In Reply:

We appreciate Dr. Xue *et al.*'s interest in our paper. Several points are made that require clarification. First, the notion that occurrence and severity as well as duration of acute kidney injury (AKI) in the early postoperative period after cardiac surgery is responsible for major adverse kidney events has been called into question by studies that demonstrated that only part of the risk for major adverse kidney events comes from an early AKI in the postoperative period.[1] These patients are also at risk for late AKI and progression of underlying chronic kidney disease and risk for death unrelated to AKI.

Second, the authors were concerned that we did not use the correct Kidney Disease: Improving Global Outcomes criteria to diagnose and stage AKI, suggesting that we used an absolute serum creatinine increase of 0.3 mg/dl or more within a 72-h time window. This is not correct. Although our primary outcome was the occurrence of AKI within 72 h after cardiac surgery, we applied the full Kidney Disease: Improving Global Outcomes criteria[2] and used an absolute serum creatinine increase of 0.3 mg/dl or more only if it occurred within a 48-h timeframe. In other words, if a patient had a 0.3 mg/dl increase but the rate of rise was slower than 48 h they would only be classified as AKI if they reached a 50% increase in serum creatinine by 72 h or they met urine output criteria. The authors correctly stated that we did not adjust the serum creatinine concentrations for fluid balance. This might have influenced the incidence of AKI, but it should not have influenced the absolute difference of AKI between the groups, given that this was a double-blinded randomized trial and the amount of fluid application and subsequent dilution of serum creatinine concentrations should have been comparable between the groups. Also, the effect of "re-classification" using fluid-balance to adjust creatinine would be expected to be less when one includes urine output criteria as we did.

Finally, the authors are concerned that important predisposing factors for AKI have not been reported in our two papers.[3,4] Randomization guarantees, however, that patient allocation to interventions is left purely to chance. Patient characteristics that may affect outcome are expected to be equally distributed between treatment groups so that any outcome difference can be assumed to be due to the intervention. In the original paper,[3] we reported several prognostic variables showing the generalizability of our study and success of the randomization.

Research Support

The study was funded by the German Research Foundation (Bonn, Germany; grant Nos. ZA428/6-1 and ZA428/10–1; to Dr. Zarbock) and the Else Kröner Fresenius Stiftung (Bad Homburg, Germany; grant No. 2016_A97).

Competing Interests

Drs. Zarbock and Kellum have received grant support and lecture fees from Astute Medical (San Diego, California), unrelated to the current study. They have filed a patent application on the use of the biomarkers together with remote ischemic preconditioning.

Alexander Zarbock, M.D., John A. Kellum, M.D. University Hospital Münster, Münster, Germany (A.Z.). zarbock@uni-muenster.de

References

1. Greenberg JH, Zappitelli M, Devarajan P, Thiessen-Philbrook HR, Krawczeski C, Li S, Garg AX, Coca S, Parikh CR; TRIBE-AKI Consortium: Kidney outcomes 5 years after pediatric cardiac surgery: The TRIBE-AKI study. JAMA Pediatr 2016; 170:1071–8
2. KDIGO AKI Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2: 1–138
3. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, Wolf B, Goebel U, Schwer CI, Rosenberger P, Haeberle H, Görlich D, Kellum JA, Meersch M; RenalRIPC Investigators: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: A randomized clinical trial. JAMA 2015; 313:2133–41
4. Zarbock A, Kellum JA, Van Aken H, Schmidt C, Küllmar M, Rosenberger P, Martens S, Görlich D, Meersch M: Long-term effects of remote ischemic preconditioning on kidney function in high-risk cardiac surgery patients: Follow-up results from the RenalRIP trial. Anesthesiology 2017; 126:787–98

(Accepted for publication September 20, 2017.)

What Is the Role of Cytokines during Ventilator-induced Lung Injury?

To the Editor:

We are pleased that Lex and Uhlig[1] come to the same conclusion we published more than 15 yr ago,[2] that the role of inflammatory cytokines is minor (if there is indeed any role at all) during ventilator-induced lung injury (VILI). However, we and Dr. Uhlig have had different perspectives on that matter for years. Indeed, in response to an article we wrote on the role of cytokines during VILI,[3] Uhlig did not agree with our contention that cytokine secretion by the lungs is a by-product without physiologic significance. In contrast, he emphasized the importance of cytokine mediators in the pathogenesis of VILI.[4]

We believe that the article by Lex and Uhlig[1] and the accompanying editorial[5] omitted some key references that illustrate the role of mediators in lung injury in a broader context. For example, cytokines might be important in VILI only in the setting of another source of inflammation,[6] and von Bethmann *et al.*[7] demonstrated that inflammatory cytokines and prostanoids may be produced by the lungs during low tidal volume (noninjurious) ventilation. Therefore it is not possible to determine the exact role of cytokines in the development of VILI, because their elevation, when observed, may be either a cause (which we think unlikely) or a consequence of lung overdistension, and the results of experimental studies (including those by Uhlig) are often

inconsistent.[3] Finally, even if mediators play a role in propagating lung injury, the most important clinical aspect is that simply reducing tidal volume has resulted in a marked reduction in mortality from adult respiratory distress syndrome, whereas to date all clinical trials of antimediator therapies in critically ill patients have been negative.

Competing Interests

The authors declare no competing interests.

Didier Dreyfuss, M.D., Georges Saumon, M.D. Louis Mourier Hospital, Colombes, France (D.D.). didier.dreyfuss@aphp.fr

References

1. Lex D, Uhlig S: One-hit models of ventilator-induced lung injury: Benign inflammation *versus* inflammation as a by-product. Anesthesiology 2017; 126:909–22
2. Ricard JD, Dreyfuss D, Saumon G: Production of inflammatory cytokines in ventilator-induced lung injury: A reappraisal. Am J Respir Crit Care Med 2001; 163:1176–80
3. Dreyfuss D, Ricard JD, Saumon G: On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. Am J Respir Crit Care Med 2003; 167:1467–71
4. Uhlig S, Ranieri M, Slutsky AS: Biotrauma hypothesis of ventilator-induced lung injury. Am J Respir Crit Care Med 2004; 169:314–5; author reply 315
5. Takata M, Wilson MR: If we ask a mouse about biotrauma, will it give us a sensible answer? Anesthesiology 2017; 126:766–7
6. Bouadma L, Schortgen F, Ricard JD, Martet G, Dreyfuss D, Saumon G: Ventilation strategy affects cytokine release after mesenteric ischemia-reperfusion in rats. Crit Care Med 2004; 32:1563–9
7. von Bethmann AN, Brasch F, Nüsing R, Vogt K, Volk HD, Müller KM, Wendel A, Uhlig S: Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med 1998; 157:263–72

(Accepted for publication September 20, 2017.)

In Reply:

We thank Drs. Dreyfuss and Saumon for their comments on our recent work on one-hit models to study the biotrauma hypothesis.[1] I agree that our study supports some of his earlier concerns and that my view has been too simplistic. However, it is important to note that our recent work does not discredit the biotrauma hypothesis itself. What our work suggests is that the biotrauma hypothesis is difficult to study in one-hit models using ventilation as the only hit, because in such models, there is either mild inflammation without lung injury or severe mechanical injury followed by secondary inflammation. One-hit models, therefore, do not well recapitulate the clinical situation where injured and inflamed lungs are exposed to a second proinflammatory stimulus, namely ventilation.

To me, the biotrauma hypothesis still offers a relevant explanation for the findings of the low tidal volume Acute Respiratory Distress Syndrome Network (ARDSnet) trial.[2] In that study, neither barotrauma, oxygenation, nor hypercapnia correlated with mortality—only inflammation did.[2,3] Similar correlations were found in a second, independent trial.[4,5] For obvious reasons, such studies cannot be repeated, and we will need complex and more realistic experimental animal models mimicking intensive care unit–like conditions to understand the complex interplay between ventilation and inflammation in patients with adult respiratory distress syndrome. In contrast to Dr. Dreyfuss, I believe that such studies are possible.

Competing Interests

The author declares no competing interests.

Stefan Uhlig, Ph.D., Rheinisch-Westfälische Technische Hochschule, RWTH Aachen University, Institute of Pharmacology and Toxicology, Aachen, Germany. suhlig@ukaachen.de

References

1. Lex D, Uhlig S: One-hit models of ventilator induced lung injury: Benign inflammation *versus* inflammation as a by-product. Anesthesiology 2017; 126:909–22
2. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8
3. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP; NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network: Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005; 33:1–6; discussion 230–2
4. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999; 282:54–61
5. Ranieri VM, Giunta F, Suter PM, Slutsky AS: Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–4

(Accepted for publication September 20, 2017.)

Anesthesia, Consciousness, and Language

To the Editor:

I was fascinated to read the recent paper and editorial concerning anesthesia and consciousness, and I wondered whether we might learn more about the effects of anesthesia if we consider one of the brain's most impressive faculties—that of human language.[1,2] There have been a number of reports of patients fixating on a second language while under the effects of anesthesia, either during sedation or sometimes for hours postoperatively.[3–8] In all cases, the switching of the production of speech to exclusively the patient's second language appears to be a direct and involuntary effect of anesthesia, one that spontaneously