Exercise-Induced Pulmonary Hemorrhage—An Occupational Hazard of High-Speed Exercise

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1. Introduction

Exercise-induced pulmonary hemorrhage, or EIPH as it is better known, is defined as bleeding from the lungs during exercise. This hemorrhage results in the accumulation of varying volumes of blood in the pulmonary interstitium and airways. Veterinary thinking regarding EIPH has evolved greatly over the last 45-50 years. The advent of flexible fiberoptic tracheoendoscopy (TE) and the seminal work of Pascoe et al. introduced the term “exercise-induced pulmonary hemorrhage” and showed that the prevalence of EIPH in Thoroughbred racehorses was >50% based on a single post-race endoscopic examination. Previously, EIPH had been generally regarded as infrequent and characterized by post-exercise epistaxis. The initial study by Pascoe et al. was followed by a series of additional reports based on TE that indicated that the prevalence of EIPH after racing was similar in Standardbred and Quarter Horse racehorses. Horses were regarded as “bleeders” or “non bleeders” and EIPH was considered to be an abnormality or a disease. It was widely presumed that EIPH impaired performance and post-exercise TE became a common diagnostic test in horses that had trained or raced poorly.

Subsequent studies involving multiple post-race TE of Thoroughbreds and/or the counting of red blood cells (RBC) or visually evaluating the color from post-exercise bronchoalveolar lavage fluid (BALF) led to the recognition that the prevalence of EIPH was greater than had been thought when based on results of a single post-exercise TE. Additional reports of EIPH in horses engaged in other high-speed activities such as polo, barrel racing, endurance racing, and steeplechasing supported the suggestion that EIPH is associated with any equine performance involving high-speed exercise. These publications and others documenting evidence of EIPH in the lungs of 18-22 month-old Thoroughbreds in early training and post-race in other 2-yr-olds have led to the realization that the fundamental cause of EIPH must be physiologic rather than pathologic. To think otherwise implies that all horses that exercise at high speed have some degree of pulmonary pathology, regardless of their age, when they first experience EIPH. Such a premise appears to be untenable, with no evidence to support it. However, the presence of blood in the airways and pulmonary interstitial tissues does have a pro-inflammatory effect, particularly in the face of repeated hemorrhagic episodes. In some cases this inflammation is markedly progressive and results in severe pathology that could be career ending or life threatening with episodes of EIPH, when based on a grade or score reflecting severity, tending to become more severe as the number of lifetime race.
starts increases. Under these circumstances, the affected areas of lung can justifiably be regarded as diseased and the presence of these inflammatory changes probably exacerbates the severity of EIPH. However, this does not mean that the underlying cause of EIPH per se is a disease.

While post-exercise TE remains the most widely accepted test for assessment of EIPH, it has been recently shown that it is a relatively insensitive test when compared to BAL. Based on a study of 102 horses that underwent both TE and BAL after a simulated race, about 40% of horses that had EIPH based on analysis of BALF were negative on TE; in other words, TE was associated with a large number of false negative diagnoses of EIPH. In contrast, the sensitivity of BAL approached 1.0, with 99/102 horses positive for EIPH based on a BAL red blood cell count > 992 cells/μl recovered BAL fluid and/or TE. This strongly suggests that EIPH is a ubiquitous event in Thoroughbred racehorses and that its underlying cause is likely linked to the physiologic responses to high-speed exercise that characterizes these events (i.e., EIPH is an occupational hazard for horses engaged in these types of sports).

2. The Pathophysiology of EIPH

The fundamental cause of EIPH is generally regarded as being pulmonary capillary stress failure. This occurs when the capillary transmural pressure (Ptm; the difference in pressure between the inside and outside of the capillaries) exceeds a threshold value. According to cadaveric studies this threshold lies between 75 and 100 mmHg in equine lungs, higher than the equivalent values in rabbits and dogs. Ptm recently measured during high-speed treadmill exercise was reported to exceed mean maximum values of 160 mmHg in some horses. One of the principal reasons that horses competing at high speed or maximal exercise intensities are such elite athletes is due to the volume of RBCs stored in the spleen while at rest and the ability of these animals to autotransfuse or “blood dope” themselves with these cells in response to sympathetic nervous stimulation. Their circulating blood volume increases by up to 50% as a result. This ability to increase circulating blood volume appears to be central to the ubiquitous nature of EIPH in equine athletes undergoing strenuous exercise. Pulmonary arterial hypertension always develops in horses exercising at high or maximum speed (multiple reports >120 mmHg with mean pressures > 90 mmHg; summarized by West et al), with this hypertension widely proposed to be responsible for the intravascular pressures associated with pulmonary capillary stress failure. However, arterial pressures rarely, if ever, result in increased capillary pressure, whereas only mild increases in venous pressures can result in increased intravascular capillary pressures. One of the principal determinants of pulmonary venous and capillary pressure is left atrial (LA) pressure. Volume expansion-related increases in left atrial pressure, particularly end diastolic pressure, probably exert a greater effect on pulmonary capillary pressure than the direct effects of pulmonary blood volume expansion. Further insight into understanding how marked increases in LA and pulmonary venous pressures play a key role in EIPH can be gleaned from the pathophysiology of the left-sided cardiac failure. Increases in pulmonary venous and capillary pressures are a hallmark of classic left-sided diastolic heart failure due to the inability of the LA to fully accommodate blood volume during diastole (i.e., volume overload). This form of heart failure is characterized by increased LA diastolic pressure and left ventricular filling pressure, increased pulmonary venous and capillary pressure, and pulmonary arterial hypertension.

Horses galloping at high speed are clearly not in heart failure per se. However, the effects of the splenic contraction-induced rapid expansion of the circulating blood volume on the left heart could be equated with a transient left-sided diastolic failure condition. One of the causes of this diastolic dysfunction is volume overload secondary to a marked increase in circulating blood volume. The most characteristic clinical sign in these cases is a marked increase in LA diastolic and left ventricular filling pressures and pulmonary artery wedge pressure (PAW). PAW is an excellent, albeit indirect, measure of LA pressure. At rest, the LA of a horse typically has a mean pressure of 3–8 mmHg, while that of maximally galloping horses measures in the range of 50–70 mmHg. If the pressure in the LA is that high, then it is inherent that in order for there to be adequate blood flow through the pulmonary circulation, the pulmonary venous and capillary pressures must be higher than LA pressure. Under these conditions, Ptm exceeds the threshold for pulmonary capillary stress failure and EIPH occurs. Direct measurement of LA pressure in exercising horses is technically extremely difficult. Left ventricular filling or end diastolic pressure (LVED) is, however, a valid indicator of LA pressure. The left ventricle of equine athletes is relatively stiff and lacking in compliance, making it almost impossible for horses to accommodate a large increase in circulating blood volume at high heart rates without an associated increase in LVED. Horses galloping on a treadmill with heart rates greater than 200 bpm have marked increases in left ventricular diastolic pressures. Pressures in the latter study were significantly correlated with EIPH score, BALF RBC, PAW, and Ptm. When 14L of blood was acutely removed and horses exercised at the same speed, the LVED, PAW and Ptm decreased as did the severity of EIPH according to both EIPH score and BAL red blood cell number. Replacement of the previously removed blood was associated with a return of these respective pressures to their initial values with EIPH significantly more severe than following blood volume depletion. These data strongly suggested that
there is a close link between circulating blood volume and EIPH. Furthermore, because of the autotransfusing capability of the spleen and its importance relative to the ability to gallop fast despite the impact it has on LVED and P\textsubscript{fr}, it is hard to imagine that horses can be athletically competitive at high speed without experiencing some degree of EIPH (i.e., it is an occupational hazard).

3. EIPH and Performance

As understanding of the factors responsible for EIPH grows, the critical question regarding the condition is moving from “Is it a bleeder or not?” to “How bad was it?” The degree or severity of EIPH is usually assessed by applying a widely accepted grading scale that was first published in 2005.\textsuperscript{21} This score is usually based on a single TE that almost always takes place 30–90 mins after the completion of exercise. There are 5 grades that can be assigned: 0, 1, 2, 3, and 4, with the prevalence of grades 3 and 4 EIPH being <0.1 (10%) in any population of horses that exercises regularly at high speed.\textsuperscript{36} Several studies involving large numbers of flatracing horses have indicated that a horse’s performance will be adversely affected by grade 4 EIPH.\textsuperscript{36–38} The largest of the three studies also suggested that EIPH was more likely to reduce performance if the grade was \( \geq 3 \), when a different statistical model was applied to the dataset.\textsuperscript{36} In this instance, horses with EIPH \( \geq 3 \) were significantly faster in the early and middle sections of a race but then slowed as compared to those with EIPH \(< 3 \), which tended to accelerate their average speed over the last 600 m of a race. It is also notable that there was considerable variability in the finishing positions of individual horses in all 3 studies,\textsuperscript{36–38} regardless of EIPH grade, meaning that horses with EIPH \( \geq 3 \) can and do win races or finish in the placings. However, when horses with grades \( \geq 3 \) are considered as a population, they are less likely to win.\textsuperscript{36–38} Whether they are also less likely to finish second or third is equivocal when the results of these three studies are compared. Applying a population finding to an individual is an inexact science. Horses with grade 0 EIPH based on TE can have a dark red appearing BALF with a very high BALF RBC.\textsuperscript{8,9} TE EIPH grade is only weakly correlated with BALF RBC,\textsuperscript{8} with about 1/3 of grade 0 cases being false negatives.\textsuperscript{8} This might not matter from the perspective of whether undetected EIPH could have affected performance, as it is unlikely that these false negative TE cases were severe enough, based on BALF RBC, to have adversely impacted performance. There is currently no BALF RBC scale that relates EIPH severity to BALF RBC. There is a wide range of BALF RBC numbers associated with any given EIPH TE grade,\textsuperscript{8,9} and it may be that while BAL greatly reduces the number of false negative diagnoses of EIPH, it is no better than TE when it comes to assessing the severity of EIPH. It is generally assumed that the severity of EIPH and the likelihood that it will interfere with performance is dependent on the amount of EIPH. However, there is still no accurate way to quantitate the volume of blood present in the airways and pulmonary interstitium following a bout of EIPH, as determining BALF RBC is, at best, semi-quantitative. Instillation of 100 ml of autologous blood into the dorsocaudal region of each lung about 30 mins before a supramaximal treadmill run to fatigue reduced horses’ ability to perform, based on a decrease in maximum oxygen consumption and run time to fatigue.\textsuperscript{39} This was in contrast to another study in which infusion of the same area of just the right lung with 100 ml autologous blood failed to demonstrate any significant effect on the same parameters.\textsuperscript{40} Each of these studies involved 6 Thoroughbreds, and it may have been that this relatively small number of subjects meant that very large changes in measured variables were required before statistical significance was detectable. Extrapolations based on the number of erythrocytes in circulating blood at the end of exercise and the number of BALF RBC suggest that volume of blood collected by BAL is a lot less than 100 ml. In summary, there is little doubt that EIPH can affect performance in some horses. What proportion of horses might be affected is unclear although, based on the largest study, this appears to be <10% of the total number of horses racing.\textsuperscript{36} The relationship between EIPH and performance is further clouded by the fact that the severity of EIPH in an individual horse can vary from start to start when based on TE EIPH grade.\textsuperscript{41} Therefore, it may be that even when EIPH does impair performance, it does so intermittently. The extent to which an occurrence of EIPH grade \( \geq 3 \) in an individual horse is predictive of future episodes of equivalent or worse severity requires investigation, even though the severity of EIPH tends to worsen as the cumulative number of race starts increase when populations of horses are considered as a whole.\textsuperscript{14,23}

Acknowledgments

The Author has been a recipient of research funds from the Grayson-Jockey Club Research Foundation and some of the work supported by that organization is cited in this paper.

Declaration of Ethics

The Author has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest

The Author has no conflicts of interest.

References


