Exercise-induced pulmonary haemorrhage: risk factors, clinical signs and prevention

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ABSTRACT

An occupational hazard for many horses that perform intensely, exercise-induced pulmonary haemorrhage has huge financial implications for the racing industry, as well as being a serious animal welfare issue. Studies show virtually all racehorses will exhibit it, and a grading system is in place to help vets and owners determine how serious an individual incidence is. The author discusses the clinical signs, impact on performance, pathophysiology, risk factors and preventive strategies for a limiting and potentially serious condition in performance horses

Exercise-induced pulmonary haemorrhage (EIPH) is a performance-limiting condition of racehorses that also affects horses involved in other high-intensity pursuits, such as polo and eventing.

Occasionally, cases occur in horses used for other disciplines, such as showjumping and dressage. EIPH has huge financial implications for the racing industry and presents an animal welfare issue.

The condition is likely to be progressive and horses exhibiting repeated episodes develop permanent pulmonary pathology.

Clinical signs

Figure 1. Epistaxis is a sign of severe EIPH, but the majority of cases go unnoticed unless endoscopy is performed following racing.

Clinical signs are limited to poor performance, stopping during exercise, epistaxis (**Figure 1**) and sudden death during exercise. Subclinical disease is extremely common.

No consensus exists on what constitutes EIPH, but it is most often defined as the presence of visible blood in the trachea on endoscopic examination[1]. However, some horses with no visible blood in the airways on endoscopy will have marked haemorrhage in the more distal airways sufficient to cause red discolouration of tracheal wash (**Figure 2**) or bronchoalveolar lavage fluid (BALF; **Figure 3**), or produce radiodense streaks in the caudodorsal lung fields.

Around 50% to 75% of Thoroughbred racehorses will have visible evidence of haemorrhage on endoscopy performed two hours after racing[2,3] and it has been suggested if every racehorse was scoped after every race, 100% would be considered to be suffering from EIPH. Only 1% to 4% of race-starting horses will develop epistaxis[4].

When post-race cytology of BALF is performed, erythrocytes or haemosiderophages will be identified in virtually all racehorses[5,6], and a level that is diagnostic of EIPH has not been agreed. Pulmonary haemorrhage was judged to have contributed to death in 50 of 143 racehorses examined postmortem in an international study[7], and 60% of racehorse deaths were attributed to pulmonary haemorrhage in a study in Australia[8]. However, cause and effect has not been demonstrated and will be difficult to demonstrate when the majority of horses exhibit a degree of pulmonary haemorrhage during racing.

As virtually all racehorses exhibit pulmonary haemorrhage, the severity of haemorrhage needs to be considered when determining its significance. The following grading system has become accepted[5]:

- **Grade 0**. No blood detected in the pharynx, larynx, trachea or mainstem bronchi viewed from the tracheal bifurcation.
- **Grade 1**. One or more flecks of blood or two or fewer short (less than one quarter the length of the trachea), narrow (less than 10% of the tracheal surface area) streams of blood in the trachea or mainstem bronchi visible from the tracheal bifurcation.
- **Grade 2**. One long stream of blood (greater than half the length of the trachea) or more than two short streams of blood occupying less than a third of the tracheal circumference.
- **Grade 3**. Multiple, distinct streams of blood covering more than a third of the tracheal circumference, with no blood pooling at the thoracic inlet.
- **Grade 4**. Multiple coalescing streams of blood covering more than 90% of the tracheal surface, with blood pooling at the thoracic inlet.

Effects on performance

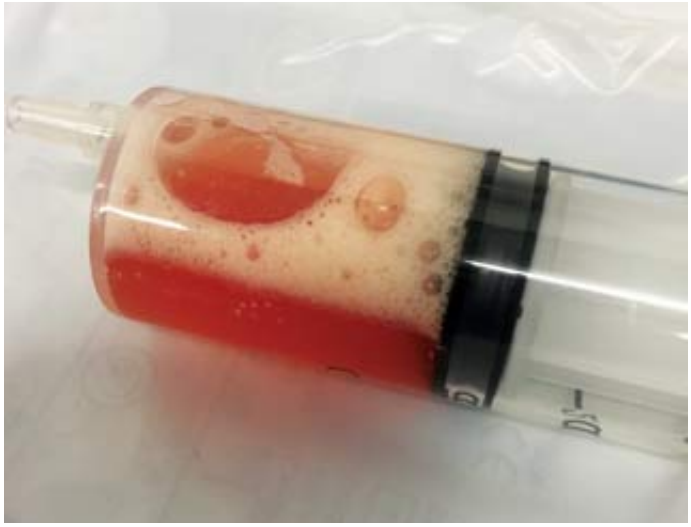

Figure 2. Blood is often visible within the lower airways and may be even more obvious when a tracheal aspirate is collected.

Early investigations of EIPH and performance were low powered, had a variable quality of study design and produced conflicting results. Two more robust prospective studies have been performed in Victoria, Australia[2] and South Africa[9], looking at 744 and 1,000 Thoroughbred flat racehorses, respectively.

In the Australian study, horses with EIPH of grade 2 or greater were four times less likely to win and two times less likely to finish placed in the first three. They also finished significantly further behind the winner than horses that had not bled.

Horses categorised as grade 0 or 1 were three times more likely to be in the top 10% for earnings. In South Africa, horses without EIPH were twice as likely to win, finished an average of one length

ahead of horses with EIPH and were twice as likely to be in the highest 10% for race earnings.

In the Australian study, no association was recorded between a single episode of EIPH of equal or less than grade 3 and earnings, total number of starts, wins, or placings achieved during a horse's career. However, horses with severe (grade 4) EIPH had shorter career duration, lower earnings and fewer starts than horses that had not been diagnosed with EIPH. Epistaxis, another indicator of severe EIPH, has been associated with lower career earnings in Thoroughbreds in the UK[10].

Pathophysiology

It is the current consensus EIPH occurs as a consequence of stress failure of the pulmonary capillaries resulting from excessive pressures across the wall of the capillary. This may be the result of increased, positive blood pressure in the capillary, increased negative pressure in the alveoli or both.

Pulmonary arterial and venous blood pressures will increase three to four fold during strenuous exercise as a result of increased cardiac output. Pulmonary pressures attained during galloping frequently exceed those causing capillary failure in vitro[4] and are highest in the caudodorsal lung lobes where EIPH typically occurs.

A further factor that may increase EIPH risk is veno-occlusive remodelling, which may occur as an adaptation to exercise and/or EIPH and is most pronounced in the caudodorsal lung lobes. Increased collagen deposition and smooth muscle hypertrophy occur in small diameter veins, increasing their strength and stiffness, but reducing their diameter and, hence, increasing their resistance to blood flow[11,12]. This resistance may further increase capillary pressures and increase the risk of capillary failure and subsequent haemorrhage.

Diastolic pressures in the left side of the heart will have a major influence on pulmonary venous and, hence, pulmonary capillary pressures. Therefore, cardiac dysfunction may contribute to the development of EIPH. Paroxysmal atrial fibrillation is the cardiac abnormality most commonly associated with EIPH.

In addition to increasing positive blood pressure within the capillaries, exercise can increase the negative pressure within the alveoli over 10 fold[13]. Partial obstruction of the upper airway results in a further, potentially marked, increase in negative pressure[14], making static and dynamic causes of upper respiratory tract dysfunction potential factors in the development of EIPH.

Despite this theoretical and logical association, horses with recurrent laryngeal paralysis in Hong Kong were no more likely to develop EIPH than matched cohorts prior to surgery; after surgery they were more likely to develop epistaxis[15].

Although lower airway inflammation has been associated with EIPH[16,17] and experimental induction

of inflammation increases severity of EIPH[18], the significance of lower airway inflammation in the development of EIPH remains contentious, and expert opinion remains divided[1]. Airway inflammation has the potential to cause airway narrowing, resulting in more negative alveolar pressures and a greater risk of capillary failure.

When haemorrhage occurs, blood constituents will have pro-inflammatory effects and may cause a spiral of increasing inflammation and haemorrhage.

Instillation of blood into the airways causes a mild inflammatory response for up to two weeks[19]. When blood enters the interstitium, it may promote the development of the fibrotic lesions that typify EIPH.

An association between EIPH and inheritance has been suggested in Thoroughbreds[20,21]. However, the quality of evidence is weak and insufficient to conclude the condition is heritable[1].

No evidence is available to show clotting disorders contribute to the development of EIPH[22].

Risk factors

A number of investigations of EIPH risk factors have been performed in different racing jurisdictions, often with conflicting results[4]. Possible risk factors include:

- greater intensity of exercise
- higher speed of exercise
- racing rather than training exercise
- cumulative racing volume
- age (likely compounded by racing volume)
- steeplechasing/hurdling rather than flat racing
- males (possibly compounded by age and retirement of females)
- ambient temperature of less than 20°C

Prevention

While it has not been the subject of study, rest from racing is likely to be the most effective treatment, albeit an unpopular one. Rest will prevent further bleeding and associated inflammation, haemosiderin accumulation, fibrosis, and remodelling.

Furosemide

Furosemide has been used widely in the treatment of EIPH for more than 40 years, despite its definitive mechanism of action in EIPH being unknown. Furosemide is a loop diuretic that reduces intravascular volume and limits the increase in right atrial pressure, as well as pulmonary arterial,

venous, and capillary pressures. Furosemide also has direct effects within the lungs, as it causes smooth muscle dilation of both pulmonary veins (reducing increases in capillary pressure) and bronchi (reducing negative pressure changes in the alveoli).

The evidence supporting use of furosemide was generally weak and contradictory prior to a placebo-controlled, blinded, crossover study of Thoroughbred racehorses in South Africa[3]. In the trial, 167 horses were raced twice over the same distance one week apart. Each horse received 500mg furosemide IV, four hours before one race, and a saline placebo four hours before the other. After receiving furosemide, horses were less likely to bleed and less likely to bleed severely.

Figure 3. Bronchoalveolar lavage is not performed routinely in racehorses, but will identify haemorrhage that is not observed on endoscopy and tracheal wash alone.

Two-thirds (81 of 120) of the horses that bled after receiving saline bled by at least a grade less after receiving furosemide. A meta-analysis of 11 studies that included a total of 5,653 horses provided further evidence of the effectiveness of furosemide[23]. Furosemide cannot be used in the UK prior to racing and can only be used to reduce the incidence of EIPH during training. The optimal dose and timing of furosemide in relation to exercise has not been determined, but doses

of 0.5mg/kg (“low dose”) to 1mg/kg (“high dose”) are typically used two to four hours before exercise.

Water deprivation is sometimes practised in association with use of furosemide, but cannot be condoned as it compromises welfare and is potentially damaging to the public perception of racing.

Vasodilators

Vasodilatory drugs, including phosphodiesterase inhibitors (for example, pentoxifylline or sildenafil), angiotensin-converting enzyme inhibitors (like enalapril), alpha-2-adrenergic agonists (such as clonidine), and nitric oxide analogues have not been demonstrated to be effective in reducing the development of EIPH[24-26].

Procoagulants

Drugs such as aminocaproic acid, oestrogens, aspirin, bioflavonoids and vitamin C, which inhibit fibrinolysis and, therefore, promote clot formation, are ineffective[27-29], as clotting disorders are not a feature of EIPH.

Nasal strips

External nasal strips are designed to limit the collapse of the upper airways, increasing air flow and limiting the development of negative pressure within the terminal airways. Evidence pertaining to their effects is mixed, and further higher-quality field trials are needed. Some investigations of their use have reported a reduction in the number of erythrocytes in BALF, while others have failed to identify a difference in endoscopic findings[30-32].

Nasal strips are not permitted under the rules of racing, but are permitted under the rules of the Fédération Equestre Internationale.

Anti-inflammatories

Lower airway inflammation may be a factor in the development of EIPH, so its investigation and treatment is logical, but has not been evaluated critically.

Cytological assessment of BALF provides a more sensitive and reliable means of assessing lower airway inflammation than cytology performed on tracheal aspirates, but is not popular in horses in training.

If evidence of lower airway inflammation is identified on either tracheal wash or BALF cytology, or on the gross appearance of the airways, it should be treated with inhaled or systemic glucocorticoids. Air hygiene will be central to the management of lower airway inflammation.

Conclusion

EIPH is an occupational hazard for horses performing intense exercise. It is associated with poor performance, prematurely terminates racing careers and presents a huge cost to the racing industry.

Furosemide is an effective preventive measure in some horses, but cannot be used prior to racing in the UK. No effective alternatives exist. Factors that may contribute to the development of EIPH, for example, cardiac arrhythmias, dynamic collapse of the upper airway and lower airway inflammation, should be investigated and treated or managed where possible.

Rest from high-intensity exercise is likely to reduce the risk of recurrence and progression.

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