

provide hard evidence to support the idea that goal-directed colloid infusion is the best method of managing these cases. The methodology is critically flawed in at least four ways.

First, these anesthetized pigs were hypotensive (baseline blood pressure = 57–60 mmHg) and tachycardic (heart rate = 110–117 beats/min) in baseline conditions, relative to well-established normal values for either conscious or anesthetized animals.^{3,4}

Second, the resuscitation was disparate; 250 ml of colloid is not the same resuscitation strategy as 250 ml of crystalloid. An intravascular equivalent of 500–750 ml crystalloid bolus should have been the comparator.

Third, there is no justification for the intraoperative mixed venous oxygen saturation target of 60, given the baseline value of 48–50.

Fourth, neither the threshold microcirculatory blood flow nor the tissue oxygen tension associated with anastomotic breakdown is established, so the excess blood flow or oxygen in the goal-directed group could be good, bad, or indifferent.

This study only demonstrates that inadequate fluid resuscitation is worse than adequate fluid resuscitation. The crystalloid group virtually never achieved the “goal” of mixed venous oxygen saturation > 60%; as the authors note themselves, six of nine animals in the group never achieved the goal over the entire experiment. The average of 1,794 ml per animal in the goal-directed crystalloid group indicated that each animal received the 250-ml bolus every 30 min (the maximum allowed) over the entire 4-h experiment, in contrast to the colloid group, which got a bolus every hour on average; this was about twice the colloid volume infused over the experiment and yet was still inadequate. The inability to achieve the goal in the crystalloid group does shed light on another debate, though. It suggests that the correct conversion is indeed 3 ml crystalloid to 1 ml of colloid, not 2:1.

The unexpected finding that the wet/dry ratio was not different in colloid *versus* crystalloid is also obviously related to the fact that in the goal-directed crystalloid group, fluid resuscitation was inadequate. Since, by the authors' own primary measure of mixed venous oxygen saturation, fluid resuscitation was not achieved in most goal-directed therapy crystalloid animals, adrenergic tone was likely increased throughout the experiment, and the very sensitive intestinal vasculature had vasoconstriction-limited perfusion—consistent with the decreased PO_2 of the intestinal tissue noted in the study. On the other hand, if the resuscitation had been adequate, it is probable that the wet/dry ratio would have been greater in the crystalloid group. It is not clear what effect appropriate resuscitation might have had on the primary measure of intestinal and perianastomotic tissue PO_2 , as an appropriate crystalloid comparator would have had more edema counteracting the positive effect of more perfusion. Regardless, it is impos-

sible to attribute the different PO_2 of the tissue in this study to fluid choice *versus* resuscitation adequacy, especially since the baseline condition was abnormal.

Then there is the issue of the measurement taken: Trying to identify a single and infallible parameter that predicts outcome in resuscitation is the search for the holy grail of critical care. Can we use a single number as a crystal ball and if so, which one? For all bedside clinicians the quest goes on. While variations in microcirculatory parameters like perianastomotic PO_2 tension increases our body of knowledge, it does not explain by itself better clinical outcome. As the authors point out, the lactate level in all groups was no different, which represents payment of the oxygen debt without any systemic sequelae. Why was resuscitation adequacy not comparable, but the endpoint of lactate not different? Could the colon possess protective mechanisms similar to those in effect with ischemic preconditioning of the cardiac muscle? The assertion that the use of goal-directed therapy with colloids accounts for improved patient outcomes because of the mechanism described is again not supported by the findings.

Furthermore, we believe that the journal has done the anesthesia community a mild disservice by publishing an editorial highlighting and lauding this critically flawed, albeit well-intentioned article, as “evidence” of the benefit of colloid goal-directed therapy. We need the information it seeks to convey, and believe a well-done study will support both the editorial and the paper. We just need a much better protocol and more insight when interpreting the results. In any case, we can hopefully all agree with another famous philosopher who said, “*It ain't over 'till it's over.*”⁵

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In Reply:—We thank the editor for giving us the opportunity to respond to the letter by Lubarsky *et al.*, and appreciate their critical appraisal of our article.¹

Lubarsky *et al.* conclude that our study did not bring hard evidence that goal-directed colloid fluid therapy is the best method of managing major abdominal surgery. We did not mean to indicate that our study would bring such hard evidence. Rather, as indicated in our introduction, the purpose of our study was to “study if goal-directed fluid therapy with colloids increases perianastomotic tissue oxygen tension and perfusion in comparison to a goal-directed crystalloid and a restricted crystalloid fluid therapy.”¹ Our conclusion states: “Goal-directed colloid fluid therapy significantly increased microcirculatory blood flow and tissue oxygen tension in healthy and injured colon compared to crystalloids.”¹ We thus feel that Lubarsky *et al.* considerably overinterpreted our data. Our study's aim was to investigate physiologic mechanisms that may explain some of the benefits of

the already demonstrated superiority of goal-directed colloid therapy in a multitude of well-conducted clinical studies^{2–4} and in a recent metaanalysis.⁵

Lubarsky *et al.* were concerned that our animals were hypovolemic. During preparation and before randomization, all animals received 3 ml · kg⁻¹ · h⁻¹ of Ringer's lactate, reflecting a typical restrictive fluid therapy used in clinical studies.⁶ Lubarsky *et al.* also note that fluid therapy with 250 ml of colloids is not equivalent to 250 ml of crystalloids. We agree that a 250 ml bolus of crystalloids every 30 min may appear conservative if we were treating severely hypovolemic or septic subjects. However, at this stage of the experiments, after completing surgery and instrumentation, the animals were hemodynamically stable. They had minimal blood and fluid loss (the abdominal wound was closed to limit fluid evaporation from the wound) and good diuresis. Our aim was to mimic clinical conditions and treatments, and we therefore administered 250 ml of crystalloids when mixed venous

oxygen saturation was below 60%, which is comparable to approximately 600–700 ml in adult patients. At our institution a typical intravenous fluid bolus in clinical anesthesia is 500 ml of Ringer's lactate or 500 ml of colloids. If we had chosen a protocol as suggested by Lubarsky *et al.*, the crystalloid goal-directed therapy (GDT) group would have received a 750-ml bolus, which would be comparable to a $\approx 1,700$ -ml bolus in humans. Such large fluid therapy could have led to fluid overload in these animals and would have been considered clinically not applicable. We have shown in an earlier study in a similar pig model as used in the present study⁷ that even larger amounts of crystalloids administered ($20 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) than in the present crystalloid GDT group did not affect tissue oxygen tension in the colon.

Concerning blood volume in the two GDT groups, we believe that it was similar in the two groups as judged by the hemoglobin values. The hemoglobin values were comparable in the two GDT groups before and after the experiment and significantly lower than in the fluid restricted group at the end of the study, suggesting similar-grade hemodilution. In addition, data on pulse pressure variation and stroke volume (measured with PICCO; Pulsion Medical Systems GmbH, Munich, Germany) that were not presented in this paper support this opinion, since pulse pressure variation and stroke volume were virtually identical in the two GDT groups at the end of the study. In the fluid-restricted group, pulse pressure variation remained high and stroke volume low throughout the experiments.

Concerning the choice of mixed venous oxygen saturation as a main goal during fluid therapy, we agree there are other, more clinically practical methods available for human studies, and we certainly do not suggest that clinicians should insert pulmonary artery catheters in patients undergoing routine colon surgery. However, for the purpose of this study we considered this method reliable, as the parameter has been shown to be independently associated with clinical outcome.⁸ In our pilot studies measuring mixed venous oxygen saturation resulted in minimal variability and reproducible results. We concede that the target of 60% for mixed venous oxygen saturation seems rather low in patients, but it is ambitious in pigs, as they have a distinctly lower hemoglobin concentration, a species-specific higher hemoglobin oxygen affinity, and an increased body temperature as compared with humans.⁹

Finally, we disagree with the statement by Lubarsky *et al.* that “no threshold tissue oxygen tension with anastomotic breakdown is established.” We know at least of two well-designed studies^{10,11} that deal with this very question and that have been referenced in our publication. In these studies, gut tissue oxygen tension is directly correlated to anastomotic breakdown, and a critical value of 20–25 mmHg was

established. This critical value was also used in our study to standardize anastomotic conditions.

We are convinced that neither the editorial by Kehlet and Bundgaard-Nielsen¹² nor our original article are a disservice done to the anesthesia community, and conclude paraphrasing the words of the great scientist John Tukey “*An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem.*”

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