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Initial *In Vivo* Evaluation of the DexAide Right Ventricular Assist Device

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Abstract

Objectives: Despite the increasing use of left ventricular assist devices for patients with end-stage congestive heart failure, no implantable, centrifugal right ventricular assist devices (RVADs) are available for those patients with significant right ventricular failure. The DexAide RVAD was developed to provide an implantable RVAD option to surgeons. The aim of this study was to evaluate pump performance in an acute *in vivo* model.

Methods: The DexAide RVAD, developed as a modified CorAide™ left ventricular assist device, was implanted between the right ventricle and the pulmonary artery in four healthy calves. Pump speed was varied from 1,800 rpm to 3,600 rpm. RVAD performance was analyzed acutely at baseline and under conditions of low circulating volume, high contractility, high pulmonary arterial pressure, vasodilation, and low contractility.

Results: Pump flow was well maintained even under conditions of high pulmonary arterial pressure and vasodilation, with the exception of low circulating volume. Under all conditions, pulmonary arterial pressures were not affected by changing pump speed.

Conclusions: The DexAide RVAD demonstrated acceptable hemodynamic characteristics for use as an implantable RVAD in the initial acute studies. Further studies are ongoing to examine the biocompatibility of the pump under chronic conditions.

Keywords

ventricular assist device; right ventricular failure; circulatory support

Introduction

The use of implantable left ventricular assist devices (LVADs) has been increasing to serve the growing population of patients with end-stage congestive heart failure [1]. However, up to 39% of patients have significant right ventricular (RV) failure, which limits the utility of implantable LVAD therapy [2-4]. Such patients commonly require prolonged inotropic support or support with a right ventricular assist device (RVAD). Clinically available RVADs, such as

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the Bio-Pump® (Medtronic, Inc., Minneapolis, MN), CentriMag® Ventricular Assist System (Levitronix GmbH, Zurich, Switzerland), Abiomed BVS 5000® (ABIOMED, Inc., Danvers, MA), and Thoratec® VAD (Thoratec Corp., Pleasanton, CA), are not implantable devices and have several limitations, among which are poor blood compatibility, high infection rates, poor long-term durability, need for anticoagulation drugs, need for long hospital stays, high mortality, and a less than ideal post-surgical quality of life. Although the Thoratec® IVAD (Thoratec Corp., Pleasanton, CA) is an implantable VAD approved for clinical use, the IVAD is a pneumatic pump and the system consists of a large portable driver not ideal for use outside of the hospital setting. The prognosis for patients receiving LVAD support who also require external RVAD support has been poor [3].

We developed the CorAide™ LVD-4000 Assist System (Arrow International, Reading, PA), an implantable, third-generation, centrifugal pump as an LVAD [5-9]. The rotating assembly, the only moving part, is fully suspended without mechanical contact or wear during operation. The CorAide blood pump demonstrated excellent biocompatibility and reliable, effective system performance in a series of 24 chronic *in vivo* experiments that included 12 experiments without any anticoagulation therapy [7-9], and an initial clinical study was initiated [10]. Recently, the National Heart, Lung and Blood Institute, National Institutes of Health, funded the development of an implantable RVAD (BRP 5R01HL074896) based on modifications to the CorAide left ventricular assist system. The purpose of this initial *in vivo* study was to evaluate the Cleveland Clinic's DexAide blood pump, a new, small, implantable RVAD, in an acute animal model.

Materials and Method

DexAide Blood Pump

The Cleveland Clinic's DexAide blood pump, an implantable centrifugal blood pump, was developed by modifying the design of the CorAide LVAD, reducing the size of each primary impeller, decreasing the number of primary impellers from seven to five, and redesigning the volute housing. Like the CorAide LVAD, the DexAide consists of only three major components: volute housing assembly, a rotating assembly, which contains a permanent magnet ring and primary and secondary impellers, and a stator assembly. Detailed device design and the initial *in vitro* data have been published [11].

Surgical Procedure for RVAD Implantation

From August 2004 through April 2005, four healthy calves, weighing between 97.4 kg and 102.0 kg (100.1 ± 1.9 kg), received an RVAD implant. This study was performed under authorization by the Institutional Animal Care and Use Committee of the Cleveland Clinic Foundation. The animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

Animals were anesthetized with intramuscular ketamine (10 mg/kg) and inhalation of isoflurane and were ventilated through an endotracheal tube. Anesthesia was maintained with isoflurane. The arterial blood pressure and electrocardiogram were continuously monitored. Through a 5th left thoracotomy, a pericardiotomy was performed. The pulmonary artery was exposed and then partially clamped with a side clamp. A 14-mm Hemashield® outflow graft, a collagen-impregnated woven Dacron® graft (Boston Scientific, Natick, MA), was anastomosed to the pulmonary artery in an end-to-side fashion. After heparinization (300 U/kg), an arterial cannula (22 Fr.) was inserted into the left carotid artery, and a two-stage venous cannula (28-36 Fr.) was inserted into the left jugular vein and advanced into the right atrium. With the beating heart emptied under cardiopulmonary bypass (CPB) support, a

ventriculotomy for the inlet cannula was performed at the outflow portion of the right ventricle with a core-cutting device. A metallic or malleable inlet cannula was inserted into the right ventricle, and the RVAD was connected to the outflow graft and inflow cannula. Two ultrasonic perivascular flow probes (Transonic Systems, Inc, Ithaca, NY) were placed around the outflow graft and the distal pulmonary artery to monitor pump flow and cardiac output, respectively. After clearing all air from the pump, CPB was discontinued and the RVAD was started. The RVAD was placed in the chest cavity and secured to the diaphragm.

Hemodynamic Studies

Pump speed was varied from 1,800 rpm to 3,600 rpm using an external controller. Right atrial pressure, right ventricular pressure, pulmonary arterial pressure, left atrial pressure, aortic pressure, cardiac output, and pump flow data were measured under each condition described below and each pump speed. RVAD performance was analyzed acutely at baseline and under conditions of high pulmonary arterial pressure, high contractility, low contractility, vasodilation, and low circulating volume. High pulmonary arterial pressure was induced by a vascular tourniquet placed distal to the pulmonary anastomosis. High contractility was induced by an infusion of 2-3 $\mu\text{g/kg/min}$ of dobutamine. Low contractility was induced by an esmolol bolus of 500 $\mu\text{g/kg}$. Vasodilation was induced by an infusion of 0.5-3 $\mu\text{g/kg/min}$ of nitroprusside. Low circulating volume was induced by withdrawing circulating blood from the animal into the CPB reservoir. At the conclusion of the experiment, each animal was sacrificed with an overdose of sodium pentobarbital and potassium chloride.

The hemodynamic variables were recorded using a PowerLab data acquisition system (AD Instruments, Inc., Mountain View, CA) and analyzed using a custom-made Visual Basic program on Excel software (Excel 2000, Microsoft Corporation, Redmond, WA). All values were expressed as mean $\pm$ standard deviation. One-way repeated-measures analysis of variance was used to assess the differences between each condition. When the differences were determined to be significant, they were further analyzed by the Tukey-Kramer test. Differences were considered significant at $p < 0.05$. Correlations between pump speed and pump flow were calculated by linear regression analysis.

Results

The anatomical fit of the RVAD was acceptable in all four calves (Figure 1). Pulsatility of the pulmonary arterial pressure gradually diminished when pump speed was increased (Figure 2). There was no significant difference in pump flows in each condition. The averaged pump flows correlated well with the various pump speeds under all conditions except vasodilation and low circulating volume (Figure 3). Pump flows at 2,600 rpm, 3,000 rpm, and 3,600 rpm during vasodilation were 4.6 ± 0.5 L/min, 4.7 ± 1.0 L/min, and 5.3 ± 1.5 L/min, respectively. Pump flows at 2,600 rpm, 3,000 rpm, and 3,600 rpm under low-volume conditions were 4.6 ± 0.7 L/min, 4.6 ± 0.4 L/min, and 4.7 ± 0.3 L/min, respectively. Pump flow under conditions other than vasodilation and low volume was well correlated with pump speed ($r = 0.871$, $p < 0.0001$). The cardiac output measured during baseline was 8.7 ± 2.0 L/min and under conditions of high pulmonary arterial pressure, high contractility, low contractility, vasodilation, and low circulating volume, cardiac output was measured at, 8.8 ± 2.4 L/min, 13.2 ± 3.4 L/min ($p < 0.0001$), 7.7 ± 2.1 L/min, 7.8 ± 2.6 L/min, 5.8 ± 1.4 L/min ($p < 0.0001$), respectively.

The averaged right atrial pressures through 2,000 rpm and 3,200 rpm under the condition of high pulmonary arterial pressure were significantly higher ($p < 0.05$) than those under low-volume states (Figure 4). Right atrial pressures decreased under all conditions when the pump speed was increased. The averaged pulmonary arterial pressures under the condition of high pulmonary arterial pressure were significantly higher ($p < 0.05$) than those under other

conditions (Figure 5). The pulmonary arterial pressures were not affected by changes in pump speed during all conditions.

Discussion

In the present *in vivo* study, we tested the DexAide RVAD under various hemodynamic conditions. This study revealed that (1) pump flow correlated well with pump speed, even during the condition of high pulmonary arterial pressure; (2) pump flow was limited by the available circulating volume, as expected; and (3) pulmonary arterial pressure remained approximately constant with pump speed.

The flow of centrifugal pumps [12,13] or axial pumps [14,15] used as LVADs is affected by the pressure gradient between inflow and outflow. Therefore, it is essential to maintain low or normal systemic vascular resistance for patients supported by these pumps [16]. However, the blood pressure within the pulmonary artery is less than the blood pressure within the systemic arteries. With mean pressure between 20 and 50 mm Hg in the pulmonary artery, pump flow correlated well with pump speed. If there is adequate volume in the RV, adjusting pump flow to the clinician's intention is quite simply performed by changing the RVAD speed.

In this study, pump flow was limited under conditions of vasodilation and low volume when the pump flow was increased. In these conditions, the right atrial pressure decreased to less than 5 mm Hg. Although the animals were intubated and anesthetized and had normal heart function in this acute study, maintaining the right atrial pressure above 5 mm Hg was necessary to maintain sufficient pump flow.

Compared with the development of implantable LVADs, there are few reports of implantable RVADs. The Gyro centrifugal pump, suspended by two pivots, has been developed as an implantable LVAD and RVAD [17,18], and animal experiments are ongoing. The Jarvik 2000 FlowMaker® (Jarvik Heart, Inc., New York, NY) has been developed as an implantable LVAD [19]. This pump was also used as an “off-label” implantable RVAD for life-saving purposes in a human clinical case [20]. In August 2004, the Thoratec® IVAD (Thoratec Corp.) [21] was approved by FDA not only for use as an implantable LVAD, but also for the application as an implantable RVAD. However, there are some limitations of the Thoratec® IVAD for long-term use. The IVAD is pneumatically operated and the pump system consists of a large driver not ideal for use outside of the hospital. As a result, a smaller, implantable RVAD system for patients with right ventricular failure is desperately needed.

There is no commercially available implantable RVAD in the United States. An implantable RVAD system for patients with right ventricular failure is desperately needed.

In conclusion, the DexAide RVAD demonstrated acceptable hemodynamic characteristics for use as an implantable RVAD. Further studies are ongoing to examine how well it performs in terms of biocompatibility (hemolysis and thrombogenicity) under chronic conditions similar to those seen clinically.

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Figure 1.

Anatomical fit of the *DexAide* right ventricular assist device. The inflow cannula was inserted into the right ventricular outflow tract, and the outflow was anastomosed to the pulmonary artery through a left thoracotomy. LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; RVAD, right ventricular assist device.

Figure 2. Representative pulmonary arterial pressure waveforms during baseline (Figure 2a) and condition of high pulmonary arterial pressure (PAP) (Figure 2b).

Figure 3.
Relationship between pump speed and averaged pump flow.

Figure 4.
Relationship between pump speed and averaged right atrial pressure.

Figure 5.
Relationship between pump speed and averaged pulmonary arterial pressure.