Peer Review File

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Reviewer A:

1. Comment: The authors described that patients with distal disease and malignancy involving other organs were excluded in line133, page 5, and actually performed PEA for patients with high PVR and those who required concomitant procedure. I was wondering how the authors considered operative risks in selecting PEA candidates.

   Reply: We are grateful to the reviewer for the comment. The PEA programme in Bulgaria discussed every case with the large UK centre. The plan of this collaboration was to exclude malignancy and distal disease. However, addition of a second procedure in some patients was unavoidable and directly supervised by an experienced PEA surgeon. There were extensive discussions between the surgical and cardiology teams from both countries regarding the two patients with the additional mitral valve replacements (Patient 4 and 6). Patient 9 had an imaging suggestive of a myxoma and recurrent thrombotic seedlings on the tumour. Patient 10 had found out about our programme himself and requested surgery at any risk. His case was discussed in detail and in view of young age, recent diagnosis, and rapid deterioration, the patient was made aware that he is unlikely to survive a transfer to a large centre, yet surgery is of very high-risk.

   Changes to text: We clarified the manuscript by adding "Although the initial plan was to avoid patients with malignancy, the clinical deterioration of two patients who had tumour in the pulmonary vessels (1 myxoma and 1 vascular sarcoma) warranted surgery in the local centre as opposed to transfer to a larger centre. The patient with myoxma was complicated by recurrent seedlings of thromboembolism and organisation. The other patient had vascular sarcoma which was complicated by thromboembolism and organisation of the thrombus. The rest of the patients had organised thromboembolic disease only."

2. Comment: The authors described that one patient had worsening exercise tolerance due to vasculitis in line 169-171 in page 7. I did not understand which patient the authors meant and what vasculitis meant. Despite excellent results of follow-up RHC in all patients, the patient had worsened exercise tolerance. I was wondering whether the authors excluded differential diagnosis of recurrent pulmonary embolism.

Reply: Patient 3 underwent pulmonary endarterectomy in 2017. She had initial good recovery and resumed normal daily activities including cycling. However, in 2020 she was also diagnosed with vasculitis and her exercise capacity worsened again.

Changes to text: 'Patient 3 improved initially and resumed physical exercise, including cycling. However, she was also diagnosed with vasculitis 3 years later and exercise tolerance worsened again. Repeat CTPA did not show recurrence of thromboembolism.'

3. Comment: Some important pre and postoperative data seemed missing, such as gender, WHO functional class, and administration of PH targeted medicine. In addition, I suppose case number should be added in Figure 1.

   Reply: We are grateful to the reviewer for this comment. We have added Gender, WHO functional class, and use of Sildenafil. At the time endothelin antagonists and soluble guanylate cyclase (sGC) stimulators were not available in Bulgaria. Now they are. We added case numbers in the figure.

   Changes to text: We have added rows with Gender, WHO functional class and use of pulmonary vasodilators in the table. We added case numbers in the figure.
   We have added the three suggested references.

Reviewer B

1. Comment: Why choosing for central and not peripheral ECMO ? Was it VA or VV central ECMO ?

   Reply: We are grateful to the reviewer for this comment. Following advise from the larger centre from UK, we used Central VA ECMO for immediate postoperative mechanical support.The reasons were: cannulation was already in place; Central ECMO provides best circulatory and oxygenation support, including for RV in the face of high afterload.

   Changes to text: We clarified in the manuscript that we used Central VA ECMO as initial haemodynamic and respiratory support.

2. Comment: I quote : "The first patient developed immediate renal failure but was successfully extubated on the first post-operative day. However, on the following day he developed respiratory failure as well. During the planned re-intubation on the following day there was a failure to secure airway and subsequent cardiac arrest from which they could not be resuscitated.

Some centers specialized in PEA for CTEPH do run systematically VV-ECMO for 48-72 hours post procedure ….This could perhaps have saved this patient…..VV-ECMO is also without risks…

Reply: We are grateful to the reviewer for this suggestion and are in complete agreement. VV ECMO would have saved this patient's life. However, during the last visit the patient was awake, mobilizing in the chair, had no haemodynamic or respiratory compromise and hence no indication for ECMO. On the following day the PEA team were not informed of respiratory compromise. Tracheal intubation was attempted but failed which resulted in a cardiac arrest. The management of the patient was investigated and underwent root cause analysis.

Changes to text: 'The first patient recovered well and was extubated in good cardiorespiratory status on postoperative day 1. He had developed immediate renal failure which did not require treatment, and was in negative fluid balance. However, on postoperative day 2, he developed respiratory failure. The PEA team was not informed. The ICU team attempted but failed re-intubation which resulted in cardiac arrest.'

Reviewer C:

1. Comment: ・What was the cause of death for the two deaths discharged?

   Reply: We are grateful to the reviewer for the comments. The reported cause of death for patient 7 was respiratory arrest and patient 10 was multiorgan failure.

   Changes to text: The first patient recovered well and was extubated in good cardiorespiratory status on postoperative day 1. He had developed immediate renal failure which did not require treatment, and was in negative fluid balance. However, on postoperative day 2, he developed respiratory failure. The PEA team was not informed. The ICU team attempted but failed re-intubation which resulted in cardiac arrest. The second patient had pre-operative diagnosis of a tumour invading pulmonary artery bifurcation and the main branches. He had symptoms of right ventricular and liver failure. The surgery was deemed of higher risk (7) and was expedited with a satisfactory surgical result. However, the patient developed multi-organ failure and died on post-operative day 7.

2. Question: Why has PEA not been performed in Bulgaria?

Reply: Due to lack of appropriate training and resource, PEA was not performed until 2017. Patients were referred overseas. Now there is a national program.

Changes to text: NA

3. Question: How many physicians in Bulgaria are capable of performing pulmonary endarterectomy (PEA) ?

   Reply: There is a team of referring physicians, single trained surgeon, team of anaesthetists and intensive care physicians.

   Changes to text: NA