Cardiothoracic Surgery

Division Photo

J. Duffy, P.Manning, P. Eghtesady

Division Data Summary

Research and Training Details	
Number of Faculty	3
Number of Support Personnel	15
Direct Annual Grant Support	$209,091
Peer Reviewed Publications	5
Clinical Activities and Training	
Number of Clinical Fellows	1
Number of Other Students	4
Inpatient Encounters	314
Outpatient Encounters	195

Significant Publications

Baker RS, Lam CT, Heeb EA, Eghtesady P. J Thorac Cardiovasc Surg. 2009 Mar;137(3):714-22.

OBJECTIVE: Fluid shifts have been suggested to occur with fetal bypass. The degree or mechanisms behind these volume changes (or location) have not been defined. We characterized the preceding and correlated the findings to plasma vasopressin concentrations, the critical peptide of osmoregulation. METHODS: Seventeen ovine fetuses (105-111 days' gestation) were started on bypass and followed 2 hours after bypass. Hemodynamics and volume replacements needed to maintain minimum reservoir volume during bypass and normal physiologic parameters after bypass were recorded. Serial blood samples were collected to assess gas exchange and vasopressin levels. Changes in total tissue water content were measured for several organs and the placenta. Plasma volume, fluid shifts, and osmolarity were calculated. RESULTS: Hematocrit values decreased by 15 minutes of bypass to 28% from 33% and then increased to 34% by 120 minutes after bypass, corresponding to a decreased fetal plasma

volume of 79 to 72 mL/kg by 120 minutes after bypass. The majority of volume shifts (approximately 100 mL/kg) occurred during bypass, but additional volume replacements were required after bypass to maintain normal hemodynamics, resulting in overall losses of 0.8 mL x kg(-1) x min(-1). Losses were not accounted for by placental or organ edema. Vasopressin levels increased dramatically with bypass (39-51.5 pg/mL) and were strongly predicted by increased fetal plasma volumes (R(2) = 0.90), whereas osmolarity was not significantly associated with plasma volumes. CONCLUSION: Fetal bypass leads to significant fluid shifts that correlate strongly with increasing vasopressin levels (but not changes in osmolarity). The placenta is not the primary site of volume loss. Rehydration of the fetus is necessary after bypass.

Duffy JY, McLean KM, Lyons JM, Czaikowski AJ, Wagner CJ, Pearl JM. Crit Care Med. 2009 Feb;37(2):577-83.

OBJECTIVE: The hypothesis is that partial nuclear factor-kappaB (NF-kappaB) inhibition can alleviate cardiopulmonary dysfunction associated with ischemia and reperfusion injury following cardiopulmonary bypass and deep hypothermic circulatory arrest (CPB/DHCA) in a pediatric model. DESIGN: Animal case study. SUBJECTS: Two-week-old piglets (5-7 kg). INTERVENTIONS: Piglets received 100 microg/kg of SN50, a peptide inhibitor of NF-kappaB translocation and activation, 1 hour before CPB. The control group received saline. Animals were cooled to 18 degrees C with CPB, the piglets were in DHCA for 120 minutes, and the piglets were then rewarmed on CPB to 38 degrees C and maintained for 120 minutes after CPB/DHCA. MEASUREMENTS: Sonomicrometry and pressure catheters collected hemodynamic data. Transmural left and right ventricular tissues were obtained at the terminal time point for determination of NF-kappaB activity by enzyme-linked immunosorbent assay. Data are expressed as mean +/- sd. MAIN POINTS: Oxygen delivery was maintained at 76 +/- 13 mL/min at baseline and 75 +/- 5 mL/min at 120 minutes after CPB/DHCA (p = 0.75) in SN50-treated animals vs. 99 +/- 26 mL/min at baseline and 63 +/- 20 mL/min at 120 minutes in the untreated group (p = 0.0001). Pulmonary vascular resistance (dynes.sec.cm) increased from 124 +/- 59 at baseline to 369 +/- 104 at 120 minutes in the untreated piglets (p = 0.001) compared with SN50-treated animals (100 +/- 24 at baseline and 169 +/- 88 at 120 minutes, p = 0.1). NF-kappaB activity was reduced by 74% in left ventricles of SN50-treated compared with SN50-untreated animals (p < 0.001). Plasma endothelin-1 (pg/mL), an important vasoconstrictor regulated by NF-kappaB, increased from 2.1 +/- 0.4 to 14.2 +/- 5.7 in untreated animals (p = 0.004) but was elevated to only 4.5 +/- 2 with SN50 treatment (p = 0.005). CONCLUSIONS: Improvement of cardiopulmonary function after ischemia/reperfusion was associated with the reduction of NF-kappaB activity in piglet hearts. Maintenance of systemic oxygen delivery and alleviation of pulmonary hypertension after CPB/DHCA in piglets administered SN50, possibly through a reduction of circulating endothelin-1, suggest that selective inhibition of NF-kappaB activity may reduce ischemia and reperfusion injury after pediatric cardiac surgery.

Giuliano JS Jr, Lahni PM, Bigham MT, Manning PB, Nelson DP, Wong HR, Wheeler DS. Intensive Care Med. 2008 Oct;34(10):1851-7. Epub 2008 May 31.

OBJECTIVE: The aim was to investigate the effects of cardiopulmonary bypass (CPB) on plasma levels of the vascular growth factors, angiopoietin (angpt)-1, angpt-2, and vascular endothelial growth factor (VEGF). DESIGN: The design was a prospective, clinical investigation. SETTING: The setting was a 12-bed pediatric cardiac intensive care unit of a tertiary children's medical center. PATIENTS: The patients were 48 children (median age, 5 months) undergoing surgical correction or palliation of congenital heart disease who were prospectively enrolled following informed consent. INTERVENTIONS: There were no interventions in this study. MEASUREMENTS AND RESULTS: Plasma samples were obtained at baseline and at 0, 6, and 24 h following CPB. Angpt-1, angpt-2, and VEGF levels were measured via commercial ELISA. Angpt-2 levels increased by 6 h (0.95, IQR 0.43-2.08 ng mL(-1) vs. 4.62, IQR 1.16-6.93 ng mL(-1), P < 0.05) and remained significantly elevated at 24 h after CPB (1.85, IQR 0.70-2.76 ng mL(-1); P < 0.05). Angpt-1 levels remained unchanged immediately after CPB, but were significantly decreased at 24 h after CPB (0.64, IQR 0.40-1.62 ng mL(-1) vs. 1.99, IQR 1.23-2.63 ng mL(-1), P < 0.05). Angpt-2 levels correlated significantly with cardiac intensive care unit (CICU) length of stay (LOS) and were an independent predictor for CICU LOS on subsequent multivariate analysis. CONCLUSIONS: Angpt-2 appears to be an important biomarker of adverse outcome following CPB in children

Heeb EA, Baker RS, Lam C, Basu M, Lubbers W, Duffy JY, Eghtesady P. Ann Thorac Surg. 2009 Mar;87(3):841-7.

BACKGROUND: We previously showed cyclic guanosine 3',5'-monophosphate (cGMP) levels increase with fetal cardiac bypass despite derangements in the placental nitric oxide pathway. The natriuretic peptides, atrial (ANP), brain (BNP), and c-type (CNP), are common indicators of cardiac distress, and an alternative pathway for cGMP generation. We hypothesized that these natriuretic peptides may account for the paradoxic rise in cGMP seen with fetal bypass. METHODS: Six ovine fetuses, 106 to 118 days' gestation, underwent cardiac bypass for 30 minutes and were followed for 120 minutes after bypass. Fetal plasma samples were collected before bypass, during bypass,

and 30 and 120 minutes after bypass for natriuretic peptide analysis. Results were compared with 6 sham bypass fetuses and cGMP values from another 14 bypass fetuses (to avoid confounding effects of excess blood sampling). Fetal hemodynamics and metabolics were correlated to ANP, BNP, and CNP values. Statistical analysis was by analysis of variance, Student's t test, and best-fit correlations, with significance set at p = 0.05 or less. RESULTS: The ANP, BNP, and CNP increased with fetal bypass (674 +/- 133 pg/mL, 151 +/- 52 pg/mL, and 295 +/- 45 pg/mL, respectively), remaining elevated after bypass, whereas sham concentrations remained stable at pre-bypass levels. Changes in ANP, BNP, and CNP positively correlated with rising cGMP. There was positive correlation between ANP and CNP and rising fetal lactate levels, but not to other physiologic parameters associated with placental dysfunction. CONCLUSIONS: There is a substantial rise in natriuretic peptides seen with fetal bypass, likely in part a reflection of myocardial dysfunction. Further, the natriuretic peptide pathway may account for the paradoxic rise in cGMP seen with fetal bypass.

Nguyen MT, Dent CL, Ross GF, Harris N, Manning PB, Mitsnefes MM, Devarajan P. Pediatr Nephrol. 2008 Aug;23(8):1317-26. Epub 2008 May 28.

Proteomic analysis has revealed potential early biomarkers of acute kidney injury (AKI) in children undergoing cardiopulmonary bypass (CPB), the most prominent one with a mass-to-charge ratio of 6.4 kDa. The objective of this study was to identify this protein and test its utility as a biomarker of AKI. Trypsin-digested protein bands were analyzed by tandem mass spectrometry (MS/MS) to identify the protein in urine samples. Surface-enhanced laser desorption/ionization time-of-flight analysis and a functional activity assay were performed to quantify urinary levels in a pilot study of 106 pediatric patients undergoing CPB. The protein was identified as aprotinin. Urinary aprotinin levels 2 h after initiation of CPB were predictive of AKI (for functional assay: 92% sensitivity, 96% specificity, area under the curve of 0.98). By multivariate analysis, the urinary aprotinin level 2 h after CPB was an independent predictor of AKI (beta = 0.001, $P < 0.0001$). The 2 h urinary aprotinin level correlated with serum creatinine, duration of AKI, and length of hospital stay. We concluded that urinary aprotinin levels 2 h after initiation of CPB predict the development of AKI and adverse clinical outcomes.

Division Highlights

Jodie Duffy, PhD

Presentations:

Myocardial cantractile dysfunction is associated with fetal cardiac bypass in a sheep model. American Heart Association Scientific Sessions. New Orleans, LA. Circulation 118:S543.

Activation of inflammatory and apoptotic pathways in human donor heart dysfunction. American Heart Association Scientific Sessions. New Orleans, LA.

Pirooz Egthesady, MD, PhD

Presentations:

Cyclic Nucleotide Analog Infusion does not Improve Fetal-Placental Hemodynamics or Placental Function with Fetal Cardiac Bypass. 5th International Conference on Pediatric Circulatory Support Systems and Pediatric Cardiopulmonary Perfusion. Dallas, TX.

Mini-Epidemics of Hypoplastic Left Heart Syndrome. AmericanCollege of Cardiology, 58th Annual Scientific Session. Orlando, FL. Selected for “Best Poster” Competition.

Myocardial Contractile Dysfunction is Associated with Fetal Cardiac Bypass in a Sheep Model. American Heart Association, Scientific Sessions. New Orleans, LA.

Role of Nitric Oxide in the Increased Vascular Resistance Following Fetal Cardiac Bypass. American Heart Association Research Symposium. New Orleans, LA.

Ventricular Septal Defects. Thoracic Teaching Program. University of Cincinnati, Cincinnati, OH.

Faculty Members

Peter B. Manning, MD, Professor ; *Director, Cardiothoracic Surgery; Co-director The Heart Center*

Jodie Y. Duffy, PhD, Research Associate Professor

Research Interests: Reoxygenation and Reperfusion Injury with Cardiopulmonary Bypass

Pirooz Eghtesady, MD, Associate Professor ; *Surgical Director, Cardiac Transplantation*
Research Interests: Fetal Cardiac Surgery

Trainees

- **Lynn Huffman, MD,** PGY-4, University of Cincinnati

Significant Accomplishments

The Division of Cardiothoracic Surgery

Cardiothoracic Surgery is comprised of 2 surgical faculty,1 research faculty, 4 perfusionists, 3 nurse practitioners, 2 physician assists, 2 research assists and 3 administrative support staff dedicated to the surgical care of children with cardiac problems. Based solely at CCHMC the Division has formed a strong collaborative relationship with the leadership in Cardiothoracic Surgery at UC. An integrated component of The Heart Institute, the Division has a high profile nationally as a leader in managing cardiac problems in children.Our vision is to be a national and international leader in ped cardiothoracic surgery, research and teaching.Our clinical programs provide excellent care with morbidity and mortality rates rivaling any national program.The Division is a primary key to the Ped Cardiology and Ped Critical Care fellowship training programs.Close interaction with these fellows occurs daily, mainly in the Cardiac ICU and in weekly teaching conferences.The Division serves as one of the main rotations of UC's Cardiothoracic Surgery program with a fellow rotating 4 to 6 mths a year.Our research efforts continue to grow with faculty collaboration with Cardiology and other faculty on clinical research projects.The Division's clinical focus is on surgical management of cardiac problems from birth through adolescence. We are involved in the Fetal Cardiology with prenatal counseling of families of children with congenital heart defects. We focus on complete corrections of cardiac defects in the newborn period, management of complex single ventricle cardiac anomalies and techniques to limit transfusion exposures.The Division performs all levels of open and closed heart surgeries, cardiac transplant and ECMO support.The annual BMCH review of state-wide data revealed that CCHMC continues to perform the highest volume of newborn open heart procedures in OH. With conventional operating rooms and a state-of-the-art Hybrid Suite CCHMC provides multiple treatment modalities.

Research Program - Jodie Duffy, PhD

The lab currently has several projects underway investigating reoxygenation and reperfusion injury associated with cardiopulmonary bypass during repair of congenital heart disease and cardiac transplantation. The program includes mechanistic studies using proteomics, gene therapy, protein and gene expression arrays, and novel *in vitro* models of reperfusion injury. The lab has identified several myocardial proteins influenced by hypoxia and reoxygenation that allow investigations to focus on novel pathways. Gene therapy was integrated into the model with optimized delivery of target gene expressing adenoviral system directly into the coronary arteries to provide high levels of calpastatin gene expression in the myocardium. An R01 grant funded by NIH to investigate the role of the calpain/calpastatin pathway in reperfusion injury incorporates large animal studies with *in vitro* characterization of the cellular pathways that answer clinically-relevant questions.

The important combination of clinical investigations, animal model studies, and basic cellular research provides an opportunity for translation into solutions for problems confronting patients. A collaborative R21 grant proposal investigating the role of vasopressin in the placental dysfunction associated with fetal cardiac bypass is currently funded by the NIH. Collaboration between Drs. Eghtesady and Duffy focus on translational efforts for fetal bypass by understanding the cellular processes. A novel non-invasive preconditioning procedure, periodic acceleration, is under investigation for use as therapy to reduce ischemia and reperfusion injury in pediatric surgery patients. Joint collaborators from Children's Hosp of Philadelphia and Mt Sinai Medical Center are examining the piglet model used in Dr. Duffy's program to progress this translational study. A R21 proposal is under current consideration by NIH.

Research Program - Pirooz Eghtesady, MD

Our group continues to work toward clinical translation of fetal cardiac surgery. We recently pioneered an experimental model of fetal intracardiac surgery that may eventually be used to facilitate in-utero repair of select pathologies. We have also begun studying the pathologic mechanisms and markers involved in myocardial dysfunction associated with fetal cardiac surgery and bypass. Current studies funded by The Thrasher Foundation and The American Heart Association use combined in-vivo and in-vitro techniques to investigate the role of nitric oxide/cGMP signaling and natriuretic peptides in vascular dysfunction. These studies have suggested a novel role for vasopressin, which is the subject of a submitted R21 proposal. Another R21 application in October 2008 will examine the ideal fetal cardioplegia to alleviate myocardial dysfunction associated with fetal cardiac bypass. An R01 application in February 2009 will examine the role of calcium handling in fetal myocardial dysfunction associated with fetal cardiac bypass.

We are also continuing our research into pathogenesis of hypoplastic left heart syndrome (HLHS), a defect associated with significant neonatal, mortality and morbidity. Over the past year the group completed an epidemiologic analysis of the Pediatric Hospital Information Systems database (1996-2006 in 32 children's hospitals across the U.S.), which demonstrated that the occurrence of HLHS presents as "mini-epidemics" with a seasonal distribution, data supportive of our novel hypothesis suggesting that HLHS is an expression of rheumatic heart disease in the fetus, caused by the maternal antibodies to strep throat that cross the placenta and alter fetal heart valve development. To test this hypothesis, the research team is conducting ongoing studies, using IRB-approved protocols, in pregnant women recruited from the Fetal Care Center at Cincinnati Children's Hospital. These studies are the subject of an R01 application to be submitted in Oct 2008.

Division Publications

1. Duffy JY, McLean KM, Lyons JM, Czaikowski AJ, Wagner CJ, Pearl JM. Modulation of nuclear factor-kappaB improves cardiac dysfunction associated with cardiopulmonary bypass and deep hypothermic circulatory arrest. *Crit Care Med.* 2009; 37: 577-83.
2. Baker RS, Lam CT, Heeb EA, Eghtesady P. Dynamic fluid shifts induced by fetal bypass. *J Thorac Cardiovasc Surg.* 2009; 137: 714-22.
3. Heeb EA, Baker RS, Lam C, Basu M, Lubbers W, Duffy JY, Eghtesady P. Role of natriuretic peptides in cGMP production in fetal cardiac bypass. *Ann Thorac Surg.* 2009; 87: 841-7.
4. Nguyen MT, Dent CL, Ross GF, Harris N, Manning PB, Mitsnefes MM, Devarajan P. Urinary aprotinin as a predictor of acute kidney injury after cardiac surgery in children receiving aprotinin therapy. *Pediatr Nephrol.* 2008; 23: 1317-26.
5. Giuliano JS, Jr., Lahni PM, Bigham MT, Manning PB, Nelson DP, Wong HR, Wheeler DS. Plasma angiopoietin-2 levels increase in children following cardiopulmonary bypass. *Intensive Care Med.* 2008; 34: 1851-7.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

EGHTESADY, P

Role of Nitric Oxide in the Increased Placental Vascular Resistance Following Cardipulmonary Bypass
American Heart Association - National
SDG0535292N — 07/01/05 - 06/30/09 — $59,091 / $236,364

Mechanisms of Vasopressin-Mediated PVR Following Fetal Bypass
National Institutes of Health
R21 HL 093683 — 04/01/09 - 03/31/11 — $150,000 / $275,000

Current Year Direct **$209,091**

Total $ 209,091