

## Role of Hydrogen Peroxide in Propofol Restoration of Microvascular Function Impaired by High Glucose

*To the Editor:*—I read with great interest the recently published article by Nakahata *et al.*,<sup>1</sup> “Propofol Restores Brain Microvascular Function Impaired by High Glucose *via* the Decrease in Oxidative Stress.” 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.<sup>1</sup> 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<sup>2</sup> that is complicated by hypertrophic cardiomyopathy in the rat.<sup>3</sup> 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.*<sup>1</sup> 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 prooxidant in proportion to the available antioxidants (such as the intracellular antioxidant enzymes: superoxide dismutase and glutathione peroxidase) and subsequently result in oxidative injury (oxidative stress). Therefore, a more suitable title for the study of Nakahata *et al.*<sup>1</sup> 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,<sup>4</sup> a potent endogenous antioxidant that converts hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) to water (H<sub>2</sub>O) catalyzed by glutathione peroxidase (*i.e.*, 2GSH + H<sub>2</sub>O<sub>2</sub> → GSSG + 2H<sub>2</sub>O, where GSSG represents glutathione disulfide). Acute high glucose<sup>5</sup> as well as chronic hyperglycemia<sup>6</sup> 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).<sup>7</sup> As such, a small dose of hydrogen peroxide can significantly aug-

ment TNF-α cellular toxicity, which can be attenuated by treatment with propofol.<sup>7</sup> Propofol has been shown to attenuate hydrogen peroxide-induced myocardial dysfunction in rats.<sup>8</sup> 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.*<sup>1</sup> 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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*In Reply:*—We appreciate Dr. Xia's comments regarding our article.<sup>1</sup> 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.<sup>2,3</sup> Considering these previous results, we conducted our study to evaluate the involvement of superoxide in the malfunction of cerebral microvessels induced by high glucose.<sup>1</sup> 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.<sup>4</sup> 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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## Lost in Translation: The Mallampati Score?

“Originally there were three Mallampati grades; a fourth was added by Samssoon and Young.”—Pilkington *et al.*<sup>1</sup>

*To the Editor:*—We read with interest the recent editorial commentary by Isono<sup>2</sup> referencing the article by Kodali *et al.*<sup>3</sup> Isono states: “The Mallampati classification is a rough estimate of the tongue size relative to the oral cavity. . . . In addition to difficult tracheal intubation, Mallampati class 3 or 4 is an independent predictor for difficulty of mask ventilation during anesthesia induction and presence of obstructive sleep apnea.”<sup>2</sup> In contrast, Kodali *et al.* state: “In the first study, we used the conventional Samssoon modification of the Mallampati score to evaluate airway changes.”<sup>3</sup> We believe that while Kodali *et al.* correctly identify the Samssoon–Young modification of the Mallampati score, which changed the original 3-point scale of Mallampati to a 4-point scale,<sup>4,5</sup> the editorial comment represents the latest example of the Mallampati score being “lost in translation.”

Other examples of the confusion this change generated can easily be found. Farcon *et al.*,<sup>6</sup> in their report on changing airway score during labor, state: “For this reason, a Mallampati evaluation of the airway with or without the Samssoon–Young additions is performed . . . on admission of the pregnant woman to hospital.” However, they then confuse the issue by stating: “A repeat airway evaluation . . . revealed marked edema of the lower pharynx giving rise to a Mallampati score of III–IV.” In contrast, Pilkington *et al.*<sup>1</sup> (quoted above), in their study of airway changes in pregnancy, clearly noted the difference between the original Mallampati score out of 3 and the addition of a fourth grade by Samssoon and Young.

In chapter 21 of *Snyder and Levinson’s Anesthesia for Obstetrics*, Stackhouse and Bainton<sup>7</sup> appropriately outline both the original Mallampati classification and the score’s modification by Samssoon and Young. However, their figure 21.1 carries the confusing legend: “Mallampati classification. Pictorial classification of the pharyngeal structures as seen when conducting the examination.” Fortunately, the situation is redeemed by an acknowledgment that follows: “Adapted from Samssoon GLT, Young JRB . . .”

Malinow,<sup>8</sup> writing in Norris’s *Obstetric Anesthesia*, 2nd Edition, first cites Samssoon and Young’s retrospective review of “seven parturients who previously experienced failed intubation.” He then references the article by Rocke *et al.*,<sup>9</sup> who “calculated the relative risk of difficulty at tracheal intubation *versus* a Mallampati class 1 airway.” However, table 3, which lists “Relative risk of factors associated with difficulty at tracheal intubation as compared with an

uncomplicated Mallampati class 1 evaluation,” includes as an “anatomic feature—Mallampati 4.” Yet Rocke *et al.* clearly state: “We have therefore evaluated the Mallampati test as modified by Samssoon and Young in a large obstetric population undergoing cesarean section under general anesthesia.”<sup>9</sup>

Watanabe and Handa’s<sup>10</sup> chapter titled “Difficult and Failed Intubation” in the *Textbook of Obstetric Anesthesia* edited by Birnbach, Gatt, and Datta includes an illustration (fig. 32-1) of four upper airway views (class I–IV) said to originate from the original 1985 article by Mallampati *et al.*<sup>4</sup>

Similarly, Kuczkowski, Reisner, and Benumof’s<sup>11</sup> chapter, “The Difficult Airway: Risk, Prophylaxis, and Management,” in the latest edition of Chestnut’s *Obstetric Anesthesia Principles and Practice* also includes an illustration (fig. 31-4) of four upper airway views (class I–IV) once again said to originate from the original 1985 article by Mallampati *et al.*

In a recent review titled “Airway Problems in Pregnancy,” Munnur and Suresh<sup>12</sup> state that the Mallampati classification “evaluates the size of the tongue relative to the size of the oropharyngeal cavity. It is divided into four classes based on the oropharyngeal structures seen on opening the mouth: . . . ; and class IV, only hard palate.” In addition, both Pilkington *et al.* and Rocke *et al.* are misquoted as having used the “Mallampati scores” to report on the incidence of “Mallampati class IV airways.”

In a later article, these same authors, joined by de Boisblanc,<sup>13</sup> offer a clearer text rendition of the modification of the original Mallampati score by Samssoon and Young. However, figure 1 illustrates four airway classes with the legend: “Difficulty of intubation based on Mallampati classification. Adapted from Mallampati SR: A clinical sign to predict difficult tracheal intubation: A prospective study. *Can J Anaesth* 1985; 32: 429.” It seems that Mallampati’s six coauthors were lost in translation too.

In a lighter vein, Doyle and Wilson provide a similar illustration (no mention of its origin) in a continuing medical education program\* on management of the difficult airway published in *Anesthesiology News*.<sup>14</sup>

In the interests of historical accuracy, we think it is important to clearly differentiate between the original 3/3 Mallampati score and 4/4 modification thereof published subsequently by Samssoon and Young. By so doing, the Mallampati score may emerge from its current situation of being “lost in translation” because of the confusion introduced by the Samssoon–Young modification and may thereby assume its proper and important place in the history and practice of anesthesia.

\* Available at: <http://www.CMEZone.com>. Accessed May 14, 2008.

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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.*<sup>1,2</sup> 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.<sup>3</sup> 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.<sup>4</sup> After the milestone article was published in 1985, Samssoon 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.<sup>5</sup>

For reasons of historical accuracy and because of the fundamental differences between them, a clear distinction between the 3/3 Mallampati score<sup>4</sup> and the 4/4 Samssoon-Young score<sup>5</sup> is necessary. As Drs. Downing and Baysinger indicated in their letter, confusion was introduced after the article was published by Samssoon 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.<sup>4</sup> Samssoon 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.<sup>5</sup> Clearly, the two airway classification systems are totally different.

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

Levinson's *Anesthesia for Obstetrics*, 4th edition. Edited by Hughes SC, Levinson G, Rosen MA. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 375-6

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textbooks, including those mentioned by Drs. Downing and Baysinger, and original articles, even by Pilkington *et al.*<sup>6</sup> and Kodali *et al.*,<sup>2</sup> 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 Samssoon-Young score. Despite using Mallampati's anatomical landmarks, some anesthesia textbooks and even review articles use a figure published in the article of Samssoon 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.*<sup>4</sup> assume that the uvula is concealed by the tongue base first, whereas Samssoon and Young<sup>5</sup> 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 nonanesthesia 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.<sup>1</sup> 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.<sup>2</sup> In a recent review of 858 thoracoabdominal aneurysm repairs (1990–2006), Dr. Etz *et al.*<sup>2</sup> 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 management of postoperative paraplegia in this setting.<sup>3</sup>

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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## What Is Simple Is Perhaps Not Always the Truth

*To the Editor:*—This letter is in response to the interesting article on venous physiology<sup>1</sup> published in your journal. While the article expands on the thoughts of Arthur Guyton<sup>2</sup> on these matters, it does not acknowledge the presence of other views<sup>3</sup> 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.<sup>4</sup> Guyton's opponents opine that circulatory work<sup>5</sup> (integral function of instantaneous pressure and volume decrement) is the elixir of venous flow. To the practicing clinician, the import of either the potential energy in the form of venous volume (Guyton) or a potential energy in the form of an energy derived from ventricular work propelling venous return is only of academic interest; in both models, venous flow ceases very soon after the pump stops! The mean circulatory filling pressure (strictly speaking, the pressure when cardiac output is zero in an experimental model) is therefore critically dependent on pump function. Even as we quibble about physiologic niceties, in the intact animal, the heart as a pump not only affects the fluid mechanics of blood flow; it also affects, and is in turn affected by, the neurohormonal milieu in which it works.<sup>6</sup> Failure of pump function leads to an assortment of chemical mediators that can potentially affect the venous capacity and venous compliance.<sup>7</sup>

Because teleologically the cardiopulmonary apparatus works to perfuse the systemic circulation, it also seems to make more physiologic sense that the venous circuit ends at the pulmonary vein–left atrial level. The right ventricle and the pulmonary circulation are nicely coupled, but either can play rogue (pulmonary hypertension or right ventricular myocardial infarction). The left heart may not then fill adequately. One might argue again that the  $VR = MSFP - RAP/R_v$  relation explains this ( $VR =$  venous return,  $MSFP =$  mean systemic filling pressure,  $RAP =$  right atrial pressure,  $R_v =$  cumulative venous resistance) because the gradient for venous return is decreased when the right atrial pressure is high. I could equally argue that interventric-

ular dependence has compromised left ventricular function and therefore resulted in less work done by it in pushing the blood around! All in all, any analysis of venous function that stops at the right atrium is seemingly not complete.

Arguably, the concept of the splanchnic circulation being a potential booster pump to the larger venous circulation outside it (on account of its large volume and high compliance) is elegant; how well does this model work in clinical practice? Although it offers an elegant explanation of the increase in filling pressure with aortic clamping<sup>8</sup> or the ability to maintain vital perfusion early on with exsanguinating trauma, as the physiologic setting becomes complex (heart failure, septic shock) it becomes increasingly difficult to apply. The author himself points out that adrenergic stress could affect both the changes in stressed volume (the currency of the circulation, in principle) and the effect on mobilization of this very volume. This 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.<sup>9,10</sup> The circulation seems to be among the vulnerable in terms of ischemia<sup>11</sup>; one cannot imagine a situation of circulatory stress where a *decreased* splanchnic arteriolar resistance with a *decreased* resistance to hepatic outflow (working like an “arteriovenous fistula”) can potentially contribute to an *increased* mean circulatory filling pressure. From this perspective, the two-compartment model has limited application in our understanding of most clinical situations causing a circulatory imbalance.

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*

splanchnic ischemia is expected to trigger gut cell death,<sup>12</sup> 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.<sup>13</sup> 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

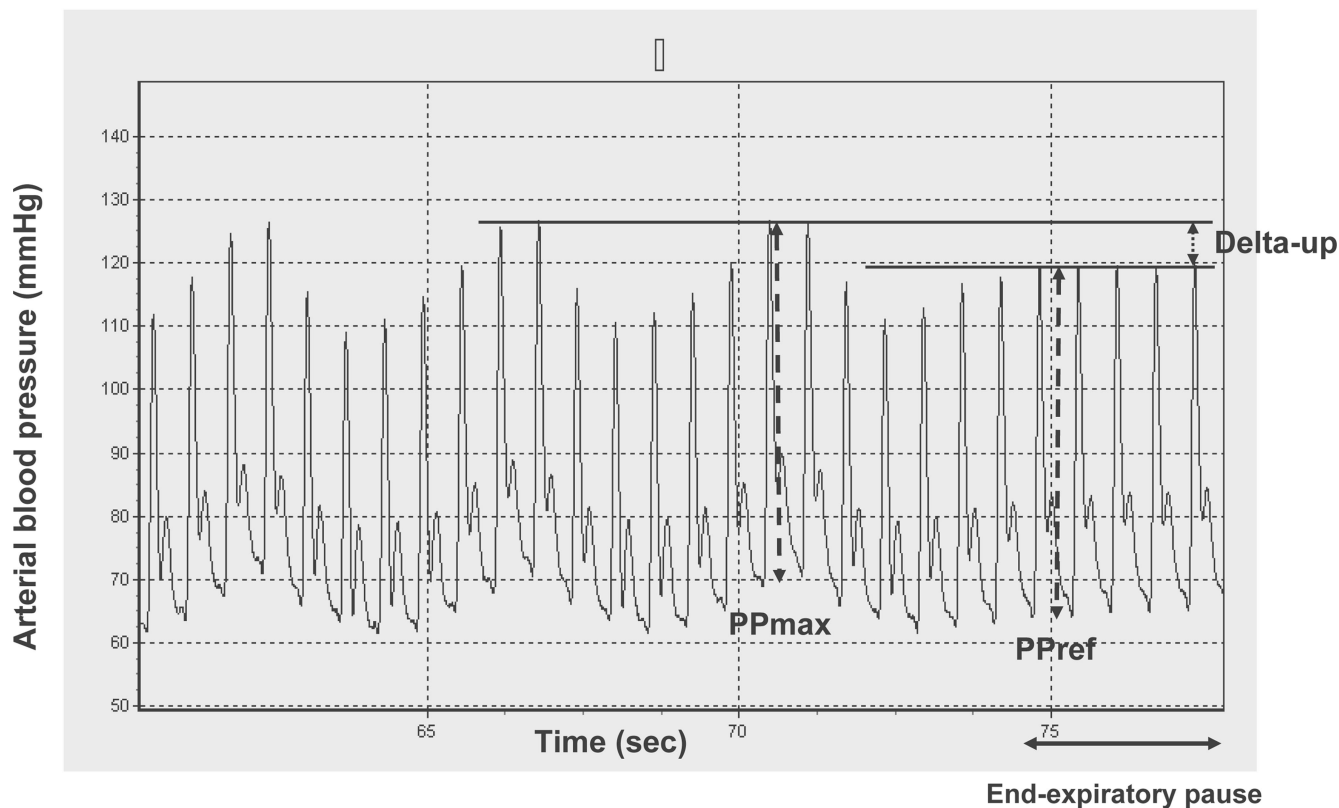
*To the Editor:*—We read with interest the recent review by Dr. Gelman on venous function and central venous pressure. In the paragraph on systolic blood pressure and pulse pressure variations, Dr. Gelman describes the effects of positive-pressure ventilation on ventricular and stroke volumes and states 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.<sup>1</sup> This deflection is called "delta-up" and is usually around 2-4 mmHg.<sup>1</sup> Delta-up has effectively been described as reflecting the inspiratory increase in LV stroke volume.<sup>2</sup> However, delta-up actually quantifies the inspiratory increase in systolic blood pressure<sup>2</sup> and may thus result either from an increase in LV stroke volume or an increase in extramural aortic pressure related to the increase in pleural pressure.<sup>3</sup> Unlike the systolic blood pressure, the pulse pressure is directly proportional to LV stroke volume.<sup>3</sup> 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 investigated whether delta-up and deltaPP-up behave similarly among ventilated patients. We recently reviewed 298 arterial blood pressure curves recorded immediately before or after fluid challenges in 35 mechanically ventilated patients (21 men and 14 women, mean [± SD] age of 55 ± 14 yr) in the intensive care unit (n = 17) or in the operating room (n = 18). Delta-up was measured as previously described (fig. 1).<sup>4</sup> 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 ( $\geq 1$  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.<sup>3,5</sup> 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.**

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*In Reply:*—I agree with Dr. Augoustides that my review article<sup>1</sup> “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.”<sup>1</sup> (P735) 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.*<sup>2</sup> 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.<sup>3,4</sup> Compared with the classic work of Guyton, Brengelmann and also Levy<sup>5</sup> 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 review<sup>1</sup> (P737) as well as the two-compartment model<sup>(pp739-41)</sup> 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 Rothe<sup>6</sup> 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



of the overall circulatory system “that stops at the right atrium is seemingly not complete.” I also agree. The review in question focuses only on the venous system,<sup>1</sup> (p735) not on “the overall circulatory system.” The fact that the review does not discuss in detail heart and pulmonary circulation should not be construed to say that I do not believe that these parts of the circulation are important. The review describes the venous system itself in more detail than the work by Levy and Brengelmann does; the latter focuses more on the overall cardiovascular system than on the details of the venous system *per se*. If I had introduced the concept described by Brengelmann, I would have had to delete something else that in my mind is more relevant to the focus of the review.

In the third paragraph of his letter, Dr. Jayant says that the two-compartment model described in my review “offers an elegant explanation of the increase in filling pressure with aortic clamping.” Then Dr. Jayant says that “as the physiologic setting becomes complex (heart failure . . .) it becomes increasingly difficult to apply.” Not at all. As I mentioned in my review,<sup>1</sup> (p737) a decrease in cardiac output due to cardiac failure would decrease flow from the splanchnic arteries, decrease volume within splanchnic veins, and shift this volume to the systemic circulation, increasing preload and recruiting the Frank-Starling mechanism.

A few lines later, I am afraid Dr. Jayant does not properly distinguish the two compartments within the venous system: “working like an arteriovenous fistula” in my example is related to a decrease in arterial resistance in the fast (main) compartment rather than to a decrease in resistance to hepatic outflow (slow compartment). Despite that these specific examples that Dr. Jayant lists in this paragraph fit quite well (and can be easily explained by) the two-compartment model, I agree conceptually that not all physiologic and pathophysiologic observations can fit this model. Models rarely if ever explain everything.

In the same paragraph, Dr. Jayant separates changes in stress volume from the mobilization of this volume; then he says, “This is an either/or function.” I disagree. This is the same function: Mobilization of blood volume from the splanchnic system is an increase in stress volume secondary to the shift of blood from unstressed volume.

In the fourth paragraph of his letter, Dr. Jayant writes that “increased intrathoracic pressure increases transmural central venous pressure.” This is wrong in most situations and is certainly wrong in the situation when an increase in intrathoracic pressure is due to routine controlled ventilation in a patient with normal heart function and blood volume. In such a situation, transmural CVP does not increase; only intramural CVP does. When intramural CVP is increased, the sympathetic nervous system is moderately activated, leading to an increase in splanchnic arterial resistance (associated with a passive recoil of splanchnic veins) as well as active constriction of the splanchnic veins (veins are much more sensitive to sympathetic stimulation than arteries),<sup>7</sup> working in concert with squeezing the abdominal venous system by the shift of the diaphragm downward and increasing intraabdominal pressure. These responses increase stressed volume and then MCFP, which maintains the baseline pressure gradient for venous return (MCFP – CVP). This does not lead, as Dr. Jayant suggests, to splanchnic ischemia. If it did, we would be dead before we started walking: Every time we stand up, a low degree of sympathetic stimulation occurs, and blood shifts from the splanchnic veins into the systemic circulation to increase stress volume and MCFP, maintaining normal transmural CVP and venous return. Only a high degree of sympathetic nervous tone might lead to severe arterial constriction within the splanchnic vasculature, which might jeopardize blood supply to the gut. Dr. Jayant writes “most would agree that significant abdominal hypertension calls for only one therapeutic modality: early abdominal decompression.” I disagree only with the word *most*: I would say that *all* would agree with this notion. Therefore, the whole point here is the degree of increase in sympathetic nervous system discharge: A low degree is absolutely needed for every moment of survival, whereas a high degree is dangerous.<sup>1</sup> (pp739,741,744)

Finally, I am happy that Dr. Jayant, having a very critical mind, agrees with me that “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.<sup>1</sup> (p744) 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.<sup>8</sup>

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.<sup>1</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup>

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.<sup>12</sup> Therefore, mainly based on the simplicity and usefulness of using the SPV, this section of the review<sup>1</sup> 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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## Fospropofol Assay Issues and Impact on Pharmacokinetic and Pharmacodynamic Evaluation

*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 propofol<sub>FP</sub>. Several pharmacokinetic and pharmacodynamic studies have shown that propofol<sub>FP</sub> demonstrated differences in pharmacokinetic and pharmacodynamic profiles compared with propofol in a lipid solution.<sup>1-5</sup> We have recently discovered an assay problem that may have affected the measurement of propofol<sub>FP</sub> plasma concentrations in previously published studies. In the earlier studies,<sup>1-4,6</sup> 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 propofol<sub>FP</sub> concentrations obtained in previous studies<sup>1-4,6</sup> 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 propofol<sub>FP</sub> 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

This study was funded by a grant from MGI Pharma, Inc., Bloomington, Minnesota.

*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

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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question, and determines how the error influences the conclusions, we will retract these previously published articles.

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