Pleth Variability Index in Orthopedic Surgery: Comment

To the Editor:

At first glance, the recent 447-patient randomized controlled trial in major orthopedic surgery with new goal-directed fluid management methodology[1] may revitalize the debate, although no effect was demonstrated. Importantly, the concept of goal-directed fluid management has been discussed for more than a decade and, although initially promising, still remains debatable.[2,3]

However, a closer look on the methodology of the study[1] again shows that the gold standard of an randomized controlled trial in perioperative medicine may not always be the "gold standard" when it is performed in a clinical setup that limits the potential interaction between the intervention and the outcome.[4] Thus, the trial had a primary outcome on length of stay which was similar between the groups (about 6 days), which is very far from common practice in many international centers with length of stay around 1 to 3 days in optimized pathways.[5,6] Interpretation is therefore difficult, because there was no information about perioperative care principles or why the patients were hospitalized, and as such the actual impact of the optimized fluid management on length of stay will be probably be negligible, as other factors clearly will determine length of stay. The power analysis assumes a reduction in length of stay from 6 to 5 days, but it is difficult to understand from the assumed focus on fluid management *per se versus* the known impact of care traditions (pain management, mobilization, physiotherapy). Finally, it is surprising that patients with high comorbidities or recommended to a cardiac output monitor were excluded, which essentially may represent those patients who may benefit from goal-directed fluid management.[3]

In summary, this is another perioperative outcome randomized controlled trial interventional study which unfortunately prevents sufficient interpretation by not considering available evidence-based care principles shown for many years to reduce length of stay in the specific surgeries investigated.[7]

Competing Interests

Dr. Foss has received teaching fees from Edwards Lifesciences (Irvine, California). Dr Kehler declares no competing interests.

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To the Editor:

In the recent issue of Anesthesiology there is an article[1] and an accompanying editorial[2] that provide us with somewhat contradictory conclusions. The study[1] did not find any difference in outcome of intermediate risk orthopedic surgery between the patients who received goal-directed hemodynamic therapy or usual treatment determined by an anesthesiologist in charge of the case. Maheshwari and Sessler[2] correctly stated that future studies should include patients who undergo surgery requiring more severe volume changes than patients in the reported study did,[1] possibly implying that such group of patients would do well regardless of the goal-directed hemodynamic therapy.

Despite no differences in outcome the patients who were treated with goal-directed hemodynamic therapy received 1.5 times more fluid than the patients in the controlled group.[1] Basic physiology of venous system helps to elucidate the possible reason for the difference.

The blood within the venous vasculature may be under zero pressure (unstressed volume) or under pressure above zero (stressed volume).[3,4] It is important to keep in mind that the stressed volume and unstressed volume are virtual volumes; they are not separated by a membrane, they are different only by being under pressure above zero or not. When a fluid infusion starts, the infused fluid "enters" the unstressed volume because transmural pressure there is lower than in the stressed volume, by definition. Infused fluid gradually increases unstressed volume that eventually reaches "the point of conversion of unstressed volume-to-stressed volume." The unstressed volume does not affect hemodynamics, whereas stressed volume does (stressed volume is one of the main determinants of flow within the venous vasculature). Therefore, the amount of fluid infused before the point of conversion of the unstressed volume-to-stressed volume does not affect hemodynamics, is not needed, and may represent overloading at that time. When the point of conversion of unstressed volume-to-stressed volume is reached, the whole blood in that chamber (that part of venous vasculature), together with the infused fluid, constitutes the stressed volume that increases preload affecting the hemodynamics. Any vasodilating insults that occur before the points of conversion of unstressed volume-to-stressed volume increase the unstressed volume that does not affect hemodynamics but may be associated with an increase in the amount of infused fluid and represent overloading at that moment. Clinicians have to remember that the unstressed volume represents the reservoir of volume that can be partially mobilized within seconds by converting the unstressed volume to stressed volume.

Small doses of a vasoconstrictor constrict mainly veins, not arteries, and therefore do not jeopardize tissue perfusion.[4] However, they decrease the unstressed volume, thereby decreasing the amount of overload during goal-directed hemodynamic therapy. Two clinical studies[5,6] are in agreement with the speculations above. Moreover, the study by Nakamoto *et al.*[6] showed that a vasopressor increases the responsiveness to fluid challenge. This is apparently attributable to a decrease in unstressed volume (induced by a vasopressor), leading to sooner conversion of the unstressed volume to stressed volume and thereby decreasing the amount of fluid infused before the point of conversion of unstressed volume-to-stressed volume.[7]

Thus, the goal-directed hemodynamic therapy *per se* helps to prevent underfilling, whereas small doses of a vasopressor may effectively diminish overloading of the vasculature.

Competing Interests

The author declares no competing interests.

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Pleth Variability Index in Orthopedic Surgery: Reply

In Reply:

We thank Kehlet and Foss[1] and Gelman[2] for their correspondence and interest in our randomized study on goal-directed fluid management published in Anesthesiology.[3] Limitations in our choice of hospital length of stay as a clinically significant primary outcome were rightly raised. One such limitation, highlighted by Kehlet and Foss, is its variability among health care systems but also within time according to the evolution of care. The primary outcome of the OPVI (Optimization using the Pleth Variability Index) study (real length of hospital stay after knee or hip arthroplasty) was chosen by the OPVI group as a clinically relevant surrogate measure of postoperative morbidity. The length of hospital stay used to calculate the sample size was based on the 2014 national French database, the year the study was approved by the ethics committee.[4] We agree that nowadays the length of stay is substantially shorter because of progressive implementation of enhanced recovery after surgery protocols in many surgical procedures, recently including knee and hip arthroplasty.

Another issue raised was the study population. The OPVI trial included intermediate-risk surgical patients because they represent the wide majority of patients worldwide and because they were not previously evaluated in this setting. It was deemed ethical for our group to exclude high-risk surgical patients because the Pleth Variability Index was not yet validated as a hemodynamic monitoring device at the time of our study.

Gelman emphasized that patients who were treated with goal-directed hemodynamic therapy received more fluids than the patients in the control group. Indeed, in the OPVI trial, twice as many patients received a fluid loading in the Pleth Variability Index group than in the control group, and the cumulative volume of fluid infused throughout the surgery was significantly larger in the Pleth Variability Index group than in the control group, whereas we observed no difference in regard to vasopressor use. We advance two theories to explain this. On the one hand, this result could be related to the fact that the study population did not benefit from using the hemodynamic algorithm through dedicated monitoring, as suggested by the low volumes of fluid loading used and the low incidence of postoperative complications. On another side, the Pleth Variability Index may not be reliable enough to allow effective hemodynamic optimization in a surgical setting. Using a cut-off value of 13% to discriminate preload dependency may not be sufficiently precise and suited to individualized goal-directed hemodynamic therapy. Dynamic changes in Pleth Variability Index or arterial pulse pressure variation may be more precise than a universal value of 13%, because many confounding factors are known to increase or decrease this cut-off value.[5] Further studies are necessary to assess Pleth Variability Index in patients who undergo surgery requiring larger volume loadings,[6] using changes in Pleth Variability Index more than a static cut-off value, to further specify the clinical utility of this device.

Competing Interests

The authors declare no competing interests.

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Postoperative Hypotension and Myocardial Injury: Comment

To the Editor:

We have read with great interest the observational cohort study "Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury," by Liem *et al.*[1] In this study the authors examined postoperative hypotension after noncardiac surgery as a risk factor for myocardial injury by defining multiple mean arterial pressure (MAP) thresholds and different characterizations of blood pressure exposures. We commend the authors for further emphasizing the association between postoperative hypotension and myocardial injury and stressing the potential benefit of postoperative continuous blood pressure monitoring. May we ask the authors to provide some additional details that will help address some concerns and will better put their findings into clinical perspective? First, the secondary outcome of 30-day all-cause mortality was not compared between patients with *versus* patients without myocardial injury. May we kindly ask the authors to provide baseline characteristics including 30-day all-cause mortality stratified for myocardial injury and no myocardial injury? Second, the authors concluded that postoperative duration under a MAP threshold of 75 mmHg was associated with increased risk of myocardial injury. We are concerned that the corresponding figure 3 may lead some readers to falsely interpret the results, because the association between duration under a MAP threshold of 75 mmHg and myocardial injury was only significant for a duration of more than 635 min. Additionally, for a duration of more than 635 min under a MAP threshold of 75 mmHg, CIs are gradually increasing. Moreover, when comparing duration under MAP for five different thresholds, duration under a threshold of 75 mmHg did not remain significant. Please consider highlighting alternative thresholds that might be better supported by your data. Third, previous studies have additionally adjusted for use of cardiovascular medications before surgery (*i.e.*, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, calcium channel blocker, β-blocker, statin, diuretics, aspirin, oral anticoagulants).[2–4] We are concerned that not adjusting for preoperative cardiovascular medication may have led to an overestimation of the association between hypotension and injury or death. Please provide a sensitivity analysis adjusting for those important confounders. This will help clinicians to further understand the impact of postoperative hypotension on myocardial injury.

Competing Interests

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