Physiology of Fetal Circulation

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Disclosure

• Plagiarism = Copy material from one source

• Research = Copy material from multiple sources
Outline

- Arrangement of fetal circulation
- Different segments of fetal circulation
  - Placenta – pulmonary circulation
- Developmental changes
- Transition at birth

Function of Circulatory System

- Provide oxygen and nutrient supply to the tissues
- Adjust the oxygen supply to the metabolic needs of the tissues
- Return deoxygenated blood and CO₂ to the organ of gas exchange
Normal Fetus

Fetal Circulation
Normal Fetal Circulation

Placental Circulation
Arrows indicate sites of arterio-venous shunts in the placenta.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>PO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Uterine art</td>
<td>90-100</td>
</tr>
<tr>
<td>Inter-villous space</td>
<td>50</td>
</tr>
<tr>
<td>Umbilical artery</td>
<td>20</td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>30-35</td>
</tr>
</tbody>
</table>

**Hb-O₂ Dissociation Curve**

Fetal Hb=70% Term Neo
P50= 20-HbF, 28-HbA
90%= 45-HbF, 60-HbA
### Hb-O₂ Dissociation Curve

<table>
<thead>
<tr>
<th>Factor</th>
<th>Right Shift</th>
<th>Left Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>DPG</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>p(CO₂)</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>pH (Bohr effect)</td>
<td>low (acidosis)</td>
<td>high (alkalosis)</td>
</tr>
<tr>
<td>Type of Hemoglobin</td>
<td>adult hemoglobin</td>
<td>fetal hemoglobin</td>
</tr>
</tbody>
</table>
Oxygen Content of Blood at Different Levels of Oxygen Tension

<table>
<thead>
<tr>
<th>PO₂ (torr)</th>
<th>SO₂ (%)</th>
<th>O₂ Combined with Hb (ml/100ml)</th>
<th>O₂ dissolved in plasma (ml/100ml)</th>
<th>Total O₂ content per 100ml of blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 (Hb=16)</td>
<td>65</td>
<td>13.95</td>
<td>0.075</td>
<td>14.01</td>
</tr>
<tr>
<td>90 (Hb=16)</td>
<td>100</td>
<td>21.4</td>
<td>0.3</td>
<td>21.74</td>
</tr>
<tr>
<td>90 (Hb=12)</td>
<td>100</td>
<td>16.08</td>
<td>0.3</td>
<td>16.38</td>
</tr>
<tr>
<td>600 (Hb=16)</td>
<td>100</td>
<td>20.1</td>
<td>1.8</td>
<td>21.9</td>
</tr>
</tbody>
</table>

Hb binds 1.34 ml O₂/gm
Dissolved O₂ = 0.3 ml/100 mmHg

Right Lobe

Left Lobe

Liver

Right hepatic vein

Ductus venous

Portal vein

Inferior vena cava

Placenta

Superior vena cava

Right Atrium

Left hepatic vein

Ductus venosus

Umbilical Vein

30-50% of UV

Blood across DV

30-50% of UV

Blood across DV

Left hepatic vein

Ductus venous

10-20 cm/s

3-9 mmHg

60-80 cm/s

Foramen ovale valve

LA

RA

IVC

PV

Umbilical vein
Normal Fetal Circulation

### Percent Combined Output

<table>
<thead>
<tr>
<th></th>
<th>20 Wks</th>
<th>30 Wks</th>
<th>38 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined output</td>
<td>210 ml/min</td>
<td>960 ml/min</td>
<td>1900 ml/min</td>
</tr>
<tr>
<td>Left Ventr</td>
<td>47</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Right Ventr</td>
<td>53</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>PFO</td>
<td>40</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Lungs</td>
<td>5</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>
Developmental Limitations

- 30% of fetal (premature) myocardial cell consists of myofibrils (60% of adult myocyte)
- Myofibrils less Ca\(^{++}\) sensitive
- Mitochondrial size & complexity less in fetus
- More dependent on carbohydrate for energy

Fetal/neonatal myocardial physiology

<table>
<thead>
<tr>
<th></th>
<th>Fetus/ Neonate</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>HR dependent</td>
<td>SV &amp; HR</td>
</tr>
<tr>
<td>Starling response</td>
<td>limited</td>
<td>normal</td>
</tr>
<tr>
<td>Compliance</td>
<td>less</td>
<td>normal</td>
</tr>
<tr>
<td>Afterload compensation</td>
<td>limited</td>
<td>effective</td>
</tr>
<tr>
<td>Ventricular interdependence</td>
<td>high</td>
<td>relatively low</td>
</tr>
</tbody>
</table>
Changes at birth

- SVR increases suddenly
- Pulmonary flow increases by 10-fold
- Left ventricle-increases in pre-load & after-load
- Increased oxygen supply- improved left ventricular performance
Response to Physiologic Stimuli

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>PDA</th>
<th>Pulm Artery</th>
</tr>
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<tbody>
<tr>
<td>Hypoxia</td>
<td>Dilate</td>
<td>Constrict</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Dilate</td>
<td>Constrict</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Constrict</td>
<td>Dilate</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Constrict</td>
<td>Dilate</td>
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</table>
PGE2 Effects on PDA

- Low PO2
- High luminal pressure
- Placental PGE2

Endothelial Cell

- COX
- PGE2

Smooth Muscle Cell

- EP2
- EP3
- EP4

- cAMP
- K+ATP
- Relaxation

- K+
- PDE3
- AMP
Fetal Pulmonary Circulation

- 40-Fold increase in # small blood vessels in 3 trimester
- Increase in smooth muscle layer around small PA
- Increase in responsiveness of PA to stimuli
Low PO2

↑ET-1, EET, TxA2

↓NO, PGI2

↑Ca++

↓cGMP, cAMP

↓K+Ca, Kv

Endothelin Effects on Vessel

Pre-pro-ET-1 → Big-ET1 (92 AA) → ECE (21 AA) ET-1

↑eNOS

↑Ca++ Contr

↓Ca++ Relax

ET-A

ET-B

NO
Vascular Resistance (mmHg/ml/min/kg)  Arterial Pressure (mmHg)  Blood Flow (ml/min/kg)

95 136          Birth 1-3 6 days Age

80% decrease in 24 h
Transition of Lung at Birth

Fetus

Newborn

Transition in Pulm Flow

Left pulm flow (ml/min)

BL  Drain lg  Dist  Dist+O2
Oxygen & Pulmonary Flow

Fetal $\text{PO}_2$ 22 27 47
Oxygen & Pulmonary Flow

Fetal PO2  22  27  47
Pulmonary flow and Maturation of NOS & COX
Reactive Oxygen Species

![Diagram of reactive oxygen species](image)

- NOX, NOS
- eNOS
- \( \text{O}_2^- \)
- SOD
- \( \text{H}_2\text{O}_2 \)
- \( \text{H}_2\text{O} + \text{O}_2 \)
- Peroxynitrite
- cGMP
- Constriction
- Vasodilation
Regulation of cGMP
Postnatal Circulation
Summary

• Fetal circulation uniquely adapted to the intra-uterine life- Low PO$_2$ and non-respiring lungs
• Preparation for post-natal adaptation occurs throughout fetal life
• Understanding these adaptations essential to management of infants in NICU
Normal Post Natal Circulation

Normal Transition

Systemic Blood Pressure

Pulmonary arterial pressure

Right Atrium

Left Atrium
Ductus Venosus Shunt

• 30-50% of umbilical venous blood shunted thru DV
• Percent shunted declines with gestation
• Rest of umbilical venous blood-left and right lobes of liver
• Left hepatic vein (65% Sat)-across PFO
• Portal venous blood (40% Sat) mostly to right lobe of liver
PDA - Compensatory Mechanism?

Hox 1,2 → CO

ET-1

Oxygen ↓ Pressure

Cyp 450

Lumen

EC

SM

Low PO2 Lumen pressure

PDA Physiology

↑ Kv

↑ cGMP

↑ cAMP

↑ Ca++

↓ Kv
Flow Across PDA

- Regulated by PVR in the fetus
- Response to blood gas changes - opposite to pulmonary circulation
- Response to vasoactive substances - PGE2, NO, ATP, K+ channel blockers etc similar to pulmonary vessels
Breath NO Levels - Infants

![Bar graph showing breath NO levels for preterm and term infants.](image)

- Nasal NO
- Ex NO-Vent

Parts per billion

Preterm

Term

- Williams et al Ear Hum Dev ’03
- Leipala et al Eur J Ped ‘04

Diagram of liver venous system:

- Right Lobe
- Left Lobe
- SVC
- RA
- LA
- LHV
- RHV
- Portal Vein
- UV
- IVC
- DAo
Fetal Pulmonary Artery

Low PO2
↑Lumen pressure

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<th>VSM</th>
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<td>↑Lip Oxy</td>
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<td>↓Cox1,2</td>
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<td>↑ET-1</td>
<td>↑Cyp 450</td>
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<td>EET</td>
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Maturation of vasodilator system during gestation

Estrogen
Steroids
Shear Stress

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Basal ATP levels in fetus

![Bar chart showing Blood ATP and Plasma ATP levels for PA and LA with SAT 59% and SAT 81% respectively.]

Advantages of sheep model

- Gest age 140 days
- Carry single or twins
- Fetus large enough for instrumentation
- Uterus is quiescent
Superoxide Dismutases

EC-SOD

CuZn-SOD

Mn-SOD

cell membrane

oxidases

mitochondria

O$_2^-$ $\rightarrow$ H$_2$O$_2$

O$_2^-$ $\rightarrow$ H$_2$O$_2$

O$_2^-$ $\rightarrow$ H$_2$O$_2$

Endo

SMC

O$_2$

Dist

NOS

NO

COX

PGI2

K$^+$

GC-cGMP

AC-cAMP

34