

Training related risk factors for exercise induced pulmonary haemorrhage in British National Hunt racehorses

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Abstract

Background: Exercise induced pulmonary haemorrhage (EIPH) is an important condition of horses performing high intensity exercise, with reported prevalence among racehorses of up to 95%, based on the detection of blood on tracheobronchoscopy. Previously identified risk factors include age, sex, season, race type, years spent in racing and lower airway inflammation.

Objectives: To estimate the prevalence of EIPH in British National Hunt racehorses as indicated by two outcome measures: presence of tracheal blood on tracheobronchoscopy, and presence of moderate-large (significant) proportions of haemosiderophages in tracheal wash (TW) fluid; and to identify training-related risk factors for these indicators of EIPH.

Study design: Prospective longitudinal study.

Methods: Data from tracheobronchoscopy and TW cytology were analysed using univariable and multivariable mixed-effects logistic regression.

Results: 1184 observations, from 177 horses, were analysed. The prevalence of tracheal blood was 7.2% (95%CI: 5.8, 8.8) and significant haemosiderophages in TW fluid was 36% (95%CI: 33.3, 38.8). Increased time in training was significantly associated with increased odds of EIPH. For each additional year spent in training the odds of tracheal blood and presence of significant proportions haemosiderophages increased approximately 1.5-fold (OR = 1.5; 95%CI: 1.1-2.0; $P = .005$; and OR = 1.5; 95%CI: 1.3, 1.8; $P < .001$, respectively). Current inflammation was associated with previous haemorrhage, but not current haemorrhage.

Main limitations: There are no standardised measures for quantification of TW cytological parameters for EIPH diagnosis. Few horses were examined following jumping. Recent racing dates were not included in analysis.

Conclusions: Increasing time in training was a risk factor for both indicators of EIPH. Current inflammation was associated with previous haemorrhage, but not current or future haemorrhage, suggesting that haemorrhage leads to inflammation but not that inflammation leads to haemorrhage. Overall, our findings are consistent with the

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capillary stress failure theory of EIPH. The development of standardised measures for TW cytological diagnosis of EIPH is warranted.

KEYWORDS

EIPH, horse, National Hunt, racehorse

1 | INTRODUCTION

Exercise-induced pulmonary haemorrhage (EIPH) is defined as bleeding that occurs in the lungs during exercise.¹ It is an important disease of horses performing high intensity exercise, most frequently identified in Thoroughbreds and Standardbreds racing at high speed.¹

Diagnosis is based on detection of epistaxis, blood on tracheo-bronchoscopy or presence of red blood cells (RBCs) in bronchoalveolar lavage (BAL) or tracheal wash (TW) fluid.¹ Tracheobronchoscopy and tracheal washes are commonly carried out on British racing yards for evaluation and management of respiratory disease. BAL is infrequently used as it is less acceptable to trainers and owners due to a perceived invasiveness and requirement for sedation and rest following sampling.^{2,3}

The reported prevalence of EIPH in racehorses, diagnosed by visualisation of tracheal blood is high, ranging from 43% to 75% of horses on a single examination and up to 95% with repeated examinations.⁴⁻⁷ EIPH has been reported to occur most frequently following racing.⁸

EIPH may have welfare and performance implications, with conflicting evidence regarding its effect on race day performance. No association between mild to moderate haemorrhage and inferior race day performance was detected in a population of Thoroughbred racehorses in Australia⁹, while impaired performance in Thoroughbred racehorses not receiving prophylactic interventions has been reported.¹⁰ Some racing staff and veterinarians working with racehorses suggest that EIPH might be associated with superior performance, indicating greater racing effort.¹¹

Known risk factors for EIPH include increasing age, being male,¹² ambient temperature below 20°C, winter and spring,¹³ jump versus flat racing, increasing ground hardness, accumulated years spent racing,¹⁴ number of starts¹³ and lower airway inflammation.⁶

Much of the existing literature focuses on racing-related risk factors, athletic capacity, career longevity and efficacy of prophylactic interventions, usually in flat racehorses, a younger population than the National Hunt (NH) population. British Racing Statistics report that 85% of NH horses are over 5 years old, compared with less than 20% of flat racehorses.¹⁵

EIPH is a complex disease with proposed pathogeneses of pulmonary capillary stress failure¹⁶ or impact-induced trauma.¹⁷ Pulmonary capillary stress failure refers to mechanical failure of the thin blood-gas barrier in the alveoli under high capillary pressures and large negative airway pressures, as generated during intense exercise.¹⁶ A proposed mechanism for the association between inflammation and EIPH is that inflammation leads to airway obstruction resulting in increased pleural pressures and subsequent bleeding due to capillary stress failure.¹⁴ The presence of blood in the airways leads to further airway inflammation.¹⁸ The impact-induced trauma theory proposes that the force following forelimb ground strike is transmitted via the scapula and ribs

to the thorax where pressure waves are reflected along the spinal and diaphragmatic walls, leading to shearing forces within the lung parenchyma. The level of force is considered sufficient to cause oedema and haemorrhage within the lung parenchyma.¹⁷ Accumulated time in training may be a more important risk factor for EIPH than age. It has been theorised that increased pulmonary pressures during exercise leads to venous remodelling and suggested that the degree of this remodelling may depend on genetic susceptibility combined with frequency of high-pressure events occurring during strenuous exercise.¹⁹

The current study examined a population of NH racehorses with different training histories. Some entered training for the first time as 4-year-olds while others entered NH training from flat racing, where training begins at around 2 years of age. The aim was to describe EIPH in NH racehorses. The objectives were to estimate the prevalence of EIPH as indicated by two outcome measures: presence of tracheal blood and presence of moderate-large (significant) proportions of haemosiderophages in TW fluid; and to identify training-related risk factors for these outcome measures. The hypothesis was that the occurrence of EIPH would increase with time in training.

2 | MATERIALS AND METHODS

A prospective longitudinal study followed 177 healthy NH racehorses in training on five training yards over two seasons (August 2003 – April 2004).²⁰ Yards were enrolled based on willingness to participate and being within 4 hours drive of the diagnostic laboratory. Random sampling from 3 strata was used to recruit around 15 horses from each yard at the start of each season. The strata were: (1) ex-flat or ex-point-to-point racehorses entering NH training for the first time, (2) NH horses entering training for the first time and (3) older horses that had been in training on NH yards for at least 12 months. Horses were examined and sampled monthly while in training.²⁰ The total number of observations varied between individuals. The dataset was prepared using Microsoft Excel 2016 (Microsoft Excel) and analysed using Stata 14 (Stata Corporation).

Thoroughbred age, in whole years, was calculated from the year of birth, assuming a birth date of 1 January. Time in training was calculated from the date the horse entered training for the first time, based on BHA records, and categorised in yearly increments, up to 5 years or more. Autumn comprised August, September and October; winter November, December and January; and spring February, March, April and May. No sampling was conducted in June or July when participating yards had a training break. Activities on the day of sampling were recorded, with stabled, walk, horse walker, trot and swim considered low-impact activities and grouped as the reference stratum.²¹ Canter

was considered medium-impact work and gallop and jumping as high-impact work. Stabled horses were those sampled prior to work or having a rest day. Any nasal discharge was recorded as present or absent immediately prior to tracheobronchoscopic examination. Information about current medications and those administered within the previous month were recorded from yard staff.

Examination and sampling of horses took place within 90 minutes following exercise for horses exercised on the day of sampling. A standardised protocol was used. Tracheobronchoscopy, to the level of the carina, was performed without sedation using a flexible endoscope (1.4 m or 2 m). The presence and amount of visible tracheal mucus was recorded and scored from 0 to 3, where 0 = none, 1 = small amounts (isolated flecks), 2 = moderate amounts (multiple larger blobs) and 3 = large amounts, at least partly confluent.²² The presence of blood was recorded and scored in the same way. These scores were collapsed into binary variables indicating presence (score 1-3) or absence (score 0). A TW sample was collected transendoscopically, in a standard manner, from each horse undergoing tracheobronchoscopy. 30 mL of phosphate buffered saline was instilled into and aspirated from the distal trachea using a sterile polyethylene catheter. A portion of the retrieved sample was combined with an equal volume of 10% formal saline for cytological examination. Cytological assessments were performed using routine diagnostic methods adapted from those described by Whitwell and Greet (1984)²³, with samples stained with haematoxylin and eosin.²⁰ Neutrophils were recorded as a proportion of total nucleated cells and categorised as 0%–10%, 11%–25%, 26%–50% and greater than 50%. Proportions of macrophages containing haemosiderin (haemosiderophages) were scored as none (0%), occasional (<10%), small proportions (10%–25%), moderate proportions (25%–50%) or large proportions (>50%). Moderate and large proportions were classified as significant haemosiderophages, likely indicating a substantial recent bleed, for analysis.

Auto-regressive variables were created from mucus, blood, neutrophil and haemosiderophage variables to indicate the status of these variables the previous month. Where observations from the preceding month were missing, including the first months' observations, auto-regressive variables were classified as missing.

The following were used as indicators of EIPH and recent EIPH, respectively:

- Tracheal blood: the presence of grossly visible blood on tracheobronchoscopy.
- Significant haemosiderophages: the presence of moderate and large proportions of haemosiderophages in TW fluid.

2.1 | Data analysis

Descriptive statistics summarised horse characteristics and number of tracheobronchoscopic examinations. The sample-level and horse-level prevalence of tracheal blood and haemosiderophages in TW fluid were calculated, with 95% confidence intervals (CIs).

Distributions of continuous variables were checked for normality using histograms and Shapiro-Wilk test statistic and summarised accordingly, using median and interquartile range (IQR). Linearity of associations between continuous exposure variables and outcomes were assessed by examining plots of the log odds, in conjunction with Wald tests and likelihood ratio tests.

Univariable analysis with mixed-effects logistic regression, including individual horse identification (ID) as a random effect and yard as a fixed effect to account for unmeasured variation between horses and yards respectively, identified exposure variables associated with each outcome. A P -value $<.2$ was set for inclusion in further analysis.

Multivariable mixed-effects logistic regression was conducted for each outcome measure, with yard retained as a fixed effect and horse ID as a random effect, irrespective of significance. A forward stepwise manual selection process was used to identify which exposure variables should remain in the final models. The likelihood ratio test (LRT) was used to compare models and a LRT P -value of $P < .05$ used as the threshold for retention in the final models. Crude and adjusted odds ratios (ORs) were compared to assess for confounding.

3 | RESULTS

A total of 177 horses contributed 1184 observations, of which 7.4% (87) were from female and 92.7% (1097) were from male horses.

Age ranged from 3 to 11 years with a median of 5 years (IQR:4,6). Time in training ranged from zero to 6 years with a median of 2 years (IQR:1,3).

Approximately 27.7% (328) of horses entered training for the first time as 4-year-olds, 22.5% (266) entered from flat racing and 49.8% (590) had been on NH training yards for at least 12 months.

The number of tracheobronchoscopic examinations per horse ranged from 1 to 18, with a median of 7 (IQR:4,9).

Tracheal blood was observed in 7.2% (95%CI:5.8, 8.8), haemosiderophages in 72.6% (95%CI:69.9, 75.1) and significant haemosiderophages in 36% (95%CI:33.3, 38.8) of samples. No episodes of epistaxis were recorded. At the individual horse-level, tracheal blood was observed in 26% (95%CI:20, 33), haemosiderophages in 94% (95%CI:90, 97) and significant haemosiderophages in 78% (95%CI:71, 84) of horses.

3.1 | Univariable analysis

The variables identified by univariable analysis for inclusion in multivariable analysis ($P < .2$) for presence of tracheal blood were sex, age, time in training, season, work type and presence of significant haemosiderophages (Table S1). For presence of significant haemosiderophages the variables were age, time in training, season, neutrophil proportions, previous tracheal blood, current antibiotics, and previous antibiotics. (Table S2).

There was significant evidence for a linear association between time in training and odds of both tracheal blood ($P = .004$) and

significant haemosiderophages ($P < .001$), and between age and odds of significant haemosiderophages ($P < .001$).

Likelihood ratio tests for departures from linearity were not significant, so age and time in training were analysed as continuous variables.

3.2 | Multivariable analysis

The explanatory variables that remained significantly associated with the outcomes and had a significant effect on the overall fit of the final models are presented with ORs, 95% CIs and Wald P -values in Table 1 for tracheal blood and Table 2 for significant haemosiderophages.

After adjusting for the other retained explanatory variables, time in training was associated with 1.5-fold increase in the odds of tracheal blood for each additional year spent in training. Odds of tracheal blood were almost twofold higher in winter and spring than in autumn. Male horses had 85% lower odds of tracheal blood than females. The presence of significant haemosiderophages was associated with approximately 5-fold increased odds of tracheal blood. Compared with low-impact work, medium-impact work was associated with a near 10-fold increase and high-impact work with a 60-fold increase in odds of tracheal blood.

Time in training was associated with 1.5-fold increased odds of significant haemosiderophages. Odds of significant haemosiderophages were approximately 1.9-fold and 1.6-fold higher in winter and spring compared to autumn. Odds of significant haemosiderophages increased with increasing neutrophil percentages. Recent tracheal blood was associated with 3.5-fold increased odds of significant haemosiderophages.

4 | DISCUSSION

EIPH is known to vary by horse population and exercise performed, leading to difficulties in comparing prevalence between studies. In this study, the prevalence of EIPH diagnosed by blood on tracheo-bronchoscopy was lower than previous reports. EIPH has previously been shown to occur more frequently following racing compared with training.⁸ This study population was examined following training only, and therefore the lower prevalence might be explained by differences in exercise intensity.¹⁶

Cytological methods of EIPH diagnosis frequently result in higher prevalence estimates than observation of epistaxis or blood on tracheobronchoscopy.^{1,6} In the current study, the 36% sample-level prevalence of significant haemosiderophages in TW fluid was markedly higher than the 7% prevalence of tracheal blood. Similar findings have been reported in horses in flat training, with a 51% prevalence of increased haemosiderophages and 4% prevalence of tracheal blood.⁶ Examination of TW samples for haemosiderophages potentially has the advantage of reducing the influence of short-term exercise intensity on EIPH diagnosis as research examining autologous installation of blood into the airways indicates that haemosiderophages can persist in the airways for at least 28 days.^{6,24} However, although the presence of haemosiderophages in TW fluid provides evidence of previous haemorrhage into the airways, the clinically significant proportions of these cells have not been determined.¹ Furthermore, the presence of haemosiderophages in TW fluid could result from other forms of pulmonary pathology, including pneumonia or pulmonary abscessation. This was unlikely in this population as all horses were outwardly healthy and in training at the time of sampling.

Explanatory variable	Stratum	Odds ratio	95% CI	P -value*
Sex	female	Ref.		
	male	0.16	0.039-0.64	.01
Years in training		1.51	1.13-2.02	.005
Season	autumn	Ref.		
	winter	2.38	1.07-5.27	.03
	spring	2.29	1.03-5.07	.04
Work type	low impact activity	Ref.		
	medium impact work	9.80	3.02-31.81	<.001
	high impact work	60.88	16.16-229.36	<.001
Significant haemosiderophages	absent	Ref.		
	present	4.92	2.55-9.46	<.001
Yard	1	Ref.		
	2	0.29	0.073-1.19	.09
	3	1.04	0.32-3.41	>.9
	4	0.29	0.097-0.87	.03
	5	0.58	0.17-2.01	.4

TABLE 1 Final 2-level Mixed effects logistic regression model for tracheal blood, with horse-level random effect ($P < .001$) and trainer level fixed effect ($n = 1184$)

*Likelihood ratio test.

TABLE 2 Final 2-level Mixed effects logistic regression model for significant haemosiderophages, with horse-level random effect ($P < .001$) and trainer fixed effect ($n = 930$)

Explanatory variable	Stratum	Odds ratio	95% CI	P-value*
Years in training		1.54	1.33-1.79	<.001
Season	autumn	ref.		
	winter	1.86	1.22-2.91	.004
	spring	1.56	1-2.43	.051
Neutrophil percentage	0%-10%	ref.		
	11%-25%	2.44	1.36-4.38	.003
	26%-50%	8.31	4.71-14.67	<.001
	>50%	9.70	5.11-18.38	<.001
Tracheal blood previous month	Absent	ref.		
	Present	3.49	1.65-7.39	.001
Yard	1	Ref.		
	2	0.36	0.18-0.71	.003
	3	1.88	0.99-3.59	.06
	4	1.24	0.69-2.22	.5
	5	0.86	0.46-1.61	.7

*Likelihood ratio test.

The median age and age range of the current study population were slightly older than those reported in previous studies of EIPH in horses in flat racing.^{6,25-27} Age was not significantly associated with EIPH in the current study. Cumulative measures of time in racing, such as number of starts, duration of racing career, years spent racing and age have previously been identified as risk factors for EIPH.¹ This study population allowed further examination of the association between EIPH and measures of time in training by comparing horses with different training histories. The data supported significant associations between time in training and both tracheal blood ($P = .005$) and significant haemosiderophages ($P < .001$), with the odds of both increasing 1.5-fold for each additional year spent in training.

The odds of tracheal blood and significant haemosiderophages were increased in both spring and winter, compared to autumn. Others have suggested that this could be attributed to shorter term accumulated racing and training, as these months correspond to the end of the NH racing season.⁶ Season is also a proxy measure for variations in ambient temperature and previous studies have demonstrated an increased risk of EIPH during colder weather.⁵

The type of exercise performed prior to tracheobronchoscopy was significantly associated with tracheal blood. Compared to low-impact activities, the odds of tracheal blood were increased for medium- and high-impact work. However, wide confidence intervals indicate that the OR estimates are imprecise, and these figures should be interpreted with caution. The observation of increasing odds of EIPH with increasing percussive impact of exercise undertaken corroborates previous studies where an increased risk of epistaxis was found following jump racing compared with flat racing, consistent with a theory of impact-induced trauma contributing to EIPH.¹⁴ In the current study, due to low numbers of horses jumping prior to tracheobronchoscopy, it was not possible to distinguish jumping from other high-impact exercise. Anecdotally, EIPH has

been associated with swimming,¹³ a low-impact activity, suggesting a mechanism other than percussive impact. The association between swimming and EIPH could not be examined further in the current study due to low numbers of horses swimming and none having tracheal blood following this activity.

The presence of >20% neutrophils in TW samples indicates airway inflammation.²⁸ The odds of significant haemosiderophages increased with increasing proportions of neutrophils in this study, consistent with observations that blood instilled into the airways leads to inflammation.¹⁸ However, we found no association between current inflammation or inflammation in the previous month and current tracheal blood. This suggests that inflammation associated with presence of significant haemosiderophages resulted from previous bleeding inducing pulmonary inflammation rather than current inflammation being a risk factor for current or future bleeding. These findings are consistent with a systematic review concluding there was low-quality evidence that EIPH leads to inflammation and very low-quality evidence that inflammation causes EIPH.¹¹ Haemosiderophages are a recognised cytological indicator of prior pulmonary haemorrhage and their presence in TW samples has been used in previous studies to indicate EIPH.⁶ The current study demonstrated fivefold increased odds of tracheal blood if horses had evidence of recent haemorrhage into the airways. As discussed by others, the high pulmonary pressures reached during intense exercise are sufficient to lead to capillary stress failure.¹⁹ Over time this leads to remodelling of the small pulmonary veins, resulting in reduced lumen diameters and further increased pressures. This is consistent with the conclusions drawn by another study which demonstrated moderate to high-quality evidence that EIPH is progressive.¹¹ This can also be related to the theory that horses that experience EIPH tend to be elite athletes and are therefore likely to exert themselves to the point of experiencing EIPH.¹⁵ Genetic variants associated with increased EIPH risk may have been maintained

in the Thoroughbred racehorse population due to enhanced muscle development and cardiovascular performance.¹⁹

The current lack of standardised measures for the quantification of cytological indicators of EIPH prevent direct comparison of results between studies. A limitation of the current study is that cytology was performed on TW samples, rather than BAL samples. Numerous studies have demonstrated poor agreement between TW and BAL cytology in the investigation of the lower airways, with BAL cytology reported to reflect lower airway disease more closely.²⁹⁻³¹ However, given the routine use of TW cytology in British racehorse populations the current study aimed to describe the frequency and risk factors for these routinely available outcome measures without attempting to re-define or validate the use of TW samples for diagnosis of EIPH. In relation to the classification of haemosiderophages for analysis, up to 94.7% of healthy racehorses in training have been shown to have some haemosiderophages on tracheal wash,²³ with a similar figure of 94% demonstrated in the current study. In another study haemosiderin was present in approximately 20% of alveolar macrophages in BAL samples from horses that experienced only mild haemorrhage, not detectable on tracheobronchoscopy, with the percentage of haemosiderophages increased for up to 3 weeks following strenuous exercise and returning to baseline levels after around 4 weeks.³² Therefore, given a lack of standardisation for diagnosis of EIPH based on TW cytology, moderate and large proportions of haemosiderophages, representing a proportion of $\geq 25\%$, were subjectively categorised as "significant" for the purposes of this analysis in order to distinguish horses that had recent substantial haemorrhage from those that had recent smaller haemorrhages, or substantial haemorrhages occurring more than a month ago. As horses were examined monthly, bleeds experienced a month or more previously would have been evident on the previous examination. This threshold reduced the likelihood of recording the same episode of EIPH, based on small numbers of residual haemosiderophages, twice.

A further limitation of our study is that horses were examined following training, not on race days, and few after jumping. Specific information about duration or intensity of work performed prior to examination or other training-related risk factors were not available for analysis. Racing history, such as recent race dates, results or days between race starts, was also not accounted for. No variables related to medication remained in the models. This may have been influenced by inaccuracies in the data and missing data and should therefore be interpreted with caution.

In conclusion, this study demonstrates significantly increased odds of EIPH with increasing time in training. It provides further support for the association between bleeding in the previous month and current inflammation,⁶ but not between current bleeding and previous inflammation, suggesting that inflammation observed may have resulted from previous haemorrhage, rather than being a risk factor for current or future haemorrhage. These findings support the capillary stress failure theory of EIPH, with increased time in training resulting in cumulative remodelling of the pulmonary vasculature, increasing susceptibility to EIPH through capillary stress failure with ongoing training. Cytological examination of TW samples was a more

sensitive indicator of EIPH than tracheobronchoscopy alone and the development of standardised measures would contribute to improved detection of EIPH, particularly during training. Although EIPH in racehorses may not be avoidable, identification of horses at risk could contribute towards improved preventive measures in the future.

ETHICAL ANIMAL RESEARCH

Ethics approval was obtained from the Royal Veterinary College Clinical Research Ethical Review Board (URN SR2018-1607).

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CONFLICT OF INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

T. McGilvray and J. Cardwell contributed to the study design and study execution. T. McGilvray performed the data analysis and prepared the manuscript with contributions by J. Cardwell. Both authors approved the final version of the manuscript.

INFORMED CONSENT

Owner consent was given for inclusion of the horses in the study.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/evj.13448>.

DATA ACCESSIBILITY STATEMENT

The data that support the findings of this study are available from the authors on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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