Pulmonary Arteriovenous Malformations After the Bidirectional Glenn and the Role of VEGF

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DISCLOSURES: NONE

Background
- PAVMs first recognised during follow-up after classical Glenn shunt, in ipsilateral lung
- Early BDG part of standard surgical sequence in staged Fontan palliation
- What causes the development of PAVMs in some children?

Physiology of PAVMs
- Intrapulmonary right to left shunt proximal to the gas exchange units
- Can become evident as early as a few weeks after BDG
- Lesions tend to progress with time

METHODS OF DETECTION
- Angiography
- Radionuclide study
- Contrast echocardiography: more sensitive, detect right to left shunts even in the absence of clinically evident PAVMs

Recruitment of pre-existing vessels versus Angiogenesis

Recruitment and dilation of pre-existing vascular channels
- Pulmonary arteriovenous shunting in the normal fetal lung
  - McMullan DM, 2004
Rapid onset of PAVMs (72 hours) after Kawashima procedure

Not true angiogenesis, but recruitment of preexisting vessels

**Angiogenesis**

- Increased microvessel density in the lungs after BDG, even in the absence of clinical evidence of PAVMs
- Continuing angiogenic stimulus, early after BDG
- Development of symptomatic PAVMs associated with histologic transitions

**Microvessel density**

- **Sparse data:** Weber Osler Rendu complex vs BDG vs hepatic cirrhosis
- Greatly increased number of new vessels extending into the periphery of the lung
- Connections between pulmonary arterioles and vascular lakes proximal to the capillary level

**Microvessel Density: rat model**

**Histology**

**Lung Biopsy Micrographs**

Duncan BW, 1999
Freedom from PAVMs

Srivastava D, 1995

14 year old, post Fontan, gradually worsening O2 saturations

Selective angiography

Many hours & devices later

25 year old; status post-Fontan for TA

Possible Etiologic Mechanisms

- Develop whenever hepatic effluent does not perfuse pulmonary arteries directly
- Occur bilaterally after BDG and with isolated drainage of hepatic veins to common atrium (Kawashima procedure)
- Surgical redirection of hepatic venous flow to the PAs causes PAVMs to regress …
Effect of Incorporation of Hepatic Veins after Kawashima Operation

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PVRI (%)</th>
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<tbody>
<tr>
<td>Post-BCPA</td>
<td>85%</td>
</tr>
<tr>
<td>PA/MH Diagnoses</td>
<td>76%</td>
</tr>
<tr>
<td>Hospital Discharge</td>
<td>78%</td>
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<tr>
<td>Max IV</td>
<td>92%</td>
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<td>Most Recent Follow-Up</td>
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McElhinney, 2005

...but not always

Diffuse bilateral AVMs

Unilateral progression despite incorporation of hepatic blood

Vettukattil J, 2002

Specific Angiogenic Factors: VEGF

- VEGF a potent stimulator of endothelial proliferation & angiogenesis
- Increased VEGF in SVC and systemic artery after BCPA
- Increased expression of VEGF & its receptor in lung biopsy specimens after BCPA

VEGF mRNA expression for CPA versus control lung

Rat model classical Glenn Shunt

<table>
<thead>
<tr>
<th>Time after CPA</th>
<th>% Increase Over Control</th>
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<tbody>
<tr>
<td>2 months</td>
<td>50</td>
</tr>
<tr>
<td>8 months</td>
<td>190</td>
</tr>
<tr>
<td>12 months</td>
<td>220</td>
</tr>
</tbody>
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Mumtaz MA, 2005

Arterial oxygen saturation versus serum VEGF

Rat model classical Glenn Shunt

Suda K, 2004

Clinical correlates: Hypothesis

- Systemic VEGF levels would fluctuate during the course of various surgical alterations in patients with univentricular hearts
- Each patient as his/her own control
Methods

• VEGF (1) in the OR, prior to BDG (no additional sources of pulmonary blood flow) (age 13.4 ± 6.1 months)

• VEGF (2) at cardiac catheterization, prior to completion of Fontan (non-fenestrated lateral tunnel/ extracardiac conduit TCPC) (age 3.4 ± 1.2 years)

• VEGF (3) at >1 month after Fontan completion

Results

• VEGF (1) vs VEGF (2) vs VEGF3
  - (24.4 ± 28.3 pg/ml) vs (112.4 ± 68.5) vs (48.8 ± 27.1)

• O₂ saturation levels
  - 82% (74-85%) vs 79% (65-87%) vs 97% (91-100%)

• Inverse correlation of O₂ saturation with VEGF levels poorest just prior to TCPC

Problems

• No significant relationship in VEGF levels between patients with abnormal vessels (arteriovenous or venovenous) and those without

• Most patients with hypoxemia secondary to structural heart disease do not develop PAVMs
**Other mediators of Angiogenesis: Endothelial Oxidative stress**

- PA banding versus CPA:
  - Both result in upregulation of VEGF1 and its receptor.
  - Only CPA associated with ↑ endothelial oxidative stress in affected vascular bed:
    - ↑ HIF-1α, hemoxygenase 1 (HO1) and glucose transporter 1 (GLUT1).

**Other mediators of Angiogenesis: Impaired vasoconstriction**

- ↓ ACE mRNA & protein expression in shunted lung after classical Glenn shunt
  - Within 1 week
- ↓ Angiotensin II in the right pulmonary vein
  - Within 1 week
- ↑ Angiotensin II receptor mRNA (type 1 & type 2) and protein expression
  - Within 1 week
- AV shunting uniformly detectable by bubble contrast echocardiography at 6 weeks after Glenn shunt.

**Role of the liver**

- Formation of inhibitor(s) of angiogenesis
  - Hepatocyte conditioned media strongly inhibitory for endothelial cell proliferation
- Degradation of an angiogenic substance which would not be removed from the pulmonary circulation after BDG
- Hepatopulmonary syndrome and role of orthotopic liver transplantation

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**The Liver, Pulmonary Hypertension & Disordered Angiogenesis**

- PHT in 2% of patients with cirrhosis & portal hypertension (portopulmonary syndrome)
- Severe PHT may be reversible by liver transplantation
- Liver disease related PHT and PAVMs seem to be mutually exclusive

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**Candidate Factors**

- Plasminogen: precursor of angiostatin
- Collagen XVIII: precursor of endostatin
- Both inhibit endothelial cell proliferation, angiogenesis and tumor growth

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**Candidate Factors**

- ↑ plasma Endothelin -1 and ↑ endothelial NOS
  - In vivo: rat cirrhosis model (CBD ligation)
- Pulmonary microcirculatory vasodilation associated with gas exchange abnormalities
  - Zhang M, 1999
Pulmonary angiogenesis in hepatobiliary syndrome

- Rat cirrhosis model:
  - Angiogenesis, with increased microvessel density
    - VEGF-A
    - VEGFR-2
  
  Zhang J, 2009

**Maintenance of Pulmonary Vascular Tone by Blood Derived from the IVC**

- Sham CPA
- CPA + pulsatile flow

Ikai A, 2005

Many Inputs – Common Effector Mechanisms?

- VEGF
- Oxidative Stress
- Angiotensin II

- Hepatic influence: All of the above +
  - Plasminogen
  - Collagen XVIII
  - Endothelin 1 → NOS

Endothelial Notch4 gene activation and lung AVMs

- Essential for vascular morphogenesis and arteriovenous specification
- Embryonic expression of Notch4 gene largely restricted to endothelial cells
- Effects of VEGF & HIF-1α are mediated by Notch signalling

Uyttendaele H, 1996
Notch4* can be (re) expressed in young/adult mammals

- Endothelial expression of constitutionally active Notch4* elicits reversible AVMs in adult mice
- Cessation of Notch4* expression reverses these pathophysiological effects

Miniati D, 2010

To conclude...

- Durability of BDG not likely to be limited by development of clinically relevant cyanosis
- PAVMs after BDG a bed-to-bench paradigm, searching for an explanation
5 month old, increasing cyanosis 3 weeks after BDG

Native LPA