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Original Article

An Experimental Study on Pumpless Extracorporeal Membrane Oxygenation (ECMO) Support in a Canine Model

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This study was carried out to determine whether an extracorporeal membrane oxygenation (ECMO) support could be sufficiently conducted by the right ventricle alone from the viewpoint of the hemodynamics and blood gas state. Six infant dogs underwent a bypass between the left pulmonary artery and left atrium with an in-line oxygenator after a left pneumonectomy. Partial ECMO support was conducted simply by opening the circuit, and total ECMO support was conducted by ligating the right pulmonary artery. After the establishment of partial ECMO, approximately one-third of the right ventricular output was passively shunted through the bypass circuit, and the cardiac index and central venous pressure did not change. The mean pulmonary arterial pressures increased significantly. After a complete ligation of the right pulmonary artery, all 6 dogs survived for 12 h, but the cardiac output and blood pressure decreased significantly. The blood gas state was sufficiently maintained throughout the experiment. The results suggest the possibility of using the pumpless ECMO support. However, the flow resistance of the membrane oxygenator proved to still be too high for use in a total pumpless ECMO. Further studies on long-term ECMO and the development of a membrane oxygenator with a considerably low flow-resistance are needed.

Key words: pumpless ECMO, implantable artificial lung, pulmonary bypass

The only current treatment for end-stage pulmonary diseases is a lung or heart-lung transplantation, with the major limitation of transplantation being a shortage of organ donors [1, 2]. Extracorporeal life support techniques are commonly used today to treat patients with severe respiratory and/or cardiac failure [3]. The device, however, is so large that the patient is unable to carry out his/her normal daily activities. It has been suggested in several reports that a pumpless implantable artificial lung could conceivably be useful not only as a bridge to lung transplantation, but also as a means of pulmonary support for patients with acute respiratory failure [4, 5]. We thought that the limitation of daily activities for such patients could be improved by means of a pumpless implantable artificial lung placed between the right heart and the left heart if a membrane oxygenator can be sufficiently perfused by the native right ventricle (RV) alone with an appropriate gas exchange.

The purpose of the present study was to determine whether an extracorporeal membrane oxygenaton (ECMO) system placed between the left pulmonary artery (PA) and left atrium (LA) of the heart

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could be perfused by RV alone, and also to evaluate the effectiveness of a pumpless ECMO support from the viewpoint of the hemodynamics and blood gas state in an experimental canine model.

Materials and Methods

Artificial lung. A commercially available extracapillary-perfusion membrane oxygenator $9.8 \times 5.4 \times 3.6$ cm in size (MENOX EL2000, Kuraray Co. & Dainippon Ink and Chemicals Inc., Tokyo, Japan) was used in this study. The oxygenator consisted of double-layered polyolefin hollow fibers with a priming volume of 50 ml and a total membrane surface area of 0.4 m^2, having a low flow resistance of 45 mmHg at a maximum blood flow rate of 2.0 l/min (Kuraray Co. Ltd. internal technical manual). The oxygenator was preprimed with heparinized crystalloid fluid (4 U/ml).

Pumpless ECMO circuit. Six infant mongrel dogs, weighing 4.8 to 7.7 kg (mean weight, 6.5 kg), were used in the present study. The animals were initially anesthetized by the intramuscular administration of ketamine hydrochloride (10 mg/kg) and atropine sulfate (0.025 mg/kg), with additional intravenous thiopental sodium (10 mg/kg). The animals were then intubated, paralyzed with pancuronium bromide (2 mg), and placed on a mechanical ventilator (Model 613, Harvard Apparatus, Holliston, MA, USA) at a respiratory rate of 15 bpm and a tidal volume of 20 ml/kg. Anesthesia was maintained with a mixture of 50% oxygen, 50% nitrous oxide, and halothane (0.5%). A femoral arterial line was established to measure

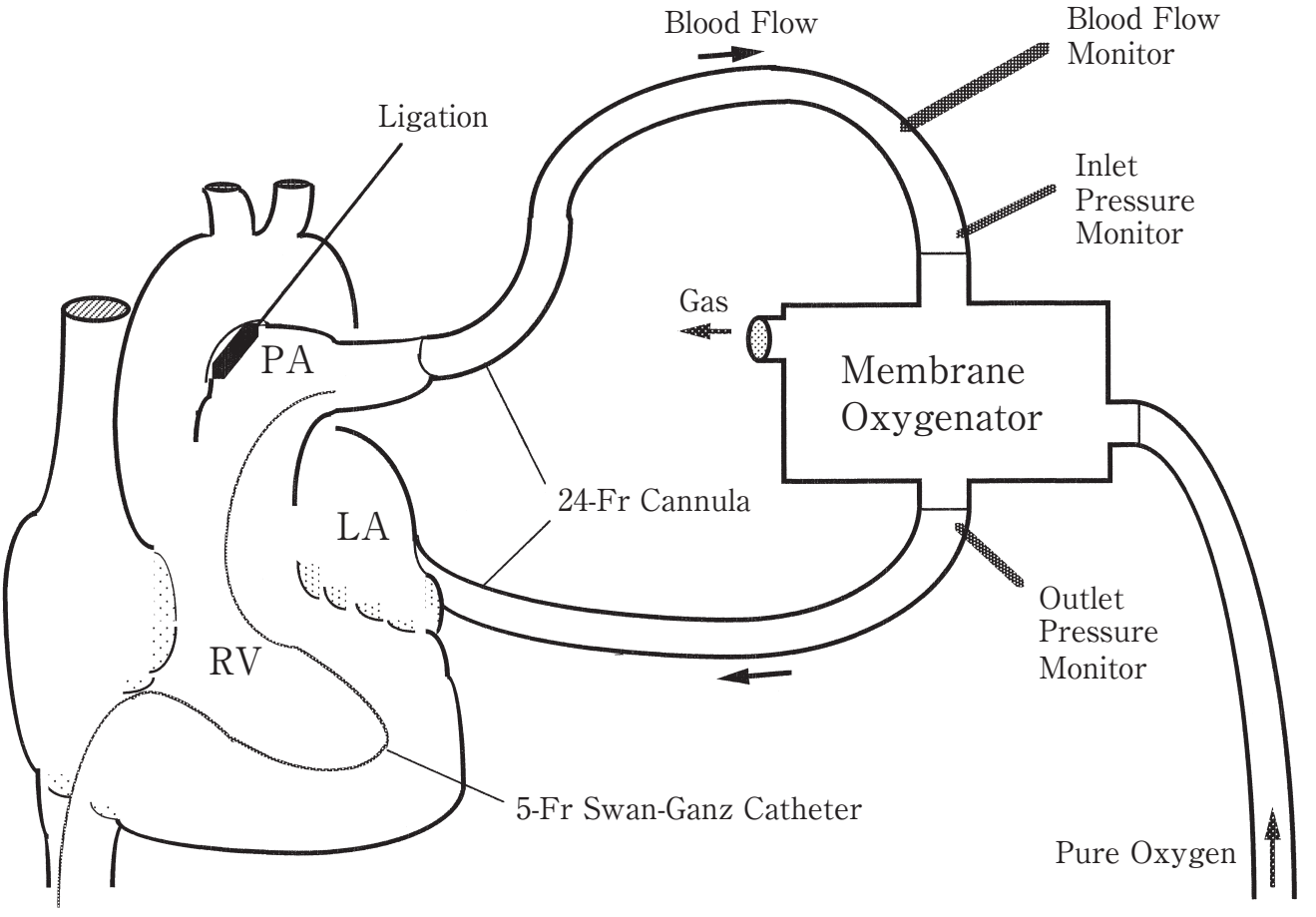

Fig. 1 Schematic illustration of the experimental ECMO circuit. PA, pulmonary artery; LA, left atrium; RV, right ventricle.

the arterial blood pressure and to draw blood samples. A 5-Fr Swan-Ganz thermodilution-cardiac output catheter was also placed from the femoral vein into the PA for measurement of the mean pulmonary arterial pressure (MPAP; mmHg), mean right atrial pressure (MRAP; mmHg), and cardiac output (CO; expressed as CI; l/min/m^2) as well as for drawing venous blood samples.

Left pneumonectomy was performed through a left fourth intercostal thoracotomy. The oxygenator was placed in the bypass circuit between the left PA and LA using two 24-Fr cannulae after the intravenous administration of sodium heparin (200 U/kg) (Fig. 1). Additional heparin was given as necessary to maintain the activated clotting time longer than 400 sec. The animals were supported without any inotropic agents throughout the experiments.

(1). Partial pulmonary bypass using an oxygenator (partial pumpless ECMO support): The partial pumpless ECMO support was commenced by opening the circuit, with the native pulmonary circulation preserved. Anesthesia was changed from a mixture of 50% oxygen, 50% nitrous oxide, and halothane (0.5%) to room air and halothane (0.5%) with the same mechanical ventilation set-up being preserved. Pure oxygen was supplied to the membrane oxygenator with the gas blender at flow rates of 1 to 2 l/min, and the sweep gas outflow port was briefly suctioned to prevent occlusion by condensation. The animals were observed for a duration of 1 h.

(2). Total pulmonary bypass using an oxygenator (total pumpless ECMO support): For the animals undergoing partial ECMO support, the right PA was ligated to divert the right ventricular output to the device, and a total PA-to-LA bypass driven by the RV alone was begun. After ligating the right PA, the gas anesthesia was changed to the intravenous administration of ketamine HCl (7.5 mg/kg/h) and mechanical ventilation was discontinued by removing the endotracheal tube. The incision was closed after 6 h, and the hemodynamics and blood gas state were observed for a period of 12 h. Each animal was euthanized by injecting a lethal dose of pentobarbital (80 mg/kg) intravenously after assessment. A postmortem examination of the lungs in the animals and of the circuit in order to identify any thrombus was performed.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Data acquisition. Hemodynamic changes were studied by the indices of MRAP, MPAP, the mean arterial blood pressure (MABP; mmHg), and CO (CI). The blood pressures as well as inlet and outlet pressures of the oxygenator were measured using a Polygraph 360 (NEC Co., Tokyo, Japan), and CO was measured by the thermodilution method using a Cardiac Output Monitor with a Printer (COM-2P-100, Baxter Healthcare Co., Irvine, CA, USA). A blood gas analysis, expressed as oxygen (O_2), saturation (%) and arterial carbon dioxide tension ($PaCO_2$) with a hemoglobin measurement was carried out using a Blood Gas System™ (Ciba Corning Diagnostic Corp., Medfield, MA, USA). To examine the oxygenator performance, the rate of blood flow through the oxygenator (device blood flow: DBF; ml/min) was measured using an ultrasonic blood flow meter (T201, Transonic System Inc., Ithaca, NY, USA). The flow resistance (mmHg/l/min) of the membrane oxygenator was calculated using these data. To assess the O_2 transfer of the oxygenator, the formula as described by Boonstra *et al.* [6] was used, and the CO_2 transfer was determined from a Van Slyke nomogram [7]. The activated clotting time was measured with a blood coagulation timer (Hemocron™ 400, International Technidyne Co., Edison, NJ, USA). All data were obtained at the following time points: before the bypass operation, at 1 h after the establishment of partial ECMO support, and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after ligation of the right PA.

Statistical analysis. Serial quantitative data were compared by nonparametric one-way repeated measures analysis of variance (ANOVA) to determine the effect of the study group and time. When the p ratio of the ANOVA was significant ($p < 0.05$), the differences between the data at each time and those at baseline were tested by the paired 2-tailed t test. All data in the text, tables, and figures are presented as the means ± the standard deviations.

Results

The pulmonary bypass circuit with an in-line oxygenator was successfully established in the 6

dogs, all of which were available for analysis. After the induction of partial ECMO support, the averaged bypass blood flow through the device and CO were 332 ± 99 ml/min and 1062 ± 266 ml/min; the averaged percentage of the device blood flow rate in CO was $34 \pm 16\%$. The MPAP increased significantly from 16.3 ± 4.7 mmHg before ECMO support to 19.7 ± 6.3 mmHg ($p < 0.05$), while the MRAP did not show significant change (Table 1). The MABP decreased from 100.7 ± 16.0 to 89.5 ± 17.7 mmHg, and the CI slightly decreased from 2.97 ± 0.36 to 2.75 ± 0.74 l/min/m^2; however these changes were not significant. Arterial O_2 saturation and the $PaCO_2$ level did not show any remarkable change.

After the establishment of total pumpless ECMO support there were significant differences (ANOVA) in hemodynamics with respect to the MABP, MPAP, CI, and hemoglobin value. The MABP decreased from 100.7 ± 16.0 mmHg before ECMO to 66.0 ± 13.0 ($p < 0.005$), 62.8 ± 16.9 ($p < 0.05$), 62.8 ± 15.1 mmHg ($p < 0.005$), and 46.0 ± 15.1 mmHg ($p < 0.001$) at 1 h, 4 h, 8 h and 12 h, respectively. The MPAP increased from 16.3 ± 4.7 mmHg before ECMO to 32.8 ± 9.3 ($p < 0.05$), 27.0 ± 7.2 ($p < 0.05$), 26.2 ± 6.0 mmHg ($p < 0.05$), and 22.8 ± 6.7 mmHg (not significant) at 1 h, 4 h, 8 h and 12 h, respectively. The MRAP remained relatively stable but was on an increasing trend. The CI showed a significant decrease from 2.97 ± 0.36 l/min/m^2 before ECMO to 1.65 ± 0.22 l/min/m^2 at 1 h ($p < 0.005$) and to 1.26 ± 0.21 l/min/m^2 at 12 h ($p < 0.001$). The hemoglobin value decreased from 12.0 ± 2.1 g/dl before ECMO to 9.1 ± 3.6 g/dl at 12 h. However, blood gas analysis revealed that the arterial O_2 saturation and $PaCO_2$ levels were sufficiently maintained throughout the experiment, presenting a mean O_2 transfer rate of 42.1 ± 11.2 ml/min and a CO_2 transfer rate of 37.4 ± 11.2 ml/min with a mean blood flow rate of 500 ± 142 ml/min. There were no significant differences (ANOVA) in the O_2 transfer rate, CO_2 transfer rate, and flow resistance data over the duration of the total pumpless ECMO support (Table 2). The average flow resistance of the membrane oxygenator in the total ECMO support was calculated to be 25.2 ± 9.5 mmHg/l/min. Thrombogenesis within the membrane oxygenator was observed in 2 of the 6 cases, and the membrane oxygenator was noted to resister increased mean flow resistance at the maximums of 40.4 mmHg/l/min and 41.7 mmHg/l/min in total ECMO support, respectively. In these cases, the blood flow rates through the device were as low as 250 ml/min and 230 ml/min in partial ECMO support respectively, and both air embolus and macroscopic thrombus were noted inside the membrane oxygenator. No plasma leakage of the oxygenator was observed. A postmortem examination of the lungs in the 6 animals revealed no macroscopic thrombus in the pulmonary vascular system.

Discussion

Two types of implantable artificial lungs have

Table 1 Data from pumpless ECMO support

Variable	Before ECMO (n=6)	Partial ECMO (n=6)	Total ECMO			
			1 h (n=6)	4 h (n=6)	8 h (n=6)	12 h (n=6)
MABP (mmHg)	100.7 ± 16.0	89.5 ± 17.7	66.0 ± 13.0 †	62.8 ± 16.9*	62.8 ± 15.1 †	46.0 ± 15.1††
MPAP (mmHg)	16.3 ± 4.7	19.7 ± 6.3*	32.8 ± 9.3*	27.0 ± 7.2*	26.2 ± 6.0*	22.8 ± 6.7
MRAP (mmHg)	4.0 ± 1.1	5.0 ± 2.3	5.7 ± 1.6	5.5 ± 0.8	6.0 ± 1.3	6.5 ± 2.2
Cadiac Index (l/min/m^2)	2.97 ± 0.36	2.75 ± 0.74	1.65 ± 0.22 †	1.41 ± 0.20††	1.48 ± 0.39 †	1.26 ± 0.21††
Hemoglobin (g/dl)	12.0 ± 2.1	11.7 ± 3.4	12.2 ± 3.3	11.5 ± 3.1	9.7 ± 3.4	9.1 ± 3.6
SaO_2 (%)	99.6 ± 0.2	99.6 ± 0.5	99.8 ± 0.1	99.8 ± 0.2	99.7 ± 0.3	99.7 ± 0.2
$PaCO_2$ (mmHg)	27.7 ± 6.3	2.8 ± 6.2	26.3 ± 9.0	31.2 ± 9.3	33.5 ± 14.1	42.5 ± 20.2

Data are means ± standard deviations. Significance: *$p < 0.05$, **$p < 0.01$, †$p < 0.005$, ††$p < 0.001$ versus each baseline before ECMO. MABP, mean arterial blood pressure: MPAP, mean pulmonary arterial pressure: MRAP, mean roght atrial pressure: SaO_2, arterial oxygen saturation; $PaCO_2$, arterial carbon dioxide tension.

Table 2 Gas exchange performance of the device

Variable	Partial ECMO (n=6)	Total ECMO			
		1 h (n=6)	4 h (n=6)	8 h (n=6)	12 h (n=6)
VO_2 (ml/min)	27.6 ± 7.2	45.5 ± 10.5	42.6 ± 9.0	42.8 ± 10.9	34.1 ± 14.3
VCO_2 (ml/min)	36.7 ± 20.3	42.7 ± 11.2	38.2 ± 14.9	40.7 ± 13.2	36.3 ± 11.4
DBF (ml/min)	332 ± 99	555 ± 81	475 ± 102	491 ± 134	397 ± 87*
DFR (mmHg/l/min)	17.0 ± 12.4	26.8 ± 7.8	26.6 ± 8.7	23.1 ± 11.0	24.1 ± 10.8

Data are means ± standard deviations. Significance: *$p<0.05$, versus baseline 1 h after induction of total ECMO. VO_2, oxygen transfer rate of the membrane oxygenator; VCO_2, carbon dioxide transfer rate of the membrane oxygenator; DBF, device blood flow; DFR, device flow resistance.

been developed, an intravenous membrane oxygenator type and an intrathoracic artificial lung type [5, 8]. The pumpless ECMO system used in the present study was one of the latter types, which has the advantage of sufficient gas exchange. Patients would have no limitation of daily activities if an intrathoracic implantable artificial lung could be clinically used in the future. However, this type has shortcomings, in that a thoracotomy is a necessity and bleeding due to heparinization can occur. In cases with a functional disorder such as a decline in the gas exchange performance, thrombogenesis, and air thrombus in the device, it would be better to keep the artificial lung out of the pleural cavity rather than to implant the whole device into the pleural cavity, so as to be able to immediately exchange a malfunctioning artificial lung. Thus, the artificial lung was positioned paracorporeally in the present experiment.

Regarding the experimental preparations, cannulation was used for blood access in the canine model because we had observed gradual bleeding at the anastomotic sites between the left PA and expanded polytetrafluoroethylene graft in our preliminary study. The membrane oxygenator used in the present study was MENOX™ EL2000, and its expected pressure drop at a flow rate of 1 l/min, which was considered to correspond to a cardiac index of more than 2 l/min/m^2 for such small animals, was calculated to be about 24 mmHg (Kuraray Co. Ltd. internal technical manual). Therefore, we thought that the RV with a MPAP higher than 24 mmHg could perfuse the membrane oxygenator without causing the development of a low cardiac output syndrome.

After induction of a partial bypass, approximately one-third of the RV output was passively shunted through the bypass circuit, and the MPAP increased significantly. However, marked cardiac dysfunction resulting from increased afterload was not observed. The MABP, MRAP, and cardiac index did not show significant change, and the gas exchange was sufficient for the body.

The animals were able to tolerate the acute excessive pressure overload by ligation of the right PA. The membrane oxygenator was able to supply O_2 and CO_2 at average gas transfer rates greater than 30 ml/min with a small membrane surface area of 0.4 m^2 during the bypass and provided sufficient gas exchange for the body. These results are similar to those reported by Cook *et al.* [9] and Vaslef *et al.* [10] for their prototypes of implantable artificial lungs. After ligation of the right PA, the animals sustained with stable blood gas data, but cardiac failure persisted during the duration of total ECMO support. Although we hypothesized that the RV pressure would help to drive the artificial lung without causing low output syndrome by means of a bypass from the PA to LA with an in-line membrane oxygenator, the animals showed remarkable impairment in cardiac function in response to the total pumpless ECMO. These results suggest that the flow resistance of the membrane oxygenator was still too high for use in a total pumpless ECMO. A reduction in the resistance of an artificial lung is necessary to obtain a high enough device blood flow rate without impairing cardiac function, while the flow resistance is reported to be high in current

membrane oxygenators as well as in our device [11, 12]. There have been several reports on development of low pressure-loss implantable artificial lungs in which the values of resistance were 3.5 mmHg/l/min and 2.5 mmHg/l/min [9, 13]. It is expected that a low pressure-loss implantable artificial lung, such as a device with a reduction in the hollow-fiber density, will be developed and become commercially available for use in total ECMO bypass surgery in the near future. However, clot formation and bubbling in the membrane oxygenator was observed in 2 of the 6 cases, in which the flow resistance increased remarkably. However, the hemoglobin values showed a decreasing trend. It is impossible to overlook the problem of bleeding due to heparinization for long-term survival. Determination of the optimum dose of heparin, means of anticoagulation, and regulation of sweep gas flow seem to be necessary for preventing bleeding or clot formation.

From a clinical point of view, diversion of the whole RV output to the device might have some shortcomings in the long term because a malfunctioning artificial lung could be more easily changed with a partial bypass than with a total bypass. Furthermore, lung function not only involves gas exchange but is also associated with immunity, neuropeptide activity, and drug metabolism [14–16]. Accordingly, a partial bypass is thought to function better physiologically than a total bypass. Further investigation is needed to determine the effects of a long-term bypass for a period of weeks or months.

Although the effects of a long-term bypass need to be investigated, the results suggest the possibility of a pumpless partial ECMO support between the PA and LA with a membrane oxygenator. Low pressure-loss implantable artificial lungs, which enable placement of the device in the body, are currently being developed [17, 18]. Further studies on the applicability of a pumpless implantable ECMO device should be conducted to determine whether a pumpless ECMO between the right heart and left heart is an effective treatment modality or can be used as a bridge to lung transplantation in patients with end-stage pulmonary diseases.

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References

1. Rich S: Medical treatment of primary pulmonary hypertension. A bridge to transplantation? Am J Cardiol (1995) 75: 63A-66A.
2. Cooper JD: Herbert Sloan Lecture, Lung transplantation. Ann Thorac Surg (1989) 47: 28–44.
3. Ichiba S and Bartlett RH: Current status of extracorporeal membrane oxygenation for severe respiratory failure. Artif Organs (1996) 20: 120–123.
4. Bodell BR, Head JM, Head LR and Formolo AJ: An implantable artificial lung. JAMA (1965) 191: 125–128.
5. Mortensen JD: Afterword: Bottom-line status report: Can current trends in membrane gas transfer technology lead to an implantable intrathoracic artificial lung? Artif Organs (1994) 18: 864–869.
6. Boonstra PW, Akkerman CW, Tigchelaar I, Gu YJ, Huyzen R and Eijgelaar A: Heparin surface treatment does not impair gas and heat transfer of an extracorporeal circuit. Perfusion (1992) 7: 109–114.
7. Van Slyke DD and Sendroy JJr: Line charts for graphic calculations by the Henderson-Hasselbalch equation and for calculating plasma carbon dioxide content from whole blood content. J Biol Chem (1928) 79: 781–798.
8. Macha M, Federspiel WJ, Lund LW, Sawzik PJ, Litwak P, Walters FR, Reader GD, Borovetz HS and Hattler BG: Acute in vivo studies of the Pittsburgh intravenous membrane oxygenator. ASAIO J (1996) 42: 609–615.
9. Cook KE, Makarewicz AJ, Backer CL, Mockros LF, Przybylo HJ, Crawford SE, Hernandes JM, Leonard RJ and Mavroudis C: Testing of an intrathoracic artificial lung in a pig model. ASAIO J (1996) 42: M604–609.
10. Vaslef SN, Cook KE, Leonard RJ, Mockros LF and Anderson RW: Design and evaluation of a new, low pressure-loss, implantable artificial lung. ASAIO J (1994) 40: 522–526.
11. Kawaharada N, Umami T, Tanaka H, Nakakura H, Ajiki H and Komatsu S: Clinical evaluation of extracapillary blood flow type hollow fiber membrane oxygenators, "MENOX(AL-2000)", "MINIMAX" in comparison with "CAPIOX-II20". Jpn J Artif Organs (1993) 22: 974–978 (in Japanese).
12. De Vroege R, Wagemakers M, Te Velthuis H, Bulder E, Paulus R, Huybregts R, Wildevuur W, Eijsman L, Van Oeveren W and Wildevuur C: Comparison of three commercially available hollow fiber oxygenators: Gas transfer performance and biocompatibility. ASAIO J (2001) 47: 37–44.
13. Fazzalari FL, Montoya JP, Bonnell MR, Bliss DW, Hirschl RB and Bartlett RH: The development of an implantable artificial lung. ASAIO J (1994) 40: 728–731.
14. Wright JR: Immunomodulatory functions of surfactant. Physiol Rev (1997) 77: 931–962.
15. Kitamura S: Lung and neuropeptides. Jpn Kokyu To Junkan (1989) 37: 477–482 (in Japanese).
16. Lundberg JM, Alving K and Matran R: Pulmonary physiology and pharmacology of neuropeptides. Ann N Y Acad Sci (1991) 629: 332–339.
17. Zwischenger JB, Anderson CM, Cook KE, Lick SD, Mockros LF and Bartlett RH: Development of an implantable artificial lung: challenges and progress. ASAIO J (2001) 47: 316–320.
18. Sato H, Taga I, Kinoshita T, Funakubo A, Ichiba S and Shimizu N: In vitro evaluation of a newly developed implantable artificial lung. Acta Med Okayama (2006) 60: 113–119.