Published in final edited form as:

J Heart Lung Transplant. 2013 January ; 32(1): 112–119. doi:10.1016/j.healun.2012.10.011.

Pre-clinical Evaluation of the Infant Jarvik 2000 Heart in a Neonate Piglet Model

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Abstract

BACKGROUND—The infant Jarvik 2000 heart is a tiny hermetically-sealed intracorporeal axial-flow ventricular assist device (VAD) designed for circulatory support for neonates and infants. The anatomic fit, acute biocompatibility and hemodynamic performance of the device were evaluated in a neonate piglet model.

METHODS—The infant Jarvik 2000 heart with two different blade profiles (low-flow blade design and high-flow blade design) was tested in 6 piglets (8.8±0.9 kg). Using a median sternotomy, the pump was placed in the left ventricle through the apex without cardiopulmonary bypass. An outflow graft was anastomosed to the ascending aorta. Hemodynamics and biocompatibility were studied for 6 hours.

RESULTS—All six pumps were implanted without complication. Optimal anatomic positioning was found with the pump body inserted 2.4 cm into the left ventricle. Hemodynamics was stable throughout the 6 hours. The pump flow increased from 0.27 L/min to 0.95 L/min at increasing speeds from 18 krpm to 31 krpm for the low-flow blade design, while the pump flow increased from 0.54 L/min to 1.12 L/min at increasing speeds from 16 krpm to 31 krpm for the high-flow blade design. Under higher speeds, over 80% of flow could be supplied by the device. Blood chemistry and final pathology demonstrated no acute organ injury or thrombosis for both the blade designs.

CONCLUSIONS—The Infant Jarvik 2000 heart is anatomically and biologically compatible with an acute neonate piglet model. This *in vivo* study demonstrates the future feasibility of this device for clinical use.

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Conflict of Interest

Robert Jarvik is an employee of Jarvik Heart, Inc. All other authors have no financial conflicts to disclose.

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Keywords

Ventricular assist device; Mechanical circulatory support; Pediatric patients; Hemodynamics; Biocompatibility

Introduction

Each year in the North America, approximately 400 children undergo heart transplantation. However, the number of heart transplants performed has been stagnant for more than a decade due to donor scarcity.^{1,2} The mortality of infants waiting for a heart transplant is reported at 25% to 30%, which is the highest among all pediatric and adult patients.³ Mechanical circulatory support devices (MCSs) are used to sustain these young patients as “bridge to recovery” or to heart transplant.^{4,5} In 2004, the pneumatic paracorporeal Berlin Heart EXCOR became the first ventricular assist device (VAD) that can be used for infants or neonates in the United States.^{6,7} It is available in a variety of sizes suitable for children between 3 kg and adult-size. The extracorporeal blood pump and cannula restrict the movement of the patient and increase complications during the long term application. Morbidity from stroke or anticoagulation was reported relatively high in the U.S. EXCOR experiences.^{8,9} The need for alternative second generation mechanical circulatory support systems specifically designed for infants and neonates led to the “Pediatric Circulatory Support Program” (PCSP) from the National Institutes of Health (NIH) in 2004, followed by the Pumps for Kids, Infants, and Neonates program (PumpKIN) in 2010.^{10,11}

The adult Jarvik 2000 VAD is distinguished from the other clinical VADs in its intra-ventricular location. The ergonomic efficiency of this design makes it ideal for the pediatric application. The clinical performance of the Adult Jarvik 2000 heart particularly with a novel cone type bearing has resulted in high expectations for the Pediatric Jarvik 2000 models.¹² With the support of the NHLBI PumpKIN program, a child and an infant size Jarvik 2000 heart are under development. We have reported the *in vivo* performance of the child Jarvik 2000 in a pediatric ovine model.^{13,14} In the present study, the anatomic fit, acute biocompatibility and hemodynamic performance of the infant Jarvik 2000 heart were evaluated in a piglet animal model.

Materials and Methods

Device Description

The infant Jarvik 2000 VAD is a tiny hermetically-sealed intracorporeal axial-flow VAD designed for circulatory support for neonates and infants (Figure 1A). It is designed to be placed in the cavity of the left ventricle (LV) and can directly pump blood from the LV to the aorta through an outflow graft (Dacron or PTFE). It is the size of an AA battery (10.5mm diameter, 5.2 cm long, 4 ml in volume and weighs 11 grams) and can provide pump flow up to ~3L/min with input power below 6 watts (Figure 1A). To design an optimized blade set for this low-flow patient group, two different blade profiles (the low-flow blade design and the high-flow blade design) were tested in the current study (Figure 1B).

Surgery

Six piglets (8.8±0.9 kg) were used in this acute study, hence three animals for each blade profile. Anesthesia was induced with fentanyl (10ug/kg), midazolam (0.2mg/kg) and maintained with isoflurane (1-3 %). A median sternotomy was made and the pericardium was opened to expose the heart. Systematic anticoagulation was achieved by administration of heparin (100-300 unit/kg) to produce the Activated Clotting Time (ACT) of about 300

seconds. The Dacron outflow graft was anastomosed to the ascending aorta with 6-0 Prolene sutures in an end-to-side fashion. A fixative cuff was sewn on to the apex of the heart using 4-6 2-0 Ti-Cron sutures with PTFE felt. The apex tissue within the cuff was removed via a coring device. The infant pump was inserted into the LV and initiated after de-airing from the outlet graft (Figure 2). Echocardiography was performed to verify the position of the pump in the left ventricle. A necropsy study was performed 6 hours after implantation of the device to evaluate the anatomic fit of the pump and end-organ damage of the liver, lungs, spleen and kidneys. The implanted components were retrieved for analysis of thrombotic events.

All the animals were treated in compliance with the “Guide for the Care and Use of Laboratory Animals” (National Institutes of Health publication 85-23, revised 1996). All surgical procedures and postoperative care were approved by the Institutional Animal Care and Use Committee of the University of Maryland at Baltimore.

Hemodynamic data collection

The central venous pressure (CVP), arterial blood pressure (ABP), left atrial pressure (LAP), left ventricle pressure (LVP), right ventricle pressure (RVP), and pulmonary artery pressure (PAP) were measured throughout the experiment. A 14-mm ultrasonic perivascular flow probe (Transonic Systems Inc., NY) was placed on the main pulmonary artery to measure the total cardiac output (CO). An 8-mm flow probe (Transonic Systems Inc., NY) was placed on the pump outflow graft to monitor the pump flow. The hemodynamic variables were recorded using a Dataq data acquisition system (DI-720, Dataq Instruments, OH) and analyzed using a custom-made Matlab program (Mathwork, MA).

Echocardiograms

An intraoperative echocardiogram was performed with a Sonos 5500 machine (Philips Medical, Andover, MA). Data was collected at pre-and post-implantation at varying pump speeds. Short axis view at mid-level of papillary muscle was used as the standard view to calculate the fractional area change. These areas were calculated at end-diastole (ED area) and end-systole (ES area). As the rotational speed was increased, the hemodynamic and echocardiographic data, as well as pump flow and cardiac output were collected simultaneously.

Biocompatibility Evaluation

Blood samples were collected at baseline, after implantation, and every two hours during the 6-hour study period. Blood samples were sent to a veterinary laboratory (Antech Diagnostics, Lake Success, NY) for blood chemistry and complete blood count (CBC). Measurement of plasma free hemoglobin (PFH) was carried out with a modified cyanomethemoglobin method for colorimetric determination of hemoglobin. Platelet activation was evaluated by the percentage of P-selectin (CD62P) positive platelets and plasma soluble P-selectin. P-selectin expression on platelets was quantified with flow cytometry. Plasma soluble P-selectin levels were measured by enzyme-linked immunosorbent assay (ELISA) developed in our lab as described.^{13,14}

Statistical Analysis

Data are presented as mean $\pm$ standard error of the mean (mean $\pm$ SE). A value of $p < 0.05$ was considered statistically significant. Differences between the intervals were evaluated using the Student t test.

Results

Study summary

All six pumps were successfully implanted without complication. All implantation procedures were finished within 30 minutes and average blood loss during implantation was 30 ± 15 ml. The 6 animals remained hemodynamically stable throughout the acute evaluation of the device.

Anatomic fit

The size of piglet hearts in this study (LV shorter than 6 cm in length) nearly matches that of the human infants. In the first two cases, the pumps were inserted completely into the LV (~3.0 cm in length). Endocardial bruising of the papillary muscles was found at necropsy. In the last four cases, the pumps were inserted into the LV ~2.4 cm in depth. As a result, there were no bruises found on the surface of the papillary muscles (Figure 3A, B). The diameter of the ascending aorta is ~0.9 cm in these animals, making it suitable to anastomose the outlet grafts in an end to side fashion. After six hours, the chest was closed to evaluate anatomic fit in the chest. As shown in Figure 3C,D, the device was well accommodated in the chest without suppression of the heart or the graft.

Pump flow

The pump flow and cardiac output (CO) were monitored continuously for 6 hours. The pump flow increased from 0.27 L/min to 0.95 L/min at increasing speeds from 18 krpm to 31 krpm for the low-flow blade design (Figure 4A), while the pump flow increased from 0.54 L/min to 1.12 L/min at increasing speeds from 16 krpm to 31 krpm for the high-flow blade design (Figure 4B). The Jarvik 2000 infant VAD with the high-flow blade design generated a higher flow compared to the Jarvik VAD with the low flow blade design at the same pump speed. The ratio of pump flow to cardiac output was increased accordingly. Under a higher speed, over 80% of flow was supplied by the device.

Echocardiographic Data

All the infant Jarvik pumps were well positioned inside of the LV apex as verified by the intra-operative echocardiogram. They were neither touching the septum or free wall of the LV nor interfering with the mitral valve or chordae tendineae. The LV size was reduced with an increase in the pump speed. The short axis views of the LV areas at different rotational speeds are shown in Figure 5A-D. Calculated areas at end-diastole (ED area) and end-systole (ES area) are shown in Figure 5 E,F. The reduction of the area corresponds well with the increase in pump speed, indicating effective unloading of the LV.

Hemodynamics

Hemodynamic data of the left heart and the right heart were recorded with increasing pump speeds (Figure 6). The mean LVP decreased, while the mean ABP and LAP did not change significantly (Figure 6A). The hemodynamics of the right heart (RVP, PAP, and CVP) had no significant changes with increased pump speeds as shown in Figure 6 B.

Typical hemodynamic traces in one animal with high-flow blade design at pump speeds of 0, 16, 21, 27, and 31 krpm are shown in Figure 6C. The pump flow increased from 0.54 L/min to 1.13 L/min with an increase in the pump speed from 16 krpm to 31 krpm. The LV pressure was fully unloaded at the pump speed of 31 krpm, while the aortic pressure became pulseless and LA pressure also decreased.

Hematology and Biocompatibility

All blood chemistry results related to the liver function and kidney function, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), creatinine and urea nitrogen were in the normal range at baseline and every two hours after the pump implantation. PFH did not increase during the 6-hour study period after implantation compared to the baseline (7.3 ± 0.9 mg/dL vs. 8.8 ± 1.1 mg/dL, $P > 0.05$). The LDH level remained stable (715 ± 31 U/L vs. 655 ± 17 U/L, $P > 0.05$). The platelet activation marker (percentage of P-selectin positive platelets and plasma soluble P-selectin) was not increased at the end of the experiments ($0.34 \pm 0.03\%$ vs. $0.43 \pm 0.03\%$, $P > 0.05$). There were no differences in the blood chemistry, PFH, and P-selectin positive platelets of the animals with the two different blade designs.

Necropsy

The typical pictures of heart, lung and devices at necropsy are shown in Figure 7A. In the first two cases, there were small areas of bruising on the surface the papillary muscles (Figure 7B). There was no evidence of endocardial injury to the interventricular septum and left ventricle in the last four cases. There was no gross evidence of infarction or thromboembolic events in the kidney, liver, and spleen. No gross thrombus formation was visible in the grafts (Figure 7C). The pumps were free of thrombosis or any materials in the areas close to the front bearing and the rear bearing (Figure 7D).

Discussion

The United Network for Organ Sharing (UNOS) reports that of the 1600 and more infants added to the heart or heart/lung transplant lists over the last decade, fewer than 50% received a donor organ.¹⁵ The use of MCSDs as a bridge to transplantation has been shown to decrease wait list mortality and improve the efficiency of organ allocation in children.^{4,16} MCSDs has also been used successfully as a bridge to recovery in children.⁵ However, current device options for infants and children are quite limited, particularly in regards to duration of the support.

Extracorporeal membrane oxygenation (ECMO) is only capable of providing support for days to, at most, a few weeks. This becomes a significant limitation when ECMO is used for the youngest patients who often require significant time on circulatory support until a suitable donor organ becomes available.¹⁷ The Berlin Heart Excor VAD became the first pediatric specific VAD in the United States to gain widespread use as a bridge to transplant for small children and infants. Since becoming available in a wide range of sizes, ranging from 10 to 80 mL, the Excor VAD provides circulatory support options for pediatric patients ranging from 2.5 kg infants to adolescents. Hetzer reported that discharge from the hospital after either weaning from the system or heart transplantation was achieved for 35% in the early time period (devices implanted between 1990 and 1998) and for 68% in the late time period (devices implanted between 1999 and 2004).⁹ Morales et al. reported that overall mortality with the Excor VAD was 23% in the initial multicenter North American experience and the Excor VAD bridged 70% patients to transplant and 7% to recovery.¹⁸ Although the clinical results of the Excor VAD are improved and encouraging, the Excor VAD is an extracorporeal device. The blood pump and the cannulae are outside of the body and restrict the movement of the patient, increasing long-term complications. Intracorporeal placement of a VAD allowing ambulation and improved nutrition will represent a significant advancement over early devices, as it has in adults. Additionally, the low-flow regions behind the Excor's valves are predisposed to forming thrombus. Morbidity from stroke or anticoagulation has been high and central nervous system adverse events ranged between 48% and 63% in the early U.S. Excor VAD experiences.⁸

The Adult Jarvik 2000 VAD has been successfully used in patients for over 10 years.^{19,20} In 2008, Westaby et al. reported that the first patient implanted with Jarvik 2000 VAD had achieved 7.5 years event-free survival.²¹ However, children are not necessarily "small" adults.¹⁰ The design of the pediatric Jarvik 2000 VADs is based on the Adult Jarvik 2000 but is not simply a miniaturization of the adult-size device. The pediatric models require new blade designs for the lower flow and pressure requirements of children and infants. The child-size model is a 35-g, 10-mL version of the Jarvik 2000 heart for long-term support in children weighing 15 to 25 kg. The infant-size blood pump is a smaller 11-g, 4-mL pump intended for 3- to 15-kg children. To our knowledge, it is the smallest pump used in the pre-clinical studies. The conical design of the Child Jarvik 2000 bearings has nearly eliminated complications such as thrombotic events and bearing fracture seen in previous animal studies.¹³ All animals with the high-flow Infant Jarvik 2000 heart or low-flow pump showed good hemodynamics and biocompatibility in the current study, suggesting that the device is an improvement beyond pediatric ECMO or the Excor VAD. The Jarvik 2000 infant heart with the high-flow blade design had higher current and power consumption but could generate a higher flow compared to the Jarvik heart with the low-flow blade design at the same pump speed. Both blade designs will be used for further studies in the future.

In summary, The Infant Jarvik 2000 maintained adequate circulatory support while unloading the LV and was anatomically and biologically compatible with an acute neonate piglet model. This preclinical, *in vivo* study demonstrated the acute safety and the future feasibility of this device

The major limitation of this study remains that this is only an acute study. It is impossible to evaluate complications of long-term VAD use that are seen clinically, such as infection, hemolysis and thrombosis. The long-term biocompatibility of the device needs to be tested in a chronic animal experiment. The challenge of managing a VAD-implanted piglet from a husbandry standpoint, impairs the ability to obtain suitable data. There are no reports of a long-term survival VAD study using a piglet model. Although the piglet model was well suited to access anatomic fit and acute hemodynamics, sheep will likely be used for chronic *in vivo* studies in the future.

Acknowledgments

Funding Sources

This study was supported in part by the National Institutes of Health (Contract Number: HHSN268201000013C).

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Figure 1. The infant Jarvik 2000 VAD. A, The pump and the low-flow blade; B, the low-flow blade design (left) and the high-flow blade design (right).

Figure 2.
The procedure of implantation of the infant Jarvik 2000 VAD in the piglet model

Figure 3.
Anatomy fitting of the infant Jarvik 2000 VAD in the LV (A,B) and in the chest (C,D)

A**Low-flow Design**

B**High-flow Design** **Figure 4.**

Pump Flow at increasing pump speeds. A, the low-flow blade design; B, the high-flow blade design.

Figure 5.

The short axis views of echocardiograms of the piglet implanted with a Jarvik 2000 infant pump at four pump speeds. The LV volume decreased with the increase of the pump speed (A, pump off; B, 20,000 rpm; C, 26,000 rpm; D, 28,000 rpm). The areas calculated at end-diastole (ED area) and end-systole (ES area) by echocardiography. E, the low-flow blade design; F, the high-flow blade design.

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Figure 6. Hemodynamic effects of the Jarvik 2000 infant heart to the left heart (A) and the right heart (B). Typical hemodynamic traces in an animal with the high-flow blade design at five different pump speeds (C).

Figure 7. Necropsy findings of the heart, lung and the device. A, The lungs, heart, and devices. B, Small areas of bruise on the surface the papillary muscles in the first two cases. C, Graft. D, The removed pump.