Author’s response to reviews

Title: Cardiopulmonary bypass time is an independent risk factor for acute kidney injury in emergent thoracic aortic surgery: a retrospective cohort study

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Author’s response to reviews:

Dear Prof. Vipin Zamvar and the Editorial Board:

On behalf of my co-authors, we greatly appreciate the careful review and comments from both you and the reviewers. We believe that by implementing the suggested changes, we now have a stronger manuscript titled “Cardiopulmonary bypass time is an independent risk factor for acute kidney injury in emergent thoracic aortic surgery: a retrospective cohort study.” (ID: JCTS-D-19-00045) for possible publication in the “JOURNAL OF CARDIOTHORACIC SURGERY”. We look forward to your positive response to the revised work submitted here.

We present here point-to-point responses for each comment and have revised our manuscript accordingly. Revised portions were marked in red in the paper.
Responds to the reviewer’s comments:

Reviewer #1:

This study by Xu and colleagues examine the association between CPB time and postoperative AKI in 115 patients undergoing thoracic aortic surgery for acute aortic dissection. The authors conclude that CPB time is an independent predictor of AKI after thoracic aortic surgery in patients with acute aortic dissection.

I would like to make a few comments.

Question 1: Authors need to detail the patient's characteristics about acute aortic dissection:

Stanford classification or DeBakey classification, presence or absence of malperfusion, presence or absence of renal artery dissection or occlusion, presence or absence of preoperative shock or AMI.

Is there any difference in preoperative patient background mentioned above between patients with and without postoperative AKI?

Response: Special thanks for your constructive comments! It is absolutely true that in our study protocol we included these confounder factors, such as age, gender, diabetes mellitus, hypertension, preoperative hemoglobin, hematocrit, preoperative sCr, preoperative BUN, eGFR, CPB time, aortic cross clamp time, circulatory arrest time, nasopharyngeal temperature at circulatory arrest, rectal temperature at circulatory arrest, reoperation for bleeding. These confounder factors were selected based on our prior studies, clinical experience and from others examining risk factors for AKI. Following the reviewer’s advice, we added the confounder factors (renal artery dissection or occlusion, Penn class, kidney malperfusion, AMI, preoperative shock) to the revised manuscript. Revised portions were marked in red in the paper. Besides, in our study, the patients included were all acute DeBakey I aortic dissection.

The presence or absence of malperfusion was based on the Penn classification which was established and subsequently validated in the last decade. Preoperative shock was defined as a systolic blood pressure < 90 mmHg. Patients with ST elevation on a 12-lead electrocardiogram associated with wall hypokinesis at the corresponding region on echocardiography were considered to have AMI. Renal malperfusion was diagnosed as at least one renal artery dissection with creatinine rise 50% above the normal upper limit. Thank you for your suggestion. We agree that there are some correlations between these variables and postoperative AKI. We have added these data to our revised manuscript. Please see the revisions to the manuscript on page 4, lines 123-130 and table 1 and table 2. As table 2 showed, there was no significant difference in this background between patients with and without postoperative AKI.

Question 2: Authors need to describe circulatory arrest temperature. Did all patients undergo total arch replacement with FET? Company information about FET and artificial vascular graft
should be added. Is there any difference in surgical procedure between patients with and without postoperative AKI?

Response: We apologize that we did not provide detailed information regarding these. In table 1, nasopharyngeal temperature (℃) and rectal temperature (℃) were the circulatory arrest temperature. Our revised manuscript was marked in red in the paper. Over the past decade, our protocol of hypothermic circulatory arrest has evolved considerably as we accrued more experience, and now we routinely perform arch surgery at 20-25 ℃. Moreover, there was no difference between 2 groups in nasopharyngeal temperature and rectal temperature at circulatory arrest (p=0.143 and p=0.356) from table 2. Therefore, the variation in hypothermic circulatory arrest temperature had limited effects on postoperative AKI.

Aortic total arch procedure combined with an elephant trunk implant is a preferred choice to treat acute DeBakey Type I aortic dissection at our center. All patients were undergone total arch replacement with FET in our study. This part was revised and marked in red. Please see the revisions to the manuscript on page 4, lines 94-96. The procedure refers to total arch replacement using a tetra-furcate vascular graft combination with implantation of a special stented graft into the descending aorta. The procedure involves deployment of an open stent graft, Cronus® (MicroPort, Shanghai, China) into the descending aorta and total arch replacement with a 4-branched vascular graft (Maquet Cardiovascular, Wayne, NJ). This surgery was called Sun’s procedure in China. Our revised manuscript has added this information and was marked in red. Please see the revisions to the manuscript on page 6, lines 159-168.

The method of aortic total arch procedure combined with a frozen elephant trunk implant was the same. Whether to perform an aortic valve replacement depended on the condition of the aortic valve. If the classification of aortic regurgitation was moderate or severe, we preferred to perform Bentall procedure (aortic valve replacement combined with ascending aorta replacement). If there was only mild regurgitation, we preferred to perform ascending aorta replacement only. There were no significant differences in surgical procedure between 2 groups as showed in table 2 (P=0.979).

Question 3: What variables were included in the multivariable analysis to conclude that CPB time was an independent variable for postoperative AKI? If the difference in the variables mentioned above was present, that would be a confounding variable.

Response: Thank you for your advice. We have clarified that multiple logistic regression models were used to evaluate the associations between CPB time and postoperative AKI. We constructed three models: (1) adjusted for none; (2) adjusted for demographics: age; gender; BMI; diabetes mellitus; smoking history; eGFR; (III) adjusted for age; gender; BMI; diabetes mellitus; smoking history; eGFR; BUN; preoperative sCr; hemoglobin; aortic cross clamp time. Our covariates were selected based on our prior studies, clinical experience and from others examining risk factors for AKI, not based on the p value of univariate analysis. According to the recommendations of the article published by NEJM (PMID:11291666), whether the concomitant variable was adjusted was determined depending on the following principle: if, when added to this model, the variable changed the matched odds ratio by at least 10% then an adjustment was
made. Following the reviewer’s suggestion, we have added these variables (renal artery dissection or occlusion, Penn class, kidney malperfusion, AMI, preoperative shock) to our revised manuscript and re-done the data analysis. The results were showed in table 3 of revised paper and marked in red. When we additionally adjusted for renal artery dissection or occlusion, Penn class, kidney malperfusion, AMI, preoperative shock, Bentall+TAR+FET and combined with aortic bypass surgery, the results indicated that no effect size of AKI varies by more than 10% (OR=1.171; 95% CI:1.002-1.368; P=0.047). Although the effect size after adjusting these variables was not significantly different compared with original version (OR=1.163; 95% CI:1.020-1.326; P=0.024), we still modified the figure in our paper and marked it in red. Thanks again for your professional advice.

Reviewer #2:

Congratulations on the study, it is very important to evaluate the impact of extracorporeal circulation specifically on aortic surgeries.

Question 1: Regarding aortic diseases, it is important that the incidence of different aortic diseases in the studied population be reported, as well as a more detailed description of the repair technique, since they may directly interfere with renal perfusion.

Response: Thank you for pointing out this important issue. We totally agree with you. In our study, we included all patients who underwent emergent thoracic aortic surgery for acute DeBakey I aortic dissection. All the study patients received aortic total arch replacement surgery combined with a frozen elephant trunk implant. The method of aortic total arch procedure combined with a frozen elephant trunk implant was the same. Whether to perform an aortic valve replacement depended on the condition of the aortic valve. If the classification of aortic regurgitation was moderate or severe, we preferred to perform Bentall procedure (aortic valve replacement combined with ascending aorta replacement). If there was only mild regurgitation, we preferred to perform ascending aorta replacement only. If the blood pressure of the upper and lower limbs differed significantly and the signs and symptoms of lower limbs ischemia were presented, the ascending aorta to femoral artery bypass surgery was performed. There were no significant differences in surgical procedure between 2 groups as showed in table 2 (P=0.979). The method of this operation has been described in detail by our research team (PMID: 21339481; 21377701; 16399301). We apologize that we did not describe the surgical details. We have added the detailed description of the repair technique to the article and marked it in red. Please see the revisions to the manuscript on page 5, lines 151-180.

Question 2: Another point of attention, especially in cases of dissection of the A-type aorta, is the involvement of the visceral arteries, especially of the renal arteries, which may directly affect the outcomes. Clarifying these issues will certainly further improve the study, congratulations again for the work.
Response: Thank you for your advice. We strongly agree to your comments. According to your suggestion, we added these variables to our revised manuscript. Please see the revisions to the manuscript on page 4, lines 123-130 and table 1 and table 2. The involvement of the visceral arteries was based on the Penn classification (the visceral arteries malperfusion with ischemia) which was established and subsequent validated through the last decade. The involvement of the renal arteries included renal artery dissection or occlusion and kidney malperfusion. Renal malperfusion was diagnosed when there was at least one renal artery dissection with creatinine rise 50% above the normal upper limit. We have added these data to the modified version. Besides, we have added AMI, preoperative shock, Bentall+TAR+FET and combined with aortic bypass surgery. Following your suggestion, we have re-done the data analysis. These variables were also included in the multivariable analysis. The results were showed in table 3 of the revised paper and marked in red. When we additionally adjusted for these variables, the results still remained significant (OR=1.171; 95% CI:1.002-1.368; P=0.047). Although the effect size after adjusting these variables was not significantly different compared with the original version (OR=1.163; 95% CI:1.020-1.326; P=0.024), we still modified the figure in our paper and marked it in red. Please see table 3. Thanks again for your professional advice.

We tried our best to improve the manuscript and made some changes to the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked it in red in our revised paper. We sincerely appreciate the Editors/Reviewers’ professional work earnestly, and hope that the corrections will address the reviewers’ comments.

This manuscript has not been published before, nor is it being considered for publication elsewhere in any language. There are no conflicts of interest regarding this work. All authors have read the revised manuscript and approved its submission to JOURNAL OF CARDIOTHORACIC SURGERY. Once again, thank you very much for your comments and suggestions.

Should anything further be required, please do not hesitate to contact me.

Thank you very much!

Best regards

Yours sincerely,

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