fauces, and uvula; class 3, soft palate and base of uvula; and class 4, soft palate not visible. Clearly, the two airway structures seen as follows: class 1, soft palate, fauces, uvula, and pillars; class 2, faucial pillars, soft palate, and uvula; class 3, faucial pillars and soft palate; and class 4, soft palate not visible. Clearly, the two airway structures seen as follows: class 1, soft palate, fauces, uvula, and pillars; class 2, faucial pillars, soft palate, and uvula; class 3, faucial pillars and soft palate; and class 4, soft palate not visible.

The question is whether we have been accurately translating the difference between them for modifying and reshaping the Mallampati score; regretfully, we have not done well so far. There are confusions everywhere, but most of us do not realize them. Most anesthesia textbooks, including those mentioned by Drs. Downing and Baysinger, and original articles, even by Pilkington et al. and Kodali et al., describe a “modified” Mallampati score with four classes defined by the three anatomical landmarks used by Mallampati et al. The fourth is added as a condition that the soft palate is not visible. Clearly, the “modified” Mallampati score differs from the Samsoon-Young score. Despite using Mallampati’s anatomical landmarks, some anesthesia textbooks and even review articles use a figure published in the article of Samsoon and Young, introducing additional confusion. This confusion is possibly derived from the variability and complexity of the upper airway anatomy among patients. For example, it is difficult to determine the upper margins of the faucial pillars and the uvula. Mallampati et al. assume that the uvula is concealed by the tongue base first, whereas Samsoon and Young assume that the pillars are concealed by the tongue base first. Because of the anatomical variability, both could be wrong or correct. Compared with difficulty in determining the class 2 airway, both class 1 and class 3 are relatively easily determined. One solution to this inherent mistranslation or confusion would be to just define class 2 as an oropharyngeal view between classes 1 and 3. Now, many clinicians and researchers in non-anesthesiology fields acknowledge the usefulness of Mallampati’s concept. I believe it is time for anesthesiologists to recognize the inherent lost-in-translation of the Mallampati score and to improve Mallampati’s concept. By doing so, Mallampati’s great work and his name will continue to live on in our medical field.

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Venous Function and Pressure: What Is Their Role in the Management of Spinal Cord Ischemia after Thoracoabdominal Aortic Aneurysm Repair?

To the Editor:—I read with great interest the excellent article by Dr. Gelman in which he discusses the function of the human venous system. Although this review is most comprehensive, it does not detail the role of venous pressure in spinal cord perfusion. This aspect deserves attention because it may influence the management of spinal cord ischemia after thoracoabdominal aortic aneurysm repair. In a recent review of 858 thoracoabdominal aneurysm repairs (1990–2006), Dr. Etz et al. described the association between postoperative paraplegia and higher mean central venous pressures in the first 5 postoperative hours. Conceptually, this observation makes sense given that net spinal cord perfusion pressure depends on the arteriovenous pressure difference.

As a result, the manipulation of central venous pressure may improve spinal cord perfusion pressure and reverse paraplegia after thoracic aortic surgery. This has already been described for cerebrospinal fluid pressure, where its drainage may significantly impact the thoracic aortic surgery. This has already been described for cerebrospinal fluid pressure, where its drainage may significantly impact the management of postoperative paraplegia in this setting.

I congratulate Dr. Gelman on his excellent article that has highlighted the importance of the venous system. I look forward to his comments about the role of venous pressure in the pathophysiology of spinal cord ischemia after descending thoracic aortic reconstruction.

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(Accepted for publication July 9, 2008.)

To the Editor:—This letter is in response to the interesting article on venous physiology published in your journal. While the article expands on the thoughts of Arthur Guyton on these matters, it does not acknowledge the presence of other views of what makes the blood go around. The Guyton school of thought says that the loss of elastic energy in driving venous return needs to be restored by the heart. Guyton’s opponents opine that circulatory work is an either/or function and it is possible that proportionate to stress, the latter effect predominates. To add to the conundrum, the dynamics of the splanchnic circulation are among the most controversy-ridden areas in our understanding of cardiovascular physiology.

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Increased intrathoracic pressure increases transmural central venous pressure. It is suggested that this is made up by squeezing the abdominal venous system (in effect increasing the intra-abdominal pressure) and by mobilizing blood from the gut by an increase in splanchnic arteriolar resistance. Both of these maneuvers are harmful because any

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splanchnic ischemia is expected to trigger gut cell death,12 possible translocation of endotoxin from the gut, and eventual multiorgan disease. It follows that the surmise that increased intra-abdominal pressure (whatever the positive effects on mean systemic filling pressure are) is not harmful is incorrect. Most would agree that significant abdominal hypertension calls for only one therapeutic modality: early abdominal decompression.13 This alone can prevent the downward spiral of organ ischemia, acidosis, and renal failure. Because the analysis of the venous circulation stops at the right atrium, it cannot account for the effects of increased intrathoracic pressures (upward motion of diaphragm with increased intra-abdominal pressure) on the pulmonary vasculature and the downstream consequences on the right heart.

The commentary on the utility or lack thereof of measured central venous pressures is, of course, timely, considering the ever-increasing evidence base of dynamic circulatory indices. However, one might add, almost in requiem, that increased central venous pressure is still a useful clinical tool in the evaluation of right heart or pericardial disease.

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Inspiratory Increases in Systolic Blood Pressure (“Delta-up”) and Pulse Pressure Are Not Equivalent

To the Editor—We read with interest the recent review by Dr. Gelman on venous function and central venous pressure. In the paragraph on systolic blood pressure and pulse pressure variations, Dr. Gelman describes the effects of positive-pressure ventilation on ventricular and stroke volumes and states that during inspiration, a temporary increase (as compared with end of expiration) in left ventricular (LV) stroke volume, pulse pressure, and systolic blood pressure occurs.3 This deflection is called “delta-up” and is usually around 2–4 mmHg.4 Delta-up has effectively been described as reflecting the inspiratory increase in LV stroke volume.5 However, delta-up actually quantifies the inspiratory increase in splanchnic blood pressure2 and may thus result either from an increase in LV stroke volume or an increase in extra-mural aortic pressure related to the increase in pleural pressure.3 Unlike the splanchnic blood pressure, the pulse pressure is directly proportional to LV stroke volume.6 It is thus the inspiratory increase in pulse pressure (which could be called “deltaPP-up”) that reflects the inspiratory increase in LV stroke volume. No study, however, has described (fig. 1).4 For each patient, the arterial pressure curve recording with the largest delta-up was then selected. In these 35 recordings, pulse pressure and deltaPP-up (the difference between maximal pulse pressure at inspiration and pulse pressure at end-expiratory pause; fig. 1) were then also measured. We found that deltaPP-up (1.6 ± 1.8 mmHg) was smaller than delta-up (5.3 ± 2.4 mmHg; P < 0.01 vs. deltaPP-up). All 35 patients had a positive delta-up (range, 2–13 mmHg), whereas deltaPP-up ranged between –1 and 8 mmHg and was positive (≥ 1 mmHg) in only 23 patients (P < 0.01 vs. delta-up). Among the 16 patients where delta-up was 6 mmHg or greater, deltaPP-up was 2 mmHg or less in 12 patients. These data show that inspiratory increases in systolic blood pressure (delta-up) and pulse pressure (deltaPP-up) are not equivalent. Extramural aortic pressure seems to be the primary determinant of delta-up in many patients. Using delta-up as an indicator of inspiration-induced increase in LV stroke volume may thus be misleading. Finally, it has been suggested that the pulse pressure variation, because it includes this inspiratory increase in LV stroke volume that is not related to fluid responsiveness, may falsely predict positive responses to volume expansion.3,5 In the current study, where the criterion for selection of arterial curves was a large delta-up, deltaPP-up was large enough to potentially result in such false-positive pulse pressure variation in only one patient (deltaPP-up = 8 mmHg [13% of the pulse pressure]; pulse pressure variation = 15%; delta-up = 13 mmHg; delta-down = 3 mmHg). This strongly suggests that this theoretical limitation of pulse pressure variation may be relevant in only a small proportion of patients. In any case, deltaPP-up, but not delta-up, should be measured to detect such occurrence.

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Fig. 1. Respiratory changes in arterial blood pressure in a mechanically ventilated patient. The difference between the maximum systolic blood pressure and the systolic blood pressure during end-expiratory pause (end of recording) defines delta-up. The difference between the maximum pulse pressure (PPmax, with pulse pressure = systolic minus diastolic pressure) and the pulse pressure during end-expiratory pause (PPref) defines deltaPP-up. In this typical example, delta-up = 7 mmHg, whereas deltaPP-up = 1 mmHg.


In Reply—I agree with Dr. Augoustides that my review article1 “does not detail the role of venous pressure in spinal cord perfusion.” The review is focused on the gross physiologic relation within the venous system.2,3 Therefore, I did not discuss the role of veins in different organs and systems. Nevertheless, the issue per se is quite important. The spinal cord injury during surgical repair of thoracoabdominal aneurysms to a great extent depends on a dramatic decrease in spinal cord perfusion pressure, which is defined as a difference between distal aortic pressure minus cerebrospinal fluid pressure or venous pressure, whichever is higher. It is clear from this simple equation that the higher the central venous pressure (CVP) is, the lower perfusion pressure would be. The work by Etz et al.2 quoted by Dr. Augoustides does not prove but is in agreement with the speculation above. Their and other observations strongly suggest that a high CVP can be dangerous for this patient population. Interestingly, similar situations can be observed in patients undergoing liver transplantation: A high CVP may jeopardize the perfusion of the transplanted liver. Therefore, I agree with Dr. Augoustides that increased intramural and transmural CVP can be detrimental to perfusion of quite a few organs, including the spinal cord. Finally, I thank Dr. Augoustides for high evaluation of my review article.

I am very thankful to Dr. Jayant for bringing to our attention an excellent and innovative work by Brengelmann.3,4 Compared with the classic work of Guyton, Brengelmann and also Levy5 have introduced an interesting and important concept emphasizing the role of the heart as a pump and shifts of blood volume within the circulatory system. Regarding the volume shifts, the discussion of the flow–pressure–volume relation in figure 3 of the review1 as well as the two-compartment model6,7–9 address this issue. Regarding pump function, Levy and Brengelmann are correct in that it is crucially important that circulation stop without a pump. The Guyton concept of mean circulatory filling pressure (MCFP) is not necessarily incorrect: Stress volume and pump function are needed to maintain MCFP, and only then (when it is maintained by stress volume and pump function) does MCFP become the driving force for venous return. This is why Rothe6 declared that the MCFP is the “pivoting pressure,” emphasizing the importance of this pressure as a driving force for venous return.

At the end of his first paragraph, Dr. Jayant correctly says that “failure of pump function leads to an assortment of chemical mediators that can . . . affect the venous capacity.” I agree. In the second paragraph of the letter, Dr. Jayant expresses the thought that analysis
Finally, I am happy that Dr. Jayant, having a very critical mind, agrees with me that the "increased central venous pressure is still a useful clinical tool in the evaluation of right heart or pericardial disease;" I say so in the review.\[744] Therefore, I would not think that my review is a requiem to the CVP; it is rather an opera; opera in Latin means "labor" or "work produced," where many parts (singing, dancing, visual art, music, and so on) are put together.\[8]

We should be thankful to Dr. Tavernier et al. for sharing with us their recent observations on the importance of an increase in pulse pressure (deltaPP-up) compared with an increase in systolic pressure (delta-up), mentioned in my review.\[1]\n
In the review, I was talking about both systolic pressure variation (SPV) and pulse pressure variation (PPV). I started the description with delta-up; however, just a few lines later I wrote about delta-down, mentioning that it is larger than delta-up and referring to the total SPV: delta-up plus delta-down. In SPV, delta-down plays a more important role than delta-up does, not only because it is larger but also because it reflects the volume status, as was shown by Dr. Tavernier et al. a decade ago.\[9] Practically, it is much easier to assess SPV than PPV. I agree that PPV is considered to be a more accurate indicator of responsiveness to fluid load than SPV is; however, the differences between them are really minimal.\[10]

For example, a relatively recent study demonstrated that the coefficients of correlation between stroke volume and SPV or PPV were exactly the same: 0.91.\[11]

Other investigators also found that SPV and PPV were the most accurate predictors of fluid responsiveness, even emphasizing that SPV was more independent of the setting of mechanical ventilation.\[12] Therefore, mainly based on the simplicity and usefulness of using the SPV, this section of the review\[1] addressed the SPV as a total, with the main component of delta-down rather than focusing only on delta-up. Obviously, I would echo the opinion of Dr. Tavernier et al. that if one has an opportunity in clinical practice to assess PPV with separation of deltaPP-up and deltaPP-down, it would ensure more accurate assessment of patient's volume status.

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To the Editor—Fospropofol disodium (GPI 15715 or Aquavan® Injection; MGI Pharma, Inc., Bloomington, MN) is a water-soluble, phosphono-O-methyl prodrug of propofol for intravenous injection. It has been evaluated for sedation during diagnostic and routine therapeutic procedures. The early evaluation studies were published mostly in Anesthesiology between 2003 and 2005.

After intravenous administration, fospropofol is rapidly metabolized by alkaline phosphatase enzymes, releasing propofolFP. Several pharmacokinetic and pharmacodynamic studies have shown that propofolFP demonstrated differences in pharmacokinetic and pharmacodynamic profiles compared with propofol in a lipid solution.1–3 We have recently discovered an assay problem that may have affected the measurement of propofolFP plasma concentrations in previously published studies. In the earlier studies,1–4,6 blood samples were collected in tubes containing sodium orthovanadate (SOV; 60 mg added as a solid powder to maintain 10 mg/ml concentration) to prevent further in vitro conversion of fospropofol to propofol by alkaline phosphatase enzymes. This was found to result in incomplete dissolution of the SOV powder and variable concentrations of SOV that affected plasma pH and caused hemolysis of many samples, leading to changes in propofol extraction recovery and storage stability. As a result, the propofolFP concentrations obtained in previous studies1–4,6 could possibly be inconsistent and unreliable, because the impact of the aforementioned factors was neither known nor controlled, and therefore, the originally reported propofol pharmacokinetic and pharmacodynamic results and the derived conclusions could be inaccurate. It was shown that the assay and stability problem was limited to quantitation of propofolFP and that it did not affect the fospropofol concentrations. The new drug application for fospropofol disodium was submitted to the US Food and Drug Administration in September 2007. The propofol assay problem was reported in detail in the New Drug Application, as were details of the revised assay methodology. Subsequent to the discovery of the problem, the sample handling procedure was standardized to reduce variation in SOV concentration (e.g., SOV was added as a solution), and improved sample handling and processing techniques that resolved the problems were developed and validated. Additional studies were then conducted using an appropriate assay to assess the pharmacokinetics and pharmacodynamics of fospropofol in healthy volunteers and patients. We plan to publish these results shortly, along with an estimate of the degree of error from the previously published studies that reported results using the old assay. We very much regret the magnitude of the originally published incorrect information and the confusion that it has and will cause in the pharmacokinetics of propofol from the use of fospropofol.

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In Reply.—This letter led to discussions among the Editors-in-Chief of Anesthesiology, Anesthesia & Analgesia, and the European Journal of Anaesthesiology regarding how to handle the previously published articles that used this assay. Our primary commitment is to our readers, including current and future investigators who are basing clinical practice and clinical investigation on these incorrect data. We have decided to publish correction statements indicating that the propofol concentration data in these articles are likely incorrect and that they should not be used. If we do not receive within 12 months a manuscript that validates the new assay, analyzes the likely error and bias in each of the six articles in question, and determines how the error influences the conclusions, we will retract these previously published articles.

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