Exercise Induced Pulmonary Hemorrhage

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INTRODUCTION

"Watch that one there, he's a bleeder." "It's just a matter of time before he becomes a bleeder." These are the recurring conversations and concern any sport horse owner is likely to encounter the longer they keep at their sport. What is a "bleeder", you ask? The answer is not the gruesome image you may currently have pictured in your head. "Bleeder" is a layman's term that has been widely used for decades to refer to horses affected by a condition scientifically known as Exercise Induced Pulmonary Hemorrhage (EIPH). It is defined as "the presence of blood in the airways of horses after exercise and includes both occult hemorrhage (evident only on tracheobronchoscopic or cytological examination of the airways) and/or epistaxis."[1] Horses affected by this condition were given the nickname "bleeders" to portray the episodes of epistaxis that sometimes occur in those affected. EIPH has been documented in horses for over 300 years. It is estimated to affect greater than 90% of race horses at some point during their career.[2] However, little progress has been made in that time period in understanding the exact mechanisms and pathophysiology behind EIPH. It is not until recently that fresh advances have begun to shed new light on understanding this puzzling condition.

HISTORY AND PRESENTATION

The clinical findings associated with EIPH are often quite vague and generally relate more to the success of the athlete than to specific clinical signs (i.e., a horse is more likely to be evaluated when it competes unsuccessfully). Although epistaxis may be part of the presenting complaint, this finding is more uncommon. Much more common are complaints of not performing up to expectations, which is often associated with sudden losses of "speed" during competition and is accompanied by swallowing efforts after intense exercise or racing. When those horses that have competed successfully have been randomly examined (usually by

endoscopic inspection of the upper airway), most if not all also exhibit some degree of EIPH. Thus the clinical presentation of EIPH is most likely to be related to either the observation of epistaxis or an unsuccessful competition with no other obvious cause for poor performance.[3]

As mentioned above, epistaxis as a presenting complaint is surprisingly uncommon. One study states, "Pescoe *et al.* reported that although some horses manifested epistaxis after exercise, far more had endoscopic evidence of pulmonary hemorrhage without epistaxis. Whereas epistaxis has a relatively low incidence of 0.8-13.5%, EIPH has an incidence of 26.5-74.5% in Thoroughbreds. Most horses afflicted with EIPH therefore do not bleed from the nostrils."[4] Perhaps this is due to lesser severity being the more common presentation of the individual affected, or perhaps this is due to the progression of the condition being observed by owners before it has reached its more extreme form.

While race horses seem to be overrepresented in cases of EIPH, essentially any horse exposed to strenuous levels of exercise is subject to present with the condition. EIPH has most commonly been observed in Thoroughbred, Standard bred, and Quarter Horse race horses, however, it has also been reported in virtually all equine breeds during different forms of intense exercise, including steeple chasing, 3-day eventing, show jumping, polo, barrel racing, reining, cutting, and draft horses. Studies have shown that its prevalence is related to intensity of exercise rather than to duration of exercise or breed.[3]

Tucker is an 8 year old, 1-Star level, 3-Day eventing Irish sport pony gelding who presented to MSU CVM Equine Services for intermittent episodes of epistaxis that was first noticed three weeks prior to presentation. One-Star or Preliminary Level cross-country fences are 3 ft. 7 in (1.09 m), 24–28 efforts, ditch 9 ft. 2 in (2.79 m), drops 5 ft. 3 in (1.60 m), 520 m/min with Stadium fences 3 ft. 7 in (1.09 m), 11–13 efforts. The bleeding began as unilateral on the

left side during cross-country training and then progressed to a bilateral presentation at a competition event. Tucker's owner reported that the epistaxis always presents after exercise. Tucker was bright and alert upon presentation. Temperature, pulse, and respiration were all within normal limits. No abnormalities were noted on physical exam. Tucker's history of epistaxis shortly after exercise was highly suggestive of EIPH, but at this point further diagnostics needed to be performed to rule out other known causes of epistaxis.

PATHOPHYSIOLOGY

The hypotheses of the proposed pathophysiology behind EIPH are widespread and often controversial. Currently the most accepted explanation is as follows: "The accepted pathophysiologic mechanism of EIPH is stress failure of the pulmonary capillaries caused by excessive trans mural pressure created by very high intracapillary pressure (predominantly caused by high blood pressure) and low intra-alveolar pressure (generated by negative intrapleural pressures associated with inspiration) produced during exercise.

Strenuous exercise in horses is associated with marked increases in pulmonary vascular pressures. Mean pulmonary arterial pressure increases from resting levels of 25 mm Hg to greater than 95 mm Hg during maximal exercise on a treadmill at speeds of greater than or equal to 14 m/s on a 5% incline. Pulmonary artery wedge pressure (which approximates pulmonary venous pressure) and estimated pulmonary capillary pressures similarly increase in magnitude during strenuous exertion. This three- to four-fold increase in pulmonary vascular pressures occurs primarily because of an increase in cardiac output. Under experimental laboratory conditions, the critical mean pulmonary arterial pressure above which mechanical disruption of pulmonary capillaries occurs is 75 to 100 mm Hg, lower than that observed in most galloping horses.[5] When one considers that even the average of galloping pressures is above the threshold

beyond which mechanical damage occurs, it can be concluded how common this phenomenon must actually be. Consistently more breaks per millimeter occur in dorsocaudal lung regions than in cranioventral lung lobes. Unlike dogs and humans the dorsocaudal lung regions of horses receive relatively greater pulmonary blood flow during exercise than cranioventral lung lobes. This likely contributes to the vulnerability of pulmonary capillaries to rupture and accounts for the typical dorsal distribution of lesions in horses with EIPH.[5]

EIPH is only reported in horses due the remarkably elevated pulmonary vascular and trans mural capillary pressures during strenuous exercise.[6] These high pressures are the result of the large increase in cardiac output (10x), increased blood viscosity (2x), and increased left atrial pressure (10x) that are normal responses to exercise in an elite equine athlete which have not yet been reported in most other domestic animals or in the human athlete.[6]

DIAGNOSTIC APPROACH AND CONSIDERATIONS

Numerous methods have been used for the diagnosis EIPH throughout the years. In the past, before the development of the endoscope, epistaxis of either unilateral or bilateral presentation was needed to diagnose EIPH. However, with the advancement of endoscopy to directly visualize the upper airways and trachea, EIPH is now routinely diagnosed endoscopically. 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.[7]

More recent medicine has developed the use of bronchoalveolar lavage as a tactic for diagnosing EIPH, as it will show evidence of bleeding at the alveolar capillary level. A scoring

system developed in 2005 by Kenneth W. Hinchcliff, BVSc, PhD, Dipl. ACVIM is currently in use today and is described as follows:

- Grade 0- No blood detected in the pharynx, larynx, trachea, or mainstem bronchi.
- Grade 1- One or more flecks of blood, or two or fewer short (less than one quarter the length of the trachea) and narrow (less than 10% of the tracheal surface area) streams of blood in the trachea or mainstem bronchi present.
- Grade 2- One long stream of blood (more than one-half the length of the trachea) or more than two short streams of blood occupying less than one-third of the tracheal circumference.
- Grade 3- Multiple, distinct streams of blood, covering more than one-third of the tracheal circumference, with no blood pooling at the thoracic inlet.
- Grade 4- Multiple, coalescing streams of blood covering more than 90% of the tracheal surface with blood pooling at the thoracic inlet.[8]

In some cases thoracic radiographs can be helpful in confirming the diagnosis of EIPH. Radiographic examination of the thorax of horses can demonstrate the presence of increased soft tissue/ fluid densities in the caudodorsal lung fields of some horses with EIPH.[1] Radiographic changes within the lung are most commonly present in the caudal tip of the lung. However, as the severity of the disease progressives, more cranial involvement of the dorsal lung fields becomes apparent.[1]

It is important to consider the different rule outs for epistaxis before diagnosing a horse with EIPH. Epistaxis after exercise generally is considered an indication of EIPH although epistaxis can result from other causes (e.g. trauma to the head or upper airways, ethmoidal hematoma, guttural pouch mycosis). There is moderate quality evidence that epistaxis during or

soon after exercise is attributable to EIPH.[1]

Because Tucker presented for unilateral progressing to bilateral epistaxis shortly after exercise, EIPH was at the top of the rule out list for possible diagnoses. However as mentioned above, other causes of epistaxis such as trauma, ethmoidal hematoma, or guttural pouch mycosis had to be ruled out first. An endoscopic exam was performed on Tucker to evaluate his airways. No signs of trauma, ethmoidal hematomas, or guttural pouch mycosis were discovered. A tracheal wash was performed to check for previous hemorrhage and revealed increased alveolar macrophages with hemosiderin staining.

Tucker was then taken to radiology to evaluate his lung fields. Thoracic radiographs revealed an increase in radiopacity in the caudal lung fields consistent with hemorrhage. Additionally there was an increase in bronchiole wall thickness suggestive of chronic inflammation. With the combination of history, tracheal wash findings, and radiographic changes consistent with EIPH, a diagnosis of EIPH could now be confirmed for Tucker.

TREATMENT AND MANAGEMENT

Furosemide has been used for more than 40 years to reduce the occurrence or severity of EIPH. The mechanism of action to reduce or prevent EIPH is not known. Furosemide is a loop diuretic that has been demonstrated to attenuate the increased right atrial, pulmonary arterial, venous, and capillary pressures considered important in the development of pulmonary capillary stress during exercise. Furosemide also has direct effects on the pulmonary veins to relax venous smooth muscle.[5] Furosemide administered approximately 4 hours before strenuous exercise is perhaps the most widely used therapy for EIPH. Antibiotics are also a mainstay of treatment, as accumulation of blood in the lungs can consequently lead to a secondary bacterial infection. An

antibiotic such as Trimethoprim-sulfadiazine with broad spectrum coverage is most commonly used.

Another common treatment often used in conjunction with furosemide focuses on reducing inflammation of the airways. Hemorrhage into interstitial tissues induces inflammation with subsequent development of fibrosis and bronchial artery angiogenesis. Treatments to reduce inflammation and promote healing with minimal fibrosis have been proposed. Corticosteroids are often administered, either by inhalation, enterally, or parenterally, in an attempt to reduce pulmonary inflammation and minimize fibrosis.[7] Other less common treatments include nasal strips, nitric oxide, bronchodilators, and stall rest.

In the past there have been conflicting results of the impact of EIPH on performance and the outlook for a continued athletic career. However, recent research has shed a more consistent light on the topic. Most studies performed can agree on the fact that EIPH horses with grades 1, 2, or 3 have minimal effect on a horse's long term performance career. Conversely, one must keep in mind the progression of the disease. Consequently, those with grade 4 have a negative prognosis on long term performance. One article sums up these findings as the following: The prognosis for racing 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.[7]

Anti-microbial therapy of Trimethoprim-sulfadiazine 30 mg/kg orally was prescribed every 12 hours for 10 days. Strict stall rest was to be implemented with no exercise or forced riding for the next three weeks after discharge. Tucker was instructed to return to work gradually after those three weeks. Dexamethasone was prescribed to be given in the muscle every day for three days, then once every other day for three total treatments. This is a corticosteroid to reduce

the pulmonary inflammation and fibrosis as described above. Finally, Clenbuterol was prescribed to be given every day for five days. This is a bronchodilator to expand the airways in attempts to alter the pulmonary hemodynamics.

CASE OUTCOME

Tucker returned to the 2-Star Level 3-Day Eventing 8 weeks following presentation. He performed well for 6 weeks. Six weeks post return to performance Tucker had substantial epistaxis during a cross-country run. He was pulled from the event. At this time he was treated for 21 days with anti-microbial therapy of Trimethoprim-sulfadiazine 30 mg/kg orally every 12 hours. Following resolution of the antimicrobial therapy, he was started on daily albuterol inhalants for 14 days with every other day treatment of dexamethasone. He was stall rested for 4 weeks with strict instructions to soak his hay and reduce dust is his stall. Following 4 weeks of stall confinement Tucker was turned out to pasture with instructions not to return to cross-country work for 6 months. Tucker returned to a lower level of Eventing following his rehabilitation.

CONCLUSION

EIPH is a disease that affects horses performing high-intensity exercise. The proximate cause of EIPH is pulmonary capillary stress failure. The pathophysiologic basis of the disease involves very high exercising pulmonary capillary pressures and very low pleural pressures created during exercise. An early and important pathologic lesion is veno-occlusive remodeling; however, whether this finding is cause or consequence of EIPH is not yet known. Moderate to severe EIPH is associated with inferior performance during a single race and there is evidence that severe EIPH and epistaxis are associated with shorter career duration. There is high-quality

evidence that furosemide is effective for reducing the severity of EIPH. Currently, there is moderate-quality evidence that EIPH is a progressive disease.[5]

REFERENCES

1. Hinchcliff, K.w., L.l. Couetil, P.k. Knight, P.s. Morley, N.e. Robinson, C.r. Sweeney, and E. Van Erck. "Exercise Induced Pulmonary Hemorrhage in Horses: American College of Veterinary Internal Medicine Consensus Statement." *Journal of Veterinary Internal Medicine* 29.3 (2015): 743-58. Web. 17 Jan. 2017.
2. Rush, Bonnie R. DVM, MS, DACVIM. "Exercise-induced Pulmonary Hemorrhage in Horses." *The Merck Veterinary Manual*. Whitehouse Station, NJ: Merck, 2016. N. pag. Web.
3. Birks, Eric K., Mary M. Durando, and Steve Mcbride. "Exercise-induced Pulmonary Hemorrhage." *Veterinary Clinics of North America: Equine Practice 19.1* (2003): 87-100. Web. 17 Jan. 2017.
4. Weideman, H., S.j. Schoeman, G.f. Jordaan, and M. Kidd. "Epistaxis Related to Exercise-induced Pulmonary Haemorrhage in South African Thoroughbreds." *Journal of the South African Veterinary Association 74.4* (2003): n. pag. Web. 16 Jan. 2017.
5. Sullivan, Stacey, and Kenneth Hinchcliff. "Update on Exercise-Induced Pulmonary Hemorrhage." *Veterinary Clinics of North America: Equine Practice 31.1* (2015): 187-98. Web. 16 Jan. 2017.
6. Erickson, Howard H., Joseph C. O'dea, John Pascoe, N. Edward Robinson, and Corrine R. Sweeney. "Exercise-induced Pulmonary Hemorrhage (EIPH)." *Journal of Equine Veterinary Science 15.11* (1995): 464-66. Web. 11 Jan. 2017.
7. Hinchcliff, Kenneth W. "Exercise-Induced Pulmonary Hemorrhage." *Advances in Equine Nutrition IV*. By Joe D. Pagan. Nottingham: Nottingham UP, 2009. 367-77. Print.
8. Larson, Erica. "EIPH and Furosemide Use in Racehorses Explained." *The Horse* (n.d.): n.

pag. The Horse. 4 Oct. 2012. Web. 11 Jan. 2017.

9. Boudreaux, Mary K., Jennifer Koehler, Perry L. Habecker, and Fabio Del Piero. "Evaluation of the Genes Encoding CD39/NTPDase-1 and CD39L1/NTPDase-2 in Horses with and without Abnormal Hemorrhage And in Horses with Pathologic Evidence of Exercise-induced Pulmonary Hemorrhage." *Veterinary Clinical Pathology 44.4 (2015): 617-25*. Web. 13 Jan. 2017.
10. Sullivan, S. L., T. Whittem, P. S. Morley, and K. W. Hinchcliff. "A Systematic Review and Meta-analysis of the Efficacy of Furosemide for Exercise-induced Pulmonary Haemorrhage in Thoroughbred and Standardbred Racehorses." *Equine Veterinary Journal 47.3 (2015): 341-49*. Web. 13 Jan. 2017.