To-and-Fro Extracorporeal Lung Assist (ECLA) through a single catheter - in Premature Goats as an Experimental Model of Infant Respiratory Insufficiency

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A new to-and-fro V-V bypass extracorporeal lung assist (ECLA) through a single catheter as a blood access was investigated for its efficacy on six premature goats delivered by Cesarean section at a gestational age of 118 $\sim$ 139 days as an experimental model of infant respiratory insufficiency, then applied to a human premature infant suffering from life threatening barotrauma that had developed from mechanical pulmonary ventilation. The extracorporeal bypass flow and the gas flow to the artificial membrane lung were controlled to keep Pa_{O_2} above 40 mmHg and Pa_{CO_2} within normal limits. The neonate's own lungs were treated with a continuous positive airway pressure of 5 $\sim$ 12 cmH_2O, apneic oxygenation or IMV. Two goats weighing 1250 g and 700 g died 2 $\sim$ 2.5 hours after birth from severe circulatory distress. However, the other four neonates which were heavier than 2000 g, were successfully weaned from ECLA, and three of these could be weaned from mechanical ventilation as well. A human infant also survived and was weaned from ECLA on the third day. (Key words: ECLA, ECMO, neonatal respiratory insufficiency, to-and-fro V-V bypass)

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Extracorporeal membrane oxygenation (ECMO) is a lifesaving modality in infants and children who are dying from severe respiratory insufficiency refractory to conventional ventilatory menagement[1–12]. However, both the venoarterial (V-A) and the venovenous (V-V) bypass require manipulation of two major vessels for blood access. Therefore, we divised a V-V bypass extracorporeal lung assist (ECLA) circuit in which blood was intermittently withdrawn and returned to-and-fro through a single catheter[13,14]. We describe here our fundamental studies using this method in premature goats as an experimental model of infant respiratory insufficiency, and a clinical case which we could save using this method.

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Materials and Methods

The Extracorporeal Perfusion Circuit

The ECLA machine is composed of a blood-gas exchange circuit and a driving power circuit. The blood-gas exchange circuit includes an artificial membrane lung and a blood reservoir incorporated in an airtight box. The power circuit includes the airtight box described above and a water reservoir and a roller pump. These are all intercon-

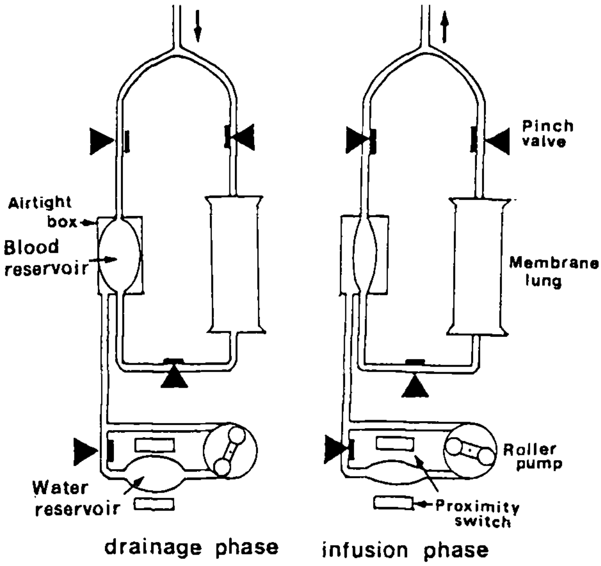

Fig. 1. Schema of our to-and-fro V-V ECLA circuit.

nected with silicon tubes (5.0 mm ID) as shown in figure 1. The water content of the reservoir exerts hydrodynamic force to the blood reservoir encased in the airtight box, positive pressure with the roller pump or negative pressure by gravity alternately. This negative pressure is controlled by the head between the blood and water reservoirs, and promotes the venous drainage.

The air-driven pinch valves incorporated into both the circuits determine the direction of blood flow. They are controlled by two capacitance proximity switches (one for maximal inflation and one for maximal deflation) placed on each side of the water reservoir. When the water reservoir inflates to a predetermined volume with water returned from the airtight box, the capacitance proximity switch energizes the pinch valves in turn and the roller pump is activated to eject the content of the water reservoir to the blood reservoir. Since both reservoirs move synchronously, the blood is infused into the vein through the artificial lung. Thus the blood is not squeezed directly by a roller pump and mechanical damage can be avoided. When the reservoir shrinks and the infusion phase comes to an end, another proximity switch stops the roller pump, opens the pinch valves on the inflow side of the water reservoir, and closes the pinch valves on the outflow side. Venous blood is drawn into the blood reservoir by negative pressure created by the water flowing down from the airtight box to the water reservoir. The rotary pump in the driving circuit was designed to respond to the on-off switch quickly. To minimize the priming volume of the blood-gas exchange circuit, an on-line heat exchanger was omitted, and the main parts of the circuit were encased in a large plastic box and kept warm from the outside by heated air. The bypass rate is controlled by setting the maximal and minimal inflation volumes of the water reservoir and the speed of the pump. The former determines the stroke volume, and the latter effects the frequency of the pumping.

A Kolobow lung with a surface area of 1.5 m^2 was used for the first animal, then a Kurare lung of 0.8 m^2 for No.2. A Mera Sirox® of 0.8 m^2 was used from No.3 on. However, in No.3, the Mera Sirox® was changed to a Kolobow lung of 0.8 m^2 four hours after the start of ECLA.

First, the extracorporeal circuit was primed with 250 ~ 350 ml lactated Ringer's solution together with 5 U/ml of heparin. This priming solution was exchanged with fresh heparinized goat blood 3 ~ 5 min before the start of ECLA to prevent the initial hemodilution. Details of the priming method of the system with blood were reported previously[14].

Experimental animals

We obtained six pregnant goats of Saanen and Shiba breeds with a gestational age of 118 ~ 139 days (term : 150 ± 1 day). Their babies were delivered by Cesarean section under halothane-nitrous oxide-oxygen anesthesia. The average weight of the goats was 2.0 ± 0.9 kg (range 0.7 ~ 3.2 kg). The corresponding gestational age in humans was uncertain, but the body weights were in the range of human premature neonates. The goats usually delivered single or twin babies, but goat No.1 had triplets and goat No.6 bore quintuplets. The neonates born from these two goats were too immature, and they died soon after delivery when their respiration was not supported (table 1).

In the experiment, a midline abdominal incision was performed on the mother goats, and the uterus was exposed over the abdominal wall. The head of the fetus was pulled out from the incised uterus, and the newborn was orotracheally intubated about 8 ~ 12 cm from the corner of the mouth while its torso was still in the uterus. The right common carotid artery was cannulated, after the administration of 200 ~ 300 units of heparin, for blood sampling and blood pressure monitoring. To test the compatibility of blood type between mother and child, 10 ml of the mother's blood was transfused to the neonate, then observed for about 15 min for any adverse reaction. When there was no transfusion reaction, we placed a thin-walled (0.3 mm) 8 ~ 12 Fr. single lumen spiral embedded catheter of segmented polyurethane into the right atrium through the right jugular vein. After the umbilical cord was cut and the newborn was placed in an incubator, a to-and-fro V-V ECLA with an artificial membrane lung was started.

Management of animals during ECLA

To institute ECLA, the bypass rate was slowly increased to allow gradual mixing between the priming blood and the recipient's blood. Nevertheless, the premature goat usually required a small amount of blood transfusion to compensate for the initial fall of blood pressure. The extracorporeal bypass rate and oxygen concentration of the insufflation gas to the membrane lung were varied to maintain the goat's systemic arterial oxygen tension slightly above 40 mmHg. The flow rate of the insufflation gas through the oxygenator was varied to adjust the Pa_{CO_2} to within the normal range. In fact, the artificial lung was ventilated with 1 to 5 l/min of oxygen and air which was humidified and warmed to about 40°C. If a flow rate of more than 3 l/min was required, suction was applied to the gas outlet of the membrane lung to accelerate the out flow and prevent a high positive pressure in the gas phase. Anticoagulation was established by the continuous infusion of heparin to maintain the whole blood activated clotting time (ACT) at 200 ~ 250 seconds. For this aim, ACT was measured every hour.

Respiration of most premature goats under ECLA was supported with a continuous positive airway pressure (CPAP) of 5 ~ 12 cmH_2O or apneic oxygenation with humidified oxygen and air. When the maturity of the lungs seemed to be improved, mechanial pulmonary ventilation, particularly intermittent mandatory ventilation with PEEP (IMV with PEEP), was started and the support of gas exchange by ECLA was gradually decreased until finally discontinued. Animals No.3 and 6 were treated under IMV with PEEP from the beginning. Weaning from the mechanical ventilation was done according to conventional methods.

Medication and parenteral nutrition were given through the ECLA circuit. For example, prophylactic antibiotics, usually peperacillin sodium (Pentcillin®) and dextrose-electrolyte solutions were given through a luer-lock incorporated into the circuit. Electrolytes were maintained at the normal range by balancing fluid intake and output. When the premature goats became reactive, their mother's milk was given through a gastric tube or by mouth.

All animals were autopsied after unexpected death or after they were killed under intravenous pentobarbital anesthesia. Macroscopic as well as microscopic examinations were done in all cases.

Table 1. Results of the to-and-fro V-V ECLA in premature goats delivered by C-section

No	Gestational age (days)	Birth weight (g)	Breed	V-V ECLA time (hrs) [Total ECLA time]	Result	Comments
1	137	2430	Saanen	24	survived	triplets
2	139	2450	Saanen	18	survived	
3	132	3190	Saanen	32	survived	
4	118	1250	Saanen	2	died	
5	124	2000	Saanen	87* [203]	improved	once weaned from ECLA died by severe pneumonia
6	120 ~ 130	700	Shiba	2* [2.5]	died	quintuplets, L/S = 1.3**

* first V-V ECLA time ** lecithin/sphingomyelin of normal range: 4 ~ 5

Table 2. Each parameter during ECLA

No	Bypass flow (ml/kg/min)	O_2 delivery by ECLA (ml/kg/min)	Pco_2 difference through the ML* (mmHg)	Neonate's respiration F_{IO_2}	Neonate's respiration PIP/PEEP (cmH_2O)	Neonate's respiration Ventilation mode	So_2 of drained blood (%)	Sa_{O_2} (%)
1	57.6	4.1	7.7	0.5	/12	CPAP	66	86
2	51.4	3.9	15.3	1.0	/10	AO	45	80
3	54.5	3.8	22.6	0.8	15/5	IMV	67	100
4	140.8	9.4	8.7	1.0	/7	AO	63	42
5	76.0	7.6	16.8	1.0	17/12	IMV	46	68
6	112.8	not measured	not measured	1.0	10/3	IMV	73	59

*ML = membrane lung

Results

Premature goats from the same litter, which received no specific respiratory care as the control, died of immaturity within a few hours. Four of the six premature goats that underwent ECLA survived and could be weaned from ECLA. Three of the four that survived (No. 1 ~ 3) were also weaned from a ventilator a few days later. The average ECLA time of survivors was 24.7 hours, with a range of 18 to 32 hours (table 1). The average bypass flow rate of the surviving group after cardiopulmonary stabilization under ECLA was 54.5 ± 3.1 ml/kg/min, when oxygen delivery by ECLA was 3.9 ± 0.15 ml/kg/min and Sa_{O_2} was above 80% (table 2). Pa_{O_2}/F_{IO_2} of the survivors improved satisfactorily (fig. 2).

In No.3, the bypass flow did not reach this desired level at the beginning of ECLA and the internal pressure of the circuit increased abnormally. When the hollow fiber artificial lung was exchanged for a new Kolobow lung, these problems were resolved. Many thrombi were found in the inflow side vestibule of the hollow-fiber-oxygenator. This might have been caused by a stagnation of blood during the long interval between the priming and active use of this oxygenator.

In No.5, endotracheal tube obstruction due to profuse secretion, occurred. Severe hypoxia continued even under V-V ECLA. Though this premature goat was weaned from ECLA after 87 hours, it suffered from aspiration pneumonia. Pa_{CO_2} increased and bradycardia often ensued probably due to accompanying hypoxia. We resumed to-and-fro V-V ECLA 53 hours after the end of the first ECLA. Normocarbia could be attained, but cyanosis was often observed without improvement during ECLA for 3 hours. The bypass method was changed from V-V to V-A. Since there was no notable improvement in respiratory function of the premature lung, the second ECLA was withdrawn

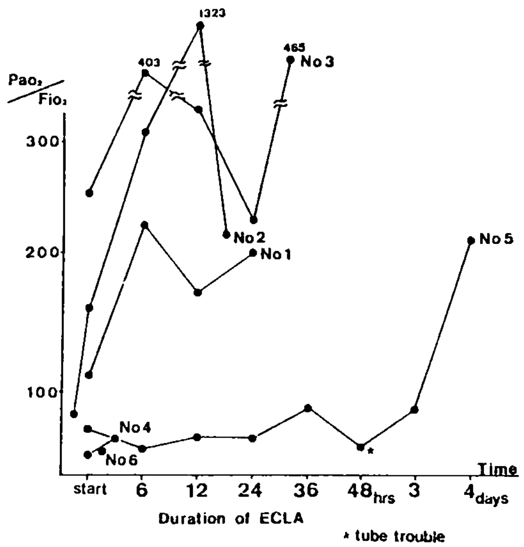

Fig. 2. Effects of the to-and-fro ECLA method on blood gases of premature goats.

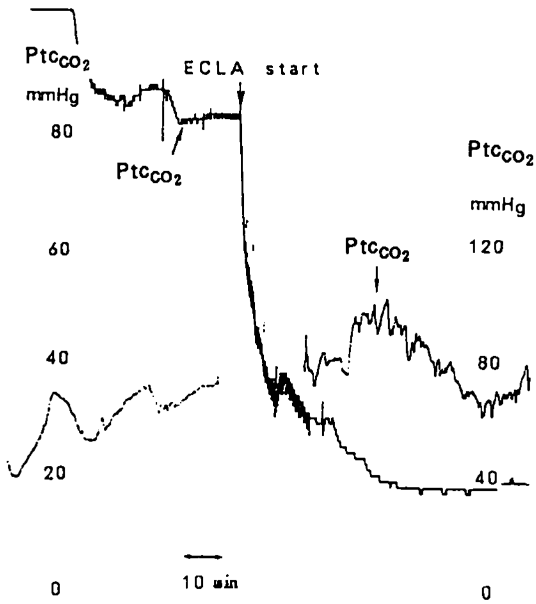

Fig. 3. Changes of $Ptco_2$ and $Ptcco_2$ before and after the start of ECLA. Three days old premature infant weighing 1980 g suffering from pneumothorax and mediastinal emphysema under mechanical pulmonary ventilation.

after 113 hours of life support. The animal died soon after the disconnection from the ECLA.

No.4 and 6 died 2 and 2.5 hours, respectively, after the initiation of ECLA. In spite of enough extracorporeal flow over 100 ml/kg/min, hypoxia lasted during the ECLA course. Oxygen saturation of the drainage blood was sometimes higher than Sa_{O_2} and suggested that a direct withdrawal of infused blood had been occurring. When cardiac arrest occurred in goat No.6, cardiac massage with manual chest compression was continued until the ECLA method was exchanged from the to-and-fro method to a V-A bypass. The lecithin/sphingomyelin ratio in goat No.6 was 1:3 and suggested that the lungs were too immature to live even under any treatment (table 2).

On autopsy, in all but goats No.1 and 4 there was no evidence of trauma due to the catheterization in the right atrium. No perforation had occurred in the cardiovascular system. The tricuspid valve and endocardium of the right ventricle were normal. The lungs of the survivors grossly appeared normal and were well aerated, though one of the lungs of goat No.1 had small bullae in the right middle and lower lobes. Microscopic examination of the survivors' lungs revealed that alveolar septae were still thick with abundant cells, but alveolar expansion was good without cell damage.

The trachea and bronchi of goat No.5 were filled with a jelly-like substance. Micrôscopically, many neutrophils and macrophages were infiltrating into the alveolar spaces and septae, and the lungs seemed not functioning due to severe pneumonia.

The foramen ovare and ductus arteriosus were still patent a few millimeters in diameter in goats No.1, 4, 5 and 6. Gross examination of the lungs in goats No.4 and 6 showed they were apparently normal but air leakage was found. The trachea and bronchi were clear without secretion. On histologic examination, alveoli were poorly developed. They did not have enough air space and some were completely atelectatic.

A portion of the aorta of goat No.6 had been torn, probably due to cardiac massage during resuscitation.

Addendum: a case of clinical application

We applied this treatment to a premature infant that weighed 1980 g and was suffering from severe RDS. During mechanical pulmonary ventilation for respiratory immaturity, the infant developed severe ventilation difficulty due to pneumothorax of the right chest and progressive mediastinal emphysema on the third day after birth. For a life threatening Pa_{CO_2} of 150 mmHg, Pa_{O_2} of 55 mmHg, and pH 6.65 under maximal mechanical ventilation, the to-and-fro V-V bypass ECLA method was applied. Under respiratory support with ECLA, blood gases were improved to within the normal range, and mechanical ventilation could be turned down to the minimum to keep the lung at rest (fig. 3). Pneumothorax and mediastinal emphysema improved within two days, and the patient was weaned from ECLA to conventional respiratory care on the third day.

Discussion

In the 1970's, the outcome of ECMO for ARDS was unsatisfactory in most cases in the United States[15]. Only Bartlett's report on neonatal ECMO published in 1976 was encouraging[1]. However, ECMO is best applied to those processes that produce acute, potentially reversible pulmonary disease, such as respiratory distress syndrome, meconium aspiration syndrome, and to persistent fetal circulation with or without a congenital diaphragmatic hernia recently[9,10,12].

The role of an artificial lung in respiratory care is not only oxygenation. By using ECLA for CO_2 elimination, we should be able to minimize the setting of mechanical ventilation to afford the lung rest to accelerate natural healing. Gattinoni et al. emphasized the significance of CO_2 removal rather than O_2 delivery and proposed a new concept of the LFPPV-$ECCO_2R$ from Italy since the late 1970's[16,17]. A new acronym $ECCO_2R$ has been proposed to replace ECMO. However, we believe that both O_2 delivery and CO_2 removal are equally essential for severely ill patients from respiratory failure. Therefore, we proposed the term "extracorporeal lung assist" ECLA[14,18,19].

The newborn lamb is widely used as a model of neonatal pulmonary failure in pediatric research. The newborn lambs born at a gestational age of 128–130 days have a very high mortality, even under mechanical ventilatory support, from respiratory failure related to surfactant deficiency and collapse of distal airways due to pulmonary immaturity[20,21]. We demonstrated that the premature goats delivered by Cesarian section also have a high mortality rate and could be used as an experimental model of infant respiratory insufficiency[22].

The V-A bypass method has been commonly used for neonatal ECLA in the United States[1–5,8–10]. V-A ECLA can provide circulatory support as well. The right internal jugular vein and the right common carotid artery are cannulated through one operative wound. Brain damage from the ligation of the carotid artery was rare[8]. However, V-A ECLA may not be completely free from neurological complications, such as embolism in the systemic circulation and ill effects due to the reduction of blood supply to the immature lungs.

V-V ECLA has been reported to be valuable for treatment of neonatal pulmonary failure[6,7,9]. V-V ECLA does not decrease pulmonary blood flow. It will not aggravate ventilation/perfusion mismatching in the lung and prevent focal pulmonary alkalosis in underperfused and mechanically hyperventilated areas. Persistent fetal circulation or pulmonary arterial hypertension pertaining to hypoxia may be resolved by a high oxygen saturation of the pulmonary arterial blood. The potentially deleterious effects of ligating the right common carotid artery are eliminated. Particulate and gaseous microemboli, if present, will be filtered and trapped by the pulmonary circulation and cause less serious complications in the vital organs such as the brain and heart. One of the disadvantages of V-V bypass is the inability to support cardiac function.

Other disadvantages of V-V ECLA from the jugular vein to the femoral vein are a longer operation time for two incision sites, infection of the groin wound and persistent leg swelling due to venous stasis. Klein et al.

chose V-V ECLA only for babies larger than 2000 g because of the technical difficulty of cannulation in the groin[7]. With our to-and-fro method the latter disadvantage of V-V ECLA is eliminated. However, to-and-fro V-V ECLA can not be used when the circulatory system is too immature as seen in No.4 and 6. A V-A bypass is indicated on patients with cardiac and respiratory failure.

V-V ECLA requires a significantly higher blood flow than V-A ECLA[6,7,23], as does the to-and-fro bypass method. This is attributable to a withdrawal of once infused oxygenated blood from the right atrium and recirculation in the ECLA circuit. This results in a relatively high oxygen content of the blood before entering the membrane lung, so less oxygen can be added to the blood, and oxygen delivery to the body is decreased. Since the infusion time in the to-and-fro sytem is short, the oxygenated blood must be ejected into the vein and carried away by the blood stream before the venous drainage cycle begins. Though Zwischenberger et al. demonstrated that their single cannula V-V ECMO could provide total respiratory support in puppies[24], normal cardiac output is essential to lessen the recirculation of oxygenated blood.

Intracranial bleeding is a frequent complication in premature infants with respiratory failure. 40.3% of premature infants, under 35 weeks of gestation and which required intensive care, had subependymal or intraventricular hemorrhage[25]. Bartlett et al. reported that the incidence of intracranial bleeding found in patients under ECMO was 38%[4]. The intracranial bleeding occurred mostly in patients who had sustained prolonged acidosis, cardiac arrest, or extreme hypoxia (Po_2 below 20 mmHg) before ECMO was instituted. Despite systemic heparinization the incidence of intracranial hemorrhage was lower in ECMO patients than in the controls[2,4].

However, because of the poor prognosis and quality of life of premature infants with intracranial hemorrhage, they are not considered good candidates for ECLA at present. Heparin bonded ECLA circuits which require little or no systemic heparinization are being developed[32–34]. This will make ECLA simpler and safer.

Our to-and-fro ECLA method has several advantages and may solve many of the problems associated with other types of ECLA. It requires only one operative field, simplifying the surgical technique. It allows the artery to remain intact and will minimize bleeding during ECLA. As the blood is not squeezed directly by a roller pump, hemolysis is minimum.

In using our system, particular attention should be paid to the follwing. If the stroke volume is increased too much, fluctuation of the blood pressure in the pulmonary artery and right ventricle will become extreme and lead to right heart failure. Sawamura et al. has recommended minimizing the pressure change by decreasing the stroke volume and increasing the stroke rate[27]. Our study showed that oxygen delivery by ECLA was 3.9 ± 0.15 ml/kg/min at a bypass flow of 54.5 ± 3.1 ml/kg/min in the survival group. This value was enough for these survivors who had some gas exchange function in their own lungs. In fact, we applied our system to an infant with severe RDS with barotrauma as described at the addendum and saved his life. If we continued conventional ventilator therapy, the infant might have died from severe mediastinal emphysema and asphyxia within several hours. Even such an infant scarcely surviving under extreme conditions of mechanical ventilation has some pulmonary function of his own, and may not need total support of gas exchange.

The to-and-fro V-V bypass ECLA method with a single cannula should become a useful life support for premature infants with respiratory insufficiency until the lung becomes mature, but the minimum necessary bypass rate must be chosen to prevent any possible side effects.

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