Dear Reviewers,

Thank you very much for reviewing the manuscript and your comments. We have revised our manuscript according to your recommendations. The changes made were highlighted in the revised manuscript.

Name of journal: World Journal of Clinical Cases

Manuscript NO: 39034

Title: Unknown Possible Complication of Extracorporeal Membrane Oxygenator : Ventilator Associated Systemic Air Embolism

Reviewer 1 (Reviewer's code: 03289764)

1. Systemic air embolism caused by broncho-venous fistula has been reported in cases with lung trauma. The reviewer read first time a paper stating air embolism from BVF caused by barotrauma of the lung. As the authors mentioned, there is no information on how high the airway pressure is is possibly dangerous. In this particular case, PEEP was 6 and PS was 20, and these numbers are within usual range. Once occurs, systemic air embolism is often lethal, and there is no effective treatment available. In this sense, prevention of this miserable complication seems to be key. The authors should mention on this.

   We totally agree with the reviewer's comment. Following sentences are added to the discussion. (Page 9)

   "Avoiding high pressure ventilation setting might help to lower the risk of this complication. Because systemic air embolism is often lethal and there is no effective treatment available, prevention of this complication is of key importance."

Reviewer 2 (Reviewer's code: 03011567)

1. Title: Please rephrase to "An unexpected complication during ECMO support: Ventilator associated systemic Air Embolism"

The title was changed as recommended. (Page 1)
The title "Unknown Possible Complication of Extracorporeal Membrane Oxygenator : Ventilator Associated Systemic Air Embolism" is changed to "An unexpected complication during ECMO support: Ventilator associated systemic Air Embolism"

2. Page 5 under ventilator settings: The FiO2 should be reading 0.8 as it is a fraction not percentage.

   "80% " was replaced with "0.8". (Page 5)

3. Given the patient received PCV a pressure control level above PEEP should be quoted, not as the authors state "pressure support of 20cm H2O". please change to inspiratory pressure above PEEP of I guess it was 20, hence a total or peak pressure of 26.

   "pressure support of 20 cm H_2O" is changed to "peak pressure of 26 cm H_2O" (Page 5)

4. Same page 5: The ECG does not only show acute inferior wall infarction but also anteroseptal tombstone ST elevation, so I presume this ought to be changed to acute inferior and anteroseptal wall ischaemia.

   "acute inferior wall infarction" is changed to "acute inferior and anteroseptal wall ischaemia" (Page 5)

5. Could the authors explain if a CT of the aorta and the chest was performed as well? It may have identified, coronary and aortic air.

   Unfortunately it was not performed. By the time when the Brain CT was taken,

the patient became unstable and no further evaluation was performed. Furthermore, we didn't even think the lung as a source of air embolism at that time. Venous catheter or ECMO circuit was suspected to be the source of the air embolism.

6. Discussion 2nd sentence, change to: "Several sources of air emboli are known."

   "Several origins of ..." was changed to "Several sources of..." (Page 6)

7. Discussion 2nd paragraph 2nd sentence change to: "Systemic air embolism can result from the interface between the alveoli and pulmonary veins..."

   "Systemic air embolism can result from the connection between the alveolar and pulmonary veins..." was changed to "Systemic air embolism can result from the interface between the alveoli and pulmonary veins..." (Page 6)

8. Finally I would like to ask the authors how they explain the fact that the air embolus appeared to occur at the time ECLS flow had been reduced hence negative drainage pressure should have been significantly lower at 1 versus 3.5L. Maybe this should be mentioned as an unusual fact, when the contributing factor of -ve venous pressure is discussed.

   It is a very good point to discuss. We had discussion about the same question. We speculate that the systemic air embolism in ECMO support occurs in two phases. First, when the patient is fully supported by ECMO, air can enter pulmonary vein but it is retained in the pulmonary vein, left atrium, or left ventricle depending on the patient's position. Systemic air embolism does not occur because the cardiac output is low. Even if there is left ventricular contraction, the cardiac output from the natural heart is low because most of the blood flows through the ECMO. The systemic air embolism finally takes place

when the ECMO support is lowered and thereby increasing blood flow through the natural heart. The retained air can move to the systemic arteries instantaneously if there is active left ventricular contraction and enough blood flow. This explains why the systemic air embolism took place after we decreased ECMO flow. In the case report(ref. 13) where the clinical situation is similar to ours, a large air bubble oscillating in the aortic root was described. The air bubble was detected in the aortic root right after IABP support and was not moving towards the branches of the aorta because there was no cardiac output. This phenomenon support our two phase theory.
Because this is only speculation we only added suggestion of this two phase theory to explain why the systemic air embolism occured after reduction of the ECMO flow.

Following paragraph is added to the discussion section. (page 8)
(Citation and reference numbers are changed accordingly)
"Although there are a number of factors that can increase the risk of air entrance into the pulmonary vein, it seems that the actual systemic air embolism does not occur until there is enough left ventricular blood flow. The patient did not show any sign of systemic air embolism when fully supported with ECMO. The systemic air embolism developed after we decreased ECMO flow. In the case report about ECMO-related systemic air embolism, the author described a large oscillating air bubble detected in the aortic root immediately after initiation of the IABP[13]. These clinical features suggest that the air embolism might take place in two phases. First, the air in the alveolar space enters into the pulmonary vein. It is trapped in the pulmonary vein, left atrium or left ventricle depending on the position of the patient. Secondly when there is enough left ventricular blood flow, the air bubbles move into the aorta and peripheral arteries causing systemic air embolism."