In Vivo Evaluation of the Nimbus Axial Flow Ventricular Assist System

Criteria and Methods

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Continuing in vivo trials are being conducted at the University of Pittsburgh using the Nimbus axial flow blood pump (AxiPump). To date, 14 sheep experiments have been performed to address several issues related to short-term support. Six acute experiments (<6 hr) have been performed to assess hemodynamics related to speed regulation and to determine anatomic placement of the pump and cannulae. Eight short-term survival studies lasting up to 6 days have been performed to evaluate biocompatibility and system reliability, and to establish clinical management protocols. The AxiPump has been used as a left ventricular assist device (LVAD), right ventricular assist device (RVAD), and biventricular assist device (BiVAD) with left ventricular and right atrial cannulation. The AxiPump has demonstrated the ability to assume complete support of either the pulmonary or systemic circulation, or both. We have determined that sufficient surgical access may be obtained through left lateral thoracotomy for both LVAD and RVAD insertion. In the absence of post operative anticoagulation therapy, we have detected subclinical renal cortical infarctions in 6 of 8 short-term animals. Thrombus deposition has been observed at the ventricular cannula tip in 4 of 8 cases—necessitating design changes. Two short-term experiments have been terminated because of bleeding—one due to inflow cannula obstruction and one due to cannula failure. Plasma free hemoglobin levels were all below 15 mg/dl, except for one case complicated by inflow obstruction. There has been no evidence of device failure; however, we have encountered some problems with the purge delivery circuit, which has motivated additional design and procedural changes. Future in vivo experiments will incorporate design changes identified in these early experiments and will concentrate on longer-term (12 week) performance. ASAIO Journal 1993; 39: M231-M236.

The overall goal of the joint venture between Nimbus, Inc., and the University of Pittsburgh (UoP) is to develop a chronic circulatory assist system using an axial flow blood pump (AxiPump; Nimbus, Inc., Rancho Cordova, CA).† To date, this pump has undergone in vitro testing for hemodynamic performance and durability, and several blade configuration changes have been effected to maximize hydraulic efficiency while minimizing hemolysis (index of hemolysis [I.H.] <0.0019). In its current configuration, the AxiPump can provide up to 220 mmHg pressure rise and 10 L/min flow. The operational range for this pump is between 8,000 and 13,000 rpm, and the pressure-flow (H-Q) response demonstrates relatively flat characteristics.

In Vivo Experiments

Both acute and short-term in vivo implant studies have been conducted in order to assess and optimize this system prior to initiating long-term trials.

Acute Studies

Six highly instrumented acute experiments (<6 hr) were conducted to assess hemodynamics related to pump speed regulation as well as surgical placement of the pump and cannulae. Because this pump is intended to support both the left and right circulations, left ventricular assist device (LVAD), right ventricular assist device (RVAD), and biventricular assist device (BiVAD) configurations were considered, and corresponding cannula dimensions were established.

Short-Term Studies

In preparation for long-term chronic in vivo trials, eight short-term experiments (<7 days) were conducted to identify characteristics of the system contributing to its basic performance and biocompatibility and to suggest design changes as necessary. These studies also provided the oppor-
Table 1. Experimental Matrix

<table>
<thead>
<tr>
<th>Design Variables</th>
<th>Clinical End Point</th>
<th>In Vivo Method of Evaluation</th>
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<tr>
<td>Geometric configuration (pump and cannulae)</td>
<td>Anatomic interface</td>
<td>Ease of surgical implantation</td>
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<td>Evidence of tissue trauma</td>
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<td>Infection</td>
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<td>Pump pressure and flow</td>
<td>Organ perfusion</td>
<td>Hemodynamics</td>
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<td>Average output</td>
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<td>Blood chemistry and hematology</td>
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<td>Pulsatility</td>
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<td>Global: lactate</td>
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<tr>
<td>Regulation</td>
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<td>Specific: BUN, creatinine, bilirubin, SGOT</td>
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<tr>
<td>Fluid dynamics (pump and cannulae)</td>
<td>Hemodynamics</td>
<td>Blood gases</td>
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<tr>
<td>Shear</td>
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<td>Histopathology</td>
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<td>Turbulence</td>
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<td>Edema</td>
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<td>Residence time</td>
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<td>Necrosis</td>
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<td>Cavitation</td>
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<td>Ischemia</td>
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<td>Biomaterials</td>
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<td>Thrombosis</td>
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<td>Coagulation times</td>
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<td>Platelet count</td>
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<td>Pathology</td>
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<td>Deposition</td>
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<td>Embolization</td>
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<td>Ischemia/necrosis</td>
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<td>Fluid dynamics (pump and cannulae)</td>
<td>Hemolysis</td>
<td>Plasma-free hemoglobin</td>
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<td>Shear</td>
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<td>Haptoglobin</td>
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<td>Turbulence</td>
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<td>Lactate dehydrogenase</td>
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<td>Residence time</td>
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<td>Viscosity</td>
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<td>Cavitation</td>
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<td>Erythrocyte sedimentation</td>
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<td>Erythrocyte deformability</td>
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<td>Infection</td>
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<td>Tissue smears</td>
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An opportunity to identify initial physiologic responses that may occur in the presence of pulseless, or diminished pulse, perfusion. Accordingly, protocols were developed for clinical management and device operation in both critical care and chronic support settings.

The chief criteria for system evaluation during this stage of testing were: 1) ease of implantation, 2) indication of organ perfusion, 3) absence of thrombosis, 4) minimal hemolysis, 5) unaltered hemorheology, and 6) absence of infection. The methods for identifying these end-points are discussed below.

**Materials and Methods**

Several design variables of the implanted system contribute to its in vivo performance. The key variables are listed in Table 1 along with the clinical manifestations that gauge the efficacy and safety of the design. The current in vivo studies were therefore conceived to evaluate these end-points, which could then be related as requirements for design modifications if necessary.

**Axial Flow Pump**

The prototype axial flow blood pump system (AxiPump) consists of three major elements: 1) an integrated pump/motor, 2) an inflow and outflow cannulae set, and 3) an external controller/power supply. This system has been described in detail previously. The pump, which is fabricated from 304 stainless steel, weighs 205 g and displaces 62 ml. Three such prototype pumps were fabricated for the initial in vivo studies.

**Pump Console**

Two percutaneous lines connecting the pump to the external console provide primary electric power (and motor speed control) as well as purge fluid supply to the pump bearing and seal. Approximately 15 ml per day of purge fluid is required for satisfactory lubrication. The originally specified purge fluid, 5% dextrose solution, was changed to Ringer's lactate in the most recent experiments.

The console was modified recently to add certain features. An electromagnetic interference (EMI) line filter was added for power conditioning in the electrically noisy operating room environment. Active cooling has been integrated into the console with a fan and vents. The purge pressure transducer was changed to a clinical disposable type (Medex, MX-900, Medex, Inc., Hilliard, OH). Software improvements include a self restart capability. Finally, the capability to remotely control pump speed by personal computer has been added.

**Inflow and Outflow Cannulae**

The basic cannula designs must satisfy the combined requirements of anatomic fit, biocompatibility, durability, kink
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Gore & Assoc., Flagstaff, AZ. Inflow cannula tip configurations have included blunt and tapered designs as well as various styles of caged and bullet tips. Several side hole placements were also explored in an attempt to improve flow patency and reduce apical blood stasis.

Implant Surgery

Domestic female sheep (60–100 kg) were intubated and connected to a mechanical ventilator after anesthesia with xylazine (0.3 mg/kg IM) and atropine (3 mg IM) followed by 3–4% isoflurane and oxygen. Maintenance anesthesia was with 1–2% isoflurane. An arterial line was placed in the left internal carotid artery, and a Swan-Ganz pulmonary artery catheter (Edward Critical Care, Santa Ana, CA) was inserted through the left jugular vein.

For LVAD insertion, the heart and descending thoracic aorta were exposed through a left lateral thoracotomy at the fourth intercostal space. After dividing the azygous vein, the outflow graft was anastomosed in an end-to-side fashion with 5-0 GoreTex suture to the descending thoracic aorta. Intravenous lidocaine (1.5 mg/kg) was administered and the pericardium was opened. Four pledged 3-0 Ethibond (Ethicon, Inc., Somerville, NJ) sutures were placed in a radial fashion around the left ventricular apex. A 3 French fiberoptic pressure catheter (Camino Laboratories, San Diego, CA) was inserted through the left atrial appendage. The outflow graft and inflow conduit were connected to the axial flow pump. Access to the left ventricle was obtained through either a stab incision at the apex of the left ventricle or a 5–8 mm ventriculostomy. Immediately thereafter, the pump inflow conduit was inserted into the ventricular apex and the pump started while the apical fixation sutures were secured. De-airing was achieved through an 18 gauge needle placed in the outflow graft.

RVAD insertion was performed following implantation and start-up of the LVAD. This allowed for stable insertion of the RVAD without compromising systemic flow. The outflow graft was anastomosed end-to-side to the main pulmonary artery, which was easily visualized through the left thoracotomy. The axial flow pump was connected to this graft and the inflow cannula. A double purse string suture was placed around the right atrial appendage with the heart elevated up and out of the pericardium. The inflow cannula tip was then inserted through a stab incision in the right atrium and the cannula advanced into the right ventricle through the tricuspid valve. The purse string sutures were snared down and the pump flow established. This combined procedure demonstrated good positioning of the RVAD within the right chest along the sternum.

Hemodynamic stability was maintained with appropriate fluids and pharmacologic adjuncts as necessary. Gas exchange was monitored by routine blood gas sampling. Oxygen saturation and end tidal CO₂ were also monitored continuously by capnometer/pulse oximeter (Novametrix 7000, Wallingford, CT).

All pump lines and monitoring lines were tunneled through the skin. The chest was closed and anesthesia re-
versed, allowing the animal to take food and water ad libitum as early as possible.

Post Operative Management and Physiologic Response

All animal procedures were performed under the supervision of U of P staff veterinarians and were in accordance with NIH and University guidelines for the care and use of experimental animals.

Routine anticoagulation was not used except for a heparin bolus of 1 mg/kg intravenously just before apical cannulation. Post operative management included appropriate volume replacement based on right atrial filling pressure and administration of intravenous flunixin magalazine (0.5 mg/kg) for pain.

Regular blood samples were drawn and analyzed for blood gases, electrolytes, hematocrit, blood cell counts, fibrinogen, plasma free hemoglobin, lactic dehydrogenase (LDH), liver enzymes (bilirubin and serum glutamic oxaloacetic transaminase [SGOT]), and renal function (blood urea nitrogen [BUN] and creatinine). Hemorheology tests included whole blood and plasma viscosity, erythrocyte sedimentation rate, and erythrocyte deformability.

Hemodynamic Monitoring and Flow Regulation

To assess hemodynamic performance and identify parameters relevant to pump speed regulation, arterial pressure, left atrial pressure, pump motor current, and RPM were continuously monitored. Transient measurement of pulmonary artery pressure and central venous pressure during the initial post-operative period was accomplished by Swan-Ganz catheter. In two cases, an oximetric Swan-Ganz catheter provided perioperative measurement of mixed venous oxygen saturation. Acute studies allowed the additional measurement of left and right ventricular pressure and, in one case, aortic flow.

Measurement of pump flow was accomplished by one or more of four methods. In two animals, a 12 mm perivascular ultrasonic flow probe (Transonics Systems, Ithaca, NY) was used to measure flow through the outflow graft. Because ePTFE material is not a good acoustic conductor, the graft was denucleated prior to implantation to maintain adequate signal strength during the acute interval. A more reliable flow measurement was provided by a custom designed ultrasonic transit time flow probe (Transonics Systems) incorporated with the inflow cannula. Thermodilution estimates of cardiac output were performed peroperatively in all LVAD cases as a validation of these flow probes. Finally, the pre-calibrated pump pressure flow power characteristics provided an additional validation and/or back-up measurement.

All data were acquired throughout the perioperative and recovery periods and stored to disk by high speed work station (Hewlett Packard APOLLO 3550, Hewlett Packard, Chelmsford, MA).

The current console regulates pump speed independent of hemodynamic feedback; accordingly, the pump speed was set manually to achieve satisfactory cardiac output, atrial pressures, and perfusion pressures. In the current experiments, the pump speed was periodically adjusted through its full operating range to map the hemodynamic response to incremental changes in flow. This procedure was repeated for several postural positions of the animal.

Post Mortem Examination

At the predetermined post operative day, the sheep were administered an intravenous bolus of heparin, sedated with xylazine (Rompun, Mobay, Shawnee, KS), and sacrificed. The necropsy of each animal included visual inspection, manual palpation, and serial incision of all body organs. The explanted pumps were evaluated for evidence of mechanical (structural) failure, physical deterioration, thrombus deposition, and mineralization, and they were cultured for bacteria according to well established protocols.

Results

Fourteen in vivo experiments have been conducted in which the AxiPump and cannulae were implanted into adult female sheep. These consisted of six acute studies and eight short-term survival studies of 11-141 hours duration. In all short-term survival studies, animals recovered quickly from the surgical procedure and began eating ad libitum. No detectable discomfort or loss of end organ function was noted. All cases lasting more than 3 days were electively terminated, and the sheep were in no apparent discomfort at the time of sacrifice.

Anatomic Placement

The AxiPump has been used in LVAD, RVAD, and BiVAD configurations with left ventricular and right atrial cannulation. We have determined that sufficient surgical access may be obtained through left lateral thoracotomy for both LVAD and RVAD insertion. A right thoracotomy does not provide sufficient access to the main pulmonary artery. It is apparent from the short-term studies that device location and appropriate cannulation are crucial to minimize physical trauma to the lungs. In one recent acute study, the pump was placed in the subdiaphragmatic abdominal space with the cannulae passing through the diaphragm. In this position, potential trauma to the lungs is reduced and cannula lengths are only slightly increased (4 cm).

Physiologic Response

Animal health as determined by external observations and vital signs remained normal in all surviving animals. Arterial blood gases (pH, pO2 and pCO2) generally remained within the normal range. Urine output was consistent and adequate. Electrolyte concentrations, creatinine, and BUN remained at baseline (pre-implant) values. Total serum protein and liver enzymes did not reflect any acute hepatic insult.

With regard to hemolysis, the maximum plasma free hemoglobin (PFH) observed for all cases was 27.5 mg/dl but was below 15 mg/dl for cases not involving inflow obstruction. Normalizing the latter results with respect to blood vol-
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Complications

Procedure related complications were limited to intra-thoracic bleeding in three cases, two of which caused us to discontinue the study. Hardware related complications were limited to: 1) the inflow cannula and 2) the purge delivery system. Cannula disconnection and cannula tip obstruction each accounted for the failure of one experiment; however, partial tip obstruction was observed at autopsy in at least four of eight short-term cases. Cannula insertion through a stab incision appeared more problematic in this regard than when apical coring was performed. In three cases, we were unable to maintain adequate purge pressure because of either purge line interruption external to the pump (two cases) or failure of the seal preload spring (one case).

Pathology

Post mortem findings relate mainly to the acute recovery phase following surgery. These include pulmonary atelectasis and compression from device placement (2/8), pleural effusion (1/8), and small to moderate sized isolated renal cortical infarct (6/8) that did not appear to impair renal function.

A relatively consistent finding at explant has been the presence of fibrin and thrombus deposits at the interface between the cannula and the pump (5/8). Deposits of thrombus at the site of apex cannulation were also noted (7/8). Cannula tip design and position were such that local inflammation and hematoma were consistently seen at the apical insertion site. We are currently evaluating whether this is due to an acute foreign body reaction of the myocardium or is a result of decompression of the ventricle caused by negative pressures. Further design modifications are being made to diminish this potential site of inflow obstruction and thrombus formation.

The expanded PTFE outflow cannula and aortic anastomosis were consistently found free of deposits. No remarkable findings were noted in the end organs of the abdominal viscera. The pump flow surfaces have generally been devoid of deposits; however, evidence of small (<1.5 mm) adherent deposits has been noted on the trailing edge of the stator blade in two cases.

Discussion

The promise of an axial flow blood pump for chronic circulatory support has encouraged us to pursue in vivo testing of the Nimbus AxiPump system. The advantages of the Nimbus AxiPump's small size, absence of one way flow valves, high efficiency, and minimum moving parts make it an attractive alternative to positive displacement pumps. However, several questions remain regarding the feasibility of chronic use of such systems. Specifically, the long-term effects of diminished pulse perfusion on local, neural, and humoral blood flow regulation, renal function, and lymphatic drainage have been questioned.

Because of the relative preload and afterload insensitivity of rotary blood pumps, satisfactory flow control of such pumps is also an engineering challenge. Before the question of chronic support with an axial flow pump can be answered, several concerns must be addressed to ensure long-term reliability, particularly: 1) bearing and seal integrity, 2) reliable purge delivery, 3) effective cannulation, and 4) optimal impeller design.

The AxiPump has sufficiently demonstrated high bearing and seal reliability through in vitro testing. This is supported by our short-term in vivo experience.

With regard to difficulties with purge delivery, design changes have been made to improve the manufacture of seal preload springs and the reliability of external purge connections. Additionally, check valves have been incorporated into the purge line to prevent air entrapment.

The design of the inflow cannula tips for rotary blood pumps has generally proved more problematic than the design for conventional VAD systems that fill passively. This is primarily due to the ability of these pumps to generate negative intraventricular pressures. As a result, intraventricular structures may be drawn into the cannula tip, impairing inflow patency. In light of observations of thrombus formation at the cannula tip and ventricular apex—which appears concurrently with the evidence of renal infarctions—it is likely that generation of emboli is occurring because of inadequate apical blood flow. At this point, it is not fully clear whether these observations are caused by the cannula, the pump, or other procedural variables such as cannula placement. To help resolve these ambiguities, rigorous flow visual-
ization studies are currently being performed to analyze the flow patterns existing within the inflow cannula and pump. Further acute in vivo experiments are also being conducted to ascertain additional design considerations relevant to the cannula tip. Initial results of these experiments suggest that a tapered inflow cannula would improve the flow and that a cannula tip that better stents the ventricular wall is needed.

Based on the initial in vivo and in vitro experience with the 12 mm diameter AxiPump, the next generation device has been upscaled to 14 mm and will be manufactured from corrosion resistant 6 AL-4V titanium alloy (Figure 2). This device features a redesigned inflow and outflow quick-connect coupling that will eliminate interface discontinuities that may act as nidus for thrombus deposition. Flow visualization results have been used to modify the rotor and stator blades, making them less susceptible to flow separation under low flow conditions — as experienced during our two cases of inflow obstruction.

Future in vivo experiments will concentrate on longer-term (12 week) system durability and on the extended physiologic effects of diminished pulse perfusion. Although all of the in vivo studies conducted thus far have involved healthy animals, a heart failure model is being investigated to study more realistic clinical settings and to allow us to independently vary cardiac outputs and pulsatility. This will assist greatly in the development of automatic control algorithms for speed regulation.

Finally, to address the possible complication of lung compression, anatomic placement of the AxiPump may be moved to a subdiaphragmatic location. The larger external radii featured by the new pump housing should further minimize irritation of adjacent tissue.

This initial in vivo experience with the Nimbus AxiPump has successfully demonstrated the versatility of this system for short-term circulatory support. These experiments have elucidated important design changes that will help optimize the system in preparation for chronic trials.

Acknowledgments

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References