The National Heart, Lung, and Blood Institute Pediatric Circulatory Support Program

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Abstract—Options for the circulatory support of pediatric patients under the age of 5 years are currently limited to short-term extracorporeal devices, the use of which is often complicated by infection, bleeding, and thromboembolism. Recognizing this void, the National Heart, Lung, and Blood Institute solicited proposals for the development of novel circulatory support systems for infants and children from 2 to 25 kg with congenital or acquired cardiovascular disease. Five contracts were awarded to develop a family of devices that includes (1) an implantable mixed-flow ventricular assist device designed specifically for patients up to 2 years of age, (2) another mixed-flow ventricular assist device that can be implanted intravascularly or extravascularly depending on patient size, (3) compact integrated pediatric cardiopulmonary assist systems, (4) apically implanted axial-flow ventricular assist devices, and (5) pulsatile-flow ventricular assist devices. The common objective for these devices is to reliably provide circulatory support for infants and children while minimizing risks related to infection, bleeding, and thromboembolism. The devices are expected to be ready for clinical studies at the conclusion of the awards in 2009. (Circulation. 2006;113:147-155.)

Key Words: heart-assist device ■ pediatrics ■ congenital heart defects ■ heart diseases ■ heart failure

The need for mechanical circulatory support to treat children with congenital and acquired heart disease is well established.1,2 Currently, 25% of the ≈36,000 babies born with congenital heart defects in the United States each year require invasive treatment during the first year of life.3 Although the annual mortality from heart defects in the United States has declined by 39% since 1979, nearly 1800 infants with congenital heart defects die each year.4 Acquired heart disease also affects this vulnerable pediatric population; based on National Heart, Lung, and Blood Institute (NHLBI)-sponsored Pediatric Cardiomyopathy Registry data, each year in the United States nearly 350 children under 1 year of age develop cardiomyopathy,* many of whom die or require cardiac transplantation.4,5 International registry data indicate that the majority of those receiving a heart transplant under 1 year of age have a diagnosis of congenital heart disease (67%), whereas the remainder have some form of cardiomyopathy (33%).6 A particular problem in this age group is the high mortality rate suffered by infants awaiting transplantation; the United Network for Organ Sharing (UNOS) reports that of the more than 1600 infants added to the heart or heart/lung transplant lists over the last decade, fewer than 50% received a donor organ.7 During this same period, 68% of the more than 3000 children between 1 and 18 years listed for cardiac transplantation underwent successful transplantations.

The use of mechanical circulatory support devices (MCSDs) as a bridge to transplantation has been shown to decrease waiting list mortality and improve the efficiency of organ utilization in children.8 MCSDs have also been used successfully as a bridge to recovery in children, especially in the management of acute fulminant myocarditis or postcardiomyotomy heart failure.9–14 However, current MCSD options for infants and children are quite limited, particularly in regard to duration of support. Extracorporeal membrane oxygenation (ECMO), which remains the only form of mechanical circulatory support available at most pediatric tertiary care centers in the United States, is capable only of providing support for days to, at most, a few weeks. This becomes a significant limitation when ECMO is used for the youngest patients, those who often require significant time on circulatory support until a suitable donor organ becomes available.

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*Based on the incidence rate of 8.34/100 000 for New England and the Central Southwest regions and extrapolated to the US national total of 4 113 000 live births for the 12 months ending November, 2004.

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Achieving effective mechanical circulatory support in children involves addressing important population-specific technological challenges that do not exist in adults. One fundamental design challenge arises from the need to provide circulatory support for the entire range of patient sizes encountered in pediatrics, from newborns to adolescents. In addition, because of the substantial growth that a child may experience while on circulatory support, pediatric MCSDs intended for chronic use should retain the capacity to increase output to match circulatory requirements as the child grows. Also, owing to the small size of the vasculature in children, cannulation strategies must be capable of providing required cardiac support while preserving the integrity of small and often fragile blood vessels.

Although size constraints are the most obvious challenge for the development of pediatric MCSDs, significant anatomic and physiological differences between pediatric and adult patients must also be considered during the design of circulatory support devices for children. For example, congenital cardiac malformations demonstrate a vast number of various combinations of anatomic abnormalities that may significantly affect cannulation. Transposition of the great arteries, dextrocardia, and abnormalities of the systemic veins are a few of the anatomic features that, when present alone or in combination, may require substantial creativity in planning for appropriate cannulation strategies.\textsuperscript{15} Survival beyond infancy is increasing in the population of patients with single-ventricle physiology who are successfully palliated with the Fontan procedure. The “Fontan pathway,” the most common surgical sequence for single-ventricle patients, consists of a neonatal palliative procedure, followed by a biventricular surgical sequence for single-ventricle patients, completion of a neonatal palliative procedure, followed by a biventricular surgical sequence for single-ventricle patients, with the Fontan procedure. These patients provide substantial management challenges owing to the multisystem nature of complications that may develop secondary to systemic venous hypertension (cirrhosis, protein-losing enteropathy) and because these patients often have some of the most significant anatomic abnormalities encountered. Finally, circulatory support with left ventricular assist devices (LVADs), which is frequently successful in the management of relatively isolated left ventricular failure in adults, may not be as likely to succeed in children. Pediatric heart failure is more often characterized by right ventricular or biventricular failure and pulmonary disease (especially pulmonary hypertension). Consequently, strategies that provide biventricular support within the size limitations imposed by the small size of the pediatric thorax assume greater importance in MCSDs designed for pediatric applications.\textsuperscript{1,16}

Devices Currently Available for Pediatric Applications

The options for mechanical circulatory support for pediatric patients in the United States are currently limited to a handful of devices. Although no MCSD has received premarket approval from the Food and Drug Administration (FDA) for specific use in pediatric patients, various devices have been used to provide acute and chronic circulatory support in the pediatric population. This is possible through off-label use of FDA-approved adult devices, compassionate use of investigational adult ventricular assist devices (VADs), the use of devices that have received an FDA Humanitarian Device Exemption, the use of devices fabricated from FDA-approved components (such as ECMO circuits), and devices that are approved on a case-by-case basis by the FDA for emergency use.\textsuperscript{1,17} The current FDA-approved adult devices that have been used in pediatric patients include the Thoratec Ventricular Assist Device and the Heartmate LVAD (Thoratec Laboratories Corp), and the Abiomed BVS 5000 (Abiomed, Inc).\textsuperscript{18–21} Historically, these FDA-approved adult VADs have typically been limited to pediatric patients with body surface areas of at least 0.7 m\textsuperscript{2} for extracorporeal devices and 1.4 m\textsuperscript{2} for implantable devices.\textsuperscript{1} However, because of their smaller sizes, a number of the current group of investigational implantable adult devices, such as the MicroMed DeBakey VAD (MicroMed Technologies, Inc), the Jarvik 2000 Flowmaker (Jarvik Heart, Inc), and the Thoratec Heartmate II VAD, provide additional options for larger pediatric patients, for whom the use of such devices qualifies as a “compassionate treatment.”\textsuperscript{22–24} The Micromed DeBakey VAD Child was granted a “humanitarian device exemption” from the FDA in February 2004 and was approved for use in pediatric patients 5 to 16 years old who have a body surface area between 0.7 and 1.5 m\textsuperscript{2} and who are in New York Heart Association class IV end-stage heart failure, are refractory to medical therapy, and are listed as candidates for cardiac transplantation.\textsuperscript{25} It is the only intracorporeal circulatory support device available in the United States exclusively designated for use in children. The device utilizes the same pump as the adult Micromed DeBakey VAD, although the inflow cannula and outflow graft have been redesigned to allow implantation in smaller pediatric patients.

Although first reported as appropriate for prolonged circulatory support in the early 1970s, ECMO remains the most commonly used method for mechanically supporting the circulation of pediatric patients.\textsuperscript{3} ECMO circuits typically consist of a roller or centrifugal pump that drives blood through a membrane oxygenator, a blood warmer, and a filter. The number of cases of pediatric cardiac ECMO use in the United States reported to the Extracorporeal Life Support (ECLS) Registry has increased from approximately 400/year in 1999 to 500/year in 2004, primarily owing to an increase in neonatal cardiac ECMO use during this time period.\textsuperscript{26–28} Although some centers report cardiac ECMO survival rates as high as 70%, the average has remained ≈40% since its early use.\textsuperscript{1,26} However, because ECMO is only capable of providing circulatory support in the acute setting, its usefulness is limited. ECMO circuits have been used for up to 30 days; however, the likelihood of adverse events increases significantly with longer duration of ECMO support. Most ECMO runs are limited to substantially shorter time periods (5 to 10 days). Although ECMO has provided the only option for many pediatric patients with heart failure refractory to medical management, serious adverse events, such as hemorrhage and neurological complications, are common and may be
suitable devices, a limited experience that involves implantation. However, because of the absence of other options for chronic circulatory support in children in the United States with body surface areas <0.7 m² are quite limited. The Berlin Heart Excor VAD (Berlin Heart AG), an extracorporeal device made in sizes ranging from 10 to 80 mL, is available only for emergency use in the United States, and as such, it requires a petition to the FDA before each implantation. However, because of the absence of other suitable devices, a limited experience that involves >20 pediatric implants in the last 3 years in the United States has been accumulated on the device. Because it is available in a wide range of sizes, the Excor VAD provides circulatory support options for pediatric patients ranging from 2.5-kg infants to adolescents. The device is intended to address severe ventricular failure resulting from acute fulminant myocarditis, cardiomyopathy, postcardiotomy failure, post-transplantation graft failure, and end-stage congenital heart disease.  

This extracorporeal device utilizes cannulas with a polyester velour coating at the site of skin entry to minimize the risk of infections. Patients supported by the Excor VAD have been managed with warfarin sodium anticoagulation in the majority of cases.

The NHLBI Pediatric Circulatory Support Program

Overview of the Program

Recognizing the limitations of circulatory support devices for small children and the common complications of infection, thromboembolism, and cannulation problems, the NHLBI issued a Broad Agency Announcement (BAA) entitled “Pediatric Circulatory Support” in November 2002. This BAA solicited contract proposals to develop novel circulatory support systems for infants and children with congenital and acquired cardiovascular disease who experience cardiopulmonary failure and circulatory collapse. The types of devices intended to be developed under the BAA included left and right VADs, ECMO systems, and other novel bioengineered systems for children ranging in weight from 2 to 25 kg.

Among the technical requirements detailed in the solicitation were that each system should: (1) be able to be routinely deployed and functioning in less than 1 hour after the decision to initiate support; (2) minimize the priming volumes; (3) include cannulation strategies to accommodate potential variations in patient anatomy; (4) minimize exposure to blood products; (5) minimize risks of infection, bleeding, hemolysis, and thrombosis; and (6) be capable of providing support for up to 6 months, depending on the intended application.

Evaluation Criteria, Review, and Awards

Thirteen proposals were submitted to NHLBI and subsequently reviewed by a panel of scientists with expertise in pediatric cardiology, pediatric cardiac surgery, biomedical engineering, biocompatibility, and biostatistics. To objectively rank the proposals with regard to their potential to successfully develop the proposed devices while meeting the clinical and performance goals, each proposal was evaluated on the following criteria: (1) concept and theory; (2) innovation; (3) research, design, development, and manufacturing; (4) plan for testing and evaluation; and (5) capabilities of offeror. Per the BAA, secondary consideration of the costs of individual projects was made to fund an overall program that provided the best value to the government.

On the basis of the evaluation of the proposals, 5 contracts were awarded by the NHLBI to provide a comprehensive program for the development of a family of novel pediatric circulatory support devices. The 5 projects awarded include an implantable mixed-flow VAD designed specifically for patients up to 2 years of age (the PediaFlow VAD), another mixed-flow VAD that can be implanted intravascularly or extravascularly depending on patient size (the PediPump), compact integrated pediatric cardiopulmonary assist systems (the pCAS), apically implanted axial-flow VADs (the Pediatric Jarvik 2000 Flowmaker), and pulsatile-flow VADs (the Penn State PVAD). The 5 contracts totaling $22,399,727 for the 5-year program duration were awarded on March 30, 2004. The pediatric circulatory support devices funded by the NHLBI contracts are described below.

Descriptions of the Programs Supported by the NHLBI’s Pediatric Circulatory Support Program

The PediaFlow VAD (University of Pittsburgh)

The PediaFlow VAD (Figure 1) is an implantable, magnetically suspended mixed-flow turbodynamic blood pump being developed by a consortium consisting of the University of Pittsburgh, Carnegie Mellon University, Children’s Hospital of Pittsburgh, LaunchPoint, LLC, and World Heart Corpora-
tion. It is being designed and developed to provide chronic (6 months) circulatory support to patients from birth to 2 years of age (3 to 15 kg body weight) with congenital or acquired heart disease. Anticoagulation therapy while patients are on the device is intended to be limited to antiplatelet medications (with the option for warfarin sodium if clinically indicated). The device is being designed to provide a flow rate range from 0.3 to 1.5 L/min and will be limited to a maximum weight of 30 g, a maximum volume of 5 mL, and a maximum priming volume 0.5 mL to help achieve the goal of being fully implantable. Only a single percutaneous lead crossing the skin for energy transmission will be required. The PediaFlow VAD’s “smart” sensor-based controller will continuously monitor cardiac status for potential “bridge-to-recovery” applications. The controller will also continuously monitor the performance of the PediaFlow device and support either continuous or pulsatile flow modes. The PediaFlow cannula sets will be designed to be suitable for both left and right ventricle cannulation.

The PediaFlow pump is based on rotary blood pump technology. The device blood flow path will be designed to optimize hemocompatibility; minimize shear-induced blood trauma, flow separation, and stagnation regions; and avoid cavitation. The PediaFlow pump is intended to be implanted in the left upper abdomen, in the anterior abdominal wall behind the left rectus abdominus muscle. As shown in Figure 1, inflow to the pump is through the left ventricular apex, with outflow to the ascending aorta. The same pump may be used for either left or right heart assistance, or 2 pumps may be used together to provide biventricular support. The pump locations will allow easy access for component change in the event of pump malfunction or for removal in case of ventricular recovery, thus obviating the need for a repeat sternotomy.

The ultimate safety and efficacy of the PediaFlow VAD will depend on the hemocompatibility of the flow path. This is particularly challenging considering the program’s goal for minimal anticoagulation and a wide range of operation. The PediaFlow design will be optimized with advanced 3D design methods and experimental and computational fluid dynamics (CFD) analysis that will incorporate new blood-damage models based on neonatal blood rheology and coagulation. To this end, a blood shearing instrument has been developed by the investigators to simulate human hemodynamic conditions expected with the PediaFlow pump and to refine blood-damage models.32

The blood-contacting surface plays a significant role in the biocompatibility of the pump. Thus, in addition to the Ti6Al4V ELI and commercially pure titanium alloys currently used in most rotary VADs, other materials are being considered. These include injection-moldable ceramics and polymers, as well as alternative titanium alloys, such as Ti6Al4Nb. Injection-moldable materials may offer manufacturability and cost advantages over machined titanium alloys. Over 30 potential coatings and surface treatments have been identified for application to the base material selected from the options mentioned above to enhance biocompatibility.

In vivo evaluation of the PediaFlow VAD will be conducted in the pediatric ovine model. Initially, 15-kg lambs will be used, with progressively smaller animals to be used for subsequent studies to simulate the intended clinical population. A number of assays to measure hemolysis, erythrocyte fragility, blood cell activation, thrombosis, and inflammation will be applied in these studies to assess PediaFlow hemocompatibility in addition to standard measures of end-organ function and cellular counts.

The PediPump (The Cleveland Clinic Foundation)
The PediPump VAD is a magnetic bearing–supported, rotary dynamic circulatory support pump designed specifically for children.33 The enabling technology for the PediPump is derived from an adult “catheter” pump in development by The Cleveland Clinic’s Department of Biomedical Engineering and Foster-Miller Technologies, Inc. Because its capabilities are packaged into a small size, the resulting basic pump design provides support for the entire range of patient sizes encountered in pediatrics.

The pump rotating assembly consists of an impeller in the front, front and rear radial magnetic bearings, and a motor rotor magnet in its center (Figure 2). Blood enters axially at the inlet and is turned to exit the pump at an intermediate angle through the pump outer shell (blood flow path is demonstrated by the arrows). Reprinted with permission from The Cleveland Clinic Foundation. Copyright 2005.

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first intravascular and extravascular prototypes have already been generated and are being used to optimize impeller design with solid 3D computer-aided design modeling and CFD studies. The best-performing impeller and stator have been manufactured in stereolithography, and their combined performance has been evaluated in a hydraulic test stage with an externalized motor. Design of test loops for pump prototypes is also proceeding. The magnetic bearing design has been reviewed and detailed for the prototype. Device assembly will begin shortly after the finishing details of the thrust bearings are finalized on the basis of the durability testing results.

The second aim of the program is to perform preclinical anatomic fitting studies using computed tomography–based 3D modeling. Archived computed tomography scans from children with congenital heart disease have been converted into 3D digital models with Mimics software (Materialise). These digital renderings have been used subsequently to generate to-scale physical models by a variety of rapid prototyping techniques. Standard stereolithography methods have been used to create rigid physical models, whereas flexible physical models have been generated with a 3D printer, ZPrinter 310 System (Z Corporation), that utilizes starch-based powder to create rigid, thin-walled physical models derived from the on-screen renderings. The accurate modeling provided by these tools is expected to enable preoperative planning on a case-by-case basis, which will be of particular importance for patients with anatomic abnormalities of the great arteries and veins.

The last aim of the program is to perform animal implantations for characterization and reliability testing of the device. Careful assessment of the physiological impact of the PediPump and the ensuing host response will be determined from the studies. Animal implantations will begin after the ongoing basic engineering and anatomic studies.

**Pediatric Cardiopulmonary Assist System (Ension, Inc)**

Ension’s pCAS is being developed in collaboration between Ension, Inc, the University of Louisville, Seare BioMatrix Systems, and Fluent, Inc. The goal of this program is to improve on the current state of ECMO by decreasing clinical complications of this therapy and improving the possibility for parent-child contact and bonding during support.

The blood-contacting component of the pCAS, shown in Figure 4, is based around a compact, paracorporeal rotary flow device capable of simultaneously pumping blood and providing oxygenation. The device rotor is fabricated from layers of microporous hollow fibers that include a custom coating to both increase fiber life and minimize requirements for systemic anticoagulation.

The paracorporeal design of the pCAS affords modularity, which allows a separate device for each target patient population and the possibility of device exchange during the support period. Such modularity also permits the patient to be “upgraded” from the neonatal-sized device to the child-sized device as growth or support needs change. In addition to steady flow, the pCAS will include an option to deliver pulsatile flow at the higher heart rates of the intended patient population.

The hardware and control schemes of the pCAS will regulate both pump flow and oxygenation on the basis of inputs from a suite of sensors. These sensors include an off-the-shelf oxygen analyzer integrated with a custom-designed, photo-acoustic carbon dioxide analyzer developed at Ension. An ultrasonic-based blood flow sensor will be used in conjunction with a high-fidelity pressure transducer mounted distal to the device to provide input needed for the blood flow control scheme. Because oxygenation is directly

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**Figure 3.** A. Intravascular PediPump deployed as a biventricular assist device for patients weighing >15 kg. Pumps are demonstrated placed across both semilunar valves to position the inlet below valve level while blood is ejected above the valve to provide biventricular support. B. Extravascular, intracorporeal PediPump deployed as a biventricular assist device for patients weighing <15 kg. Biventricular support is provided by inlet cannulation of the right and left ventricles with outlet cannulation of the corresponding great artery. Corresponding LVAD and right VAD deployment of either the intravascular or extravascular versions would be achieved by removing the pump from the unsupported ventricle. Reprinted with permission from The Cleveland Clinic Foundation. Copyright 2005.

**Figure 4.** The Ension pCAS system. The blue and red arrows show the blood inflow and outflow paths, respectively. Gas exchange occurs in the rotor’s microporous hollow fibers.
dependent on blood flow, a complex control algorithm to regulate this interdependency will be developed.

Ension and its partners are also conducting research encompassing (1) rheological characterization of human and animal neonatal and pediatric blood; (2) computational modeling of blood flow, mass exchange, and blood damage within the pCAS device; and (3) in vitro and animal testing including inflammatory response assays. Researchers at the University of Louisville are focusing on rheological characterization as the basis of an improved fluid model for computational design work and the functional evaluation of pCAS prototypes. This work includes in vitro evaluations in a mock circulatory loop approximating the anatomic and hemodynamic features of a 1-year old infant, while also allowing the option of different cannulation sites and sizes, and the creation of ventricular failure conditions for the evaluation. In addition, the University of Louisville will also be responsible for all facets of the comprehensive acute and chronic animal evaluations of the pCAS device.

Fluent, Inc, a flow-modeling company with relevant experience in biological flows, is performing the CFD modeling of the pCAS device for Ension. The goal of this work is to use a CFD model as a design tool that may be leveraged to guide refinement of pCAS design iterations. The team’s development program focuses first on calculation and validation of the blood flow field, forming a foundation for subsequent oxygenation, decarbonation, and blood-damage calculations.

Seare Biomatrix Systems, Inc, a company that specializes in surface modifications to promote healthy device-tissue interface, has partnered with Ension to texture the exterior cannula surface used in the pCAS application. The spatially specific, porous material with an integrated biologic component (SeareMatrix) is intended to promote the development of a soft tissue in-growth with neovascularity. This tissue-engineered interface should provide anchoring of the cannulas and an infection-resistant barrier while being easy to surgically dissect at the time of cannula removal. Early research efforts will focus on optimizing the interface material porosity for the size of the cannulas to be used for percutaneous placement in children.

**The Pediatric Jarvik 2000 (Jarvik Heart)**

Two models of a Pediatric Jarvik 2000 axial-flow blood pump are being developed by Jarvik Heart, Inc in collaboration with the University of Maryland, Mississippi State University, and Whalen Biomedical, Inc. The design of the Pediatric Jarvik 2000 is based on the Jarvik 2000 VAD, which has been implanted in more than 100 patients in the United States and Europe over the past 5 years. During the first 3 years of the program, the work will be focused on developing and testing a child-size pump for long-term support in children of ~15 to 25 kg. The child-size model is a 35-g, 10-mL miniaturized version of the Jarvik 2000 blood pump. In years 4 and 5 of the program, the work will shift toward developing a still smaller 12-g, 4-mL infant-size blood pump. The infant-size model is intended for 3- to 15-kg children. These small child and infant Jarvik 2000 models are intended to be versatile. These devices, through various creative surgical techniques, are being designed to be implantable in any of the normal heart’s 4 chambers to provide the chronic mechanical left, right, or biventricular support needed by children with compromised cardiac function.

Prototypes of the child and infant Jarvik 2000 models are shown in Figure 5 with the adult Jarvik 2000 VAD. Despite the similarity in appearance, the pediatric devices will not simply be scaled-down models of the adult device. The pediatric models require new blade designs for the lower flow and pressure requirements of children and infants. Hydrodynamic test results (Figure 6) demonstrate that prototype infant and child-size Jarvik 2000 models provide desired cardiac outputs while functioning under expected operating conditions. These results have been confirmed in initial animal test results that showed that the child model pumps approximately 1 to 2.5 L/min. The animal study also revealed that the pump fits well in the apex of small sheep, the animal model selected to simulate the size and anatomy of a 15- to 25-kg child.
Further pump design refinements will be made using advanced CFD methods together with flow visualization and ex vivo hemolysis testing to achieve acceptably low blood damage in these very small pumps. Also as part of the project, a small microprocessor-based programmable control system will be developed with consideration of human factors so that it can be worn by children with adult supervision.

The encouraging clinical performance of the adult Jarvik 2000 VAD has resulted in high expectations for the Pediatric Jarvik 2000 models. The first destination-therapy recipient on a Jarvik 2000 VAD remains in excellent health after 5 years of circulatory assistance, the longest of any patient with any single heart-assist device. To date, no bearing failures have occurred in any patient, the few patients who experienced device-related infections were all successfully treated, and the incidences of thrombus, thromboembolism, and hemolysis have been acceptably low. Given the design and clinical results to date for the adult device, the reliability of the pediatric Jarvik 2000 VADs is targeted to exceed 10 years.

**Pediatric Ventricular Assist Device (Penn State)**

The Penn State Pediatric Ventricular Assist Device (PVAD), is a pulsatile, pneumatically actuated blood pump based on the design principles of the adult-sized Pierce-Donachy VAD, which was developed at Penn State and is now known as the Thoratec VAD, a product of the Thoratec Corporation. The PVAD, which underwent initial development in 1986 under the direction of William S. Pierce, MD, in collaboration with 3M Corporation, is intended to be used for left, right, or biventricular support for up to 6 months. The device is intended primarily for paracorporeal placement (Figure 7) but will also be implantable for bridge-to-transplantation applications. The PVAD (Figure 8) is being developed in 2 sizes: a 12-mL dynamic stroke volume size for infants ranging in weight from 5 to 15 kg and a 25-mL stroke volume size for children 15 to 35 kg in weight. The flow rate ranges of the infant- and child-size devices are 0.5 to 1.3 L/min and 1.3 to 3.3 L/min, respectively. Each of the pumps will consist of a seamless segmented polyether polyurethaneurea (SPEUU) blood sac positioned within a rigid titanium case, mechanical heart valves, and cannula connectors. Both bileaflet and monoleaflet mechanical heart valves in the 17- to 21-mm size range for the infant-size device and the 19- to 23-mm size range for the child-size device will be evaluated for use in the devices. The pump shape will encourage the development of a vortex flow pattern, which will efficiently maintain high wall shear rates to help prevent thrombus formation. The PVAD will be controlled by a new portable biventricular pneumatic driver, which will be developed in collaboration with Minnetronix, Inc based on actuator technology developed by Penn State for electrically powered implantable blood pumps.

Device biocompatibility of the PVAD systems is another area of focus. In addition, using advanced fluid dynamic techniques to identify areas that are prone to thrombus deposition, hemolysis, or platelet activation, surface-modified SPEUU materials (Polymer Technology Group) are being investigated in an effort to increase thromboresistance without compromising fatigue life. Polymer surface morphology will be measured by scanning electron micrography, and bulk mechanical properties will be measured by dynamic mechanical analysis. In vitro methods of assessing blood compatibility are being used to supplement animal experiments. Platelet adhesion and reactivity under a range of shear rates is measured with a rotating disk system with immunofluorescent labeling of the cell membrane protein CD41, the α<sub>Ⅰb</sub> integrin chain of the glycoprotein IIb/IIIa complex. Further tests that assess the activity of biomaterial-adherent platelets in supporting formation of the coagulation complexes are also being developed. Material-induced activation of the intrinsic pathway of blood coagulation is being assessed by an in vitro assay that looks at the response of plasma to procoagulant material stimuli. Small tubes for this testing will be fabricated from the test polymers using the same procedures by which blood sacs are fabricated. Coagulation, measured by time to formation of a fibrin clot, will be assessed by testing the samples in recalcified, citrated human plasma.

During the development of the PVAD devices, animal studies will be performed to evaluate hemodynamic performance and biological effects, primarily thrombogenesis and
hemolysis. The 12-mL PVAD will be evaluated in 5- to 15-kg goats and the 25-mL PVAD in 15- to 35-kg goats. Pumps will be implanted in the preperitoneal space via a left thoracotomy, with cannulation of the left ventricle and descending aorta. Hematologic studies will be performed to detect alterations to blood-formed elements, evidence of activation of the hemostatic system, and hemolysis. Thrombus formation on the blood sac will be assessed by (1) postexplantation gross examination, (2) histological analysis, and (3) multiscale surface analysis (including scanning electron microscopy, immunofluorescent labeling of platelets and fibrinogen, and atomic force microscopy). Embolization will be assessed by clinical laboratory values throughout the study and examination of the major organs at autopsy for evidence of infarctions.

Future Directions

The objective of the NHLBI Pediatric Circulatory Support Program is to support the development of the family of pediatric MCSDs described above so that these novel devices will eventually provide effective options for clinical therapy. As evidenced in their descriptions, the PediPump, Pediatric Jarvik 2000 Flowmaker, PediaFlow VAD, Penn State PVAD, and pCAS each have unique characteristics to address the biocompatibility, cannulation, control, capacity, infection, reliability, and deployment issues specific to pediatric patients with congenital or acquired heart disease. As a result, each of the devices is expected to have unique applications based on patient size, expected duration of support, intention of therapy as a bridge to transplantation or to aid in recovery, and type of heart disease. Together, these 5 MCSDs are expected to provide the missing effective options for the vulnerable, small pediatric patients who are currently limited to short-term extracorporeal VADs and cumbersome conventional ECMO. Clinical evaluations are expected to begin at or before the conclusion of the development program in 2009.

Acknowledgments

Please see the online-only Data Supplement at http://circ.ahajournals.org/cgi/content/full/113/1/147/DC1.

Disclosures

Dr.s Baldwin and Hoke are employees of NHLBI and are the Project Officers for NHLBI’s Pediatric Circulatory Support Program. Dr. Borovetz is the Principal Investigator (PI) for the contract awarded to the University of Pittsburgh. The University of Pittsburgh licenses technology to WorldHeart, Inc. Dr. Borovetz does not receive any proceeds from the licenses. Dr. Duncan is the PI for the contract awarded to The Cleveland Clinic and is a member of the Advisory Board for the DeBakey VAD Child, a product of MicroMed Technologies, Inc. Mr. Gartner is the PI for the contract awarded to Emision, Inc., the company that intends to commercialize the pCAS. He is also President and retains ownership interest in Emision, Inc. Dr. Jarvik is the PI for the contract awarded to Jarvik Heart, Inc and is President and a shareholder of Jarvik Heart, Inc. Dr. Weiss is the PI for the contract awarded to The Pennsylvania State University.

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