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## Short-term outcomes of EXCOR Paediatric implantation

Motoki Komori <sup>a</sup>, Takaya Hoashi <sup>a,\*</sup>, Heima Sakaguchi<sup>b</sup>, Kenta Imai<sup>a</sup>, Naoki Okuda<sup>a</sup>,  
Norihide Fukushima <sup>c</sup>, Kenichi Kurosaki<sup>b</sup> and Hajime Ichikawa<sup>a</sup>

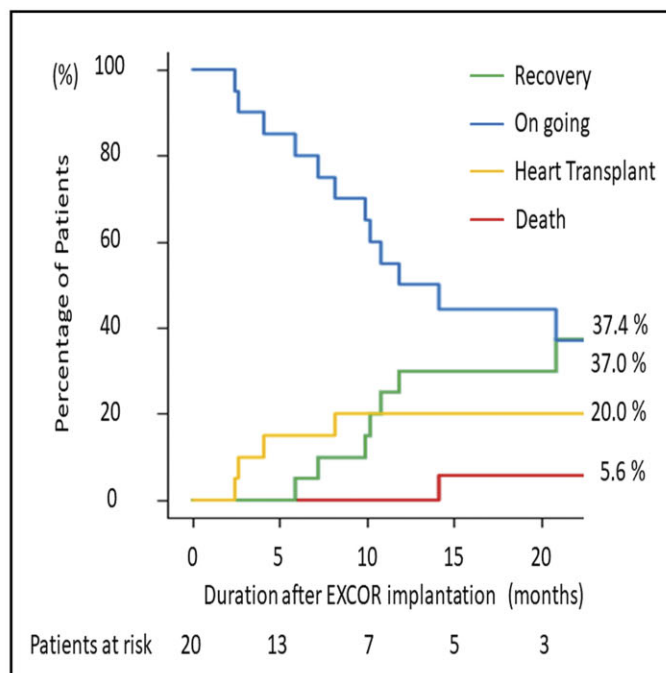
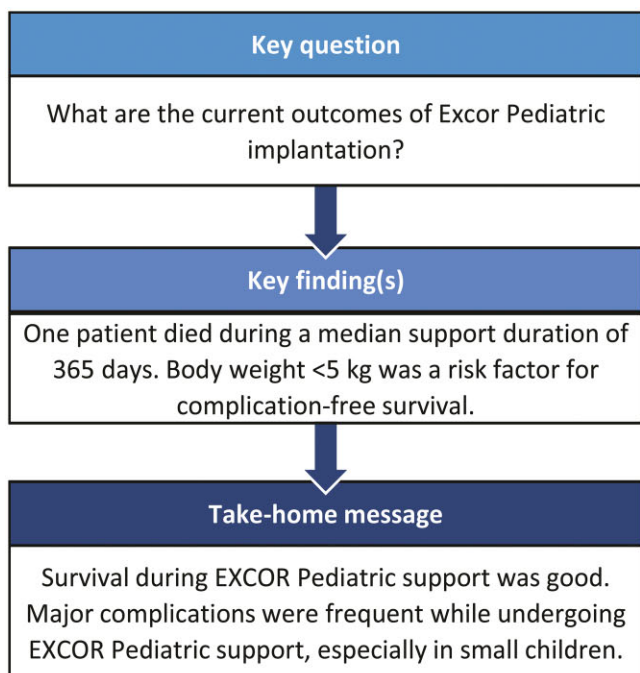
<sup>a</sup> Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan

<sup>b</sup> Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan

<sup>c</sup> Department of Pediatric Transplantation, National Cerebral and Cardiovascular Center, Osaka, Japan

\* Corresponding author. Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, 6-1, Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan. Tel: +81-6-6170-1070; fax: +81-6-6170-1348; e-mail: thoashi@surg1.med.osaka-u.ac.jp (T. Hoashi).

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### Abstract

**OBJECTIVES:** The aim of this study was to review a single institution's experience with EXCOR Paediatric implantation.

**METHODS:** Patients <15 years old who underwent EXCOR implantation as a bridge to transplantation between 2015 and 2021 were enrolled. Major adverse events included death, cerebrovascular event resulting in sequelae, major infection (sepsis or surgical site infection requiring open sternal irrigation or device removal) and device malfunction requiring surgical treatment.

**RESULTS:** Overall median age and weight for all 20 children at implantation were 10.8 (interquartile range, 7.9–33.2) months and 6.3 (4.6–10.2) kg. Ten patients (50%) weighed <5 kg. Primary diagnoses were dilated cardiomyopathy in 13 patients, fulminant myocarditis in 3, restrictive cardiomyopathy in 2 and congenital heart disease in 2. Two patients required biventricular assist support. The median support time was 365 (241–636) days. Six patients (30%) were supported for >20 months. One patient died. Seven patients underwent heart

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transplant. Heart transplant has not been performed in the last 1.5 years. Five patients were weaned from EXCOR support after native myocardial recovery, including a patient with dilated cardiomyopathy who recovered after 24 months of EXCOR support. Major complication-free survival at 6, 12 and 18 months were 79.3%, 49.6% and 38.6%, respectively. Body weight <5 kg at implantation was a risk factor for decreased major complication-free survival.

**CONCLUSIONS:** Survival during EXCOR Paediatric support was good, but it prolonged the wait time for a heart transplant. The number of major complications increased over time and was not negligible, especially in small children.

#### ABBREVIATIONS

|       |   |
|-------|---|
| BIVAD | Biventricular ventricular assist device |
| DCM   | Dilated cardiomyopathy                  |
| LVAD  | Left ventricular assist device          |
| VAD   | Ventricular assist device               |

## INTRODUCTION

The EXCOR Paediatric ventricular assist device (VAD) (Berlin Heart, Berlin, Germany) was introduced in Japan in 2015 as a bridge to heart transplant, with the expectation of increasing paediatric heart transplant donors after the low number of organ transplants in 2010. Since 2015, EXCOR has been the only insurance-reimbursed durable mechanical circulatory support device for children.

Our institution's first years' experience was reported in 2016 [1], and the number of patients who underwent EXCOR implantation has since increased. The objective of this study was to review the current situation for EXCOR Paediatric VAD support in children with end-stage heart failure due to various heart diseases, focusing on competing patient outcomes and the occurrence of major complications.

## MATERIALS AND METHODS

### Ethics and data availability statements

The National Cerebral and Cardiovascular Center Institutional Review Board approved this retrospective study (R19092, 20 December 2019).

### Patients

Patients <15 years old with end-stage heart failure who underwent EXCOR Paediatric VAD implantation at our centre from 2015 to 2021 were enrolled into this study.

### Anticoagulant protocol (medication and pump exchange)

On the basis of postoperative antithrombotic therapy guidelines from a prospective VAD trial [2] and the recommendations from a current multicentre study [3], an institutional postoperative anticoagulation and antiplatelet regimen was established. During the early postoperative period, unfractionated heparin was continuously infused to maintain the activated partial thromboplastin time of over 60 s. After restarting tube feeding, warfarin was administered to control the prothrombin time-international

normalized ratio within 2.5–3.0. Concomitantly, 5 mg/kg/day of aspirin plus 3 mg/kg/day of dipyridamole was used for antiplatelet therapy.

An LED light was used to check the internal surfaces of the pump and cannulae for attached thrombi every 4 h, which was essential. If a free-floating thrombus of any size was detected, the pump was immediately exchanged under sterile conditions in the operating room. If the thrombus was small (<3 mm) [4], whitish and immobile (small fibrin deposits), careful observation was continued without a pump exchange and anti-coagulation therapy was adjusted.

### Cannulae exit site care protocol

To date, there are no guidelines for VAD exit-site care. Daily scheduled disinfection around the cannulae exit sites is performed using benzalkonium chloride. Cannulae are stabilized using adhesive tape and bandages to reduce friction between the fabric of the cannula and the surrounding abdominal wall. Recently, a newly developed wound dressing material, Sorbact (Abigo Medical, Askim, Sweden), has been applied to eliminate the 'biofilm' that forms around cannulae exit sites [5, 6].

### Ventricular assist device explantation (recovery) protocol

When a monthly transthoracic echocardiogram revealed left ventricular ejection fraction >45% and left ventricular end-diastolic diameter <100% of the predictive normal on VAD, pump-off testing by cardiac catheterization was performed to assess left ventricular recovery. According to the previous report [7], VAD explantation was performed if a cardiac index >2.8 l/min/m<sup>2</sup>, left ventricular end-diastolic pressure <12 mmHg, central venous pressure <10 mmHg and mean pulmonary artery wedge pressure <13 mmHg were confirmed by off-pump testing. At that time, a dobutamine stress test and saline injection test were secondarily performed to examine a cardiac response to exercise or a response to increasing volume preload (diastolic function).

### Study method

This was a retrospective, non-randomized, single institutional study. A competing outcomes analysis was initially performed for a heart transplant, native myocardial recovery, ongoing support with device or death. The end point was then set at death and major complications, and risk factors for major complication-free survival were assessed. Major complications were defined as life-threatening complications, such as cerebrovascular accident, major infection (sepsis or surgical site infection requiring open sternal irrigation or device removal) and device malfunction requiring acute surgical treatment. Therefore, surgical bleeding requiring

chest re-entry, or pump exchange for thrombus formation, was not included. We examined possible risk factors such as: (i) body weight at implantation <5 kg; (ii) age at implantation <1 year old; (iii) VAD support duration >1 year; (iv) congenital heart disease as a fundamental diagnosis; (v) biventricular VAD (BiVAD) support; and (vi) surgical era. In addition, patients who showed an unusual clinical course were presented.

## Statistical analysis

All data are shown as the median with the interquartile range for continuous variables or as the number with % for categorical variables. The major complication-free survival rate was estimated using the Kaplan–Meier survival curve, and risk factors were analysed using the log-rank test. Due to the small sample size, a multivariate analysis could not be conducted. Statistical analyses were performed using the SPSS statistics package, version 19 (SPSS Inc., IBM Corp., Armonk, NY, USA). *P*-values <0.05 were considered statistically significant.

## RESULTS

### Patients

Among 56 paediatric patients with end-stage heart failure, 20 patients who were treated at our centre during the study period were identified (Table 1). Only 1 patient underwent heart transplant immediately without device support. No patient underwent alternative procedures, such as pulmonary artery banding. The median age and weight at surgery were 10.8 (7.9–33.2) months and 6.3 (4.6–10.2) kg. Ten patients (50%) were <5 kg at device implantation. Twelve patients (60%) were aged <1 year at device implantation. The main diagnoses were dilated cardiomyopathy (DCM) in 13 patients, fulminant myocarditis in 3, restrictive cardiomyopathy in 2 and congenital heart disease in 2. While 18 patients underwent left ventricular assist device (LVAD) implantation only, 2 patients required BiVAD support. Concomitant surgeries were aortic valve plasty, tricuspid valve annuloplasty and foramen ovale closure in 1 patient each.

### Competing outcomes

Follow-up was completed in all patients, and the median VAD support time was 365 (241–636) days. Ten patients (50%) were supported for >12 months, and 6 patients (30%) were supported for >20 months (Fig. 1).

Seven patients underwent heart transplant. Three patients underwent heart transplant in Japan, while 4 patients went abroad. Heart transplant has not been performed in the past 1.5 years due to a serious donor shortage during the coronavirus disease 2019 pandemic.

One patient with DCM who underwent BiVAD implantation at 5 months of age died 15 months later due to sepsis, as previously reported [8]. At 1 year after BiVAD implantation, septic shock derived from bacterial translocation and subsequent protein-losing enteropathy occurred. Both VADs were removed and replaced with central veno-arterial extracorporeal membrane oxygenation, without any improvement.

Five patients showed left ventricular recovery and were successfully weaned from LVAD support, and their LVAD was

**Table 1:** Patient characteristics (*n* = 20)

| Variables  | Median (interquartile range) or <i>n</i> (%) |
|--|--|
| Female   | 14 (70)                                      |
| Diagnosis  |  |
| Dilated cardiomyopathy                                       | 13 (65)                                      |
| Fulminant myocarditis  | 3 (15)                                       |
| Restrictive cardiomyopathy                                   | 2 (10)                                       |
| Congenital heart disease                                     | 2 (10)                                       |
| Tricuspid valve dysplasia, after biventricular repair        | 1  |
| Critical aortic stenosis, after balloon aortic valvuloplasty | 1  |
| Age at EXCOR implantation (months)                           | 10.8 (7.9–33.2)                              |
| <1 year  | 12 (60)                                      |
| Weight at EXCOR implantation (kg)                            | 6.3 (4.6–10.2)                               |
| <10 kg   | 14 (70)                                      |
| LVEDD at EXCOR implantation (% predictive normal)            | 178% (145–200)                               |
| LVEF at EXCOR implantation (%)                               | 19.5% (16.9–29.0)                            |
| Serum BNP (pg/ml)  | 3297 (1784–6980)                             |
| Pre-EXCOR ECMO support                                       | 10 (50)                                      |
| Associate syndrome   |  |
| Barth syndrome   | 1 (5)  |
| Neurofibromatosis  | 1 (5)  |
| OXPHOS disorder  | 2 (10)                                       |
| VAD support type   |  |
| LVAD   | 18 (90)                                      |
| BiVAD  | 2 (10)                                       |
| EXCOR pump size  |  |
| 10 ml  | 13 (65)                                      |
| 15 ml  | 3 (15)                                       |
| 25 ml  | 2 (10)                                       |
| 30 ml  | 2 (10)                                       |
| Cannulation site, LVAD, inflow                               |  |
| Left ventricular apex  | 20 (100)                                     |
| Cannulation site, RVAD, inflow                               |  |
| Right atrium   | 2 (100)                                      |
| Concomitant procedure  |  |
| Closure of foramen ovale                                     | 4 (20)                                       |
| Tricuspid valve annuloplasty                                 | 2 (10)                                       |
| Aortic valve repair  | 1 (5)  |

BiVAD: biventricular assist device; BNP: brain natriuretic peptide; ECMO: extracorporeal membrane oxygenation; LVAD: left ventricular assist device; RVAD: right ventricular assist device; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; OXPHOS: oxidative phosphorylation; VAD: ventricular assist device.

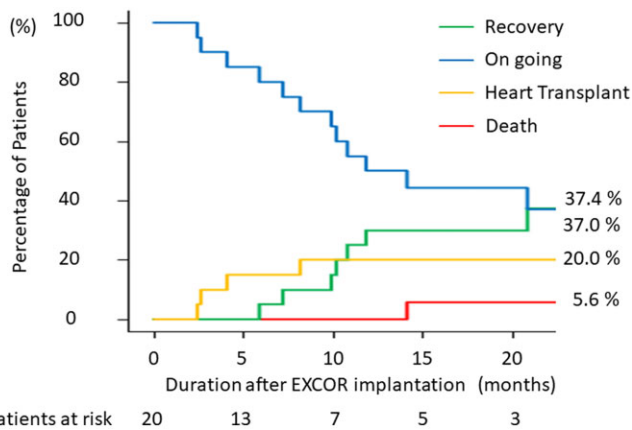
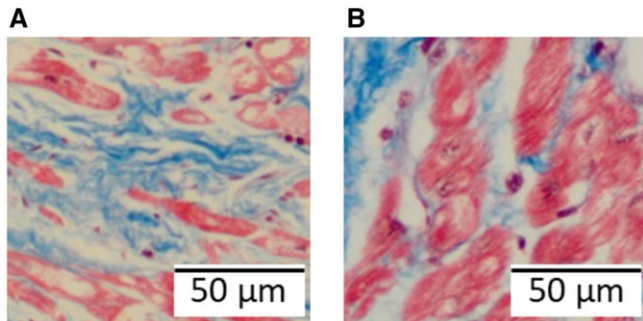
explanted at 2, 2.1, 4, 8.3 and 24 months after implantation. An 8-month-old girl with DCM whose interstitial fibrosis in the left ventricle was decreased at LVAD removal showed late recovery (24 months after LVAD implantation) (Fig. 2).

### Complications

Major complication-free survival rates at 6, 12 and 18 months were 79.3%, 49.6% and 38.6%, respectively (Fig. 3A) (Table 2). A univariable analysis was performed for baseline predictors of death or major complications (body weight at VAD implantation <5 kg, age at VAD implantation <1 year, VAD support duration >1 year, congenital heart disease, BiVAD), and the results showed that body weight <5 kg at implantation was the only factor associated with major complication-free survival (*P* = 0.003, Fig. 3B).

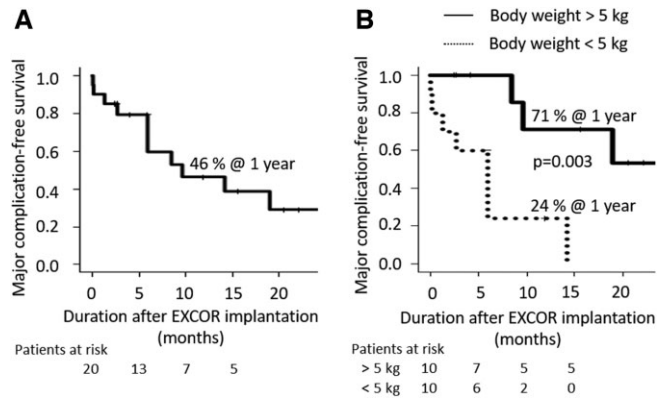
**Table 2:** Total number of death and complications ( $n = 20$ )

| Variables   | $n$ (%) |
|---|---------|
| Death   | 1 (5)   |
| Cerebrovascular event                                   |         |
| Haemorrhage   | 8 (40)  |
| Stroke  | 2 (10)  |
| Major infection   |         |
| Sepsis  | 1 (5)   |
| Cannulation site infection requiring surgical treatment | 6 (30)  |
| Devise malfunction requiring surgical treatment         |         |
| Pump exchange for thrombus formation                    | 6 (30)  |
| Membrane rupture  | 2 (10)  |
| Cannula dislocation                                     | 1 (5)   |

**Figure 1:** Competing outcomes (death, heart transplant, recovery, or ongoing support) in patients undergoing EXCOR Paediatric implantation.**Figure 2:** Photomicrographs ( $\times 500$ , scale bar =  $50 \mu\text{m}$ ) of Masson's trichrome staining at the mid-mural layer of the left ventricular wall at (A) EXCOR implantation and (B) removal 24 months later.

There were 6 exit-site infections for which surgical debridement was required (Fig. 4A). Among them, 2 patients had an infection that extended along the outflow cannula  $>1$  year after VAD implantation, which resulted in mediastinitis (Fig. 4B). Therapeutic effects of open sternal irrigation was limited, and the cannula was exchanged under cardiopulmonary bypass.

Eight patients developed intracranial Haemorrhage and 2 patients developed stroke. Among them, 3 patients (30%) had neurological sequelae. Early intracranial Haemorrhage ( $n=6$ ) occurred within 2 months after implantation. However, late

**Figure 3:** Major complication-free survival (A) and results by body weight (B).

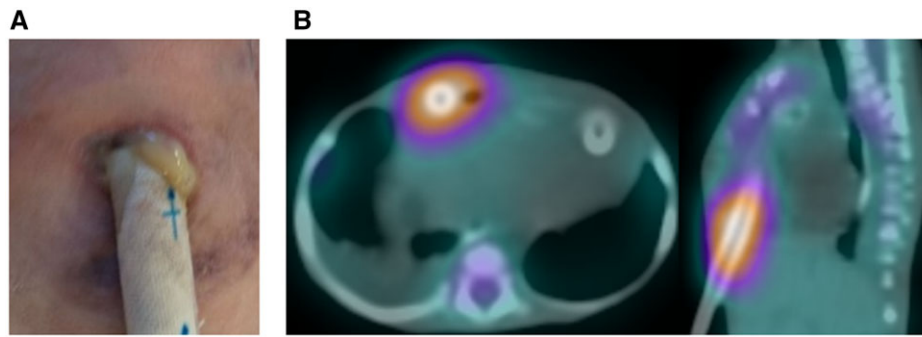
intracranial Haemorrhage ( $n=2$ ) tended to occur during surgical intervention due to unstable anti-coagulation conditions. Among the 6 pump exchanges, 2 pump exchanges were performed due to stroke. In both cases, part of a small whitish, but mobile, thrombus around the outflow connector disappeared just before developing paralysis. The median run-time of the pump exchange was 225 (200–253) days. The EXCOR ventricle pump size was chosen based on the patient's weight. A 10-ml pump was then used for 14 patients, a 15-ml pump was used for 2 patients, a 25-ml pump was used for 2 patients and a 30-ml pump was used for 2 patients.

Two patients experienced rupture of blood pump membranes. Two-layered membranes simultaneously ruptured in 1 patient 258 days after EXCOR implantation. In another patient, all three-layered membranes ruptured 293 days after EXCOR implantation. Blood travelled through to the driveline, so both the inflow and outflow cannulae were clamped quickly. The pump and line were immediately exchanged under sterile conditions. Fortunately, embolic stroke did not occur.

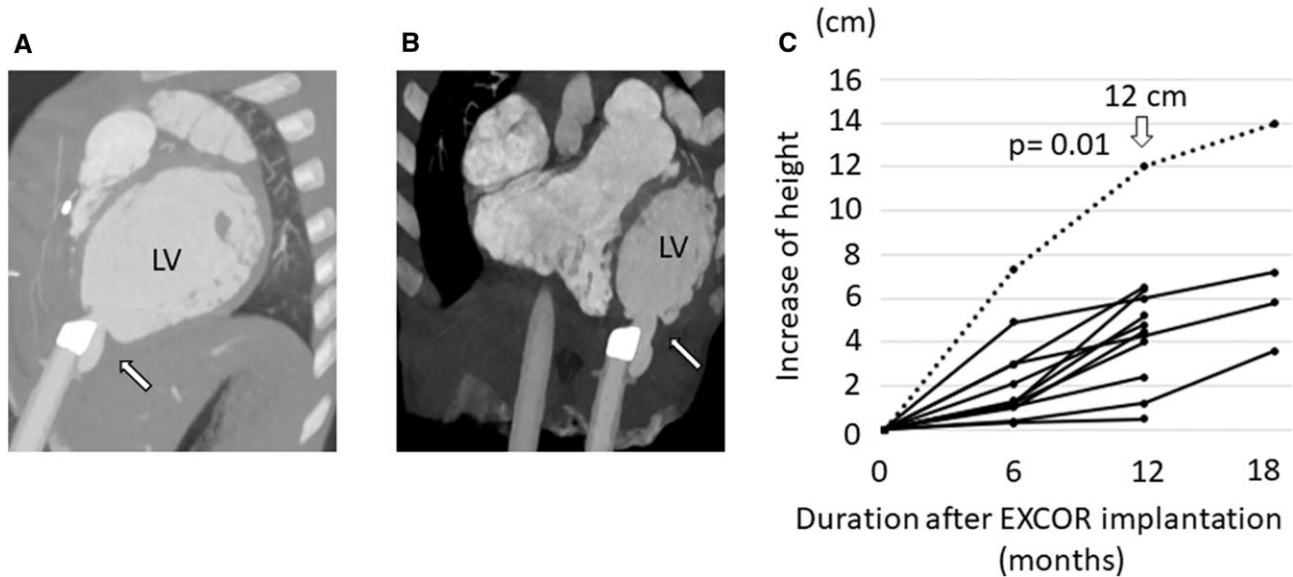
Inflow cannula dislocation was observed in an 11-kg girl with DCM (Fig. 5A and B). Her height increased 12 cm in the first 12 months after EXCOR implantation, which is significantly greater than that of other long-support patients (Fig. 5C). Left ventricular suction events frequently occurred, and a computed tomography scan showed detachment of the inflow cannula from the left ventricle apex, which resulted in pseudo aneurysm formation. Emergent revision of the inflow cannula was performed without any complications. This patient also showed a mismatch between calculated cardiac output and the volume pumped by the EXCOR ventricle at that time, so the pump size was increased from 10 to 15 ml.

## DISCUSSION

There is a chronic paediatric heart transplant donor shortage in Japan [9], and this lack of donors has become even more serious due to the corona virus disease 2019 pandemic [10]. However, the VAD program was started in Japan, and children supported by EXCOR Paediatric must wait longer for heart transplantation than usual. As a result, 30% of this study cohort were supported by EXCOR for  $>20$  months. Although previous studies included a few patients who were supported by EXCOR for  $>500$  days [11–14], the influence of a long EXCOR support period remains



**Figure 4:** Representative macro findings of (A) exit site infection and (B) gallium scintigraphy of outflow cannula infection.



**Figure 5:** Inflow cannula detachment was confirmed by (A) sagittal and (B) coronal views of contrast-enhanced computed tomography. (C) Increase in height of patients who received EXCOR ventricular assist device support for over 12 months ( $n=11$ ). The dotted line represents a patient who developed inflow cannula detachment.

unclear. Because EXCOR is not designed for a year-long (or longer) support period, new VAD-related complications or exacerbation of existing complications are a concern.

Low body weight is a well-known risk factor for increased mortality. Miera *et al.* [15] analysed 1832 children supported by EXCOR, and a body weight at EXCOR implantation  $<10$  kg was a significant risk factor, while body weight  $<5$  kg was the highest risk factor for mortality. The prognostic outcomes in both weight groups were reported to significantly improve in accordance with the surgical era (2000–2012 vs 2013–2017). Data from Paedi-EUROMACS analysed 341 VAD support patients including 193 who underwent pulsatile VAD, and a body weight at EXCOR implantation  $<20$  kg was identified as a risk factor for increased mortality [16]. Whereas risk factors for increased mortality could not be identified due to the low mortality rate in our cohort, our finding was similar to that of other reports, which showed that life-threatening complication-free survival decreased over time, and body weight at EXCOR implantation  $<5$  kg was also a risk factor for increased mortality.

In addition, intracranial Haemorrhage during the early period (i.e. within 2 months after implantation) may be caused by uncontrolled systolic hypertension. However, unlike adult patients, a longer duration of pulsatile VAD support for small

paediatric patients caused frequent life-threatening complications. In our cohort, major exit-site infection occurred in 30% of patients, neurological sequelae remained in 15% of patients and device malfunctions other than thrombus formation requiring pump exchange occurred in 15% of patients, which were comparable with current reports [15, 17, 18]. Small children will grow and develop rapidly after VAD implantation. Fixation of the driveline is difficult when toddlers start standing, walking and jumping, which makes the exit site unstable, and it also promoted bacterial colonization in 6 patients in the present cohort. Adhesion of the fabric around the cannulae to the subcutaneous soft tissue often became loose, which may have permitted bacterial invasion into the mediastinum along with the cannulae in 2 patients. Rapid somatic growth during infancy may gradually pull the cannulae out of the heart, which results in detachment of the inflow cannula from left ventricular apex in some patients. Multilayer membrane rupture in a blood pump is rare, but it can occur [19, 20]. Both multi-layer membrane ruptures in our cohort occurred within 1 year of EXCOR implantation, and they appeared to be caused by polyurethane membrane deterioration. The VAD pump rate was set at 120 beats per minute in a patient who experienced a simultaneous three-layer rupture. The VAD pump rate,

therefore, should be set as slow as possible to extend the device durability, but a low pump rate has been identified as a risk factor for pump thrombus and stroke in pulsatile VADs [21]. It is recommended that the EXCOR blood pump be exchanged once per year. However, simultaneous three-layer rupture is a life-threatening complication. Both the duration and VAD pump rate should be taken into consideration when deciding upon the timing of a scheduled pump exchange.

However, prolonged VAD support occasionally promotes sufficient native ventricular function recovery, which allows the patient to be weaned off VAD support [14, 22]. Thus, there should be no hesitation about a longer waiting time with VAD support if patient safety can be guaranteed. In addition to factors associated with VAD-promoted myocardial recovery in adults [23], age <2 years at VAD implantation, with a myocarditis diagnosis, and less myocardial fibrosis are thought to be predictors for recovery of left ventricular function during VAD support in children [14, 24]. However, the specific factors that promoted late recovery in this study have not been identified. Unlike the patients whose left ventricular function did not recover, the fibrotic area decreased in a patient who showed late recovery, as shown in Fig. 4. Matsumiya *et al.* [22] reported that when the changes in fibrosis are small, myocardial recovery is more likely. Miyagawa *et al.* [25] reported that the disturbances in the matrix metalloproteinases/tissue inhibitor system and renin-angiotensin-aldosterone system contribute to the changes in fibrosis after LVAD implantation, although the mechanism of LVAD-induced remodelling is not fully understood. Additional surgical experience is required to address this question.

## Limitations

This was a retrospective single-centre study involving a limited number of patients who underwent EXCOR Paediatric implantation. Thus, proper statistical analysis was not conducted.

## CONCLUSION

Survival during EXCOR Paediatric support was good, but the major complications that occurred were not negligible, especially in small children. While the lack of donors has become more serious due to the corona virus disease 2019 pandemic, left ventricular function recovery long after EXCOR implantation was an interesting phenomenon.

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## Author contributions

**Motoki Komori:** Writing – original draft. **Takaya Hoashi:** Conceptualization; Formal analysis; Investigation; Methodology. **Heima Sakaguchi:** Project administration; Supervision. **Kenta Imai:** Data curation. **Naoki Okuda:** Data curation. **Norihide Fukushima:** Supervision. **Kenichi Kurosaki:** Supervision. **Hajime Ichikawa:** Supervision.

## Reviewer information

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