DEVELOPMENT OF AGGRESSIVE TREATMENT TO ADMINISTER DRUGS DIRECTLY INTO THE TRACHEA OF PATIENTS ON ECMO

Yusuke Inoue, Yasushi Sato, Takeshi Terazawa, Tomoki Nagayoshi, Yoshiaki Takewa

Advanced Medical Engineering Research Center, Asahikawa Medical University, Japan

Background

Severe cases of novel coronavirus infection (COVID-19) cause acute respiratory distress syndrome (ARDS); there is no treatment for ARDS and patients are fitted with extracorporeal membrane artificial lungs (ECMO). The increase in the number of patients on ECMO during a pandemic will result in medical collapse due to a shortage of medical staff, hospital beds, and medical equipment. In addition, ECMO is not a device to treat the lungs, but rather a medical device that rests the patient's own lungs and promotes recovery. Therefore, patients with ECMO need a long hospital stay before they can recover. Early weaning from ECMO and improving the life-saving rate is an urgent issue. We have drafted a new treatment modality that promotes early pulmonary recovery by administering drugs directly into the lungs through the trachea. To evaluate the efficacy and safety of this new treatment using ECMO, an experimental animal model of the same size as humans is needed, but there are no experimental animal models available to evaluate the proposed new treatment. In addition, large animal experiments using viruses such as COVID-19 are extremely difficult. Therefore, the purpose of this study is to establish a large animal model that can evaluate aggressive pulmonary therapies that administer drugs transbronchially on ECMO support and to evaluate their efficacy.

Methods

Twelve adult Saanen goats were used. Anesthesia was induced with ketaral and maintained via mechanical ventilation with isoflurane in oxygen gas. After heparin was injected via vein as anticoagulation, the right carotid artery and right jugular vein were exposed, a de-bleeding cannula was inserted from the vein into the right atrium area, and a sending cannula was inserted into the carotid artery. Next, a centrifugal pump and a membrane artificial lung primed by saline were connected to the cannula. Lipopolysaccharide (LPS) as an endotoxin was then injected intravenously (70-100ug/kg) to induce sepsis and create a model of acute lung disease[1-4]. Pressure sensors and catheters were used to continuously measure pressure in the pulmonary artery, left ventricle, and aorta in an observational manner. Oxygen saturation before and after lung and in the artificial lung was measured intermittently. X-ray angiography was performed to observe pulmonary blood flow. Hourly lung tissue sampling was performed to histologically evaluate alveolar, bronchiolar and vascular morphology. In order to minimize the influence of individual animal differences in evaluating the effects of the drug, different conditions were set up and compared in the left and right lungs. Using a two-way intubation tube, only the left lung was administered the therapeutic drug through the trachea, while the right lung was not administered the drug as a control. 2 hours after administration of LPS, the drug (nafamostat mesylate 150 mg) was administered into the lung through the trachea.

Results

Immediately after LPS was administered intravenously, there was a rapid increase in pulmonary arterial pressure. Pulmonary arterial pressure required 30 - 60 minutes to return to normal values. A few minutes after the pulmonary artery pressure increased, aortic pressure decreased gradually. Angiography at that time showed markedly reduced pulmonary artery blood flow. Blood gas studies also showed a marked decrease in the partial pressure of oxygen in the blood immediately after the introduction of LPS. When blood flow could no longer be maintained due to the decrease in aortic pressure, ECMO was driven to maintain blood flow, and peripheral blood oxygen saturation recovered to the normal range after ECMO was driven. Histological evaluation showed blood and plasma leakage around blood vessels and inflammation in the lungs treated with LPS compared to normal lungs. The degree of inflammation was lower in the left lung treated with the therapeutic agent than in the right lung that was not treated.

Conclusions

Results of 12 animal studies showed that after endotoxin (LPS) administration, pulmonary hypertension due to vasoconstriction and a marked decrease in pulmonary blood flow and blood oxygen saturation were induced. Histological evaluation showed plasma leakage from peribronchial vessels after LPS administration. Comparison of the left and right lungs showed a difference in the degree of inflammation, allowing evaluation of the efficacy of this treatment method. We succeeded in establishing a model of acute severe lung disease caused by endotoxin and in creating an animal model in which the new treatment method could be evaluated.

References

1. M. Engel, et al. Respir Res, 21: 209, 2020
2. Matute-Bello G, et al. Am J Physiol Cell Mol Physiol, 295: L379-99, 2008
3. Rosenthal CDO, et al. Crit Care Med. 26(5):912-6, 1998
4. Lindenkov PHH, et al. Ped Res, 57(3):371-7, 2005