Author’s response to reviews

Title: Intraoperative TOE guided management of newly diagnosed severe tricuspid regurgitation and pulmonary hypertension during orthotopic liver transplantation: a case report demonstrating the importance of reversibility as a favorable prognostic factor.

Authors:

Brett Pearce (brett.pearce@austin.org.au)

Raymond Hu (raymond.hu@austin.org.au)

Fiona Desmond (fiona.desmond@austin.org.au)

Daniel Banyasz (daniel.banyasz@austin.org.au)

Robert Jones (robert.jones@austin.org.au)

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Author’s response to reviews:

Dear Editors,

RE: Response to Reviewer’s comments  (Revision: Case Report) - Intraoperative TOE guided management of newly diagnosed severe tricuspid regurgitation and pulmonary hypertension during orthotopic liver transplantation: a case report demonstrating the importance of reversibility as a favorable prognostic factor

It is with great pleasure that we re-submit our extensively revised manuscript in keeping with the suggestions of the four reviewers. In particular, we would like to draw your attention to following major areas:

- Acknowledgement of prior case reports where newly diagnosed severe pulmonary hypertension has been successfully managed intraoperatively; and subsequent re-focus of our manuscript on severe tricuspid regurgitation, which has not been well covered in the literature

- Table 1, which specifies in detail the role of intraoperative TOE in the diagnosis and management of severe TR in this context
- Figures 3 and 4, demonstrating our recommended approach to unexpected severe TR and PHT in OLT surgery; and a global view of the multi-systems causes and effects of severe TR and PHT with an intraoperative and OLT waitlisted patient perspective

We hope that with these major revisions we have adequately addressed the reviewers concerns. Please also see the response to the reviewers comments below which outlines in detail the revisions we have made.

We feel that this case report should be published as it is unique. To our knowledge it is the first case report of successful liver transplantation in a patient with severe TR. The severity of the TR with venous pressures greater than 100mmHg and the rarity of intra-operative diagnosis of PHT and TR as well as the patient’s successful management with TOE makes this in our opinion a compelling case report.

We declare that none of the authors have competing interests.

All authors have approved the manuscript for submission.

The content of the manuscript has not been submitted elsewhere nor published elsewhere.

It is intended that this case report be published in the special edition of BMC Anaesthesiology focusing on transplantation.

Regards,

Dr Brett Pearce

Reviewer reports:

Hisham Hosny (Reviewer 1): Thanks for giving me the chance to review this case report. The case sounds interesting and is worth considering, however some rephrasing might help to clarify the message more.

The title:

To an extent seems to be misleading and doesn't support the take-home message of the report. To me, the message is: patients with recently diagnosed pulmonary hypertension are more likely to survive transplantation based on the relative reversibility of their disease. This should be well elaborated in the title esp that PHT is considered a contraindication to surgery.
We thank Reviewer #1 for redirecting our attention to the crux of our case report and how the title should reflect this. We have altered the title to reinforce the focus of the report on reversibility of unexpected severe tricuspid regurgitation and associated PHT, and the use of intraoperative TOE in facilitating this.

Case:
I did not understand what authors meant by the age of the patient being 45-50

The inclusion of an age bracket rather than a specific age was suggested by our ethics reviewer in order to protect patient confidentiality. Following these comments they have agreed that this was confusing and have allowed us to use the patient’s age in years which has been amended in the manuscript.

Discussion:
In general is quiet redundant and needs to focus on the main learning points in the case; e.g. the principle diagnostic tool in this case is TOE, this should be clear in the discussion esp with the inaccuracies encountered with the PAC in the presence of severe TR.

We agree with Reviewer #1 regarding the lack of direction in our first submission and have performed a major revision of the manuscript highlighting the critical role of TOE (in particular the specific indices required for diagnosis and reversibility of severe TR and PHT and how reversibility may be assessed) and specific statements detailing the limitations of the use of PAC with severe TR and how TOE may overcome this (Discussion, Paragraph 1).

Again, reversibility is the key of success in this case and every effort should be made to stress on this key player.

We thank Reviewer #1 for specifying this weakness in our initial submission. The entire manuscript has been re-directed to highlight reversibility of severe TR (more so than severe PHT, which we acknowledge has been dealt with in other case reports) in the Case Presentation and Discussion.

References:
Many references are more than 10 yo and don't add much to the more recent ones.
We have rationalised the references used in our re-submission to retain recent references over more outdated ones dealing with the same topic referenced.

Hassan Mohamed Hassan Sayed Ahmed, EDIAC, FCAI, Ph.D. (Reviewer 2): I reviewed with interest this well written case report. I have the following concerns:

1- Successful orthotopic liver transplant in patients with severe pulmonary hypertension had been previously reported in many occasions, hence the report is not novel


We thank Reviewer #2 for pointing out the prevalence of successful case reports of OLT in severe PHT. We have acknowledged the valuable contributions made by previous authors in this field who have managed unexpected PHT on-table on day of surgery (Discussion, paragraph 1; paragraph 5). However, in almost all of these, the pulmonary hypertension was diagnosed and managed in the pre-operative phase and was not associated with severe TR. Our case report is unique for several reasons. Firstly, it is the only documented case of successful liver transplantation in a patient with severe TR. The central venous pressures in excess of 100mmHg demonstrate the severity of the condition which is also unique. We have also provided echocardiography pictures demonstrating this severity and its resolution with our interventions. The other rare and interesting feature of this case report is that the diagnosis of PHT and TR was made on the operating table. We only found two case reports of severe undifferentiated PHT, both apparently without significant TR and only one of which had used TOE. We believe therefore that our case is unique. Moreover it may provide a valuable resource by helping to provide a framework for a clinician dealing with these unexpected difficult problems with limited experience.

2- The presence of severe pulmonary hypertension is associated with poor prognosis and long term survival in liver transplantation, hence the meticulous cardiovascular assessment prior to transplantation is deemed essential. Therefore, the reliability of an 18 mo echo seems to be quite inappropriate.

We agree with Reviewer #2 that the lack of more regular TTE assessment of this patient contributed to the unexpected severe TR and PHT seen at operation. We have included in the discussion reference to the variable TTE screening intervals recommended by various...
institutions, and our recommendations subsequent to this case report, for having a high index of suspicion for TR and PHT in OLT waitlisted patients. The explanation in our case was loss to follow up after a repeat TTE request due in part to the remote place of residence of the patient. This has been specified in the Case Presentation.

I congratulate the authors on the successful anesthetic management of this challenging case and its long term survival. Even so, it may not be suitable for a full paper but potentially may be publishable as a Letter.

We hope that the extensive revision we have made addressing Reviewer #2’s concerns has qualified our submission for consideration as a full Case Report.

Mohamed Ismail, FEBA, ABHSA, DESA, FCAI (Reviewer 3): Patients with PHT have higher post-transplant mortality rate. The report exhibits how difficult the decision-making could be, while facing such situation of newly discovered PHT in theatre. The authors have stressed on the fact that preoperative testing required to avoid such dreadful dilemma. Cole et al [Hepatology 2003] found that pulmonary hypertension can develop in this cohort of patients within duration ranging from 2 to 5 months, which might suggest TTE screening every 3 months in patients on liver transplant list. Moreover, preoperative diagnosis would give the chance to improve pulmonary haemodynamic measurements with means of vasodilatation, diuretics and/or ultrafiltration.

We agree with Reviewer #3 that an earlier TTE would have identified this patients severe TR and PHT prior to the operative theatre and permitted optimisation that may well have prevented her presentation in pulmonary hypertensive crisis on day of surgery. This has been specified in the text (Discussion, Paragraph 2 and 3). We have also emphasized the rapidly progressive and dynamic nature of TR and PHT in our major revision (Discussion, Paragraph 3) and hence reinforced the range of frequencies suggested by various institutions on the recommended timing of TTE in the OLT waitlist population (Discussion, Paragraph 3), as well as drawing the attention of the reader to how TR and PHT onset may masquerade as deteriorating hepatic function (Discussion, Paragraph 3).

The authors, additionally, suggested that PHT not associated with smooth muscle hypertrophy and fibrosis might have satisfactory outcome after transplant due to the reversible nature of the condition. This should be taken into account while screening those patients as it could affect the patient's wait list position.

We have emphasized the importance of potential reversibility of preoperatively identified PHT by right heart catheterisation and the way the information may be used to influence earlier timing of transplantation (Discussion, Paragraph 3).
Ahmed Abdelaal Ahmed Mahmoud, MD., FCAI (Reviewer 4): Thanks for the opportunity to review this case report.

The following major concerns must be addressed clearly while presenting the case report;

What is the age of the patient? I think there was a confusion between a pressure 45-50 and the age of the patient. Please correct and clarify.

We apologise to Reviewer #4 for this ambiguity. As stated above the use of an age bracket had been specified by our ethics committee to protect patient confidentiality. Following these comments they have agreed that this was confusing and have allowed us to use the patient’s age in years which has been amended in the manuscript.

Please use generic names and not trade names e.g. albumin and not "albumex". Apply this to all the manuscript.

Trade names have been removed completely from our re-submission as per Reviewer #4’s request.

3. Authors should describe their local institutional protocol for assessment and follow up of the patients waiting for liver transplant. Was that protocol followed or not and if not, what are the reasons? Does this cases report has led to change in the preoperative assessment protocol in their center or not?

We have now included a description of how screening TTE is ordered in our usual institutional practice in the text (Discussion, Paragraph 3), as well as consideration given to repeating TTE when right heart dysfunction may present as hepatic decompensation. Also in the resubmission is a description of how our patient was lost to follow up regarding her repeat ordered TTE at time of re-presentation (Discussion, Paragraph 3). Finally, we make recommendations in the context of other guidelines and intercurrent illness for when repeat TTE should be considered (discussion, Paragraph 3)

4. Authors mentioned that the patient was scheduled for urgent transplant due to acute deterioration of her chronic liver condition, has the patient been assessed during the acute deterioration or not? Was the patient in the ward or intensive care for the deterioration?
We have included descriptions of the nature of our patient’s presentation and ICU admission in the text as suggested by Reviewer #4 (Case Presentation, Paragraph 2).

5. Did the patient present any clinical signs and symptoms of PHT before induction of anaesthesia or not? Considering this high pulmonary and central venous pressures, there must have been clinical signs for the underlying condition, has the patient been assessed clinically or not?

Our patient was assessed by multiple expert clinicians on a daily basis in the ICU and the ward. We have reviewed the notes and although there were some signs or symptoms associated with these conditions, these were non-specific. It is of course regrettable that a TTE was not ordered but it seems there was no specific indication to order one.

Our revised manuscript summarises this. “Clinical signs of TR and PHT are that of right heart failure and non-specific, and easily attributable to worsening hepatic function” (Discussion, Paragraph 3)

The signs and symptoms that were present prior to transplantation include a deterioration in liver and renal function, and tender hepatosplenomegaly. Retrospectively these have been attributed to impaired organ perfusion secondary to severe venous hypertension. It is however worth noting that they are relatively findings in this population. The poor response to terlipressin was perhaps another clue to the presence of TR and PHT but this is not well described the literature as we have alluded to in the case report (Discussion, Paragraph 3)

6. The description of the PHT and its rapid resolution, especially with increasing the fraction of inspired inhaled anaesthetic, gives the impression that inadequate level or technique of anaesthesia may have precipitated an acute hypertensive pulmonary crisis in a susceptible patient (having the history of PHT). Did the authors considered this in the differential diagnosis of the case or not? What was the analysis of vital signs, etCO2, inspired and expired inhaled anaesthetic, BIS values, was the PHT associated with haemodynamic instability or not?

We have specified the MAP, CI, etCO2 and targeted BIS range during the time of initial diagnosis of PHT as suggested by reviewer #2 (Case Presentation, Paragraph 3) and specified our decision making process prior to deciding to increase the Fi (isoflurane) despite acceptable BIS values. We have also included consideration of inadequate anaesthesia depth into our recommendation diagram on approach to unexpected severe TR and PHT on-table at time of surgery (Figure 3). The patient in fact improved in systemic haemodynamics after manoeuvres were instituted to correct TR and PHT; this has been specified in the text (Case Presentation, Paragraph 3 and 4).
7. Although the case report may be interesting, yet it is poorly presented with no differential diagnosis was discussed at all.

We agree with Reviewer #4 that our initial submission was lacking structure and comprehensive diagnostic approach. We hope that this has been addressed by our complete re-work of the manuscript, with the specific causes of PHT and TR and how intraoperative TOE in conjunction with other modalities may assist this. The new Figure 3 is a stepwise approach we recommend to others who may face the same on-table situation, and Figure 4 summarises how a multi-systems approach to diagnosis and management may assist prognosis and achieve a successful operative outcome.

8. Any case report must deliver a new message to the readers, which is not adequately written here.

We hope that our re-worked manuscript, in particular our stepwise recommended approach to unexpected severe TR and PHT in Figure 3, and the re-focused conclusions in the Abstract and Discussion, have helped to formalise and deliver a new message to readers.

9. Did the authors consider a bedside echo in the following cases or as a new addition to their institutional protocol?

As Reviewer #4 has surmised, we did in fact consider this option, but did not have a qualified member of staff available to perform this test. We have specified this in the text (Case Presentation Paragraph 2). As TTE is not a skill currently possessed by the majority of our anaesthesia department, and false positive findings potentially misleading in this context, we are hesitant to incorporate bedside TTE as a requirement to our institutional protocol.

I recommend the case report to be presented in a more systematic way with a focus on the differential diagnosis of the PHT crisis and a focus on any possible anaesthetic technique that may have triggered PHT.

We agree with Reviewer #4 that this was grossly lacking in our initial submission and hope that the extensive revision, with inclusion of Figure 3 detailing our recommended approach to such a crisis of PHT and severe TR, and inclusion of the possibility of inadequate anaesthesia into the diagnostic approach, has addressed any concerns.

Authors should focus on delivering a clear message to the readers about systematic thinking, decision making and protocol modifications when handling these patients for such major complex surgeries.
As Reviewer #4 has suggested we believe our extensively revised manuscript has now included stepwise and detailed descriptions of our actions and subsequent recommendations on the pre- and intra-operative pathways that should be considered in such cases. In particular, we feel that inclusion of Table 1 detailing specific intraoperative TOE indices on assessment of TR; and inclusion of Figures 3 and 4 providing both algorithmic and a birds-eye view of approaches to unexpected TR and PHT, have achieved these goals.