iNO in neonates with cardiac disorders

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Terminology

• PAP  Pulmonary artery pressure

• PVR  Pulmonary vascular resistance

• PHT  Pulmonary hypertension

- PAP > 25, PVR >3, in the absence of LV failure

- Systolic PAP more than 50% systemic systolic arterial pressure
PHT in cardiac neonates

• Remember the basics....

Pressure = Flow x Resistance

PHT (‘high pressure’) occurs in neonates:

1. Where pulmonary blood flow is high
2. Where pulmonary vascular resistance is high
High pulmonary blood flow

- $\uparrow$Flow $\times$ Resistance $\gg$ $\uparrow$Pressure

- Occurs in congenital heart lesions where blood can shunt from **Left $\gg\gg$ Right**
- PDA
- Septal defects (ASD, VSD, AVSD)
- Truncus arteriosus *(rare)*
- Aorto-pulmonary window *(rare)*
High PVR or obstruction
‘increased resistance’

$\leftrightarrow$Flow $\times$ ↑Resistance $\gg$ ↑Pressure

1. Long standing high PBF causes changes which eventually lead to muscular hypertrophy and eventually fibrosis, raising PVR

- Unoperated high-flow cardiac lesions (VSD, AVSD etc)

2. Obstructive lesions $\gg$ obstructed pulmonary veins
Most common lesions associated with PH after definitive surgical repair in neonates and infants

- Unrestrictive VSD > 6 months age
- AVSD > 6 months age
- Transposition + VSD > 6 months age
- TAPVD with obstruction
- Truncus arteriosus
- Aortopulmonary window
- Neonatal presentation of Scimitar syndrome
Other indications for iNO in cardiac neonates and infants

• **Acute right ventricular failure**
  – post cardiac transplantation

• **Lowering PVR in ‘low resistance’ settings**
  “cavo-pulmonary’ circulations”
  - Glenn (SVC-PA shunt)
  - Total cavo-pulmonary connection (Fontan)
  - Right ventricular failure

• **PVR reversibility testing** pre-cardiac transplant or pre-late corrective surgery
Early Clinical Studies with iNO

Cardiac

- Wessel et al, Circulation 1993

- Postop endothelial dysfunction noted by minimal response to ACH

- 80 ppm iNO reduced PVR
Hemodynamic Changes with Inhaled Nitric Oxide in TAPVC

Baseline

- HR: 149 b/min
- CI: 2.3 l/min/m²
- BP: 62 mmHg
- SVR: 23.5 U/m²
- mPAP: 35.6 mmHg
- PVR: 11.5 U/m²
Fig. 3. Mean percentage change in PVRI and SVRI after exposure to increasing doses of inhaled NO (2, 10, and 20 ppm), with intervening 0-exposure control periods, in seven subjects with PAP/SAP ratio $\geq 0.50$. 
Fig. 4. Percentage change in PVRI for both the low and high PAP/SAP ratio groups after exposures to increasing doses of inhaled NO (2, 10, and 20 ppm) with intervening control periods.
Fig. 1. Correlation of initial PVR/SVR ratio and maximal percentage change after exposure to inhaled NO ($r = -0.82$, $p < 0.001$).
Randomized Clinical Trials of iNO

  - iNO significantly reduced mean PAP in patients with postop PHTN
- Morris et al, Crit Care Med, 2000
  - iNO plus hyperventilation reduced mean PAP in children with postop PHTN
Randomized Clinical Trials of iNO

- iNO significantly reduced systolic PAP/SAP
- Miller et al, Lancet, 2000
- iNO significantly reduced time until extubation readiness
- Reduction in pulmonary hypertensive crises
RCT’s iNO for PHT in children with cardiac disease

<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
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<tbody>
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<td>Day 2000</td>
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Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease (Cochrane Review) Bizarro and Gross, 2014

- Only the 4 RCTs included (Russell / Morris / Day 2000 / Miller 2000)
- Total of 162 patients
- No difference in mortality, number of PHT crises, physiologic outcomes between iNO and placebo groups
- Limitations of meta-analysis addressed including small sample size, methodology
- Larger RCTs need to address important outcomes
Day et al. 2000

- 40 infants with systolic P pulmonary > 50% P systemic after CPB
- Randomised to conventional management alone or iNO 20 ppm
- Small reduction in PAP/ SAP ratio at 1 hour
- Failed to demonstrate a reduction in incidence of pulmonary hypertensive crisis (OR 0.80, 95% CI 0.15 to 4.18; P = 0.79)
- Small study
- Low incidence of PH

124 infants at risk of post-op pulmonary hypertension
Randomised to iNO or placebo gas on admission to ICU following cardiac surgery

Figure 4: Median pulmonary vascular resistance index by treatment group over time after surgery until eligible for extubation

Figure 2: Relative risk (95% CI) of PHTC in nitric oxide compared with placebo group
Miller et al. 2000  
Post-operative course

Figure 3: Hazard ratios (95% CI) for postoperative course with differences in median times. 

- $T_{cr}$ = time to criteria for weaning; $T_w$ = time weaning; $T_g$ = time on study gas; $T_{ext}$ = time to extubation; $T_{icu}$ = time in intensive-care unit.
<table>
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<th>Demography</th>
<th>Nitric oxide (n=63)</th>
<th>Placebo (n=61)</th>
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<td>Sex (male/female)</td>
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<td>28/33</td>
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<td>Median (IQR) age (months)</td>
<td>3 (1–5)</td>
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<td>Down’s syndrome</td>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Nitric oxide (n=63)</th>
<th>Placebo (n=61)</th>
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</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>29 (46%)</td>
<td>19 (31%)</td>
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<tr>
<td>Atrioventricular septal defect</td>
<td>18 (29%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>8 (13%)</td>
<td>13 (21%)</td>
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<tr>
<td>Total anomalous pulmonary venous drainage</td>
<td>6 (9%)</td>
<td>11 (18%)</td>
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<tr>
<td>Other</td>
<td>2 (3%)</td>
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**Haemodynamics (median [IQR])**

| | Nitric oxide | Placebo |
|----------------|----------------|
| Pulmonary artery pressure (mm Hg) | 20 (17–22) | 20 (18–25) |
| Systemic artery pressure (mm Hg) | 66 (59–72) | 60 (54–71) |
| Pulmonary vascular resistance index (dynes s cm⁻¹ m²⁻¹) | 212 (159–253) | 223 (182–398) |
| Systemic vascular resistance index (dynes s cm⁻¹ m²⁻¹) | 1181 (1014–1349) | 1272 (950–1510) |

There were no significant differences between groups in any of these characteristics.

**Table 2: Baseline characteristics**
Comparison 1: Inhaled nitric oxide versus placebo or conventional management
Mortality prior to discharge.

Control
n/N

Odds Ratio
M-H, Fixed, 95% CI

Odds Ratio
M-H, Fixed, 95% CI

DAY

MILLER

FAVOURS TREATMENT
FAVOURS CONTROL
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 CHD. We have observed no differences with respect to mortality, number of PHTC, arterial oxygenation, or changes in haemodynamics with the use of postoperative iNO. There are no data to determine the effects of iNO and its definition should be refined.
iNO and the Fontan circulation

Fig 1. Changes in $\text{SaO}_2$ (a) and TPG (b) from baseline with exposure to iNO (20 ppm for 15 minutes) in all 15 patients studied. Dashed lines represent patients with baseline $\text{SaO}_2 \leq 85\%$; solid lines, patients with $\text{SaO}_2 > 85\%$. One patient is missing from b due to the absence of a left atrial catheter. Values expressed as mean±SEM. *Baseline compared with initial trial of iNO, $P<.01$. 

Goldman et al. 1996
Vasodilator testing of pulmonary vascular reactivity

- Cardiac transplant assessment
- Assessment of operability (TCPC/Fontan or late repairs of VSD etc.)
- Primary PHT Rx

Fig. 2 Acute responders to the evaluated treatments
Acute right ventricular failure after pediatric cardiac transplant: Predictors and long-term outcome in current era of transplantation medicine

Aparna Hoskote, MD, MRCP, a Catherine Carter, MSc, MPH, RN, b Phillip Rees, MB, FRCP, b Martin Elliott, MD, FRCS, c Michael Burch, MD, FRCP, FRCPCH, b and Katherine Brown, MPH, MRCP a

Recommend management of RV failure peri-operatively with iNO and other vasodilators
Why not talk about ‘Advances in PICU management of PHT’?

We now better understand perioperative Pulmonary Hypertension

Because we understand PH we can:
- Usually avoid trouble
- Better manage if not avoidable

Management strategies are cursed by
- “Knowledge”
- “Opportunity”
Diagnosis and Management of Postoperative Pulmonary Hypertensive Crisis

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

A. Steady state

B. During crisis

C. Tolazoline (1 mg/kg/hr)

Circulation 1979;60:1640-1644
PVR $\uparrow$ RV stroke volume $\downarrow$ RV hypertension $\downarrow$ Cardiac output $\downarrow$ Reduced tissue oxygen delivery $\uparrow$ O$_2$ extraction $\downarrow$ PBF $\downarrow$ CO$_2$ clearance $\downarrow$ PaO$_2$

$\downarrow$ PvO$_2$

TRIGGER:
Pain, Hypoxia, Low cardiac output

Metabolic acidosis

Respiratory acidosis

R $\gg$ Shunt $\downarrow$ PaO$_2$
## Basic management of Acute Perioperative PHT

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<td><strong>A</strong></td>
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<tr>
<td>AVOID</td>
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<td><strong>B</strong></td>
<td><strong>E</strong></td>
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<tr>
<td>BREATHING</td>
<td>EXTRAS</td>
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<tr>
<td><strong>C</strong></td>
<td><strong>F</strong></td>
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<tr>
<td>CARDIAC OUTPUT</td>
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Basic management of Acute Perioperative PHT

A

Ensure good case selection

AVOID

Ensure ‘early’ surgery

Good basic intensive care management

Appropriate analgesia / sedation
Basic management of Acute Perioperative PHT

B

BREATHING

Avoid / treat alveolar hypoxia
ALVEOLAR HYPOXIA

Alveolus

SvO₂ 50% (30mmHg)

60mmHg

50mmHg

Pulmonary arteriole

ALVEOLAR NORMOXIA

Alveolus

SvO₂ 75%

60mmHg

150mmHg

110mmHg

Pulmonary arteriole
Oxygen

- God’s pulmonary vasodilator
- Selective
- Relatively non-toxic
- Inexpensive
- Easily titrated / delivered

- Does not achieve maximal pulmonary dilation in many clinical situations
Fig. 17-14. Changes in pulmonary vascular resistance with changes in Pao₂ and arterial pH. (From Rudolph AM, Yvan S: Response of the pulmonary circulation to hypoxia and H⁺ ion changes. J Clin Invest 45:399-405, 1966, with permission.)

BASICS

- Open the lung
- Avoid acidosis
Fig. 17-16. Changes in pulmonary vascular resistance with changes in lung volumes. At low lung volumes, atelectasis causes collapse of arterioles with increase in resistance. With hyperinflation and high lung volumes, capillaries in alveolar septa are compressed, increasing resistance. (From West JB: Respiratory Physiology (ed 3). Baltimore, Williams & Wilkins, 1979, p 39, with permission.)
Alveolar and Extra-Alveolar Vessels

- Alveolus
- Alveolar capillary
- Extra-alveolar vessels

- High alveolar volume
- Normal alveolar volume
Basic management of Acute Perioperative PHT

C
CARDIAC OUTPUT

Structured approach to diagnosis and management of LCO
LOW CO

SvO₂ 50% (30mmHg)

Alveolus

150mmHg

110mmHg

Pulmonary arteriole

ADEQUATE CO

SvO₂ 75%

60mmHg

Alveolus

150mmHg

110mmHg

Pulmonary arteriole
Basic management of Acute Perioperative PHT

D
Drugs

Ensure vasodilatory ‘milieu’
- PDEIII inhibitor
- Nitroglycerine

Consider low-dose inotropic support
- Echo guidance
IV (± Oral) Vasodilators

- Alpha adrenergic blockers
- Beta 2 adrenergic agonists
- Prostacyclin, Iloprost
- Calcium channel blockers
- Nitrates (nitroglycerine, sodium nitroprusside)
- Phosphodiesterase inhibitors
  - (III = milrinone etc; V = sildenafil etc;)
- And others........

- Many drugs widely used and ‘understood’..... but....
- Mostly non-selective, leading to systemic hypotension
Exogenous nitric oxide delivery to the lung

Alveolus

Hb + NO ----> NO-Hb ----> metHb

O2 L-arginine

NO synthase

L-citrulline

Guanylate cyclase

GTP cGMP

Ca<sup>2+</sup>

Fibre relaxation / vasodilatation

EC

Hb + NO ----> NO-Hb ----> metHb
Basic management of Acute Perioperative PHT

Deeper sedation

EXTRAS

Inhaled nitric oxide
  – Max. dose 20 ppm
  – Or other ‘specific’ pulmonary vasodilator

Refractory PH
  – ECMO if available
iNO and Cardio-Pulmonary Bypass

• NO given to patients with compromised endogenous NO production results in decreased vascular resistance, decreased inflammation and decreased tissue damage

**Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children—a randomized trial**

Paul A. Checchia, MD, FCCM, FACC, Ronald A. Bronicki, MD, Jared T. Muenzer, MD, David Dixon, PhD, Steve Raithel, BS, CCP, Sanjiv K. Gandhi, MD, and Charles B. Huddleston, MD

RCT 16 infants CPB: iNO 20ppm or Air/ O2 only

• Duration of post op ventilation
• ICU length of stay
• Cardiac troponin levels all reduced in iNO group
Recommendations for the use of iNO in a peri-operative setting

- iNO is an effective selective pulmonary vasodilator in children following cardiac surgery

- No high quality clinical trials show major differences in clinical outcomes from elective use of iNO

- It is reasonable to use iNO in situations where raised PVR is likely to cause harm as part of a structured approach to manipulating PAP/PVR:
  - Acute pulmonary hypertension
  - Reversibly raised PVR in cavo-pulmonary circulations
  - Acute RV dysfunction – post-transplant, LVAD, etc.

- Future applications: ?? Routine use during CPB