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Closing in on the PumpKIN Trial of the Jarvik 2015 Ventricular Assist Device

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Abstract

Background—The Infant Jarvik Ventricular Assist Device (VAD) has been developed to support the circulation of infants and children with advanced heart failure. The first version of the device was determined to have elevated hemolysis under certain conditions. The objective of this work was to determine appropriate modifications to the Infant Jarvik VAD that would result in acceptably low hemolysis levels.

Methods—*In vitro* hemolysis testing revealed that hemolysis was related to the shape of the pump blade tips and a critical speed over which hemolysis would occur. Various design modifications were tested and a final design was selected which met the hemolysis performance goal. The new version was named the Jarvik 2015 VAD. Chronic *in vivo* tests, virtual fit studies, and a series of other performance tests were carried out to assess the device's performance characteristics.

Results—*In vivo* test results revealed acceptable hemolysis levels in a series of animals and virtual fit studies showed that the device would fit into children 8 kg and above, but could fit in smaller children as well. Additional FDA-required testing has been completed and all of the data are being submitted to the FDA so that a clinical trial of the Jarvik 2015 VAD can begin.

Conclusions—Development of a Jarvik VAD for use in young children has been challenging for various reasons. However, with the hemolysis issue addressed in the Jarvik 2015 VAD, the device is well-poised for the start of the PumpKIN clinical trial in the near future.

Keywords

Ventricular Assist Device (VAD); Continuous-flow device; Pediatrics; Mechanical Circulatory Support (MCS); Pediatrics Heart Transplantation

1. Introduction

The need for circulatory support devices for small children with advanced heart failure, most of whom will need a heart transplant, is substantial and has been growing over the past decade. According to the Organ Procurement and Transplantation Network [1], 236 children below the age of 6 years received heart transplants in 2015. This is a 52% increase over the past decade. However, nearly a fifth of children awaiting a donor heart die each year [2]. A recent publication reveals that mortality of children on the cardiac transplant waiting list has decreased by more than 50% since 2005, the time when pediatric-specific ventricular assist devices (VADs) were introduced and which are now used to bridge 20% of pediatric patients to transplant [3]. However, that publication also shows that an etiology of congenital heart disease and weights below 10 kg are the two greatest risk factors for mortality for children on the heart transplant waiting list. This was the case before pediatric-specific VADs were available and is still true [3]. Consequently, the availability of effective circulatory support

devices for small children, especially those with congenital heart disease, remains an unmet need.

In 2004, with the paucity of devices at that time and the documented public health need for a device to specifically support the circulation of small children with heart failure, the NHLBI launched the Pediatric Circulatory Support Program. Through five separate contracts, this program supported the development of five novel circulatory support systems for infants and children from 2 to 25 kg with congenital or acquired cardiovascular disease [4,5]. The devices included an implantable mixed-flow VAD designed specifically for patients up to 2 years of age, another mixed-flow VAD designed to be implanted intravascularly or extravascularly depending on patient size, a compact integrated pediatric ECMO system, an apically implanted axial-flow VAD, and a paracorporeal or intracorporeal placed pulsatile-flow VAD. Good progress was made on these devices during the program, but significant work remained before any of them would be ready for clinical use.

To move pediatric circulatory support devices from the developmental stage to clinical application, the NHLBI launched the Pumps for Kids, Infants, and Neonates (PumpKIN) program in January 2010 when contracts were awarded to four different pre-clinical contractors: Ension, Inc. (PI: Mark Gartner, Ph.D), the University of Pittsburgh (PI: Harvey Borovetz, Ph.D.), the University of Maryland, Baltimore (PI: Bartley Griffith, M.D.), and Jarvik Heart, Inc. (PI: Robert Jarvik, M.D.). The awards were made to support the work necessary to receive Investigational Device Exemptions (IDEs) from the Food and Drug Administration (FDA) for these four different pediatric circulatory support devices with a target of October 2013. Three of the four contracts were awarded to contractors who had been part of the Pediatric Circulatory Support Program. The contract to the University of Pittsburgh was to develop the PediaFlow Ventricular Assist System (VAS) with their consortium partners, the Children's Hospital of Pittsburgh, Carnegie-Mellon University, LaunchPoint Technologies, and WorldHeart, Inc. The contract to the University of Maryland was to develop the Pediatric-Pump Lung (PediPL) with their corporate partner, Levitronix LLC. The contract to Ension, Inc. was for the pediatric Cardiopulmonary Assist System (pCAS) and the contract to Jarvik Heart was for the Infant Jarvik 2000 VAD, the predecessor to the Jarvik 2015 VAD. It should be noted that when the PumpKIN Program began, the Berlin Heart EXCOR Pediatric VAD, a pediatric-specific VAD used to bridge children with weights as low as 3 kg to cardiac transplantation, was only being used in the United States under compassionate use granted by the FDA. Berlin Heart eventually received approval of its Humanitarian Device Exemption application in 2011 to commercially distribute the EXCOR Pediatric VAD as a bridge to transplant in pediatric patients in the U.S.

NHLBI awarded a contract to the New England Research Institutes, Inc (NERI) in April 2012 to be the Data and Clinical Coordinating Center (DCCC) for the PumpKIN clinical trials of the circulatory support devices for which IDEs were granted. In this capacity, NERI has overall responsibility for the operation of the trials and provides the necessary administrative guidance, oversight, and support to achieve the objectives of the trials. Their initial tasks involved coordination and writing of the protocols and the manuals of operations and procedures for the trials and providing these and other needed clinical information to the

four device contractors for their IDE applications. Because two devices were ventricular assist systems (the PediaFlow and the Infant Jarvik 2000) and two were compact extracorporeal membrane oxygenator (ECMO) systems (the PediPL and the pCAS), two very different protocols were developed for the two types of devices. While many parts were similar for the protocols of similar devices, each was distinct based on the characteristics of the specific device.

Funding on the PediaFlow device was halted before the contract ended after WorldHeart was acquired by HeartWare International, Inc. in August, 2012. Following the acquisition, HeartWare decided not to assume the responsibilities that WorldHeart had agreed to under their subcontract to the University of Pittsburgh. Without a way to remedy the contract with the University of Pittsburgh, it was terminated in early 2013.

In the second quarter of 2013, the remaining three contractors requested supplemental funds and time to complete the work and obtain IDEs by the contract end date (January 2014). Additional funding and time to obtain the IDEs were provided to Jarvik Heart and the University of Maryland. Ension was not provided any supplemental funding due to the costs and timing to complete a substantial amount of additional work on the pCAS and the reality of budget constraints resulting from federal budget sequestration in 2013.

It should also be noted that in August 2011 Thoratec Corp. acquired the medical division of Levitronix LLC and became the University of Maryland's new corporate partner in the work on the PediPL device. However, in November 2013, Thoratec terminated its sub-award agreement with the University of Maryland. These setbacks made it impossible to submit the IDE application by the contract's end in January 2014. However, Thoratec agreed to transfer the IP back to the University of Maryland and to be an original equipment manufacturer (OEM) supplier as needed in the event that the University of Maryland wished to pursue the completion of the work on the PediPL.

Due to various technical challenges, Jarvik Heart also did not achieve the goal of obtaining an IDE by the end of their contract in January 2014. At this point, NHLBI opted to allow NERI, under their DCCC contract, to serve as an administrative center where they would subcontract with one or more of the PumpKIN device contractors to complete the remaining work on their devices until IDEs were approved. At that time, a decision was made to limit the PumpKIN clinical studies to the first VAD and ECMO system to receive approval. Proposals were invited from each of the four original PumpKIN device contractors and proposals were submitted by Jarvik Heart, the University of Maryland, and Ension, Inc. Upon review of the proposals, Jarvik Heart and the University of Maryland were selected by NERI based on proposed remaining work, timeline to complete the work, coordination plans, qualifications of personnel and vendors, and budget. The selection and continued funding of these two contractors was approved by NHLBI. Unfortunately, before the award to the University of Maryland was made, the University of Maryland could not obtain a guarantee from Thoratec that a company that was being set up to continue the work and produce the device would be able to commercialize the product after the trial was completed. Without such an agreement, the University of Maryland could and would not continue the

work. As a result, only Jarvik Heart received funding and continued working towards an IDE for the Infant Jarvik 2000 VAD after January 2014.

The Infant Jarvik 2000 VAD was designed for intracorporeal placement and was about the size of an AAA battery. The device had no inflow cannula since it was designed to be implanted through the apex of the heart. The outflow cannula was an 8mm ePTFE Vascutek reinforced Maxiflo™ graft (Vascutek Ltd., Inchinnan, Scotland, UK) that was anastomosed to the ascending aorta. The Jarvik Heart analog controller used to control the speed of the device was connected to the pump via six multi-stranded wires. The speed and flow of the device ranged from 18,000–28,000 rpm and 0.5 to 1.5 LPM (with an afterload of 45 mmHg), respectively.

After the requirements for the IDE submission for the Infant Jarvik 2000 VAD were completed, the IDE application was submitted by Jarvik Heart, Inc. in April 2014. A disapproval letter from the FDA received in May 2014 included questions about some of the tests that were performed. To address some of the questions, additional tests were performed. The new test results, along with additional information, clarifications, and justifications were provided in response to the FDA questions in an amendment to the IDE application in September 2014. The IDE was disapproved again specifically for the results from the *in vitro* hemolysis tests. These tests were run per the “Standard Practice for Assessment of Hemolysis in Continuous Flow Blood Pumps,” ASTM F1841-97, with deviations for testing a continuous flow VAD intended for pediatric subjects instead of adult subjects, such as a differential pressure of 45 mmHg rather than 100 mmHg. The testing was performed at the Texas Heart Institute on 6 test devices while running at the maximum intended speed of 28,000 rpm. The *in vitro* hemolysis results of the Infant Jarvik 2000 are shown in Figure 1. The mean Normalized Index of Hemolysis (NIH) over the 5-hour test for the for each ranged from 0.20 to 1.04 grams of plasma-free hemoglobin/100 liters of blood (bovine) and the overall mean for all 6 pumps over the test was 0.70 g/100 L. A Medtronic BP-50 (Medtronic, Dublin, Ireland), a centrifugal blood pump approved for pediatric use for up to 6 hours, was used as a control for the tests; the mean NIH value for the BP-50 tested on three separate days ranged from 0.003 to 0.059 g/100 L.

The PumpKIN team, consisting of NHLBI, the DCCC, and Jarvik Heart staff, had considered the hemolysis test results as too elevated before submitting the amended IDE application. Although the team anticipated the IDE application would not be approved based on the hemolysis results, the team decided to submit the application (1) to determine if the FDA identified any other engineering issues to address, (2) to obtain the FDA’s advice on the hemolysis issue as the PumpKIN team began deliberating options to address the hemolysis issue at that time and (3) to determine if the proposed clinical trial design was satisfactory to evaluate the safety and probable benefit of the device.

The objectives of the studies conducted and described below were to determine appropriate modifications to the Infant Jarvik VAD that would result in low, acceptable hemolysis levels and still meet the program goal to be for infants and children from 2 to 25 kg with congenital or acquired cardiovascular disease. Demonstration of achieving acceptable

hemolysis levels would be assessed by *in vitro* hemolysis testing and appropriate chronic *in vivo* testing.

2. Methods and Results

2.1 Redesign and Assessment of the Jarvik 2015 VAD using *In Vitro* Hemolysis Testing

The PumpKIN program contracted consultants with broad expertise relevant to VADs (computational fluid dynamics (CFD), engineering, device development, regulatory) to aid in the evaluation, assessment, and resolution of the hemolysis issue in the Infant Jarvik 2000 VAD. The group considered various causes of the hemolysis including heating, cavitation, blade clearances, bearings, and material finishes. From September 2014 through April 2015, various tests and analyses were performed to pinpoint the cause of the hemolysis and to modify the design of the pump to achieve acceptable levels. A series of *in vitro* hemolysis tests conducted at Texas Heart Institute on various minor modifications to the Infant Jarvik 2000 revealed that the hemolysis was substantially reduced by adding a radius to the impeller tips and when the impeller speed was kept below 20,000 rpms. No heating or cavitation in the pump was observed. Because running the Infant Jarvik 2000 at 20,000 rpms would limit the flow to less than 0.7 LPM, the group considered the best alternative was to increase the diameter of the pump so that it could be run at lower speeds while delivering a flow range appropriate for its use in the pediatric population for which it is intended.

Various impeller blade designs were considered, evaluated using CFD, and underwent *in vitro* hemolysis testing using prototypes. Prior to starting the *in vitro* hemolysis testing, a maximum NIH level of 0.10 g/100L was chosen as the initial goal to achieve for the next version of the Infant Jarvik VAD. Upon completion of the hemolysis testing on the various prototypes, one met the initial NIH goal over the specified pump speed/flow range and was subsequently selected as the next version of the Infant Jarvik VAD. Because the work was completed in 2015 and the new outer hub diameter of the device was 15mm, the new version of the device was initially named the “Infant Jarvik 2015 VAD” and then shortened to the “Jarvik 2015 VAD.” The results of the *in-vitro* hemolysis testing of the Jarvik 2015 VAD at high (3 L/min) and low (1 L/min) flows are shown in Figure 1 for comparison to the results of the Infant Jarvik 2000 VAD. The average NIH over the 5 hours of testing for the two pumps tested at the 1 L/min and 3 L/min flow rates was 0.040 and 0.054 g/100L, respectively. The corresponding reductions in NIH for the Jarvik 2015 VAD at the low and high flow conditions from that of the Infant Jarvik 2000 VAD are 94% and 92%, respectively.

A cutaway view of the Jarvik 2015 VAD system’s titanium axial flow pump is shown in Figure 2. As shown, the pump has two circular-arc impeller blades, a set of stator blades, and two ceramic cone bearings. Like the Infant Jarvik 2000 VAD, the Jarvik 2015 has no inflow cannula, has an 8 mm outflow cannula, and utilizes a Jarvik Heart analog controller. Figure 3 provides a comparison of the Jarvik 2015 VAD to the Infant Jarvik 2000 VAD. The Jarvik 2015 VAD is, of course, larger than the Infant Jarvik 2000 VAD due to the increased rotor hub diameter. The outer diameter is 15 mm and the overall length is 55 mm, making it about the size of an AA battery. The operating speed range of the Jarvik 2015 VAD is

10,000 to 18,000 rpms, which produces a flow range of 0.5 to 3.0 LPM at a differential pressure of 45 mmHg. With the change in hub design, a few other important design improvements were incorporated based on feedback from surgeons involved with the program. These were: (1) an elbow was placed on the outflow of the VAD to reduce the potential for kinking of the outflow graft since the flow must be redirected 180° due to placement of the pump and where the graft will be anastomosed to the aorta, and (2) the 8mm ePTFE outflow graft used previously was replaced with an 8mm gelatin-sealed, spiral-supported polyester graft by Vascutek. The gelatin-sealed polyester graft was preferred to the ePTFE in the 8 mm size due to potential issues related to bleeding (due to needle punctures during suturing) and plasma weeping through the ePTFE grafts. Of note also are the changes from a parabolic blade arc to a circular one and the increase in stator blades from three to four. Also, another change is that a radius was added to the impeller blade tips of the Jarvik 2015 VAD.

2.2 *In Vivo* Animal Studies of the Jarvik 2015 VAD

A series of animal studies were performed to assess the *in vivo* performance on the Jarvik 2015 VAD. Only key details are provided here. Detailed results have been submitted for publication (personal communication, Iki Adachi, MD, May, 2016). The implants of the device were performed in small (19–30 kg) Barbado sheep. Two non-Good Laboratory Practice (GLP) implants, which were performed to gain experience with the device and implant procedure, achieved the 30-day survival goal and eight GLP implants were performed to achieve a goal of six survivors to 60 days. The two that did not survive died from non-device-related complications (tension pneumothorax and small bowel obstruction). The devices were operated at the highest flow rate appropriate for each animal; this resulted in a pump speed range of 11,000 to 18,000 rpms in the six survivors. A flow study conducted in the 2 non-GLP sheep demonstrated favorable increases in flow (up to 3.0 L/min) in proportion to change in pump speed. Plasma-free hemoglobin and lactate dehydrogenase were monitored throughout the study; the results demonstrated minimal hemolysis despite high pump speeds and a mild anticoagulation regimen. The animals were all in good health with good weight gain over the 60-day period for the GLP study. Overall, the results demonstrated favorable biocompatibility and hemodynamic performance of the Jarvik 2015 VAD in the chronic sheep model.

2.3 Other Testing and Analyses of the Jarvik 2015 VAD

Because the Jarvik 2015 VAD increased in size over the previous version of the device, work was performed at the Arizona State University and Phoenix Children's Hospital to determine the smallest child into which the Jarvik 2015 VAD would fit. The work was done by performing virtual fits of the device using anonymized available CT and MRI data from six children with advanced heart failure who might be appropriate candidates for the device and spanning the expected potential size range [7]. The weights for the six cases were 2.6, 4.3, 8.4, 8.4, 13.6 and 16.0 kg, corresponding to a range in BSA of 0.26–0.68 m². The results indicate that the device would fit conventionally in the 8.4 kg (and larger) patients and would fit in the 4.3 kg patient if implanted using a sub-diaphragmatic pocket, i.e. a space where the pump and the outflow elbow would sit by dividing the left hemidiaphragm.

Other testing required for assessing the device and for and IDE submission to the FDA to begin the PumpKIN trial included various grafts tests, GLP *in vitro* hemolysis tests, computational fluid dynamics analyses, sterilization validation testing, and electrical safety. These have been completed and the results appear to confirm previous results or pass specific standards.

3. Discussion and Conclusions

3.1 The Long Development Path

The development of VADs to the point that they are ready for a clinical trial takes many years, even when the path is smooth, due to the required high level of engineering and design, the crucial testing and analyses needed to evaluate the design and the device's performance, and then the extensive testing and analyses required to assess the risks and to meet FDA requirements. However, this can become an extended iterative process when issues arise that indicate a problem with the performance of the device that require a redesign. This has been common for many VADs developed over the years and, unfortunately, sometimes the issues are not observed until after clinical use has begun.

Similarly, the development of the Jarvik 2015 VAD, a fully implantable continuous flow pump intended for infants and smaller children who are difficult to support with existing devices, has been long, stretching from 2004 to the present. However, most of the time it has taken was planned. The initial delays to the IDEs were not evident until 2013 and resulted in a one year delay. The issue of high hemolysis in the Infant Jarvik 2000 VAD was a setback that required an additional two years to address. While the solution to the issue was determined in approximately 6 months, to perform a variety of *in vitro* test and a series of non-GLP and GLP tests, complete the analyses of the results, and provide the necessary detailed reports required time and effort to work through, which is emblematic of device development. The delay in NHLBI's original timeline was unfortunate but necessary to complete the necessary work and demonstrate acceptable hemolysis levels. Fortunately, the hemolysis issue was determined prior to beginning a clinical trial and proved to be an important discovery that, in the end, avoided exposing patients to excessive risks.

The developmental pathway for the Jarvik 2015 has been unique in that the government has taken a lead role and, as a result, it has involved the special productive collaboration and group effort of individuals from the VAD industry, various medical, engineering, and science academic departments and companies, and small business. Through their efforts to develop the device, specifically overcome the hemolysis issue, and plan the clinical study, the Jarvik 2015 is now well-positioned for another IDE submission to the FDA to begin the clinical trial in the near future. This trial, the PumpKIN clinical trial of the Jarvik 2015 VAD, is discussed below.

3.2 The PumpKIN Clinical Study

3.2.1 Protocol Development—The protocol is an essential part of the IDE submission and was updated for the Jarvik 2015 VAD. Careful consideration was given to the size/weight range of the children for the study given the size and operating performance of the

Jarvik 2015 VAD. While the virtual fit study results indicated that the device could fit in rather small patients using the sub-diaphragmatic pocket, the data currently only sufficiently supports the use of the device for the patients for whom a flow of 1 LPM is sufficient. Using a minimum normal cardiac index (CI) of 2.5 L/min/m², the corresponding minimum BSA for that flow rate is 0.4 m². This BSA corresponds to a weight of approximately 8 kg. As a result, the clinical trial protocol was amended to the weight range of 8.0 to 20.0 kg. (The upper limit was chosen so as not to compete with VADs designed for adults but which are being used in children large enough for them.) The PumpKIN Trial Executive Committee agreed that expanding the inclusion criteria to those children with weights lower than 8 kg would be considered if sufficient evidence to do so is obtained in the future.

The PumpKIN clinical trial of the Jarvik 2015 VAD is designed as a prospective two-arm randomized controlled trial. The randomization ratio will be 1:1 between the Jarvik 2015 VAD and the control device, the Berlin Heart EXCOR VAD. Patients eligible for the trial will be limited to (among other inclusion/exclusion criteria) those with severe heart failure with two-ventricle circulation and weighing between 8 and 20 kg. The sample size is 44 per arm and the number of sites for the trial will be approximately 22. The trial has been designed to support a Humanitarian Device Exemption application to the FDA at the trial's conclusion. As such, its design is structured to assess and potentially demonstrate the safety and probable benefit of the Jarvik 2015 VAD. The primary safety endpoint is serious adverse events while on VAD support up to the first 180 days after implant, and the primary probable benefit endpoint in the trial is survival without new severe neurological impairment up to recovery or transplant, or 180 days of VAD support.

3.2.2 Plans for starting the clinical trial—The IDE for the PumpKIN trial for the Jarvik 2015 VAD was submitted in August 2016 and the NHLBI-appointed PumpKIN DSMB will meet to consider approval of the protocol in October 2016. The anticipated start date for the trial, assuming that the IDE and the protocol are approved in this time frame, is late in the first quarter of 2017.

The trial will start with a Vanguard phase at seven high-volume clinical sites, which is anticipated to enroll ten patients with five receiving the Jarvik 2015 VAD.

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Figure 1.

In Vitro hemolysis test results for the Infant Jarvik 2000 and Jarvik 2015 VADs. Results for the control device (Medtronic BP-50 Bio-Pump) are shown for comparison. The normalized index of hemolysis (NIH) is the average mass (in grams) of plasma free hemoglobin measured per 100 liters of bovine blood pumped by the device over a 5-hour period. The mean NIH results for the Infant Jarvik 2000 VADs are for its highest flow rate (1.5 L/min) and ranged from 0.2 to 1.04 g/100 L. In contrast, the mean NIH results for the Jarvik 2015 VAD ranged from 0.03 to 0.08 g/100 L across a 1 to 3 L/min flow range. The reduction in the mean NIH in the Jarvik 2015 VAD from that observed in the Infant Jarvik 2000 VAD is over 90%.

Figure 2.

The Jarvik 2015 impeller blades (green) are attached to the rotor (also green). The stator blades (blue), the housing (gray), and cone bearing rings with posts (black) are stationary and only the rotor with the attached impeller blades move. The inflow is to the left, with flow from left to right in the illustration.

Feature	Infant Jarvik 2000 VAD	Jarvik 2015 VAD

Rotor Hub Outer Diameter	3.6 mm	5.6 mm
Flowpath Inner Diameter	6.1 mm	8.9 mm
Overall Length	47 mm	55 mm
Housing Outer Diameter	11 mm	15 mm
Rotor Length	37 mm	45 mm
Outflow Direction	0°	90°
Bearing Width	2.5 mm	3.2 mm
Number of Stator Blades	3	4
Number of Impeller Blades	2	2
Blade Shape	Parabolic-arc	Circular-arc
Radiused Impeller Blades	No	Yes
Speed Range	18,000 to 28,000 rpm	~10,000 to 18,000 rpm
Flow range	~.5 to 1.5 LPM	~0.5 to 3.0 LPM
Graft	8 mm ePTFE	8 mm gelatin-sealed polyester

Figure 3.

Design features of the Infant Jarvik 2000 and Jarvik 2015 VADs. The impeller of the Infant Jarvik 2000 VAD is shown in the image. While the Infant Jarvik 2015 is larger, it features a greater flow range, radiused blade tips, a polyester outflow graft, and an outflow elbow.

Figure 4.
Central Picture Legend: The Infant Jarvik 2015 Ventricular Assist Device