8. Daga MK, Chaudhary M, Sharma B, Bhattacharjee J, Ghambhir DS, Arora N, Sudha R: Effect of esmolol on oxidant status and antioxidant activity in acute myocardial infarction. J Assoc Physicians India 2003; 51:677–80
9. Nguyen LT, Rebecchi MJ, Moore LC, Glass PS, Brink PR, Liu L: Attenuation of isoflurane-induced preconditioning and reactive oxygen species production in the senescent rat heart. Anesth Analg 2008; 107:776–82

(Accepted for publication June 29, 2009.)

Anesthesiology 2009; 111:925

In Reply:—We thank Drs. Xia and Irwin for their interest in our study on the role of β-adrenergic signaling in anesthetic postconditioning[1] 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 infarct size–reducing capacity. Apart from their effect on the interaction between β receptor activation and reactive oxygen species production[3] and scavenging,[4] β blockers can inhibit calcium/calmodulin -dependent protein kinase II[5] and phospholipase A,[6] exert membrane stabilizing effects,[7] and may even have direct effects on mitochondrial electron transport and reactive oxygen species production.[8] The role of alternative mechanisms is certainly supported by the finding that infarct size reduction by β blockade is independent of heart rate, the main determinant of myocardial oxygen consumption.[9] 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.[10] 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[11] and pharmacological[12] preconditioning can be attenuated or lost in senescent hearts, there is some evidence of preserved ischemic postconditioning in the aged myocardium.[13] 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.

Markus Lange, M.D.,* **Matthias L. Riess, M.D., Ph.D.** *Klinikum der Bayerischen Julius-Maximilians-Universität, Würzburg, Germany. lange_m@klinik.uni-wuerzburg.de

References

1. Lange M, Redel A, Lotz C, Smul TM, Blomeyer C, Frank A, Stumpner J, Roewer N, Kehl F: Desflurane-induced postconditioning is mediated by beta-adrenergic signaling: role of beta 1- and beta 2-adrenergic receptors, protein kinase A, and calcium/calmodulin-dependent protein kinase II. Anesthesiology 2009; 110:516–28
2. Riess ML: The rocky road from bench to bedside: Beta-blockers and anesthetic postconditioning. Anesthesiology 2009; 110:451–2
3. Moniri NH, Daaka Y: Agonist-stimulated reactive oxygen species formation regulates beta2-adrenergic receptor signal transduction. Biochem Pharmacol 2007; 74:64–73
4. Srivastava S, Chandrasekar B, Gu Y, Luo J, Hamid T, Hill BG, Prabhu SD: Downregulation of CuZn-superoxide dismutase contributes to beta-adrenergic receptor-mediated oxidative stress in the heart. Cardiovasc Res 2007; 74:445–55
5. Lange M, Smul TM, Redel A, Lotz C, Jazbutyte V, Schnupp V, Roewer N, Kehl F: Differential role of calcium/calmodulin-dependent protein kinase II in desflurane-induced preconditioning and cardioprotection by metoprolol: Metoprolol blocks desflurane-induced preconditioning. Anesthesiology 2008; 109:72–80
6. Trotz M, Jellison EJ, Hostetler KY: Propranolol inhibition of the neural phospholipases A of rat heart mitochondria, sarcoplasmatic reticulum and cytosol. Biochem Pharmacol 1987; 36:4251–6
7. Boucher M, Chapuy E, Duchêne-Marullaz P: Membrane stabilizing activity and β-adrenoceptor antagonist-induced bradycardia in conscious dogs. Eur J Pharmacol 1992; 211:343–9
8. Kametani R, Miura T, Harada N, Shibuya M, Wang R, Tan H, Fukagawa Y, Kawamura S, Matsuzaki M: Carvedilol inhibits mitochondrial oxygen consumption and superoxide production during calcium overload in isolated heart mitochondria. Circ J 2006; 70:321–6
9. Warltier DC, Gross GJ, Jesmok GJ, Brooks HL, Hardman HF: Protection of ischemic myocardium: Comparison of effects of propranolol, bevantolol and N-dimethyl propranolol on infarct size following coronary artery occlusion in anesthetized dogs. Cardiology 1980; 66:133–46
10. Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, Grueter CE, Qi X, Richardson JA, Hill JA, Katus HA, Bassel-Duby R, Maier LS, Olson EN: The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. Proc Natl Acad Sci USA 2009; 106:2342–7
11. Fenton RA, Dickson EW, Meyer TE, Dobson JG: Aging reduces the cardioprotective effect of ischemic preconditioning in the rat heart. J Mol Cell Cardiol 2000; 32:1371–5
12. Sniecinski R, Liu H: Reduced efficacy of volatile anesthetic preconditioning with advanced age in isolated rat myocardium. Anesthesiology 2004; 100:589–97
13. Lauzier B, Delemasure S, Debin R, Collin B, Sicard P, Acar N, Bretillon L, Joffre C, Bron A, Creuzot-Garcher C, Vergely C, Rochette L: Beneficial effects of myocardial postconditioning are associated with reduced oxidative stress in a senescent mouse model. Transplantation 2008; 85:1802–8

(Accepted for publication June 29, 2009.)

Anesthesiology 2009; 111:925–6

Goals Neither Validated Nor Met in Goal-directed Colloid *versus* Crystalloid Therapy

To the Editor:—Kimberger *et al.*[1] and the editors[2] 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."*

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

The above letter was sent to the authors of the referenced Editorial. The authors did not feel that a response was required. —James C. Eisenach, M.D., Editor-in-Chief.

*Available at http://famouspoetsandpoems.com/poets/victor_hugo/quotes. Accessed May 29, 2009.

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 impossible 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]

David A. Lubarsky, M.D., M.B.A.,† Kenneth G. Proctor, Ph.D., Miguel Cobas, M.D. †University of Miami Miller School of Medicine, Miami, Florida. dlubarsky@med.miami.edu

References

1. Kimberger O, Arnberger M, Brandt S, Plock J, Sigurdsson GH, Kurz A, Hiltebrand L: Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology 2009; 110:496–504
2. Kehlet H, Bundgaard-Nielsen M: Goal-directed perioperative fluid management: Why, when, and how? Anesthesiology 2009; 110:453–5
3. Hannon JP, Bossone CA, Wade CE: Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci 1009;40:293–8
4. Swindle MM: Swine in the Laboratory (Surgery, Anesthesia, Imaging, and Experimental Techniques), 2nd edition. Boca Raton, CRC Press, 2007
5. Berra Y: The Yogi Book: I really didn't say everything I said. New York, Workman Publishing Company, 1998

(Accepted for publication June 30, 2009.)

Anesthesiology 2009; 111:926–7

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 $ml \cdot kg^{-1} \cdot h^{-1}$ 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