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Abstract: We have evaluated the feasibility of a newly developed single-use, magnetically levitated centrifugal blood pump, MedTech Mag-Lev, in a 3-week extracorporeal membrane oxygenation (ECMO) study in calves against a Medtronic Bio-Pump BPX-80. A heparin- and silicone-coated polypropylene membrane oxygenator MERA NHP Excelung NSH-R was employed as an oxygenator. Six healthy male Holstein calves with body weights of about 100 kg were divided into two groups, four in the MedTech group and two in the Bio-Pump group. Under general anesthesia, the blood pump and oxygenator were inserted extracorporeally between the main pulmonary artery and the descending aorta via a fifth left thora cotomy. Postoperatively, both the pump and oxygen flow rates were controlled at 3 L/min. Heparin was continuously infused to maintain the activated clotting time at 200–240 s. All the MedTech ECMO calves completed the study duration. However, the Bio-Pump ECMO calves were terminated on postoperative days 7 and 10 because of severe hemolysis and thrombus formation. At the start of the MedTech ECMO, the pressure drop across the oxygenator was about 25 mm Hg with the pump operated at 2800 rpm and delivering 3 L/min flow. The PO2 of the oxygenator outlet was higher than 400 mm Hg with the PCO2 below 45 mm Hg. Hemolysis and thrombus were not seen in the MedTech ECMO circuits (plasma-free hemoglobin [PFH] < 5 mg/dL), while severe hemolysis (PFH > 20 mg/dL) and large thrombus were observed in the Bio-Pump ECMO circuits. Plasma leakage from the oxygenator did not occur in any ECMO circuits. Three-week cardiopulmonary support was performed successfully with the MedTech ECMO without circuit exchanges. The MedTech Mag-Lev could help extend the durability of ECMO circuits by the improved biocompatible performances. Key Words: Magnetically levitated centrifugal blood pump—Silicone-coated polypropylene membrane oxygenator—Extracorporeal membrane oxygenation—Percutaneous cardiopulmonary support.

In intensive care medicine, extracorporeal membrane oxygenation (ECMO) is an essential therapy for providing both cardiac and respiratory support to patients having heart and/or lung failure. The conventional ECMO systems comprising a centrifugal blood pump and a polypropylene microporous membrane oxygenator, however, cause significant risks in terms of hemolytic and thromboembolic complications. Centrifugal pumps with a mechanical bearing and a seal structure cause hemolysis and thrombus formation at the bearing and seal areas (1). During perfusion, the oxygenator located downstream captures the emboli generated by the blood pump, clogging up the pores of the membrane and shortening the lifespan of oxygenators. Anticoagulation therapy is necessary to suppress thrombus formation in the blood pumps. Such a therapy, however, can lead to bleeding complications including intracranial hemorrhage, which occurs in 7.4% of the ECMO-supported patients (7.6% of the pediatric and 2.9% of the adult cases).
ECMO-supported patients) (2). In addition, hemolysis provokes anemia and renal dysfunction. As for the oxygenators, the polypropylene microporous membrane oxygenators often develop plasma leakage in a few days, requiring exchange of the ECMO circuit (3).

The blood pump and oxygenator technologies in general have made remarkable progress during the last decade, which helped improve the ECMO performance in both adult and pediatric applications (4,5). The CentriMag blood pump (Thoratec Co., Pleasanton, CA, USA) that replaced the mechanical contact bearing of the conventional centrifugal blood pumps with a sophisticated noncontact magnetic bearing, the so-called “bearingless motor technology” (6,7), successfully reduced risks of hemolysis and thromboembolic complications in the midterm ventricular assist device (VAD) as well as ECMO applications (8,9). However, the Rotaflow Centrifugal Pump (Maquet Cardiopulmonary AG, Hirrlingen, Germany) that employs the so-called “sapphire monopivot bearing system” to support a rotating impeller (10) has found its way in pediatric applications because of its simpler, compact, easy-to-handle, and cost-effective design (11).

As for the oxygenator technology, a new membrane material polymethylpentene (PMP) became the base for a new oxygenator to improve the performance by greatly reducing the risk of plasma leakage (12). The Quadrox D (Maquet Cardiopulmonary AG) that employs PMP led to outstanding outcomes in the midterm ECMO studies (13).

Shortcomings of the new blood pump technologies also exist. The Rotaflow Centrifugal Pump may have possibilities of hemolysis and thromboembolic complications due to the monopivot bearing structure, although the significant improvement over the conventional design has been demonstrated (14). As for the CentriMag, it is extremely cost-ineffective because of its bearingless design, and each single-use pump head costs from 7000 to 12 000 USD (20–30 times more expensive than the Rotaflow) (15). In addition, although the CentriMag is approved for clinical use up to 30 days in Europe (received Conformité Européene Mark), the US Food and Drug Administration indicated the use of the CentriMag for extracorporeal circulatory support for up to 6 h, and the extended use beyond 6 h would be considered as off-label. It is of course not introduced to Japan yet.

Because of the increasing need for a reliable, cost-effective ECMO system that can be used for longer than 2 weeks in Japan, we have developed a new single-use, magnetically levitated, centrifugal blood pump, MedTech Mag-Lev (16–20). In this study, in order to demonstrate the applicability of the MedTech Mag-Lev for midterm ECMO applications, we have designed a 3-week comparative in vivo study against the Bio-Pump BPX-80 (Medtronic, Inc., Minneapolis, MN) in calves. The BPX-80 was chosen because of its conventional mechanical bearing structure and worldwide acceptance as an extracorporeal blood pump. As for an oxygenator, a heparin- and silicone-coated polypropylene membrane oxygenator was chosen because of its easier availability in Japan.

**MATERIALS AND METHODS**

**Blood pumps**

**MedTech Mag-Lev**

The MedTech Mag-Lev system consists of a single-use pump head, a reusable motor driver, and a console (Fig. 1). The core of the system is the x- and y-axis active control together with the z- and tilting-axis passive control accomplished using a pair of electromagnets and permanent magnets. The priming volume of the pump head is 21 mL, smaller than those of the CentriMag (31 mL) and the Rotaflow (32 mL), and thus may be applicable to even pediatric ECMO. A secondary flow path inside the pump head enhances washout effects to reduce thrombus formation inside the pump head. Furthermore, the biocompatible 2-methacryloyl-oxyethyl phosphorylcholine (MPC) polymer coated on the blood contacting surface of the pump head assures thrombus-free performance in the midterm operation (21).

**Bio-Pump BPX-80**

The Bio-Pump BPX-80 was used as a control pump because of its worldwide acceptance for many years and having a conventional mechanical shaft and bearing at the bottom of the cone to support the cone rotation (22). The three-layer cone is rotated through an axial magnetic coupling to the drive magnet mounted on the external motor shaft. It has a priming volume of 80 mL and heparin coating (Carmeda BioActive Surface, W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) is provided to improve the biocompatibility (23).

**Cannula**

A 5-cm-long 6-mm vascular prosthesis (Hemashield, Boston Scientific Corp., Natick, MA, USA) bonded to an 18 Fr Toyobo MERA Flexmate (Senko Medical Corp., Tokyo, Japan) was used as the outflow cannula, from the pump to the calf, which was anas-
tomosed end-to-side to the descending aorta. A 22-Fr Medtronic DLP Malleable cannula (Medtronic, Inc.) was used as the inflow cannula, from the calf to the pump, which was inserted into the main pulmonary artery. The sizes of cannula were decided to match those of the percutaneous cardiopulmonary support system. Similar cannulae were originally designed and used in the pediatric ventricular assist study using 10 kg goats, showing remarkable hemodynamic performances at low pump flow of 1.0 L/min for the duration of 30 days (24,25).

Oxygenator
A membrane oxygenator MERA NHP Excelung NSH-R (Senko Medical Corp.) was used in all calves. A heat exchanger and a gas exchanger unit are integrated as a compact size oxygenator. Its priming volume is 225 mL. The surface of polypropylene hollow fiber is coated with 0.2 μm thick silicone layer and the heparin molecules to prevent plasma leakage and thrombus formation. The biocompatibility of the silicone-coated polypropylene hollow fiber oxygenator was evaluated in animal experiments (26) and clinical studies (27). To improve the antithrombogenicity of this hollow fiber, a heparin coating was added since 2005.

Experimental animals
From July 2011 through March 2012, animal experiments with an intended duration of 3 weeks were performed in a total of six healthy male Holstein calves with a body weight of about 100 kg. Six calves were divided into two groups, four in the MedTech ECMO group and two in the Bio-Pump ECMO group. All experiments were carried out in accordance with the Guidelines for Animal Experimentation of the Tokyo Medical and Dental University, and were approved by the Institutional Animal Care and Use Committee of Tokyo Medical and Dental University.

Surgical procedures
Calves were anesthetized with an inhalational isoflurane. The left carotid artery was exposed to insert an arterial line (Radifocus Introducer IIH, RS-A40G07S, Terumo Corp., Tokyo, Japan). A triple lumen venous catheter (CS-14703, Arrow Japan Corp. Ltd., Tokyo, Japan) was inserted into the left jugular vein. Left thoracotomy was performed through the fifth intercostal space. After a bolus injection of heparin (250 IU/kg) extending the activated clotting time (ACT) to over 500 s, the descending aorta was side-clamped. A 6-mm vascular prosthesis bonded with an 18-Fr outflow cannula from the pump to the calf was anastomosed end-to-side to the side-clamped aorta with a 5-0 polypropylene continuous suture. Pericardium was then opened, followed with anastomosing 10-mm vascular prosthesis (Hemashield, Boston Scientific Corp.) end-to-side to the main pulmonary artery with a 5-0 polypropylene continuous suture. Thereafter, the inflow cannula from the calf to the pump was inserted into the main pulmonary artery toward the proximal
side through the 10-mm graft and tied with silk threads. The inflow and outflow cannula were then tunneled subcutaneously to exit at the seventh intercostal space. The blood pump and the oxygenator were connected to the inlet and outlet cannula. The ultrasonic flow probe (Transonic Systems, Inc., Ithaca, NY, USA) was attached over the inflow cannula for continuous monitoring of the pump flow. Both the pump flow and the oxygen flow rates were maintained at 3 L/min.

**Postoperative care**

Calves were postoperatively kept in a cage and watched carefully around the clock. The pump and the oxygenator were fixed to a saddle mounted on the calf’s back so that the calf could move freely in the cage (Fig. 2). The warm water was circulated through the heat exchanger unit to rewarm the calves only the day of the operation when it was required. Heparin was continuously infused, and warfarin was orally provided to maintain the ACT level at 200–240 s. The inlet and outlet port pressures of the oxygenator were measured continuously to derive the pressure drop across the oxygenator. The blood samples were analyzed to evaluate the gas exchange performance of the oxygenator. Blood samples from arterial line were obtained periodically to evaluate hemolysis, activation of coagulation, infection, and organ dysfunction of calves.

**Autopsy**

After the study duration of 3 weeks, calves were electively sacrificed and autopsy was performed to examine thrombus formation inside the pump and the oxygenator. Major organs including heart, lungs, liver, kidneys, and spleen were inspected macro- and microscopically to detect evidence of infarction.

**Data analysis**

All values were expressed as mean ± standard deviation. In comparative analysis, the Mann–Whitney U-test was used because the number of subjects was too small so that the values did not conform to a normal distribution. *P* values less than 0.05 were considered statistically significant.

**RESULTS**

**Hemodynamics, blood gases, and general findings**

A total of six calves, four in the MedTech ECMO group and two in the Bio-Pump ECMO group, were used in this study. The ACT level was maintained between 200 and 240 s in both groups by the continuous administration of heparin and warfarin. All MedTech ECMO calves successfully completed the study duration (Fig. 3A). The cumulative support time of MedTech ECMO was 2016 h. However, two Bio-Pump ECMO calves had to be terminated prematurely (Fig. 3B). Bio-Pump ECMO calf #1 could not stand up because of severe hemolytic anemia; therefore, the study was terminated on postoperative (PO) day 7. In the case of Bio-Pump ECMO calf #2, the adhesion of thrombus around the bearing area caused the pump to stop on PO day 10. The cumulative support time of Bio-Pump ECMO was 408 h.

The general conditions of the MedTech ECMO calves were in good health. The hemodynamics such as the blood pressure, the pump flow, and the pressure drop across the oxygenator were stable for 3 weeks (Fig. 3A). At the start of extracorporeal circu-
lation, the pressure drop of the oxygenator was about 25 mm Hg, and the pump flow was about 3 L/min with the rotational speed of about 2800 rpm. The rotational speed was gradually increased up to 3000 rpm, because the pressure drop slowly increased. Under 3 L/min of pure oxygen flow rate, the PO₂ at the outlet port of the oxygenator was maintained almost higher than 400 mm Hg, and the PCO₂ below 45 mm Hg in all calves (Fig. 4). Plasma leakage from the membrane oxygenator did not occur in any ECMO circuit. Abnormal neurologic signs such as paraplegia were not observed in all calves. Severe hematuria was detected on PO day 4 in the case of Bio-Pump ECMO calf #1 and PO day 9 in the Bio-Pump ECMO calf #2.

Hemolysis and hematological data
The plasma-free hemoglobin (PFH) levels in MedTech ECMO calves were less than 5 mg/dL throughout the study duration. Meanwhile, the PFH levels in Bio-Pump ECMO calves exceeded 20 mg/dL on PO day 4 and day 9 (Fig. 5). The time course changes in hematocrit and platelet counts of the two groups are shown in Fig. 6A,B by calculating the rate of changes normalized to the value at the termination of the operation. Hematocrit of both groups decreased initially, with that of the MedTech ECMO group showing an increasing tendency within 3 days postoperatively, while that of the Bio-Pump ECMO consistently decreased throughout the study duration (Fig. 6A). Platelet counts of the MedTech ECMO recovered the preoperative condition within 5 days postoperatively, while those of the Bio-Pump did not recover throughout the study duration (Fig. 6B).

Autopsy findings
The autopsy findings of the MedTech ECMO revealed no thrombus inside the pump head, cannulae, or circuit tubings (Fig. 7A). Some fibers of the heat exchanger unit in the oxygenator were found to be occluded by thrombi. Some thrombus formation was found at the surface of the hollow fibers in the transition regions between the inlet and outlet casings (Fig. 8A–C). The scanning electron micro-
scope (JSM-6460LV, Nihon Denshi Corp., Tokyo, Japan) pictures disclosed that the fibrin network adhered to the surface of the hollow fibers seemed to have captured red blood cells (Fig. 8D–F). The autopsy findings of the Bio-Pump ECMO revealed the thrombus formation around the axis of the pump head (Fig. 7B). The large emboli were found at the inlet of the heat exchanger unit. Thromboembolic occlusion of the branches of aorta, infarction of major organs, and fibrotic changes of lungs were not recognized in all calves.

**DISCUSSION**

Because of the increasing needs for a reliable, cost-effective ECMO system in Japan, we have developed a single-use, compact, cost-effective magnetically levitated, centrifugal blood pump, MedTech Mag-Lev (16–20). After demonstrating its biocompatible performance as a short-term VAD, in this study, the MedTech Mag-Lev was combined with a heparin- and silicone-coated polypropylene membrane oxygenator, MERA NHP Excelung NSH-R, to assess its feasibility for 3-week ECMO in calves. As evident from the results, the MedTech Mag-Lev together with MERA NHP Excelung showed far better performance than the mechanical bearing-supported the Bio-Pump BPX-80. Although the number of animals may be small with four, all animals of MedTech group successfully completed the study duration of 3 weeks in comparison to the prematurely terminated Bio-Pump group due to pump-related hemolytic and thromboembolic complications.

**FIG. 4.** Blood gases (oxygenator outlet port). Under 3 L/min of pure oxygen flow rate, the partial pressure of oxygen at the outlet port of the oxygenator was maintained almost higher than 400 mm Hg, and the partial pressure of carbon dioxide below 45 mm Hg in all calves.

**FIG. 5.** Plasma-free hemoglobin (PFH). The PFH levels in MedTech ECMO calves were less than 5 mg/dL throughout the study duration. Meanwhile, the PFH levels in Bio-Pump ECMO calves exceeded 20 mg/dL on postoperative days 4 and 9.
Although the magnetic bearing technology as incorporated in the CentriMag has shown safe and effective performance in Europe and the USA, it is not available in Japan. The magnetic levitation principle of the newly developed MedTech Mag-Lev is far simpler than that of the CentriMag, offering a cost-effective, reliable ECMO system (18). The priming volume of 21 mL is small enough to be used even for pediatric applications. The secondary flow path incorporated inside the pump head together with biocompatible MPC polymer coating on the blood contacting surface of the pump head assures biocompatible performance for 3 weeks.

As for the new membrane oxygenator, MERA NHP Excelung, the heparin and silicone coating to polypropylene membrane can assure prolonged performance without plasma leakage. The examination by a scanning electron microscope revealed that the silicone coating had not deteriorated despite the continuous 3-week use. Fibers of the heat exchanger unit in the oxygenator were found to be occluded by thrombus to increase the pressure drop across the oxygenator. The thrombi seen in the heat exchanger unit were probably formed in the narrow lumen of the heat exchanger fibers, not released from the MedTech Mag-Lev pump. Therefore, if the lumen diameter of the heat exchanger fibers is widened, a lower pressure drop could be expected.

Concerning the operative procedure of central ECMO approach employed in this study, it has not been reported previously. The central ECMO approach from the pulmonary artery to the descending aorta through left thoracotomy was specifically designed for this study. The peripheral approach from neck vessels, which seems easier and simpler than the central approach with thoracotomy, is usually selected in animal experiments using calves (28,29). However, when the calves bend their neck during daily events, bending and kinking of the cannula and bleeding from the cannulation site could occur. In fact, these complications were reported by other workers (29). Although our central approach was
fairly invasive, the postoperative complications have never occurred. The blood drainage from the main pulmonary artery enabled the pump flow to remain stable regardless of the calf movement.

As seen from the results, the MedTech ECMO showed stable gas exchange and pump flow without severe hemolysis and thrombus formation for 3 weeks. We are confident that the MedTech ECMO, therefore, would not require circuit exchange frequently when used in usual clinical situations. Since the actual average run time for ECMO was about 173 h (7.2 days) according to the registry report of the Extracorporeal Life Support Organization (ELSO) in 2008, our MedTech ECMO system can easily meet the requirements for clinical ECMO (30).

Finally, the recent clinical reports disclosed that the prolonged ECMO therapy was helpful in improving patients with severe diseases (31–36). The progress in antithrombogenic performance of the mechanical devices helped reduce crucial bleeding complications such as intracranial hemorrhage (37). When fulminant myocarditis causes occasional cardiogenic shock despite optimal medical managements, ECMO is considered as the first-line treatment option because of its easy and rapid setup time (31). According to the ELSO registry, the survival rate with ECMO was 61%, and 3% patients underwent heart transplantation (32). The prospective randomized trial of ECMO therapy for acute respiratory distress syndrome (ARDS) as compared with the conventional care resulted in the 6-month survival free of disability of 63 versus 47% (33). The other investigation reported the 71% survival rate in ARDS resulting from Influenza A (H1N1) (34). Lung transplantation is offered.

FIG. 7. Autopsy findings. (A) The pump head of MedTech Mag-Lev had no thrombus, and some fibers of the heat exchanger were occluded by thrombus which was made in the narrow fibers. (B) The pump head of Bio-Pump had the thrombus formation around the axis of the pump, and large emboli at the inlet of the heat exchanger were observed.

FIG. 8. Some thrombus formation was found at the surface of the hollow fibers in the transition regions between the inlet and outlet casings (A–C). The scanning electron microscope (JSM-6460LV, Nihon Denshi Corp., Tokyo, Japan) pictures disclosed that the fibrin network adhered to the surface of the hollow fibers seemed to have captured red blood cells (D–F). Scale bar = 500 μm (D), 50 μm (E), 10 μm (F).
for patients with end-stage lung disease with no other treatment options. Prolonged ECMO support is the only life-saving option for the significant primary graft dysfunction, which still occurs in 5 to 25% cases despite improved surgical and graft preservation techniques (35,36). If the results of our study in this small calf series were demonstrated in humans, the MedTech ECMO could become one important device further improving the prognosis of these diseases.

Limitations

In this experiment, there were some limitations. The most critical limitation is the small number of animals in both groups. There were four MedTech ECMO calves and two Bio-Pump ECMO calves. Therefore, rigorous statistical analysis between the two animal groups was not possible. In addition, the same number of subjects in each group is preferable to compare the two different devices. Despite this, we stopped the Bio-Pump ECMO test in just two cases only, because the Bio-Pump ECMOs resulted in severe hemolysis and thrombus formation on PO days 7 and 10. These initial results suggested that further experiments might not be profitable. Also the results reported by Someya et al. (19) suggested apparent superiority of the Mag-Lev system over the mechanical bearing pump from in vitro hemolysis study.

CONCLUSION

The MedTech Mag-Lev showed an excellent biocompatibility for the 3-week ECMO study in calves, when it was used with the heparin- and silicone-coated polypropylene membrane oxygenator. Three-week cardiopulmonary support was performed successfully without circuit exchanges. If the early results in this small number of calf experiments were demonstrated clinically, the MedTech ECMO could become one important device to improve the prognosis of severe diseases such as fulminant myocarditis, ARDS, and end-stage lung disease indicated for lung transplantation.

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