Abstract: While airway endoscopy and bronchoalveolar lavage are the methods of choice for diagnosing exercise-induced pulmonary hemorrhage (EIPH), these techniques do not allow accurate evaluation of the severity of bleeding. EIPH pathology is characterized by occlusive remodeling of pulmonary veins. Affected veins have large collagen deposits in their walls, which reduces their lumens. In the caudodorsal regions, pulmonary vein wall remodeling is associated with hemosiderin accumulation, bronchial circulation angiogenesis, and fibrosis of the alveolar interstitium, bronchovascular bundle, septa, and pleura. During exercise, venous occlusion increases regional pulmonary capillary pressure, likely causing capillary rupture and resulting in bleeding.

The relationship between strenuous exercise and bleeding in horses has been recognized since at least the early 18th century. For example, the brother of Flying Childers, one of the founding stallions of the Thoroughbred breed, was given the ignominious name Bleeding Childers because of his propensity to bleed from the nose after exercise. The source of this blood remained a mystery until the 20th century, when Cook used a rigid endoscope to inspect the nasal airways for the source of blood. Partly because Cook did not find the source of blood in the nose, he hypothesized that epistaxis after exercise originated in the lungs. By 1981, the flexible fiberoptic endoscope had become more widely available. Using this new technology, Pascoe et al reported that blood was present in the tracheas of 44% of Thoroughbreds after racing. From this study, it was concluded that the bleeding originated in the lungs, and the term exercise-induced pulmonary hemorrhage (EIPH) was coined. Subsequent studies have confirmed the prevalence of EIPH in Thoroughbreds after racing to be 47% to 75%. EIPH is not restricted to Standardbreds and Thoroughbreds; it also occurs in other breeds that perform strenuously, such as racing Quarter horses, polo ponies, and 3-day event horses. Most studies have indicated that the prevalence of EIPH increases with a horse's age. One study suggested that time in training, rather than age, correlated with EIPH. The increased incidence of EIPH associated with time in training suggests that repeated episodes of hemorrhage result in progressive pulmonary damage.

Diagnosis
Examination of the upper airway and trachea using a fiberoptic endoscope has been the method of choice for diagnosing EIPH. In general, the upper and lower respiratory tracts of horses are endoscopically evaluated within 2 hours after exercise. Investigators have attempted to quantify the degree of hemorrhage based on the amount of blood in the trachea, which can range from a few flecks of blood to multiple coalescing streams of blood covering more than 90% of the tracheal wall. This scoring system is useful, but it is not ideal because the amount of blood in the trachea after racing varies in individual horses. Thus, a single examination of an individual horse after exercise may be misleading because a horse may seem unaffected by EIPH after a specific race but may have severe EIPH after subsequent races. However, it is possible that the amount of bleeding in the lungs is consistent from race to race but that the blood is not mobilized consistently into the trachea. Thus, multiple examinations after exercise are required to fully determine the status of individual horses with EIPH. Multiple examinations are also useful because horses with severe EIPH bleed more frequently.
Other studies have used BAL to diagnose EIPH. This technique is quantitative and more sensitive than tracheal endoscopy because red blood cells (RBCs) can be detected in BAL fluid without endoscopic evidence of blood in the trachea. However, this method only samples a small portion of one lung, and the location of bleeding may be remote from the site sampled. The location of bleeding probably also varies in individual horses and from race to race. Therefore, it is no surprise that the RBC counts in BAL fluid collected from the right and left lungs of individual horses differ significantly. Further, the technique is too invasive for routine clinical use. A survey of racehorses in training found that 73% of BAL samples had evidence of free RBCs and 90% of samples had hemosiderophages. Hemosiderophages offer evidence of EIPH and can be detected in the tracheal wash fluid of virtually all vigorously exercised horses that are examined repeatedly. The presence of hemosiderophages in BAL fluid does not accurately predict when hemorrhage occurred, as hemosiderophages are cleared slowly and found in BAL fluid of horses for at least 5 weeks after exercise.

Effects on Pulmonary Function and Performance
Changes in pulmonary function caused by EIPH can be demonstrated by ventilation and perfusion imaging of lung fields using radioactive nucleotides. In a study of five horses with confirmed EIPH, radiographic opacities in the caudodorsal lung field correlated with regions of ventilation/perfusion mismatch. Therefore, it is not surprising that EIPH affects performance. In a large study of Thoroughbreds, Hinchcliff et al documented that even modest EIPH affects performance. Horses were graded on a scale from 0 (unaffected) to 4 (most severely affected). There was a significant association between the presence of grade ≥2 EIPH and (1) lower odds of winning or finishing in the first three positions, (2) finishing a longer distance behind the winner, and (3) a lower likelihood of being in the 90th percentile or higher for race earnings.

Pulmonary Pathology
Studies of the pathology of equine EIPH, while not numerous, have been important in the evolution of understanding the pathogenesis of this disease. The first extensive investigation of the gross and histologic features of EIPH was performed more than 20 years ago. The investigators described the clinical features of 26 horses with EIPH and the pathologic lesions of 19 of them. The reported gross lesions included bilateral, symmetric dark discoloration of the pleura of the caudodorsal lung (Figure 1), with the underlying lung tissue described as firmer than normal lung tissue. Histologically, the primary findings were described as scattered bronchiolitis, hemosiderophage accumulation, fibrosis, and angiogenesis. Based on this study, it was suggested that EIPH results from bronchiolitis, with the bleeding arising from bronchial circulation proliferation in response to chronic airway inflammation. In a 1993 study on the ultrastructure of alveoli in horses with EIPH, West et al detected tears in the alveolar capillary wall. This study involving three horses has been the basis for the most widely mentioned hypothesis for the pathogenesis of EIPH, namely that exercise-induced alveolar capillary hypertension results in capillary wall stress failure. However, the reported histologic lesions of EIPH suggest that the pathogenesis is more complex than simple capillary wall tearing.

The Role of Pulmonary Veins
In another article, we confirmed the caudodorsal lung's predilection for lesion development in EIPH. In the study, we identified a constellation of histologic findings (i.e., hemosiderin accumulation, interstitial fibrosis, pleural and septal fibrosis, foci of angiogenesis that occur together with a previously unrecognized pulmonary venous lesion) that may
have important implications in the pathogenesis of EIPH. The most dramatic of these venous changes is regional veno-occlusive remodeling of small branches of intrapulmonary veins (FIGURE 2). Affected veins have large collagen deposits in their walls, causing thickening of the vein wall and reduction of the venous lumen. In the caudodorsal regions, where lesions are more severe, pulmonary vein wall remodeling is associated with hemosiderin accumulation, bronchial vasculature angiogenesis, and fibrosis of the alveolar interstitium, bronchovascular bundle, septa, and pleura. The lesions in these regions are far more severe than previously reported. While collagen accumulation around pulmonary veins can occur alone, significant hemosiderin accumulation, angiogenesis, and fibrosis of pulmonary structures do not occur without coincident venous remodeling. The spatial association between hemosiderin accumulation and characteristic lesions of EIPH suggests that bleeding during exercise arises from foci centered around venous remodeling. All of the studies of the pathology of EIPH involved severely affected horses, and results should be cautiously extrapolated to mildly affected horses.

**Venous Hypertension and Vein Wall Remodeling**

What could cause such marked venous remodeling in horses with EIPH? Veins are thin-walled vessels designed to function as low-pressure, high-volume conduits for blood flow. Experimentally, high venous pressure, even for short periods of time, elicits remodeling of the vessel wall.23 This remodeling is important for preventing catastrophic rupture. Racehorses train and race frequently, and, in strenuously exercising horses, pulmonary veins are subjected to pressures as high as 80 mm Hg.24 (In horses, normal venous pressure at rest is about 20 mm Hg; in other species, the increase in pulmonary vascular pressure with exercise is much smaller—often less than half that in horses.) These data suggest that repeated bouts of high pulmonary venous pressure in strenuously exercising horses might be responsible for the vein wall fibrosis and remodeling observed in these studies.

**FIGURE 3** presents a diagram of our proposed pathogenesis of EIPH. First, high-intensity exercise results in high pulmonary vascular pressure. In exercising horses, pulmonary blood flow is preferentially distributed to the caudodorsal lung regions; therefore, it is possible that pulmonary venous pressure is particularly high in these regions. Repeated bouts of high vascular pressure result in pulmonary vein wall remodeling, including collagen deposition in the vein wall. This remodeling causes narrowing of the venous lumen as well as regional venous occlusion. During exercise, venous occlusion results in regionally severe increases in pulmonary capillary pressure, capillary rupture, and bleeding. The bleeding causes deposition of blood in the alveoli and pulmonary interstitium, a local influx of macrophages, and conversion of RBCs to hemosiderin by the macrophages. Hemosiderin accumulation in tissues, rather than only being present in the airway,26 causes fibrosis in the interstitium, septa, and pleura. This also results in bronchial vasculature angiogenesis, which may exacerbate bleeding during exercise. Lastly, regional venous occlusion in the caudodorsal region results in diversion of blood flow to other lung regions and extension of the EIPH lesion in a cranial direction.

If this proposed pathogenesis is correct, it could greatly affect how EIPH is managed, helping to reduce its incidence or even preventing it altogether. For example, confirming a pivotal role for pulmonary vein remodeling in the pathogenesis of EIPH should lead to new research on venodilators. Preliminary data from another laboratory suggest that venodilators significantly reduce the severity of EIPH.27 A better understanding of the pathobiology of EIPH may help researchers devise strategies to reduce the associated severity of bleeding and chronic pulmonary effects.

**Treatment**

When evaluating the effectiveness of a treatment for EIPH, clinicians should be mindful of the limitations of the diagnostic techniques.
Box 1. Proposed Treatments for Exercise-Induced Pulmonary Hemorrhage

Some evidence of effectiveness in reducing EIPH (referenced articles)
- Furosemide
- Nasal strips
- Phosphodiesterase inhibitors (E4021)
- Concentrated equine serum
- Omega-3 fatty acids

No evidence of effectiveness
- Rest (not studied, but often tried)
- Aminocaproic acid
- Hesperidin bioflavonoids
- Citrus bioflavonoids
- ET-1 antagonists
- Bronchodilators (clenbuterol)
- Air quality (bedding)
- Water vapor
- Pentoxifylline
- Nitric oxide (may increase EIPH)

(i.e., tracheal endoscopy, BAL) and should not be surprised by variability in study results.

In North America, furosemide is the most popular drug for treating EIPH. Several studies have demonstrated that furosemide decreases the amount of bleeding. However, furosemide does not stop bleeding, and, in many treated horses, blood is still observed in the trachea after high-intensity exercise. The drug decreases pulmonary vascular pressure (probably partly by decreasing plasma volume and partly by venodilation) in horses exercising on a high-speed treadmill, so this is probably the mechanism by which the drug exerts its effect.

In addition, furosemide likely enhances the performance of horses independent of its effect on pulmonary hemorrhage. The drug’s diuretic effect causes horses to lose a significant volume of water, weigh less, and therefore race faster.

A nasal dilator device (nasal strip) has become popular. The nasal strip dilates the nose and reduces upper airway resistance. The nasal strip also diminishes EIPH, probably by reducing inspiratory pressure in the alveoli. Reduction of this pressure during exercise reduces the pressure difference across the pulmonary capillary wall (pulmonary capillary pressure minus alveolar pressure); therefore, the capillaries are less likely to rupture. Because the device has no adverse effects, it is likely to prove useful in a multipronged approach to preventing EIPH. BOX 1 summarizes the proposed treatments for EIPH.

In the future, therapeutic regimens may significantly decrease vascular pressure in exercising horses, particularly in pulmonary veins. This would reduce inward remodeling and scarring of pulmonary veins and reduce venous obstruction. Further, pharmacologic intervention may ameliorate the interstitial fibrosis characteristic of the EIPH lesion.

References

23. Johnson JE, Perkett EA, Meyrick B. Pulmonary veins and bronchial vessels undergo...


1. Which statement regarding EIPH is correct?
   a. Only severe EIPH (grade 4/4) significantly affects performance in racing Thoroughbreds.
   b. It is widely accepted that increasing age is not associated with increased prevalence of EIPH.
   c. With multiple (three) endoscopic evaluations, the reported postrace prevalence of EIPH in racehorses is 100% on at least one evaluation.
   d. EIPH is exclusive to typical racehorse breeds, namely the Thoroughbred and Standardbred.

2. The method of choice for evaluating EIPH in racehorses is
   a. endoscopic evaluation of a horse's trachea within 2 hours after racing.
   b. examination of BAL fluid.
   c. quantification of epistaxis.
   d. complete blood count and quantification of anemia.

3. Which statement regarding BAL and EIPH is true?
   a. BAL always yields similar numbers of RBCs from the left and right lungs.
   b. The presence of hemosiderophages in BAL fluid makes it possible to determine the timing of bleeding episodes relative to time of sampling.
   c. BAL is only useful as a diagnostic tool if it is performed within 2 weeks after exercise.
   d. BAL fluid can be used only to evaluate the amount of blood in a small portion of one lung.

4. Which statement regarding EIPH and performance is true?
   a. Any amount of EIPH causes poor performance.
   b. Only severe EIPH (grade 4 or epistaxis) impairs performance.
   c. EIPH does not affect performance.
   d. Modest EIPH (grade 2) adversely affects performance.

5. Pulmonary blood flow in exercising horses is
   a. preferentially distributed to the caudodorsal lung regions.
   b. preferentially distributed to the cranioventral lung regions.
   c. preferentially distributed to the cranial lung regions.
   d. distributed uniformly throughout the lungs.

6. Which statement regarding veno-occlusive remodeling is incorrect?
   a. Because veins are inherently compliant and thinly walled, when they are exposed to repeated or continuous high intraluminal pressure, they remodel, presumably to prevent overdistention and rupture.
   b. In EIPH, veno-occlusive remodeling is primarily localized in the cranioventral lung region.
   c. In horses with a diagnosis of EIPH, veno-occlusive remodeling lesions are often associated with hemosiderin, fibrosis, and bronchial angiogenesis.
   d. None of the above is incorrect.

7. Vein wall remodeling in EIPH
   a. primarily involves smooth muscle hypertrophy.
   b. primarily involves collagen deposition.
   c. does not reduce the venous lumen.
   d. enlarges the venous lumen.

8. Obstruction of pulmonary veins results in ____________ pulmonary capillary pressure.
   a. a decrease in
   b. no change in
   c. an increase in
   d. none of the above

9. Which statement(s) regarding furosemide and EIPH is/are true?
   a. Furosemide is a popular prophylactic therapy for EIPH in North America and has been shown to reduce the severity of bleeding.
   b. Furosemide prevents EIPH.
   c. Furosemide likely improves racing performance.
   d. a and c

10. For which of the following therapies is there some evidence of effectiveness in reducing the severity of EIPH?
    a. aminocaproic acid
    b. pentoxifylline
    c. nasal strips
    d. bioflavonoids