Ketamine-(Dex)Medetomidine, Hyperglycemia, Glycocalyx, and Vascular Permeability

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To the Editor

Guerci et al[1] used an in vivo rat model of hemorrhagic shock to investigate the clinically relevant question whether breakdown of the glycocalyx results in increased vascular permeability. They found that the induction of hemorrhagic shock increased levels of glycocalyx breakdown products but did not change vascular permeability, as indicated by a similar retention ratio of 0.8 for infused Alexa 70 kDa albumin (Figure 3B). The dichotomy between glycocalyx breakdown and vascular permeability argues against a significant role for glycocalyx in regulating vascular permeability. This conclusion is surprising because of the large body of literature reporting that these 2 processes are interconnected. What factor(s) sets this study apart? We suggest that one factor could be hyperglycemia in all groups because of the use of medetomidine in the anesthetic regimen.

Ketamine-(dex)medetomidine anesthesia is a preferred anesthetic regimen for small animals because of its favorable effects on hemodynamics. But a negative aspect of this regimen is the development of hyperglycemia.[2] α-2-Agonists, such as medetomidine, not only impair insulin release from the pancreatic β cells but also increase glucagon release from the α cells.[2] The decrease in the insulin/glucagon ratio results in decreased glucose uptake and increased glucose production by the liver. Although blood glucose levels were not reported, it is likely that they were ≥14 mmol/L. In a very recent article using a rat model with similar dosage of dexmedetomidine as was used in Guerci et al,[1] glucose concentration increased above 20 mmol/L.[3] Previous work demonstrated that increasing blood glucose levels to 25 mmol/L caused increased vascular permeability, as reflected by increased disappearance of the 70 kDa fluorescence dextran marker from the blood.[4] That study showed that with normoglycemia the retention ratio of the 70 kDa marker is approximately 1.0, whereas with acute or chronic hyperglycemia the ratio decreased to approximately 0.8 (Figure 2 of Zuurbier et al[4]).

As stated above, a retention ratio of 0.8 was observed for all experimental groups in Guerci et al.[1] It is therefore likely that vascular permeability was already increased in the sham control group before the induction of a hemorrhagic shock. This then offers the possibility that additional degradation of the glycocalyx could not further increase vascular permeability. Studies in normoglycemic animals are needed to adequately test this explanation of the observed dichotomy between degradation of glycocalyx and vascular permeability.

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REFERENCES

1. Guerci P, Ergin B, Uz Z, et al. Glycocalyx degradation is independent of vascular barrier permeability increase in nontraumatic hemorrhagic shock in rats. *Anesth Analg*. 2019;129:598–607.
2. Zuurbier CJ, Koeman A, Houten SM, Hollmann MW, Florijn WJ. Optimizing anesthetic regimen for surgery in mice through minimization of hemodynamic, metabolic, and inflammatory perturbations. *Exp Biol Med (Maywood)*. 2014;239:737–746.
3. Wirtz MR, Jurgens J, Zuurbier CJ, et al. Washing or filtering of blood products does not improve outcome in a rat model of trauma and multiple transfusion. *Transfusion*. 2019;59:134–145.
4. Zuurbier CJ, Demirci C, Koeman A, Vink H, Ince C. Short-term hyperglycemia increases endothelial glycocalyx permeability and acutely decreases lineal density of capillaries with flowing red blood cells. *J Appl Physiol (1985)*. 2005;99:1471–1476.

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In Response

We read with interest the comments by Zuurbier[1] on our study[2] published in *Anesthesia & Analgesia*. The author suggested that hyperglycemia-induced glycocalyx shedding secondary to the anesthetic regimen used would contribute to the increased vascular barrier permeability (VBP) in the controls of our study. Therefore, it may introduce a bias in the observed results, impairing the interpretation of the data.

To date, there is no consensus on laboratory experimental science on the anesthetic regimen used for hemorrhagic shock models. Each anesthetic technique has qualities and flaws. We acknowledge the potential negative effects of (dex-)medetomidine on blood glucose levels by its α-2 agonist action, as previously demonstrated in other species. Nevertheless, we mitigate the impact of hyperglycemia on the increase in VBP.

First, we emphasized that there is a gradation in terms of VBP injury during shock. Thus, the injury to VBP has several stages, starting from glycocalyx degradation (eg, altered mechanotransduction), followed by microcirculatory disturbances, and ultimately by cell-to-cell disruption that alters VBP. We suggested that glycocalyx degradation per se is not a sufficient trigger to cause hyperpermeability in this model. Thus, the analysis of VBP should be integrative, or it should rely on multiple parameters.

Zuurbier et al[3] explored the deleterious effects of hyperglycemia on the glycocalyx. Interestingly, in their study, they used a similar (to ours) anesthetic regimen in their controls without noticeably experiencing hyperglycemia (≈5 mmol/L).[3] On the contrary, while using the same strain of mice (C57BL/6) with the same anesthetic regimen, higher blood glucose levels were observed.[4] Surprisingly, these inconsistencies between the 2 studies were not addressed in their comments, and they remain yet unexplained.

We measured blood glucose levels during a series of experiments. Although blood glucose levels may increase (up to 17 ± 3 mmol/L; n = 5) shortly after surgery, they returned to normal values (5.65 ± 3 mmol/L; n = 4) at the end of the experiment (≈3 hours) in the control group. Blood glucose levels were transiently affected, and anesthesia was maintained with infusion of ketamine alone in our study.