Challenges in the Acute Post-operative Management of Pulmonary Hypertension after Congenital Heart Surgery

Lara Shekerdemian
Section Head of Critical Care, Texas Children’s Hospital
Professor of Pediatrics, Baylor College of Medicine

CASE REPORT

Diagnosis and Management of Postoperative Pulmonary Hypertensive Crisis

John Wheeler, M.D., Barbara L. George, M.D., Donald G. Mulder, M.D., and Jay M. Jarmakani, M.D.

SUMMARY: In this paper we discuss two infants and one child who experienced a previously unreported complication after complete correction of a large, unresectible ventricular septal defect. Two patients had documented pulmonary hypertensive crises and severe right-heart failure secondary to hypoxia and pulmonary vasoconstriction. These crises were associated with significantly increased right ventricular (RV) peak systolic and end-diastolic pressures and right-to-left shunting via a foramen ovale which, in turn, exaggerated the hypoxia. The crises were treated successfully with tolazoline in the second and third patients. RV pressures returned to normal values and have remained normal up to 12 months postoperatively in the second patient. Although the RV pressures decreased with tolazoline in the third patient, they never reached normal values. Postoperative monitoring of pulmonary artery and RV pressures in infants with large ventricular septal defects is essential when unexplained complications are encountered. Tolazoline proved to be very effective in the treatment of two patients with pulmonary vasoconstriction secondary to hypoxia.
Pulmonary Hypertension after Congenital Heart Surgery

Is it still a problem?
Pathophysiology
Therapeutic targets
Future directions

Failed extubation after cardiac surgery in young children: Prevalence, pathogenesis, and risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>31.4 (4.5,218)</td>
<td>.0005</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>4.7 (1.3,16.6)</td>
<td>.0179</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest</td>
<td>4.2 (1.1,15.7)</td>
<td>.035</td>
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</tbody>
</table>

Sensitivity vs. Specificity

J Thorac Cardiovasc Surg 2001
Pediatr Crit Care Med 2002
### Clinical Investigations

**Risk factors for long intensive care unit stay after cardiopulmonary bypass in children**

Kate L. Brown, MRCP, Deborah A. Ridout, MSc; Allan P. Goldman, MRCP; Aparna Hoskote, MRCP; Daniel J. Penny, MD, FRCP

<table>
<thead>
<tr>
<th>Post operative Model</th>
<th>Adjusted IRR</th>
<th>95% CI for IRR</th>
<th>P value</th>
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<tbody>
<tr>
<td>CPR</td>
<td>1.31</td>
<td>0.98, 1.74</td>
<td>0.069</td>
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<tr>
<td>Arrhythmia</td>
<td>1.68</td>
<td>1.33, 2.14</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Pulmonary hypertension</strong></td>
<td>1.68</td>
<td>1.17, 2.41</td>
<td>0.003</td>
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<tr>
<td>Renal failure</td>
<td>2.13</td>
<td>1.52, 2.98</td>
<td>&lt;0.001</td>
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<tr>
<td>Sepsis</td>
<td>2.48</td>
<td>1.87, 3.29</td>
<td>&lt;0.001</td>
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<td>Chylothorax</td>
<td>2.77</td>
<td>1.96, 3.91</td>
<td>&lt;0.001</td>
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<td>Diaphragm palsy</td>
<td>3.56</td>
<td>2.10, 6.31</td>
<td>0.002</td>
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<tr>
<td>Complications Score</td>
<td>1.80</td>
<td>1.65, 1.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed sternal closure</td>
<td>1.74</td>
<td>1.42, 2.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Causes of Death After Congenital Heart Surgery**

Marsha Ma, MD, Kimberlee Gauvreau, ScD, Catherine K. Allan, MD, John E. Mayer, Jr, MD, and Kathy J. Jenkins, MD, MPH

Tufts University School of Medicine, and Departments of Cardiology and Cardiovascular Surgery, Children’s Hospital Boston, Harvard Medical School, Boston, Massachusetts

- **Background.** There has been little research about the causes of death after congenital heart surgery.
- **Methods.** To determine whether mode of death differs after congenital heart surgery, we evaluated the cause of death for 100 consecutive postoperative deaths at our institution. Mode of death was determined based on retrospective chart review including available autopsy reports. Low output states were categorized into ventricular failure: inadequate postoperative physiology (technically adequate surgery and ventricular function, but persistent low cardiac output; pulmonary hypertension; and atrioventricular valve regurgitation.
- **Results.** There was considerable anatomic diversity among patients who died; 46 patients had single-ventricle physiology. The vast majority of patients (n = 79) were in the intensive care unit before surgery. Surgical repairs were revisited at initial operation in 22 cases; 7 patients died in the operating room. Seventy-three patients had technically adequate surgical procedures, 23 had residual anatomic defects, and 4 were indeterminate. Thirty patients underwent additional surgical and catheter-based procedures, although some were classified as rescue procedures performed to address minor anatomic or physiologic abnormalities as last hope to rescue the patient from impending demise. Of 100 deaths, most (n = 52) were due to low cardiac output: 24 inadequate postoperative physiology, 19 ventricular failure, 1 pulmonary hypertension, and 1 valvar regurgitation. Other significant causes of death included sudden cardiac arrest (n = 11), sepsis (n = 11), and procedural complications (n = 8).
- **Conclusions.** More than half of the deaths were due to low cardiac output, but not exclusively ventricular failure.

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**Causes of Death After Congenital Heart Surgery**

- Inadequate post-op physiology
- Ventricular Failure
- Pulmonary hypertension
- Cardiac Arrest
- Sepsis
- Complication
- Brain Injury
- Respiratory Failure
- Arrhythmia
- Bleed/Clot
- Other

Critic Care Med 2003
Double Patch Closure of Ventricular Septal Defect With Increased Pulmonary Vascular Resistance

William M. Novick, MD, A. Tayfun Gurbuz, MD, Donald C. Watson, MD, Vasily V. Lazorishnets, MD, Alexander N. Perepeka, MD, Ivan Malic, MD, PhD, Branko Marinovic MD, Bruce S. Alpert, MD, and Thomas G. D'Isessa, MD

Le Bonheur Children's Medical Center, University of Tennessee, Memphis, Tennessee; Kyiv Institute of Cardiovascular Surgery, Kyiv, Ukraine; and Rebro University Hospital Zagreb, Zagreb, Croatia

Background: Closure of a large ventricular septal defect (VSD) in children with elevated pulmonary vascular resistance is associated with significant morbidity and mortality. Pulmonary hypertensive episodes continue to be a major cause of postoperative morbidity and mortality. We designed a fenestrated flap valve double VSD patch in an effort to decrease the morbidity and mortality associated with the closure of a large VSD with elevated pulmonary vascular resistance.

Methods: Eighteen children (mean age, 5.7 years) with a large VSD and elevated pulmonary vascular resistance (mean, 11.4 Wood units) underwent double patch VSD closure using moderate hypothermic cardiopulmonary bypass and cardiopulmonary arrest. The routine VSD patch was fenestrated (4 to 6 mm) and on the left ventricular side of the patch, a second, smaller patch was attached to the fenestration along its superior margin before closure of the VSD.

Results. All children survived operation and were weaned from inotropic and ventilator support within 48 hours postoperatively. Postoperative pulmonary artery pressures were significantly lower than preoperative values. One child died 9 months postoperatively.

Conclusions. Closure of a large VSD in children with elevated pulmonary vascular resistance can be performed with low morbidity and mortality when a flap valve double VSD patch is used.

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Pathophysiology of Post-operative PH: Pulmonary Endothelial Dysfunction

- Exaggerated endothelium-dependent vasoconstriction
- Impaired endothelium-dependent vasodilation
- Abnormal interaction between vascular smooth muscle and endothelium
- Imbalance between dilator and constrictor pathways

Selective endothelial dysfunction in conscious dogs after cardiopulmonary bypass

4-week lambs
- Shunted lambs have increased basal NO-cGMP activity
- 30% decrease in NO metabolites after CPB
- No difference in NOS activity

Alterations in Endogenous Nitric Oxide Production After Cardiopulmonary Bypass in Lambs With Normal and Increased Pulmonary Blood Flow

- 4-week lambs
- Shunted lambs have increased basal NO-cGMP activity
- 30% decrease in NO metabolites after CPB
- No difference in NOS activity
Alterations in Nitric Oxide Production in 8-Week-Old Lambs with Increased Pulmonary Blood Flow

8-week lambs, no CPB
- Selective impairment of endothelium-dependent dilation
- No increased in basal NO activity

The Role of ET-1 after CPB

LUNG TISSUE IrET-1 (pg/gm)

ET-1 and Pulmonary Hypertension after Surgery for Congenital Heart Disease

PULMONARY VASCULAR RESISTANCE

V Mohan Reddy, Circulation 1997
Komai J Thorac Cardiovasc Surg 1993
ET-1 and Pulmonary Hypertension after Surgery for Congenital Heart Disease

Principles of Management of Pulmonary Hypertension after Cardiac Surgery

**Pre-emptive management**
- Before surgery
  - Identify at-risk patients
  - Early surgery
- Pre-operative therapy
- Intra-operative measures
- Post-operative measures
  - Anticipatory intensive care

**Early Intervention**
Intra-operative Measures

Objectives: A prospective randomized study was performed to test whether removal of endostatin-1, by ultrasound techniques, will reduce pulmonary hypertension after operations for congenital heart disease. Methods: Twenty-four patients with pulmonary hypertension (systolic pulmonary/systemic arterial pressure ratio > 0.40) undergoing cardiac operations were randomized into a control group (n = 12) having conventional ultrafiltration and an experimental group (n = 12) undergoing dilutional ultrafiltration during and after modified ultrafiltration after cardiopulmonary bypass. Plasma endostatin-1, nitric oxide metabolites, and cyclic guanosine monophosphate were assayed before bypass, 10 minutes into bypass, after bypass, and 3, 6, and 12 hours after the operation in both groups, as well as in the ultrafilters and after modified ultrafiltration in the experimental group. Both groups received ß-blockers (chlopamizide and/or propranolol) postoperatively using the same guidelines. Results: The ultrafilters contained significant amounts of endostatin-1 (1.81 ± 0.06 mmol dilutional and 6.44 ± 1.87 mmol modified ultrafiltrate). Endostatin-1 and the pulmonary/systemic pressure ratio were significantly lower in experimental compared with control patients. Nitric oxide metabolites and cyclic guanosine monophosphate increased similarly in both groups for 12 hours after the operation (p = not significant). Three of 12 control patients (25%) but no experimental patients had pulmonary hypertensive crises (p = 0.07). The experimental patients required significantly less ventilatory support (67 ± 47 hours vs 178 ± 139 hours for control patients, p = 0.048). Conclusions: Dilutional and modified ultrafiltration reduce endostatin-1 and the pulmonary/systemic pressure ratio postoperatively and may become an important adjutant for preventing pulmonary hypertension after operations for congenital heart disease among high-risk patients. 14: Thomas, Cardiovasc. Surg. LG, 1979, 115:317-27

Pre-emptive Management for at-risk Patients:
Post-operative Ventilation

Pre-emptive Management
Pre-sedate before Suction
Pre-emptive Management
Pre-sedate before Suction

Hickey et al Anaesth Analg 1985

Pre-emptive Therapy: iv Milrinone

Deb, Crit Care Med 2000

Current Therapies for Post-operative Pulmonary Hypertension: Inhaled Nitric Oxide

Nitric Oxide...... what’s the evidence?
Nitric oxide for respiratory failure in infants born at or near term (Review)

Finer N, Barrington KJ

Authors' conclusions

On the evidence presently available, it appears reasonable to use inhaled nitric oxide at an initial concentration of 20ppm for term and near term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults (Review)

Afshari A, Brok J, Möller AM, Wetterslev J

Authors’ conclusions

INO cannot be recommended for patients with AHRF. INO results in a transient improvement in oxygenation but does not reduce mortality and may be harmful.
What About Congenital Heart Disease?

Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease (Review)

Bizzarro M, Gross I

AUTHORS’ CONCLUSIONS

Implications for practice

The results of this meta-analysis do not appear to show any significant clinical benefit with the use of postoperative iNO to treat pulmonary hypertension in children with congenital heart disease.

While there may be a reduction in MPAJ in some subjects, we have observed no differences with respect to mortality, number of PHTC, or improved arterial oxygenation occur with that reduction. There are no data to determine the effects of treatment with iNO on length of intensive care unit or hospital stay, long-term mortality, and neurodevelopmental disability. Furthermore, the
**Limitations of Inhaled Nitric Oxide**

- Non-responders
- Partial responders and tachyphylaxis
- Rebound pulmonary hypertension on discontinuation
- Limited evidence in our patient population
- Availability
- Cost

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**Non-Responders to Inhaled Nitric Oxide**

15 Infants with PH post-op

- 40ppm NO for 30 min
  - 5 Responders
  - 10 Non-Responders

- Re-Investigated
  - Anatomic Obstruction (10)
  - Reintervention (6)
Partial Responders:
Augmenting the Response to Nitric Oxide

- Prepro-ET-1
- Big ET-1
- ET-A
- L-Arginine
- NO
- NOS
- ECE
- Nucleotides
- cGMP
- GCy
- PDE 5
- Sildenafil
  - PDE-5 inhibitor
  - Reduces cGMP breakdown
  - Increases endogenous c-GMP
**Rebound Pulmonary Hypertension: Occurs at the Lowest Doses**

In Healthy Lungs:
- Acute increase in PVR on stopping iNO
- Inhaled NO reduces endothelial NOS activity
- Acute reduction in cGMP on stopping iNO

**Pathophysiology of Rebound Pulmonary Hypertension**

*In Healthy Lungs:*
- Acute increase in PVR on stopping iNO
- Inhaled NO reduces endothelial NOS activity
- Acute reduction in cGMP on stopping iNO
Nitric oxide exposure inhibits endothelial NOS activity but not gene expression: a role for superoxide

A. MacDuff Sheehy, Michael A. Burson, and Stephen M. Black
Department of Pediatrics, University of California, San Francisco, California 94143-0106

Nitric Oxide
- Stimulates xanthine oxidase
- Increase in peroxynitrite
- NOS inhibition
- Mechanism for withdrawal

Am J Physiol 1998

Inhaled nitric oxide increases endothelin-1 levels: A potential cause of rebound pulmonary hypertension

Jeffrey M. Pearl, MD; David P. Nelson, MD, PhD; Jenni L. Raake, RRT; Peter B. Manning, MD; Steven M. Schwartz, MD; Lisa Koons, RN; Thomas P. Shinley, MD; Hector R. Wong, MD; Jodie Y. Duffy, PhD

Inhale nitric oxide increases endothelin-1 levels: A potential cause of rebound pulmonary hypertension

Am J Physiol 1998

Sildenafil Prevents Rebound Pulmonary Hypertension after Withdrawal of Nitric Oxide in Children

Poongundran Namachivayam, Ulf Theilen, Warwick W. Butt, Sian M. Cooper, Daniel J. Penney, and Lara S. Shekerdemian

Sildenafil Prevents Rebound Pulmonary Hypertension after Withdrawal of Nitric Oxide in Children

Prevention of Rebound

Am J Respir Crit Care Med 2006

Am J Respir Crit Care Med 2006
Alternatives to Nitric Oxide: Targeting the Endothelium

Brief Communication

Intravenous Sildenafil Lowers Pulmonary Vascular Resistance in a Model of Neonatal Pulmonary Hypertension

Lara S. Shekerdemian, Hanne B. Ravn, and Daniel J. Penny

DOI 10.1007/s00134-003-1066-4

Christian Stocker
Daniel J. Penny
Christian P. Beizard
Andrew D. Cochrane
Rodrigo Soto
Lara S. Shekerdemian

Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery

Am J Respir Crit Care Med 2002
i-v Sildenafil 'at risk' patients, early post-CPB:
- Reduces PVR
- Systemic vasodilation
- Increased V/Q mismatch

Enteral sildenafil in 100 patients with severe post-op PHT, 66 already on iNO
- 66 receiving iNO
- Stepwise dose increase to 2mg/kg
- Continued for 5-7 days after extubation
- Well tolerated
- No significant desaturation
- No rebound
**Endothelin-A Receptor Blockade and Inhaled Nitric Oxide in a Porcine Model of Meconium Aspiration Syndrome**

LARA S. SHEIKERDAM, DANIEL J. PENNY, PIA K. BVHAMMER, JAYNE A. READER, AND HANNE B. RAVN

Pandiatric Intensive Care Unit (I.S.S.), Department of Cardiology (D.J.P.), Royal Children’s Hospital, Parkville, Victoria 3052, Australia, Department of Anesthesia and Intensive Care (P.K.B., H.B.R.), and Institute of Experimental Research, University of Aarhus, Denmark, and Department of Vascular Biology (I.K.), Institute of Child Health, London WC1, England

**ABSTRACT**

Acute neonatal pulmonary hypertension is associated with increased activation of the endogenous endothelin pathway. We investigated the role of selective endothelin-A receptor blockade using prepro-ET-1 at a glomerul model of meconium aspiration syndrome. Meconium aspiration was induced in 18 anesthetized piglets. Six controls received no intervention. Six piglets received 1 g/kg PQ-123 at 120 min, with the addition of 20 ppm of inhaled nitric oxide (NO) at 240 min. Six controls received NO therapy at 120 min, but were given 1 g/kg PQ-123 at 240 min. The total study duration was 300 min. Mean pulmonary artery pressure increased in acute pulmonary hypertension and elevated endothelin-1 levels in all animals. There were no changes in pulmonary hemodynamics or endothelin-1 levels between 30-30 min in controls. In the group receiving PQ-123 first, this agent alone reduced the pulmonary artery pressure and pulmonary vascular resistance, and the subsequent addition of inhaled nitric oxide further reduced pulmonary artery pressure. In the group first receiving nitric oxide alone, this restored the pulmonary artery pressure, and the addition of PQ-123 resulted in a fall in pulmonary vascular resistance. Endothelin-1 levels increased with both agents. PQ-123 was found to be a highly effective pulmonary vasodilator and augmented the effects of nitric oxide in this model of acute pulmonary hypertension. (Pediatr Res 56: 355-358, 2004)

**Abbreviations**

PQ-123, persistent pulmonary hypertension of the newborn
NO, nitric oxide
ET, endothelin
NO, inhaled nitric oxide

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**The endothelin antagonist BQ123 reduces pulmonary vascular resistance after surgical intervention for congenital heart disease**

Ingram Schulte-Neick, MD
Jia L, MD
Jayne A. Reader, MD
Lara Sheikerdam, MD
Andrew N. Redington, MD
Daniel J. Penny, MD

**Objective:** Postoperative pulmonary hypertension in children after surgical intervention for congenital heart disease has been attributed to failure of the pulmonary endothelium to provide adequate vasodilation. Although we have shown that the impaired vasodilatory component attributable to the eNOS-serine kinase pathway is almost completely reversible, a nonreversible component persists, implying an additional vasorestrictive mechanism in postoperative pulmonary endothelial dysfunction. In this study of children after surgical intervention for congenital heart disease, we measured endothelin-1 levels and used BQ123, a selective endothelin-A receptor antagonist, together with inhaled nitric oxide to determine the effects of dysfunctional pulmonary endothelial vasodilation from endothelium-derived pulmonary vasorelaxation.

**Methods:** All children were examined early after surgical intervention in the intensive care unit. Pulmonary vascular resistance (wresting by respiratory mass spectrometry), as well as arterial and venous endothelin-1 levels (measured by means of a quantitative enzyme-linked immunosorbent assay), were determined in 12 children (age range: 3.3-15.7 months; median age: 6.5 months) with intracardiac shunting defects at baseline and during ventilation with a fraction of inspired oxygen of 0.6 with additional BQ123 (0.1 mg/kg infused over 20 minutes) and with inhaled nitric oxide (20 ppm).

**Results:** Pulmonary vascular resistance decreased from 7.7 ± 3.4 to baseline at 0.2 ± 0.8 Woods units (P < 0.05) at a fraction of inspired oxygen of 0.6 with additional BQ123 (0.1 mg/kg infused over 20 minutes) and with inhaled nitric oxide (20 ppm).
Endothelin Receptor Antagonists

- Minimal data on non-investigational use early after cardiac surgery

Challenges in the Management of Post-Operative Pulmonary Hypertension

- Pulmonary hypertension still a significant cause of post-operative morbidity
- Major problem in many settings
- Pre-emptive management is the best approach
  - Identify at-risk patients
  - Good, basic intensive care

Challenges in the Management of Post-Operative Pulmonary Hypertension

- Nitric oxide remains the only widely available selective pulmonary vasodilator, but many limitations
  - Cost
  - Tolerance
  - Rebound
  - Lack of evidence
- Early re-investigation of non-responders
- Careful weaning protocols - prevent rebound
  - Slow wean, increase FiO2, single dose enteral sildenafil
- Alternative therapies for acute PH are limited