

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 criteria² 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.

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Competing Interests

Drs. Zarbock and Kellum have received grant support and lecture fees from Astute Medical (San Diego, California), un-

related to the current study. They have filed a patent application on the use of the biomarkers together with remote ischemic preconditioning.

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

To the Editor:

We are pleased that Lex and Uhlig¹ 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 Uhlig¹ and the accompanying editorial⁵ 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