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Effect of the Pulsatile Extracorporeal Membrane Oxygenation on Hemodynamic Energy and Systemic Microcirculation in a Piglet Model of Acute Cardiac Failure

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Abstract

Objective: The objective of this study was to compare the effects of pulsatile and non-pulsatile extracorporeal membrane oxygenation (ECMO) on hemodynamic energy and systemic microcirculation in an acute cardiac failure model in piglets.

Methods: Fourteen piglets with a mean body weight of 6.08 ± 0.86 kg were divided into pulsatile (n = 7) and non-pulsatile (n = 7) ECMO groups. The experimental ECMO circuit consisted of a centrifugal pump, a membrane oxygenator, and a pneumatic pulsatile flow generator system developed in-house. Non-pulsatile ECMO was initiated at a flow rate of 140 mL/kg/min for the first 30 min with normal heart beating, with rectal temperature maintained at 36°C. Ventricular fibrillation was then induced with a 3.5 V alternating current to generate a cardiac dysfunction model. Using this model, we collected the data on pulsatile and non-pulsatile groups. The piglets were weaned off ECMO at the end of the experiment (180 min after ECMO was initiated). The animals did not receive blood transfusions, inotropic drugs, or vasoactive drugs. Blood samples were collected to measure hemoglobin, methemoglobin, blood gases, electrolytes, and lactic acid levels. Hemodynamic energy was calculated using the Shepard's energy equivalent pressure. Near-infrared spectroscopy was used to monitor brain and kidney perfusion.

Results: The pulsatile ECMO group had a higher atrial pressure (systolic and mean), and significantly higher regional saturation at the brain level, than the non-pulsatile group (for both, $p < 0.05$). Additionally, the pulsatile ECMO group had higher methemoglobin levels within the normal range than the non-pulsatile group.

Conclusions: Our study demonstrated that pulsatile ECMO produces significantly higher hemodynamic energy and improves systemic microcirculation, compared to non-pulsatile ECMO in acute cardiac failure.

Introduction:

Mechanical circulatory support systems have successfully improved clinical outcomes in patients with cardiac and respiratory dysfunctions (1). Extracorporeal membrane oxygenation (ECMO) is widely used for respiratory and circulatory support, especially in critical cases such as acute cardiac dysfunction, cardiac resuscitation, and acute respiratory distress syndrome (2 - 4). Previously, the gold standard of the ECMO circuit consisted of a membrane oxygenator and roller pump (5). Currently, the gold standard consists of a polymethylpentene (PMP) membrane oxygenator and centrifugal pump, more commonly referred to as ECMO 2 (4, 6). The current ECMO pump, which is mainly a non-pulsatile centrifugal pump, is smaller and non-occlusive, has a lower priming volume, and is operational at lower membrane oxygenator inlet pressures, thus reducing blood cell damage (7). However, its disadvantage is that peripheral tissue perfusion is low and a higher pump flow output of 20%-30% is thus required to match the bioavailability of a pulsatile pump (8). Additionally, tissue oxygenation and exchangeability in the membrane oxygenator are less effective compare with a pulsatile pump (8). Only a few centrifugal pumps can generate pulsatile flow; however, lower pulsatility and back-flow issues, obstruct the development of centrifugal pumps for pulsatile use in clinical practice (4, 9, 10).

Recently, the novel i-cor system (Xenios AG, Heilbronn, Germany) introduced in the USA, uses a diagonal pump and is the first extracorporeal life support (ECLS) system that is able to deliver electrocardiogram triggered pulsatile diastolic augmentation in the descending aorta for adult patients (11). An in -vivo study clearly demonstrated better renal function and systemic vascular tone in the pulsatile group than in the non-pulsatile group (11).

The theoretical advantages of pulsatile flow during acute and chronic mechanical circulatory support have also been well established (12). Under identical flow and pressure levels, pulsatile flow generates significantly more hemodynamic energy, which may be one of the reasons for better vital organ protection during the pulsatile mode of support (13, 14).

In this study, we investigated the effects of pulsatile and non-pulsatile ECMO on hemodynamic energy and systemic microcirculation in a piglet model of acute cardiac failure using a pulsatile ECMO system developed in-house. It was

hypothesized that pulsatile ECMO would be more effective for improvements in systemic circulation than non-pulsatile ECMO.

Materials and Methods:

Fourteen piglets with a mean body weight of 6.08 ± 0.86 kg were used for experiments and divided into 2 groups; pulsatile ($n = 7$) and non-pulsatile ($n = 7$) ECMO groups. The Animal Care and Use Committee of the Okayama University of Science (Okayama, Japan) approved the experimental protocol. All experimental animals were handled in accordance with Federal Law and guidelines of the “Guide for the Care and Use of Laboratory Animals, Eighth Edition” prepared by the National Institutes of Health (NIH Publication, 2011).

Experimental Design

The experimental ECMO circuit (Figure 1) consisted of a centrifugal pump (HPM-15; MERA, Tokyo, Japan), a membrane oxygenator (Excelung-prime KIDS, MERA), and pneumatic pulsatile flow generator system that we developed for this study (Figure 2). We used a 10 Fr ultra-thin-wall cannula (Fem-Flex; Edwards Life Sciences, CA, USA) via the ascending aorta and a 16Fr straight cannula (DLP; Medtronic, MN, USA) via the right atrium. The circuit was primed with 250 mL acetate Ringer’s solution. The pump rate was maintained at 60 beats per minute (bpm) during pulsatile ECMO.

We generated pulsatile flow using a pneumatic pulsatile flow generator system developed in-house (Figure 2). The pulsatile generator system was driven at a rate of 60 bpm. The ECMO flow was set at 140 mL/kg/min as full support flow during experimental study for both pulsatile and non-pulsatile ECMO. Figure 3 shows the pulsatile waveform. TS 410 transit-time tubing flow probes (Transonic Systems, NY, USA) were used to measure the flow rate in the arterial and venous lines. A cardio-press in line pressure monitor (JMS, Tokyo, Japan) was used to measure pre- and post-pneumatic pulsatile flow generator pressures. For the procedure, each piglet was pretreated with 10 mg midazolam and placed on the surgical table. A tracheotomy was performed and a 7 Fr. endotracheal tubes was inserted. The endotracheal tube was connected to a respirator, and anesthesia was maintained using 2.5 % sevoflurane. An intravenous (IV) fluid route was established at the right internal jugular vein. We administered 0.2mg/h pancuronium to maintain anesthesia with Ringer’s acetate solution. The respirator was maintained at a rate of 20 times/min, with a tidal volume

of 7-10 mL/kg/respiration, and with 100 % oxygen. Near-infrared spectroscopy (INVOS; Covidien, MA, USA) was used to monitor frontal lobe and kidney regional oxygen saturation levels. An electrocardiogram (ECG) monitor, pulse oximeter (Nihon Kohden, Tokyo, Japan), and rectal temperature probe were also used. To monitor hemodynamic data, an 18G catheter containing a TruWave MP5300 pressure monitoring set (Edwards Life Sciences, CA, USA) was inserted via the right carotid artery. Following set-up of the hemodynamic and perfusion monitoring equipment, 3 mg/kg of heparin sodium was administered. Anticoagulation was accomplished via drip infusion of heparin sodium to maintain an activated clotting time (ACT) of 160-200 s during the experiment. In addition, an 8 Fr. Foley catheter (Covidien, MA, USA) was placed in the urinary bladder to monitor output during the experiment. Subsequently, a median sternotomy was performed, the pericardium was opened, and the experimental ECMO circuit was connected.

We initiated non-pulsatile ECMO at the flow rate of 140 mL/kg/min for the first 30 min under normal cardiac rhythm. Rectal temperature was maintained at 36°C during the experiment using an HHC-51 heater cooler unit (MERA, Tokyo, Japan). Ventricular fibrillation, as a model of cardiac dysfunction, was then induced using a 3.5 V alternating current. Once the cardiac dysfunction model was established, data on heart rate, arterial pressure (systole, diastole and mean), regional saturation of oxygen (rSO₂), blood gases (pH, PaO₂, PaCO₂, lactate [Lac]), base excess [BE], HCO₃⁻, SaO₂, SvO₂), arterial blood sampling (hemoglobin, methemoglobin, erythrocytes, leukocytes, thrombocytes), ECG monitoring, and arterial pressure wave forms, were collected for both pulsatile and non-pulsatile ECMO groups. We weaned off ECMO at the end of the experiment (180 min after ECMO was initiated). The animals did not receive blood transfusions, inotropic drugs, or vasoactive drugs.

Blood sampling and hemodynamic profile

Blood sampling was performed using the i-STAT System (Abbott Laboratories, Abbott Park, IL, USA) with the i-STAT CG4+ (pH, PaO₂, PaCO₂, Lac) and CG8+ (SO₂, BE, HCO₃⁻) cartridge test. Erythrocyte, thrombocyte, and leukocyte levels were measured using a Celltac α MEK-6450 (Nihon Kohden, Tokyo, Japan)

Methemoglobin levels were measured using an AVOXmeter 4000 (International Technidyne Corporation, Toms River, NJ, USA).

Arterial blood (for measurement of hemoglobin, methemoglobin, erythrocytes, leukocytes, and thrombocytes) was sampled at 9 time points: (1) after induction of anesthesia, (2) just before ECMO (5 min after heparin administration), (3) 10 min after ECMO, (4) 30 min after ECMO, (5) 60 min after ECMO, (6) 90 min after ECMO, (7) 120 min after ECMO, (8) 150 min after ECMO, (9) 180 min after ECMO. At each time point, 2.5 mL of blood was withdrawn. Two milliliters of the blood sample was used for ACT measurement and the remaining 0.5 mL was used for blood gas analysis, electrolyte measurement, and lactic acid.

The hemodynamic profile included measurements of the heart rate and arterial blood pressure (systolic, diastolic, mean). Data were fed via a USB port into Labview 2009 software for Windows (Japan National Instruments, Tokyo, Japan), and collected at 20-s intervals with 1000 samples/s. We used USB-6008 (Japan National Instruments), as an analog- to- digital converter, to input flow and pressure measurement data into a personal computer for hemodynamic data analysis.

Hemodynamic Energy Calculation

Utilizing the Shepard's energy equivalent pressure (EEP) formula (15) and data from simultaneous flow (f) and pressure (p) readings, values for EEP, surplus hemodynamic energy (SHE) and total hemodynamic energy (THE) were calculated in the interval time (t_1 and t_2) as follows.

$$EEP(mmHg) = \frac{\int_{t_1}^{t_2} fp dt}{\int_{t_1}^{t_2} f dt}$$

$$SHE(ergs/cm^3) = 1332 * (EEP - meanpressure)$$

$$THE(ergs/cm^3) = 1332 * EEP$$

Statistical Analysis

Data were analyzed using SPSS software for windows version 20 (SPSS Inc., IL, USA). All data were expressed as mean and standard deviation. The Student-t test and Tukey-Kramer test were used to evaluate differences between groups. A p-value of

<0.05 was considered to have statistical significance. Sample Power 3.0 (SPSS Inc., IL, USA) was used for all data to determine the number of samples necessary in each of the two groups being compared. Power analyses were conducted for multiple analysis of variance (MANOVA), with a significance level of 0.05, and a power of 0.6.

Results:

Table 1 represents the hemodynamic pressure and energy change data in the pulsatile and non-pulsatile ECMO groups. The pulsatile ECMO group produced significantly higher hemodynamic energy than the non-pulsatile group ($p < 0.05$, Table 1). After induction of ECMO, arterial blood pressure decreased in both groups (Table 1). At between 90 and 180 min of the ECMO, systolic arterial pressure was significantly higher in the pulsatile ECMO group, at each time point (all $p < 0.05$, respectively) (Table 1). Similarly, mean arterial pressure was significantly higher in the pulsatile ECMO group at between 120 and 180 min, at each time point (all $p < 0.05$, respectively) (Table 1). EEP, SHE, and THE were significantly higher in the pulsatile ECMO group at between 60 and 180 min, at each time point (all $p < 0.05$, respectively) (Table 1).

Table 2 represents peripheral tissue perfusion data of the pulsatile and non-pulsatile ECMO groups. At between 60 and 180 min of ECMO, near-infrared spectroscopy monitoring showed that the pulsatile ECMO group had significantly higher regional saturation at the level of the frontal lobes, in comparison to the non-pulsatile ECMO group, at each measurement time point (all $p < 0.05$, respectively) (Table 2).

After induction of ECMO, the pH level decreased in both groups (Table 2). At between 120 and 180 min of ECMO, the pulsatile ECMO group showed a significantly higher pH level than the non-pulsatile ECMO group (all $p < 0.05$, respectively) (Table 2).

After induction of ECMO, the acid -BE level decreased in both groups (Table 2). At between 90 and 180 min of ECMO, the pulsatile ECMO group showed significantly higher acid base excess level than non-pulsatile ECMO group at each measurement time point (all $p < 0.05$, respectively) (Table 2).

After induction of ECMO, blood lactate concentration gradually increased in both groups (Table 2). At between 60 and 180 min of ECMO, the pulsatile ECMO group showed significantly lower blood lactate concentrations than the non-pulsatile ECMO group at each measurement time point (all $p < 0.05$, respectively) (Table 2).

Discussion:

Recently, new pulsatile perfusion devices have been developing in Europe (16-18). However, in Japan, a good pulsatile ECMO generator system using a centrifugal pump is not yet available. The pulsatile flow generator system described in this study is easy to set up as it only connects to the arterial line with a pneumatic system, and it is easy to alternate between pulsatile and non-pulsatile flow. The principle of the drive console of our pneumatic system is based on the intra-aortic balloon pump (IABP). Hence, we can adapt perfusion flow to cardiac function by choosing a flow setting that is in pulsatile or non-pulsatile mode; we can set pulsatile flow during cardiac dysfunction with pulsatile flow mode ECMO, and change to non-pulsatile flow during cardiac recovery conditions under normal cardiac rhythm, using continuous non-pulsatile flow mode ECMO. Our pneumatic system can also trigger the arterial pulse pressure monitor and ECG. In a clinical setting, our pulsatile generator system does not need a special drive console; as a simple alternative, an IABP or ventricular-assist device console can be used to drive our pneumatic pulsatile generator system. Therefore, we believe our pulsatile perfusion generators are highly versatile, without the need for a specific console to control the system.

Based on the findings of the present study, we emphasize that pulsatile ECMO has a significant advantage over non-pulsatile ECMO. Pulsatile ECMO produces higher hemodynamic energy than non-pulsatile ECMO. Moreover, our results demonstrated that pulsatile ECMO produces methemoglobin levels within the normal range, compared to non-pulsatile ECMO. Roberts et al. reported that an increase in methemoglobin level is associated with an increase in nitric oxide (19). This indicates that pulsatile flow produces more nitric oxide than nonpulsatile flow (19-24). Nitric oxide secretion causes systemic vasodilation by diffusing into vascular smooth muscle cells (19, 21). Nitric oxide secretion from the endothelium is stimulated by the mechanical shear stress of pulsatile flow acting on vessel endothelium (25). For this reason, pulsatile blood flow may reduce systemic vascular resistances and maintain better circulation in microvessels by increasing nitric oxide secretion.

In cases of acute cardiac failure, cardiac output rapidly decreases; this leads to the maintenance of blood flow to important organs, such as the brain and heart, by reducing blood flow to peripheral organs such as the kidneys and systemic

microcirculation (8, 26). Generally, near-infrared spectroscopy is used to monitor brain and kidney perfusion in perioperative management (27, 28). In the present study, near-infrared spectroscopy monitoring showed lower regional oxygen saturation at the level of the kidneys, compared with the frontal lobes, with non-pulsatile ECMO. In contrast, pulsatile ECMO can maintain regional oxygen saturation at both kidney and frontal lobe levels. This indicates that pulsatile flow can prevent brain and kidney perfusion. Our results demonstrated that pulsatile ECMO prevents increases in blood lactate concentration; therefore it could prevent metabolic acidosis and maintain adequate oxygen delivery in keeping with the primary physiological goal of ECMO, in comparison to non-pulsatile ECMO. Therefore, these factors confirm that compared with non-pulsatile ECMO, pulsatile ECMO improves microcirculation.

Limitations of the present study are that we evaluated the effect of pulsatile ECMO on hemodynamic energy and microcirculation under severe acute cardiac failure model, without any blood transfusion and vasoactive agents, with normothermic perfusion, and had only 3 hours of perfusion research on ECMO. However in the near future, we intend to compare physiological data with a longer perfusion time. We intend to evaluate different types of centrifugal pumps and oxygenators to generate adequate pulsatility, using our pneumatic pulsatile flow generator system. We also intend to compare the physiological and hemodynamic data in clinical settings, using our pneumatic pulsatile generator system and novel i-cor system or delastream- DP3 (Medos, Stolberg, Germany). We intend to develop a better pulsatile generator system, making it more compact, with a portable IABP console.

Conclusions:

Continuous perfusion has less hemodynamic energy than pulsatile perfusion. Hence, adequate continuous perfusion requires more high-flow perfusion or volume overloading. In conclusions, the results of our study indicate that pulsatile ECMO produces significantly higher hemodynamic energy and improved systemic microcirculation, compared to non-pulsatile ECMO in acute cardiac failure.

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Disclosure: I declare on behalf of myself and all authors the following:

We have no material, financial, or other relationship with any healthcare-related business or other entity whose products or services may be discussed in, or directly affected in the marketplace by, this manuscript.

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Figure legend**Figure 1. Experimental Pulsatile and Non-Pulsatile ECMO circuit**

The experimental ECMO circuit consisted of an HPM-15 centrifugal pump (MERA, Tokyo, Japan), Excelung-prime KIDS (MERA) as a membrane oxygenator, and pneumatic pulsatile flow generator system that we developed for this study. We used 10 Fr. Fem-Flex ultra-thin-wall cannula (Edwards Life Sciences, CA, USA) via the ascending aorta and a 16Fr. DLP straight cannula (Medtronic, MN, USA) via the right atrium. The circuit was primed with 250 mL acetate Ringer's solution.

Figure 2. Pneumatic pulsatile flow generator system developed in-house

This pneumatic pulsatile flow generator system has a 25 mL pillow bag, made of poly-vinyl chloride, inside a 120 mL cylinder cone. Blood is inside of and air is outside pillow bag. We can control the air- pressure, rate, and timing with electrocardiogram to produce the pulse wave.

Figure 3. Pulsatile Waveform

This is an arterial pressure waveform of pulsatile flow during pulsatile ECMO. Pulse rate is 60 bpm.

Table 1. Hemodynamic pressure and energy changes with Pulsatile vs. Non-pulsatile ECMO

After 30 min of ECMO, we established a cardiac dysfunction model.

Table 2. Peripheral tissue perfusion data with Pulsatile vs. Non-pulsatile ECMO

After 30 min of ECMO, we established a cardiac dysfunction model.

Figure 1. Experimental Pulsatile and Non-Pulsatile ECMO circuit

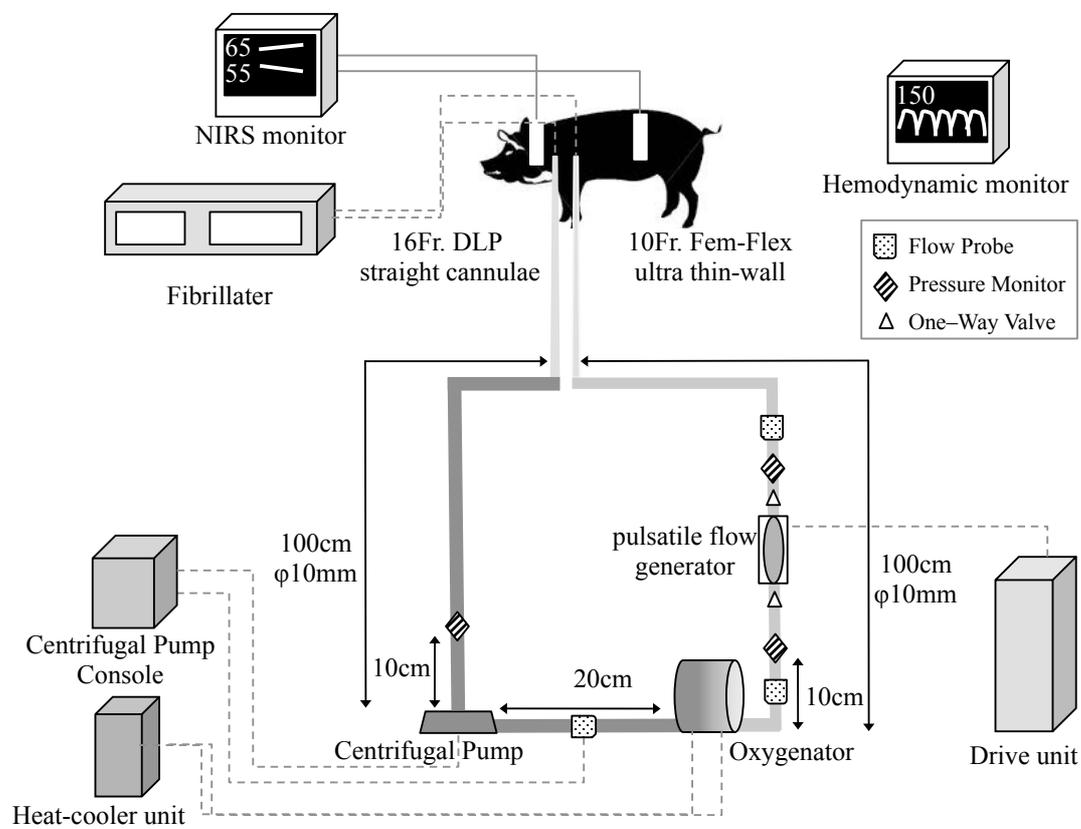


Figure 2. Pneumatic pulsatile flow generator system developed in-house

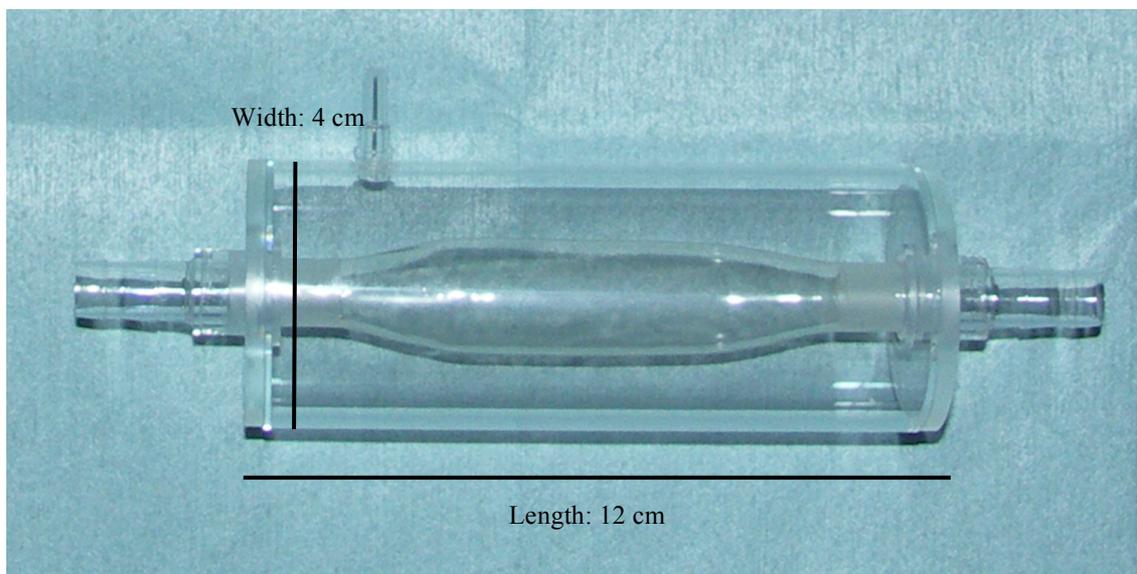


Figure 3.

