Inducible intrapulmonary arteriovenous shunt pathways: Real or Imaginary

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Novel Concepts that Challenge Conventional Wisdom

- Inducible intrapulmonary shunt pathways are REAL and maybe IMPORTANT in health and disease.
- Inducible intrapulmonary shunt pathways maybe parallel vascular networks with NOVEL and CONTRADICTORY regulatory mechanisms.

Pulmonary gas exchange during exercise in healthy humans is NOT perfect

Potential contributors to the gas exchange dysfunction seen with exercise include:

- Ventilation/Perfusion Inequality
- Diffusion Limitation
- Right-to-Left shunt
  - Intracardiac shunts
    - Patent Foramen Ovale (PFO)
    - Atrial Septal Defect (ASD)
  - Post-pulmonary venous admixture
  - Thebesian circulation
  - Bronchial circulation
  - Intracardiac shunts
    - Physiologic (atelectasis and alveolar flooding)
    - Anatomic (Intrapulmonary arteriovenous pathways)

Ventilation/Perfusion Inequality and Shunt determined with MIGET

Eldridge et al J Appl Physiol 1996
Diffusion capacity and capillary transit time during exercise

Johnson et al Handbook of Physiology, 1996

Why should we reconsider arteriovenous intrapulmonary shunts despite findings from 100\% \(O_2\) test and MIGET that discount them?

- Gledhill et al (1977) suggested that a 2\% intrapulmonary shunt would completely account for the difference between MIGET predicted and measured \(A\dot{D}O_2\).
- Morphologic studies showing arteriovenous intrapulmonary shunts.
  - De Busscher (1947), Kucsko (1953), Weibel (1959), and von Hayek (1960)
  - Microsphere studies (human and animal) showing passage of large spheres (25-200\(\mu\) in diameter) through the pulmonary circulation.
  - Pitzmetal (1948), Rahn (1952), Parker (1956), Tobin (1950a, 1950b, 1953, 1966)

Hit by a Bus

- 11 year old boy run over by a school bus.
- Admitted to PICU with significant pelvic fractures, pelvic hemorrhage, ureter disruption and bladder injury.
- Placed on ventilator with low pressures but had large \(O_2\) requirement with \(S_{O_2} \approx 80\%\) on 100\% \(O_2\). Clear chest X-ray and no apparent lung injury. Normal heart sounds and no murmur. Had clubbing of the fingers.
- Echocardiogram showed normal cardiac anatomy and function. Contrast study suggested a pulmonary arteriovenous malformation.

The Lung as a Biological Filter

Case Report: Angiography

Hit by a bus: Saline Contrast Echocardiogram

Delayed highly dense left heart opacification. Diagnostic for Large Pulmonary Arteriovenous Malformation (PAVM).
Contrast Echocardiography During Exercise

- Recruited 26 healthy non-smoking subjects (15M/11F, aged 23-48 yrs, %VO\textsubscript{2max} range 78-200%). However, resting echocardiograms revealed PFO’s in 3 subjects. These 3 subjects were excluded from the exercise studies.
- Incremental cycle ergometer exercise, with contrast bubble injection and apical 4-chamber echo study during the last minute of each 2 minute stage.

Discoveries and Speculations

- Intrapulmonary arteriovenous shunts are recruited during exercise in healthy humans.
- These shunt pathways may contribute pulmonary gas exchange dysfunction.
- Inducible intrapulmonary shunts pathways may be distinct vascular conduits that open under conditions of stress.
Manohar and Goetz. Intrapulmonary arteriovenous shunts of > 15 µm in diameter probably do not contribute to arterial hypoxemia in maximally exercising Thoroughbred horses. J Applied Physiol, 2005

Results:

No evidence of shunt in resting animals.

In 5 of 6 exercising animals we found microspheres in the arterial blood or tissue. Suggesting the recruitment of intrapulmonary shunt pathways.

Calculated exercising shunt fraction found to be 1.4 ± 0.8 % cardiac output.

Methods:

Cardiac output during rest and exercise.

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10.8 million 25 µm stable isotope-labeled microspheres (BioPAL) were injected into a vein @ rest (N=8) and during high intensity exercise (6-8mph 10% grade N=6). Arterial blood was continuously collected @ 10mL/min during and for 3 min after the injection. After euthanasia tissue samples were obtained from the heart, liver, kidney, & skeletal muscle and analyzed for microspheres. Shunt fraction was calculated from the known microsphere injection, cardiac output, right renal blood flow, and # microspheres found in the kidney samples.

Stickland, Lovering, & Eldridge. Exercised induced arteriovenous intrapulmonary shunting in dogs. AJRCM, 2007

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Methods:

Recruited 11 healthy nonsmoking males subjects. Four were found to have previously unrecognized PFO and were excluded from the study. The remaining 7 subjects completed a maximal treadmill exercise study.

On separate days the subjects were injected with 99mTcMAA (0.057mCi/kg) @ rest (standing) or during the last minute of a 3 minute maximal treadmill exercise bout. Within minutes of the injection the subjects underwent quantitative whole body planar gamma scanning in the supine position. Shunt fraction was calculated from the whole body lung ratio.

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**Shunt fraction determination using whole body ⁹⁹mTcMAA scanning**


**Does alveolar hypoxia modulate arteriovenous intrapulmonary pathways?**

- 14 healthy male (18-49 years) were recruited, 5 subjects had abnormal screening resting contrast echocardiograms (4 PFO’s and 1 PAMV).
- Remaining 9 subjects completed 2 progressive contrast echo exercise studies to max (FI\(O_2\)=0.209 & FI\(O_2\)=0.12).
- Collected arterial blood gases during the last 30 sec of each workload.

**Influence of inspired oxygen tension on A-a\(DO_2\) and recruitment of intrapulmonary arteriovenous shunting**


**Effect of hyperoxia**

Consistent finding in all 9 subjects tested

Lovering et al. J Physiol 2008

**Defining IPAV Pathways in the Developing Lung using our Right Heart Catheterization Piglet Model and Microsphere Infusion Method**

**IPAV Recruitment as a function of age and mixed venous oxygen tension**

Bates and Eldridge in prep 2010
Inducible intrapulmonary shunt pathways are REAL and are IMPORTANT in health and disease. They are likely important in a variety of pediatric diseases, including Pediatric Stroke, Neonatal Pulmonary Hypertension, Bronchopulmonary Dysplasia and Hepatopulmonary Syndrome.

Inducible intrapulmonary shunt pathways maybe parallel vascular networks with NOVEL and CONTRADICTORY regulatory mechanisms and thus challenge our current understanding of lung vascular structure, function and regulation.

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Enthusiastic human subjects

Supernumerary artery with baffle valve

From: Shaw et al JAP 86:2348, 1999