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EIPH – Have we changed our thinking about its pathophysiology and treatment?

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PREVALENCE

EIPH has been documented to occur in horses performing many types of strenuous exercise including flat and timber racing, steeple-chasing, polo and rodeo events.2,26,27,39,47,49,53,54,58 It has also been documented to occur in racing camels, in racing Greyhounds and in elite human athletes undertaking ultra-marathons or strenuous cycling.1,15,30,31,37 In horses, the prevalence of EIPH varies between 40-85% and is a function of the diagnostic method used; the length of time elapsing after exercise when the examination was performed and the number of times the horse was examined after different exercise bouts. In one endoscopic study of 258 Thoroughbred and 296 Standardbred racehorses, Birk and colleagues5 reported a 75% prevalence of EIPH for either group indicating that neither the gait nor the breed was a primary determinant of EIPH. When multiple endoscopic exams of the same horse were conducted on different days, a 95% prevalence rate of EIPH was found.

When the diagnosis of EIPH was based upon presence of erythrocytes or hemosiderophages in either the tracheal wash or bronchoalveolar lavage (BAL) fluid, then virtually 100% of horses involved in intense exercise develop EIPH.12 In contrast, the prevalence of epistaxis (occurring during or shortly after exercise) is reported to be much less, ranging from 0.1 to 14%. Epistaxis is more common in older horses, in horses racing shorter distances < 1600 m and in steeple-chase racers.54,56

ETIOPATHOGENESIS

The source of the bleeding is from the caudodorsal lung regions.45 As the severity of EIPH increases, more craniodorsal areas become involved: Cranioventral lung regions are spared. In the initial description of EIPH in Thoroughbred racehorses, O’Callaghan (1987) noted a bluish-brown discoloration of the dorsal lung tissue and pleura. Histopathologically, scattered bronchiolitis, hemosiderophage accumulation in the airspaces and interstitium, interstitial fibrosis and alveolar epithelialization were found.45,46 The discrete regional lung involvement has led to the development of numerous hypotheses to explain EIPH such as upper airway obstruction, locomotory-induced lung trauma, exercise-induced hyperviscosity, coagulopathy, small airway inflammation, stress failure of the pulmonary capillaries and veno-occlusive disease.10,18,50,52,59-61 It is possible that aspects of many different mechanisms contribute to EIPH. In the most widely held theory—that of stress failure of the pulmonary capillaries—it is proposed that exercise-induced increases in transmural pressure (the pressure difference between the pulmonary capillary and the alveolar lumen) exceed the tensile strength of the pulmonary capillary wall causing it to rupture and release RBCs into the interstitium and alveoli. Excessive transmural pressures develop during high intensity exercise as a result of the (1) the large cardiac output and the high conductance of the pulmonary vasculature (increasing pulmonary capillary pressure) and (2) the very negative intra-alveolar inspiratory pressure.
pressures that generate high airflows. Since the initial report by West,60 others have found that as the mean pulmonary arterial pressure increases (as a function of treadmill exercise), so too does the severity of EIPH. Transmural pressures and bleeding severity also increase when horses run on an incline as compared to a flat surface. Transmural pressures increase in horses with upper airway obstructions (more negative inspiratory pressures) but an association between the severity of EIPH and the presence of an upper airway obstruction14 remains unproven. Small airway disease (bronchiolitis)—an intrathoracic resistance—is thought to be contributory by requiring more negative inspiratory pressures to be generated. Inflammation alters compliance of lung units which could promote abnormal shear stresses and tissue damage. McKane and Slocombe (2010) reported that when inflammation was induced in cranioventral lung segments, horses bled from those segments following strenuous exercise. Recently, Williams (2008) proposed that EIPH is a pulmonary veno-occlusive disease after finding in the caudodorsal lung regions of EIPH-affected horses, prominent intralobular veins surrounded by and/or obscured by collars of mature collagen. Venous remodeling, co-localized with hemosiderosis, angiogenesis, interstitial and interlobular fibrosis typical of EIPH, was not detected in the cranioventral lung regions61 or in the lungs of the control horses. These findings led investigators to hypothesize that strenuous exercise is associated with the development of high regional pulmonary vascular pressures in the caudodorsal lungs (p referential distribution of blood flow during exercise) which promotes regional pulmonary vein remodeling and venous occlusion. The increased resistance to blood flow is transmitted upstream causing an increase in pulmonary capillary pressure, capillary rupture (stress failure) and bleeding into the interstitium and alveoli. The accumulation of haemosiderin within the interstitium and airspaces is thought to initiate inflammation (involving reactive oxygen species) and secondary interstitial fibrosis. Defects in coagulation as a cause of EIPH have also been proposed based upon the findings that (1) strenuous exercise suppresses platelet reactivity (demonstrated ex vivo); (2) platelet reactivity from EIPH-positive horses is attenuated compared to EIPH-negative horses and platelet numbers in EIPH-positive horses are less than those of EIPH negative horses. Giordano and colleagues (2010) used thromboelastography (TEG) to examine coagulation and fibrinolysis in Standardbred racehorses with and without EIPH. In both control and EIPH positive horses coagulability decreased after racing. However, rarely were there statistical differences in the TEG parameters between the bleeders and controls suggesting that this was not the primary cause of EIPH.

Less supportive evidence exists for the role of locomotory forces on the development of EIPH. Schroter (1998) proposed that concussive forces of forelimb impact during exercise were transmitted through the scapulae and chest wall and “focused” onto the narrow caudodorsal lung region. However Jones and colleagues (2002), studying exercising horses with implanted pleural pressure catheters, were unable to detect differences in intrapleural pressure excursions at the various regions in the thoracic cavity. Furthermore, horses performing strenuous swimming exercise—an exercise which lacks forelimb concussion—also experience EIPH.

EIPH AND ATHLETIC PERFORMANCE

In many of the earlier reports in the literature, the effect of EIPH on athleticism was inconsistent with studies citing no effect, a negative or even a positive effect on performance. Differences in the conclusions probably reflect the statistical methods used (non-randomization of study population), the case definition of EIPH, and confounding effects of pre-race medications. In a recent randomized, controlled study of 744 Australian Thoroughbred racehorses that received no pre-race medication, the investigators reported that horses with endoscopic bleeding scores of 0 or 1 were 4 times as likely to win and nearly 2
times as likely to finish in the first 3 positions compared to horses with more severe pulmonary bleeding (grades ≥ 2). In that study, approximately 55% of the horses examined had endoscopic evidence of EIPH. A similar study has not been performed for Standardbred racehorses but one suspects that the results would be similar. In a treadmill study of horses investigating the effect of airway disease on performance, Sanchez and Couetil (2005) reported that horses with EIPH exhibited more severe exercise-induced hypoxemia and hypercapnia as compared to controls. This suggested to them that pulmonary bleeding reduces gas exchange. Interestingly, the gas exchange alterations did not impact upon laboratory parameters of performance—total run time, distance to fatigue or peak running speed. Severe pulmonary bleeds have resulted in fatalities of horses racing or training. In one study conducted over a two-year period, Gunson reported (1988) that the cause of sudden death in 9 of 11 Thoroughbred racehorses was attributed to EIPH. (They excluded from their study racehorses dying from fractures.) In another study of Australian Thoroughbred racehorses conducted over a 3.5 year period, Boden reported (2005) that 60% of all sudden deaths in racehorses were attributed to acute pulmonary edema, congestion and hemorrhage, compatible with EIPH.

**Diagnostic Tests:**

Tracheobronchoscopic scoring of pulmonary hemorrhage using a scale ranging from 0 to 4 has been described and allows good agreement between evaluators. Endoscopy is performed between 30 and 90 minutes following exercise and grades are assigned based upon the amount of blood observed in the trachea.

- **Score 0:** No blood in pharynx, larynx, trachea or mainstem bronchi.
- **Score 1:** One or more flocks of blood or two or fewer short (< ¼ length of trachea) narrow (< 10% of tracheal surface) streams of blood in the trachea or mainstem bronchi.
- **Score 2:** One long stream of blood (> ½ the length of the trachea) or > two short streams of blood occupying more than ⅓ of the tracheal circumference.
- **Score 3:** Multiple distinct streams of blood covering more than ⅓ of the tracheal circumference, no blood at the thoracic inlet.
- **Score 4:** Multiple coalescing streams of blood covering more than 90% of tracheal surface with blood pooling at thoracic inlet.

Cytological examination of bronchoalveolar lavage fluid (BALF). Enumeration of erythrocytes in the bronchoalveolar lavage fluid (BALF) post-exercise has been used but the relationship between RBC count and the severity of hemorrhage has not been established. Some of the investigational studies are marred because dilutional effects of the BAL were not addressed. Meyer and co-workers (1998) reported that in horses performing strenuous treadmill exercise, mean BALF erythrocyte counts more than doubled from the pre-exercise values of 0.9 x 10⁶ cells/mL to 2.5 x 10⁶ cells/mL post-exercise. Horses exercising with an upper airway obstruction (recurrent laryngeal neuropathy) developed significantly greater increases in post-exercise BALF RBCs, averaging 18 x 10⁶ cells/mL. In that same study, a significant increase in BALF erythrophages (macrophages containing RBCs) was not detected until 1 week post-exercise but remained prevalent for at least 3 weeks. As the engulfed erythrocytes are degraded, the breakdown product of hematin, hemosiderin, can be scored and provides another means of documenting EIPH. Doucet and Viel (2002) developed hemosiderin scores (maximum score = 400) based upon the intensity of the cytoplasmic staining in BALF pulmonary macrophages isolated from EIPH negative and EIPH positive Standardbred racehorses. The average score for the control horses was 22, that of the EIPH positive horses was 198. They noted that for a total hemosiderin score > 75, the sensitivity and specificity for detecting EIPH was 94% and 88%, respectively, provided that the horse had not had a prior history of pulmonary abscessation or pleuropneumonia. The percentage of pulmonary macrophages that are hemosiderophages has also been used to diagnose EIPH. Scores range from 1 (1-9% of macrophages are hemosiderophages) to 5 (> 60% of macrophages are hemosiderophages)
and a score ≥ 1 is considered to be positive for EIPH.

**Thoracic radiography.** In some horses that bleed, unstructured interstitial nodular densities are found in the caudodorsal lung field.44 However, most clinicians agree that radiographic changes do not correlate with clinical signs of EIPH.12 **Thoracic ultrasound.** In a field study of 157 Thoroughbred and Standardbred racehorses in training, Ferrucci and colleagues (2009) compared the diagnostic accuracy of ultrasound compared to endoscopy or cytological examination of the BALF in horses with EIPH. They diagnosed EIPH by the presence of comet tail artifacts in the 10th-17th intercostal spaces, assigning a score that reflected the number of spaces involved. They concluded that ultrasound was highly sensitive (86%) but lacked specificity (26%) compared to post-exercise endoscopy (sensitivity=73%, specificity=88%).

**Treatment and/or prevention of EIPH.** Assessing the efficacy of treatments aimed at reducing or preventing EIPH has been problematic for several reasons: the exact cause of EIPH remains unknown; an accurate method of quantitating pulmonary bleeding is lacking and well-controlled randomized studies of large numbers of horses are difficult and expensive to undertake.

**Reducing pulmonary artery pressures during exercise.** Furosemide remains one of the most widely studied and most frequently administered drugs for the treatment and/or prevention of EIPH. In experimental studies, pre-treatment with furosemide (500 mg, 4 hours pre-exercise) reduced right atrial, pulmonary artery and pulmonary capillary pressures16 during exercise and post-exercise BALF erythrocyte numbers.35, 21 The hemodynamic alterations are mediated by reductions in blood and plasma volume and perhaps also, a reduction in pulmonary blood flow to the caudodorsal lung lobes.17 Hemodynamic effects as well as increases in mass-specific maximal oxygen consumption4 are thought to be responsible for the enhanced athletic performance of racehorses receiving this drug. In North American field studies of Thoroughbred racehorses, those receiving furosemide were more likely to win or finish in the top 3 positions compared to untreated racehorses. The magnitude of the furosemide effect on a 6-furlong race time was 0.56 seconds, equivalent to a 3 to 6 length difference.23 In another well controlled study of 193 Thoroughbred racehorses performing in South Africa, investigators found a significant reduction in the incidence and endoscopic severity of EIPH in horses that had received 500 mg of intravenous furosemide compared to horses receiving placebo.30 Another drug that reduces pulmonary vascular pressures is nitric oxide (NO). This vasoactive agent, produced by endothelial cells through the action of NO synthase on L-arginine, induces vascular smooth muscle relaxation. In lab studies, inhaled NO (80 ppm) attenuated exercise-induced increases in pulmonary artery pressures but exacerbated EIPH, as evidenced by BALF RBC numbers.35 The latter effect was attributed to an increase in pulmonary vascular conductance—which does not occur with furosemide. Thus pulmonary capillary beds most prone to EIPH remain exposed to high intraluminal pressures.35 Interestingly, nitroglycerin, a “precursor of nitric oxide”, did not attenuate exercise-induced pulmonary hypertension when administered either orally or intravenously.25, 41 Similarly, sildenafil citrate, which reduces pulmonary vascular pressures in a number of species including man by inhibiting the breakdown of intracellular cGMP, was ineffective in attenuating pulmonary artery hypertension in horses strenuously exercising on a treadmill.9 Thus these studies suggest that simply reducing pulmonary arterial pressures is not sufficient for reducing bleeding.

**Reducing airway resistance particularly in the upper respiratory tract, the site of the greatest impediment to airflow, decreases transmural pressures by reducing peak inspiratory alveolar pressures.** Surgical correction of upper airway obstructive disorders should be undertaken in athletic horses. The FLAIR nasal strip is an externally applied adhesive strip used to prevent or reduce collapse of the nasal passages. At least two laboratory studies of horses have demonstrated a reduction in EIPH.
severity (based upon BALF RBC counts) in the absence of pulmonary arterial pressure changes.\textsuperscript{21,35} In another lab study of exercising Thoroughbreds, Goetz and colleagues (2001) reported that EIPH still occurred in horses wearing the nasal strips but failed to report the severity of EIPH either endoscopically or by BALF erythrocyte counts. In a California field study of 23 Thoroughbreds (ages 2-4, mean 3) that raced with or without the nasal strip, the post-race BALF RBC counts were halved in the treated horses (\(P=0.054\)). When considering only those horses with severe bleeding, post-race BALF RBC counts were significantly lower in the treated group compared to controls.\textsuperscript{57} Controlled, randomized field studies with larger numbers of horses are required to further establish the efficacy of the nasal strip in preventing or reducing EIPH.

As inflammatory airway disease (IAD) is often reported on histopathological evaluation of pulmonary tissues isolated from horses with EIPH, one logical approach is to administer bronchodilators or corticosteroids to IAD-affected horses. No studies exist that demonstrate the efficacy of clenbuterol, albuterol or glucocorticoid administration on preventing or reducing EIPH. Theoretically, reducing inhaled particulates from bedding or hay should decrease airway inflammation but studies demonstrating this approach as an effective means of preventing or reducing EIPH have not been conducted.

\textbf{Improving capillary integrity.} Capillary fragility predisposes to vascular breaks and pulmonary bleeds, especially when capillaries are subjected to high vascular pressures. Hesperin and citrus bioflavinoids, administered with the intent to improve capillary integrity of pulmonary vasculature, were not found to be efficacious in preventing EIPH.\textsuperscript{55} Carbazochrome salicylate is an oxyepinephrine derivative that is used for the treatment of hemorrhage secondary to capillary fragility syndrome in humans. This drug is also routinely administered to racehorses (Kentucky Red). In a study of Standardbred horses performing strenuous treadmill exercise, intravenous treatment with carbazochrome salicylate (100 mg) and furosemide (250 mg) was no more efficacious than furosemide alone in preventing EIPH, based upon BALF RBC counts. However, the investigators cautioned that the conclusions were based upon a small sample size and that larger field investigations were warranted.\textsuperscript{48}

\textbf{Targeting coagulopathies or fibrinolysis.} Aminocaproic acid is a potent inhibitor of fibrin degradation and has been administered with the aim of reducing or preventing EIPH. When administered at a dose of 2 or 7 gram IV 4 hours prior to strenuous treadmill exercise, no beneficial effect in preventing EIPH was demonstrated.\textsuperscript{8}

\textbf{REFERENCES}


