

Peer Review File

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Review Comments

Reviewer A:

I have some comments on this report and I thank the authors for reading and considering them.

- 1. To me, the main problem of your report is that you are not describing in detail your experience on LT to underline the relevance of cardio-thoracic cooperation, I believe your manuscript would be enriched if you'd present in detail all procedures in your experience where MCS or cardiac procedures were performed.*

Response:

We appreciate these important suggestions. Please see our additions in each section noted following.

Introduction” section.

At our institution, those cases have generally been supported by cardiovascular surgeons for establishment of extracorporeal circulation and concomitant cardiac surgery, as well as vascular anastomosis in difficult cases, with the five- and 10-year survival rates for cadaveric-donor lung transplant recipients 72.1% and 65.4%, respectively.

“Integrated cardiothoracic approach to complex lung transplant” section.

At our institution, MCS strategy and pump-on timing are generally discussed preoperatively by the lung transplantation team. Based on recipient condition, a CPB has been used for 34 patients and VA-ECMO for 36. A CPB was generally used for those with idiopathic or secondary PH including conditions treated by concomitant cardiac surgery, while an unplanned CPB was performed for an atrial procedure due to bleeding in one case that required intraoperative conversion from ECMO to CPB and in another for removal of atrial thrombus. Theoretically, use of a closed circuit and centrifugal pump for ECMO is less invasive, and also reduces inflammatory responses and the necessity for full heparinization as compared to a CPB. A study that compared ECMO and CPB cases concluded that the former is associated with lower occurrence of primary graft dysfunction (PGD), fewer blood transfusions after a lung transplantation procedure, and a shorter stay in the intensive care unit (8), thus recently we have attempted to use ECMO as much as possible.

In the “Complex vascular anastomosis during lung transplant procedure” and “Concurrent cardiac surgery”, we have added case information.

In addition, in the “Development of LDLLT” and “Combined heart and lung transplantation” sections, details regarding technical aspects of lung transplantation have been added.

2. *Lung transplantation process not only includes surgical procedures as could be deducible from the sentences in lines 78-82. Selection and physical improvement of potential candidates for lung transplant is paramount and usually a responsibility of pulmonologists and rehabilitation specialists. At least, the role of those and other specialists (intensive care physicians) should be mentioned in the text.*

Response:

We agree with the reviewer and are grateful for these good suggestions. Those sentences have been changed, as follows.

A lung transplant is a complex procedure that carries a high risk of perioperative complications, some of which can be fatal, and success is dependent on the involvement of a team comprised of general thoracic surgeons, cardiac surgeons, cardiologists, anesthesiologists, perfusionists, operating room staff, pulmonologists, intensive care physicians, rehabilitation specialists, transplant nurse coordinators, and social workers, with their expertise and different perspectives used in a collaborative effort to ultimately benefit the patient. The technically challenging surgical procedures, appropriate preoperative preparations, optimization of the patient, and selection of a suitable donor, as well as management of postoperative complications are important for the success of lung transplantation, thus utilization of a multidisciplinary team is indispensable.

Furthermore, we have added text regarding the role of other specialists and also revised Figure 1 (Figure 3 in revised version).

3. Your sentence in line 189 is arguable. Proficiency in difficult techniques is not depending on the surgeon’s certification but on his/her personal expertise.

Response:

We’d concur with the reviewer’s points. Indeed most of all the UNOS-certified cardiothoracic transplant fellowship programs in North America consist of one-year training; however, it is clear that such training alone is not good enough to be qualified to handle complex lung transplant procedures as addressed in this section.

In addition, under the limited number of lung transplants in Japan, whereas quite a few of thoracic surgeons have been trained through the fellowship programs not only in North America but also in

Europe, it remains challenging for them to continue to develop their technical proficiency as well as appropriate decision making on MCS options under urgent circumstances after they go back to Japan. All of these backgrounds contributed to facilitating our unique approach with integrated cardiothoracic expertise and efforts in order to prioritize the optimal outcomes and best benefits for the patients who undergo lung transplantation in Japan.

Accordingly, the sentence regarding the “Surgery training program” has been deleted and the following added.

It is not uncommon for general thoracic surgeons in Japan to receive lung transplantation training and gain experience as a surgical trainee at high volume centers in other countries, as it is difficult to receive formal cardiovascular surgery or lung transplantation training in their own country (5). Under the limited number of lung transplants in Japan, whereas quite a few of thoracic surgeons have been trained through the fellowship programs not only in North America but also in Europe, it remains challenging for them to continue to develop their technical proficiency as well as appropriate decision making on MCS options under urgent circumstances after they go back to Japan. All of these backgrounds contributed to facilitating our unique approach with integrated cardiothoracic expertise and efforts in order to prioritize the optimal outcomes and best benefits for the patients who undergo lung transplantation in Japan.

Reviewer B:

We appreciate the opportunity to review the article “Integrated cardiothoracic team approach for complex lung transplantation procedures in Japan – current status and future directions”. This article is related to the practices used in Japan, where the training of thoracic surgeons is different compared to other countries. It is more of an informative article, and the scientific merit is low (unless there is an Edition of JTD focusing on analyzing practices worldwide).

We intend to provide constructive feedback to the authors. Please see the below comments:

Introduction:

- 1. Lines 57 to 76 look interesting as describes Lung transplantation in Japan. A suggestion would be for the authors to expand more about the revised Organ Transplant Law – line 67 – as this is an important topic.”*

Response:

We really appreciate this important suggestion. The following has been added to the revised version of the manuscript.

Although the number of patients with lung transplantations has increased since 2011 in Japan, the year following enforcement of the revised Organ Transplant law, which permits organ donation from brain-dead donors based on family consent even if the patient has not declared their intention to donate organs or in child cases,

2. *From lines 78 to 98, the authors described the rationale for the integrated cardiothoracic team approach, with little to comment on.*

Integrated cardiothoracic approach to complex lung transplant

Response

Based on the reviewer's helpful comments, those sentences have been revised, as follows.

The technically challenging surgical procedures, appropriate preoperative preparations, optimization of the patient, and selection of a suitable donor, as well as management of postoperative complications are important for the success of lung transplantation, thus utilization of a multidisciplinary team is indispensable. In addition, surgical knowledge, techniques, and patient management related to cardiovascular surgery are necessary for successful lung transplantation, especially in regard to management of mechanical circulatory support (MCS), vascular anastomosis in difficult cases, and concomitant cardiac surgery.

3. *When the authors mentioned "precise MCS..." line 108, what comes after is tedious since the authors describe MCS and how cardiac surgeons have a significant role. This may be the case for Japan, but in other places, Thoracic Surgeons do the same situations without compromising outcomes.*

Response

We have deleted sentences related to the MCS discussion.

4. *The discussion about "CPB vs. ECMO in the current era" also seems somehow out of scope here. The description of central ECMO, advantages of CPB via sternotomy, peripheral ECMO and its disadvantages, closed circuit for ECMO, ECMO vs CPB, and several other discussions within this point becomes tedious since this information is available in many papers. You could just mention that conversions from off-pump to ECMO/CPB are done by cardiac surgeons in Japan.*

Response

Accordingly, discussion about CPB vs. ECMO has been deleted and information regarding our strategy has been added, as shown following.

At our institution, MCS strategy and pump-on timing are generally discussed preoperatively by the lung transplantation team. Based on recipient condition, a CPB has been used for 34 patients and VA-ECMO for 36. A CPB was generally used for those with idiopathic or secondary PH including conditions treated by concomitant cardiac surgery, while an unplanned CPB was performed for an atrial procedure due to bleeding in one case that required intraoperative conversion from ECMO to CPB and in another for removal of atrial thrombus. Theoretically, use of a closed circuit and centrifugal pump for ECMO is less invasive, and also reduces inflammatory responses and the necessity for full heparinization as compared to a CPB. A study that compared ECMO and CPB cases concluded that the former is associated with lower occurrence of primary graft dysfunction (PGD), fewer blood transfusions after a lung transplantation procedure, and a shorter stay in the intensive care unit (8), thus recently we have attempted to use ECMO as much as possible.

5. *In “Complex vascular anastomosis....” In line 168, there is a good discussion about issues with anastomosis, and the authors concluded that these techniques are better supported by a cardiac surgeon – line 189. Not much to comment on since these are particularities of the author’s center/Japan.*

Response

Based on the reviewer’s helpful comments, we have deleted that from the revised version.

6. *In “Concurrent Cardiac Surgery” is where we see the need for cardiac surgery, and it is the best section of this study since it is, we believe, the topic that is common in most centers.*

Response

According to comments from Reviewer A, details focusing on some specific cases have been added to the revised version.

7. *In “Development of LDLLT” and “Combined heart and Lung transplantation”, it is important to bring focus to the importance of the synergistic approach by the authors.*

Response

Technical surgical aspects regarding LDLLT have been included in the revised version, as follows. Various techniques for anastomosis of the PA in cases with a size mismatch, such as plication for the PA of the recipient and autopericardial patching for that of the donor, have been reported by experienced centers in Japan (26). Although vascular anastomosis is performed by thoracic surgeons in most lung transplant centers in Japan for a standard LDLLT, at our institution when the PA caliber

mismatch is too great for performing anastomosis of the PA, such vascular anastomosis is performed by cardiac surgeons to prevent a vascular complication.

8. *The authors could work on technical surgical aspects more. What cardiac surgeons do differently? What are their cannulation strategies for intraoperative support? What are the particularities in LDLLT that cardiac surgeons do? What are the techniques for patching used by our cardiac colleagues? This would enrich the paper, instead of being a descriptive article. Why don't you focus on the technical aspects of the cardiac surgeon's contributions?*

Response

We sincerely appreciate this important suggestion. The manuscript has been duly revised so that it highlights the technical aspects with regards to the contribution of cardiac surgeons' involvement to complex lung transplantation including concurrent cardiac surgeries and LDLLT. Details about technical surgical aspects regarding MCS, complex vascular anastomosis, concurrent cardiac surgery, and LDLLT, as well as combined heart and lung transplantation procedures have been added to the revised version.

Thank you for the opportunity to review your research. As we mentioned before, this review article has low scientific merit. It could only be considered for publication under special circumstances, like, for example, an edition about "practices of lung transplantation around the world". During the article, the reading becomes tedious as the authors move to, for example, ECMO discussions, which are important, but tend to move away from the focus of this article. We believe the authors aimed to bring some interesting/relevant data to the reader since these are practices applicable in Japan/in the author's Center.

Response

The aim of this report is, 1) to briefly introduce the history of lung transplantation in Japan with its unique religious and cultural backgrounds regarding organ donation as well as its developing processes, and 2) to share our experiences with the integrated cardiothoracic approach for complex lung transplantation procedures which have been facilitated through such unique circumstances including surgical training systems in Japan different from those in North America and Europe. Although the number of our transplants remains limited, through our experiences, we expect that the integrated cardiothoracic approach is so solid and safe that it can be applied for other small transplant centers or those who are planning to start lung transplant programs in other developing countries, leading to optimal transplant outcomes and further increasing the number of lung transplants worldwide.

With this aim on the top, according to the reviewer, we duly revised the manuscript by deleting the paragraph delineating MCS and highlighting the technical aspects in complex lung transplantation. Thank you very much for all the reviewer's thoughtful comments.

Reviewer C:

Thank you for the opportunity to review this interesting article from the Osaka group, giving us their perspective on the role of cardiac surgeons in lung transplantation.

Overall this paper highlights important areas where the skills of a cardiac surgeon can be very valuable, usually in challenging aspects of lung transplant, and readers of the JTD will no doubt find this educational.

Response:

We are grateful for the supportive comments from the reviewer.

Some minor comments:

line 133: 'vena cava inferior'- it is more often referred to as 'inferior vena cava'

Line 142- suggest to explain clearly what is the cause of 'Harlequin effect'

Response:

Discussion regarding CPB vs. ECMO has been deleted from the revised version, including that sentence.

line 241- 'aortopulmonary window closure'-> do you mean closure of patent ductus arteriosus?

Response:

We apologize for the confusion. The condition was "aortopulmonary (AP) window defect", which has been added to information presented regarding that case.

lines 270-272 and lines 277-279: The same sentence is duplicated in the same paragraph

Response:

Thank you for pointing this out. We have deleted one of those duplicate sentences.

Reviewer D:

Well written.

Just like cardiologists and cardiac surgeons have a heart team concept for the treatment of structural valve disease this sounds a similar co-operation between thoracic and cardiac surgeons.

While some centers are predominantly run by thoracic surgeons some have exclusively cardiac surgeons performing lung transplant. However the more the merrier and obviously the patient stands to benefit from increased input.

Response:

We are grateful for the supportive comments from the reviewer.

Reviewer E:

This review paper is well described about how the thoracic and cardiovascular surgeons collaborate for lung transplant procedures. I totally agree with the authors. We definitely require help of a cardiovascular surgeon for managing the extracorporeal support during the transplant procedure. Cardiovascular surgeon can also help us perform complicated transplant procedure, which requires cardiac repair such as ASD, VSD, PDA, IHD, and giant PA aneurysm. Furthermore, cardiovascular surgeon can frequently help us perform small vascular anastomosis in pediatric living-donor lung transplantation.

Response:

We are grateful for the supportive comments from the reviewer. Based on the good suggestion, we have added details regarding a case with a giant PA aneurysm to the revised version of the manuscript.

Minor comment:

Kyoto group previously reported a successful on-pump beating CABG concomitant with LDLLT (Ueyama K. Heart Lung. 2019;48:166-68), so the authors can put this paper in the reference.

Response

Based on the reviewer's helpful suggestion, we have added the Kyoto group study and describe it as shown following.

Ueyama et al. reported the first beating CABG case performed concomitant with bilateral LDLLT in Japan.

Reviewer F:

The reviewer is honored to review a mini-review article about integrated cardiothoracic team approach for complex lung transplantation procedures in Japan. This paper is written based on the experiences at Osaka University in Japan. The Osaka University team is the only team which can perform heart-lung transplantation in Japan. They also perform several difficult lung transplantations with concomitant cardiac surgery. Their policy of lung transplantation can be informed through this manuscript. In this meaning, the topic of this manuscript is really interesting, but some of the statements might be specially related to Osaka University. The manuscript is potentially acceptable in its current form. But there are several points to be revised, as follows:

Response:

We are grateful for the supportive comments from the reviewer.

1) *In vascular anastomosis in cadaveric lung transplantation, it is true that a thoracic surgeon needs some help by a cardiac surgeon in a difficult case. However, thoracic surgeons can perform difficult anastomoses by themselves. Therefore, the reviewer advised that the authors should rewrite the sentence (Line 179-181), as follows: "In such cases, ... for thoracic surgeons. They can ask cardiac surgeons to help performing the anastomosis or even let cardiac surgeons perform it." The reviewer also advised that they should cite a recently published paper focusing on the pulmonary arterial anastomosis (PMID 34647099).*

Response:

We sincerely appreciate these important comments and suggestions. In the revised version of the manuscript, details of a typical case of giant PA aneurysm, for which anastomosis is often difficult for thoracic surgeons and generally performed by a cardiac surgeon, have been included.

2) *Regarding LDLLT, vascular anastomosis seems to be performed by thoracic surgeons in most lung transplant centers in Japan for the standard LDLLT. As the authors cited a reference #27, there is a potential vascular complication, but this complication might be a rare one. To prevent a potential misunderstanding, the reviewer advised that the authors should add some comments that vascular anastomosis are generally performed in most lung transplant centers by a thoracic surgeon in Japan. This would also lead to future directions written by the authors (Line 332-) Of course, the reviewer agrees that the thoracic surgeons need some help in performing vascular anastomosis of LDLLT especially for a difficult case.*

Response:

We fully agree with the reviewer and have changed the related sentence, as follows.

Although vascular anastomosis is performed by thoracic surgeons in most lung transplant centers in Japan for a standard LDLLT, at our institution when the PA caliber mismatch is too great for performing anastomosis of the PA, such vascular anastomosis is performed by cardiac surgeons to prevent a vascular complication.

3) *In donor surgery for LDLLT, the authors documented that they need support by cardiac surgeons (Line 306). It is all right in terms of safety, but thoracic surgeons can perform these procedures by themselves (PMID 31605611, 28186281). This would also lead to future directions written by the authors (Line 332-). Please add some comments related to this to prevent potential misunderstanding.*

Response:

This sentence has also been changed, as shown following

When a complex pulmonary arterioplasty for the remaining arterial stump of the donor is necessary, that is performed at our institution with an autopericardial graft with support provided by a cardiac surgeon to avoid vascular complications.

We also added a sentence to the “Future directions” section, as follows.

The unique situation in Japan has led to development of LDLLT and it is considered that thoracic surgeons can benefit from learning about LDLLT procedures used at experienced lung transplant centers.

4) *Regarding figure 1, the message of this figure is somewhat difficult to understand. For example, “lung transplant assessment and testing” might be “Assessment and testing for lung transplantation”? “lung transplants” might be “lung transplantation”. “Critical care after lung transplantation” might be shared with intensivists as well as cardiac surgeons. Please reconsider these wordings.*

Response:

Based on the reviewer’s helpful comments, we have changed Figure 1, as shown following.

