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Investigation of the biological effects of artificial perfusion using rat extracorporeal circulation model

Yutaka Fujii, Mikiyasu Shirai, Shuji Inamori, Yoshiaki Takewa and Eisuke Tatsumi

Abstract— **Extracorporeal circulation (ECC) is indispensable for cardiac surgery. Since difficulty in clinical research keeps the knowledge insufficient, it is desirable to have a miniature ECC system for small animals. We aimed to establish a miniature ECC system and apply the system to the rat for investigating biochemical changes. The ECC system consisted of a membranous oxygenator (polypropylene, 0.03 m^2), tubing line (polyvinyl chloride) and roller pump. Priming volume of this system is only 15 ml. Rats were divided into the SHAM group and the ECC group. ECC pump flow was initiated and maintained at 70 ml/kg/min. We measured the serum cytokine levels of tumor necrosis factor-α, interleukin (IL)-6, and IL-10, and biochemical markers (lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase) before, 60, and 120 min after the initiation of ECC. In addition, we measured the wet-to-dry weight (W/D) ratio of the left lung tissues. During ECC, blood pressure and Hb were maintained around 80 mmHg and 10g/dl, the serum cytokine levels and biochemical markers were significantly elevated in the ECC group compared with the SHAM group. The W/D ratio increased significantly more in the ECC group compared with that in the SHAM group. These data suggest that ECC promotes organ damages and systemic inflammatory response. This rat ECC model is considered to be equivalent to the already established human ECC and useful for studying the mechanism of pathophysiological changes during artificial perfusion.**

I. Introduction

Extracorporeal circulation (ECC) is indispensable for cardiac surgery [1]. Despite the fact that ECC is traumatic to blood components and non-physiologic, its influence has not been fully elucidated. Since difficulty in clinical research and animal experiments keeps the knowledge insufficient, it is desirable to have a miniature ECC system for small animals to study the mechanism of pathophysiological changes in the circulation during ECC. Therefore, in this study, we measured the serum cytokine levels of tumor necrosis factor-α, interleukin (IL)-6, and IL-10, and biochemical markers (lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase) before, 60, and 120 min after the initiation of CPB. In addition, we measured the wet-to-dry weight (W/D) ratio of the left lung tissues.

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II. Materials and Methods

A. Animal

The study was approved by the National Cerebral and Cardiovascular Center Research Institute Animal Care and Use Committee, and all procedures met the National Institutes of Health guidelines for animal care.

Sprague-Dawley rats (male 400-450 g) were housed three per cage under a 12-h light-dark cycle with food and water available ad libitum.

B. Anesthesia, surgical preparation, and ECC

The animals were anesthetized with pentobarbital spdium (50 mg/kg body weight, intraperitoneal injection) and placed in the supine position with rectal thermocouple in place. Then, orotracheal intubation was performed using a 14G cannula (Insyte BD Medical, Sandy, UT, USA) and rats were ventilated with a respirator (Model SN-480-7, Shinano Seisakusho Co., Ltd, Tokyo, Japan). Ventilation was volume controlled at a frequency of 70/min, a tidal volume of 8-10 mL/kg body weight, and 40 % of inspired oxygen fraction. Rectal temperature was maintained at 36 ℃ throughout the experiment. Arterial blood pressure was monitored (Model 870, PowerLab system, AD Instruments, Castle Hill, NSW, Australia) via the femoral artery, which was cannulated with polyethylene tubing (SP-31 Natsume Seisakusho Co., Ltd, Tokyo, Japan). The left common carotid artery with a polyethylene tubing (SP-55 Natsume Seisakusho Co.) to serve as the arterial inflow cannula for the ECC circuit. 500 IU/kg heparin sodium was administered after placement of this cannula. A 16 G cannula (Insyte BD Medical) was advanced through the right external jugular vein into the right atrium and served as a conduit for venous outflow .

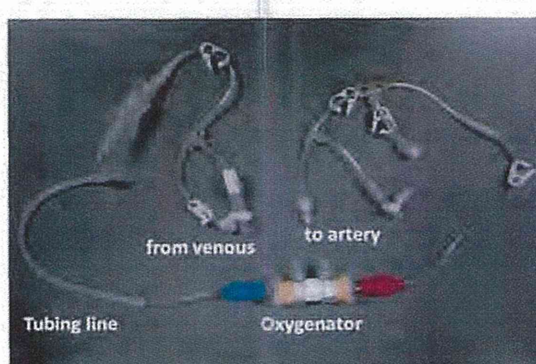

Figure 1. The small animal ECC system.

The ECC circuit consisted of a membranous oxygenator (Senko Medical Co., Ltd, Osaka, Japan), tubing line (Senko Medical Co., Ltd) and roller pump (Micro tube pump MP-3 Tokyo Rikakikai Co., Ltd, Tokyo, Japan). The ECC circuit was primed by 14 ml of Ringer's solution bicarbonate and 1 ml (1000 IU) of heparin, total priming volume was 15 ml (Fig.1). Figure 2 shows the small animal ECC model schema.

C. Experimental design

The animals were divided into two groups: SHAM group (n=5), ECC group (n=7). The SHAM group received surgical preparation only without ECC. ECC pump flow was initiated and maintained at 70 mL/kg/min. Arterial pressure of carbon dioxide (PaO_2) and arterial pressure of oxygen (PaO_2) were maintained at 35-45 mmHg and 300-400 mmHg, respectively. Blood samples were collected at three defined time points, before ECC (pre-ECC), 60 min after initiation of ECC and 120 min after initiation of ECC (end-ECC).

To evaluate the inflammatory responses, TNF-α, IL-6, and IL-10 were measured (ELISA kit, R&D Systems, Minneapolis, MN, USA). The biochemical markers for evaluating organ damage (17), LDH, AST, and ALT were measured (DRI-CHEM 7000, Fujifilm, Kanagawa, Japan). Blood gases, pH, hemoglobin concentration, and electrolytes were also measured. Animals in which the hemoglobin level declined to less than 7 g/dL at any point were excluded from the study. All animals were sacrificed at the end of ECC by myocardial potassium injection and the left lung was harvested and divided into three parts. The superior third was used for the calculation of W/D ratio. The lung block was weighed before and after desiccation for 72 h in a drying oven at 70°C.

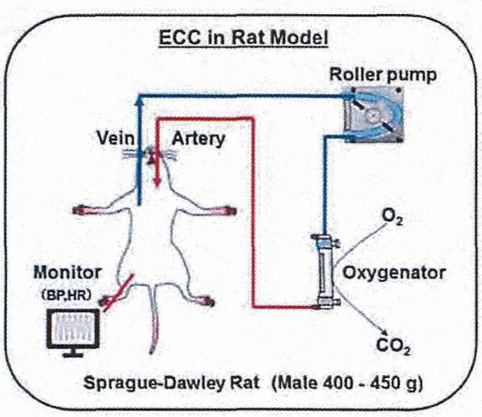

Figure 2. The small animal ECC model schema.

D. Statistics

All data are expressed as mean ± standard deviation. Comparison among groups was performed using analysis of variance. Fisher Protected Least Significant Difference post hoc test was used for subsequent comparison between groups at the same time. All statistical analyses were performed using Stat-View 5.0 (Abacus Concepts, Berkeley, CA, USA). Significance was set at $P < 0.05$.

III. Results

Table I shows the changes in hemodynamic variables, Hb concentration and PaO_2 and $PaCO_2$ in SHAM and ECC groups during experiments. Mean arterial pressure (MAP) and Hb were significantly decreased during experiment in ECC groups.

TABLE I. HEMODYNAMIC VARIABLES, HB AND BLOOD GAS PARTIAL PRESSURES BEFORE AND DURING ECC

	Group	Pre-ECC	ECC 60 min	ECC 120 min
MAP (mmHg)	SHAM	103 ± 3	100 ± 5	104 ± 3
	ECC	105 ± 5	80 ± 3 †	76 ± 3 †
HR (beat/min)	SHAM	385 ± 15	385 ± 11	381 ± 7
	ECC	406 ± 9	358 ± 8	363 ± 8
PaO2 (mmHg)	SHAM	113 ± 8	106 ± 7	105 ± 6
	ECC	103 ± 8	464 ± 17 †	461 ± 16 †
PaCO2 (mmHg)	SHAM	38 ± 1	37 ± 1	40 ± 1
	ECC	40 ± 1	37 ± 1	36 ± 1
Hb (mg/dL)	SHAM	15.3 ± 1.0	15.2 ± 0.5	14.5 ± 0.4
	ECC	15.4 ± 0.2	10.1 ± 0.5 †	9.8 ± 0.4 †

Variables are expressed by mean ± standard error.
† $P < 0.05$ versus SHAM group at the same time.

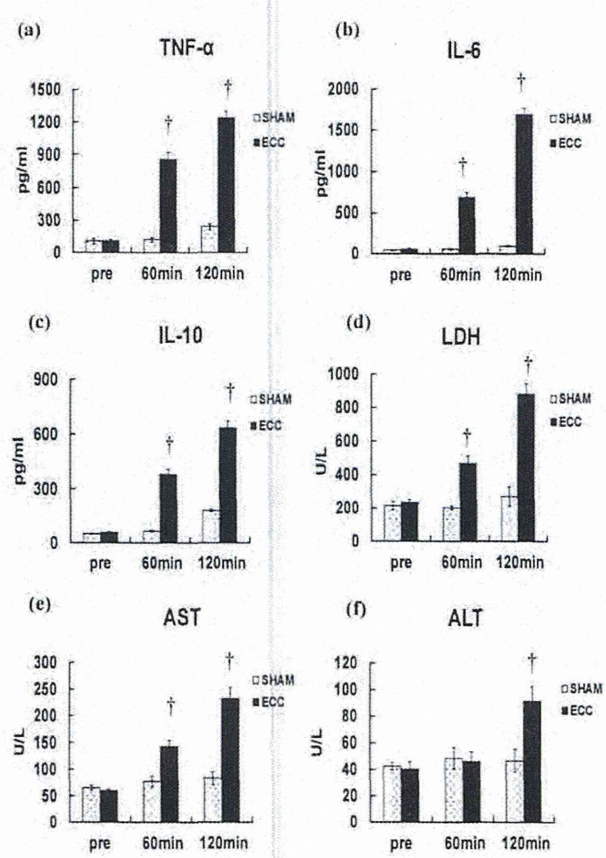

Figure 3. Serum TNF-α (a), IL-6 (b), IL-10 (c), LDH (d), AST (e), ALT(f).
† $P < 0.05$versus SHAM group at the same time periods.

The PaO2 level was much higher in the ECC group (~460 mmHg) than in the SHAM group (~130 mmHg), while no statistical difference was found in the PaCO2 level between these groups.

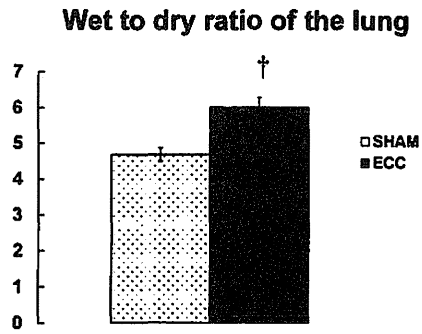

Figure 4. Wet to dry ratio of left lung at the end of ECC.
† P < 0.05versus SHAM group

Before ECC, the serum levels of inflammatory and biochemical markers were not statistically different among the SHAM and ECC groups. Serum inflammatory and biochemical markers remained unchanged during experiment periods in the SHAM group. In the ECC group, the cytokines and increased significantly, reaching a maximum (TNF-α : 1237 ± 62 pg/ml , IL-6 : 1695 ± 73 pg/ml, IL-10: 632 ± 40 pg/ml) at the end of ECC (Fig. 3a-c)

In the ECC group, the levels of biochemical markers significantly increased (LDH : 447±48 U/L, AST : 143±12 U/L, ALT : 46±7 U/L) 60 min after the ECC initiation and increased further (LDH : 882±62 U/L, AST : 233±20 U/L, ALT : 92±11 U/L) 120 min after the ECC initiation (Fig. 3d-e).

The ECC groups showed significantly higher W/D ratio than the SHAM group. (SHAM group : 4.68±0.08, ECC group : 6.01±0.10) (Fig.4).

IV. Discussion

In this study, our small animal ECC system was able to maintain adequate levels of blood gases ($PaCO_2$:35-45 mmHg, PaO_2: 300-400 mmHg), Hb (around the 10 g/dl level) and blood pressure (Mean arterial pressure more than 70 mmHg). Previous models have required high priming volumes to achieve acceptable hematocrit concentrations during the experiment. On the other hand, our model offers the advantage of a low priming volume not requiring transfusion in ECC group rats. Most previous research was performed in isolated heart models (e.g., Langendorff's method) [2]. By using our small animal ECC model, due to its minimal invasiveness and ease of recoverability, short- and long-term effects of ECC time, temperature (hypothermic condition), blood contact surface area and potentially also direct gene transfer on myocardial function and histological outcomes can be assessed better than in isolated heart models. While these models allow investigating the immediate effects of therapeutic interventions or different cardioplegia solutions, they preclude the assessment of long-term histological, biochemical, or functional outcomes. Survival studies using dogs or pigs [3,4] have been performed but are limited due to sample size and costs.

The present data showed that during the serum cytokine levels (TNF-α, IL-6 and IL-10) and biochemical markers (LDH, ALT, AST) were significantly elevated in the ECC group compared with the SHAM group, indicating that organ damage and a systemic inflammatory response occurred in our rat ECC model. During ECC, blood pressure and Hb were maintained around 80 mmHg and 10 g/dl, respectively. From these data, our rat ECC model is considered to be equivalent to the established human ECC, which is often associated with systemic inflammation and organ damage [5-7].

The significant systemic inflammatory responses occurred, reaching a maximum at the end of ECC. Additionally, the biochemical markers reflecting organ damages significantly increased 60 min after the ECC initiation and increased further 120 min after the ECC initiation. The significant increase in the W/D ratio which suggests pulmonary edema [8] is consistent with the previous clinical data [9]. From these data, our rat ECC model is considered to be equivalent to the established human ECC, which is often associated with systemic inflammation and organ damage [10].

It has been suggested that the factors responsible for the inflammatory response during ECC are blood contact with the surface of the extracorporeal circulation unit, endotoxemia, surgical trauma, ischemic reperfusion injury, and blood loss [11]. Many studies showed the walls of the ECC circuit activate white cells, platelets and the complement system. The increase in cytokines, such as interleukins and necrosis factor [12], aggravates the inflammatory response [13]. These complex interactions during ECC lead to further inflammation [13]. In our rat ECC models, the insufflation of hydrogen which selectively reduces the hydroxyl radical could decrease the levels of serum cytokines and biochemical markers, and the W/D ratio of the lung, suggesting that this radical contributes toward promoting the systemic inflammatory responses and organ damages during ECC [8].

Our previous study showed the selective reduction of hydroxyl radical with hydrogen gas attenuates both pro- and anti-inflammatory cytokines, suggesting that this radical acts to non-selectively increase these cytokines [8]. In addition, our new finding is that this increase in the W/D ratio was attenuated with hydrogen gas insufflation. Because ECC increases pulmonary vascular permeability, it is possible that hydrogen gas insufflation attenuates the injury of pulmonary vascular endothelium by scavenging reactive oxygen species and reducing the increase in vascular permeability during ECC. Although the detailed mechanism of the abovementioned anti-inflammatory effects of hydrogen gas insufflation was not elucidated in the previous study[8], this treatment may potentially serve as a novel clinical intervention in reducing the ECC-induced systemic inflammation. Solution of the inflammation mechanism during ECC require future research.

We have to study of due to its minimal invasiveness and ease of recoverability, short- and long-term effects of ECC time, temperature (hypothermic condition), blood contact surface area and potentially also direct gene transfer on myocardial function and histological outcomes. In addition, the model allows for the investigation of unique animal strains with varying susceptibility to myocardial injury depending on either their genetic background or disease (e.g., diabetes, old age, hypertension).

There are some limitations to this current model. Although our model closely resembles current clinical standards with respect to the ECC circuit, a number of potentially important differences to the clinical setting are present. Median sternotomy, direct surgery on the heart involving aortic cross-clamping, and cardiac arrest with the use of cardioplegia were not performed. Similarly, the absence of significant atheromatous disease and the complex comorbidities seen in patients undergoing coronary artery bypass graft surgery are limitations.

V. Conclusion

In this study, we developed a miniature ECC model and applied the system to the rat. In our rat ECC models, we demonstrated that adequate levels of blood gases and Hb, and blood pressure were maintained and that the systemic inflammatory response and organ damages including pulmonary edema were induced associated with the production of cytokines. We considered that our rat ECC model is equivalent to the established human ECC, which is often associated with systemic inflammation and organ damage. This miniature ECC model could be a very useful approach for studying the mechanism of pathophysiology during ECC and basic assessment of the ECC devices.

Acknowledgment

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Application of a Search Algorithm Using Stochastic Behaviors to Autonomous Control of a Ventricular Assist Device

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Abstract— **A ventricular assist device (VAD) is a device with mechanical pumps implanted adjacent to the patient's native heart to support the blood flow. Mechanical circulatory support using VADs has been an essential therapeutic tool for patients with severe heart failure waiting for a heart transplant in clinical site. Adaptive control of VADs that automatically adjust the pump output with changes in a patient state is one of the important approaches for enhanced therapeutic efficacy, prevention of complications and quality of life improvement. However adaptively controlling a VAD in the realistic situation would be difficult because it is necessary to model the whole including the VAD and the cardiovascular dynamics. To solve this problem, we propose an application of attractor selection algorithm using stochastic behavior to a VAD control system. In this study, we sought to investigate whether this proposed method can be used to adaptively control of a VAD in the simple case of a continuous flow VAD. The flow rate control algorithm was constructed on the basis of a stochastically searching algorithm as one example of application. The validity of the constructed control algorithm was examined in a mock circuit. As a result, in response to a low-flow state with the different causes, the flow rate of the pump reached a target value with self adaptive behavior without designing the detailed control rule based on the experience or the model of the control target.**

I. INTRODUCTION

A Ventricular Assist Device (VAD) is a device with mechanical pumps implanted adjacent to the patient's native heart to provide circulatory support (a left ventricular assist device, for example, pumps blood from the left ventricle to the aorta to assist blood flowing). Advanced hardware technology has enhanced the reliability of VAD long-term use, such as clinical application of implantable continuous flow VADs [1]. Accordingly, mechanical circulatory support using VADs has been an essential therapeutic tool for patients with severe heart failure waiting for a heart transplant [2]. On the other hand, considering about new treatment to recover cardiac function including destination therapy (DT) [3] or combination with myocardial regeneration therapy [4], there are many issues to solve, such as further device miniaturization, durability and antithrombogenicity improvements, circulation-control abnormality regardless of the improved treatment effects and stable blood flow, and various complications. To solve these issues, advanced software functionality such as VAD drive control may be equally important as hardware improvements. Many researchers have conducted studies on bypass flow control using cardiovascular mathematical models as well as continuous flow VAD optimization such as development of a function to change rotation speed via synchronization with the patient's heart rate [5-8]. Variations in rotation speed are expected to produce clinical effects including cardiac function recovery and complication prevention. Some devices have been already equipped with control functions to prevent outflow sucking and maintain bypass blood flow. At clinical sites, however, devices are usually used in a fixed rate or rotation number. Major reasons that the VAD automatic control functions are not used in practice are because of the difficulties in long-term stable measurement of biological information and modeling of complex circulatory systems controlled by the autonomic nerve or humoral factors. An algorithmic error consequent to an unexpected complex circulation behavior may cause dangerous device operation. These problems are likely to be solved when VADs are equipped with flexibly adaptive control like human body.

A recent physiological study has demonstrated that searching behaviors based on noise (or fluctuations) including muscle molecular level movement and heart rate variability play an important role in human adaptability [9-13]. Moreover, some researchers attempted to apply this mechanism to artificial object control such as robots or communication systems [14-17]. The objective of the present study was to realize ventricular assist devices which flexibly can response to unexpected changes. The mechanism of human adaptive behaviors was used to enable VADs to deal with the situations in which accurate modeling was considered difficult. Furthermore, this study was conducted to propose the application of a searching algorithm to VAD control using stochastic behaviors and to verify the beneficial effects on VAD control by this method according to the results of flow control. As the first step to investigate the benefits of this proposed method, continuous flow pumps, simple systems, were used to perform mock circulation tests.

II. MATERIALS AND METHODS

A. Control Algorithm

Kashiwagi et al. proposed formula (1) called "attractor selection model" as a mathematical model to explain human sensing behaviors using noise [9].

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