In summary, we applaud Dr. Kertai *et al*. for their enlightening study and opinions on AKI and short-term mortality after cardiac surgeries. However, it is of utmost importance for us readers to keep alerted of the conclusions this study intended to present, in order to avoid overreliance on the statistical results while neglecting the possible biologic implausibility. We expect the authors to further address and explore on the above issues.

## Competing Interests

The authors declare no competing interests.

**Shangyi Hui, M.D., Chunhua Yu, M.D.** Peking Union Medical College Hospital, Beijing, China (C.Y.). yuchh@pumch.cn

## References

1. Kertai MD, Zhou S, Karhausen JA, Cooter M, Jooste E, Li YJ, White WD, Aronson S, Podgoreanu MV, Gaca J, Welsby IJ, Levy JH, Stafford-Smith M, Mathew JP, Fontes ML: Platelet counts, acute kidney injury, and mortality after coronary artery bypass grafting surgery. Anesthesiology 2016; 124:339–52
2. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J: The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004; 44:1453–62
3. Goren O, Matot I: Perioperative acute kidney injury. Br J Anaesth. 2015; 115(suppl 2):ii3–14
4. Walsh M, Garg AX, Devereaux PJ, Argalious M, Honar H, Sessler DI: The association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery. Anesth Analg 2013; 117:924–31
5. Brienza N, Giglio MT, Marucci M, Fiore T: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 2009; 37:2079–90
6. Mörtberg J, Blombäck M, Wallén H, He S, Jacobson SH, Spaak J: Increased fibrin formation and impaired fibrinolytic capacity in severe chronic kidney disease. Blood Coagul Fibrinolysis 2016; 27:401–7
7. Campo G, Valgimigli M, Ferraresi P, Malagutti P, Baroni M, Arcozzi C, Gemmati D, Percoco G, Parrinello G, Ferrari R, Bernardi F: Tissue factor and coagulation factor VII levels during acute myocardial infarction: Association with genotype and adverse events. Arterioscler Thromb Vasc Biol 2006; 26:2800–6

*(Accepted for publication April 28, 2016.)*

---

*In Reply:*

We appreciate comments from Drs. Hui and Yu regarding our published article titled "Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery."[1] The letter indicated that "despite the elaborate statistical analysis and the innovative perspectives," they were concerned over "the study design and the interpretation of statistical results" of our study. More specifically, the letter highlighted that information on perioperative blood loss was not included in the logistic regression analysis and "suggest focusing more attention on perioperative blood loss, rather than platelets reduction in future research studies on postoperative acute kidney injury." In support of their statement, Drs. Hui and Yu critiqued that significant blood loss is an independent risk factor for postoperative acute kidney injury (AKI) and in-hospital mortality after cardiac surgery. However, all studies cited in support of their statement did not directly test blood loss as a predictor of AKI. For example, one study defined significant blood loss as a need for large volume of blood transfusion (administration of more than or equal to 5 units of packed erythrocytes within 1 day of surgery)[2]; another reviewed risk factors and management of AKI without discussing the role of blood loss for predicting perioperative AKI[3]; another study was conducted in patients undergoing noncardiac surgery and investigated the role of perioperative hemoglobin as a predictor of AKI[4]; and the last citation was a meta-analysis of studies about the effects of perioperative hemodynamic optimization for postoperative renal dysfunction.[5] Although several studies have found transfusion and anemia to be associated with AKI in cardiac surgery, none have addressed blood loss itself as a predictor.[6–8] Further, the incidence of major bleeding requiring reoperation after elective coronary artery bypass grafting surgery is reported to be around 2.1%,[9] and therefore given this low incidence, it is unlikely that major bleeding and/or blood loss accounted for a higher risk for AKI in our study. In addition, accurate measurement of blood loss intraoperatively in cardiac surgery with the use of cardiopulmonary bypass has limitations. Similarly, chest tube outputs after surgery is not a reliable method of capturing blood loss because the hemoglobin content in the chest tube is not measured.

Drs. Hui and Yu also alluded that our study did not explore the functions of the whole set of serum coagulant components on AKI from a "broader view, other than focusing on the single variable of platelet count." Again, in support of their statement, they reference two studies conducted in nonsurgical populations—one on increased fibrin formation and impaired fibrinolysis capacity in severe chronic kidney disease[10] and the other on the role of tissue factor and coagulation factor VII levels in patients with acute myocardial infarction.[11] We are not aware of any studies to date to indicate that increased fibrin formation, impaired fibrinolysis capacity, tissue factor, or coagulation factor VII levels play a significant role in the development of postoperative AKI after cardiac surgery. Further, many of these factors of coagulation are not routinely measured during and after cardiopulmonary bypass in patients undergoing cardiac surgery. On the contrary, previous studies indicated that contact activation during and after cardiopulmonary bypass can lead to formation of circulating microaggregates (adhesions among leukocytes, activated platelets, and endothelial cells), and along with persistent thrombin generation, microaggregates may

produce ongoing microvascular plugging that manifest clinically as end-organ injury such as AKI.[12] The involvement of activated platelets in the formation of these microaggregates can manifest in the reduction in platelet counts as reasoned in our study. Thus, measuring intra- and postoperative platelet counts, which is readily available and is a routinely performed laboratory test in patients undergoing cardiac surgery, may be used as an indicator of ongoing platelet activation/consumption that may prognosticate end-organ injury such as AKI.

Finally, the letter suggests, "readers to keep alerted of the conclusions" of our study "in order to avoid overreliance in the statistical results while neglecting the possible biologic implausibility." It should be noted first that our hypothesis and our analysis strategy sought to reveal the independent effect of postoperative thrombocytopenia, separate from any overlap with patient- and procedure-related effects. Thus, using contemporary statistical methods for adjusting for those covariable effects on outcome is critically important. Second, as also highlighted in the accompanying editorial to our article,[13] platelets reflect biologic complexity of poorly buffered inflammation, and in depth research of that biocomplexity may allow hypothesis-driven studies to sprout out from the findings of our observational study. Of note, we agree that since we were not able to measure markers of inflammation and microthrombosis in our current study, future studies that are prospective in design and of sufficient size are needed to define the context of platelet activation, thrombocytopenia, and inflammation-related ischemic complications in coronary artery bypass grafting surgery.[1]

## Competing Interests

The authors declare no competing interests.

**Miklos D. Kertai, M.D., Ph.D., Shan Zhou, M.D., Jörn A. Karhausen, M.D., Mary Cooter, M.Sc., Edmund Jooste, M.B.Ch.B., Yi-Ju Li, Ph.D., William D. White, M.Sc., Solomon Aronson, M.D., M.B.A., Mihai V. Podgoreanu, M.D., Jeffrey Gaca, M.D., Ian J. Welsby, M.D., Jerrold H. Levy, M.D., Mark Stafford-Smith, M.D., Joseph P. Mathew, M.D., M.H.Sc., Manuel L. Fontes, M.D.** Yale School of Medicine, New Haven, Connecticut (M.L.F.). manuel.fontes@yale.edu

## References

1. Kertai MD, Zhou S, Karhausen JA, Cooter M, Jooste E, Li YJ, White WD, Aronson S, Podgoreanu MV, Gaca J, Welsby IJ, Levy JH, Stafford-Smith M, Mathew JP, Fontes ML: Platelet counts, acute kidney injury, and mortality after coronary artery bypass grafting surgery. Anesthesiology 2016; 124:339–52
2. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J: The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004; 44:1453–62
3. Goren O, Matot I: Perioperative acute kidney injury. Br J Anaesth 2015; 115(suppl 2):ii3–14
4. Walsh M, Garg AX, Devereaux PJ, Argalious M, Honar H, Sessler DI: The association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery. Anesth Analg 2013; 117:924–31
5. Brienza N, Giglio MT, Marucci M, Fiore T: Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 2009; 37:2079–90
6. Karkouti K, Wijeysundera DN, Beattie WS; Reducing Bleeding in Cardiac Surgery (RBC) Investigators: Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. Circulation 2008; 117:478–84
7. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, Beattie WS: Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. Anesthesiology 2011; 115:523–30
8. Karkouti K, Grocott HP, Hall R, Jessen ME, Kruger C, Lerner AB, MacAdams C, Mazer CD, de Medicis É, Myles P, Ralley F, Rheault MR, Rochon A, Slaughter MS, Sternlicht A, Syed S, Waters T: Interrelationship of preoperative anemia, intraoperative anemia, and red blood cell transfusion as potentially modifiable risk factors for acute kidney injury in cardiac surgery: A historical multicentre cohort study. Can J Anaesth 2015; 62:377–84
9. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS: Trends in isolated coronary artery bypass grafting: An analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg 2012; 143:273–81
10. Mörtberg J, Blombäck M, Wallén Å, He S, Jacobson SH, Spaak J: Increased fibrin formation and impaired fibrinolytic capacity in severe chronic kidney disease. Blood Coagul Fibrinolysis 2016; 27:401–7
11. Campo G, Valgimigli M, Ferraresi P, Malagutti P, Baroni M, Arcozzi C, Gemmati D, Percoco G, Parrinello G, Ferrari R, Bernardi F: Tissue factor and coagulation factor VII levels during acute myocardial infarction: Association with genotype and adverse events. Arterioscler Thromb Vasc Biol 2006; 26:2800–6
12. Rinder CS, Mathew JP, Rinder HM, Greg Howe J, Fontes M, Crouch J, Pfau S, Patel P, Smith BR; Multicenter Study of Perioperative Ischemia Research Group: Platelet PlA2 polymorphism and platelet activation are associated with increased troponin I release after cardiopulmonary bypass. Anesthesiology 2002; 97:1118–22
13. Spiess BD: Platelets reflect biologic complexity. Anesthesiology 2016; 124:265–6

*(Accepted for publication April 28, 2016.)*

# Epidurals and Chronic Postsurgical Pain: Is It Lack of Evidence or Poor Design?

*To the Editor:*

We read with great interest the large, retrospective database review of perioperative epidural use for abdominal surgery by Ladha *et al.*[1] We agree that studying anesthetic techniques that might have an impact on the incidence of persistent postsurgical pain is an important area, and is one in which large, well-controlled studies are lacking. Indeed, the large sample population was a strength of the study. However, we have serious concerns about the design of the study. First, and perhaps