WHAT IS EIPH?
Exercise induce pulmonary hemorrhage (EIPH) has been recognized in performing Thoroughbred racehorses dating far back to the mid 18th Century. Eclipse (1764-1789) descended from the line of Bartlett's Childers who was renamed from Bleeding Childer's who never lost a race and sired 334 winners. Although EIPH is a major health concern in a variety of performance horses, its significance on overall peak performance has yet to be determined, based on the observation that many elite athletes have at one time or another demonstrated pulmonary hemorrhage. The condition has been reported in Quarter Horses, Thoroughbreds, Standardbreds, as well as in horses competing in disciplines other than racing such as cutting, roping, reining, jumping, polo, and even in pulling events performed by draft horses. EIPH poses the greatest concern to the racing industry because of the financial implications resulting from decreased performance, lost training days, necessity for pre-race medications and removal of horses from racing.

EIPH is characterized by pulmonary hypertension, alveolar edema formation, rupture of pulmonary capillaries, intra-alveolar hemorrhage and the presence of blood within the airways. Although recognized as a disease of multifactorial etiologies, lower airway inflammation, upper airway obstruction, exercise-induced hyperviscosity, mechanical stress of respiration and locomotion-induced redistribution of blood flow in the lung, alveolar pressure fluctuations, and pulmonary hypertension have all been reported to play a role in disease development. One study that clearly demonstrates pulmonary as compared to bronchial pulmonary system to be responsible for disease development, revealed that microspheres (10 and 15 micron diameter) injected into the jugular vein (pulmonary arterial perfusion) reached the alveoli, in contrast spheres injected directly into the left atrium (bronchiolar perfusion) were not identified in the alveoli. These data support the hypothesis that pulmonary perfusion contributes to EIPH whereas bronchiolar blood flow is unlikely to be involved in the pathogenesis of EIPH.

DIAGNOSIS OF EIPH
Original diagnostic methods involved visualization of blood from the nostrils in affected horses (true epistaxis). We now recognize that very few of the horses suffering from EIPH demonstrate overt epistaxis and visualization of the
lower airways in combination with bronchoalveolar lavage are more appropriate methods of diagnosis. When repeated endoscopic procedures are performed on an individual horse, the rate of EIPH has been reported to be as high as 82-95%.

Bronchoalveolar lavage is the preferred diagnostic method at this time because it will detect the presence of hemorrhage at the level of the alveoli and small airways. The procedure is relatively easy to perform with either an 3M endoscope or specifically designed cuffed BAL tube. The advantage of this technique is accurate identification of the cytologic population in the terminal airways and alveolar spaces. Multiple investigations have demonstrated good correlation between BAL cytologic findings when compared with histopathologic analysis of lung biopsy samples. Sensitivity is greater for BAL cytology when compared with endoscopy or tracheal lavage cytology.

CLINICAL MANAGEMENT OF EIPH

Due to the multifactorial etiology of EIPH therapeutic management is challenging, at best. Identifying the most likely underlying etiologies contributing to disease are likely to enhance the therapeutic success rate. For instance, if lower airway inflammation appears to be playing a role in a bleeder, resolution of the inflammation (specifically) may improve the tendency for pulmonary hemorrhage.

Furosemide: The most commonly administered therapy for EIPH is furosemide (1 mg/kg IV 4 hours pre race). Furosemide acts by reducing the exercise induced increases in right atrial, pulmonary arterial, pulmonary wedge, and pulmonary capillary pressures in addition to showing a reduction in the number of RBCs identified on BAL cytology. Horses that were run at 95% of their aerobic capacity were shown to have a 90% reduction in EIPH when furosemide was administered according to the prerace conditions (previously listed). The predominant feature of this therapy believed to contribute to the favorable response was associated with a significant reduction in mean pulmonary arterial pressure. This reduction in pulmonary vascular pressure is compatible with a reduction in stress failure of the pulmonary capillaries, reduced transcapillary filtration, reduced accumulation of lung water during exercise, and overall reduced EIPH.

Functional changes observed in response to furosemide administration result from reduced circulating blood and plasma volume. Some authors have also suggested a theory of redistribution of pulmonary blood flow following furosemide administration to also contribute to reduced pulmonary hemorrhage. Spacial differences in pulmonary blood flow have been reported both in vivo and in vitro. Methacholine challenge in vitro has demonstrated a greater vasodilatory function in dorsally located vasculature when compared to more ventrally located vasculature in the equine lung. Correspondingly, following an episode of EIPH radiographic evidence of disease is characterized by a caudodorsal distribution of increased radiopacity, consistent with dorsally distributed hemorrhage. Interestingly, investigations looking at the spacial relationship of pulmonary blood flow in response to furosemide administration have revealed that following intravenous microsphere injection, exercising horses demonstrate reduced dorsal pulmonary blood flow following furosemide administration.

Furosemide remains a controversial topic when discussing pre-race medications for racehorses, because of the potential for performance enhancement following drug administration. Although legal for use in North and South America as well as in the Philippines and Saudi Arabia, the mechanisms for enhanced performance remain unclear, but likely relates to reduced body weight, reduced pulmonary vascular pressures, and bronchodilation. Nonetheless, furosemide remains a commonly administered medication for the management of clinical EIPH. Recent investigations failed to reveal evidence for bioavailability following oral administration of furosemide tablets (1.0 mg/kg PO); therefore systemic administration in athletic horses should remain via the parenteral route.

Nasal dilators: As much as 40-50% of the pulmonary resistance can be located within the nasal passages. Similar to strategies to reduce the resistance of air flow in the upper airways in people, a nasal dilator devise has been designed for use in athletic performance horses. The FLAIR™ nasal dilator strip has been introduced for use in horses to reduce the collapse of the nasal passages and to decrease upper airway resistance. In particular, a goal of reduction of upper airway resistance has been to lower intrapleural and alveolar pressure swings that may contribute to high pulmonary capillary transmural pressures and EIPH. Clearly demonstrated from investigations on exercising racehorses on the treadmill, were data that showed a significant reduction in oxygen uptake and carbon dioxide production when the nasal dilator was applied. In addition, BAL cytology revealed a 33% reduction in EIPH in horses wearing the nasal dilator. When multiple investigations are compared, the overall reduction in EIPH has been reported to be 40-50% reduction in EIPH for treated horses. The reduction in pulmonary oxygen uptake and EIPH demonstrated with the nasal strip is attributed to reduced inspiratory resistance, reduced inspiratory muscle work, and less negative intrapulmonary pressure swings. The nasal strip may act to shunt the oxygen savings from the reduced work of breathing to the locomotary muscles to enhance the time to fatigue, thus improving performance.

Application of the nasal strip has been universally approved by various performance horse jurisdictions such as for flat and harness racing, Federation Equestrian International, United States Equestrian Federation, National Reining Association, United States Equestrian Team, United States Polo Association, National Barrel Horse Association, and the American Quarter Horse Association.

ADDITIONAL THERAPIES

Concentrated equine serum is commercially marketed as Seramune® to be used for treatment of failure of passive transfer in foals. Although this product has been successfully used for this purpose, some individuals have applied it for use in other conditions, such as EIPH. The protocol that is currently being investigated involves both intravenous as well as intratracheal administration on a repeated dosing protocol. The proposed mechanism of effect is for altered pulmonary immune function following administration. Although a limited number of horses have been investigated there appears to be some reduction in EIPH based on BAL cytology. What remains to be determined is the mechanism of this effect, altered leukocyte phagocytic activity in the lower airways may be involved in increased RBC removal following an episode of hemorrhage, but many features of this treatment strategy (safety and efficacy) remain to be determined.

Additional alternative treatments have been investigated that include procoagulant agents (vitamin K, oxalic acid, conjugated estrogens, and aminocaproic acid), antihypertensive drugs (enalapril, nitric oxide donors /
analogue), rheologic agents (pentoxyphylline), bronchodilators (clenbuterol, albuterol, ipratropium), and anti-inflammatory drugs (corticosteroids, cromolyn sodium). None of these treatments have demonstrated therapeutic benefit in horses with EIPH. In addition, prolonged periods of rest from strenuous exercise have not reduced the severity of bleeding in affected horses. Dietary supplements (hepseridin-citrus bioflavinoids) to improve capillary strength have not been successful in reducing the severity of EIPH or enhancing performance.

It is unlikely that an ideal therapeutic agent for EIPH (eliminate pulmonary hemorrhage without impairing race performance) will be developed until the etiopathogenesis of the disease is completely understood. At this point, it appears that EIPH results from “stress failure” of the pulmonary vascular system, and the presence of blood in the pulmonary parenchyma stimulates a self-perpetuating inflammatory response. Given the universal occurrence of EIPH in horses that exert a maximal level of effort, it is unlikely that a single agent will completely eliminate the problem in horses that perform high intensity exercise.

REFERENCES