Congenital Diaphragmatic Hernia
ECMO or NO?

Matthew Harting

[Image of Matthew Harting]
Wine

The secret of enjoying a good wine:

3. No role for ECMO
Global Warming

No role for ECMO
Who am I to give advice...
CDH ± ECMO

• CDH primer
• CDH management pre-ECMO
• Indications for ECMO
• VV vs VA
• Prognosis
• Timing of surgery in relation to ECMO
• How long should we keep this patient on?
• The “opportunity” of ECMO management
Initial management

Room air / nasal cannula oxygenation

Pressure-limited ventilation

High-frequency oscillatory ventilation

Extracorporeal membrane oxygenation
- <48 hours
- Nearing decannulation
- After decannulation (varies by center)

Operative repair

Initial targets
- Predural oxygen saturation >85%*
- Adequate tissue oxygen delivery'
- Adequate tissue perfusion'
- PaCO₂: 45-70
- pH: >7.2

Targets met?

Pre-operative targets
- Resolution of hypoxia (FiO₂ ≤50%)§
- Blood pressure normalization
- Adequate tissue oxygen delivery'
- Adequate tissue perfusion'
- Stabilization³ of pulmonary hypertension

Targets met?

Operative repair
Pressure-limited ventilation

Congenital Diaphragmatic Hernia: Survival Treated With Very Delayed Surgery, Spontaneous Respiration, and No Chest Tube

New York, New York

<table>
<thead>
<tr>
<th>Immediate surgery</th>
<th>Limited stabilization</th>
<th>Prolonged stabilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>82%</td>
<td>75%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Albaiceta et al. Critical Care 2011
Driving pressure

Higher plateau pressure: not always risky

Higher PEEP: not always protective
Dear God,

Thank you for the baby brother but what I prayed for was a puppy.

Joyce

Sick CDH

HFOV? iNO?
High Frequency Oscillatory Ventilation

Initiation of HFOV: MAP: 17, Hz: 10, Amp: 36

Operative repair; C defect

pH

CO₂
High Frequency Oscillatory Ventilation

O₂
VICI trial

Conventional Mechanical Ventilation Versus High-frequency Oscillatory Ventilation for Congenital Diaphragmatic Hernia

A Randomized Clinical Trial (The VICI-trial)

Kitty G. Snoek, MD,* Irma Capolupo, MD, PhD,† Joost van Rosmalen, PhD,‡ Lieke de Jongste-van den Hout, MD, PhD,* Sanne Vijffhuize, MD,* Anne Greenough, MD,§ René M. Wijnen, MD, PhD,* Dick Tibboel, MD, PhD,* and Irwin K.M. Reiss, MD, PhD*,
CDH EURO Consortium

• 171 patients enrolled over 5 years
• Randomized to initial ventilation strategy
  – Conventional (91) vs HFOV (80)

VICI trial

- Mortality: no difference

- Length of ventilation, ECMO, iNO, sildenafil, vasoactive med req, & mode of ventilation failure ALL favored conventional ventilation


\[ p=0.19 \]
inhaled Nitric Oxide (iNO)

- 53 pts randomized (±iNO) – no difference in survival or ECMO need

- Significant improvement in survival – ALL pts with PPHN
- CDH subset – no clear survival advantage

Finer et al (for NINOS). *Pediatrics* 1997
inhaled Nitric Oxide (iNO)

Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia

3367 Infants with CDH

3117 Echocardiogram results

2174 With PH
t

943 Without PH
t

1613 Received iNO

561 Did not receive iNO

343 Received iNO

600 Did not receive iNO

Putnam et al. JAMA Pediatrics 2016
inhaled Nitric Oxide (iNO)

- Highly variable among centers (0-100%)
- 36% of patients without pHTN received iNO
- 60% of all CDH pts treated with iNO
- Propensity score:
  - Matched 10 clinically relevant variables
  - ATE: 0.15 (95% CI: 0.1-0.2)

Putnam et al. JAMA Pediatrics 2016
CDH Study Group staging

Defect A

Defect B

Defect C

Defect D

Lally et al. J Pediatric Surgery 2013
ECMO indications

- Failure of pressure-limited conventional ventilation
- \( \approx 2 \text{ kg, } 32-34 \text{ wks EGA, } < \text{ G I-II IVH, Concomitant abnormalities?} \)

Harting et al. APSA NAT 2016
CDH + CHD

• Perhaps outcomes (short term) are not so dismal...

ECMO for respiratory failure

Review of 4 RCTs (236 total infants)

Objective: Determine if ECMO is effective for neonates with respiratory failure

Strong benefit for ECMO – RR: 0.44 (95% CI: 0.31-0.61)

NNT: 3

Unknown benefit for CDH

Mugford et al. Cochrane Systematic Reviews 2008
ECMO for CDH

- Meta analysis of 21 retrospective studies (2043 pts)
- **Objective**: Determine if ECMO is effective for neonates with CDH

*Morini et al. Eu J Pediatric Surgery 2008*
### a) Short term mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>ECMO</th>
<th>No ECMO</th>
<th>RR</th>
<th>95% CI</th>
<th>NTotal</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor</td>
<td>39/109</td>
<td>8/16</td>
<td>0.716</td>
<td>0.413 - 1.241</td>
<td>125</td>
<td>0.273</td>
</tr>
<tr>
<td>Bergamo</td>
<td>4/29</td>
<td>4/12</td>
<td>0.414</td>
<td>0.123 - 1.390</td>
<td>41</td>
<td>0.151</td>
</tr>
<tr>
<td>Birmingham</td>
<td>9/20</td>
<td>12/15</td>
<td>0.562</td>
<td>0.326 - 0.972</td>
<td>35</td>
<td>0.036</td>
</tr>
<tr>
<td>Boston</td>
<td>81/176</td>
<td>11/20</td>
<td>0.837</td>
<td>0.546 - 1.283</td>
<td>196</td>
<td>0.446</td>
</tr>
<tr>
<td>Charlottesville</td>
<td>14/42</td>
<td>10/19</td>
<td>0.633</td>
<td>0.346 - 1.159</td>
<td>61</td>
<td>0.153</td>
</tr>
<tr>
<td>Detroit</td>
<td>36/75</td>
<td>16/24</td>
<td>0.720</td>
<td>0.498 - 1.040</td>
<td>99</td>
<td>0.111</td>
</tr>
<tr>
<td>Gainesville</td>
<td>13/67</td>
<td>10/12</td>
<td>0.233</td>
<td>0.134 - 0.403</td>
<td>79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Houston</td>
<td>10/32</td>
<td>21/62</td>
<td>0.923</td>
<td>0.496 - 1.716</td>
<td>94</td>
<td>0.798</td>
</tr>
<tr>
<td>Indianapolis</td>
<td>15/46</td>
<td>37/65</td>
<td>0.873</td>
<td>0.359 - 0.913</td>
<td>111</td>
<td>0.011</td>
</tr>
<tr>
<td>Kasugai</td>
<td>7/33</td>
<td>9/21</td>
<td>0.495</td>
<td>0.217 - 1.126</td>
<td>54</td>
<td>0.089</td>
</tr>
<tr>
<td>Lille</td>
<td>28/85</td>
<td>40/52</td>
<td>0.428</td>
<td>0.305 - 0.600</td>
<td>137</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>9/31</td>
<td>30/58</td>
<td>0.561</td>
<td>0.307 - 1.027</td>
<td>89</td>
<td>0.040</td>
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<tr>
<td>Nijmegen</td>
<td>16/37</td>
<td>12/18</td>
<td>0.649</td>
<td>0.396 - 1.062</td>
<td>55</td>
<td>0.103</td>
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<tr>
<td>Philadelphia</td>
<td>11/30</td>
<td>22/32</td>
<td>0.533</td>
<td>0.315 - 0.902</td>
<td>62</td>
<td>0.011</td>
</tr>
<tr>
<td>Pittsburg</td>
<td>14/31</td>
<td>24/62</td>
<td>1.167</td>
<td>0.709 - 1.921</td>
<td>93</td>
<td>0.551</td>
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<tr>
<td>San Diego</td>
<td>13/33</td>
<td>22/45</td>
<td>0.806</td>
<td>0.480 - 1.353</td>
<td>78</td>
<td>0.405</td>
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<tr>
<td>Shizuoka</td>
<td>6/34</td>
<td>12/26</td>
<td>0.382</td>
<td>0.166 - 0.883</td>
<td>60</td>
<td>0.017</td>
</tr>
<tr>
<td>St Louis</td>
<td>38/101</td>
<td>59/102</td>
<td>0.650</td>
<td>0.481 - 0.879</td>
<td>203</td>
<td>0.004</td>
</tr>
<tr>
<td>Stockholm</td>
<td>11/73</td>
<td>27/65</td>
<td>0.363</td>
<td>0.196 - 0.672</td>
<td>138</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Combined (19)</strong></td>
<td>374/1084</td>
<td>386/726</td>
<td>0.596</td>
<td>0.505 - 0.703</td>
<td>1810</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### b) Long term mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>ECMO</th>
<th>No ECMO</th>
<th>RR</th>
<th>95% CI</th>
<th>NTotal</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor</td>
<td>9/34</td>
<td>8/16</td>
<td>0.529</td>
<td>0.252 - 1.114</td>
<td>50</td>
<td>0.101</td>
</tr>
<tr>
<td>Bergamo</td>
<td>4/29</td>
<td>4/12</td>
<td>0.414</td>
<td>0.123 - 1.390</td>
<td>41</td>
<td>0.151</td>
</tr>
<tr>
<td>Charlottesville</td>
<td>17/42</td>
<td>10/19</td>
<td>0.769</td>
<td>0.438 - 1.350</td>
<td>61</td>
<td>0.376</td>
</tr>
<tr>
<td>Indianapolis</td>
<td>18/46</td>
<td>37/65</td>
<td>0.887</td>
<td>0.453 - 1.044</td>
<td>111</td>
<td>0.065</td>
</tr>
<tr>
<td>Kasugai</td>
<td>6/21</td>
<td>9/21</td>
<td>0.667</td>
<td>0.289 - 1.540</td>
<td>42</td>
<td>0.334</td>
</tr>
<tr>
<td>Lille</td>
<td>34/85</td>
<td>40/52</td>
<td>0.520</td>
<td>0.385 - 0.702</td>
<td>137</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Newcastle upon Tyne</td>
<td>17/48</td>
<td>41/81</td>
<td>0.700</td>
<td>0.451 - 1.085</td>
<td>129</td>
<td>0.093</td>
</tr>
<tr>
<td>St Louis</td>
<td>39/101</td>
<td>59/102</td>
<td>0.668</td>
<td>0.496 - 0.898</td>
<td>203</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Combined (8)</strong></td>
<td>144/406</td>
<td>208/368</td>
<td>0.625</td>
<td>0.534 - 0.731</td>
<td>774</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Favours ECMO**
ECMO for CDH

Extracorporeal Membrane Oxygenation in Infants with Congenital Diaphragmatic Hernia: A Systematic Review of the Evidence

• Meta analysis of 21 retrospective studies (2043 pts)
• Objective: Determine if ECMO is effective for neonates with CDH
• Strong benefit for ECMO

Venovenous vs Venoarterial

Now we know we should, but how should we?
Advantages of VV ECMO support

- Cannulation/decannulation is simpler
- No injury / cannulation of the carotid artery
- Oxygenated blood to the heart and lungs
  - Oxygen is a potent pulmonary vasodilator
- Pulsatile blood flow to organs
- Physiologic pulmonary blood flow
- Circuit micro-emboli trapped in lungs
- No change to afterload
Disadvantages of VV ECMO

• Does not support profound cardiac failure
• Large cannula challenging to place in small patients
• Requires more “attention”
• Must maintain with a lower oxygen saturation than normal
• Conversion to VA... sucks.
Venovenous vs Venoarterial


Venovenous Versus Venoarterial Extracorporeal Membrane Oxygenation in Congenital Diaphragmatic Hernia

Outcome analysis of neonates with congenital diaphragmatic hernia treated with venovenous vs venoarterial extracorporeal membrane oxygenation
Predicting who will require ECMO

- 29-33% of CDH patients require ECMO

Jancelewicz et al. accepted APSA 2017

Apgar, 1 min
PaCO₂, highest

A
B

ROC Curve for Model
Area Under the Curve = 0.8216

ROC Curve for Model
Area Under the Curve = 0.7722

0.82
0.77

Jancelewicz et al. accepted APSA 2017
Predicting mortality

• Overall mortality is 50%

Guner et al. accepted APSA 2017
Predicting mortality

Guner et al. accepted APSA 2017
Surgical timing

• Repair ON ECMO
  – Early
  – Late

• Repair AFTER ECMO

• Repair BEFORE ECMO
Repair on ECMO

• Repair early
  – Allow pulmonary expansion
  – Supported during post-operative inflammation / edematous phase
  – Enteral nutrition

• Disadvantages
  – Hemorrhage, Coag/Anticoag mgmt
Repair after ECMO

• Minimal bleeding risk
• Know they are a likely survivor
• Disadvantages
  – Post-operative deterioration
• What if they can’t liberate?
Surgical timing

Congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: does timing of repair matter?☆

Repair after ECMO

Repair on ECMO

Surgical timing

Congenital diaphragmatic hernia: to repair on or off extracorporeal membrane oxygenation?

Richard Keijzer\textsuperscript{a,1}, Dorien E. Wilschut\textsuperscript{a,1}, Robert Jan Houmes\textsuperscript{a}, Kees P. van de Ven\textsuperscript{a}, Lieke van den Hout\textsuperscript{a}, Ilona Sluijter\textsuperscript{a}, Peter Rycus\textsuperscript{b}, Klaas M. Bax\textsuperscript{a}, Dick Tibboel\textsuperscript{a,*}

- Bleeding complications comparable (with a protocol)

Surgical timing

• Early repair is feasible, safe, and may have some advantages

Surgical timing

- Repair very early (prior to ECMO) may have a survival advantage
- Minimizes bleeding risk
- Optimizes pulmonary expansion

Length of ECMO run for CDH

- LLD: median = 9.5 days
- LLU: median = 11 days
- Right: median = 13.7 days

Kays et al. JACS 2015
The opportunity
The opportunity

Pulmonary artery

Adventitia
VSMCs
Internal elastic lamina
Endothelium
The opportunity

Foundation for stem cell-based therapies
If you are not going to use ECMO

• What are you going to do when conventional ventilation fails?
• Why does conventional ventilation fail?
  – Suboptimal management
  – Pulmonary hypertensive crisis

These are recoverable events!
ECMO for CDH - certainly

- Standard protocol
- Pressure-limited strategy (CMV)
- Do not use iNO
- VV or VA ECMO (Bad right CDH → VA ECMO)
- Repair early (aggressive strategy)
EMCO Team

 UTHealth McGovern Medical School
 MEMORIAL HERMANN ECMO Team
 Children's MEMORIAL HERMANN Hospital