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PENN STATE HERSHEY - CENTER FOR PEDIATRIC CARDIOVASCULAR RESEARCH

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Introduction

Over the past five years at Penn State Hershey we have established a multi-disciplinary research team with the goal to improve the outcomes for children undergoing cardiac surgery with cardiopulmonary bypass and mechanical circulatory support. The Penn State Hershey - Center for Pediatric Cardiovascular Research has been established with the collaboration of teams from multiple academic departments and representing multiple disciplines. This center combines basic science, engineering, and clinical applications under the unified mission of pediatric cardiovascular research. Scientists and clinicians in the center represent the departments of Pediatrics, Surgery, Bioengineering, Anesthesiology, Comparative Medicine, Public Health Sciences, Pharmacology, and Obstetrics & Gynecology.

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Our major objective is the development of novel technologies and methodologies to be used in minimizing the adverse effects of cardiovascular operations and cardiopulmonary bypass in neonates, infants, and children. Particular attention will be focused on reducing the associated morbidities of cerebral, myocardial, pulmonary, and renal injury.

Our long term aspirations are to: 1) establish The *Penn State Hershey - Center for Pediatric Cardiovascular Research* as a leading center for further development of novel treatments and cutting edge devices for cardiovascular health in pediatric populations, both at the Penn State Hershey Children's Hospital and at other pediatric heart centers around the world; 2) educate more bioengineers, medical students, residents, post-doctoral fellows and junior faculty members in pediatric cardiovascular research; and 3) ensure that our international conference continues to be the leading conference for defining the problems of current mechanical circulatory support systems in pediatric patients and suggesting appropriate solutions for these pediatric cardiac patients.

History and Rationale

The rich history of research and development in mechanical circulatory support devices at Penn State Hershey should facilitate the recognition of this Center as an ideal proving ground for new technology in the field of pediatric cardiopulmonary bypass and mechanical circulatory support. In this environment, translational research can be conducted with absolute scientific objectivity and freedom from commercial bias.

Within the past five years, our pediatric cardiac research group has generated over 271 publications (98 articles and 173 abstracts), over 124 national and international presentations and invited lectures, as well as over \$7.5 million in grants. Additionally, we have trained dozens of medical students, post-doctoral fellows, and undergraduate and graduate biomedical engineering students.

The Penn State Hershey College of Medicine, Department of Pediatrics contributed over \$600,000 in funds to support the creation of the new pediatric cardiac research laboratory. Many research components in the lab (e.g., heart-lung machines, heater and cooler units, advanced ultrasound devices) are identical to the clinical instruments used in our pediatric cardiac operating room. In addition, we are testing several new heart pumps and oxygenators for future clinical studies in pediatric patients in the United States and around the globe.

Current Projects

Impact of Pulsatile CPB on Vital Organ Recovery (Clinical/Basic Science/Engineering)

This study is designed to investigate the effects of pulsatile flow versus conventional non-pulsatile flow on systemic inflammation, and cerebral, myocardial, renal, and pulmonary recovery in neonates, infants, and children during CPB (1–5).

Discovery Proteomics during Pediatric Cardiac Surgery (Clinical/Basic Science)

These studies use state-of-the art 2-D gel electrophoresis, liquid chromatography, and mass spectrometry along with Multi-Analyte Profile immunoassays to identify altered serum proteins resulting from CPB perfusion modes. In addition, these studies may lead to the identification of specific preclinical markers that are associated with short and long-term outcomes that can be used to further optimize strategies for CPB in high-risk pediatric populations (6).

Microdevices for Measuring CPB Systemic Inflammation (Engineering/Basic Science)

This study is designed to develop a novel approach to measuring plasma cytokine and complement concentrations in real-time within a microfluidic analytical system during cardiopulmonary bypass procedures (7–8).

Microfluidic Dialysis Platforms for Monitoring Cardiopulmonary Bypass Systemic Inflammation (Engineering/Basic Science)

The objective of this study is to design microanalytical devices capable of continuously measuring antigen-substrate binding by employing microfabrication techniques and designing a microfluidic immunoassay platform that is able to measure concentrations of pro-inflammatory cytokines and complement in vitro (9).

Neonatal Aortic Arch Hemodynamic and Perfusion during Cardiopulmonary Bypass (Engineering)

The objective of this study is to evaluate and quantify detailed, patient-specific, three-dimensional (3D) pulsatile hemodynamics, mechanical loading, and perfusion characteristics of neonatal aortic arches during cardiopulmonary bypass (10).

Microemboli Detection and Classification by Innovative Ultrasound Technology during Cardiopulmonary Bypass Procedures (Clinical/Engineering)

The objective of this study is to detect and classify the number and size of gaseous microemboli during normothermic, hypothermic, and deep-hypothermic cardiopulmonary bypass (11–13).

Application of real time intra operative neurologic monitoring on management of pediatric cardiopulmonary bypass (Clinical)

The objective of this research is to incorporate advanced neurologic monitoring techniques using a multi specialty team approach to proactively identify and mitigate high risk periods during pediatric cardiopulmonary bypass (14).

Noninvasive Cardiac Imaging (Clinical)

The noninvasive cardiac imaging laboratory at Penn State Hershey Medical Center is dedicated to the development and clinical application of novel techniques to assess cardiac function. A main focus has been tissue Doppler imaging and strain rate imaging (15). We study the effect of cardiopulmonary bypass surgery on the recovery of left and right ventricular regional function. Tissue Doppler imaging is particularly useful to assess diastolic function quantitatively. Another project is imaging support of the development of a pediatric ventricular assist device. In the clinical arena, the laboratory is developing quantitative stress echocardiography for children using strain rate imaging. These techniques have been used in adults but have not been adapted for routine clinical use in children yet. Finally, we use three-dimensional echocardiography to better assess heart valve function.

Comparison of Eight Different Pediatric 10 FR Aortic Cannulae during Pulsatile vs. Non-Pulsatile Perfusion in a Simulated Neonatal Model of CPB (Engineering/Clinical)

The purpose of this investigation is to compare the surplus hemodynamic energy levels generated by eight pediatric aortic cannulae with different geometries during pulsatile and non-pulsatile perfusion modes in an in vitro neonatal model of CPB (16).

Effects of CPB on Blood Viscoelasticity during and after Open-heart Surgery in Neonates and Infants (Clinical/Basic Science)

The objective of this study is to determine the changes in blood viscoelasticity during and after cardiopulmonary bypass procedures in pediatric cardiac patients (17).

Pediatric Mechanical Circulatory Support (Engineering/Clinical/Basic Science)

Under the leadership of William Weiss, PhD, and as part of the prestigious five-year, five-institution NIH contract, Penn State has developed a pneumatic, pulsatile pediatric ventricular assist device, based on the design of the adult-sized Pierce-Donachy (Thoratec®) VAD. The Pediatric VAD exists in two sizes: an Infant VAD with a dynamic stroke volume of 12–14 ml, and a Child VAD with a 25–30 ml stroke volume. Under the NHLBI Contract Program “Pediatric Circulatory Support “, we have completed the design requirements, pump design, and cannula design. A custom valve has been designed and is currently being manufactured in house. The first phase of animal testing has been completed (15 studies). Manufacturing processes have been developed and 11 pumps are currently in process. Our research and development activities continue to focus on reducing the risk of thromboembolism, by drawing in relevant expertise in biomaterials, fluid dynamics, and hematology. In addition to the necessary device development tasks, we also plan to continue research in VAD thrombosis and anticoagulation that will contribute to the best possible clinical results (18).

Medos Pulsatile DP1 Device for ECLS (Engineering/Clinical)

The purpose of this investigation is to evaluate the performance of a new CPB/ECMO circuit and hollow-fiber membrane oxygenator during pulsatile perfusion and chronic use (19).

Levitronix Pulsatile Centrifugal Pump (Engineering/Clinical)

The objective of this study is to quantify the pressure-flow waveforms generated by the Levitronix centrifugal pump (approved in Europe for use up to 30 days) in terms of hemodynamic energy levels (20–22).

Fifth International Conference on Pediatric Circulatory Support Systems & Pediatric Cardiopulmonary Perfusion (Clinical/Basic Science/Engineering)

The main objective of this conference is to focus on the current problems associated with pediatric cardiac patients during and after acute or chronic cardiac support. In this conference, we bring together as many distinguished physicians and scientists as possible, in order to precisely define the current problems and to suggest solutions with novel approaches. This is the only national/international conference to focus solely on pediatric cardiac patients (23).

Ecuador Mission Program

Over the last ten years, the Penn State Hershey Children’s Hospital has annually deployed a team of specialists (including pediatric heart surgeons, cardiologists, anesthesiologists, intensivists, perfusionists, nurses, and medical students) to perform life-saving heart surgery for children at the Hospital de los Niños in Guayaquil, Ecuador. In addition to the providing a charitable clinical service, the team also continues to provide direct education to the local surgeons and clinicians, with the goal of fostering an independent, self-sustaining pediatric heart surgery program at the children’s hospital.

Animal models will be developed for testing the new devices

With the help of collaborators from the Department of Comparative Medicine (Ronald Wilson, VMD, MS, and Elizabeth Carney, DVM), we will develop animal models for testing new pediatric heart pumps, oxygenators, cannulae, etc. for acute and chronic support (24).

Summary

With the creation of the Penn State Hershey - Center for Pediatric Cardiovascular Research, we strive to become one of the leading centers for the innovation and development of novel devices and treatments for congenital heart surgery. We also seek to educate more bioengineers, medical students, residents, post-doctoral fellows, and junior faculty members in pediatric cardiovascular research. Finally, we seek to continue the growth of our conference (The International Conference on Pediatric Mechanical Circulatory Support Systems and Pediatric Cardiopulmonary Perfusion - <http://www.hmc.psu.edu/childrens/pedscpb/>), in order to provide a scientific venue for the pioneering research being performed in pediatric mechanical circulatory support and cardiopulmonary perfusion.

Our website (<http://www.pennstatehershey.org/web/childrensheartgroup/research/overview>) includes an overview of all of our current projects (clinical, basic science, and bioengineering), publications, presentations, as well as national and international collaborators affiliated with our center. Investigators interested in collaborating with us on current or new projects should send an e-mail to aundar@psu.edu.

Special thanks go to all those who support our collaborative efforts, both intellectually and financially each year. This includes significant financial support from the Penn State Hershey Children's Hospital and Penn State Hershey College of Medicine, the National Heart Lung and Blood Institute, and the National Institute of Health Office of Rare Diseases. Furthermore, we are most grateful to our dedicated students, sponsors, faculty, and national and international collaborators which make the formation of such an establishment possible.

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