In Reply.—We thank Drs. Xia and Irwin for their interest in our study on the role of β-adrenergic signaling in anesthetic postconditioning and in the accompanying editorial view.² We agree with Drs. Xia and Irwin that, besides their energy-sparing effect, several alternative mechanisms of β blockers might be responsible for their infant size-reducing capacity. Apart from their effect on the interaction between β receptor activation and reactive oxygen species production³ and scavenging,⁴ β blockers can inhibit calcium/calmodulin-dependent protein kinase II⁵ and phospholipase A², exert membrane stabilizing effects,⁶ and may even have direct effects on mitochondrial electron transport and reactive oxygen species production.⁷ The role of alternative mechanisms is certainly supported by the finding that infant size reduction by β blockade is independent of heart rate, the main determinant of myocardial oxygen consumption.⁸ It is entirely conceivable that the combination of different cardioprotective principles at different time points during reperfusion might provide additive protective effects. In this context, it is of interest that calcium/calmodulin-dependent protein kinase II is necessary for desflurane-induced postconditioning, whereas prolonged postischemic calcium/calmodulin-dependent protein kinase II blockade might attenuate adverse effects of ischemia/reperfusion injury, including remodeling.⁹ Thus, it might be reasonable to apply anesthetic postconditioning at the onset of reperfusion and to initiate β blockade later during reperfusion. However, further basic research and clinical studies will be necessary to determine an optimized cardioprotective approach and to identify the possible clinical consequences of these experimental findings.

The rabbits used in this study were between 8 and 12 weeks of age and weighed between 2.5 and 3.0 kg. Although cardioprotection by ischemic and pharmacological preconditioning can be attenuated or lost in senescent hearts, there is some evidence of preserved ischemic preconditioning in the aged myocardium.¹⁰ Thus, the impact of aging on the cardioprotective effects of β blockade, anesthetic postconditioning and their interaction with reactive oxygen species needs to be determined in future studies.

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References


11. Śniadowski R, Liu H. Reduced efficacy of volatile anesthetic preconditioning with advanced age in isolated rat myocardium. Anesthesiology 2004; 100:809–17


To the Editor.—Kimberger et al.¹ and the editors² are to be commended for attempting to shed light on an important topic: What is the optimal intraoperative fluid and resuscitation target? Many experienced physicians, including us, who provide anesthesia for major intraabdominal surgery have evolved over time from crystalloid-only, “show me the proof” physicians to those being in philosophical agreement with both the author and the editorial writers—goal-directed therapy with colloid is best in intestinal cases. We believe this produces less gut edema without compromising gut or other critical organ perfusion (not to mention reducing the anesthesiologist’s aural discomfort from the oft repeated surgeon lament that the anesthesia team is “drowning” the patient). Indeed, Victor Hugo once said, “All the forces in the world are not so powerful as an idea whose time has come.”³

Unfortunately, despite our hope to the contrary, all the forces in the world may have to wait a little longer, because this study does not
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. Three, four. 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 bad, good, 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 P_{O_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 P_{O_2}, as an appropriate crystalloid comparator would have had more edema counteracting the positive effect of more perfusion. Regardless, it is impossible to attribute the different P_{O_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 P_{O_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 ’til it’s over.’

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References


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