Exercise-induced pulmonary haemorrhage

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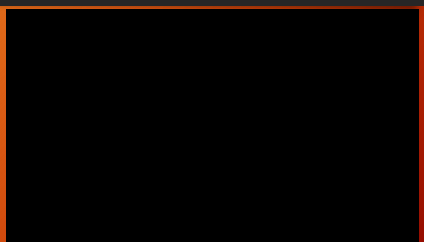
Greenslopes Lung Function

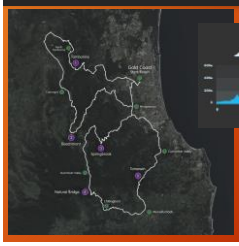
Outline

- Case presentation
- Horses
- Pathophysiology
- EIPH in humans
- Conclusions

Case – Peaks Challenge Gold Coast



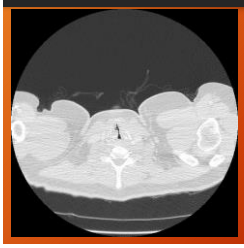
Case – Peaks Challenge Gold Coast

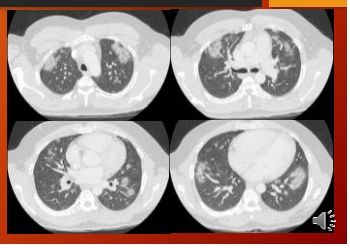


Case – presentation July 2015

- 38 year old male
- Training for 5 months since February 2015
- Intensity increased to >200 km rides
- Symptomatic half way through, while ascending Mt Nebo
- chest tightness and discomfort
- breathlessness with minor wheeze
- higher than expected pulse rate
- cough & small volumes of bright haemoptysis.

Case - CT





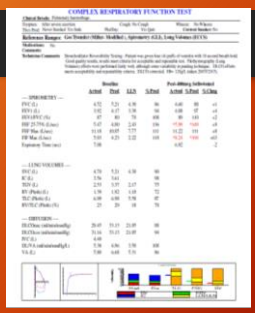
Case

- Symptoms rapidly improved.
- Bronchoscopy – normal.
- BAL:

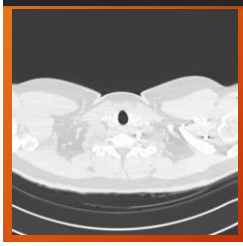
Case

- Symptoms resolved rapidly.
- Chest x-ray showed resolution.
- Echo – normal LV and RV function. Normal RVSP
- Lung function:

Case



Case – May 2016



- Training for Peaks Challenge Gold Coast 2016
- 2nd climb up Mt Nebo

Exercise-induced pulmonary haemorrhage

EIPH

- Well-known entity in racehorses
- Originally reported rate <3%
- Bronchial washes by flexible bronchoscopy showed occurrence >70% of racehorses on at least one occasion after three consecutive races

exercise-induced pulmonary hemorrhage: where are we now? Veterinary Medicine research. David C. Poole

- *Abstract:* As the Thoroughbreds race for the final stretch, 44 hooves flash and thunder creating a cacophony of tortured air and turf. Orchestrated by selective breeding for physiology and biomechanics, expressed as speed, the millennia-old symphony of man and beast reaches its climax. At nearly 73 kilometres per hour (45 mph) over half a ton of flesh and bone dwarfs its limpet-like jockey as, eyes wild and nostrils flaring, their necks stretch for glory. Beneath each resplendent livery-adorned, latherin-splattered coat hides a monstrous heart trilling at 4 beats per second, and each minute, driving over 400 L (105 gallons) of oxygen-rich blood from lungs to muscles. Matching breath to stride frequency, those lungs will inhale 16 L (4 gallons) of air each stride moving >1,000 L/min in and out of each nostril – and yet failing. Engorged with blood and stretched to breaking point, those lungs can no longer redden the arterial blood but leave it dusky and cyanotic. Their exquisitely thin blood-gas barrier, a mere 10.5 μm thick (1/50,000 of an inch), ruptures, and red cells invade the lungs. After the race is won and lost, long after the frenetic crowd has quieted and gone, that blood will clog and inflame the airways. For a few horses, those who bleed extensively, it will overflow their lungs and spray from their nostrils incarnadining the walls of their stall: a horrifically poignant canvas that strikes at horse racing's very core.

EIPH in horses – ventilation

- An elite horse achieving VO2 of 90 L/min with a 3 L dead space and a respiratory rate of 130 breaths per minute, to maintain PaCO2 of 40 mmHg would necessitate ~2,400 L/min ventilation.
- However, horses permit hypercapnia to 60 mmHg, therefore reducing ventilation requirement to 1,700 L/min.
- Peak flow rates of 120 L/min requires very low alveolar negative pressures exceeding -100 cm H2O.

EIPH in horses – circulation

- Mean left atrial pressure as high as 70 mm Hg! Required to deliver the very high cardiac output.
- Left ventricle emptying into an enormous afterload - mean aortic pressure of 240 mm Hg
- Pulmonary artery pressure 120 mm Hg!
  - Despite reduction in pulmonary vascular resistance
  - Due to the high left atrial and therefore pulmonary venous pressures.
- capillary pressure – 100 mm Hg!

EIPH in horses

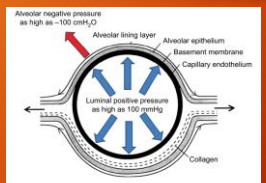


Figure 6 Schematic depicting cross-section of a pulmonary capillary.
Notes: Alveolar negative and capillary luminal positive pressures summate across the perilously thin (0.5 μm total thickness, 50 nm basement membrane thickness) blood-gas barrier. Pressures shown are for maximal exercise in the horse.

EIPH in humans

- Considered rare in humans but perhaps under-recognised.
- Pushing the limits
- Strenuous exercise can be dangerous – hyperthermia, electrolyte imbalances, rhabdomyolysis leading to kidney failure, chest pain, sudden cardiac death, bronchoconstriction, pneumothorax
- Pulmonary oedema and haemoptysis also described.

EIPH in humans

- Pulmonary capillary walls have a dilemma.
- must be extremely thin for efficient gas exchange
- immensely strong to resist the mechanical stresses during heavy exercise.

EIPH - pathophysiology

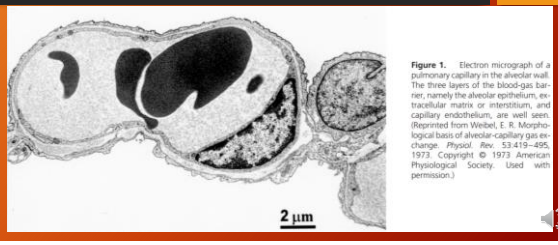


Figure 1. Electron micrograph of a pulmonary capillary in the alveolar wall. The three layers of the blood-gas barrier, namely the alveolar epithelium, extracellular matrix or interstitium, and capillary endothelium, are well seen. (Reprinted from Weibel, E. R. Morphological basis of alveolar-capillary gas exchange. *Physiol. Rev.* 53:419–495, 1973. Copyright © 1973 American Physiological Society. Used with permission.)

EIPH - pathophysiology

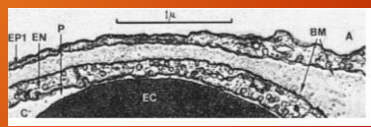


Figure 2. High-power electron micrograph showing the thin portion of the blood-gas barrier. A, alveolar space; EP1, epithelium; BM, basement membrane; EN, endothelium; P, plasma; C, capillary; EC, erythrocyte. (Reprinted from Gehr, P., M. Bachofen, and E. R. Weibel. The normal human lung: Ultrastructure and morphometric estimation of diffusion capacity. *Respir. Physiol.* 32:121–140, 1978. Copyright © 1978 Elsevier. Used with permission.)

EIPH - pathophysiology

Figure 3. High-power electron micrograph showing the blood-gas barrier in the rat. The electron-dense region in the center of the extracellular matrix contains much of the type IV collagen. EP, epithelium; ENDO, endothelium; LRE, lamina rara externa; LD, lamina densa; LRI, lamina rara interna. [Adapted from Vaccaro, C. A., and J. S. Brody. Structural features of alveolar wall basement membrane in the adult rat lung. *J. Cell Biol.* 91:427–437, 1981.]

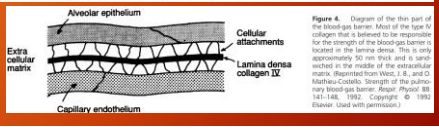


Figure 4. Diagram of the thin part of the blood-gas barrier. Most of the type IV collagen that is believed to be responsible for the strength of the blood-gas barrier is located in the lamina densa. This is only approximately 50 nm thick and is sandwiched in the middle of the extracellular matrix. (Reprinted from West, J. B., and O. Mathieu-Costello. Strength of the pulmonary blood-gas barrier. *Respir. Physiol.* 88:141–148, 1992. Copyright © 1992 Elsevier. Used with permission.)

EIPH - pathophysiology

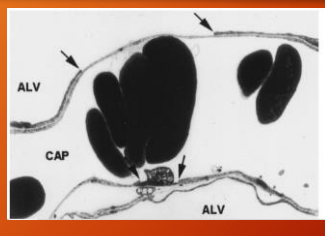


Figure 8. Another example of stress failure showing disruptions of both the alveolar epithelial layer (top) and capillary endothelial layer (bottom). A blood platelet is adhering to the exposed basement membrane below. [Adapted from West, J. B., K. Tsukimoto, O. Mathieu-Costello, and R. Prediletto. Stress failure in pulmonary capillaries. *J. Appl. Physiol.* 70:1731–1742, 1991.]

EIPH - pathophysiology

- BGB strength is from the basement membranes & LD - type IV collagen is an important component.
- Collagens are well known to be some of the strongest soft tissues in the body.
- Ultimate tensile strength of basement membrane approximately 1x10^6 N/m^2, a very high value.

EIPH in humans

- Total area of the blood-gas barrier (BGB) is 50-100 m^2
- For more than half of this enormous area, thickness is only 0.2-0.3 mm – the pulmonary capillary wall.

EIPH in humans

- Early measurements of pulmonary vascular pressures suggested that they did not increase on exercise; this erroneous notion is still cited in some textbooks
- Pulmonary artery wedge pressures up to 30 mm Hg during intense exercise with a mean pulmonary artery pressure as high as 37 mmHg.
- Studies of the pressures in small pulmonary blood vessels in animals by micropuncture have shown that the capillary pressure is about halfway between arterial and venous pressure, and much of the pressure drop occurs in the capillary bed.
- Taking into account of the hydrostatic pressure gradient between midlung and the bottom, the transmural pressure of some of the capillaries is approximately 40 mmHg.
- Using the Laplace relationship and assuming most stress is borne by the thin layer of type IV collagen in the middle of the ECM, the calculated stress approaches the ultimate tensile strength of type IV collagen.

EIPH in humans

- First report of haemoptysis in human athletes published in 1979 - Comrades' Marathon in South Africa - two marathon runners developed dyspnoea, bloodstained frothy sputum, and bilateral pulmonary oedema during a 90-km race
- Haemoptysis and pulmonary oedema was described in eight swimmers taking part in a time trial
- Survey of community triathletes from a national North American triathlon organization: 1.4 % of 1,400 participants reported cough with production of pink, frothy, or bloody secretions during a swim

EIPH in humans

- Hopkins et al. studied six elite cyclists who had a history suggestive of lung bleeding.
- 4 km uphill sprint at maximal effort to give a mean heart rate of 177 beats/min
- Within 1 h of finishing, the volunteers underwent bronchoalveolar lavage. Control group of 8 non-exercising non-athletes.

EIPH in humans

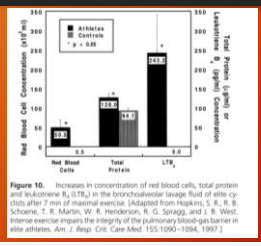


Figure 10. Increases in concentration of red blood cells, total protein and leukotriene B_4 (LTB_4) in the bronchoalveolar lavage fluid of elite cyclists after 7 min of maximal exercise. [Adapted from Hopkins, S. R., R. B. Schoene, T. R. Martin, W. R. Henderson, R. G. Spragg, and J. B. West. Intense exercise impairs the integrity of the pulmonary blood-gas barrier in elite athletes. *Am. J. Resp. Crit. Care Med.* 155:1090–1094, 1997.]

EIPH in humans

- Only absolute maximal wall stresses in pulmonary capillaries will result in ultrastructural changes.
- Study repeated - six elite cyclists exercised at 77% of maximal VO2 for 1 h and then underwent BAL. (controls were eight non-exercised non-athletes).
- Concentrations of red blood cells, total protein, and LTB4 in the BAL fluid were not increased.

EIPH in humans - conclusions

- Due to high transmural capillary pressure (+/- shear stress from lung expansion)
- Occurs only during the most intense exercise when the transmural pressure approaches tensile strength limit of type 4 collagen.
- Does not occur at submaximal exercise.
- Unanswered question – does adaptation of the capillary basement membrane occur in response to exercise training?

Questions?