Pulmonary Vasodilator Treatments in the ICU Setting

Lara Shekerdemian

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

CASE REPORT

Diagnosis and Management of Postoperative Pulmonary Hypertensive Crisis

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

Postoperative Mortality in Children After 101,885 Anesthetics at a Tertiary Pediatric Hospital

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BACKGROUND: Mortality is a basic measure for quality and safety in anesthesia. There are few anesthesiology-related mortality data available for pediatric practice. Our objective for this study was to evaluate in-hospital mortality after pediatric anesthetics in children.

METHODS: Children <18 years old who had an anesthetic between January 1, 2003, and August 30, 2008, at the Royal Children’s Hospital, Melbourne, Australia, were included for this study. Data were analyzed by matching a database for every anesthetic performed with an accurate electronic record of mortality of children who had been in a Royal Children’s Hospital patient. Causes of death among children dying within 30 days and 24 hours of an anesthetic were identified and the patient’s anesthetic record was reviewed. The cause of death was defined as the underlying cause of death, whereby a panel of three anesthesiologists all agreed that anesthesia or for patients under 1 year of age, the underlying cause of death was anesthesia-related.

RESULTS: During this 6-month period, 559,885 anesthetics were administered to 45,291 children. The overall 24-hour mortality from any cause after anesthesia was 0.34 per 10,000 anesthetics delivered and 30-day mortality was 0.95 per 10,000 anesthetics delivered. The incidence of death was highest in children <20 days old. Patients undergoing cardiac surgery had a higher incidence of death in children <20 days old. The overall 24-hour mortality from any cause after anesthesia was 0.34 per 10,000 anesthetics delivered and 30-day mortality was 0.95 per 10,000 anesthetics delivered.

CONCLUSIONS: Anesthesia-related mortality is higher in children with heart disease and in particular those with pulmonary hypertension. The lack of anesthesia-related deaths in children
Factors in the ICU

- RV LV Hypoxia K+ Ca++ K+ Ca++

Management of Pulmonary Hypertension After Cardiopulmonary Bypass

- The lungs: ventilation
- The endothelium & smooth muscle: vasodilators
- The heart: RV supportive measures

Endothelium-Dependent Pathways

Use of Inhaled Nitric Oxide and Acetylcholine in the Evaluation of Pulmonary Hypertension and Endothelial Function After Cardiopulmonary Bypass

- Change in PVR (mm Hg)
Pulmonary Vasodilators in the ICU

- Targeting the endothelium
  - NO-cGMP pathway
  - PGI₂ pathway
  - ET-1 pathway
- Considerations
  - Delivery
  - Selectivity
  - Cost
**Effects of inhaled versus intravenous vasodilators in experimental pulmonary hypertension**

D. Walmrath, R. Schermuly, J. Pilch, F. Griminger, W. Seeger

![Bar chart showing effects of different vasodilators](image)

**The Nitric Oxide Pathway**

- **NOS** (Nitric Oxide Synthase)
- **cGMP** (cyclic Guanosine Monophosphate)

![Diagram of the Nitric Oxide Pathway](image)

**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 MPAP 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

![Graph showing effects of inhaled nitric oxide after cardiac surgery](image)

**Inhaled Nitric Oxide after Cardiac Surgery**

- 10 children after surgery for CHD
- Median age 6 months
- 42% reduction in PVR
**Nitric Oxide Is Superior to Prostacyclin for Pulmonary Hypertension After Cardiac Operations**
Allan P. Goldman, MRCP, Ralph E. Delius, MD, John E. Deanfield, FRCP, and Duncan J. Macrae, FRCA
Cardiothoracic Unit, Great Ormond Street Hospital for Children, London, United Kingdom

**Problems with Inhaled Nitric Oxide:**
Cost (and availability)

*Editor—Evidence based medicine is the gold standard for practice, and pharmaceutical companies appreciate the power of evidence based medicine. A positive result in a randomised controlled study produces pressure to use a specific agent regardless of cost.*

High costs seem to predominate in intensive care. Over the past 10 years several expensive treatments have been launched and subsequently failed. Inhaled nitric oxide (INO) was the reverse, being initially inexpensive, and is of proved efficacy in reducing morbidity.

Recently, two randomised controlled studies have shown improved oxygenation1 and a reduction in the need for extracorporeal membrane oxygenation with the use of inhaled nitric oxide in neonates with persist-

**Problems with Nitric Oxide:**
Rebound
Alternatives to Nitric Oxide

- **Prostacyclin** - systemic / inhaled
- **Sildenafil** - enteral / parenteral
- **Endothelin receptor antagonists** - systemic

### The Prostacyclin Pathway

![Pathway Diagram]

**Endothelium** → **Prostacyclin synthase** → **Prostacyclin**

### Aerosolized Iloprost

![Aerosol Delivery System]

- **Drug delivery**
- **Nebulizer**
- **Expiration line**
- **Mouthpiece**

Variable Iloprost dose at mouthpiece depending on nebulizer type and characteristics.
Inhaled Nitric Oxide Versus Aerosolized Iloprost in Secondary Pulmonary Hypertension in Children With Congenital Heart Disease

Vasodilator Capacity and Cellular Mechanisms

Peter C. Rimemsberger, MD; Isabelle Sphir-Scherper, MD; Michel Berner, MD; Edgar Jaeggi, MD; Atiendyos Kalangos, PhD, MD; Beat Friedli, MD; Maurice Begetti, MD

15 children
5 post-op CHD
10 pre-op
Equivalent potency

Conclusion: In medical setting with limited access to the nitric oxide, inhaled iloprost is considered to be an effective alternative treatment for postoperative PHC in children undergoing congenital heart surgery.

Augmenting the Nitric Oxide Pathway

Nitric Oxide Pathway

Vessel Lumen
Endothelial Cells
Smooth Muscle
GTP
sGCy
Nitric Oxide
iNO then sild
sild then iNO

PVR
432
Systolic BP
70 60 50
PaO2
150 120 90
20 min 40 min 0 min

Infants at risk of PHT
Pulmonary vasodilation
Systemic vasodilation
Increased intrapulmonary shunt
Not intolerable but need for caution

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

Conclusion: In medical setting with limited access to the nitric oxide, inhaled iloprost is considered to be an effective alternative treatment for postoperative PHC in children undergoing congenital heart surgery.
**Intravenous sildenafil for postoperative pulmonary hypertension in children with congenital heart disease**

- Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children
  - 66 pulmonary hypertensive infants receiving iNO
    - Closure of septal defects / Cavopulm shunts
    - Stepwise dose increase
    - 5-7 days
    - Well tolerated
    - No desaturation or rebound

**The Management of Rebound**

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

- Less selective than iNO
- Greater selectivity for pulmonary vasculature in the presence of PHT
- Has been investigated in aerosolized form
- Useful in prevention of rebound

Pharmacokinetics and safety of intravenously administered citrulline in children undergoing congenital heart surgery: Potential therapy for postoperative pulmonary hypertension

- Single dose on CPB
- 2nd dose 4hrs post-op
- +/- 48hr infusion
- Safe, well tolerated
- Efficacy
Endothelin-1 Pathway

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

In large parts of the world, particularly in developing countries, iNO and ECMO are not readily available due to high costs and lack of a sufficient infrastructure.
**Pulmonary Vasodilators in the Intensive care Unit**

- Acute severe crises less common in many regions, with early surgery, pre-emptive management
- More 'insidious' post-operative PHT is still a problem
- Increasing interest in alternatives to iNO
  - Cost, availability, rebound
  - Selectivity needs to be considered
    - Pulmonary Vs systemic
    - Ventilated Vs non-ventilated regions
    - Presence / absence of lung injury
    - Careful use of systemic agents early after surgery

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**To Be Discussed**

- The scope of the problem
- Pathophysiology of pulmonary hypertension in the ICU
- Management in CHD
- Acute intervention
- Alternatives to iNO

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**Influence of state of inflation of the lung on pulmonary vascular resistance**

- Whittenberger J Appl Physiol 1960

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

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