combined with TEA does not necessarily indicate that all organs were adequately perfused and well oxygenated. Critical decreases in oxygen supply (the product of blood flow and arterial oxygen content) in some organs could be masked by increases in oxygen supply in other organs. Canine studies in our laboratory and others have demonstrated widely heterogeneous changes in regional blood flow during ANA.[2–4] The findings showed that the blood flow increases in the heart, brain, and spinal cord were sufficient to maintain oxygen supply until hematocrit was reduced to less than 10% but that the flow responses in the peripheral organs resulted in decreases in oxygen at a much higher hematocrit.[4] Noteworthy was that renal blood flow remained constant during ANA, with the result that oxygen supply decreased in parallel with hematocrit; at a hematocrit of 10%, renal oxygen supply was only one fourth of the baseline value.[4] Because of a diffusive shunt for oxygen (owing to the close proximity of the interlobar arteries and veins), much of the oxygen supplied to the kidney bypasses the tissue.[5] Thus, unlike the body as a whole, the kidney cannot increase oxygen extraction to compensate for decreases in oxygen supply. A rat study has demonstrated that both renal $Vo_2$ and tissue $Po_2$ declined in parallel during progressive decreases in hematocrit.[6] These findings suggest that the kidneys may be at particular risk of hypoxic damage during ANA. The systemic endpoints used by Pape *et al.* were not sensitive to this potentially severe, localized imbalance between oxygen supply and demand.

The limited blood flow responses during ANA in the peripheral organs, including the kidney, are consistent with a countervailing vasoconstrictor mechanism to offset the effect of local metabolic vasodilation. Engagement of the sympathetic nerves has been suggested, based on their role in the reflex response to other systemic cardiovascular stresses, such as hemorrhagic shock,[7] and the ability of diluted blood to stimulate the arterial chemoreceptors,[8] which would provide the sensory limb for activation of the these nerves. Reflex activation of the sympathetic nerves operates to support aortic pressure, and, because it is selective to the peripheral organs, blood flow redistributes toward the heart and brain. The attenuation of this pathway by TEA might favor perfusion of the kidney and other peripheral beds under sympathetic control during ANA, but it would do so at the expense of a decrease in perfusion pressure, which could jeopardize blood flow and oxygen supply to the heart and brain. These regional responses must be evaluated before it can be concluded that it is safe to use TEA in the context of ANA.

A second issue relates to the pig model used by Pape *et al.* A limitation of this model was that the baseline hemoglobin was only 7.7 ± 0.8 g/dl, which is considered severe anemia in the human. This value for hemoglobin yielded a proportionally low value for arterial oxygen content (approximately 10 ml/dl) and a high value for the systemic oxygen extraction ratio (approximately 55%). This baseline condition would be expected to reduce the adaptive capability of the systemic circulation to the stress of ANA. The clinical applicability of the current findings must remain an open question.

Apart from the above concerns, the authors have offered provocative and interesting findings, which can serve as a springboard for further studies focusing on the tolerance of individual organs, such as the kidney and heart, to both ANA alone and combined with TEA. The use of an animal model with a hemoglobin concentration closer to that of the human would enhance the clinical relevance of such studies.

## Competing Interests

The author declares no competing interests.

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*In Reply:*

We thank Dr. Crystal for his interest in our article entitled "Thoracic Epidural Anesthesia with Ropivacaine Does Not Compromise the Tolerance of Acute Normovolemic Anemia in Pigs,"[1] and we do very much appreciate his comments. In summary, Dr. Crystal addresses two important points: first, the limitation of the whole-body approach applied in our

experimental model and, second, the relatively low hemoglobin concentrations at baseline.

Before taking up these comments, we would like to rectify a methodological issue. Dr. Crystal states that whole-body oxygen consumption ($V_{O_2}$) was calculated according to Fick equation. Actually, $V_{O_2}$ was directly measured using a metabolic monitor. This is an important detail, as in the presence of oxygen supply dependency, the reverse Fick method becomes imprecise resulting in underestimation of $V_{O_2}$.[2] Of note, the onset of oxygen supply dependency was the indicator of our target parameter $Hb_{crit}$.

Our experiments were performed in juvenile pigs. Physiologic hemoglobin values in pigs range from 7 to 8.5 g/dl, and we agree with Dr. Crystal's objection that this would be considered as severe anemia in men. The comparatively high oxygen-extraction rate ($O_2$-ER) at baseline indicates that animals were adapted to these hemoglobin levels. Nevertheless, in previous studies as well as in the present study, we still observed increases of $O_2$-ER compensating for progressive hemodilution.[1,3,4] Inasmuch, data interpretation should rather aim at the evaluation of physiologic mechanisms maintaining tissue oxygenation than at the extrapolation of absolute values to the clinical setting.

Although our study was not designed to investigate anemia tolerance on the organ-specific level, we are aware that this point represents a major limitation. Recently, Lauscher *et al.*[5] studied organ-specific anemia tolerance by investigating molecular markers of tissue hypoxia in several organs at different stages of anemia. Consistently with Dr. Crystal's findings,[6] renal tissue oxygenation was found impaired, before whole-body $Hb_{crit}$ was met, as indicated by increased levels of pimonidazole binding and vascular endothelial growth factor. These findings are elucidated by Dr. Crystal's comments describing the characteristics of renal perfusion and oxygen extraction during acute anemia. Regarding these essential compensatory mechanisms during acute anemia, the kidney differs fundamentally from other organs, indicating that further investigation of renal anemia tolerance might be of particular interest. This is the case because the evidence is amounting that a restrictive transfusion practice is associated with decreased renal morbidity, for example, in patients undergoing cardiac surgery.[7]

In our experimental study, the institution of thoracic epidural anesthesia (TEA) resulted in a decrease in vascular resistance and $O_2$-ER. Particularly in the light of the preexisting anemia, this finding may be interpreted as an indicator of improved tissue perfusion because $V_{O_2}$ remained constant after epidural injection of 0.2% ropivacaine. This interpretation, however, raises the question, how TEA might have influenced perfusion pressure and regional blood flow to and within the organs and whether these phenomena might be dose dependent. Although our data cannot answer these questions, we do very much appreciate Dr. Crystal's considerations on (re)distribution of regional blood leading to the conclusion that this point deserves further research.

We agree that many points need to be clarified before drawing the conclusion that TEA is safe at the lowest acceptable level of acute anemia, and we would like to emphasize that we abstained from drawing such conclusions in our article. What we found out is that, on the whole-body level, essential mechanisms of acute anemia are maintained despite sympathetic block induced by TEA. We would be honored if this finding had provoked interest in further research.

## Competing Interests

The authors declare no competing interests.

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# Inappropriate Trial of Cervical Epidural Injections

*To the Editor:*

We were excited to see the multicenter, randomized, comparative-effectiveness study of cervical epidural steroid injections comparing conservative treatment or combination treatment for cervical radicular pain by Cohen *et al.*[1] published in Anesthesiology. However, we are concerned regarding the potential flaws with the study's concept and design as well as the techniques used to examine the outcomes.

Pertinent information is missing in the introduction. The authors state that for cervical radiculopathy, two