Regional Blood Flow Distribution from the Proximal Arterial Cannula during Veno-Arterial Extracorporeal Membrane Oxygenation in Neonatal Dog

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ABSTRACT. Extracorporeal membrane oxygenation (ECMO) is frequently used for treatment of patients with severe hypoxemia due to life-threatening respiratory failure. Due to this hypoxemia, the myocardium of these patients is insufficiently provided with oxygen, and consequently their cardiac function commonly deteriorates. But veno-arterial (V-A) ECMO provides oxygenated blood to the coronary arteries from ECMO circuit insufficiently. To increase the coronary blood flow distributed from ECMO, we placed the arterial cannula 1 cm above the aortic valve and evaluated the regional blood flow from the proximal arterial cannula in comparison with the distal cannula.

Eight neonatal dogs weighting 1.8–2.5 kg were supported by V-A ECMO. The regional blood flow from the arterial cannula was measured by injection of colored microspheres into ECMO circuit. The site of the arterial cannula was changed under fluoroscopy. The bypass flow was maintained at either 50 or 100 ml/min/kg. We found that the coronary blood flow distributed from the proximal arterial cannula was significantly higher than that from the distal cannula. The proximal arterial cannula appears necessary to provide sufficient oxygenated blood to the coronary circulation during V-A ECMO. Therefore, it is expected that the increased cardiac function may improved, and that the survival rate of the patients with retarded cardiac function due to severe hypoxemia may increase by proximal placement of the arterial cannula during V-A ECMO.—KEY WORDS: artificial placenta, colored microsphere, coronary blood flow, extracorporeal membrane oxygenation, neonatal canine.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is frequently used for treatment of life-threatening respiratory failure. Several researchers have developed an “artificial placenta” using ECMO experimentally since the 1960 [1, 9, 11, 12, 15]. In small animal practices, ECMO is scarcely used in veterinary medicine. ECMO is only used in veterinary clinic as a part of the cardio-pulmonary bypass circulation as far as we know.

We demonstrated that the veno-arterial (V-A) ECMO was inadequate for efficient distribution of oxygenated blood into the coronary circulation of the fetal lamb [3]. Kinsella et al. have reported that more than 90% of the coronary blood flow is distributed from the left ventricle during V-A ECMO [5]. Therefore, it seemed difficult for V-A ECMO to distribute oxygenated blood to the coronary arteries. Since the artificial placenta has only one source of oxygen, it is important to provide oxygenated blood to the coronary circulation during V-A ECMO.

Due to the hypoxemia, the myocardium of these patients is insufficiently provided with oxygen, and consequently their cardiac function commonly deteriorates. It is necessary to distribute the oxygen to the myocardium sufficiently. To obtain a sufficient coronary oxygenation from V-A ECMO, the tip of the arterial cannula was placed 1 cm above the aortic valve. We examined the regional blood flow of the heart and other organs during V-A ECMO with proximal placement of the arterial cannula in neonatal dogs using colored microspheres. Simultaneously, we investigated applications for veterinary use.

MATERIALS AND METHODS

Animal: Eight mongrel neonatal dogs within 1 month old were used in this study. Their body weight ranged between 1.8 to 2.5 kg. The animals were subjected to the experiment, after checking their fitness clinically by preoperative examination, including physical examination, clinical laboratory evaluation, and radiography of the thorax. The experiment was carried out in accordance with the Guide for Animal Experimentation, Faculty of Agriculture, Kagoshima University.

Surgical procedure: The dogs fasted for 24 hr before surgery. The animals were anesthetized with 25 mg/kg of pentobarbital sodium intravenously, and intubated with a cuffed endotracheal tube, and ventilated mechanically throughout the experiment. The peak air pressure was set at 12 mmHg, and the respiratory rate was set between 8 and 15 times per minute. Topical 1% lidocain was used as necessary to dilate the vessel and to insert the cannula easily. An incision was made in the neck of each dog, and either a 6F or 7F cannula was inserted into the left jugular vein in a caudal direction until the tip of the cannula was placed in the right atrium. A 6F polyvinyl cannula was inserted into the left femoral vein in a cranial direction until the tip was placed in the vena cava. These two cannulae placed in the jugular and femoral vein were used for withdrawal blood during ECMO. These venous cannulae were connected to each other by a Y-shape connector. Either a 6F or 7F cannula was inserted into the left carotid artery until the tip of the cannula was 3–4 cm above the aortic valve fluoroscopically, and it was used to return blood to the dog.
during ECMO. This site of the cannula 3–4 cm above the aortic valve is used clinically. The arterial cannula was fixed loosely so as to move the tip of the cannula. An incision was made in the chest wall and a 6F polyvinyl cannula was placed into the left atrium via the left auricular appendage for injection of colored microspheres. This cannula was removed after single injection of colored microspheres.

A cannula was placed into the aortic arch for taking a reference blood sample to calculate the coronary blood flow. To measure the cerebral blood flow, a 24-gauge IV cannula was inserted into the right jugular vein caudally preventing cranial blood flow. To measure the blood flow in other organs in the lower body, a reference blood sample was taken via a cannula placed in the abdominal aorta. Three sites were used to take the reference samples.

ECMO circuit (Fig. 1): The extracorporeal circuit was filled with 200 ml of heparinized blood of another dog before the experiment. The dog was connected to the ECMO and blood was withdrawn from the right atrium and caudal vena cava, oxygenated by membrane oxygenator (Mera Silox S 0.5, Mera, Tokyo), and warmed to 38 to 39°C by heat exchanger. The blood was returned to the aorta through the cannula inserted into the left carotid artery.

Microspheres preparation: Nonradioactive colored polystyrene microspheres (E-Z Trac, Interactive Medical Technologies, Los Angeles) were used to measure the regional blood flow [8]. Vials obtained from the manufacture contained approximately $1 \times 10^7$ microspheres per milliliter. The suspension contains thimerosal (0.01%), bacteriostat, and Tween 80 (0.05%) hydrophobic sphere to prevent aggregation. Red, yellow, blue, green, and orange were the selected colors. The amount of injected microspheres into each neonatal dog was 0.2 ml, containing $2 \times 10^6$ microspheres, and it was diluted to 1 ml by saline. Vigorous vortex agitation of the stock vial for 1 min was done immediately before the aliquot was withdrawn. The microspheres were withdrawn into a 1-ml syringe with a 23-gauge needle. The syringe was continuously agitated until injection.

Experimental protocol: The red microspheres were injected via the cannula placed in the left ventricle as control before connecting to ECMO. Each animal was connected to ECMO, and the roller pump was started.

After stabilization of ECMO flow rate at 50 ml/min/kg, the blue microspheres were injected into the cannula of the second bubble trap of ECMO circuit. The yellow microspheres were injected at ECMO flow of 100 ml/min/kg. ECMO was stopped, and the arterial cannula was advanced caudally until the tip of the cannula was located 1 cm above the aortic valve (Fig. 2). After restarting ECMO, the green and orange microspheres were injected at ECMO flow rate of 50 and 100 ml/min/kg, respectively.

Reference samples were simultaneously withdrawn for 70 sec from three sites using a precalibrated syringe pump (Harvard Apparatus, Dover, Mass) set at withdrawal rate of 2.0 ml/min starting 10 sec before microsphere injection. Another blood sample was taken for measurement of pH, PCO₂, and PO₂. The heart rate and aortic blood pressure were measured continuously via the cannula inserted into the femoral artery, which was connected to previously calibrated, sterile pressure transducers (Polygraph 360 system and Rectigraph 8K6174, Sanei Sokki, Tokyo).

After the experiment, the animals were euthanized and autopsy was performed. The heart, brain, liver, kidney, and adrenal gland were removed and weighed. According to the measurement techniques of the colored microspheres, we calculated the regional blood flow [8].

Statistical analysis: All values are expressed as the mean ± SD. The significance of differences among parameters was determined by analysis of variance, and Scheffe’s method was used for simultaneous multiple comparisons. P<0.05 was considered significant.

RESULTS

The coronary blood flow distributed from the left ventricle before starting ECMO was 2.40 ± 0.67 ml/min/g. After starting ECMO, the coronary blood flow distributed from the proximal and distal arterial cannulae at ECMO flow 50 ml/min/kg was 4.65 ± 4.08 ml/min/g, and 1.57 ± 2.08 ml/min/g, respectively (Fig. 3). The differences were significant. The coronary blood flow at 100 ml/min/kg from the proximal and distal arterial cannula were 4.69 ± 3.68 ml/min/g.

Fig. 1. Veno-arterial extracorporeal membrane oxygenation (ECMO). Blood is withdrawn from the right atrium (RA) through two cannulae inserted into the femoral vein and the jugular vein, and is returned into the aorta through cannula inserted into the carotid artery.
An "artificial placenta" using ECMO has been developed since the 1960 [1, 11, 12, 15]. Kuwahara et al. have recently performed an umbilical artery to umbilical vein ECMO in goat fetus [9]. This route is similar to the physiologic circulation in the fetus. However, the bypass blood flow of this route depends on the blood volume coming from the umbilical artery cannula, blood volume coming from the left ventricular output. Since any decrease in the left ventricular output reduces the bypass blood flow during umbilical artery to umbilical vein ECMO, it may be difficult to consistently maintain a sufficient blood flow. In consideration of this demerit, we selected a V-A ECMO. The bypass withdraw from the right atrium, can pool the most quantity of the blood in the body. The V-A bypass may potentially

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\text{Coronary blood flow during before and during ECMO. The coronary blood flow distributed from the left ventricle before starting ECMO (pre-ECMO, \(\bar{\mu}\)). ECMO bypass flow is set at 50 ml/kg/min (\(\bar{\mu}\)) or 100 ml/kg/min (\(\bar{\mu}\)).}
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Values are means ± SD. * P<0.05.

DISCUSSION

An “artificial placenta” using ECMO has been developed since the 1960 [1, 11, 12, 15]. Kuwahara et al. have recently performed an umbilical artery to umbilical vein ECMO in goat fetus [9]. This route is similar to the physiologic circulation in the fetus. However, the bypass blood flow of this route depends on the blood volume coming from the umbilical artery cannula, blood volume coming from the left ventricular output. Since any decrease in the left ventricular output reduces the bypass blood flow during umbilical artery to umbilical vein ECMO, it may be difficult to consistently maintain a sufficient blood flow. In consideration of this demerit, we selected a V-A ECMO. The bypass withdraw from the right atrium, can pool the most quantity of the blood in the body. The V-A bypass may potentially

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\text{Regional blood flow (ml/min/g) distributed from the arterial cannula before and during ECMO}
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<table>
<thead>
<tr>
<th>Organ</th>
<th>Pre-ECMO (N)</th>
<th>50 ml/min/kg</th>
<th>100 ml/min/kg</th>
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</thead>
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<tr>
<td></td>
<td>Distal (N)</td>
<td>Proximal (N)</td>
<td>Distal (N)</td>
</tr>
<tr>
<td>Brain</td>
<td>1.17 ± 0.88 (7)</td>
<td>1.02 ± 0.65 (8)</td>
<td>0.97 ± 1.1 (8)</td>
</tr>
<tr>
<td>Heart</td>
<td>2.39 ± 1.66 (7)</td>
<td>1.57 ± 2.08 (7)</td>
<td>4.65 ± 4.08 (7)</td>
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<tr>
<td>Adrenal grand</td>
<td>4.17 ± 3.30 (7)</td>
<td>3.39 ± 3.08 (7)</td>
<td>7.16 ± 9.23 (7)</td>
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<tr>
<td>Liver</td>
<td>0.76 ± 0.46 (7)</td>
<td>0.63 ± 0.70 (7)</td>
<td>0.88 ± 0.84 (7)</td>
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<tr>
<td>Kidney</td>
<td>2.51 ± 2.33 (6)</td>
<td>2.00 ± 2.41 (6)</td>
<td>0.96 ± 1.03 (6)</td>
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Values represent mean ± standard deviation. No significant difference was noted. a) Numbers of animals. b) Arterial cannula is placed distally. c) Arterial cannula is placed proximally.
withdraw blood independently from the left ventricular output.

Nevertheless V-A bypass provides oxygenated blood to the coronary circulation insufficiently. Many researchers suggested that V-A ECMO could not directly oxygenate the coronary blood [13, 17]. Kinsella et al. demonstrated that approximately 90% of the coronary blood flow was provided from the left ventricle and the remainder of the coronary blood flow was distributed from ECMO [5]. We investigated whether the proximal cannula can provide sufficient oxygenated blood to the coronary artery. We found that the proximal cannula could provide oxygenated blood 3–4 times as the distal cannula did. This indicated that it was possible to provide sufficient oxygenation to the heart. The increase of the distributed blood from ECMO may be attributed to the increase the retrograde flow from the proximal arterial cannula reaching the coronary arteries against the left ventricular output.

The bypass flow is considered to increase the regional blood flow. Seeker-Walker et al. reported that an 85% of the bypass flow was required for a 25%-increase in the oxygenated blood flow to the coronary arteries (% bypass = 100 × bypass flow/bypass flow + left ventricular output) [16]. However, such an 85% bypass is impossible in the living body. If the left ventricular output is 0, 85% bypass is possible. On the other hand, the coronary arterial flow decreased as the bypass flow increased [4]. Two reports showed that was difficult to increase the coronary blood flow distributed directly from ECMO by adjusting the bypass flow. We should find another way to increase the coronary blood flow except changing the bypass flow. In this study, the blood flow at ECMO flow of 50 ml/min/kg did not differ from that at 100 ml/min/kg at both cannula sites. High-flow ECMO reduce cardiac function [6, 19]. The low-flow ECMO may be recommended, if high and low-flow ECMO provide the same blood flow.

Thirty percent of the survivors appear to have some injury in the central nervous system after ECMO [7]. If ECMO itself is the cause, it is thought that ECMO effects the cerebral blood flow. The results of cerebral blood flow measurement during ECMO are not same among the researchers. Santillan et al. and Henriklesen et al. have reported increased cerebral flow during cardiopulmonary bypass [2, 14]. We recently demonstrated that the oxygen tension in the cerebral arterial blood was increased by V-A ECMO in the fetal lambs [3]. However, a decreased in the cerebral blood flow of the rhesus monkey has been reported by Lees et al. [10]. No significant difference was noted in the newborn lambs [18]. Smith et al. indicated two reasons for these different findings [17]. One is the vascular anatomy among the animals used in these experiments. The other is the duration of undergoing ECMO. Long-term ECMO dilates the cerebral vessels by regulatory mechanisms. This study did not solve the problems, but indicated that the proximal cannula did not effect the cerebral flow.

ECMO has been used in experimental animals, however it has scarcely been used in veterinary practice. We
encounter the cases with the pulmonary edema due to congenital heart disease or valvular disease. Oxygen inhalation or ventilation is required in severe cases. If this is not effective, we may consider the application of ECMO for these animals, to support the pulmonary function temporarily until the pulmonary edema can be controlled, because ECMO can provide the oxygen to the blood independently of the pulmonary status. This study demonstrated that ECMO might be of potential use in small animal practice.

Patients undergoing ECMO appear to have severe hypoxemia caused by cardiopulmonary failure. Due to this hypoxemia, the myocardium of these patients is insufficiently provided with oxygen, and consequently their cardiac function commonly deteriorates. The purpose of ECMO is to provide oxygen to the patients and to improve the hypoxemia. It was impossible to provide the oxygenated blood to coronary circulation sufficiently during usual V-A ECMO with distal placement of arterial cannula. Formerly V-A ECMO might be unsuitable for an artificial placenta, because it had only one source of oxygen and could not provide sufficient blood flow to the heart. Nevertheless this study suggested that the proximal arterial cannula could increase the coronary blood flow sufficiently. This study may solved this problem by placing the arterial cannula proximally. Therefore, it is expected that the survival rate of the patients with retarded cardiac function due to severe hypoxemia may increase by proximal placement of the arterial cannula during V-A ECMO.

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REFERENCES