Author's response to reviews

Title: A Dual Therapy of Off-Pump Temporary Left Ventricular Extracorporeal Device and Amniotic Stem Cell for Cardiogenic Shock

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Author’s response to reviews:

Reviewer #1: The authors provide details of a novel surgical technique for temporary VAD implantation which they feel limits myocardial inflammation, thereby promoting grafting of intra-myocardial stem cell transplant and subsequent myocardial recovery.

Comment 1) However, the manuscript lacks sufficient evidence to back-up these premises. There is no presentation of inflammatory parameters in the peri-surgical phase and no report of myocardial biopsies to assess inflammatory infiltrates. Furthermore, the reported improvement in ejection fraction from 10 to 30% over a two week period is commonly seen in patients who suffer acute myocardial infarction due to initial "stunning" of the ventricle. Therefore, the LV improvement in conjunction with stem cells is completely circumstantial and there is a complete lack of evidence of a cause and effect relationship. Indeed, I suspect the ventricle would have improved without the stem cells.

Our response: We thank the reviewer for this comment. We want to demonstrate that the inflammation from minimally invasive off pump cannulation approach is less than full sternotomy, which has been widely accepted in CTS. Unfortunately we don’t have concrete evidence to support stem cell injection provided better recovery than establishing temporary circulatory device. However, utilizing stem cell in the acute setting is a fairly new concept which we cited in Ref. 8 and 13. These 2 studies utilized bone marrow stem cells whereas we used
amniotic stem cell. We just want to point out that direct stem cell injection is safe to utilize and might promote myocardial functional recovery.

Our modification to the manuscript: We added the following:

- minimally invasive off pump approach minimizes sternotomy-induced myocardial inflammation

- This observed clinical improvement is concurrent to bone marrow stem cell studies reported by Gojo et al [8] (EF improved from 6.4 to 40%) and Miyagawa et al [13] (EF improved from 22 to 32%). Aside from safe to use, we think that direct stem cell injection may provide myocardial functional recovery but further study is highly warranted in the future.

Comment 2) Finally, the successfulness of the novel surgical approach is unclear. The patient suffered significant neurological deficits due to strokes and was discharged to a rehab facility. The authors provide no information regarding the long-term outcome of the patient or the degree of (if any) neurological recovery.

Our response: We thank the reviewer for this comment. Based on this pre op condition, avoiding sternotomy is potentially very favorable to future surgical interventions such as LVAD implant or heart transplant. We meant successful as providing enough support for her to recover from acute decompensation without compromising support. We simply want to report that this minimally invasive off pump approach is feasible and that it might have concomittantly provide a favorable hemodynamic environment for stem cell therapy. The patient was fully recovered by POD13 but we waited a few days too late to decannulate her. Unfortunately, she suffered from stroke which possibly caused by clot dislodgement from 3/8x3/8 connectors.

Our modification to the manuscript: We added the following:

- fibrin clots developed in both the inflow and outflow cannula connectors prompting for an urgent decannulation

- possibly due to clots dislodgement from the support/plumbing system or thrombotic occlusion of the right brachiocephalic trunk, right common carotid, right internal, and right vertebral arteries resulting in left sided hemiplegia.

Reviewer #2: INTERMACS 1 profile patients offer an extremely difficult group of patients mandating some tough decision making and management options. In that respect, the case report offers an interesting case of managing a patient using extracorporeal short term VAD as bridge to decision/recovery. Unfortunately final outcome, as is often the case, was complicated by ischaemic cerebral event.
Comment 1) The language in the article needs to be closely looked at since there are numerous spelling mistakes.

Our response: We thank the reviewer for this comment. We have closely looked at the spelling mistakes and grammatical error. They can be found in the tracking changes.

Comment 2) The authors should clarify the reasons to go down the short term versus long term VAD option and what was the right heart function?

Our response: We thank the reviewer for this comment. The right heart function was good via TEE. However, she was in INTERMACS profile 1 when she presented to our hospital. Temporary device should be more appropriate device choice in this case which we discussed in the introduction.

Our modification to the manuscript: We added the following:

- Right heart was functional prompting for a CentriMag LVAD placement as Bridge-to-Decision/Recovery.

Comment 3) If there was a need to go down short term route as bridge to decision/recovery, when is the ideal time to intervene and escalate to next level?

Our response: We thank the reviewer for this comment. We believe 3 days to 7 days is a reasonable timeframe. However, it really depends on the each patients.

Our modification to the manuscript: We added the following:

Comment 4) Authors have stated that there was hyperperfusion of right carotid system and final outcome involves thrombotic event affecting the right carotid system. How can they be confident that these two are not related?

Our response: We thank the reviewer for this question. We have clarified the outcome. Please see our response to reviewer 1, Comment 2 and the addition below.

Our modification to the manuscript: We added the following:

- fibrin clots developed in both the inflow and outflow cannula connectors prompting for an urgent decannulation

- possibly due to clots dislodgement from the support/plumbing system or thrombotic occlusion of the right brachiocephalic trunk, right common carotid, right internal, and right vertebral arteries resulting in left sided hemiplegia.