In Reply:

Conflict of interest is managed using a variety of strategies, but they all begin with disclosure. I absolutely agree with Dr. Kempen's insistence that important competing interests must be identified and believe that there could have been more transparency regarding competing interests of the individuals who prepared this editorial which appeared in the January 2014 issue.[1]

The journal style changed with the January issue in two manners relevant to competing interests. First, we now only publish the individual's institution, but not their position in that institution (*e.g.*, fellow, resident, student, assistant professor, and so on). In the submission of this editorial, the authors listed their positions at the American Board of Anesthesiology (ABA) as Director or Chief Assessment Officer, but those were removed in the new style and their institution information printed in the editorial merely states ABA. This statement provides transparency that the authors are associated with the ABA, whether they are paid employees, receive other compensation, or are unpaid. Second, we have consolidated all competing interests into one place, at the end of articles including editorials. Although the authors' affiliation with the ABA was already declared, Dr. Kempen is correct that the competing interest statement should have reiterated what was present on the title page—that the authors are associated with the ABA. This would also apply to the editorial by Dr. Gambill, Chief Learning Officer at the American Society of Anesthesiologists, who describes American Society of Anesthesiologists' efforts to meet the educational needs of its members.[2]

I thank Dr. Kempen for his comments and take responsibility for any confusion there might have been caused between the authors' affiliations and the competing interest statement.

Competing Interests

Dr. Eisenach has received fees for consultation to Aerial Biopharma (Morrisville, North Carolina) and Adynxx (San Francisco, California) on topics unrelated to this letter, and receives salary support from the American Society of Anesthesiologists as Editor-in-Chief of Anesthesiology.

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Is Norepinephrine Infusion during Intraoperative Period Justified?

To the Editor:

The study by Wuethrich *et al.*[1] has interesting physiological background and important clinical implications. Veins, particularly splanchnic veins, are much more compliant than arteries.[2,3] Density of α-adrenergic receptors within the veins is much higher than in the arteries.[4] Therefore, veins are more sensitive to sympathetic activation than arteries.[4,5] The reported study has demonstrated that the use of relatively small doses of norepinephrine is not associated with any clinical or biochemical signs of tissue hypoperfusion.[1]

Sympathetic nervous system and α-adrenergic receptors play the main role in maintaining a certain ratio between stressed (Vs) and unstressed (Vu) blood volumes.[2,3] α-Adrenergic agonists induced constriction of compliant veins, resulting in a decrease in Vu and a concomitant increase in Vs.[3,6] General and, particularly, epidural anesthesia decreases the overall sympathetic discharge followed by venodilation, increase in Vu, and decrease in Vs, which could lead to a decrease in venous return and cardiac output. In addition, controlled ventilation with concomitant increase in intrathoracic pressure might decrease venous return and therefore must be associated with an increase in Vs to maintain adequate hemodynamics. The body achieves this by several mechanisms, main and immediate of which is an increase in sympathetic discharge. Such compensation also might be impaired to different degrees by general and epidural anesthesia. This study illustrates that norepinephrine induced reduction in enlarged Vu and restoration of the Vs can maintain adequate hemodynamics. Fluid infusion also can restore the Vs. Thus, an increase in Vs can be achieved by an increase in fluid load (to fill up an increased venous capacity) and/or by restoration of the sympathetic tone that would reduce the increased Vu. The use of norepinephrine in this situation decreases the Vu but not the blood flow to the tissues. The current study demonstrates clinical benefits of such an approach.[1]

Clinical implications of these observations are also important. Use of relatively small doses of vasopressors to restore what has general and epidural anesthesia impaired seems logical. The clinical advantage of such an approach is relatively simple: it allows avoiding additional, not needed infusion of fluid. However, the clinician should realize that such approach might decrease the margin of safety. The main function of the Vu is to serve as a reservoir of blood to be mobilized when needed, for example, during blood loss. However, when the mobilization of blood from Vu to Vs is approximately complete, hemodynamics deteriorate. We all have observed the initial blood loss of 800 to 900 ml not being associated with serious hemodynamic consequences; however, when blood loss

reaches approximately 1 l, even minor additional blood loss quickly leads to hemodynamic deterioration. This happens at the time when Vu becomes very low. Low Vu *per se* is not harmful, but unexpected blood loss in condition of decreased Vu could lead quickly to hemodynamic deterioration.

Routine use of such technique might aggravate other unexpected complications. For example, some minor cardiac insufficiency might need an increase in preload to maintain adequate cardiac output. An already decreased Vu might postpone the effective treatment of such unexpected complications. Other events, such as compression of inferior caval vein, unexpected pneumothorax, and others, could also result in a decreased ability of the body to respond adequately and timely. Also, use of norepinephrine in situations during anesthesia and surgery might confuse a clinician and delay correct clinical diagnosis or one or another deviation from the expected uncomplicated course.

Finally, the differences between the experimental (norepinephrine infusion) and control groups in this study are quite drastic; the dramatic degree of these differences partially might be due to the overloading of the patients in the control group: the protocol rather than the clinical situation required infusion of fluid to a greater extent than usually is done in clinical setting. We hardly ever infuse up to 8 to 9 l of fluid during surgical procedures that are not associated with severe blood loss.

The main lesson from this interesting study is that the administration of small doses of vasopressors during anesthesia and surgery is physiologically justified because it can counteract the iatrogenic impairment of sympathetic nervous system and may provide our patients with certain advantages. However, such techniques might become dangerous when some deviations from the expected clinical course occur. As always, vigilance and clinical judgment remain to be crucially important in patient care.

Competing Interests

The author declares no competing interests.

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In Reply:

Dr. Gelman summarizes very elegantly the pathophysiologic background of our norepinephrine/low-volume study[1]: general and, particularly, epidural anesthesia induce venodilation, especially of splanchnic veins (capacitance veins), which can lead to a decrease in venous return and cardiac output. These side effects can be counteracted by restoring the sympathetic tone of the plegic veins to the preoperative normal physiological status by continuous administration of low-dose norepinephrine. This avoids the need for additional unnecessary infusion of fluid that may cause interstitial edema with all its negative consequences (postoperative bowel dysfunction, pulmonary dysfunction, and cardiac arrhythmia).[2–4]

We agree with Dr. Gelman's conclusion that the difference in results of our study between the two patient groups is quite drastic and favor administration of continuous low-dose norepinephrine instead of infusion of greater fluid volumes as in the control arm. Indeed, Dr. Gelman is right when he says that such a difference could also have been caused by overloading with too much fluid in patients in the control arm. Generous fluid administration (*i.e.*, iatrogenic hypervolemia) can cause destruction of the endothelial glycocalix layer, the most important part of the vascular barrier that regulates homeostatic functions. This impairment of homeostasis leads to edema (third space shifting), and the fluid accumulation will not be readily mobilized in case of acute bleeding. Our patients, however, were not given up to 8 to 9 l of fluid as stated by Dr. Gelman. The 6 $ml \cdot kg^{-1} \cdot h^{-1}$ given to our control patients accords with most anesthesia guidelines recommended in reference textbooks[5] (including a fluid bolus of 6 ml/kg after activation of the epidural catheter during induction of anesthesia) and resulted in a median overall fluid load of 4.3 l per patient for a median time of surgery of 6.5 h.[1]

We also agree with Dr. Gelman's concern that the use of vasoactive agents might reduce the margin of safety if they are used to compensate for intraoperative blood/fluid loss. This, however, was not the case for the patients in our study. Blood loss was monitored continuously (including weighing of all used gauze, sponges, suction contents, *etc.*) and replaced (as mentioned in the article) in addition to the basic fluid supplementation of 2 $ml \cdot kg^{-1} \cdot h^{-1}$ of balanced Ringer's solution.