Acta Medica Okayama

Experimental study on veno-venous extracorporeal membrane oxygenation for respiratory failure after lung transplantation.

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Abstract

Extracorporeal Membrane Oxygenation (ECMO) has been adopted as a means of strong respiratory support. In lung transplantation, reimplantation response is still a serious problem. It causes severe respiratory failure which is refractory to mechanical ventilation in some cases. The purpose of this study was to evaluate the effects of veno-venous ECMO after lung transplantation using a canine autotransplantation model. The autotransplantation model was created by keeping the left lung in a warm ischemic state for 2 h. After reperfusion, the right pulmonary artery was ligated. The following two groups were studied: Group 1, Control group, (no ECMO group) (n = 6). After reperfusion, both lungs were ventilated without ECMO. Group 2, ECMO group (n = 7). After reperfusion, veno-venous ECMO support was introduced with reduction of mechanical ventilation. In the no ECMO group, four of the animals died within 210 min after reperfusion. In the ECMO group, two of the animals died of severe pulmonary edema. Data of blood gas analyses (PaO2, PaCO2, and SvO2) after reperfusion were significantly better in the ECMO group, whereas there were no significant differences in both shunt fraction and pulmonary vascular resistance index. In this model with severe pulmonary edema induced by warm ischemia, veno-venous ECMO contributed to the improvement of hypoxemia and hypercapnia, but did not improve pulmonary hemodynamics.

KEYWORDS: extracorporeal membrance oxygenation(ECMO), warm ischemia, reimplantation response, lung transplantation, pulmonary edema, veno-venous ECMO

Experimental Study on Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure after Lung Transplantation

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Extracorporeal Membrane Oxygenation (ECMO) has been adopted as a means of strong respiratory support. In lung transplantation, reimplantation response is still a serious problem. It causes severe respiratory failure which is refractory to mechanical ventilation in some cases. The purpose of this study was to evaluate the effects of veno-venous ECMO after lung transplantation using a canine autotransplantation model. The autotransplantation model was created by keeping the left lung in a warm ischemic state for 2 h. After reperfusion, the right pulmonary artery was ligated. The following two groups were studied: Group 1, Control group, (no ECMO group) ($n = 6$). After reperfusion, both lungs were ventilated without ECMO. Group 2, ECMO group ($n = 7$). After reperfusion, veno-venous ECMO support was introduced with reduction of mechanical ventilation. In the no ECMO group, four of the animals died within 210 min after reperfusion. In the ECMO group, two of the animals died of severe pulmonary edema. Data of blod gas analyses (PaO_2, $PaCO_2$, and SvO_2) after reperfusion were significantly better in the ECMO group, whereas there were no significant differences in both shunt fraction and pulmonary vascular resistance index. In this model with severe pulmonary edema induced by warm ischemia, veno-venous ECMO contributed to the improvement of hypoxemia and hypercapnia, but did not improve pulmonary hemodynamics.

Key words : extracorporeal membrane oxygenation (ECMO), warm ischemia, reimplantation response, lung transplantation, pulmonary edema, veno-venous ECMO

Human lung transplantation remains in the developmental stage, with several basic problems yet to be solved. One such problem is reimplantation response, which occurs as the result of ischemia-reperfusion. This response consists of pulmonary edema, which reaches a peak wihtin 3 days after transplantation and regresses over the next 3 weeks (1). It sometimes causes respiratory failure which is refractory to maximal ventilatory support, resulting in death in the first week. Cooper and coworkers, from their clinical experiences of extracorporeal membrane oxygenation (ECMO) before and after a lung transplantation, reported that postoperative support with a membrane oxygenator could play a useful role in the management of future transpalnt recipients (2–4). ECMO has been used successfully in the treatment of reversible cardiorespiratory failure in neonates since reported by Bartlett and co-workers in 1977 (5, 6). The current survival of

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ARDS patients treated with ECMO has also improved compared with past experiences (7–10).

Prospective observations from the 1974–1977 ECMO trial demonstrated a survival of 9 percent (8). Increased survival of ARDS patiens has been reported after the use of low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO₂R). The current survival rate increased to 49 % by Gattinoni *et al.* and 45 % by Suchyta *et al.* (9, 10). It may be reasonable to combine the rapidly advancing therapies, lung transplantation and ECMO (11). The purpose of this study was to evaluate the veno-venous ECMO after lung transplantation, using a canine autotransplantation model.

was ligated to cause the full cardiac output to flow to the injured left lung.

In the animals receiving ECMO, a 16–20 Fr drainage cannula was placed in the right atrium via the right internal jugular vein. In addition, a 14 Fr cannula was inserted into the left femoral vein. Cannulation procedures were performed prior to reperfusion of the left lung. This allowed blood to be drained from the right atrium using a roller pump (MERA HAL-100, Senko Medical Co., Tokyo), circulated through a reservoir, a membrane oxygenator (Cobe Cml Ultra, Cobe laboratories Inc., CO. U.S.A.), and a heat-exchanger, and then returned to the animal via the left femoral vein (Fig. 1). The ECMO circuit was primed with 400 ml of lactated Ringer's solution, and then exchanged with heparinized whole blood obtained from a dog sacrificed the day prior to the experiment. The animals were given a bolus injection of sodium heparin 100 units/kg prior to cannulation, and heparinization was controlled to maintain

Materials and Methods

Animal preparation. Thirteen mongrel dogs (8–16 kg) were used. After intramuscular injection of atropine sulfate (0.025 mg/kg) and ketamine hydrochloride (10 mg/kg), anesthesia was induced by intravenous injection of pentobarbital sodium (20 mg/kg) and pancuronium bromide (0.2 mg/kg). The dogs were intubated with a 7.5 mm cuffed endotracheal tube, and ventilated using a Harvard ventilator model 613. An arterial catheter was inserted into the right femoral artery for blood sampling and measurement of systemic arterial pressure. A 5 French (Fr) Swan-Ganz catheter was placed in the main pulmonary artery via the right femoral vein for pressure monitoring and evaluation of cardiac output.

The autotranplantation model was created by the following procedure. Following left thoracotomy at the fifth intercostal space, complete hilar stripping of the left lung was performed. The left main bronchus was cut, and the right pulmonary artery was taped. After a bolus injection of sodium heparin 100 units/kg, the left pulmonary artery and veins were clamped to maintain the left lung in a warm ischemic state. The left lung was deflated during this period. A 16 gage venous catheter was placed directly in the left atrium for pressure monitoring. Then, ventilation was fixed at a tidal volume of 20 ml/kg, a rate of 20/min, F₁O₂ of 1.0, and positive end expiratory pressure (PEEP) of 4 mmHg. Two hours later, the left lung was reperfused after reanastomosis of the left main bronchus. Five minutes later, the right pulmonary artery
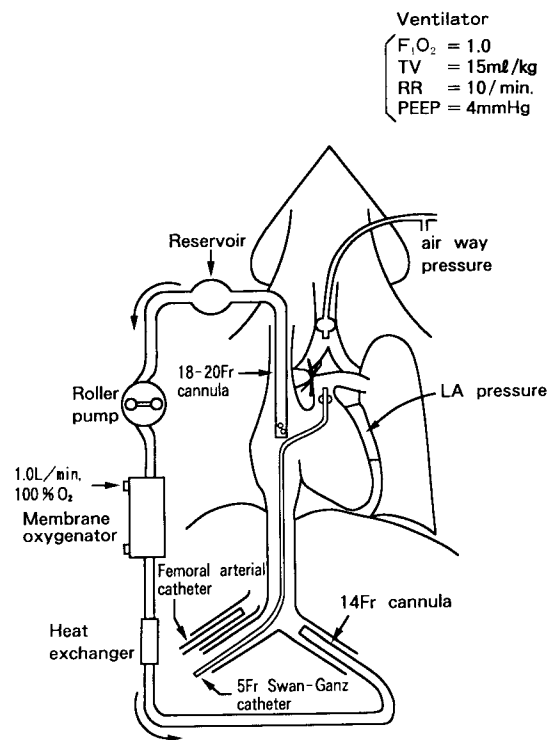

Fig. 1   Schematic representation of veno-venous ECMO circuit system. Blood is drained from the right atrium and infused into the left femoral vein.

activated clotting time (ACT) at about 300 sec during perfusion (Hemocron 400). ECMO was introduced following ligation of the right pulmonary artery and bypass flow was maintained at 40% of baseline cardiac output assessed during warm ischemic period.

The animals received maintenance fluid (5% glucose in lactated Ringer's) at 4 ml/kg/hr. Blood temperature was maintained at 37°C. Sodium bicarbonate was given if necessary to correct metabolic acidosis.

Study group. Two groups of animals were studied. In dogs in the no ECMO group ($n = 6$), both lungs were ventilated without ECMO. In the ECMO group ($n = 7$), after ligation of the right pulnorary artery, veno-venous ECMO was introduced. After the ECMO system reached 40% of baseline cardiac output value, ventilation was reduced to a tidal volume of 15 ml/kg, a rate of 10/min, F_iO_2 of 1.0, and PEEP of 4 mmHg.

Laboratory determinations. Arterial and pulmonary blood gases including systemic arterial oxygen tension (PaO_2), arterial oxygen saturation (SaO_2), arterial carbon dioxide tension ($PaCO_2$), pulmonary arterial (mixed venous) oxygen tension (PvO_2), and pulmonary arterial (mixed venous) oxygen saturation (SvO_2) were assessed every 30 min for 300 min (Blood Gas System, type 280, Ciba-Corning Diagnostic Co., Tokyo). Shunt fraction (cardiac output passing through the non-aerated lung) was calculated by the following equation.

$$\dot{Q}_s / \dot{Q}_t = \frac{C_{AO2} - C_{aO2}}{C_{AO2} - C_{vO2}} \times 100 \quad [\%], \text{ where}$$

$\dot{Q}_s / \dot{Q}_t$; shunt, C_{AO2}; oxygen content of blood from ideally ventilated alveoli, C_{aO2}; oxygen content of arterial blood, C_{vO2}; oxygen content of mixed venous blood.

Cardiac output was determined by the thermodilution technique by injecting 5 ml of 4°C 5% glucose solution through the Swan-Ganz catheter. Cardiac output was calculated by a cardiac output computer and converted to cardiac index (C.I.). Hemodynamic data including mean systemic arterial pressure (mAOP), mean pulmonary arterial pressure (mPAP), mean right and left atrial pressure (mRAP, mLAP) and airway pressure were recorded every 30 min for 300 min (Polygraph 360 system Nihondenki-Sanei Co., Tokyo). Pulmonary vascular resistance index (PVRI) was calculated by the following equation.

$$\text{PVRI} = 79.92 \times (\text{mPAP} - \text{mLAP})/\text{C.I.}$$
$$[\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^2]$$

All baseline values were assessed during the warm ischemic period when the right lung was perfused. The baseline value was assessed in order to evaluate the respiratory function in normal state of the animal.

Statistical analysis. Data are given as mean and standard error of the maen (mean ± SEM). The survival data were compared using Cox-Mantel test. Comparisons between groups were perfomed by unpaired t test, and comparisons between baseline value and the value at 120 min after reperfusion in each group were perfomed by paired t test. Differences were considered statistically significant at p values < 0.05.
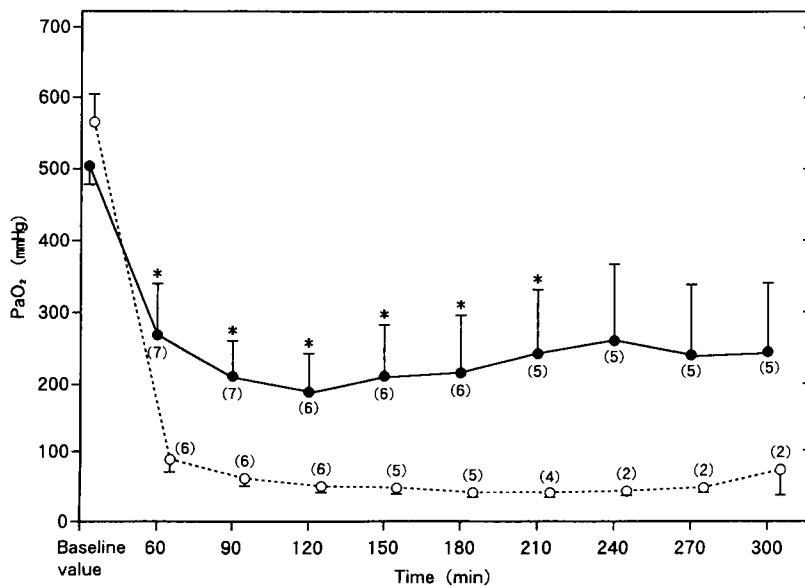
Results

Survival. In the no ECMO group, two of the six animals survived for 300 min. The other four animals died of respiratory failure due to severe pulmonary edema (120 min, 180 min, 210 min, 210 min). In the ECMO group, five of the seven animals survived for 300 min. The other two animals died (90 min, 180 min). The animal that died at 90 min had severe circulatory insufficiency immediately after ligation of the right pulmonary artery. There was no statistically significant difference in 300 min survival rate between the two groups (Fig. 2).

Blood gas analyses. There was no significant difference in baseline values of each parameter between the two groups. In the no ECMO gruop, PaO_2 was 567.5 ± 38.1 mmHg at baseline, and significantly decreased to 50.6 ± 9.8 mmHg at 120 min after reperfusion. In the ECMO group, PaO_2 was 505.3 ± 25.3 mmHg at baseline, and significantly decreased to 186.0 ± 55.7 mmHg at 120 min, and at about the same value thereafter. There was a significant difference between the two groups ($p < 0.05$) (Fig. 3). In the no ECMO group, $PaCO_2$ was 30.6 ± 4.4 mmHg at baseline, and significantly increased to 82.5 ± 15.1 mmHg at 120 min with progressive deterioration. In the ECMO group, $PaCO_2$ was 24.3 ± 1.2 mmHg at baseline, and increased to 40.0 ± 3.0 mmHg at 120 min, and controlled at a stable level. There was a significant differece between the two groups at 60, 90, and 120 min ($p < 0.05$) (Fig. 4). In the no ECMO group, SvO_2 was $87.9 \pm 1.8\%$ at

216   Ichiba *et al.*
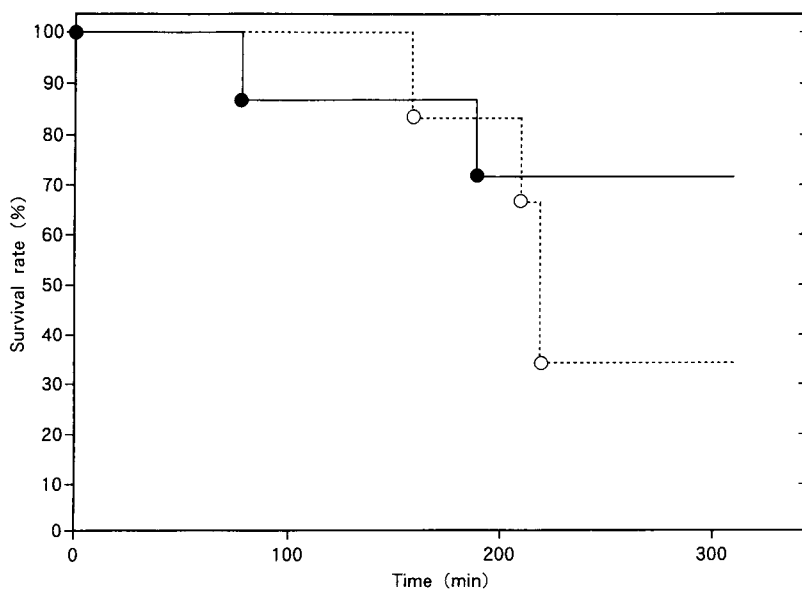
Fig. 2   Survival curves after reperfusion with no significant difference between the two groups. (●): ECMO group ($n = 7$), (○): no ECMO group ($n = 6$),

Fig. 3   Systemic arterial oxygen tension (PaO_2) in the two groups. The results are presented as the mean $\pm$ SEM. The numbers in parentheses are survivors in each group. (●): ECMO group, (○): no ECMO group. ✱: Difference from another group at $p <$ 0.05.
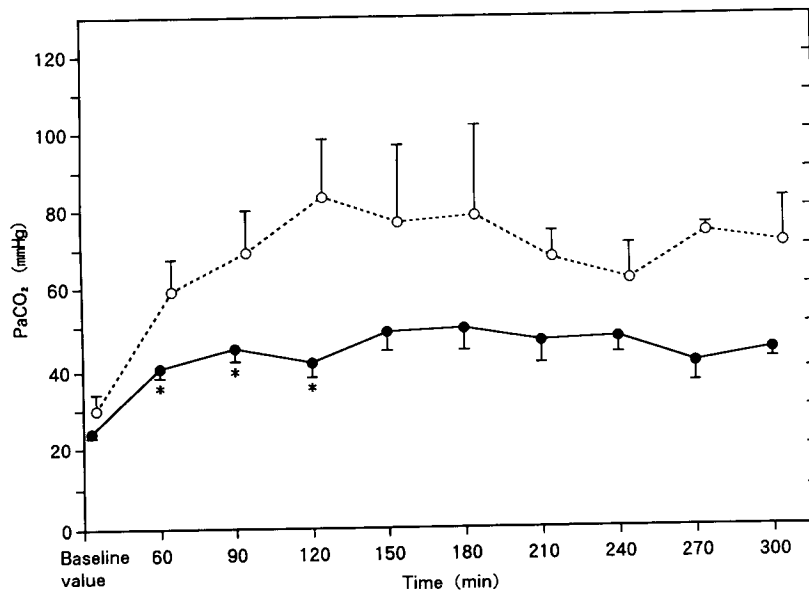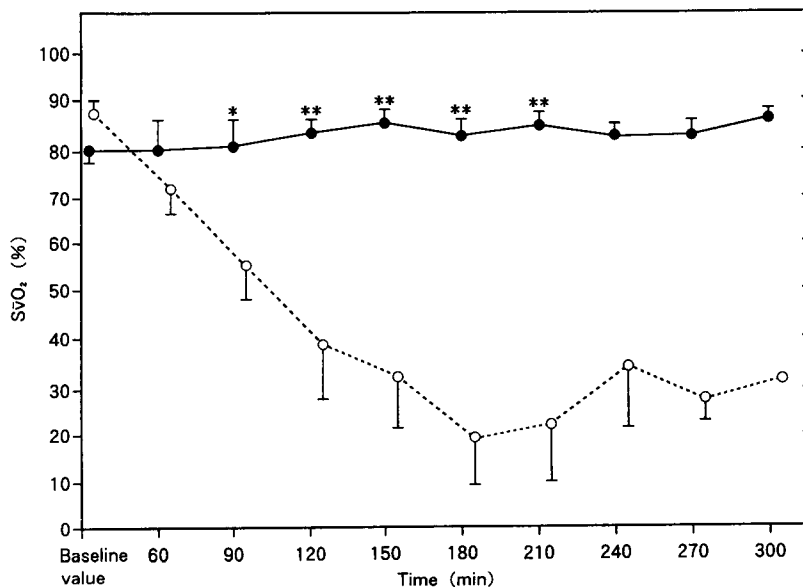
Fig. 4 Systemic arterial carbon dioxide tension ($PaCO_2$) in the two groups. The results are presented as the mean $\pm$ SEM. ($\bullet$): ECMO group, ($\bigcirc$): no ECMO group. $*$: Difference from another group at $p < 0.05$.

baseline, and significantly decreased to $38.7 \pm 11.1 \%$ at 120 min with progressive deterioration. In the ECMO gruop, SvO_2 was $80.7 \pm 3.0 \%$ at baseline, and $84.0 \pm 2.2 \%$ at 120 min, and could be controlled at a stable level. There was a significant difference between the two groups ($p < 0.05$ at 90 min, $p < 0.01$ after 120 min) (Fig. 5). In the no ECMO group, shunt fraction was $13.3 \pm 4.3 \%$ at baseline, and significantly increased to $52.9 \pm 9.0 \%$ at 120 min, and to $62.4 \pm 8.8 \%$ at 180 min. In the ECMO group, shunt fraction was $12.6 \pm 1.4 \%$ at baseline, and significantly increased to $46.0 \pm 5.7 \%$ at 120 min, to $46.9 \pm 7.6 \%$ at 180 min, and to $40.2 \pm 11.3 \%$ at 240 min (Fig. 6). The shunt fraction tended to increase progressively in the no ECMO group. The ECMO group tended to be maintained at a lower shunt fraction than the no ECMO group, but there was no statistically significant difference between the two groups.

Hemodynamics. There was no significant difference in baseline values of all parameters between the two group. In the no ECMO group,

mean aortic pressure (mAOP) was 98.8 ± 4.6 mmHg at baseline and 80.7 ± 10.7 mmHg at 120 min. In the ECMO group, mAOP was 101 ± 4.6 mmHg at baseline, and decreased to 62.1 ± 9.1 mmHg at 120 min. In the no ECMO group, cardiac index (C. I.) was 3.39 ± 0.37 l/min/m², and significantly decreased to 2.31 ± 0.43 l/min/ m² at 120 min. In the ECMO group, C.I. was 2.78 ± 0.15 l/min/m² at baseline, and significantly decreased to 1.81 ± 0.32 l/min/m². In the no ECMO group, pulmonary vascular resistance index (PVRI) was 374 ± 70 (dynes· sec·cm^{-5}·m²) at baseline, and significantly increased to 1309 ± 317 at 120 min. In the ECMO group, PVRI was 539 ± 88 at baseline and significantly increased to 1191 ± 272 at 120 min (Fig. 7). There was no statistically significant difference in any hemodynamic parameter between the two groups after reperfusion.

Ichiba *et al.*

Fig. 5 Mixed venous oxygen saturation (SvO_2) in the two groups. The results are presented as the mean $\pm$ SEM. ($\bullet$): ECMO group, ($\circ$): no ECMO group. Difference from another group at ($*$: $p < 0.05$, $**$: $p < 0.01$).
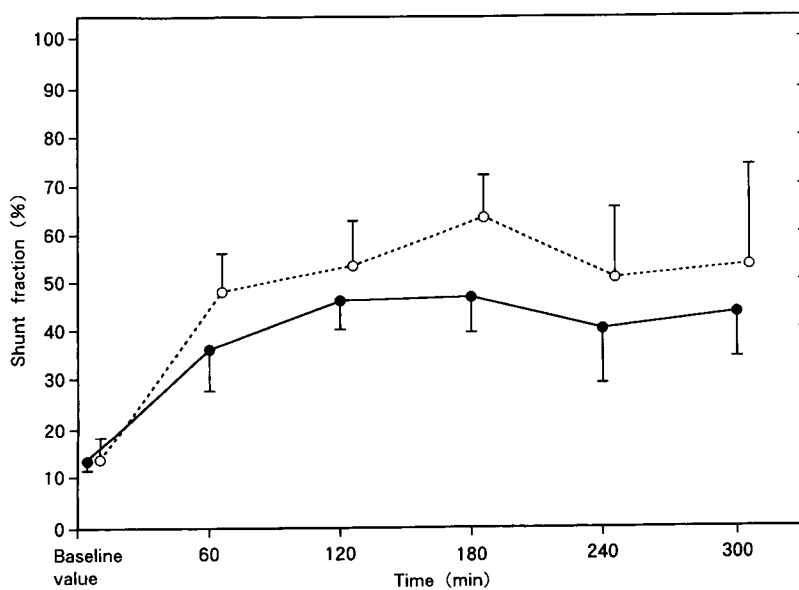
Fig. 6 Shunt fraction in the two groups with no significant difference. The results are presented as the mean $\pm$ SEM. ($\bullet$): ECMO group, ($\circ$): no ECMO group.
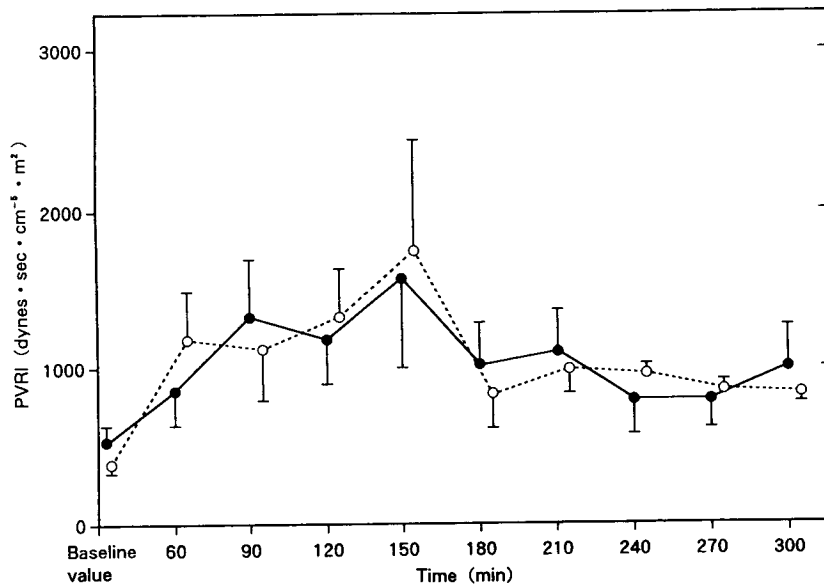
Fig. 7   Pulmonary vascular resistance index (PVRI) in the two groups. The results are presented as the mean ± SEM. (●): ECMO group, (○): no ECMO group.

Discussion

Reimplantation response in lung transplantation consists of pulmonary edema, which is mainly caused by the oxygen free radicals, arachidonic acid metabolites, the complement system, and leukocyte products produced by ischemia-reperfusion injury (12,13). This presents as severe ventilation-perfusion imbalance and high pulmonary vascular resistance. In this study, the animals had severe impairment of gas exchange and an immediate increase of pulmonary vascular resistance after reperfusion of the lung, mainly as the result of vascular compression and vascular congestion due to high permeability pulmonary edema (14).

In the ECMO group, arterial blood gases were significantly better than those in no ECMO group. Mixed venous oxygen saturation (SvO_2) was stabilized at about 80–90 %, and removal of carbon dioxide was excellent in all animals receiving ECMO. In veno-venous ECMO, significant

reductions of $PaCO_2$ can be obtained even a bypass flow rate of 20 % (16). But a higher bypass flow rate is required for sufficient oxygen supply because of the recirculation phenomenon (15). Recirculation phenomenon becomes marked at flow rates exceeding 40 % (16). In this study, we fixed the bypass flow rate at 40 % of the baseline cardiac output, but actual bypass flow rate was greater than 40 % because of decrease in cardiac output after reperfusion.

Physiological evaluation of the extent of ventilation-perfusion imbalance is performed by measuring the shunt fraction. When the ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) is low, increase of mixed venous oxygen content contributes to the sharp increase of terminal capillary oxygen content, because the blood gas composition from areas with decreased $\dot{V}/\dot{Q}$ is similar to that of mixed venous blood (17). It is considered that high mixed venous oxygen saturation produced by veno-venous ECMO could contribute to a significant improvement of hypoxemia during

severe pulmonary edema.

Hypoxic vasoconstriction plays an important role in blood flow distribution during pulomonary edema, causing flow to be shunted away from the most severely injured areas where oxygen tension is the lowest (18). We hypothesized that high mixed venous oxygen saturation might reverse vasoconstriction, resulting in lower pulmonary vascular resistance in this model. However, one concern is that the highly increased mixed venous saturation may have the same effect by increasing blood flow to the areas of the greatest damage, possibly increasing the edema (19). Yanos and coworkers studied oleic-acid induced edema in dogs and concluded that high mixed venous oxygenation associated with veno-venous ECMO with reduction of pulmonary ventilation increased arterial oxygenation and lowered pulomonary arterial pressure, but could not find a significant difference in pulmonary edema (20). In this study, we were unable to demonstrate a reduction of pulmonary vascular resistance by mixed venous oxygenation because of the severe pulmonary damage. We considered that the severe pulmonary damage in this model deteriorated the functions of regulating its pulmonary vascular tone.

In summary, increased mixed venous oxygen saturation produced by veno-venous ECMO contributed to the significant reduction of hypoxemia, but could not lower pulmonary vascular resistance in warm ischemic pulmonary edema. Veno-venous ECMO is considered to be effective for arterial oxygenation and removal of carbon dioxide but not for improvement of hemodynamics in severe respiratory failure after lung transplantation.

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