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EXERCISE-INDUCED PULMONARY HEMORRHAGE

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Epidemiology

Exercise-induced pulmonary hemorrhage (EIPH) occurs in horses that race at high speeds, such as Thoroughbred and Standardbred racehorses. The disease is almost unknown in endurance horses or draft breeds. As a general rule, the more intense the exercise or higher the speed attained, the greater the proportion of horses with EIPH.

The prevalence of EIPH varies with the method used to detect it and the frequency with which horses are examined. Almost all Thoroughbred racehorses in active training have hemosiderophages in bronchoalveolar lavage fluid, indicating that all have some degree of EIPH (McKane et al., 1993). The prevalence of EIPH decreases when diagnosis is based on endoscopic examination of horses after exercise or racing.

EIPH is very common in Thoroughbred racehorses with estimates of prevalence, based on a single endoscopic examination of the trachea and bronchi, of 43 to 75% (Pascoe et al., 1981a; Raphel and Soma, 1982; Mason et al., 1983). The prevalence increases with the frequency of examination, with over 80% of horses having evidence of EIPH on at least one occasion after three consecutive races (Sweeney et al., 1990). When examined after each of three races, 87% of Standardbred racehorses have evidence of EIPH on at least one occasion (Lapointe et al., 1994), suggesting that EIPH is as common in Standardbred racehorses as it is in Thoroughbred racehorses.

History and Presenting Complaint

Poor athletic performance or epistaxis (bleeding from the nostrils) are the most common presenting complaints for horses with EIPH. Epistaxis due to EIPH occurs during or shortly after exercise and is usually first noticed at the end of a race, particularly when the horse is returned to the paddock or winner's circle and is allowed to lower its head.

Failure of racehorses to perform to the expected standard (poor performance) is often attributed to EIPH. Many horses with poor performance have cytologic evidence of EIPH on microscopic examination of tracheobronchial aspirates or bronchoalveolar lavage fluid or have blood evident on endoscopic examination of the tracheobronchial tree performed 30 to 90 minutes after strenuous exercise or racing (McKane et al.,

1993; Martin et al., 1999). Severe EIPH undoubtedly results in poor performance and, on rare occasions, death of Thoroughbred racehorses (Gunson et al., 1988).

We recently completed a study of Thoroughbred horses racing in Melbourne, Australia. The study involved endoscopic examination of 744 horses after racing. There was a clear association between presence and severity of EIPH and performance; horses with any more than a fleck of blood in the airway had poorer performances than unaffected horses. These horses were not racing after administration of furosemide (Lasix, Salix) as use of this drug is not permitted on race day in Australia. However, it is important to recognize that EIPH is very common in racehorses and it should be considered the cause of poor performance only after other causes have been eliminated.

Diagnosis of EIPH

There are a variety of techniques available for determining the presence and severity of EIPH including direct visualization of the airways through a flexible endoscope or examination of bronchial lavage fluid or tracheal aspirates for evidence of hemorrhage. The utility of these diagnostic tests varies and choice of examination technique depends on the time between the horse racing and the examination, and the desired sensitivity of the test. For instance, tracheobronchoscopic examination is most appropriate if a horse is examined within 1-2 hours of exercise, whereas examination of airway washings is most appropriate if the examination is days to a week after strenuous exercise. Radiography, pulmonary scintigraphy, and lung function tests are useful in eliminating other respiratory diseases as a cause of poor performance, but are minimally useful in confirming a diagnosis of EIPH or in determining the severity of hemorrhage.

Observation of blood in the trachea or large bronchi of horses 30-120 minutes after racing or strenuous exercise provides a definitive diagnosis of EIPH. The amount of blood in the large airways varies from a few small specks on the airway walls to abundant blood covering the tracheal surface. Blood may also be present in the larynx and nasopharynx. If there is a strong suspicion of EIPH and blood is not present on a single examination conducted soon after exercise, the examination should be repeated 60-90 minutes later. Some horses with EIPH do not have blood present in the rostral airways immediately after exercise, but do so when examined 1-2 hours later. Blood is detectable by tracheobronchoscopic examination for 1-3 days in most horses, with some horses having blood detectable for up to 7 days.

A grading system can be used to estimate the severity of EIPH following bronchoscopic examination (Pascoe et al., 1981b; Mason et al., 1983; Pascoe et al., 1985; Lapointe et al., 1994). A commonly used grading system has four levels from 0 (no hemorrhage visible) to 3 (streak of blood >5 mm wide).

The presence of red cells or macrophages containing either effete red cells or the breakdown products of hemoglobin (hemosiderophages) in tracheal or bronchoalveolar lavage fluid provides evidence of EIPH. Detection of red cells or hemosiderophages in tracheal aspirates or bronchoalveolar lavage fluid is believed to be both sensitive and

specific in the diagnosis of EIPH (Fogarty and Buckley, 1991; McKane et al., 1993). Examination of airway fluids indicates the presence of EIPH in a greater proportion of horses than does tracheobronchoscopic examination after strenuous exercise or racing. The greater sensitivity of examination of airway fluid is likely attributable to the ability of this examination to detect the presence of small amounts of blood or its residual products and the longevity of these products in the airways. Recent studies have reported on the use of red cell numbers in bronchoalveolar lavage fluid as a quantitative indicator of EIPH (Meyer et al., 1998; Langsetmo et al., 2000; Geor et al., 2001; Kindig et al., 2001). However, this indicator of EIPH severity has not been validated or demonstrated to be more reliable or repeatable than tracheobronchoscopic examination and visual scoring.

Pathophysiology and Etiology

Ultimately, the cause of EIPH is rupture of alveolar capillary membranes with subsequent leakage of blood into interstitial and alveolar spaces (West et al., 1993). The source of blood in such instances is the pulmonary circulation. Bleeding from bronchial circulation during exercise has been suggested based on histologic evidence of bronchial angiogenesis in horses that have experienced previous episodes of EIPH (Pascoe, 1996). Whether there is a contribution of the bronchial circulation to EIPH has not been determined. Hemorrhage into the interstitial space and alveoli, with subsequent rostral movement of blood into the airways, results in blood in the trachea and bronchi and, infrequently, epistaxis.

Rupture of alveolar capillaries occurs secondary to an exercise-induced increase in transmural pressure (pressure difference between the inside of the capillary and the alveolar lumen). If the transmural stress exceeds the tensile strength of the capillary wall, the capillary ruptures (West and Mathieu-Costello, 1994). The proximate cause of alveolar capillary rupture is the high transmural pressure generated by positive intracapillary pressures (largely attributable to capillary blood pressure) and the lower intraalveolar pressure (generated by the negative pleural pressures associated with inspiration). During exercise, the absolute magnitudes of both pulmonary capillary pressure and alveolar pressure increase, with a consequent increase in transmural pressure (West and Mathieu-Costello, 1994; Ducharme et al., 1999). Other theories of the pathogenesis of EIPH include small airway disease, upper airway obstruction, hemostatic abnormalities, changes in blood viscosity and erythrocyte shape, intrathoracic shear forces associated with gait, and bronchial artery angiogenesis (Pascoe, 1996; Schroter et al., 1998). It is likely that the pathogenesis of EIPH involves several processes, including pulmonary hypertension, lower alveolar pressure, and changes in lung structure, that summate to induce stress failure of pulmonary capillaries.

Regardless of the cause, rupture of pulmonary capillaries and subsequent hemorrhage into airways and interstitium cause inflammation of both airways and interstitium with subsequent development of fibrosis and alteration of tissue compliance. Heterogeneity of compliance within the lungs, and particularly at the

junction of normal and diseased tissue, results in development of abnormal shear stress with subsequent tissue damage. These changes are exacerbated by inflammation and obstruction of small airways with resulting uneven inflation of the lungs (Robinson and Derksen, 1980). The structural abnormalities, combined with pulmonary hypertension and the large intrathoracic forces associated with respiration during strenuous exercise, cause repetitive damage at the boundary of normal and diseased tissue with further hemorrhage and inflammation. The process continues for as long as the horse performs strenuous exercise (Pascoe, 1996).

Treatment and Prognosis

Therapy for EIPH is controversial in that many treatments are used but none are backed by conclusive evidence of efficacy in horses under field conditions (i.e., racing). Therapy for EIPH is usually a combination of attempts to reduce the severity of subsequent hemorrhage and efforts to minimize the effect of recent hemorrhage.

Treatment of EIPH is problematic for a number of reasons. Firstly, the pathogenesis of EIPH has not been determined, although the available evidence supports a role for stress failure of pulmonary capillaries secondary to exercise-induced pulmonary hypertension (see below).

Secondly, there is a lack of information using large numbers of horses under field conditions that demonstrates an effect of any medication or management practice (with the exception of bedding) on EIPH. There are numerous studies of small numbers of horses (<~40) under experimental conditions, but these studies often lacked the statistical power to detect treatment effects, and the relevance of studies conducted on a treadmill to horses racing competitively is questionable. Treatments for EIPH are usually intended to address a specific aspect of the pathogenesis of the disease and will be discussed in that context.

PREVENTION OF STRESS FAILURE OF THE PULMONARY CAPILLARIES

Stress failure of pulmonary capillaries, and subsequent hemorrhage, is believed to occur as a result of the high transmural pressures in pulmonary capillaries that develop in the lungs of horses during strenuous exercise. Consequently, there is interest in reducing the pressure difference across the pulmonary capillary membrane in an effort to reduce EIPH. Theoretically, this can be achieved by reducing the pressure within the capillary or increasing (making less negative) the pressure within the intrathoracic airways and alveolus.

FUROSEMIDE (LASIX, SALIX)

Furosemide administration as prophylaxis of EIPH is permitted in a number of racing jurisdictions worldwide (Anonymous, 2002). Within the United States and Canada, almost all Thoroughbred, Standardbred, and Quarter Horse racing jurisdictions permit

administration of furosemide before racing. Approximately 85% of all Thoroughbred racehorses in the United States and Canada receive furosemide at some stage in their careers, and on average, 75% of horses in a race receive furosemide (Gross et al., 1999). Although accurate numbers are not available, it appears that a smaller proportion of Standardbred and Quarter Horse racehorses receive furosemide before racing. Furosemide is administered to 22-32% of Standardbred racehorses and 19% of racing Quarter Horses in two racing jurisdictions (Sime et al., 1994; Soma et al., 1996; Soma et al., 2000).

The efficacy of furosemide in treatment of EIPH is uncertain. While field studies of large numbers of horses do not demonstrate an effect of furosemide on the prevalence of EIPH (Sweeney et al., 1990; Birks et al., 2002), studies of Thoroughbred horses running on a treadmill provide evidence that furosemide reduces the severity of EIPH (Geor et al., 2001; Kindig et al., 2001). Under field conditions, based on tracheobronchoscopic evaluation of the severity of bleeding, furosemide has been reported to reduce or have no influence on the severity of bleeding (Pascoe et al., 1985; Birks et al., 2002). This apparent inconsistency may be attributable to measurement of red blood cell counts in bronchoalveolar lavage fluid of horses that have run on a treadmill not being representative of effects of furosemide under field conditions. The weight of evidence from field studies does not support a role for furosemide in preventing or reducing the severity of EIPH.

Furosemide is associated with superior performance in both Thoroughbred and Standardbred racehorses (Gross et al., 1999; Soma et al., 2000). Thoroughbred horses treated with furosemide were 1.4 times as likely to win a race and earn more money, and had a standardized 6-furlong race time 0.56 to 1.09 seconds less than untreated horses (Gross et al., 1999). Similarly, furosemide reduced one-mile race times of Standardbred pacers by 0.31 to 0.74 seconds (Soma et al., 2000).

NITRIC OXIDE

Nitric oxide is a potent vasodilator in many vascular beds. Administration of nitroglycerin (a nitric oxide donor) reduces pulmonary artery pressure of standing horses but does not affect pulmonary artery pressure of horses during intense exercise (Manohar and Goetz, 1999). L-arginine is a nitric oxide donor with no demonstrated efficacy in reducing pulmonary capillary pressure or EIPH in horses. Sildenafil, a phosphodiesterase inhibitor that accentuates the effect of nitric oxide and is used in the treatment of erectile dysfunction in men, has been administered to horses in an apparent attempt to reduce EIPH. However, its efficacy in preventing EIPH or reducing pulmonary capillary pressure has not been demonstrated.

INCREASING ALVEOLAR INSPIRATORY PRESSURE

Recently, the role of the nares in contributing to upper airway resistance, and hence lowering inspiratory intrapleural pressure during intense exercise, has attracted the

attention of some investigators. Application of nasal dilator bands (Flair® strips) reduces nasal resistance by dilating the nasal valve (Holcombe et al., 2002), and reduces red cell count of bronchoalveolar lavage fluid collected from horses after intense exercise on a treadmill (Geor et al., 2001; Kindig et al., 2001). However, the effect of this intervention in horses racing competitively has not been demonstrated.

The role of small airway inflammation and bronchoconstriction in the pathogenesis of EIPH is unclear. However, horses with EIPH are often treated with drugs intended to decrease lower airway inflammation and relieve bronchoconstriction. Beta-adrenergic bronchodilatory drugs such as clenbuterol and albuterol are effective in inducing bronchodilation in horses with bronchoconstriction, but their efficacy in preventing EIPH is either unknown or, in very small studies, is not evident. Clenbuterol does not alter the hemodynamic responses of horses to exertion or attenuate exercise-induced arterial hypoxemia in normal horses (Slocombe et al., 1992; Manohar et al., 2000). Ipratropium, a parasympatholytic drug administered by inhalation, showed promised in a very small study (2 horses) of preventing EIPH (Sweeney et al., 1984). Corticosteroids, including dexamethasone, fluticasone, and beclomethasone administered by inhalation, parenterally, or enterally, reduce airway inflammation and obstruction, but have no demonstrated efficacy in preventing EIPH. Cromolyn sodium (sodium cromoglycate) has no efficacy in preventing EIPH (Hillidge et al., 1987).

Reducing Inflammation

Hemorrhage into interstitial tissues induces inflammation with subsequent development of fibrosis and bronchial artery angiogenesis (O'Callaghan et al., 1987; McKane and Slocombe, 1999; McKane and Slocombe, 2002). The role of these changes in perpetuating EIPH in horses is unclear but likely is of some importance. Treatments to reduce inflammation and promote healing with minimal fibrosis have been proposed. Rest is an obvious recommendation and many racing jurisdictions have rules regarding enforced rest for horses with epistaxis. While the recommendation for rest is intuitive, there is no information that rest reduces the severity or incidence of EIPH in horses with prior evidence of this disorder.

Similarly, corticosteroids are often administered, either by inhalation, enterally or parenterally, in an attempt to reduce pulmonary inflammation and minimize fibrosis. Again, the efficacy of this intervention in preventing or minimizing severity of EIPH has not been documented.

Excessive Bleeding

These is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis (Bayly et al., 1983; Johnstone et al., 1991). Regardless, aminocaproic acid, a potent inhibitor of fibrin degradation, has been administered to horses to prevent EIPH. The efficacy of aminocaproic acid in preventing EIPH has not been

demonstrated. Similarly, estrogens are given to horses with the expectation of improving hemostasis although effect of estrogens on coagulation in any species is unclear. There is no evidence that estrogens prevent EIPH in horses.

Vitamin K is administered to horses with EIPH presumably with the expectation that it will decrease coagulation times. However, as EIPH is not associated with prolonged bleeding times, it is unlikely that this intervention will affect the prevalence or severity of EIPH.

PLATELET FUNCTION

Aspirin inhibits platelet aggregation in horses and increases bleeding time (Kopp et al., 1985). Seemingly paradoxically, aspirin is sometimes administered to horses with EIPH because of concerns that increased platelet aggregation contributes to EIPH (Mahony et al., 1992). There is no evidence that aspirin exacerbates or prevents EIPH.

CAPILLARY INTEGRITY

Capillary fragility increases the risk of hemorrhage in many species. Various bioflavinoids have been suggested to increase capillary integrity and prevent bleeding. However, hesperidin and citrus bioflavinoids have no efficacy in prevention of EIPH in horses (Sweeney and Soma, 1984). Similarly, vitamin C is administered to horses with EIPH without scientific evidence of any beneficial effect.

Overview of Treatment

Selection of therapy for horses with EIPH is problematic. Given that most horses have some degree of pulmonary hemorrhage during most bouts of intense exercise, the decision must be made not only as to the type of treatment and its timing but also which horses to treat. Moreover, the apparent progressive nature of the disease with continued work highlights the importance of early and effective prophylaxis and emphasizes the need for studying factors, such as air quality and respiratory infections, that incite the disorder.

The currently favored treatment for EIPH is administration of furosemide before intense exercise. Its use is permitted in racehorses in a number of countries. Increasingly persuasive laboratory evidence of an effect of furosemide to reduce red cell count in bronchoalveolar lavage fluid collected from horses soon after intense exercise supports the contention that furosemide is effective in reducing the severity of EIPH in racehorses. However, it should be borne in mind that neither the relationship between severity of EIPH and red cell count in bronchoalveolar lavage fluid nor the efficacy of furosemide in reducing severity of EIPH in racehorses in the field have been demonstrated. In fact, there is strong evidence that furosemide does not reduce

the prevalence of EIPH and other evidence that it does not reduce the severity of EIPH under field conditions. The association between furosemide administration and superior performance in Standardbred and Thoroughbred racehorses should be considered when recommending use of this drug.

Rest is an obvious recommendation for horses with EIPH, but the hemorrhage is likely to recur when the horse is next strenuously exercised. The duration of rest and the optimal exercise program to return horses to racing after EIPH is unknown, although some jurisdictions require exercise no more intense than trotting for 2 months. Firm recommendations cannot be made on duration of rest because of a lack of objective information.

Although a role for lower airway disease (either infectious or allergic) in the genesis of EIPH has not been demonstrated, control of infectious diseases and minimization of noninfectious lower airway inflammation appears prudent.

Prognosis

The prognosis for racing for horses with clinically significant EIPH is guarded because of the progressive nature of the disease. Horses that have experienced severe EIPH on one occasion are likely to do so again regardless of treatment. However, the risk of horses experiencing a repeated bout of severe hemorrhage and the effect of EIPH on career longevity are unknown.

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