Pulmonary arterio-venous fistulas

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Typical patient presentation

- KB was cyanotic at birth due to a hypoplastic right ventricle.
- She had a modified B-T shunt in infancy, and a bidirectional Glenn operation at 3 years of age.
- By 10 years of age she had become increasingly cyanotic, with an arterial oxygen saturation of 69%; at cardiac catheterization extensive bilateral pulmonary arterio-venous shunting was observed.
- Immediately after completing the single ventricle repair her arterial oxygen saturation was 69%. It returned to normal after about 6 months.

Pulmonary angiogram
Injection of agitated saline into LPA

Before

After

Detecting anatomic intra-pulmonary shunts

1. IV/PA injection of radio-labeled macro-aggregated albumin (\(^{99}\text{mTcMAAA}\)). Very sensitive, but results vary with particle size. Quantifiable.
2. Contrast echocardiography. Sensitive, cannot quantify exactly
3. Pulmonary angiography:
   - Blush due to increased number of tiny vessels
   - May show details of fistulae. Much less sensitive than first two methods
4. Measure AaD while breathing 100% oxygen

Normal venous admixture

- Contrast echocardiography
  - Usually none at rest, may appear with exercise
- Respiratory gas techniques
  - Shunt of 3-5% of cardiac output with heavy exercise
- Radiolabeled microspheres
  - <6% of cardiac output

Diseases with abnormal venous admixture

- After Glenn, Kawashima, or Fontan operations
  - More with Kawashima, but may be absent
- Rarely in congenital cardiovascular diseases without surgery
- Isolated pulmonary arterio-venous fistulas, especially with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)
- Liver disease (hepato-pulmonary syndrome)

- Are there any common factors?
Post-surgical pulmonary arterio-venous fistulas

- Occur in >50% of subjects after Glenn or Kawashima operations
- Incidence increases with time
- In original Glenn, fistulas only on side of operation
- In bidirectional Glenn or Kawashima operations fistulas are bilateral
- Fistulas usually disappear after completing the Fontan operation

Possible mechanisms

- Decrease or absence of inferior vena caval return to lungs, depending on lesion and operation
- Decreased pulsatility—unlikely because fistulas usually disappear after completing the Fontan
- In Kawashima operation only hepatic venous return does not go directly to the lungs. Therefore likely that exclusion of hepatic venous drainage is responsible

CHD without surgery

1. Pulmonary arterio-venous fistulas rare in CHD
2. Occasionally with left atrial isomerism
3. Isolated drainage of IVC or hepatic veins to left atrium

Hepatic factors in pulmonary arterio-venous fistulas

- Pulmonary arterio-venous fistulas are often associated with failure of hepatic vein blood to perfuse lungs in first circulation
- These fistulas usually disappear when hepatic venous blood is re-routed to lung, including Fontan patient with hepatic blood flow directed almost exclusively to one lung
- Suggests a deficiency of a short-lived anti-angiogenic factor or an excess of a short-lived angiogenic factor
Putative hepatic factor

Isolated pulmonary arterio-venous fistulas
- Uncommon to present in childhood
- Sometimes plexiform lesions
- Sometimes large aneurysms
- Usually associated with Hereditary Hemorrhagic Telangiectasia (HHT)

Importance of HHT
Natural equilibria in body:
1. Many cells and molecules undergo replacement after characteristic times - 120 days for red blood cells, 5 days for myosin.
2. Equilibrium may be static until disturbed e.g. blood pro- and anti-coagulant activity
One of these may be true for lung blood vessels, with balanced angiogenesis and anti-angiogenesis related to endoglin and ALK1.

Lessons from HHT
Transforming growth factor-β
BMP receptor II
-Endoglin
ALK3
ALK5
ALK6
BMP2-BMP7-GDF5
BMP-9, BMP-10
Smad 2/3
EC
SMC
Migntion
Proliferation
Differentiation
Migration
Proliferation
Activation
Maturation
Hepato-pulmonary syndrome

- Defined as “an arterial oxygenation defect induced by intrapulmonary vascular dilatations (IPVD) associated with hepatic disease”
- Occurs in any liver disease, mainly cirrhosis (in 15-30%)
- Pathology characterized by hugely dilated capillaries as well as pulmonary arterio-venous fistulas. Cyanosis due to diffusion defect as well as Va/Q mismatch and fistulas
- Lung contains CD68(+) macrophages that produce VEGF and PDGF

Are mechanisms of Glenn and Kawashima pulmonary arterio-venous fistulas similar to those for hepato-pulmonary syndrome?
Is diseased liver producing excess angiogenic factor or decreased anti-angiogenic factor?

Possible factors

- VEGF and endoglin produced by many cells and tissues
- VEGF increased in cyanotic heart disease
- Angiopoietin-1 widely produced by pericytes and smooth muscle cells, angiopoietin-2 in endothelial cells
- Angiostatin is produced from plasminogen in the liver, but half-life is 15 min
- Endostatin is produced from soluble collagen XVIII from liver, but has long half-life. Cannot be dismissed because of recent finding that endostatin decreases and collagen XVIII increases after Glenn operation

Angiotensin
Conclusions

- Hepatic factor affected by first pass circulation in the lungs
  - Excess of angiogenic factor(s)
  - Deficit of anti-angiogenic factor(s)
- With multiplicity of factors involved in angiogenesis, it would not be surprising to find more than one factor involved
- Whether the involved factor produces pulmonary arterio-venous fistulas may depend on concentrations of other involved factors

Venous admixture

1. Produces an Alveolar-arterial gradient (AaD) of oxygen tension
2. Normal AaD 5-15 mm Hg; more in neonates
3. Usually <5% of cardiac output
4. Causes of increased AaD:
   a. Va/Q mismatch-abolished by breathing 100% oxygen
   b. Diffusion limitation-does not occur normally
   c. Lesions excluding air from alveoli-collapse, fluid, cells
   d. Anatomic connections that by-pass alveoli
      - Post-alveolar connections
        - Bronchial veins
        - Thebesian veins
      - Pre-alveolar connections-pulmonary arterio-venous fistulas
Pathology of fistulas

- Inadequately described
- Usually irregular thin walled vessels, especially subpleurally
- NB. In hepato-pulmonary syndrome
  - the pulmonary capillaries are very dilated, unlike other diseases mentioned here
  - There are CD68+ macrophages that release angiogenic factors