Author’s response to reviews

Title: Severe Systemic Inflammatory Response Syndrome in Patients Following Total Aortic Arch Replacement with Deep Hypothermic Circulatory Arrest

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Version: 2 Date: 30 Aug 2019

Author’s response to reviews:

Dear Editor:

Thank you so much for your contributed work to the review and revision of our manuscript. We have made point-to-point responses to all 4 reviewers as listed below, and revised part was highlighted red. We are not English native speaker, therefore language editing was completed and editing certificate is uploaded as supplementary material. Through this experience we have learned a lot in academic area. Hope to have another cooperation in the future!

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Dear Reviewer #1:

Thank you for your positive comments.
Question: An interesting paper. My questions are exposed in the limitations. The severity of SIRS is the etiology or the consequence of complications?
RESPONSE: We supposed that the severity of SIRS is an etiology contributing to the complications such as major adverse events (OR, 4.52; 95%CI, 3.40-6.01; P &lt; 0.001) and
longer duration of intensive care unit following repair (log-rank P < 0.001), and we depicted those in the part “Clinical Outcomes Associated with sSIRS” in RESULTS.

Dear Reviewer #2:

Great thanks were expressed for your insightful reviews.  
Question: SIRS in postoperative aortic arch surgery is frequent and often lethal. The author presents a series with a significant number of patients and very interesting data. The ischemia / reperfusion process can trigger this inflammatory reaction. Some authors have noted a relationship of this inflammatory response exacerbated with the number of leukocytes and in the elevation of the lymphocyte / macrophages ratio. Studying this data and relationship would enrich the article. The data studied by the author are generic and do not add much to current knowledge. Markers as TNF alfa, BNP and others would be useful to elucidate the whole process. I suppose the paper should be improved.  
RESPONSE: First, we feel a little regretful that this is a retrospective study, and few data associated could be obtained to elucidate the relationship between ischemia / reperfusion and the number of leukocytes, and the elevation of the lymphocyte / macrophages ratio. Your suggestion is pretty great, so we make that into our limitation part. Second, markers as TNF- α, BNP and others during the whole peri-operation were not measured routinely for a great number of patients in our clinics, the incomplete data was not suitable for scientific research and resulting in the primal imperfection of this cohort cohort; hope you will understand it, and we have this shortcoming into limitation part; please see page 11, line 339-341.

Dear Reviewer #3:

How concrete your advice is! Thanks a lot.

1-As for the diagnostic Criteria for SIRS, due to the severity of the disease and its postoperative condition, many patients remain sedated on mechanical ventilation for a longer period of time (20.0 hours on average up to 45 h), how about the evaluation in these patients?  
RESPONSE 1: There was no patient undergoing fast-track anesthesia in this study cohort, namely, all patients were transferred to the intensive care unit with tracheal intubation, and then receiving sedation and mechanical ventilation. Extubation was conducted or not depend on patients’ recovery in respiration, hemodynamics and so on. In fact, 20 hours on average in patients following TAR is normal compared with other study cohorts. As such, recent study showed that mechanical ventilation for hemiarch and aggressive arch was 44h (23.9, 106.5) and 50 hours (24, 100.5), respectively [1]. Another investigation illustrated that the duration of ventilation for patients undergoing TAR with 4-branched frozen elephant trunk prosthesis was 1.0 day (0.6-3.7), however, time for patients with acute dissection could be as high as 2.8 d (0.8-6.0) [2].  
The proportion of patients ventilated more than 72 h was 14.9% (78/522) in our study. Similarly, studies on total arch replacement showed that 14.8% (149/1005) [3] or 19.0% (16/84) [4] patients experienced prolonged ventilation >72h.


2-In the description of the technique used it would be important to inform the method of myocardial protection used as well as the cardiopulmonary bypass technical characteristics (for example if the tubes are coated) and the brands used.

RESPONSE 2: Of course, techniques to protect myocardia were used in our routine work, including blood cardioplegia, ice sprinkled on myocardial surface and hypothermic method to cool down myocardium in surgical process. However, coated tube systems were only applied to patients needing ECMO support but not in TAR. We supplemented the part “Myocardial protection” in page 5, line 151-157 to make it more detailed.

3 - Neurological complications (Stroke and paraplegia) could be placed in a separate field since they are more related to the severity of the underlying disease than to SIRS itself.

RESPONSE 3: We must acknowledge that stroke and paraplegia always gains a great deal of attention in the surgical field of TAR. In our study cohort, the epidemiology of either stroke or paraplegia in the sSIRS group was a little greater than patients without sSIRS in despite of no significance (3.6% (6/164), 1.4 (5/358), p = 0.18; 5.4% (9/164), 2.5 (9/358), p = 0.084). No further multivariable analysis was carried out to figure out the predictors of neurological dysfunction owing to the limited number of patients’ suffering them. We added more detailed information on neurological dysfunction in discussion, please see page 10, line 319-334.

Dear Reviewer #4:

We appreciate the comments a lot by you. All puzzles are made clear below.
1. The content of the introduction summarises the problems caused by SIRS and the study hypothesis but this could be worded better.
RESPONSE 1. We re-arranged the INTRODUCTION, and appreciate your advice a lot which makes this manuscript looks better and more logistic. At the same time, we asked language editing help to make it worded better.

2. The methods section is entirely satisfactory.
RESPONSE 2. Thanks a lot for your agreement for our method section.

3. Regarding the results, most patients had suffered a dissection. Did the authors look at how many of these were type A & how many type B? Also how many were acute and how many either chronic or a delayed presentation or subacute. I possibly would expect a greater inflammatory response in patients with an acute pathology. Also how many patients had evidence of malperfusion pre-operatively?
RESPONSE 3. In fact, all patients recruited were diagnosed with type A dissection, aneurysm, Marfan syndrome at our institute, without any inclusion of type B dissection; and all patients suffered acute presentation, without suffering subacute or chronic pathology. However, with multivariable logistic analysis, we did not find that type A dissection was an independent risk factor to postoperative sSIRS. We must acknowledge that in the future more work should be done to investigate the relationship of SIRS, even its severity and acute or chronic presentation in patients undergoing TAR to provide more clinical references. We have added more information on dissection and its presentation in METHODS (page 4, Line105-106) and LIMITATION part (page11, Line 346-349).
Again regretful more or less to respond that malperfusion, screened out with CT, angiography, magnetic resonance angiography and visceral ultrasound, was not routinely diagnosed in our institute. So the lack of it cannot be used to do scientific research. It is proposed that CT scan is the gold standard to diagnose malperfusion, but its accuracy can still be effected by patient weight, contrast volume, the timing of scanning and so on. Hope you will admit this flaw in our study as well. The evidence of malperfusion is of lack, stated in LIMITATION part (page11, Line 345-346).

4. The overall cohort is a young one with few patients over the age of 60. Could the authors add the total range of ages please?
RESPONSE 4. We have added the total range of age in RESULTS, and the range was 19-83 yr; in page 6, line 181. Figure 1 was depicted by us to make the distribution of age more pronounced in groups including whole cohorts, the SIRS and the no-sSIRS group.

5. In the discussion I would remove the reference to influenza vaccine as I am unsure of the relevance of this.
RESPONSE 5. We have deleted the content and related references on influenza vaccine as reviewer’s suggestion.

6. I would suggest a further paragraph on ulinastatin, as we are unfamiliar with this drug in the west.
RESPONSE 6. Ulinastatin, the anti-inflammatory agent, was used primarily at present in China, Japan and Korea. In our study, it is confirmed to be a positive administration to alleviate postoperative inflammation (OR=0.69; 95% CI 0.51–0.93; P = 0.015). To make its clinical
application more explained to readers, we have put more information on ulinastatin in a sole part in discussion. Page 9, line 295-302.

7. I concur with the remainder of the discussion and conclusions, although again some rewording and correction of grammar is required.

RESPONSE 7. I and all co-authors feel a little regretful that we are not native English-speaker, thus there occurred some language problems in this manuscript. We have asked help from professional language editing service. The certificate is uploaded as well.