The miniaturized pediatric continuous-flow device: Preclinical assessment in the chronic sheep model

Iki Adachi, MD,[a,b] Sarah Burki, MD,[a,b] David Horne, MD,[a,b] Gil G. Costas, DVM,[c] Taylor Spangler, DVM,[d] Robert Jarvik, MD,[e] John Teal, BS,[e] J. Timothy Baldwin, PhD,[f] Kurt Dasse, PhD,[g] M. Patricia Massicotte, MD,[h] Jeff Conger, BS,[c] William E. Cohn, MD,[c] and Charles D. Fraser, Jr, MD[a,b]

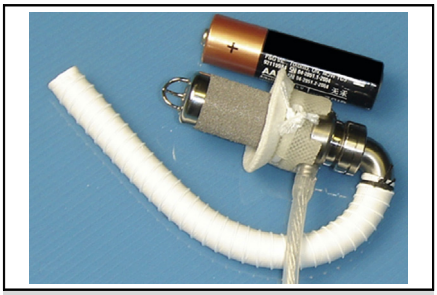
ABSTRACT

Background: The Infant Jarvik 2015 is an implantable axial-flow ventricular assist device (VAD) that has undergone the major evolutionary design modifications to improve hemocompatibility. This study was conducted in anticipation of data submission to the US Food and Drug Administration to obtain Investigational Device Exemption approval.

Methods: The VAD was implanted via a left thoracotomy in Barbado sheep (n = 10, 26 (19-34] kg). Anticoagulation was maintained with coumadin, with a target international normalized ratio of greater than the individual sheep's baseline values. The VAD was managed at the highest possible speed as clinically tolerable. Complete necropsy was performed at the end of the study.

Results: There were 2 early mortalities: tension pneumothorax (n = 1) and shower emboli of the fragmented myocardium (n = 1). The remaining 8 sheep (2 with 30-day and 6 with 60-day protocols) completed the anticipated study duration in excellent condition, with the 6 completing 60-day sheep showing appropriate weight gain during support. There were no signs of clinically significant hemolysis, with the final plasma-free hemoglobin of 2 (1-17) mg/dL. Necropsy showed old renal infarction in 7 sheep. Although thromboembolism can be the potential etiology, given the mild anticoagulation regimen, other sources of emboli were identified in 2 sheep (graft coating material and fragmented myocardium). Flow study demonstrated favorable increase in flow (up to 3.0 L/min) in proportion to change in pump speed.

Conclusions: This study has demonstrated that the Infant Jarvik 2015 VAD is capable of maintaining its functionality for an extended period of time with minimal hemolysis. (J Thorac Cardiovasc Surg 2017;154:291-300)



The Infant Jarvik 2015 ventricular assist device.

Central Message

This preclinical study has demonstrated the Infant Jarvik 2015 VAD maintains its functionality for an extended period of time with minimal hemolysis.

Perspective

Although continuous-flow devices are being used more often in children, pulsatile devices remain the only feasible options in infants due to size constraint. The Infant Jarvik 2015, the first continuous-flow device designed for small children, has demonstrated favorable hemocompatibility in this preclinical study. This study may herald the era of continuous-flow support in small children.

See Editorial Commentary page 301.

The infant Jarvik ventricular assist device (VAD) has been under development for more than a decade, as 1 of the 6 devices originally funded by the National Heart, Lung, and Blood Institute's Pediatric Circulatory Support program[1] and subsequently by the PumpKIN program.[2] The Infant Jarvik VAD is currently the only device remaining in the

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From the [a]Michael E. DeBakey Department of Surgery, Baylor College of Medicine; [b]Congenital Heart Surgery, Texas Children's Hospital; [c]Texas Heart Institute, Houston, Tex; [d]VDx Preclinical, Davis, Calif; [e]Jarvik Heart, Inc, New York, NY; [f]National Heart, Lung and Blood Institute, Bethesda, Md, [g]Geno, LLC, Cocoa, Fla; and [h]Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada.

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Address for reprints: Iki Adachi, MD, Congenital Heart Surgery, Texas Children's Hospital, Baylor College of Medicine, 6621 Fannin St, WT19345H, Houston, TX 77030 (E-mail: iadachi@bcm.edu).

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Abbreviations and Acronyms
ACT = activated clotting time
FDA = Food and Drug Administration
GLP = good laboratory practice
IDE = Investigational Device Exemption
INR = international normalized ratio
IV = intravenous
rpm = revolutions per minute
VAD = ventricular assist device

program, which certainly highlights the extremely challenging nature of VAD development, especially those for pediatric use. In particular, development of an ''implantable'' VAD suitable for infants has been an especially demanding task. Although an infant VAD must meet all of the essential criteria required for adult VADs, the infant VAD also must function at a higher pump speed without increased blood damage despite much smaller blood flow channels and clearances than in the adult device. Infants VADs also require very fine motors, precise welds of paper-thin titanium components, and optimized hydrodynamic pump blade shapes for this unique heart failure population.

The initial approach was to scale down the adult Jarvik 2000; however, animal studies revealed that thrombosis occurred in the pin bearings used in the early prototypes that were as small as a AAA battery. The breakthrough to address this issue was the development of ''cone'' bearings that enabled the infant VAD to run long-term without bearing thrombosis. The product with the cone bearings was termed the ''Infant Jarvik 2000 VAD'' (11-mm outer diameter). The Infant Jarvik 2000 was extensively tested in an acute piglet model (8 kg)[3] and in a chronic lamb model (25 kg) at a different institution. The data from these and other preclinical studies were submitted to the US Food and Drug Administration (FDA) to obtain Investigational Device Exemption (IDE) approval to initiate a clinical trial (the so-called PumpKIN trial) in August 2014. Unfortunately, in September 2014, the IDE approval was not granted, resulting in the postponement of the PumpKIN trial. The major concern raised by the FDA was significant hemolysis, as evidenced in the in vitro hemolysis test, coupled with the poor condition of the animals implanted with the Infant Jarvik 2000. Since then, the Infant Jarvik VAD has undergone major evolutionary design modifications, yielding a successful implantable infant-size VAD, named the Infant Jarvik 2015 VAD, which demonstrated a much improved hemolysis profile during in vitro testing.[4] The specific aim of this study was to test biocompatibility and hemodynamic performance of the Infant Jarvik 2015 in a chronic sheep model, with a special emphasis on addressing concerns raised by the FDA in the previous preclinical studies.

METHODS

Infant Jarvik VAD Design Change

A pump optimization effort was initiated by identifying the actual source of hemolysis using computational fluid dynamics analysis, actual pump modifications, and bench hemolysis tests. Although hemolysis was determined to be substantially decreased at pump speeds below 20,000 rpm, the Infant Jarvik 2000 was unable to produce sufficient flow and pressure at the lower speeds. The decision was made to increase the pump outer diameter to 15 mm and to redesign the blades (Figure 1). With its larger flow channels, the new pump was designed to provide a flow of up to 3 L/min at 18,000 rpm. The major differences of the old and new pumps are shown in Figure 2.

Hemocompatibility of the new pump was assessed by the bench hemolysis testing. There was more than 10-fold reduction in the normalized index of hemolysis down from >0.6 g/100 L with the old pump to <0.04 g/100 L with the new pump. The normalized index of hemolysis of the new pump is favorably compared with published data of the other devices previously developed.[5,6] Based on these results, it was felt that the Infant Jarvik 2015 should be progressed to the next phase of testing: a preclinical trial in a chronic animal model.

Animal Model

The study was approved by the Texas Heart Institute's Institutional Animal Care and Use Committee, and all sheep received humane care in accordance with Principles of Laboratory Animal Care (National Society of Medical Research) and the Guide for the Care and Use of Laboratory Animals (National Institutes of Health). We planned to complete 30 (+5) days support with the VAD in the first 2 sheep as a non-GLP (Good Laboratory Practice),[7] and 60 (+10) days support in the subsequent 8 sheep as a GLP study. In the two 30-day sheep, VAD flow measurement was conducted intraoperatively at the completion of the study immediately before euthanasia. Via a repeat left thoracotomy, the outflow graft of the VAD was exposed. A transonic flow probe (Transonic Systems, Inc, Ithaca, NY) was placed on the graft. VAD flow was measured at different levels of pump speed, starting from 11,000 to 18,000 rpm.

Implantation Procedure

In each case, the sheep was placed in a stanchion for acclimatization before surgery. Food was withheld approximately 8 to 10 hours before surgery and water was available ad libitum. An intravenous (IV) line was placed in the right internal jugular vein for hydration. The sheep was premedicated with glycopyrrolate (0.01-0.025 mg/kg subcutaneous) and

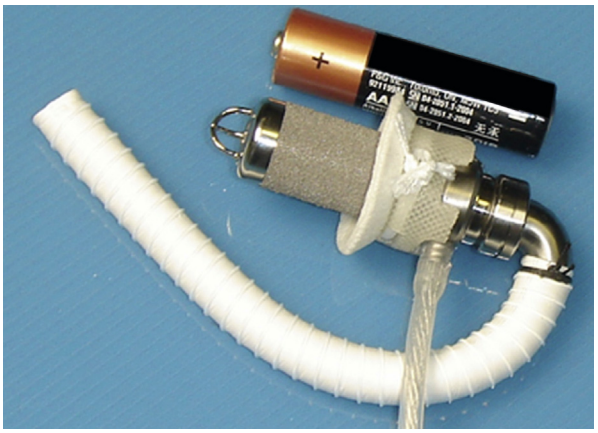

FIGURE 1. The Infant Jarvik 2015 ventricular assist device.