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.

**Simon Gelman, M.D., Ph.D.,** Brigham and Women's Hospital, Boston, Massachusetts. sgelman@partners.org

## References

1. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE: Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: A randomized clinical trial. Anesthesiology 2014; 120:365–77
2. Rothe CF: Reflex control of veins and vascular capacitance. Physiol Rev 1983; 63:1281–342
3. Gelman S: Venous function and central venous pressure: A physiologic story. Anesthesiology 2008; 108:735–48
4. Birch DJ, Turmaine M, Boulos PB, Burnstock G: Sympathetic innervation of human mesenteric artery and vein. J Vasc Res 2008; 45:323–32
5. Hainsworth R: The importance of vascular capacitance in cardiovascular control. News Physiol Sci 1990; 5:250–4
6. Caldini P, Permutt S, Waddell JA, Riley RL: Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. Circ Res 1974; 34:606–23

*(Accepted for publication May 12, 2014.)*

*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.

Whether an unexpected major blood loss would be less detrimental in an overhydrated patient with interstitial edema with decreased tissue perfusion and anesthesia/analgesia-induced venodilation and therefore unable to react adequately to an acute drop in venous pressure than it would be in a normovolemic patient under continuous low-dose norepinephrine administration with normal tissue perfusion is an often discussed but speculative question. Such controversies can only be answered by a prospective randomized trial. The results of our study speak against such speculations: No relevant impairment in tissue perfusion could be detected in the norepinephrine/low-volume group as serum lactate values and central venous oxygen saturation did not reach pathological thresholds and thus excluding a clinically relevant tissue hypoperfusion. In contrast, the number of patients with serum brain natriuretic peptide values greater than 100 pg/ml (a marker of myocardial dilation and risk for heart insufficiency) was twice that in the control arm.

Nevertheless, we fully agree with Dr. Gelman that clinical judgment and individualization of anesthesia remain the cornerstones of adequate perioperative patient management.

## Competing Interests

The authors declare no competing interests.

**Patrick Y. Wuethrich, M.D., Fiona C. Burkhard, M.D., Urs E. Studer, M.D.** University Hospital Bern, Bern, Switzerland (P.Y.W.). patrick.wuethrich@insel.ch

## References

1. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE: Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: A randomized clinical trial. Anesthesiology 2014; 120:365–77
2. Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F; Danish Study Group on Perioperative Fluid Therapy: Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens: A randomized assessor-blinded multicenter trial. Ann Surg 2003; 238:641–8
3. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. Lancet 2002; 359:1812–8
4. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I: Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 2005; 103:25–32
5. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J: Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br J Surg 2009; 96:331–41

*(Accepted for publication May 12, 2014.)*