

## Cardiothoracic Surgery



P. Manning, P. Eghtesady, J. Duffy

### Division Data Summary

#### Research and Training Details

Number of Faculty	3
Number of Research Fellows	1
Number of Support Personnel	14
Direct Annual Grant Support	\$272,432
Peer Reviewed Publications	8

#### Clinical Activities and Training

Number of Other Students	6
Inpatient Encounters	336
Outpatient Encounters	262

### Faculty Members

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

**Jodie Y. Duffy, PhD**, Research Assistant Professor

**Research Interests:** Reoxygenation and Reperfusion Injury with Cardiopulmonary Bypass

**Pirooz Eghtesady, MD**, Assistant Professor ; *Surgical Director, Cardiac Transplantation*

**Research Interests:** Fetal Cardiac Surgery

### Trainees

- **Julian Guitron, MD**, PGY-2, University of Cincinnati

### Significant Accomplishments in FY08

#### Clinical Program

The Division of Cardiothoracic Surgery at Cincinnati Children's Hospital Medical Center is comprised of two surgical faculty, one research faculty, four clinical perfusionists, three nurse practitioners, two physician assistants, two research

assistants and three administrative support staff dedicated to the surgical care of children with cardiac problems. Based completely at Cincinnati Children's Hospital Medical Center, the Division has formed a strong collaborative relationship over recent years with the leadership in Cardiothoracic Surgery at University Hospital. As an integrated component of The Heart Institute, a multi-disciplinary business unit within CCHMC, the Division has enjoyed a continually higher profile nationally as a leader in the management of cardiac problems in children.

The vision of the Division is to be a national and international leader in pediatric cardiothoracic surgical care, surgical research and teaching. The clinical programs of the Division continue to provide excellent care with morbidity and mortality rates rivaling any program nationwide.

Members of the Division of Cardiothoracic Surgery function as key faculty of the Pediatric Cardiology and Pediatric Critical Care fellowship training programs at CCHMC. Close interaction with these fellows occurs on a daily basis, primarily in the Cardiac Intensive Care Unit, in addition to a number of weekly teaching conferences in which the faculty participates. The Division serves as one of the primary rotations of the Cardiothoracic Surgery training program, based at UC, with a Fellow on the CCHMC service four to six months out of each year.

The research efforts within the Division continue to grow with two basic science laboratories presently within the Division, as well as the collaboration of Cardiothoracic Surgical faculty with Cardiology and other faculty on a number of clinical research projects.

The clinical programs in the Division of Pediatric Cardiothoracic Surgery focus on surgical management of cardiac problems from birth through adolescence. We also have become more involved in the Fetal Cardiology program, participating in prenatal counseling of families with 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 program has the capability of performing all levels of open and closed heart surgeries, including cardiac transplantation and the ability to perform ECMO support.

Clinical case volume for fiscal 2008 remained stable from the previous year. The annual review of state-wide data for pediatric cardiac programs under the auspices of BCMH revealed that Cincinnati Children's continues to perform the highest volume of newborn open heart procedures in Ohio. In addition to conventional operating rooms, Cincinnati Children's has a state-of-the-art Hybrid Suite allowing the use of multiple treatment modalities in a single site.

#### **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 October 2008.

#### **Research Program - Jodie Duffy, PhD**

The research group 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 has expanded to include mechanistic studies using proteomics, gene therapy, protein and gene expression arrays, and novel *in vitro* models of reperfusion injury. The research group has identified several myocardial proteins influenced by hypoxia and reoxygenation that allow investigations to focus on novel pathways. With funding of the NIH R03 grant by the National Institute of Child Health and Human Development, gene therapy was integrated into the animal 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. Currently, an R01 grant funded by the National Heart, Lung and Blood Institute to investigate the role of the calpain/calpastatin pathway in reperfusion injury incorporates large animal studies with *in vitro* characterization of the cellular and molecular pathways that provide an opportunity to ask and answer clinically-relevant questions. The important combination of clinical investigations, animal model studies, and basic cellular research provides the greatest opportunity for translation of data into solutions for problems confronting

cardiothoracic surgery patients. Application for continuation of NIH funding for these projects will be made in October of 2008.

A collaborative R21 grant proposal investigating the role of vasopressin in the placental dysfunction associated with fetal cardiac bypass is currently under consideration by the NIH. Collaborative efforts between the research labs of Drs. Eghtesady and Duffy focus on the translational efforts for fetal bypass by understanding the cellular processes.

## **Significant Publications in FY08**

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**Ashcraft TM, Jones K, Border WL, Eghtesady P, Pearl JM Khoury PR, Manning PB. Factors affecting long-term risk of aortic arch recoarctation after the Norwood procedure. *Annals Thoracic Surgery* 85(4)(April): 1297-401**

The purpose of this study was to identify factors predicting risk of aortic arch recoarctation after the Norwood procedure. **METHODS:** Patient records were reviewed retrospectively for consecutive patients who underwent the Norwood procedure from 1996 to 2005. Preoperative and intraoperative parameters were identified for analysis. Aortic arch recoarctation was defined by the need for catheter or surgical reintervention. Data were analyzed using survival analysis, with freedom from intervention as the outcome. Factors predicting need for reintervention were analyzed using Cox proportional hazards regression. **RESULTS:** Thirty-five recoarctations were observed in 117 patients (30%). Freedom from aortic arch reintervention at six months, one, three, and five years were 72%, 63%, 56%, and 52%, respectively. The majority of arch reinterventions occurred in the first six months (63%), involving either surgical (43%) or catheter (57%) techniques. The use of bovine pericardium showed the greatest risk for potential recoarctation (hazard ratio = 1.81 [0.90-3.64],  $p = 0.09$ ). Age, gender, weight, ascending aortic diameter, ventricular morphology, primary anatomic diagnosis, and coarctation shelf resection were not found to be predictors of recoarctation. **CONCLUSIONS:** Most interventions for aortic arch recoarctation after the Norwood procedure occur within the first six months of life. The type of patch material used for arch reconstruction appears to influence, most strongly, the long-term risk of aortic arch recoarctation.

**Lam C, Baker RS, Hilshorst J, Lombardi J, Clark KE, Eghtesady P. Role of nitric oxide pathway in placental dysfunction following fetal bypass. *Annals Thoracic Surgery* 84(3)(Sep): 917-24; discussion 924-5**

The etiology of placental dysfunction after fetal cardiopulmonary bypass remains unknown. The placental nitric oxide (NO) pathway has been implicated in this pathophysiology. We set out to examine possible perturbations in this pathway in an ovine model of fetal bypass. **METHODS:** Ovine fetuses ( $n = 14$ ) between 100 and 114 days of gestation, instrumented to measure hemodynamics and umbilical blood flow, were placed on bypass for 30 minutes and followed after bypass for 2 hours. Sham controls ( $n = 6$ ) were instrumented but did not undergo bypass. Real-time, in-vivo NO concentrations were measured in the placental circulation. To examine other components of the NO pathway, fetal plasma samples were analyzed by immunoassays for total NO metabolite and cyclic guanosine 3',5'-cyclic monophosphate (cGMP) levels. In addition, the expression of phosphodiesterase-5 was examined in placenta by immunohistochemistry. Statistical analysis was performed using analysis of variance with least significant difference post hoc tests ( $p < \text{or} = 0.05$ ). **RESULTS:** With the onset of bypass, an immediate increase occurs in umbilical NO concentrations. These return to baseline with cessation of bypass, and decline thereafter. In contrast, there was a linear increase in fetal plasma cGMP levels and a decline in NO metabolite concentrations through the post-bypass period. There was a dramatic increase in placental phosphodiesterase-5 expression with 30 minutes of bypass. The changes occur simultaneously with decreasing umbilical flows, increased placental vascular resistance, and worsening placental gas exchange. **CONCLUSIONS:** Fetal bypass leads to significant reductions in placental NO concentrations despite increases in fetal plasma cGMP and placental phosphodiesterase-5 levels, indicative of perturbations in the fetal-placental NO pathway.

**Lam C, Sharma S, Baker RS, Hilshorst J, Lombardi J, Clark KE, Eghtesady P. Fetal stress response to fetal cardiac surgery. *Annals Thoracic Surgery* 85(5) ( May): 1719-27**

A deleterious fetal stress response, although not fully elucidated, may account for poor outcomes after experimental fetal cardiac surgery. We set out to characterize this fetal stress response and its potential role in placental dysfunction. **METHODS:** Fifteen ovine fetuses at gestational day 100 to 114 were placed on extracorporeal support for 30 minutes and were then followed 2 hours after cardiopulmonary bypass. Fetal plasma samples were analyzed for vasopressin, cortisol, and beta-endorphin levels, and correlated to fetal hemodynamics and placental gas exchange. **RESULTS:** Unique temporal patterns of response were seen in release of the three stress hormones. Vasopressin demonstrated the most profound and early response followed by cortisol and beta-endorphin, the latter continuing to rise in the post-bypass period. A sharp rise in fetal mean arterial pressure and placental vascular resistance strongly correlated with rising vasopressin levels. Post-bypass deterioration of fetal gas exchange and hemodynamics correlated with the ensuing rise in cortisol and beta-endorphin. Rising fetal lactate levels correlated with elevations in all three stress hormones. **CONCLUSIONS:** Fetal cardiopulmonary bypass leads to a profound, early rise in vasopressin concentrations that strongly correlates with placental dysfunction after fetal bypass. Vasopressin may play an important mechanistic role in pathogenesis of this placental dysfunction.

**Manning PB, Rutter MJ, Border WL. Slide tracheoplasty in infants and children: risk factors for prolonged postoperative ventilatory support. *Annals of Thoracic Surgery* 85(4) (April) 1187-91; discussion 1401-2**

A single-institution experience with slide tracheoplasty for management of tracheal stenosis in children with emphasis on identifying predictors of prolonged postoperative mechanical ventilation is reviewed. METHODS: Patient characteristics, hospital course, and outcomes for children undergoing slide tracheoplasty were recorded. Univariate and multivariate analysis was performed to identify factors leading to prolonged mechanical ventilation (>48 hours postoperatively). RESULTS: Since April 2001, 40 children underwent slide tracheoplasty utilizing cardiopulmonary bypass (CPB) support at a median age of 6.2 months (range, 7 days to 15 years), and median weight of 6.1 kg (range, 1.9 to 57 kg). Thirteen patients had undergone prior operations. Thirteen patients (32.5%) were mechanically ventilated before operation. Thirteen patients underwent additional procedures at the time of the slide tracheoplasty. Mean CPB support time was 123 minutes. Seven patients required aortic cross-clamping (mean, 69 minutes). There were 2 early and 2 late deaths, none related to the tracheoplasty. One patient required repair of a recurrent tracheal stenosis, 4 patients required tracheotomy, and 3 required temporary stent placement. Twenty-one patients (52.5%) were extubated within 48 hours after tracheoplasty. Univariate and multivariate analysis revealed only preoperative mechanical ventilatory support (odds ratio 28.4,  $p = 0.015$ ) and duration of CPB support (odds ratio 1.06,  $p = 0.007$ ) to be significant predictors of the need for prolonged intubation. CONCLUSIONS: Slide tracheoplasty utilizing CPB support is a versatile and effective treatment for tracheal stenosis in children even when combined with repair of congenital cardiac anomalies. Most children can be successfully weaned from mechanical ventilatory support early after repair.

## Division Highlights

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### Jodie Duffy, PhD

#### Presentations:

Calpain inhibition regulates endothelin-1 and nitric oxide during simulated ischemia and reperfusion of isolated cardiomyocytes. International Society of Heart Research Annual Meeting. Cincinnati, OH. June 17-20, 2008.

Calpain Inhibition reduces nuclear factor-kappaB activity and apoptosis markers after cardiopulmonary bypass in neonatal piglets. American Heart Association. The Scientific Basis of Heart Failure in Children. Estes Park, CO. May 14-16, 2008.

Epigallocatechin-3-gallate moderates nitric oxide production during ischemia and reperfusion of cardiomyocytes. Society of Thoracic Surgeons Annual Meeting. Fort Lauderdale, FL. January 28-30, 2008.

Serum collected during and after fetal sheep cardiopulmonary bypass stimulates nitric oxide and endothelin-1 production by umbilical vein endothelial cells. Society of Gynecological Investigation Annual Meeting. San Diego, CA. March 26-29, 2008.

Glucocorticoid administration improves calcium handling by cardiomyocytes after ischemia and reperfusion. Society of Thoracic Surgeons Annual Meeting. Fort Lauderdale, FL. January 28-30, 2008.

### Piروز Eghtesady, MD

#### Presentations:

Fetal cardiac surgery: Mission impossible? 4th Annual International Symposium of Pediatric Mechanical Assist and Cardiopulmonary Bypass. Portland, OR. May 21-24, 2008.

Fetal surgical management of congenital heart block in a hydroptic fetus: lessons learned from a clinical experience. 4th Annual International Symposium of Pediatric Mechanical Assist and Cardiopulmonary Bypass. Portland, OR. May 21-24, 2008.

Dynamic fluid shifts induced by fetal cardiopulmonary bypass. American Association of Thoracic Surgery. San Diego, CA. May 11-14, 2008.

Role of NOS and PDE5 in placental dysfunction following fetal bypass. Society of Gynecological Investigation Annual Meeting. San Diego, CA. March 26-29, 2008.

Brain natriuretic peptide (BNP), cGMP, and fetal cardiopulmonary bypass. Society of Thoracic Surgeons Annual Meeting. Fort Lauderdale, FL. January 28-30, 2008.

Changes in fetal metabolism and oxygen delivery with fetal cardiac surgery. Society of Thoracic Surgeons Annual Meeting. Fort Lauderdale, FL. January 28-30, 2008.

## Division Publications

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1. Ashcraft TM, Jones K, Border WL, Eghtesady P, Pearl JM, Khoury PR, Manning PB. [Factors affecting long-term](#)

- [risk of aortic arch recoarctation after the Norwood procedure](#) . *Ann Thorac Surg*. 2008; 85: 1397-401; discussion 1401-2.
2. Baker RS, Lam CT, Heeb EA, Hilshorst JL, Ferguson R, Lombardi J, Eghtesady P. [A simple solution is "prime" for fetal cardiopulmonary bypass](#) . *Asaio J*. 2007; 53: 710-5.
  3. Bigham MT, Brady PW, Manning PB, Jacobs BR, Kimball TR, Wong HR. [Therapeutic application of intrapericardial tissue plasminogen activator in a 4-month-old child with complex fibropurulent pericarditis](#) . *Pediatr Crit Care Med*. 2008; 9: e1-4.
  4. Lam C, Baker RS, McNamara J, Ferguson R, Lombardi J, Clark K, Eghtesady P. [Role of nitric oxide pathway in placental dysfunction following fetal bypass](#) . *Ann Thorac Surg*. 2007; 84: 917-24; discussion 924-5.
  5. Lam CT, Sharma S, Baker RS, Hilshorst J, Lombardi J, Clark KE, Eghtesady P. [Fetal stress response to fetal cardiac surgery](#) . *Ann Thorac Surg*. 2008; 85: 1719-27.
  6. Manning PB, Rutter MJ, Border WL. [Slide tracheoplasty in infants and children: risk factors for prolonged postoperative ventilatory support](#) . *Ann Thorac Surg*. 2008; 85: 1187-91; discussion 1191-2.
  7. Pandalai PK, McLean KM, Bulcao CF, Duffy JY, D'Souza KM, Merrill WH, Pearl JM, Akhter SA. [Acute beta-blockade prevents myocardial beta-adrenergic receptor desensitization and preserves early ventricular function after brain death](#) . *J Thorac Cardiovasc Surg*. 2008; 135: 792-8.
  8. Wheeler DS, Dent CL, Manning PB, Nelson DP. [Factors prolonging length of stay in the cardiac intensive care unit following the arterial switch operation](#) . *Cardiol Young*. 2008; 18: 41-50.

## Grants, Contracts, and Industry Agreements

### Grant and Contract Awards

### Annual Direct / Project Period Direct

#### Duffy, J

##### Calpain and Calpastatin Regulation of Reperfusion Injury

National Institutes of Health

R01 HL 077653

04/01/05 - 03/31/09

\$213,341 / \$900,000

#### Eghtesady, P

##### Role of Nitric Oxide in the Increased Placental Vascular Resistance Following Cardiopulmonary Bypass

American Heart Association - National

0535292N

07/01/05 - 06/30/09

\$59,091 / \$236,364

**Current Year Direct**

**\$272,432**

**Total \$272,432**