Inhaled Nitric Oxide in Congenital Diaphragmatic Hernia

Neil Patel
Neonatologist
Royal Hospital for Sick Children, Glasgow

iNO 26th March 2015
• Pathophysiology of PH in CDH

• PH therapies in CDH – iNO and friends

• Rationalising neonatal management in CDH
ADRIAN Quinones has spent the first weeks of his life fighting for survival in the Royal Children’s Hospital.

The boy was born with a hole in his diaphragm, a genetic defect known as a diaphragmatic hernia.

Five to 10 Victorian babies are born with the condition every year.

Without immediate medical attention, babies can stop breathing, go into cardiac arrest and die within hours of birth.

Adrian’s parents Grace Castro and Leo Quinones were told about their son’s condition five weeks before he was born.

The hernias are usually diagnosed within the first 20 weeks of pregnancy, but Adrian’s was not seen until 35 weeks.

Doctors told the couple Adrian would need to be rushed to the Royal Children’s as soon as he was delivered.

So instead of sharing those first few minutes cuddling and bonding with their newborn, Grace and Leo watched helplessly as doctors whisked him away.

“Once he was out I didn’t get much of a chance to see him,” Grace said.

After asking whether he was breathing and they said ‘yes’, my body just gave up and I passed out.”

Adrian was twisted into a difficult position during the eight-hour delivery and his heart rate and body temperature were both low, making his birth even more traumatic for Grace.

“I wouldn’t change the delivery I had on anybody, but I don’t regret it because I have my son at the end of it all,” she said.

Adrian’s race for LIFE...
Congenital Diaphragmatic Hernia

• 3.5 per 10,000 pregnancies

• Defect in developing diaphragm – 85% left sided

• Herniation of abdominal contents into fetal chest

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Table 6. Comparison of Year Groups Between The Children’s Hospital, Boston, and The Hospital for Sick Children, Toronto

<table>
<thead>
<tr>
<th>Year Group</th>
<th>Boston</th>
<th>Toronto</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981 to 1984</td>
<td>9/20 (45%)</td>
<td>25/47 (53%)</td>
<td>NS</td>
</tr>
<tr>
<td>1984 to 1987</td>
<td>21/50 (43%)</td>
<td>28/54 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>1987 to 1991</td>
<td>23/52 (44%)</td>
<td>32/61 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>1991 to 1994</td>
<td>51/74 (69%)</td>
<td>37/61 (61%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Fig. 1. Congenital Diaphragmatic Hernia Study Group overall mortality by year.

Pulmonary artery pressure and outcome in CDH


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Pulmonary vasculature in CDH

Pathophysiology of pulmonary hypertension

**PULMONARY HYPERTENSION**

**RIGHT TO LEFT SHUNTING**
- Within lungs
- Atrial septum
- Patent ductus

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Pathophysiology of pulmonary hypertension

PULMONARY HYPERTENSION

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REDUCED LV FILLING

REDUCED LV OUTPUT
Pathophysiology of pulmonary hypertension

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INCREASED RV AFTERLOAD

“CARDIAC FAILURE”

REDUCED LV FILLING

REDUCED LV OUTPUT
Normal RV structure and function
RV hypertrophy and effect on LV

(A) ↓ Coronary perfusion pressure + ↑ O₂ Demand = ↓ Supply/Demand

(B) ↑↑ RV Distention & ↓ LV Filling = ↓ Cardiac Output
RV function
Tissue Doppler imaging (TDI)

- Uses pulse wave Doppler to measure myocardial velocities as assessment of myocardial function
- Allows separate assessment of systolic (contractile) and diastolic (lusitropic) function
Normal pulse wave TDI (PWTDI)

**IVV:** Isovolumic contraction velocity

**S:** Systolic ejection velocity

**E':** Early diastolic velocity (active relaxation)

**A':** Late diastolic velocity (atrial contraction)
Pulse wave tissue Doppler in CDH

Control infant

CDH with PH

- Reduced systolic velocities (IVV and S)
- Loss of diastolic E’ velocity
- Abnormal “post-systolic contraction” *

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Pulse wave tissue Doppler in CDH

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 28)</th>
<th>CDH subgroup (n = 11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricuspid Doppler velocities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E wave velocity</td>
<td>0.52 (0.13)</td>
<td>0.13 (0.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A wave velocity</td>
<td>0.55 (0.11)</td>
<td>0.63 (0.18)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Systolic PWTDI data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV IVV</td>
<td>6.6 (1.1)</td>
<td>5.2 (1.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>RV S</td>
<td>9.2 (1.9)</td>
<td>6.3 (1.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Septal IVV</td>
<td>3.4 (0.5)</td>
<td>3.5 (0.7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Septal S</td>
<td>5.0 (0.7)</td>
<td>5.0 (1.5)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Diastolic PWTDI data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV E’</td>
<td>-8.5 (2.0)</td>
<td>-3.6 (1.8)</td>
<td>0.0006</td>
</tr>
<tr>
<td>RV A’</td>
<td>-10.1 (2.5)</td>
<td>-10.8 (4.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Septal E’ wave*</td>
<td>-5.4 (1.14)</td>
<td>-3.6 (0.5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Septal A’ wave</td>
<td>-6.3 (1.3)</td>
<td>-6.4 (3.2)</td>
<td>0.561</td>
</tr>
</tbody>
</table>

Neonatology 2009;96:193–199
RV function in CDH

- Impaired early diastolic relaxation
- Impaired systolic contraction
Use of the Myocardial Performance Index to Assess Right Ventricular Function in Infants with Pulmonary Hypertension

Neil Patel · John F. Mills · Michael M. H. Cheung

Fig. 3 Right ventricular myocardial performance index \((R_{\text{MPI}})\) versus pulmonary artery pressure. The correlation between \(R_{\text{MPI}}\) and pulmonary artery pressure was poor \((R^2 = 0.05; p = 0.17)\)
Cardiac failure in CDH

- RV early diastolic and systolic dysfunction
- RV dilatation and hypertrophy
  – secondary myocardial ischaemia
- LV compression and secondary dysfunction
- Variable response to elevated PA pressure
Pathophysiology of PH in CDH

- **PULMONARY HYPERTENSION**
  - INCREASED AFTERLOAD
  - RV DIASTOLIC DYSFUNCTION AND DILATATION
  - BIVENTRICULAR FAILURE
  - REDUCED LV OUTPUT
  - REDUCED LV FILLING

- **RIGHT TO LEFT SHUNTING**
  - Intrapulmonary atrial septum patent ductus

- **HYPOXAEAMIA**
- **HYPOTENSION**
- **HYPOPERFUSION**
- **ACIDOSIS**

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Pathophysiology of PH in CDH

PULMONARY HYPERTENSION

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RIGHT TO LEFT SHUNTING atrial septum and patent ductus

HYPOXAEAMIA

HYPOTENSION

HYPOPERFUSION

ACIDOSIS

CLINICAL OUTCOMES
Right Ventricular Diastolic Function Measured by Tissue Doppler Imaging Predicts Early Outcome in Congenital Diaphragmatic Hernia

Florian Moenkemeyer, MD; Neil Patel, MD
Right Ventricular Diastolic Function Measured by Tissue Doppler Imaging Predicts Early Outcome in Congenital Diaphragmatic Hernia

Florian Moenkemeyer, MD; Neil Patel, MD

Figure 3. Receiver-operating characteristics curve for the prediction of DRS more than 21 days using right ventricular early diastolic myocardial velocity on days 1 and 2 of life (RV E′ d1–2). An averaged RV E′ d1–2 less than 4.6 cm/s predicted duration of respiratory support more than 21 days with 100% sensitivity and 88% specificity (area under the curve = 0.96; SE = 0.04; 95% CI, 0.88–1.05; p = 0.002).
The right ventricular systolic to diastolic duration ratio: a simple prognostic marker in congenital diaphragmatic hernia?

Sanjeev Aggarwal (ssanjeev@dmc.org), Paul T Stockman, Michael D Klein, Girija Natarajan

*P value < 0.05 for comparisons between CDH infants who died and Normal controls as well as CDH survivors

Acta Pædiatrica 2011 100, pp. 1315–1318

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RV diastolic function is associated with adverse outcome in CDH

Early RV function appears to be a better predictor of outcome than PA$_p$

RV function, rather than absolute PA$_p$ may determine outcome in CDH
Patterns of PH and RV function in CDH

- Repair
- ECMO
- Weaning iNO + cardiotropes off
- Weaning sedation
- Extubation
- PDA flow ratio Rl:Lr
- R->L
- L->R
- Sepsis

Graph showing changes in RV S and RV E over age with key events marked.

Graph showing PDA flow ratio Rl:Lr with directions R->L and L->R.
RV function in the first week of life in CDH

- RV diastolic velocities can stratify illness severity
- RV early diastolic velocities increase from day 1-2 to day 3-4

Moenkemeyer & Patel, PCCM October 2013
RV function after CDH repair

- In more severely affected infants RV early diastolic velocities are lower at day 3-4 post op

Moenkemeyer & Patel, PCCM October 2013

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TREATMENT OF PH in CDH

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TREATMENT OF PH IN CDH

INCREASED PVR

RIGHT TO LEFT SHUNTING atrial septum and patent ductus

RV DIASTOLIC DYSFUNCTION AND DILATATION

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HYPOXAEAMIA

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ACIDOSIS

CLINICAL OUTCOMES
Pulmonary vasodilator therapies in CDH

Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.


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Pulmonary vasodilator therapies in CDH

Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.


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**iNO and oxygenation in CDH**

Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia

The Neonatal Inhaled Nitric Oxide Study Group (NINOS)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment Group (INO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pao₂ (Torr)</td>
<td>1.1 (7.6)</td>
<td>7.8 (19.8)</td>
</tr>
<tr>
<td>OI</td>
<td>4.0 (14.8)</td>
<td>−2.7 (23.4)</td>
</tr>
<tr>
<td>A-aDo₂ (Torr)</td>
<td>−2.1 (7.9)</td>
<td>−5.6 (42.8)</td>
</tr>
</tbody>
</table>
Haemodynamic effects of iNO in CDH
RCTs iNO in CDH

NINOS study (1997)
• 53 subjects, > 34 weeks, <14 days
• iNO at 20ppm, increased to max 80ppm
• Used hyperventilation, no standardization of ventilation

Clark et al (2000)
• >34 weeks, < 4 days
• Inclusion at OI >25, randomization at OI>40
• iNO weaned to 5ppm after 24 hours, for max 96 hours
### Analysis 2.1. Comparison 2 Inhaled NO versus control in infants with diaphragmatic hernia, Outcome 1
**Death or need for ECMO.**

**Review:** Nitric oxide for respiratory failure in infants born at or near term

**Comparison:** 2 Inhaled NO versus control in infants with diaphragmatic hernia

**Outcome:** 1 Death or need for ECMO

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>iNO</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ninos 1997</td>
<td>24/25</td>
<td>23/28</td>
<td></td>
<td>60.3</td>
<td>1.17 [ 0.97, 1.41 ]</td>
</tr>
<tr>
<td>Clark 2000</td>
<td>12/13</td>
<td>17/18</td>
<td></td>
<td>39.7</td>
<td>0.98 [ 0.81, 1.19 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>38</strong></td>
<td><strong>46</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.09 [ 0.95, 1.26 ]</strong></td>
</tr>
</tbody>
</table>

- Total events: 36 (iNO), 40 (Control)
- Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 43%
- Test for overall effect: Z = 1.25 (P = 0.21)
“Infants with diaphragmatic hernia do not appear to share the benefit of iNO; indeed ......outcomes may be worse in infants with CDH who received inhaled NO compared to controls.”
57% of infants received iNO
INO use ranged from 34-92%
Peak iNO use on day 2 (38%)
48% iNO pre op, 40% iNO post op
Age at iNO: 11%>30days, 3% >60days
Why are we using (more!) iNO in CDH?

• Limitations of existing RCTs
  – conducted in older treatment eras
  – Small populations
  – Short durations of treatment
  – Didn’t account for variable patterns / timing of PH in CDH

• iNO may improve oxygenation and haemodynamics and buy time e.g. for ECMO or for repair of CDH

• iNO may be more effective in combination with new therapies
Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.
Sildenafil

- PDE-5 inhibitor
- Oral preparations introduced first to allow weaning of iNO
- IV preparation now available
Intravenous Sildenafil in the Management of Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia

Anja Bialkowski¹  Florian Moenkemeyer¹  Neil Patel¹

Table 3 Effects of IV sildenafil on physiological and echocardiographic parameters

<table>
<thead>
<tr>
<th>Cardiorespiratory parameters mean (SD)</th>
<th>Sildenafil therapy</th>
<th>*p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>24–48 h post</td>
</tr>
<tr>
<td>Fio₂</td>
<td>0.53 (0.20)</td>
<td>0.57 (0.25)</td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>12.9 (5.9)</td>
<td>12.5 (9.4)³</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)</td>
<td>51 (3)</td>
<td>53 (6)</td>
</tr>
<tr>
<td>RV TDI myocardial velocities (cm/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S' (systolic)</td>
<td>7.4 (1.7)</td>
<td>7.8 (2.0)</td>
</tr>
<tr>
<td>E' (diastolic)</td>
<td>4.4 (3.8)</td>
<td>4.3 (4.1)</td>
</tr>
<tr>
<td>RVO (mL/kg/min)</td>
<td>265 (47)</td>
<td>282 (53)</td>
</tr>
<tr>
<td>PDA RI:Lr</td>
<td>2.1 (1.1)</td>
<td>1.4 (1.1)</td>
</tr>
<tr>
<td>RVSP_{est} (mm Hg)</td>
<td>68 (18)</td>
<td>57 (7)</td>
</tr>
</tbody>
</table>

Eur J Pediatr Surg

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Sildenafil Weaning After Discharge in Infants With Congenital Diaphragmatic Hernia

Joanna Behrsin · Michael Cheung · Neil Patel

- 2005-2012, single centre experience
- 112 CDH infants
- 19 (17%) discharged on oral sildenafil

**Fig. 1** Percentage of patients receiving a sildenafil dosage higher than 1.5 mg/kg/day after discharge

Pediatric Cardiology 2013
Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.
Persistent Pulmonary Hypertension in High-Risk Congenital Diaphragmatic Hernia Patients: Incidence and Vasodilator Therapy

By Albert P. Bos, Dick Tibboel, Veronica C.M. Koot, Frans W.J. Hazebroek, and Jan C. Molenaar
Rotterdam, The Netherlands

Table 2. Alveolar-Arterial Oxygen Difference (AaDO₂), Treatment in 21 Patients With PPH

Fig 1. AaDO₂ values in nine patients after administration of prostacyclin (P).

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Milrinone: “inodilator”

- Pulmonary vasodilator
- Improved diastolic function (lusitropy)
- Improved systolic function (inotropy)
- (systemic vasodilatation)

Lakshminrusimha and Steinhorn, PCCM 2013

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Use of Milrinone to Treat Cardiac Dysfunction in Infants with Pulmonary Hypertension Secondary to Congenital Diaphragmatic Hernia:

<table>
<thead>
<tr>
<th>Duration of milrinone therapy</th>
<th>pre</th>
<th>12–24 h post</th>
<th>48–72 h post</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA flow velocity, m/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left to right</td>
<td>0.8 (1.1)</td>
<td>0.8 (0.4)</td>
<td>0.5 (0.13)</td>
</tr>
<tr>
<td>right to left</td>
<td>1.9 (0.6)</td>
<td>1.3 (0.1)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.55 (0.19)</td>
<td>0.47 (0.25)</td>
<td>0.47 (0.43)</td>
</tr>
<tr>
<td>Mean airway pressure, cm H₂O</td>
<td>11.8 (4.1)</td>
<td>10.3 (5.8)</td>
<td>8.6 (1.7)</td>
</tr>
<tr>
<td>OI</td>
<td>10.6 (5.6)</td>
<td>7.9 (6.2)</td>
<td>* 5.1 (2.6)*, **</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>52.7 (4.3)</td>
<td>53.7 (11.5)</td>
<td>51 (7.3)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>72.6 (6.3)</td>
<td>75 (20.7)</td>
<td>67 (9.9)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>42.8 (4.2)</td>
<td>43 (6.9)</td>
<td>43 (6.3)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Early diastolic velocities (E’) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI. * p < 0.05.

**Fig. 2.** Isovolumic contraction velocities (IVV) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.

**Fig. 3.** Systolic ejection velocities (SV) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.
Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.
Rationalising therapies in CDH

• Understanding of pathogenesis of PH in CDH
• Multiple pulmonary vasodilators + inodilators
• Some evidence of haemodynamic benefits
• Lack of RCT support
A rationale approach...
INCREASED PVR

hypoxia

↓ LVO / BP

(Early) RV dysfunction / hypertrophy

Severity and survival

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INCREASED PVR

hypoxia

↓ LVO / BP

(Early) RV dysfunction / hypertrophy

Severity and survival

REARLY AND REGULAR ASSESSMENT

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INCREASED PVR

hypoxia

(Late) RV dysfunction / hypertrophy

LVO / BP

REALLY AND REGULAR ASSESSMENT

TARGETED, SYSTEMATIC, EARLY THERAPY

REDUCED SEVERITY

IMPROVED SURVIVAL
Clinical assessment of PH and RV function

• Simple
• Quantifiable
• Accurate
Echocardiography
N-Terminal-pro-B Type Natriuretic Peptide as a Useful Tool to Evaluate Pulmonary Hypertension and Cardiac Function in CDH Infants

Maria J. Baptista\textsuperscript{a,c} Gustavo Rocha\textsuperscript{a} Fátima Clemente\textsuperscript{a} Luís F. Azevedo\textsuperscript{b} Dick Tibboel\textsuperscript{d} Adelino F. Leite-Moreira\textsuperscript{b} Hercília Guimarães\textsuperscript{a} José C. Areias\textsuperscript{a} Jorge Correia-Pinto\textsuperscript{a,c}

\textbf{Fig. 1.} Plasmatic NT-proBNP level is significantly increased in newborns with CDH compared to control (*p < 0.05 vs. control).

Neonatology 2008;94:22–30
Plasma vascular endothelial growth factor A and placental growth factor: novel biomarkers of pulmonary hypertension in congenital diaphragmatic hernia

Neil Patel, Florian Moenkemeyer, Susie Germano, Michael M. H. Cheung

AJP Lung Feb 2015
Evidence of effects of PH:
HYPOXIA / ↓BP / RV dysfunction

Optimise ventilation, sedation, acid-base, Ca/Mg, sepsis

First line:

iNO

Regular assessment of pulmonary pressure & cardiac (RV) function

Discharge and beyond

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Evidence of effects of PH: HYPOXIA / ↓BP / RV dysfunction

First line: iNO

Optimise ventilation, sedation, acid-base, Ca/Mg, sepsis

Second line: Sildenafil (IV) (+/or) Milrinone

BIRTH

Regular assessment of pulmonary pressure & cardiac (RV) function

Discharge and beyond
Evidence of effects of PH: HYPOXIA / ↓BP / RV dysfunction

First line: iNO

Second line: Sildenafil (IV) (+/or) Milrinone

Third line: Consider prostacyclin / ECMO (Endothelin 1 antagonist)

Optimise ventilation, sedation, acid-base, Ca/Mg, sepsis

BIRTH

Regular assessment of pulmonary pressure & cardiac (RV) function

Discharge and beyond
Regular assessment of pulmonary pressure & cardiac (RV) function

Evidence of effects of PH:
HYPOXIA / ↓BP / RV dysfunction

First line:
Optimise ventilation, sedation, acid-base, Ca/Mg, sepsis

Second line:
Sildenafil (IV) (+/or) Milrinone

Worsening hypoxia or RV dysfunction

Third line:
Consider prostacyclin / ECMO (Endothelin 1 antagonist)

PGE₁ to maintain PDA if PAP>SBP / PDA closing / RV dilated
Evidence of effects of PH: 
HYPOXIA / ↓BP / RV dysfunction

First line:
iNO

Second line: 
Sildenafil (IV) (+/or) Milrinone

Third line: 
Consider prostacyclin / ECMO (Endothelin 1 antagonist)

PGE$_2$ to maintain PDA if PAP>SBP / PDA closing / RV dilated
Targeted timing of procedures inc surgery

- repair
- ECMO
- weaning iNO + cardiotropes off
- extubation
- iNO + cardiotropes

PDA flow ratio Ri:Lr

- R->L
- L->R
A new RCT?

Newborn with CDH

Early and regular assessment of $PA_p$ and cardiac (RV) function

Targeted:
- *Systematic* pulmonary vasodilator / cardiotrope use.
- Timing of procedures: surgery, weaning, extubation

CONTROL
(current therapy)

OUTCOMES: DEATH, ECMO, DISABILITY

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Antenatal Sildenafil Treatment Attenuates Pulmonary Hypertension in Experimental Congenital Diaphragmatic Hernia

Christina Luong, Juliana Rey-Perra, Arul Vadivel, Greg Gilmour, Yves Sauve, Debby Koonen, Don Walker, Kathryn G. Todd, Pierre Gressens, Zamaneh Kassiri, Khurram Nadeem, Beverly Morgan, Farah Eaton, Jason R. Dyck, Stephen L. Archer and Bernard Thébaud

Circulation  May 17, 2011
Take home message
Fig. 1. Congenital Diaphragmatic Hernia Study Group overall mortality by year.

Thanks to

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Royal Children’s Hospital, Melbourne

Murdoch Childrens Research Institute

Florian Moenkemeyer
Michael Cheung
Michael Stewart
Joanne Behrsin
Anja Bialkowski
John Mills

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