Author's response to reviews

Title: Difference Between Pre-operative and Cardiopulmonary Bypass Mean Arterial Pressure is Independently Associated with Early Cardiac Surgery-Associated Acute Kidney Injury

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Author's response to reviews: see over
Dear Dr. Zamvar:

RE: Manuscript 8518520443895232 submission titled “Difference Between Pre-operative and Cardiopulmonary Bypass Mean Arterial Pressures is Independently Associated with Early Cardiac Surgery-Associated Acute Kidney Injury”

Thank you for giving us the opportunity to address your comments and accordingly revise our manuscript. We have reviewed the reviewers’ comments provided in your email from August 11th, 2010 and provide below a summary of the changes made to the paper (changes are highlighted in manuscript).

Responses to Review 1 (Paul Boucher) Comments:
1) Is the measurement of preoperative MAP valid? Could some perioperative factors have contributed to the result (does every anesthetist hold anti-hypertensives on the day of surgery?)

We recognize that pre-operative blood pressure measurements can vary; however, made efforts to standard our methods for measurement. We obtained two pre-operative measurements, one in pre-admission clinic and another upon admission to the hospital. These were conducted with the patients in the sitting position and measured using an automated standardized blood pressure machine. In keeping with the new CHEP (Canadian Hypertension Education Program) recommendation of 2 measurements separated by 24 hours we felt this was an adequate measurement. To strengthen the baseline measurement we added a third measurement taken from the arterial line reading from the patient in the OR prior to the administration of anesthesia. We have made mention of this in the Methods section.

In regards to your question of medications held on the day of surgery, we recognize that there may be some variability in practice. We collected data on what medication were administered on the day of surgery to each group. We found no statistical difference in either anti-hypertensives or other relevant medications. We have included a summary table of some of the important medications below.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Control (92)</th>
<th>AKI (65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker on day</td>
<td>14</td>
<td>6</td>
<td>0.27</td>
</tr>
<tr>
<td>Calcium antagonist on day</td>
<td>1</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>ACE on day</td>
<td>2</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>ARB on day</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Statin on day</td>
<td>16</td>
<td>16</td>
<td>0.27</td>
</tr>
<tr>
<td>Aspirin on day</td>
<td>39</td>
<td>27</td>
<td>0.91</td>
</tr>
<tr>
<td>Clopidogrel on day</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Thiazide on day</td>
<td>2</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>Loop on day</td>
<td>2</td>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>Spironolactone on day</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Insulin on day</td>
<td>6</td>
<td>6</td>
<td>0.52</td>
</tr>
</tbody>
</table>

2) Is it the outcome perhaps related to uncontrolled hypertension causing occult kidney disease (as a marker for propensity for renal injury) rather than a modifiable factor (MAP on CPB).

We agree with the reviewer – this could represent a plausible explanation for the observed association between delta MAP and post-operative CSA-AKI. Our data suggest that patients with high risk features for CSA-AKI, when subjected to greater changes from baseline blood pressure or greater delta MAP have higher odds of developing post-operative CSA-AKI. This relative hypoperfusion may be unmasking those with “occult” renal injury; however, modifying perfusion pressure and flow we may be able to reduce the incidence of injury. Furthermore, those with occult injury possibly due to uncontrolled hypertension or various other insults may in fact need even higher pressure/flow regiments to abate CPB related injury. However, this is only a pilot observational study and we recognize the observed association remains prone to bias. To further test this hypothesis, we recognize a randomized trial would need to be performed.

3) Side-biting clamps generally imply more manipulation of the aorta - Notwithstanding delta MAP

We agree with the reviewer’s comment – indeed use of a side-biting clamp is associated with more aortic manipulation. This is particularly important in the setting of a porcine aorta (where this practice should be entirely avoided) in which there is a higher likelihood of showering emboli to the brain and potentially the kidneys. We believe this was an important observation in our study.
4) Some of the issues surrounding the negative effects of attempting to achieve a goal MAP 26 mmHg greater than the standard in their institution were touched upon. There are others - namely bleeding, hemolysis (secondary to higher pump flows), these may also contribute to renal injury.

This is a relevant issue raised by the reviewer. First, we are not certain that the intra-operative MAP would in fact need to be increased to ≥26 mmHg of the standard intra-operative MAP – rather – if such a value is proven to be highly discriminatory in confirmatory studies – one would need to maintain the delta within this range – and this would likely result in a lower titration of intra-operative MAP. For example, is pre-operative MAP was 95 mmHg – and institutional practice was CPB MAP 50 mmHg – then intraop MAP would need to be titrated to 65-75 mmHg range.

However, we agree that the issue of operative field bleeding is important and likely one reason perhaps why CPB MAP has been historically low (50-60 mmHg). Anecdotally, there can be adequate surgical field visualization with CPB MAP ≥70 mmHg. Moreover, increased intra-operative MAP while on CPB should not directly impact anastomotic bleeding as the heightened perfusion pressure is isolated to the CPB circuit and extra-cardiac circulation.

We also agree with the reviewer’s comment on risk of hemolysis with higher perfusion pressure, in particular in the extracorporeal circuit. Notably, the average pre-operative MAP in our cohort was 88 mmHg – thus suggesting a target CPB MAP would be approximately 60-65 mmHg – which we believe would be acceptable practice. We agree there may be an increased risk for hemolysis; however, our study was not poised to comment on this and we believe this would be an important variable to examine in further prospective studies.

Responses to Review 2 (Anthony Delaney) Comments:
1. In the section describing the study definitions, the authors refer to acute kidney injury (AKI) being defined by the RIFLE criteria. In my copy of the manuscript the “urine output” has been left out of the criteria, I assume this is a minor typographical error. Can the authors please confirm that AKI as defined by the Injury category is what is referred to in this study? Or have the authors defined AKI as patients meeting any of the RIFLE criteria ie, including the Risk category. The authors might consider presenting the data for how many of the cases of AKI met each of the creatinine or urine output criteria for each RIFLE category?

We apologize this was indeed a typographical error and has been corrected in the manuscript. We used the RIFLE classification system in our study as originally defined by Bellomo et al.

2. With the above point in mind, I found it hard to understand how so many patients were diagnosed as incident cases of AKI, given the results of Table 5. The mean urine output for the first 24 hours in the group with AKI was 0.5ml/kg/hr and the mean creatinine only increased from 100 to 114. It is hard to imagine how these numbers
represent the injury category of the RIFLE “injury” criteria.
We appreciate the reviewer’s comment. Indeed – we did not target RIFLE class “Injury”
to define CSA-AKI – but only RIFLE class RISK or greater. This is consistent with the
literature and many of the prior non-RIFLE definitions used to define post-operative
CSA-AKI (i.e. SCr rise 10.0 µmol/L, 26.5 µmol/L, 44.2 µmol/L, or a 25%, 50% increase
relative to baseline etc.) We also believe this was justified given two large
epidemiologic studies (Kuitunen et al, Dasta et al) both found RIFLE class – RISK to be
independently associated with increased risk for peri-operative death.

In addition, we recognize the RIFLE criteria are in fact sensitive, in particular when using
both SCr and urine output criteria. However, these criteria are now accepted for use in
cardiac surgery to capture patients as AKI and classify severity. As the reviewer has
pointed out - the Cr rise was not as significant as the change in the urine output (which
is a sensitive). As a result the difference in Cr was 100 vs 114. Despite the urine output
being 1 cc/kg/hr vs 0.5 cc/kg/hr over the first 24 hours according to the RIFLE criteria
the urine output threshold (of <0.5 cc/kg/hr) needs to be achieved for only 6 hrs to
satisfy the AKI-R strata of injury. As such, in our study, CSA-AKI when defined by the
RIFLE criteria was diagnosed by creatinine alone in 7, oliguria alone in 51, and both in 7,
respectively. The following table shows the number of patients who fulfilled criteria for
CSA-AKI by RIFLE category.

<table>
<thead>
<tr>
<th>RIFLE category achieved</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>92</td>
</tr>
<tr>
<td>Risk</td>
<td>65</td>
</tr>
<tr>
<td>Injury</td>
<td>22</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
</tr>
</tbody>
</table>

3. There are a couple of additional points that might be worth adding to the statistical
methods. The use of an a-priori hypothesised value for the delta MAP that would be
associated with a significant increase in AKI would have greatly enhanced the
reproducibility of the multivariate model and would have reduced the likelihood for a
chance finding. Could the authors justify why an a-priori value for delta MAP was not
used in the study?

We agree with the reviewer that an a priori hypothesized value for delta MAP would
have been ideal – however – we did not have data to guide on this issue – as no other
studies in the literature have specifically evaluated the association of delta-MAP and
development of CSA-AKI. Accordingly, this study was essentially a proof of concept pilot
study. However, in the results section we examined the delta MAP as both a continuous
variable and dichotomized for simpler interpretation and notably, both were significant
by multivariable analysis. We recognize the importance of verification of these findings.

Could the authors also briefly mention why the sample size was chosen for this study?
There was no pre-specified sample size estimation for this study – as previously
mentioned - this study was essentially a proof of concept pilot study.
Finally, a minor statistical clarification. My understanding is that for multivariate logistic regression models to have sufficient power to give stable results there needs to be approximately 10 outcome events for every predictor added to the model. It appears that the authors will have included 14 predictors (i.e. those with a p<0.2) in the original multivariate model. Therefore the 65 cases of AKI would be insufficient to produce a stable model and the resulting estimates of the OR would be difficult to reproduce. The validity of the results would be enhanced if the authors followed a pre-specified analysis plan. Can the authors state whether a pre-specified analysis plan was used for this analysis, or was the analysis data driven? Was the modelling performed solely on statistical grounds or were clinical factors also considered? These factors may help readers interpret the results of the study.

These are all reasonable comments by the reviewer. We are familiar with statistical rule-of-thumb suggested by Altman for 10 events per variable included in multi-variable analysis. While we evaluated an excess of this by univariate analysis, our final model included only six covariates (this includes delta MAP – which was forced into the model). Model variables were included based on theoretical considerations (i.e. age, sex) and statistical considerations (i.e. significance). In consultation with our statistician, this process was deemed acceptable, and the final model was stable. We did have an a priori analysis, drafted by our statistician and outlined briefly in the methods section, with general objectives and hypotheses in mind, in order to examine for factors associated with CSA-AKI, in particular delta MAP. Again, we recognize this as a proof of concept pilot study – and we hope to use these data to stimulate and further guide this program of inquiry.

All authors have contributed to and have approved the final manuscript. This work has not been previously published and is not under consideration for publication elsewhere.

If there is any further information required, please contact us at your convenience. We look forward to your review.

Sincerely,

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