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

small controlled studies with fewer than 50 patients had evaluated epidural steroid injections[2,3] with one demonstrating benefit.[2] It appears that the authors have omitted a double-blind, randomized, active-controlled trial published in 2012 with a 2-yr follow-up that included 120 patients.[4] The results of this trial are important because at the end of 2 yr, significant pain relief and functional status improvement of at least 50% were observed in 72% of the patients receiving local anesthetic only and 68% of those who received local anesthetic and steroids. Furthermore, the results were even more robust if patients were selected based on their response to the initial two procedures. This trial was practical in nature, including only patients with chronic pain who had failed conservative management, and the injection was repeated only if the pain had recurred. During a 2-yr period, patients received approximately five procedures.

As the authors have stated, in patients with radiculopathy, there is minimal benefit from physical therapy and pharmacotherapy as stand-alone treatments.

Therefore, addition of conservative management as a comparative treatment factor does not contribute to better understanding the role of epidural steroid injections. Furthermore, the authors have used epidural steroids without local anesthetic. As one would expect, there was no significant difference in these groups, and the combination therapy, which was reported as successful, demonstrated only minimal improvement.

The study design was somewhat surprising in that Cohen (Bicket *et al.*)[5] had previously demonstrated that nonsteroidal solutions may have been superior to steroid solutions. Thus, it might have been more appropriate to use a local anesthetic with a steroid injection or design a group with local anesthetic alone similar to other studies. As Manchikanti *et al.*[4,6–8] have elucidated, there was no significant difference between local anesthetic alone and local anesthetic with steroids. Furthermore, another systematic review also demonstrated a lack of superiority of steroids over local anesthetic in all conditions except lumbar disc herniation; whereas short- to mid-term, there was significant improvement with caudal and lumbar interlaminar epidural injections in managing lumbar disc herniation.[9]

Trials studying interventional treatments of chronic pain need to match a treatment with the incident disease. Methodologic limitations can and will lead to an inability to demonstrate the effect of the intervention.[10,11] The study by Cohen *et al.* suffers from a failure to include local anesthetic in the treatment group and a focus on conservative therapy.

## Competing Interests

The authors declare no competing interests.

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