PPHN: Radical Thoughts about Oxygen

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History of Supplemental O₂

- Oxygen was first discovered by Carl Wilhelm Scheele, but his publication “On Air and Fire” was delayed by two years.
- Joseph Priestly typically is given credit as he published his findings first in 1774.
- Antoine Lavoisier gave it the name oxygen and proved that it was an element in 1777.
- Francoise Chaussier credited with first administration of oxygen to a neonate in 1780

Persistent Pulmonary Hypertension in the US

- 1/500 infants
- ~10% of all neonates with respiratory failure
- Few genetic factors identified
- High morbidity, mortality
- At risk for long-term sequelae

Inhaled NO and PPHN Outcome

<table>
<thead>
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<th></th>
<th>% ECMO</th>
<th>% Mortality</th>
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<td>Davidson</td>
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<td>Konduri</td>
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<td>19.2</td>
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ROS Impair Normal Transition

- PPHN
- 100% O₂
- 111 ROS
- eNOS Expression
- 111 PDE5 Activity
- Blunted cGMP Vasoconstriction

Inhaled NO

- NO Synthase
- NADPH Oxidase
- Mitochondria
- Oxygen
- SOD
- Catalase
- Glutathione Peroxidase

ROS Impair Normal Transition

- NO
- O₂⁻
- ONOO⁻
- PDE5
- Catalase
- Glutathione Peroxidase
- NO Synthase
- NADPH Oxidase
- Mitochondria
- Oxygen
- SOD
- Catalase
- Glutathione Peroxidase
**Goals of Oxygen Therapy**
- Oxygen delivery
- Pulmonary vasodilation

**24-hour Ventilation Studies**
- Servo 300 Ventilator: Tidal Volume ~ 10mL/kg
- IV Infusion of D10W with 25 mEq/L NaCl, 20mEq/L KCl, 10mEq/L NaHCO₃
- ABG, Electrolytes and Hct Analysis
- 100% Oxygen x 24 hours
- BP, HR and SpO₂
- Arterial Blood Gases and arterial to Alveolar PO₂ ratios (a/A ratios)

**Effect of Oxygen on Pulmonary Artery Contractility**
- Lakshminrusimha et al; Pediatr Res 2006
- Force of Contraction (g/g)
- Exposure to Hyperoxia Increases ROS in Lamb Lungs
- Hyperoxic Ventilation Increases PDE5 Expression in Normal Lambs
- Farrow et al; Circ Res 2008
FPASMC: Oxygen and cGMP Response to NO

Exposure to 95% O₂ Increases ROS in FPASMC

Antioxidants Reverse Hyperoxia-Induced Increases in PDE5 Activity

Antioxidants Reverse Hyperoxia-Induced Increases in PDE5 Activity
**Short Term Hyperoxia**

“When resuscitating babies at term, the NRP advises using 100% oxygen whenever a baby is cyanotic or whenever positive-pressure ventilation is required.”


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**Oxygen Concentration during Resuscitation**

- 21% oxygen (PaO$_2$ 56)
- 50% oxygen (PaO$_2$ 129)
- 100% oxygen (PaO$_2$ 408)

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**Oxygen and PVR in Control Lambs**

Lakshimrusimha et al; Pediatr Res 2007

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**Effect of Brief Hyperoxia on Pulmonary Artery Contractility**

Lakshminrusimha et al; Pediatr Res 2006

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**Resuscitation with 100% Oxygen Blunts Response to NO**

Lakshminrusimha et al; Pediatr Res 2007

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**Brief Hyperoxia and H$_2$O$_2$ Reduce ecSOD Activity in Lamb PASMC**

Wedgwood et al, Antiox Redox Sig, 2011
30 Minutes of Hyperoxia Increases PDE5 Activity

Hyperoxia Rapidly Increases Mitochondrial Oxidant Stress

30 Minutes of Hyperoxia Increases PDE5 Activity

Antenatal Remodeling Associated with PPHN

Ductal Ligation Lamb Model

Increased ROS in PPHN Pulmonary Arteries
Abnormal Stimuli (Hypoxia, Hyperoxia, Stretch)

GTP-CH

BH$_2$

O$_2^-$

NO

ONOO$	ext{-}$

eNOS Uncoupling

Nox2, Nox4 Mitochondria

Total SOD Activity in PPHN Lambs

ecSOD Activity in PPHN Lambs

Effect of Oxygen Concentration in PPHN Lambs

PPHN Lambs: Resuscitation with 100% $O_2$ Blunts Response to NO

Ventilation with 100% $O_2$ in PPHN Lambs

ROS

1DSB Fetus 100% $O_2$

PPHN

PDE5 Expression

PDE5 Activity

21% $O_2$

50% $O_2$

100% $O_2$

Control

PPHN

Activity

Expression

Control

PPHN

Activity

Control

PPHN

PDE5 Expression

PDE5 Activity

Control

PPHN

PDE5 Expression

PDE5 Activity

Control

PPHN
Catalase Improves Oxygenation in PPHN Lambs

Catalase Restores ecSOD Activity and Decreases ROS

Catalase Restores ecSOD Activity and Decreases ROS
Antioxidants Restore Low PDE5 Activity in PPHN Lambs

Intravenous Sildenafil Improves Oxygenation in PPHN

Response to Intravenous Sildenafil Without iNO

ROS Impair Normal Transition

Mitochondrial Targeting of MnSOD vs. Catalase
Increased Mitochondrial ROS Production in PPHN PASMC

Remodeled Pulmonary Vasculature in PPHN Lambs

Cytosolic Generators of ROS: Nox Isoforms

Farrow et al, Resp Physiol Neurobiol 2010

Control Ductal Ligation

Lassegue and Griendling, Arterioscler Thromb Vasc Biol 2010