Author’s response to reviews

Title: Right Ventricular Failure Following Left Ventricular Assist Device Implantation is Associated with a Preoperative Pro-Inflammatory Response

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Author’s response to reviews:

Reviewer reports:

Reviewer #1: Authors analyzed LVAD experience based on inflammatory markers such as CRP and WBC. The outcomes were obvious since high WBC group had sicker patients and more likely required RV support after LVAD.

There was no exclusion or inclusion criterial for this VAD study. I assume all LVD patient during this study period.

We thank the reviewer for the opportunity to clarify this point. We included all patients with continuous flow LVADs for the study period.

The tables were difficult to read. I am not sure why there so many concomitant surgery was done (for example, TE was seen 14.6% in low WBC group but TV procedure was done in 39.5% according to Table 5. Same way I see a lot of Aortic valve surgery (7.5% in low WBC group) comparing only 3.9% of low WBC group had severe AI. It seems to me, author put all variables in to the table, and compare between based on low or high WBC group (although the cut off the WBC count was not mentioned.)
We thank the reviewer for bringing up these important points. While severe TR was seen in 14.6% of patients. While severe TR was documented in 14.6% of the low WBC group, we also performed tricuspid procedures on patients with moderate TR, particularly if the tricuspid annulus measures >4cm. In the low and high WBC groups, the proportion of patients with moderate or greater TR was 42.3% and 44.9% respectively. Moderate TR in the low and high WBC group was 28.1% and 33.9% respectively. We have added the following in the results section to further clarify valvular findings:

“There was no difference in the distribution of valvular regurgitant pathology between the 2 groups (table 4). There was also no difference in concomitant valvular operations in the 2 groups (table 5, P>0.4). Mitral valve intervention was uncommon in our practice as its utility has remained unclear. Aortic valve intervention was performed for moderate to severe AI. Tricuspid valve procedures to improve competence was used for moderate to severe TR. In the low and high WBC groups, the proportion of patients with moderate or greater TR was 42.3% and 44.9% respectively. Moderate TR in the low and high WBC group were 28.1% and 33.9% respectively.”

The cut off for the WBC count was <10.5 K/μL in the “Low WBC” group and >10.5 K/μL in the “High WBC” group. We have now included the units as well in our manuscript.

Author speculated with SIRS but only increase of WBC and CRP was not enough to say presence of SIRS before LVAD. In the discussion, authors made points regarding IL and TNF but there were not data presented in this study.

We agree with the reviewer. However, due to the retrospective nature of this study over a long period, we do not have the tissue or plasma samples to analyze for cytokine and chemokine levels as these were unfortunately not obtained prospectively. We recently started collecting these sample prospectively and can make a more accurate determination of SIRS for future studies.

The definition of RV failure was missing.

Thank the reviewer for the reminder. We have added to the methods section:

Right ventricular failure defined as a central venous pressure >18 mmHg with a cardiac index <2.0 liters/min/m2 in the absence of tamponade, ventricular arrhythmias or pneumothorax requiring RVAD or inhaled pulmonary vasodilator (e.g. nitric oxide) or inotropic therapy for >1 week at any time following LVAD implantation [10]. Only postoperative RVF occurring during the index hospitalization following LVAD implantation was considered.

I am not sure why author chose WCB 10.5 as a cut off for comparison. WBC 10.5 is not so high.

It is reasonable to find sicker patient had poor outcomes.

I have nothing learn from this study.
Thank you for this question. We examined the lowest WBC level that would differentiate postoperative outcomes in our patient population and found that 10.5 K/μl provides differentiation between patients who will develop RVF and RVAD use versus those who did not. While 10.5 K/μl is at the higher end of the reference range, it has provided sufficient differentiation ability. Therefore, this cut off was selected for the study. This was corroborated with a ROC analysis where the area under the ROC curve (C-statistics) using WBC and CRP as a predictor for RVF were 0.661 (P=0.001) and 0.727 (P<0.001) respectively. We have added to the results section:

“We performed a “Receiver Operating Characteristics” analysis and shows that WBC and CRP was able to predict RVF with a C-statistics of 0.661 (P=0.001) and 0.727 (P<0.001) respectively.”

Reviewer #2: The article is interesting. You may consider the following:

1. Page 1 & 4> The Title: 'Right Ventricular Failure Following Left Ventricular Assist Device Implantation is Associated with a Preoperative Pro-Inflammatory Response' sounds better (if you replace 'Post' with 'Following')

Thank the reviewer for the excellent suggestion. We have changed the title as recommended.

2. Page 1 & 4> Abstract> Result> 'The high WBC group was more likely .... intra-aortic balloon pump (55.9% vs 47.2%, P=0.093)' >> the p value is not significant here.

Thank you. We have qualified this statement with: “The high WBC group was more likely to be on preoperative temporary circulatory support (17.3% vs 6.4%, P<0.001) with a trend towards greater use of an intra-aortic balloon pump (55.9% vs 47.2%, P=0.093).”

3. Page 1 & 4> Abstract> Conclusion > 'Postop RVF occurs in a pro-inflammatory setting that is established preoperatively. ....'>> This statement is too assertive considering the facts of the article, plz consider rephrasing it.

We thank the reviewer for this suggestion. We have altered the abstract conclusion to: “Postop RVF is associated with a preoperative pro-inflammatory environment. This may be secondary to the increased systemic stress of decompensated heart failure. Systemic inflammation in the decompensated heart failure may contribute to RVF after LVAD implant.”

4. Page 1 & 4> The number of patients in each group (i.e. 362 & 127) is not mentioned in 'Abstract' and 'Methods' sections, those are only found in the table part. Plz consider mentioning these figures in 'Abstract' and 'Methods' sections as well.
Thank you for this suggestion. We added the group numbers to the:

1. Abstract: The population was also separated into low (<10.5 K/ul, n=362) and high (>10.5 K/ul, n=127) white blood cell count (WBC) groups.

2. Methods sections: “We separated patients into a preoperative groups of low WBC (<10.5 K/uL, n=362) and high WBC (>10.5 K/uL, n=127).”

5. Page 8, line 3-4> 'Similarly, the high WBC group was also more likely to be on IABP (55.9% vs 47.2%, P=0.093)’ >> the p value is also not significant here.

Thank you for pointing this out. We have changed the sentence to: “Similarly, the high WBC group had a trend for more IABP (55.9% vs 47.2%, P=0.093), and also…..”

6. Page 8, line 19-21> The high WBC group (Table 5) had a longer length of intensive care unit (ICU, P=0.046) and total hospital stay (P=0.064).>> again, the p value (0.064) is not significant here.

Thank you again. We have changed the sentence to: “The high WBC group (Table 5) had a longer length of intensive care unit (ICU, P=0.046) and a trend toward longer total hospital stay (P=0.064).”

7. Please consider REWRITING 'The Conclusion' part aligning with the 'Title', 'Background' and the 'Results' of your study.

Thank you for the suggestion. The conclusion has been rewritten to closer reflect our results.

8. The 'Tables' are not clear, plz add proper Titles & headings. Plz mention whether the values are Mean±SD or Mean±SE. The values should have '±' signs in the place of ‘+’. We have moved the postoperative RVF data from table 4 to table 6 under postoperative outcomes. All means are expressed with standard deviation which is now indicated as foot note with the tables. We have updated the ‘±’ signs.

Reviewer #3: I would like to congratulate the authors on this great work. Much is lacking in the literature regarding aetiology of RHF following durable LVAD implantation. There are several questions that needs to be addressed

- Given that heart failure is a pro inflammatory state it is difficult to quantify in these group of patients how much of the raised inflammatory markers come from the "state of heart failure" itself vs. invasive procedures e.g. IABP etc. Therefore this invariably leads to great heterogeneity in the study population.
We certainly agree with reviewer. The inflammatory state may result from a combination of underlying heart failure and hypoperfusion as well as the result of temporary mechanical circulatory support prior to durable LVAD implant. We intended to demonstrate this association of inflammation and the occurrence of postoperative right heart failure but realize that causality cannot be established with this retrospective study. We hope this clinical correlative data will stimulate and add to the validity of future experiments targeting the role of inflammation and myocardial dysfunction in the setting of LVAD implantation.

While previous studies (by Anker et al and Mann et al) have linked inflammatory mediators being associated with heart failure (not necessarily in the setting of LVAD implantation), here many patients had antecedent devices such as IABP etc that could have accounted for raised inflammatory markers hence I am not certain that such a comparison is still valid. Can you please elaborate?

Thank you for this important question. Patients requiring pre-durable LVAD temporary mechanical support are often sicker patients with more severe heart failure compared with those who do not require temporary mechanical support. However, the design of this retrospective clinical study makes it very difficult to tease out which component of leukocytosis comes from the stress of greater cardiogenic shock in this high WBC group versus the temporary mechanical support itself. However, it does provide correlative data for future studies that can be designed prospectively to account for the contribution of preoperative mechanical support to the leukocytosis. There was no difference in the utilization rates of IABP between the high and low WBC groups. However, we recognize that the duration of IABP was longer by 1 day in the high WBC group.

I believe that the aim of the study may not necessarily be valid. There are plenty of mitigating factors leading to raised WCC and CRP as well as survival/mortality following MCS and I do not think that raised WCC and CRP can be looked as prognostic indicators?

Thank you for this question. The goal of this study is to demonstrate that RVF occurs in the presence of higher WBC and CRP levels to provide clinical observational evidence that a proinflammatory environment may contribute to myocardial dysfunction as was previously demonstrated in experimental studies. However, we do recognize that there are other confounding factors causing leukocytosis that can be examined in future prospective studies.

How did the investigators differentiate between active infection e.g. from a central venous line, leading to raised WCC and CRP (as sepsis increases mortality rate by itself) vs. raised WCC and CRP as a result of the organ system duress from the state of heart failure itself and patients on steroids with falsely elevated inflammatory markers?

A very important question. It is indeed not possible to identify and account for all the causes of leukocytosis in this retrospective study. Since the lab values are obtained preoperatively, we typically would not place a durable LVAD in patient with known infection preoperatively.

Patients with high CRP and WCC are clearly sicker (perhaps from other causes) and will naturally have higher risk of mortality than patients with normal inflammatory parameters. I
therefore think this comparison is confounded as there are other mitigating factors in play here. The study findings would have been more valid if the investigators had performed propensity matching. How did the authors take confounding variables into consideration in their study please?

Thank you for this question. We felt that the inflammatory response from the use of temporary mechanical support itself may contribute to right heart dysfunction and therefore have not tried to exclude temporary mechanical support. However, after removing the 45 patients who utilized preoperative temporary circulatory support in our study, we still demonstrated that the patients who experience RVF had a higher WBC (10.3+4.4 vs 8.5+2.7, P=0.002) and CRP (5.3+4.3 vs 2.9+4.2, P=0.014) level compared with those who did not experience RVF. We did not exclude the IABP group as there was no difference in the utilization of IABP between the high and low WBC groups. We have added the following to the results section under operative characteristics and postoperative outcomes:

“After excluding patients who underwent preoperative TCS, patients who had postoperative RVF had a higher preoperative WBC (10.3+4.4 vs 8.5+2.7, P=0.002) and CRP (5.3+4.3 vs 2.9+4.2, P=0.014) compared to those who did not.”

-Again it is difficult to know if the raised WCC and CRP are cause or the effect here... how was this addressed please?

Thank you again for this question. It is unfortunately not possible to determine causality given the limitations of this retrospective study. But we did exclude TCS, a known proinflammatory element, in the answer to the question above.

- Perhaps my most important query is; How can the authors please explain how their finding is likely to impact clinical practice? i.e. how are they and the wider readership are going to benefit from their findings in terms of patient management? Are the authors suggesting that if the inflammatory mediators are corrected this might reduce the risk of need for an RVAD in heart failure patients receiving a cLVAD? This needs to be clarified in the discussion and the discussion needs to be expanded. They are not adding any new information or claims in their discussion!

Thank you for this suggestion. We have added the following paragraph regarding the clinical utility of our results to the discussion:

“The association of a preoperative proinflammatory state (elevated WBC and CRP) with the occurrence of postoperative RVF provides insights into the clinical relevance of inflammation in impacting myocardial contractility. Given the limited predictive value of current post-LVAD RVF prediction models, preoperative inflammatory markers may need to be incorporated into the algorithm for improved accuracy. It is also possible that suppression of excessive preoperative inflammation can decrease the incidence of RVF and need for RVAD.”

- The authors need to acknowledge significant heterogeneity in their study in the study limitations.
Thank you for this suggestion. We have added the following to our study limitations:

We acknowledge that there are multiple preoperative factors that may cause elevations in WBC and CRP, this introduces heterogeneity into our study groups.”

-It is not clear to me why there had to be 6 tables? Can you please make an effort to merge some of these please?

Thank you for this suggestion. Tables 1 and 2 are now merged as a combined table of “Patient Demographics and Preoperative Laboratory Results”.

- Authors have not detailed anything regarding what constituted infection e.g. device infection... was this on the basis of the wound appearance, culture bacteriology swabs, blood cultures or both? The authors need to give this issue significant clarification in the methods section!

Thank you for this suggestion: We have added the following regarding device infections to the methods section:

Device infection is per criteria established by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [11]. Briefly, cutaneous site infections are defined as pain, erythema or purulent drainage at the driveline site with positive skin cultures. LVAD infection are identified with positive blood cultures combined with fever and leukocytosis not explained by other potential causes.

- The authors need to significantly expand on their methods and patient selection

We agree and have added the following to the “Patients” section of the “Methods”:

“We excluded patients who underwent pulsatile durable LVADs in our study since these have been largely replaced by pulsatile flow devices and carry a very different postoperative outcomes and complication profile. We included only patients aged 18 years or older and also included patients who needed postoperative biventricular support.”

Reviewer #4: Tang et al investigated relationship between preoperative WBC and postoperative right ventricular failure. Although there has been at least one similar previous study (Neurohumoral and inflammatory markers for prediction of right ventricular failure after implantation of a left ventricular assist device. Hennig F, Stepanenko AV, Lehmkuhl HB, Kukucka M, Dandel M, Krabatsch T, Hetzer R, Potapov EV. Gen Thorac Cardiovasc Surg. 2011 Jan;59(1):19-24), I think this thema is interesting and there may be potential for publication. However, this paper has some problems with statistics in my opinion.

1) The authors should explain why the cut-off value of WBC was 10500 in this study. I guess that ROC analysis may be better for setting a cut-off value.
Thank you for this important question. We examined the lowest WBC level that would differentiate postoperative outcomes in our patient population and found that 10.5 K/μl provides differentiation between patients who will develop RVF and RVAD use versus those who did not. While 10.5 K/μl is at the higher end of the reference range, it has provided sufficient differentiation ability. Therefore this cut off was selected for the study. This was corroborated with a ROC analysis as the reviewer suggested. The area under the ROC curve (C-statistics) using WBC and CRP as a predictor for RVF were 0.661 (P=0.001) and 0.727 (P<0.001) respectively. We have added to the results section under “Operative Characteristics and Postoperative Outcomes”:

“We performed a “Receiver Operating Characteristics” analysis and shows that WBC and CRP was able to predict RVF with a C-statistics of 0.661 (P=0.001) and 0.727 (P<0.001) respectively.”

2) In this study, a multivariate analysis was performed to find an independant factor for increased WBC. However, multivariate analysis should be performed to clarify whether increased WBC is an independant factor for postoperative right ventricular failure.

In our multivariate analysis, neither preoperative use of temporary mechanical support, preoperative intra-aortic balloon pump, nor WBC was an “independent” predictors for postop RVF in our model. This is may be due to the fact that many of these variables co-vary with other laboratory parameters. If laboratory parameters such as ALT, AST, LDH, Cr, PT, INR, PTT as well as INTERMACS profile were removed from the model, then WBC is an independent factor for postoperative RVF (P=0.017). A more acute INTERMACS profile and poorer liver-renal lab values not surprisingly contribute to the inflammatory milieu and high WBC of the pre-LVAD state.