Author's response to reviews

Title: Increased cardiac index attenuates septic acute kidney injury: a prospective observational study

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Version: 3
Date: 17 December 2014

Author's response to reviews:

We have read the reviewers' comments and modified the paper according to it. We also have one scholar from the Imperial College London to help improve the language. He suggested us to use “CI constant group” to replace “CI un-increased group” in the paper and help correct many language points. We listed all the modifications below:

To the reviewer Kenneth Shelton

The major compulsory revisions:

1. “A cutoff value of 10% increased CI would provide a sensitivity of 75% and a specificity of 89%.” This needs further explanation/clarification. This line has grammar/spelling concerns. Why was a cutoff value of 10% used for this study? (Results, Relationship between CI changes and renal outcomes, First Paragraph)

Reply:
(1) The cutoff value of 10% was decided by the Youden index which balanced the sensitivity and specificity.

(2) In this study, we used the 10% to assign patients to either CI increased group or CI un-increased group because the systemic error of thermos-dilution method (the variation for two consecutive measurements) was 10% approximately. Besides, some other research[1] also used a 10% to determine whether the CI or CO increased.

(3) Although there were two 10% in this paper, their meaning were different however.

(4) To reduce confusion, we modified it as “A cutoff value of 10% increased CI determined by the Youden index would reach a sensitivity of 75% and a specificity of 89%.”

2."In this study, the incidence of poor renal outcomes were 44% (4/9) in patients with a CI < 3.0, 10% (1/10) in patients with a CI 3.0-4.0 and 44% (4/9) in patients with a CI > 4.0. This needs further explanation/clarification. This line has grammar/spelling concerns. It is concerning that renal protection is found within such a narrow cardiac index with renal impairment both above and below this range. Is it possible that having a cardiac index between 3.0-4.0 is an indicator of less severe sepsis and that these patients are therefore less likely to develop AKI. (Discussion, Third Paragraph)

Reply:
(1) As a retrospective research [1] reported, a much low or high CI or CO may also related to high incidence of AKI. We divided the patients according to the CI value after EGDT and find a trend that patients with a CI between3.0-4.0 may have lower risk of poor renal outcome (though without significant difference, in the Table shown below).

(2) However, based on the present data, it is hard to determine a particular CI value as an indicator of less severe sepsis and less likely to develop AKI (AUROC: 0.556, P=0.115).

(3) To illustrate the problem further, we added some more data and built up a new paragraph in discussion part.

3. “Over-ambitious CI goal” This needs further explanation/clarification. As mentioned above, what other possible explanations aside from reperfusion/inflammatory damage might explain a worse outcome with higher cardiac index. Perhaps a higher cardiac index is a sign of more severe sepsis with worse oxygen extraction and higher compensated perfusion and therefore these patients are more inclined to develop AKI. Is it possible that patients with low cardiac index (low flow state) are showing signs of uncompensated sepsis?

(Discussion, Third Paragraph)

Reply:
We agree with the reviewer’s opinion that a higher CI may suggest a high severity of severe sepsis or septic shock. As shown in our research, the patient with a CI>4.0L/min/m2 has a lower MAP along with a higher ScvO2, which suggest a worse oxygen extraction and higher compensated perfusion. The lower cardiac output in the patient with a CI<3.0L/min/m2 after receiving the same dose of fluid and vasopressor suggest a uncompensated status of sepsis.

We built up a new paragraph to discuss whether a much higher or lower CI may be harmful in the discussion part.

4. "Finally, some patients received infusion of hydroxyethyl starch during resuscitation, which may affect renal function as well. However, there were no significant differences in portions or doses of hydroxyethyl starch between the two groups." It is well known that hydroxyethyl starch is nephrotoxic and
associated with renal replacement therapy in the ICU patient population. While the two groups show no significant difference in terms of dose/portion, it would be interesting to know if those patients with a cardiac index of 3.0-4.0 and less renal impairment had the same HES exposure. (Limitations, First Paragraph)

Reply:

As shown in table 4 listed above, there were no significant difference in terms of dose/portion of HES among three groups.

Minor Essential Revisions:

5. “the association between the changes of cardiac index (CI)”- This needs further explanation/clarification. This line has grammar/spelling concerns.(Abstract, Background, First paragraph)

Reply:

(1) This line contained two aspects: the first, to investigate whether increment of CI associates with better renal outcome; the second, try to determine a CI goal which may serve as an indicator of less likely of AKI.

(2) We modified it to “the association between the cardiac index (CI) and the renal outcomes”.

6. “general ICU”- Please specify clearly the patient population for this ICU (surgical vs medical, cardiac vs trauma, etc) (Abstract, Methods, First paragraph)

Reply:

(1) In China, general ICU means both surgical and medical ICU which recruits patients from emergency department, internal medicine department and surgical department.

(2) To avoid misunderstanding, we modified the “general ICU” to “surgical and medical ICU” in this paper.

7. “We studied the association between CI changes and renal outcomes”- This needs further explanation/clarification. This line has grammar/spelling concerns.(Abstract, Methods, First paragraph)

Reply: We modified it to “We studied that whether an increased CI related to a better renal outcome”.

8. “CI increased >10%”- This needs further explanation/clarification. How did you decide that a cardiac index of 10% should be used as the cutoff point? How does the PiCCO system compare to the well-established thermodilution or Fick’s method of measuring cardiac index with a pulmonary artery catheter? (Abstract, Results, First paragraph)

Reply:

(1) 10% was a widely accepted level of systemic error of thermodilution method as mentioned above. If the CI increased more than 10% after EGDT, we would have confidence to say the CI really increased. So we used 10% as a boundary to assign patient to CI increased group or not.
(2) Pulmonary artery catheter is also a good method to measure the cardiac output and frequently used in cardiac diseases in our setting.

(3) The another reason is that the in-placement of PiCCO catheter is easier and require less time than the pulmonary artery catheter.

9. “CI increased group”-This needs further explanation/clarification. This line has grammar/spelling concerns. (Abstract, Results, First Paragraph)

Reply:
Patient with a CI increment above the systemic error of thermodilution method (10%) was assign to the CI increased group.

10. “CI un-increased group”-This needs further explanation/clarification. This line has grammar/spelling concerns. (Abstract, Results, First Paragraph)

Reply:
Patient with a CI increment less than the systemic error of thermodilution method (10%) was assign to the CI un-increased group. Besides, our UK friend suggested us change “CI un-increased group” to “CI constant group”, and we accept it.

11. “with an odd ratio”- This line has grammar/spelling concerns. (Abstract, Results, First Paragraph)

Reply:
We rephrased the sentence to “The logistic regression showed that the CI percent change was associated with renal outcome, with an odd ratio of 0.003 (P=0.056) after adjustment of possible confounding factors.”

12. “had a moderate accuracy”- This line has grammar/spelling concerns. (Abstract, Results, First Paragraph)

Reply:
We rephrased the sentence to “The CI percent change would predict a good renal outcome (AU ROC 0.739, P=0.012) with moderate accuracy (sensitivity 75% and specificity 89%) when using a 10% cut-off value from Youden index.”

13. “with a sensitivity of” - This line has grammar/spelling concerns. (Abstract, Results, First Paragraph)

Reply:
We improved it as shown in the last question.

14. “the CI increased by 10% can be used as a valid tool”-This needs further explanation/clarification. This line has grammar/spelling concerns. (Abstract, Results, First paragraph)

Reply:
The moderate level of area under ROC curve indicate that the CI increased by 10% can be used as a promising tool to predict development and reversibility of
AKI in septic shock patients. And 10% was decided by the Youden index which help balance the sensitivity and specificity.

15. “right shift of renal auto-regulation, the renal hypo-perfusion”-This needs further explanation/clarification. (Background, First paragraph)

Reply:
(1) We mean the renal blood flow auto-regulation curve in this line. The mechanism of renal blood flow auto-regulation is one important way to maintain a constant renal perfusion.
(2) In sepsis, the compensatory mechanism usually impaired, and the curve shift right commonly, therefore decrease the self-compensate ability of renal perfusion.

16. “therefore decrease renal blood flow on the contrary” This needs further explanation/clarification. This line has grammar/spelling concerns. (Background, Second Paragraph)

Reply:
The another reviewer suggest modify it to “Kidney perfusion can be improved by increasing the mean arterial press (MAP), which was achieved by implement of vasopressors or fluid infusion. Vasopressors may however increase the renal vascular resistance, which may result in a decrease in renal blood flow”. It seems clearer and better, so we change it as suggested.

17 “as a remarkable sign of adequate blood supply”- This needs further explanation/clarification. This line has grammar/spelling concerns. (Background, Third Paragraph)

Reply:
Increased cardiac output was more a sign of cardiac compensation, which may provide more blood to the organs. We have modified it to “An increase in cardiac output can be interpreted as an improvement in perfusion, and is associated with restoration of renal blood flow.”

To the reviewer Kamal Medlej

The major compulsory revisions:
1. Page 5, Line 53-55: You state that “This present prospective cohort study was designed to investigate the relationship between CI and the renal outcomes, and furthermore, to evaluate the possibility of setting a CI goal for renal protection.” While you address the first question, you do not determine or comment on a CI goal. Please mention this in the discussion.

Reply:
(1) We have already attempted to set a CI goal. However, based on the current data (Figure 3), it was not enough to determine a CI goal which is less likely to develop AKI.
(2) We will add this in the discussion part.
2. Page 6, Line 64: Please provide your criteria for defining “septic shock”

Reply:

In the 2012 SSC guideline [1], the definition of septic shock was modified from a “2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference”[2]. A detail criteria was a suspected or confirmed infected infection, two or more criteria for a systemic inflammatory response, and hypotension persisting after initial fluid challenge or blood lactate >4mmol/L.


3. Page 11, Discussion: Please include a discussion of the reason(s) you believe the CI did not increase in the un-increased group. Is it because not enough fluid was given or is it because the patient was no longer fluid responsive? In this case is it possible the patient received too much fluid? Could this be related to the higher incidence of AKI.

Reply:

From the data at present, we believe the difference in fluid responsiveness may be the main cause which lead to the un-increased CI. Besides, the myocardial contractility may also help explain the un-increased CI. The patients in the CI un-increased group may lay on the flat part of starling curve and easy over loaded in this setting. We have already include a discussion in the revised version.

4. Page 11, Discussion: In Tables 2 and 3, the goal parameters of EGDT (MAP, CVP, urine output) seem mostly met in both groups even before the initiation of EGDT (except for a CVP of 6 cm H2O in the CI increased group). Please discuss this and explain why. Did these patients meet criteria for initiation of EGDT and if so what were your criteria (currently accepted criteria are persistent hypotension despite 30ml/Kg of crystalloids or a Lactate of # 4 in patients with a suspected or confirmed infection and # 2 SIRS criteria*). If the CVP was on average already at goal (10 cm H2O) in the CI un-increased group would additional fluid just be excessive at this point**?

Reply:

(1) The EGDT goals are the fundamental targets, not the endpoint of early resuscitation. Because infusion of fluid before admission to ICU, many patients (13/29) near achieved the EGDT goal on admission. We have already excluded 21 patients who diagnosed with septic shock but met all the EGDT goal on admission. In our study, when EGDT initialed, 3/29 patients met one of EGDT goals, 13/29 patients met two of EGDT goals and 13/29 met three EGDT goals.

(2) Though with a median CVP of 10mmHg, there were still an increment in GEDI after EGDT in the CI un-increased group. So we can not simply say the volume is
excessive in this point.

(3) We add some discussion about this in the discussion part.

5. Page 11, Line 160-163: The following sentence has to be rephrased as it is not clear in its present form “Moreover, the CI changes during EGDT was also related to development and progression of AKI, and a regression further confirmed that increased CI was a protective factor for the kidney, and increased CI in a range associated better renal outcomes.”

Reply:
Furthermore, the renal outcome in CI increased group was better than CI constant group, and a regression analysis has confirmed increased CI was a protective factor for kidney after adjusting any possible confounding factors.”.

6. Page 11, Line 164-166: The following sentence needs to be rephrased as it is not clear in its present form “Of note, the EGDT period was the most aggressive phase of resuscitation to correct circulation failure and the early adequate resuscitation, which is targeting an increase in cardiac output may benefit the organ perfusion.”

Reply:
We rephrased the sentence to “Though increased cardiac output may attenuate poor renal outcome, we failed to define a CI goal which has the minimal risk of AKI.”

7. Page 11, Line 169-171: The following sentence is too informal and you be rephrased “So we should weigh the advantage and disadvantage of increased CI and avoid setting an over-ambitious CI goal.”

Reply:
This paragraph was re-organised and we state it as “either a much lower or higher cardiac output may be harmful”.

8. Page 12, Line 187-188: The following sentence needs to be rephrased “Besides, the CI changes can be easily obtained through hemodynamic monitoring during EGDT, equipping itself with good applicable value in critical care departments.”

Reply:
We rephrased it to “Besides, the CI could be easily monitored at bedside, which made itself more applicable in critical care departments.”

Minor Essential Revisions
9. Page 5, Line 39: Please change to “…which aims at…”, or “…which is aimed at…”

Reply:
We modified it as advised

10. Page 5, Lines 41-44: Please revise wording of this sentence. Could be
changed to “Kidney perfusion can be improved by increasing the mean arterial press (MAP). Vasopressors may however increase the renal vascular resistance, which may result in a decrease in renal blood flow.”

Reply:
We accept the reviewer’s advice and modified it as “Kidney perfusion could be improved through increasing the mean arterial press (MAP) by implement of vasopressors or fluid infusion.”

11. Page 5, Line 48-49: Please consider changing to “An increase in cardiac output can be interpreted as an improvement in perfusion and was associated with restoration of renal blood flow.”

Reply:
We considered your advice and modified it.

12. Page 5, Line 50: Please change to “…studies have shown that…”

Reply:
We modified it as advised

13. Page 5, Line 51: Please change to “…suggesting that…”

Reply:
We modified it as advised

14. Page 6, Line 65: Please change to “Patients who required…”

Reply:
We modified it as advised

15. Page 6, Line 67: Please change to “…EGDT goals already achieved on admission…”

Reply:
We modified it as advised

16. Page 6, Line 71-72: The sentence “Patients who had already reach the EGDT goals on admission (if received adequate fluid infusion in emergency department) were also excluded.” is redundant and should be deleted.

Reply: We deleted it as advised

17. Page 6, Line 75: Please change to “After admission to the ICU, blood cultures were drawn, antibiotics were administered, and fluid infusion initiated.”

Reply:
We modified it as advised

18 Page 6, Line 76: Please change to “A pulse indicator…”

Reply:
We modified it as advised.

19. Page 6, Line 77: Please change to “…was placed…”
Reply:
We modified it as advised

20. Page 6, Line 79: Please change to “…the physician implemented the EGDT…”
Reply:
We modified it as advised

21. Page 6, Line 82: Please change to “…and allowing the patient to stabilize for 30 minutes…”
Reply:
We modified it as advised

22. Page 6, Line 84-85: Please change to “Patients were followed for 28 days, or until death, for the development of AKI.”
Reply:
We modified it as advised

23. Page 9, Line 126: Did you mean SVI instead of SI?
Reply:
Yes, it is. We admit it as a spelling mistake, and correct in mow.

24. Page 9, Line 145: Please revise or consider changing to “…and poor renal outcome was even greater.”
Reply:
We modified it as advised

25. Page 11, Line 155-156: Please change to “…cardiac output, leads to better perfusion of organs.”
Reply:
We modified it as “Hyper-dynamic circulation, characterized by high cardiac output, was common in septic shock and would lead to better perfusion of organs, including heart, brain, liver, guts, and especially the kidney”

26. Page 11, Line 157: “…Langenberg, et al, renal blood flow was observed to increase along with cardiac output.”
Reply:
We modified it as advised