EQUINE PRACTICE – MEDICINE

This paper reviews recent progress in the etiology and pathology of exercise-induced pulmonary hemorrhage (EIPH), a condition which poses an important cause of financial loss to the equine industry. It is hypothesized that all horses experience some grade of EIPH during strenuous exercise. In light of the inflammatory response in lung tissue following infusion of autologous blood and the chronic nature of EIPH in racing horses, every effort should be made to eliminate EIPH during exercise and to ameliorate the inflammatory response once hemorrhage has occurred.

Exercise-Induced Pulmonary Hemorrhage: A Review of the Etiology and Pathogenesis

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Introduction

Exercise-induced pulmonary hemorrhage (EIPH) occurs commonly in performance horses and is an important cause of financial loss to the equine industry. Although the condition has been reported in horses for over 200 years, it has been only within the past 20 years that the source of the bleeding has been documented. This paper reviews recent progress in the etiology and pathology of EIPH. Criteria for classifying the different grades of severity of the syndrome are also offered.

Etiology

During the past 20 years, several theories have been proposed about the etiology of EIPH. In 1974, Cook[1] suggested that hemorrhage from healthy lung was unlikely and that EIPH occurred in horses with chronic lung disease, possibly bronchospasm linked with the early stages of chronic bronchitis and pulmonary emphysema.

In 1980, Robinson and Derksen[2] hypothesized that pulmonary hemorrhage resulted from increased distending forces applied to lung regions not ventilated homogeneously with the rest of the lung. Because lung segments with impeded airways move asynchronously with adjacent lung tissue ventilated normally, this hypothesis was not incompatible with that of Cook.[1] Inelastic scar tissue within the lung parenchyma or pleural adhesions from previous bleeding episodes would be especially susceptible to the accentuated distending forces.

In 1987, O'Callaghan and associates[3] described an increase in bronchial artery circulation in pulmonary areas with evidence of previous EIPH episodes. They proposed that the source of subsequent hemorrhage was the fragile bronchial capillary buds

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in inflamed peribronchial connective tissue and alveolar septa.

Exercise-induced coagulopathies have been proposed to cause EIPH. Reduced platelet adhesiveness and acceleration of thrombin formation with no evidence of fibrinolysis have been reported in exercising horses.[4] One study showed no difference between the clotting profiles of EIPH-positive and normal horses.[5] However, a later study reported that platelet adhesiveness may decrease more in EIPH-positive horses than in non-bleeders following exercise.[6]

A more recent hypothesis proposed by Cook and associates[7] contends that partial respiratory tract obstruction due to recurrent laryngeal neuropathy (RLN) causes EIPH. With upper airway obstruction, a greater negative pressure than normal is created during inspiration. This, along with the presence of pulmonary hypertension during intense exercise, increases the pressure gradient across the alveolar-capillary membrane, resulting in hemorrhage of the alveolar walls.

More recent work by West and associates[8] has persuasively shown that the first step in EIPH is stress failure (microrupture) of the pulmonary capillaries, with RBCs initially entering the interalveolar spaces. The pathological significance of this step is unclear, but evidence suggests that some components in blood are very inflammatory to the alveolar tissue.[9]

The most subtle clinical evidence for EIPH is the presence of hemosiderophages in tracheal washes. Virtually 100% of horses in training show hemosiderophages in their tracheal washes,[10] confirming earlier suspicions that all strenuously exercised horses suffer some degree of lung hemorrhage.

High Blood Pressure and Stress Failure of Pulmonary Capillaries in EIPH

West and associates[8] have recently applied their research on stress failure of pulmonary capillaries (SFPC) in the human lung to the problem of EIPH in horses. The alveolar-capillary membrane is composed of the capillary endothelium, the interstitium, and the alveolar epithelium. The mechanical strength of the alveolar-capillary membrane comes from the Type IV collagen in the interstitium, which is composed of the basement membranes of the capillary endothelial and alveolar epithelial cells.

With electron microscopy, Birks and associates[11] demonstrated an extremely thin (0.535 μm) alveolar-capillary membrane in rabbit lung. At high pulmonary blood pressures, the capillaries bulged into the alveolar spaces. When transmural pressure (capillary pressure minus alveolar pressure) exceeded 40 mmHg, disruption of the pulmonary-capillary wall was observed in rabbits.[12]

In contrast, dogs have a thicker alveolar-capillary membrane (μm 0.759), and transmural pressures in excess of 68 mmHg were required to rupture the membrane.[13] Interestingly, the mean alveolar-capillary membrane thickness of horses is about 0.930 μm. In all species examined, the alveolar-capillary membrane is not uniform in thickness but consists of thin and thick portions. The thinnest walls would have the highest stresses and the greatest probability for failure. The pressure at which SFPC occurs in horses has not been determined. Failure occurs acutely when the pulmonary blood pressure is maximal, typically during intense exercise. Conservative estimates have placed pulmonary capillary pressure in horses during maximal exercise at about 95 mmHg,[14] well above the maximal pressures that can be sustained in rabbit or dog lung without creating stress failure.[12,13] During failure, ruptures appear in the endothelial lining of the pulmonary capillaries, and RBCs escape into the interstitium and alveoli.

However, this theory does not explain the fact that chronic, end-stage EIPH is confined to the dorsocaudal portions of the lung. Because of hydrostatic forces, the greatest intravascular pressures are expected in the ventral portions of the lung. Therefore, EIPH lesions would be expected in the more dependent lung regions. However, one study reported especially high blood flow to the dorsocaudal lung regions.[15] Furthermore, the important pressure measurement is not intracapillary pressure but transmural pressure. Transmural pressure may actually be higher in the dorsocaudal portion of the lung, since alveolar tissue may be squeezed between the diaphragm and lumbar muscle area during strenuous exercise. Furthermore, the dorsal alveoli are probably larger than alveoli in more dependent areas of the lung, and increasing the volume of the alveoli increases the frequency of stress failure in pulmonary capillaries.[16]

It is important to note that the horse is unique among athletic animals in its tendency to become hypoxemic during intense exercise. Even other members of the species (e.g., ponies) maintain normoxia during maximal exercise.[17] The irony concerning the equine alveolar-capillary membrane is that it is too thick to allow adequate gas exchange (physiologically, this limitation is exhibited by arterial hypoxemia during intense exercise) and too thin to protect against the high pul-

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monary capillary pressures generated during intense exercise (thus, the occurrence of EIPH). It appears that the cardiopulmonary vascular system of the racehorse approaches or has reached the physiologic limitations of mammalian systems.

Levels of EIPH

In previous literature about this disease, horses are usually labeled "EIPH-positive" or "EIPH-negative". In light of studies that suggest all racehorses in training have previous evidence of EIPH using BAL[10] and studies that have measured very high pulmonary capillary pressures in exercising horses,[18,19] there may not be any racing horses that are EIPH-negative. If "EIPH-negative" is an inaccurate label for horses, then previous studies that measured the effects of furosemide on EIPH and performance must be evaluated from a different perspective.

We view EIPH as a condition present in all horses subjected to exercise above the level of introductory training. There appear to be at least five separate levels that can be identified based on the location and severity of the pulmonary hemorrhage.

LEVEL 1

Simple rupture of capillary endothelium allows RBCs to escape into the interstitial tissue, but there is no significant loss of cells into the pulmonary alveoli.

LEVEL 2

Rupture of both capillary endothelium and alveolar epithelium allows escape of RBCs into interstitial tissue and alveoli. Following this severity of hemorrhage, hemosiderophages will be present in the fluid of subsequent BALs. Because the amount of blood released into the alveoli may be inadequate to reach the trachea, no endoscopic evidence of EIPH is detectable in Levels 1 and 2 of the disease. Presumably, horses experiencing only Level 1 or 2 of EIPH would be classified EIPH-negative following endoscopic examination.

LEVEL 3

In Level 3 of EIPH, the amount of blood flowing into the alveoli is sufficient to ascend into the trachea and be visualized with endoscopy (Fig. 1).

LEVEL 4 (EPISTAXIS)

Epistaxis occurs in 1 to 2% of racehorses and is evidence of hemorrhage severe enough to be expelled from the nares. Figure 2 is a photograph of epistaxis in a Thoroughbred shortly after finishing a race.

LEVEL 5 (DEATH)

Figure 3 shows the lungs from a horse that experienced Level 5 of EIPH during a race. The horse collapsed 400 meters out of the gate (Fig. 4), fractured C-2 and C-3 of the cervical vertebrae compressing the spinal cord (Fig. 5) as it hit the ground, and died immediately on the track. At necropsy, the entire respiratory passages (nasal cavity, trachea, and bronchi) were filled with bloody froth. The lungs were deep red to black, heavy, and firm, consistent with being blood-filled. Histopathology revealed widespread areas of hemorrhage with bleeding into alveoli, bronchioles, and bronchi. Adjoining alveoli contained erythrocytes and hemosiderin pigment, suggesting previous bleeding episodes. Death was attributed to acute pulmonary hemorrhage.

Although the progression of severity through Level 1 to Level 5 is logical, one study[20] reported that some horses died from EIPH without evidence of epistaxis. At necropsy, those horses exhibited bloody froth in the trachea; however, no blood was evident in the nares.

This five level description of EIPH integrates our knowledge of its epidemiology and pathogenesis and clearly establishes this condition as a continuum. At its least intrusive, this condition occurs in all horses in training and racing; at its most dramatic, it can result in collapse and sudden death of horses early in a race.

While Level 1 is currently not clinically distinguishable from Level 2, the singular event of this level (escape of blood into interstitial tissue) may, ultimately, be the most significant occurrence of EIPH, since it has the greatest potential to produce cumulative pathological changes. It is likely that red blood cells extravasated into the interstitium are cleared via lymphatic drainage, thereby leaving no suggestion (such as hemosiderophages) of past damage. It is also likely that the presence of hemoglobin in the interstitial tissue is more of an irritant than the presence of red cells in the alveolar sinus. Since simple infusion of autologous blood causes definite pathological changes,[21] it seems likely that Level 1 EIPH, possibly associated with minimal clinical signs, could ultimately be a very significant source of long-term pathological changes.

At the other end of the EIPH spectrum, the potential impact of Level 5 events on racing must also

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FIG. 1 — Endoscope view of blood-tinged trachea in a horse following a race. Courtesy of John R. Pascoe, University of California, Davis, California.

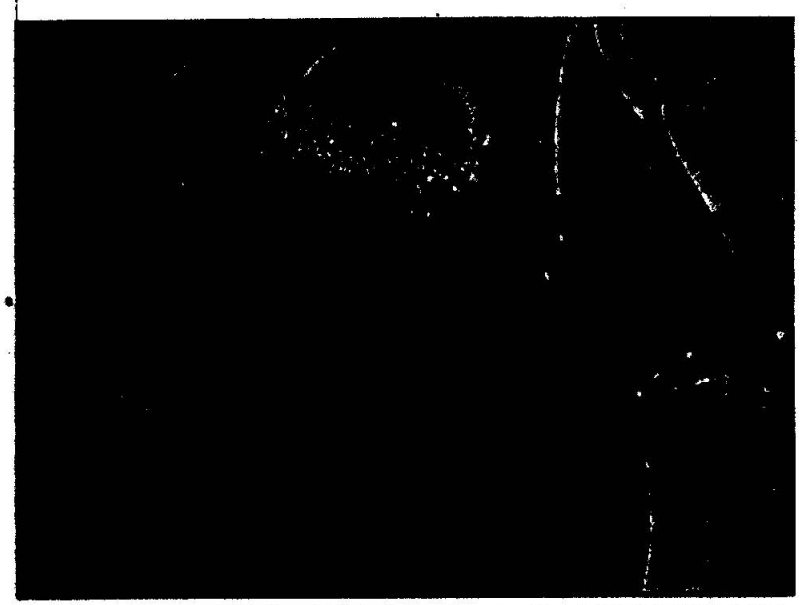

FIG. 2 — Epistaxis in a Thoroughbred after finishing a race. Courtesy of Richard H. Galley, Willow Park, Texas.

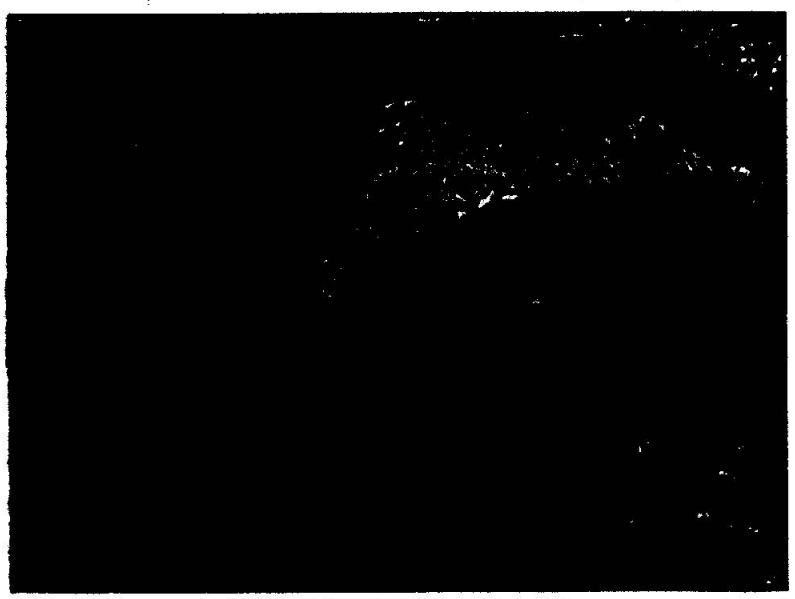

FIG. 3 — Blood-filled lungs from a horse that experienced Level 5 of EIPH during a race.

FIG. 4 — Longitudinal fracture of C-2 and fracture of cranial portion of C-3 compressing spinal cord.

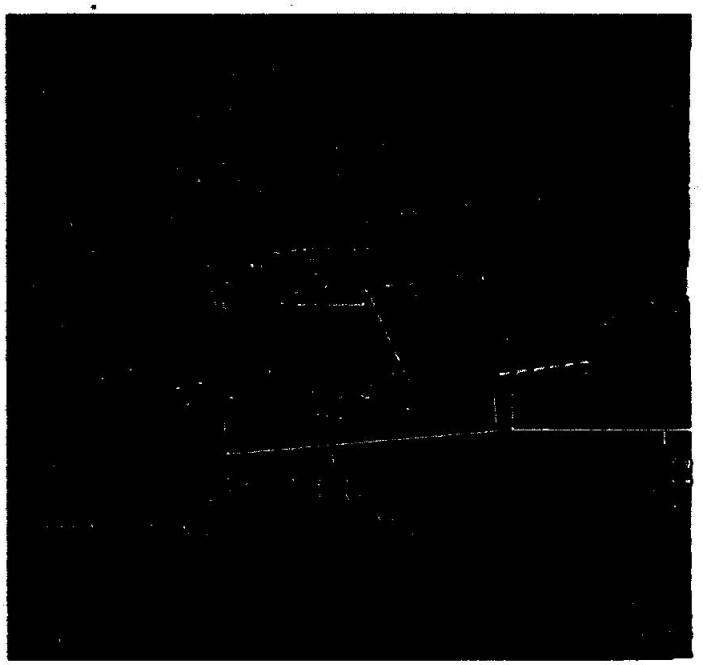

FIG. 5 — Severe discoloration of ~80% of dorsocaudal section of lung. The affected area contains dark blue staining with brown staining and irregular areas of trapped air around the margins. Reproduced with permission from O'Callaghan and associates.[3]

be understood. Massive hemorrhage into the lungs of a racing horse can lead to acute asphyxiation on the track, either during the race or very soon after the completion of the race. The impact of this spectacle is significant on the racing public, and this event needs to be recognized as one sequelae of the EIPH continuum.

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Pathology of EIPH

The first study of EIPH in a large number (813) of Thoroughbreds was from horses racing in Hong Kong and has generated several papers on this topic. Mason and associates[22] performed postmortem examinations on 26 of these horses and reported that 96% of the lungs exhibited bronchiolitis and gross lesions indicative of previous pulmonary hemorrhage.

In another paper from the Hong Kong study, O'Callaghan and associates[3] described the lung pathology in Thoroughbred racehorses of known EIPH status. The most consistent gross finding was a variable amount of dark blue, blue/grey, or blue/brown subpleural staining of lung parenchyma. The lesions were bilaterally symmetrical and typically confined to the dorsocaudal extremities of the lung. In more severely affected animals, the lesions extended cranially along the dorsal surface of the lung. The bilateral symmetry and lesion distribution indicated horizontal spread to other dorsal bronchopulmonary segments rather than proximal extension of a lesion from its distal origin. In contrast, axial spread along an affected bronchus or artery would create lesions on the ventral portion of the lung as well, which was not the case.

In more severely affected lungs, lesions covered 30 to 50% of the lung surface. Stained areas were firmer, with a spleen-like consistency and did not collapse to the same degree as did the normal lung tissue. Similarly, stained areas of the lung did not readily inflate. Another classic finding was the increased bronchial artery circulation in the discolored areas of the lung. In the most severely affected areas, there was extreme vascular hypertrophy of the bronchial arteries.

The effects of furosemide on performance and the aesthetics of horses bleeding during a race have received much attention. However, little concern has been focused on the pathology occurring in lung tissue and the effect of that pathology on future performance. Following disruption of the alveolar-capillary membrane, all of the components of blood enter the pulmonary interstitium and alveoli. Disruption of endothelial cells exposes the endothelial basement membrane, which permits the products of coagulation to accumulate in the injured tissue. This causes microthrombi and impaired microcirculation. As healing occurs, mononuclear phagocytes and mesenchymal cells (immature fibroblasts that can develop into a variety of mature cell types) enter the alveolar tissue. Repair of the interstitium also includes restoration of the extracellular matrix, with the replication of fibroblasts and the deposition of connective tissues in an ordered fashion.[9]

This fibroproliferative response is the same response that prevents surface wounds from becoming life-threatening. A fibroproliferative response to a cut in the skin is appropriate and necessary to restore the barrier between the organism and an inhospitable environment. However, the same response in the lung causes formation of scar tissue that interferes with expansion and contraction of the lungs and impedes gas exchange. In human patients that have experienced maladaptive repair of lung tissue following injury, hypoxemia is a common sequelae.[9] The hypoxemia seen in exercising horses may be initiated or worsened by sequential pulmonary fibrosis from multiple episodes of EIPH.

To better understand the effects of bleeding on lung tissue, Tyler and associates[21] infused single and multiple (5 times at 7-day intervals) doses of autologous blood and saline into specific airways of 11 horses. Reactions to infused blood varied from very mild to severe, with the lesions from multiple infusions being more severe than from single infusions, suggesting EIPH may have a cumulative effect on lung tissue. Although the lesions created in this study were less severe than those seen with naturally occurring EIPH, many similarities were observed including the presence of hemosiderophages in tissues and airspaces, bronchiolitis, and increased connective tissue.

The reduced severity of lesions seen after infusion of blood in comparison with end-stage EIPH is not surprising. If some level of EIPH occurs each time a horse is exercised strenuously, the number of hemorrhagic insults to the lung will be much greater than the number of infusions (maximum = 5 infusions) performed in these experiments. Because naturally occurring EIPH is also accompanied by membrane damage and blood components trapped in interstitial pulmonary tissue, the lesions associated with the naturally occurring disease would be more severe than those created by infusing autologous blood, which was deposited only in the alveoli.

It was concluded that bronchiolitis and increased connective tissue are sequelae rather than antecedents of the pulmonary hemorrhage seen in EIPH. Since strenuous exercise frequently causes bleeding into the lung tissue, pulmonary scarring and loss of function are likely to be common sequelae of strenuous exercise in horses.

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Surprisingly, there was also a marked reaction of lung tissue to multiple saline infusions characterized by bronchiolitis, increased formation of connective tissue, and loss of function. This suggests that even simple bronchiolar lavage carries a significant cost in terms of pulmonary function — a cost which must be weighed against the benefits of lavage as a diagnostic or therapeutic procedure.

Therefore, the pulmonary healing process appears to be a double-edged sword. Although the fibroproliferative response is required to repair lung injury, the response can also obliterate alveolar air spaces, increase alveolar-capillary membrane thickness, and reduce elasticity of alveolar tissue. All of these sequelae impair gas exchange, a critical and limiting factor in the performance horse.

Summary

Exercise-induced pulmonary hemorrhage (EIPH) was observed in the earliest Thoroughbreds and occurs worldwide in all breeds. During exercise, Thoroughbreds develop exceptionally high pulmonary blood pressures leading to stress failure of pulmonary capillaries. Stress failure of the capillary endothelium allows blood into the pulmonary interstitial tissue, the simplest microscopically identifiable lesion (Level 1) of EIPH.

Failure of the entire capillary-alveolar structure releases blood into the alveolar spaces (Level 2 of EIPH) causing the formation of hemosiderophages, the most subtle clinical sign of EIPH reported to date. All horses in strenuous training show hemosiderophages, suggesting that all race horses experience some grade of EIPH (Fig. 6). More severe hemorrhage results in the appearance of blood in the trachea (Grade 3 EIPH). Most racing horses attain this grade of EIPH if repeatedly exposed to intense exercise. A small proportion (1 to 2%) bleed from the external nares (Grade 4 EIPH), which is the classic "bleeder". Finally, a very small proportion of horses (approximately 0.067%) die acutely during a race or post-race from severe pulmonary failure (Grade 5 EIPH).

EIPH lesions are chronic and cumulative and include hemosiderophages, marked bronchiolitis, vascular hypertrophy, and increased bronchial artery circulation. Multiple infusion of autologous blood into the lungs of horses created lesions similar to but less severe than naturally occurring EIPH lesions. Sequelae of blood in the alveolar tissue includes bronchiolitis, increased connective tissue, loss of function, and neovascularization which may precipitate subsequent episodes of EIPH. It is hypothesized that all horses experience some grade of EIPH during strenuous exercise. In light of the inflammatory response in lung tissue following infusion of autologous blood and the chronic nature of EIPH in racing horses, every effort should be made to eliminate EIPH during exercise and to ameliorate the inflammatory response once hemorrhage has occurred. ■

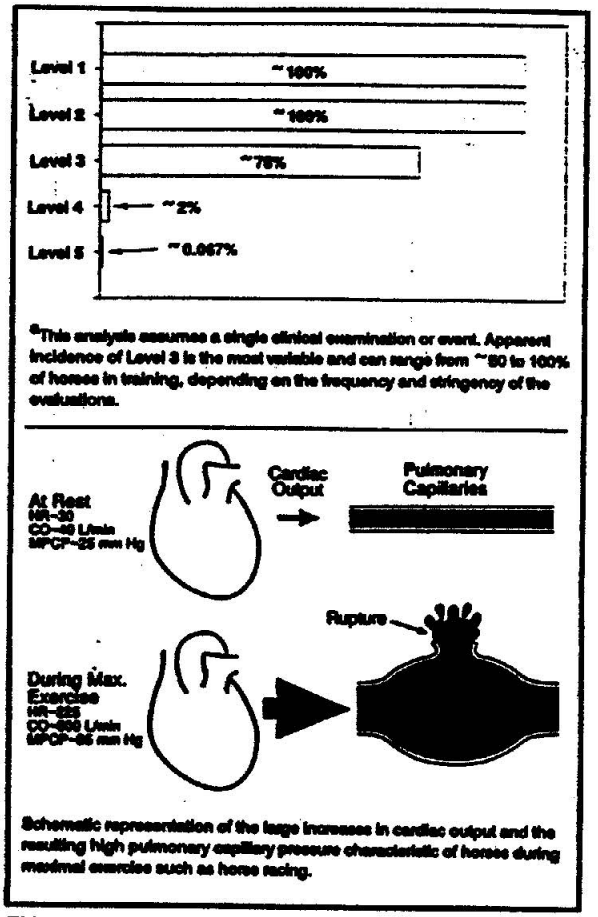

FIG. 6 — Apparent incidence of EIPH in training and racing horses.[a] HR = heart rate, CO = cardiac output, MPCP = mean pulmonary capillary pressure.

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