

Exercise-Induced Pulmonary Hemorrhage

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1. Introduction

Exercise-induced pulmonary hemorrhage (EIPH) is ubiquitous among Thoroughbred racehorses throughout the world, and there is no apparent important geographic variation in incidence of the condition.^{1–3} Although EIPH is very common, the exact incidence of the condition varies depending on the method of diagnosis and the frequency of examination. Examination of bronchoalveolar lavage fluid (BAL) or transtracheal aspirate from horses in training or racing reveals evidence (presence of red blood cells or hemosiderin-laden macrophages) of pulmonary hemorrhage in almost all such horses.^{4,5} However, bronchoscopic examination of horses after racing is currently the preferred means of detecting and quantifying EIPH in horses.⁶ Examination of Thoroughbred horses within 2 h of racing shows an incidence of EIPH of between 42% and 90%, depending on whether the horses are selected for examination because of the presence of epistaxis or other clinical abnormalities or are selected at random.^{2,7–9}

This review will consider evidence of the cost of EIPH to racing industries, the methods of assessment of the severity of EIPH, and the association of EIPH and racing performance. Results of recent studies are discussed.

2. Cost of EIPH

The cost to the industry of treating horses for EIPH has not been determined. The costs of administra-

tion of furosemide are readily estimated (see below), but the costs of other treatments, absences from racing because of EIPH, shortened racing careers, and impaired performance have not been determined. Conservatively estimated, this cost could easily exceed \$400/horse/yr (and could be as high as \$500–1000/yr). For example, costs associated with endoscopic examination (two to three examinations annually at \$50–75 each), or alternatively, herbal and hormonal treatments (\$1–5/day), easily amount to >\$400 annually. This does not include the costs associated with furosemide administration or the opportunity costs of lost racing days, poor performance, and shortened racing career. Spread over the 250,000 Standardbred and Thoroughbred racehorses starting annually in the United States, the total cost of EIPH to the Thoroughbred and Standardbred racing industries may well exceed \$100,000,000/yr.

The high incidence of EIPH in racehorses and the recognition of the adverse effect of EIPH on performance results in the widespread use of furosemide in racehorses in the United States. Ninety percent of Thoroughbred and 50–70% of Standardbred racehorses receive the drug before racing. Administration of furosemide to Thoroughbred and Standardbred horses racing in the United States incurs a cost of \$17,000,000–35,000,000 annually. Costs associated with use of furosemide are incurred not just for injection of the drug into horses before racing (“direct”

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costs) but also for diagnosis of EIPH to determine eligibility for furosemide administration, clerical and administrative costs associated with enforcing policies governing use of furosemide, such as supervision of drug administration and documentation in race records and programs, and drug testing before or after racing to ensure appropriate dosing.

The direct cost of administration of furosemide, which includes the veterinary fee and cost of drug and supplies, varies geographically but is between \$20 and \$30 for one administration.¹⁰ Costs associated with enforcement of rules governing use of furosemide, including documentation and drug testing, are estimated at an additional \$25–\$35/horse. The estimated total cost of furosemide administration is ~\$50/dose but may be as high as \$65/dose. These estimates of the total cost of furosemide use in racehorses are the same as estimates made in 1995; therefore, they are conservative estimates.¹¹

There were 444,586 starts by 107,437 horses in Thoroughbred racing in the United States in 2003.¹² Assuming that furosemide is administered to 90% of these starters and that there is no cost for horses not administered furosemide, the direct cost of furosemide administration is \$10,003,150 annually ($444,586 \times 0.9 \times \25). However, if the total costs associated with furosemide administration are considered, the annual cost for administration of furosemide in Thoroughbred racing is \$20,006,300 ($444,586 \times 0.9 \times \50) and could be as high as \$28,000,000.

Similarly, there were 635,292 Standardbred starts in the United States in 2003 as reported by the U. S. Trotting Association in October of 2004. If 50% of these horses were administered furosemide (a conservative estimate of the prevalence of furosemide administration) at a direct cost of \$25/dose, the cost to the industry would be \$7,941,000. The total cost, assuming \$50/dose, is \$15,882,000 annually.

Therefore, the cost to the racing industry of furosemide administration is over \$35,800,000 annually, and EIPH costs the racing industry over \$100,000,000 annually.

3. Assessment 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 BAL fluid or tracheal aspirates for evidence of hemorrhage. As discussed above, bronchoscopic examination during a short interval after racing is the widely accepted technique for detecting EIPH. This technique has been used by many clinicians and investigators over the past 20 yr to detect EIPH.^{2,3,7,13–17} In studies in which horses have been examined on more than one occasion, the reproducibility of the examination has been documented. Raphael and Soma⁷ found a highly significant ($p < 0.0001$) relationship between the

presence of EIPH on one occasion and during a subsequent examination after another race. Similarly, the level of agreement for detection of EIPH between examinations after consecutive racing in Thoroughbred race horses not treated with furosemide was highly significant ($p < 0.001$).¹⁴ As in Thoroughbred racehorses, there is a clear and significant association between the presence of EIPH found in consecutive examinations in Standardbred horses.¹⁸ Collectively, these data indicate that if EIPH is detected by bronchoscopic examination on one occasion, it is very likely that it will be detected during a subsequent examination.

Bronchoscopic examination can also be used to estimate the severity of EIPH through use of a grading system. The grading system first used by Pascoe et al.¹³ has been widely adopted with modifications. The grading system developed by Pascoe et al.¹⁴ uses a scale of four levels from 0 (no hemorrhage visible) to 3 (streak of blood > 5 mm wide) and its repeatability on consecutive examinations in Thoroughbred horses has been shown. Of 56 horses examined at least twice, 21 (38%) horses had identical scores on each examination, 26 (41%) had scores that differed by one grade, and 9 had scores that differed by ≥ 2 grades. These results show the repeatability for scoring severity of EIPH by bronchoscopic examination of horses.

A recent modification of the Pascoe et al.¹⁴ system of grading EIPH has been published.¹⁹ The system used the following criteria to grade EIPH (Fig. 1):

- Grade 0: no blood detected in the pharynx, larynx, trachea, or mainstem bronchi.
- Grade 1: presence of one or more flecks of blood or two or fewer short (less than one-quarter the length of the trachea) and narrow ($< 10\%$ of the tracheal surface area) streams of blood in the trachea or mainstem bronchi visible from the tracheal bifurcation.
- 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 $> 90\%$ of the tracheal surface with blood pooling at the thoracic inlet.

The repeatability of presence and severity of EIPH was assessed by examining 115 horses twice. Horses were examined within 2 h of racing, and EIPH was detected by tracheobronchoscopic examination. Presence and severity of EIPH (Grades 0–4) were evaluated later by three independent observers masked to the horse's identity. The mean difference between examinations was 0.16 grades with a standard deviation of 0.88 grades. The

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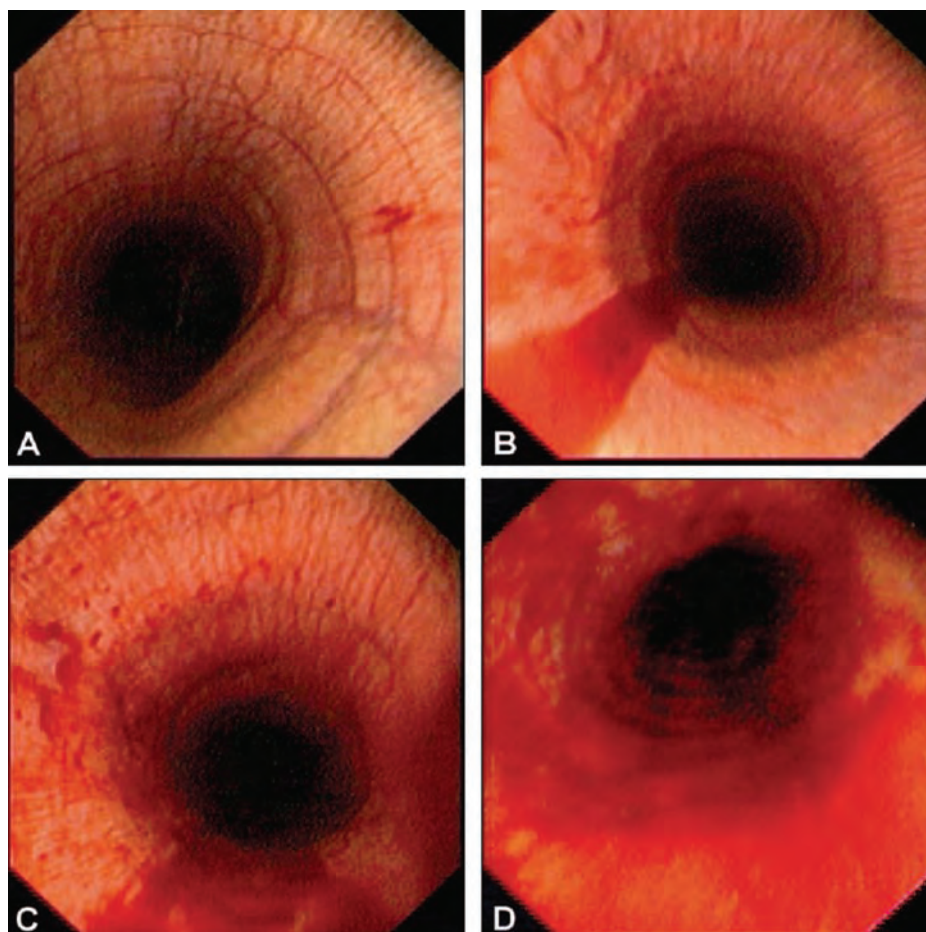


Fig. 1. Illustrative examples of grade 1 (A), 2 (B), 3 (C), and 4 (D) pulmonary hemorrhage in Thoroughbred racehorses. Grade 0, in which blood is not detected during tracheobronchoscopic examination, is not illustrated. Reprinted with the permission of the *Journal of the American Veterinary Medical Association*.¹⁹

weighted κ statistic was 0.45, indicating fair agreement between repeat studies.

The inter-observer concordance for grading severity of EIPH in Thoroughbred racehorses by tracheobronchoscopic examination was tested.¹⁹ Weighted κ statistics ranged from 0.75 to 0.80 grades. All observers agreed or two of three agreed with the third observer differing by ≤ 1 grade in 99.4% of observations. This study shows the high inter-observer reliability of tracheobronchoscopic assessment of EIPH in Thoroughbred racehorses when the examination is conducted by experienced veterinarians. The concordance among investigators is sufficient to justify use of this grading system in further studies of EIPH and in the clinical description of EIPH.

Recent experimental studies have reported on the use of red cell numbers in BAL fluid as a quantitative indicator of EIPH severity.^{20–22} However, this indicator of EIPH severity has not been validated nor proven to be more reliable or repeatable than bronchoscopic examination, and scoring and use of the technique has been associated with considerable controversy.^{23–25} Furthermore, considerable concern exists over the suitability of measuring red cell counts in BAL fluid for quantization of EIPH. This

is because only a small area of the lung is examined by lavage and there is a risk that this area of lung may not be representative of the lung as a whole, similar to the situation of BAL examination of horses with pneumonia.²⁶ In addition, studies using red cell count in BAL fluid as an indicator of severity of EIPH have all been experimental studies conducted under controlled laboratory conditions. There are no reports of the use of this indicator in horses immediately after racing, likely because of concerns about the validity of the technique and because of the logistical difficulty associated with performing the procedure at racetracks and on privately owned horses. There is little doubt that detection of red cells or hemosiderin in BAL fluid is a sensitive indicator of past hemorrhage.⁴ However, the high sensitivity of the test is attributable to the persistence of red blood cells in BAL fluid for up to 14 days after hemorrhage, whereas hemosiderin-laden macrophages are present for at least 4 wk.^{27,28} The high apparent sensitivity complicates assessment of severity of a recent episode of EIPH, because the presence of residual red cells yields an incorrectly high estimate of the red cell count attributable to the most recent episode of EIPH. For these reasons, at the present time, quantification of red

cells in BAL fluid cannot be used to estimate severity of EIPH.

4. EIPH and Race Performance

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 BAL fluid; others have blood evident on endoscopic examination of the tracheobronchial tree 30–90 min after strenuous exercise or racing.^{4,29} Severe EIPH, such as that associated with epistaxis, undoubtedly results in poor performance, and, on rare occasions, it may lead to death in Thoroughbred racehorses.^{30–32} However, the effect of less severe EIPH on race performance of Thoroughbred horses has not been conclusively determined. A relationship between finishing position and incidence of EIPH, diagnosed by bronchoscopic examination, was not detected for 191 Thoroughbred racehorses that finished in first, second, or third place.¹³ Furthermore, there was no relationship between the proportion of horses with EIPH and placing (first, second, or third versus lower placings) in another 98 horses.¹³ Similarly, Raphael and Soma⁷ did not detect a relationship between finishing position and proportion of horses with EIPH in 191 Thoroughbreds examined after racing.⁷ These results in Thoroughbred racehorses are similar to those reported for Standardbred racehorses.^{18,33}

In contrast to the studies discussed above, Mason et al.³ reported that Thoroughbred horses finishing in the first three positions had less severe EIPH than did horses finishing in lower positions. These authors examined 452 Thoroughbreds racing in Hong Kong. Some horses were examined more than one time, and the reason or means of choosing horses for examination was not provided; therefore, there may be a possibility of over-representation of poorly performing horses. Of horses finishing in the first three places, 43.9% had evidence of EIPH on bronchoscopic examination after racing, whereas 55.9% of horses finishing from fourth to fourteenth place had evidence of EIPH. The authors provide no statistical analysis of the data. Simple statistical analysis of the data presented by these authors suggests that there is a difference (χ^2 , $p < 0.05$) in the incidence and severity of EIPH of winners and losers. However, this simplistic statistical analysis may be misleading, because many of the horses were examined after more than one race. Additionally, the presence of confounding factors could not be taken into account or controlled for in our simple statistical analysis.

A recent study showed a strong association between presence of EIPH, its severity, and poor performance.³⁴ The experiment was a cross-sectional study of Thoroughbred racehorses in Victoria, Australia. This site was chosen, because day of racing use of furosemide is not permitted. Horses were

enrolled in the study before the race in which they were examined. Horses for study were identified before racing. Horses to be studied were identified during the 24–48 h preceding the race.

EIPH was detected and quantified by tracheobronchoscopic examination of unsedated horses within 120 min of racing. The examination was recorded on videotape for subsequent analysis by three individuals blinded to the identity of the horse and its race performance.

Tracheobronchoscopic examinations were performed on 744 horses competing in 202 races at 26 race meetings. During the period of study, there were 2396 starts by 1428 horses in flat races at meetings at which horses were examined. Overall, 52.1% of horses eligible for participation in the study were examined. The age distribution of the study sample did not differ significantly ($p > 0.05$) from that of the overall population of horses racing during the study period. Of the 744 horses, 306 females, 375 geldings, and 63 intact males were examined, and the distribution of sexes in the sample group did not differ ($p > 0.05$) significantly from that of the population of horses available for study. Fifty-four horses (7.3%) finished in first place, and 170 (22.9%) finished in the top three places. The proportions of horses examined that won ($p = 0.3$) or finished in the top three places ($p = 0.7$) were not different than that in the population of horses from which the study sample was drawn. Blood was detected in the airways of 412 (55.3%) horses.

Horses with EIPH graded ≤ 1 were 4.03 times more likely to win (range = 1.45–14.3 grades, 95% CI, $p = 0.006$) and 1.78 times more likely to finish in the first three positions (range = 1.05–3.07 grades, $p = 0.03$) than were horses with EIPH graded ≥ 2 .

Horses with EIPH graded ≤ 1 finished farther behind the winner than did unaffected horses (4.36 ± 1.16 m versus 2.60 ± 1.07 m, $p = 0.002$). The distance that horses with EIPH finished behind the winner was related to the grade of EIPH, and horses with higher grades finished significantly ($p = 0.025$) farther behind the winner. Post-hoc testing detected a significant difference in distance behind the winner for horses with EIPH graded 2 compared with EIPH graded 0.

Earnings were significantly associated with EIPH status. Horses with EIPH graded ≤ 1 were 3.03 times more likely to earn amounts in the top 10% (>AUD14300) of money earned (range = 1.33–7.96 grades, $p = 0.002$).

5. EIPH and Career Productivity

The incidence and severity of EIPH tend to increase with increasing age of the horse, leading to the plausible suggestion that EIPH is progressive with continued racing.³⁵ If EIPH is progressive and if the presence of EIPH is associated with reduced athletic capacity and poorer race performance, then it could be expected that young horses with more severe EIPH will have a shortened career and lower values

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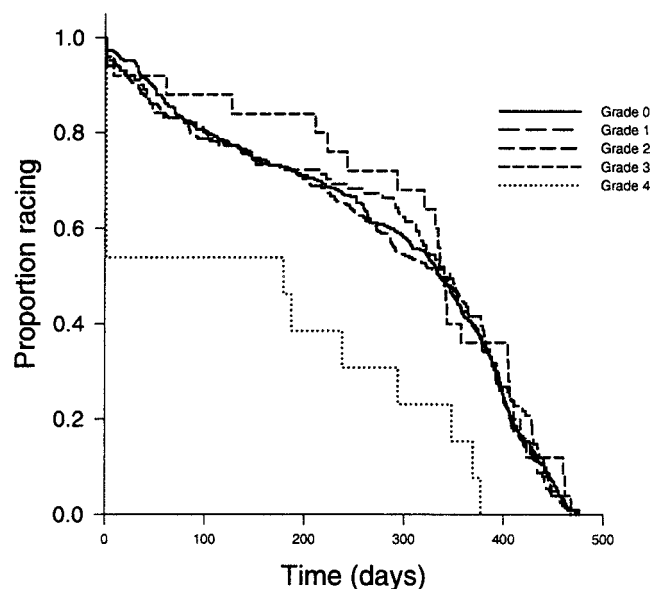


Fig. 2. Proportion of horses racing up to 480 days after examination as a function of EIPH status at day 0.

in measures of career productivity. What is unclear, however, is whether the severity of EIPH in young to mid-career racehorses is related to subsequent career performance. In other words, does the severity of EIPH in a young to mid-career horse relate to the longevity and productivity of its career?

As part of the study of race performance described above, we have an on-going study on the association between severity of EIPH (grade 0–4) and career longevity. Figure 2 is a Kaplan-Meier survival curve that depicts interim results of this study (CIs are omitted for clarity). Day 0 was the day of endoscopic examination. Grade refers to the severity of EIPH. These results are for up to 480 days after initial examination. Career longevity was significantly shorter ($p < 0.001$, log-rank test) for horses with the most severe EIPH.

6. Conclusions

EIPH is a common occurrence in racehorses. The presence and severity of the condition can be assessed by tracheobronchoscopic examination after racing. This method of assessment has excellent inter-observer agreement, and it is moderately repeatable within the same horse on separate occasions. The condition is associated with impaired performance and, possibly, with a shortened racing career.

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