Welcome to Randlab’s TechTalk

In this issue, Dr Ellie Crispe from Murdoch University takes a fresh look at an old problem and summarises some of the recent advances in our understanding and treatment of Exercise Induced Pulmonary Haemorrhage (EIPH).

We are honoured that Dr Crispe has agreed to share some of the key findings on her recent PhD studies on the epidemiology and aetiology of EIPH and to offer some key practical tips on new management strategies.

Exercise Induced Pulmonary Haemorrhage

What’s New? Can We Manage This Disease Better?

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BSc, BVMS, (PhD submitted)

Dr. Ellie Crispe graduated from Murdoch University in 2004 and worked in racetrack practice in Melbourne, Sydney and Perth before undertaking a residency in Equine Medicine and Surgery at Murdoch University. During her residency she began researching EIPH in Thoroughbred racehorses and in 2014 expanded this research into a PhD under the supervision of Assoc Professor Guy Lester. This included the most comprehensive epidemiological study of EIPH ever undertaken.

Key Points

1. Endoscopy is the preferred method of determining the impact of EIPH on race day performance and should be performed 30-120 minutes after racing.

2. Given the strong and persistent association between ambient temperature on race day and EIPH, it would be wise to avoid racing or training (fast work) horses with moderate or severe EIPH during the colder months.

3. Changing the riding tactics of horses with severe EIPH (grade 3 or 4), settling the horse in a mid-field or back marker position off the pace could potentially reduce EIPH severity.

4. Limit the number of races in a racing preparation for horses with EIPH.

5. Increase the days between races for horses with severe (grades 3 or 4) EIPH.

6. Trainers and vets should reconsider or delay racing a horse that requires a bar shoe for a short-term foot issue. Not only do horses with bar shoes typically race inferiorly to horses without bar shoes, they are more likely to have EIPH, and a higher grade of EIPH than horses racing in standard racing plates.
EIPH is a highly prevalent disease of racehorses world-wide. Recognised for centuries, there have been solid advances in our knowledge and understanding of the disease, but the cause and prevention remain elusive. Recently, there has been novel risk factors identified which potentially could be manipulated to reduce the incidence and severity of EIPH. There have also been important advances in our understanding of disease progression and the impact of EIPH on race-day and career performance.

WHAT CAUSES EIPH?
The cause of EIPH remains undetermined. The most well accepted theory is that pulmonary capillaries rupture in response to the extremely high blood pressure and extremely low alveoli pressure experienced during intense exercise \(^1\). An exquisitely thin barrier between the small vessels in the lung and alveolus (blood gas barrier; BGB) is critical for efficient gas exchange. But at the same time, the barrier needs to be strong enough to maintain structural integrity under pressure. Ultimately the BGB is neither thick enough to prevent EIPH, nor thin enough to prevent hypoxia during exercise.

WHAT IS NEW IN EIPH PATHOGENESIS?
Researchers recently identified remodelling of the small pulmonary veins in the caudo-dorsal lung occurring alongside areas of haemorrhage \(^2\). This change, termed veno-occlusive remodelling, occurs in humans and other species that experience pulmonary venous hypertension \(^3\). The remodelling leads to a collar of collagen being laid down around pulmonary veins, causing a reduction in the diameter of the vessel lumen and in some cases total vessel occlusion.

These changes do not occur in horses when blood is instilled into the airway; a model used to study the inflammatory responses to airway blood \(^4\). This indicates that the pathology associated with EIPH is not driven by the repeated physical presence of blood in the airway, but rather driven by the high blood pressure associated with exercise. The physiological consequence of this remodelling is to increase pulmonary capillary pressure upstream exacerbating the failure of the BGB, resulting in EIPH and perpetuating the veno-occlusive remodelling.

HOW COMMON IS EIPH IN THE RACEHORSE?
The prevalence of EIPH varies depending on:
(i) The sensitivity of the diagnostic modality used (endoscopy or bronchoalveolar lavage (BAL))
(ii) The intensity of the exercise (trackwork or racing)
(iii) The timing of the examination after exercise and how frequently the horse is examined.

Endoscopy should be performed 30-120 minutes after racing or galloping \(^5\).

In a recent study using tracheal endoscopy, Crispe et al found the prevalence of EIPH post-race in Australian Thoroughbreds is around 55\%\(^6\), with most horses having low or moderate volumes of blood in the trachea (Fig 1).

The prevalence of EIPH is reduced if horses are examined after trialling or track gallops \(^7\). The
prevalence of EIPH in a population increases when horses are examined on multiple occasions post-race such that all horses that have more than 7 race-starts will likely have evidence of EIPH on at least one occasion post-race\(^8\).

Cytology of BAL fluid is considered the most sensitive indicator; identifying over 90% of horses have evidence of EIPH on BAL fluid\(^8\). But the BAL should not be considered the gold standard test for EIPH. Firstly, the presence of haemosiderophages or free RBCs in BAL fluid overestimates the number and significance of EIPH positive horses. Secondly, due to the persistence of haemosiderophages in the airway, the number of haemosiderophages retrieved does not correlate with the grade of EIPH seen or volume of haemorrhage. Nor does it necessarily correlate with pulmonary haemosiderin present in post mortem lung tissue\(^{10–12}\).

The usefulness of a BAL to quantify the severity of lung haemorrhage and the contribution to poor performance remains questionable.

Lastly, EIPH is not a diffuse disease and is frequently unilateral. Passed blindly, the BAL samples only one area of the lung. A study of French trotters, which sampled the left and right lung lobe, and compared cytology, revealed that 57% of horses would be misdiagnosed as EIPH negative based on unilateral lung analysis\(^{13}\).

HOW COMMON IS EIPH IN OTHER EQUESTRIAN DISCIPLINES?
Although not frequently discussed, EIPH has been identified in almost every equestrian athletic pursuit, as well as racing camels and greyhounds and human athletes such as marathon runners and cyclists. Epidemiological surveys have been performed in polo ponies, barrel racing horses and standardbreds with a prevalence of 30%, 45% and 60%, respectively\(^{14, 15, 18}\). Although EIPH has been reported in show jumpers, eventers, dressage horses, endurance racing, western speed sports horses, draft horses pulling competitively, driving and leisure riding horses population-based surveys have not been conducted.

WHAT IS THE EFFECT OF EIPH ON RACEDAY PERFORMANCE?
EIPH has negative performance connotations in the racing industry worldwide. Surprisingly, this association has only recently been confirmed by research and poor race-day performance does not apply to all grades of EIPH. Our group recently published the results from the largest EIPH study ever conducted\(^8\).

This included 3,794 post-race endoscopy examinations from over 1500 horses and found inferior race-day performance was limited to horses with severe EIPH (grade 3 and 4). This reflected only 6.3% of all examinations\(^8\).

Horses with the highest grade of EIPH (grade 4) were less likely to finish in the first three positions, finished further from the winner, were
less likely to collect race earnings and collected less race earnings, were slower over the final stages of the race and were more likely to be overtaken by other competitors in the home straight than horses without EIPH.

But interestingly, horses with EIPH grade 1 or 2 were more likely to overtake others in the home straight, compared to grade 0 horses. To be clear, it is highly unlikely EIPH grade 1 or 2 offers an athletic advantage to these horses. A more plausible explanation is simply that horses that are ridden competitively to the finish are functioning at their maximal physiological limit, compared to horses that are eased up, and overtaken, during the finishing stages of the race because they are not in prize contention or are affected by interference in the home straight.

Another interesting finding from our study was that horses with moderate to severe EIPH (grades 3 or 4) raced the early-mid sections of the race faster than horses without EIPH. It was proposed that these horses reach the breaking threshold of the pulmonary capillaries at an earlier stage in the race compared to horses that start the race slower, compounding the severity thereafter. A study of barrel racing horses reported that horses with the most severe grade of EIPH were faster than horses without EIPH.

This finding may also reflect that rapid acceleration increases the risk of severe EIPH.

This theory is supported by evidence that horses that rapidly accelerate on a treadmill reach a higher pulmonary artery pressure than a gradual increase to the same speed. It would be judicious for trainers to instruct jockeys riding horses with a history of moderate to severe EIPH to refrain from racing in this manner.

WHAT IS THE EFFECT OF A ONE-OFF DIAGNOSIS OF EIPH OVER THE HORSE’S CAREER?

Veterinarians often consider the prognosis for clinically significant EIPH as guarded due to the disease being progressive. However, a pattern of increasing endoscopic EIPH severity over a career has not been described.

A retrospective study out of Melbourne University examined 744 records of Thoroughbred racehorses undergoing a post-race endoscopy and compared EIPH score to career performance. There was no association between any grade of EIPH and career duration, lifetime earnings or the number of wins or places. The authors concluded that a one-off diagnosis of EIPH is an unreliable predictor of overall career performance.

IS EIPH A PROGRESSIVE DISEASE?

EIPH is often described as a progressive disease- “once a bleeder, always a bleeder”. But this isn’t necessarily correct. EIPH scores can be quite erratic from one race start to the next, especially as the EIPH severity increases. In our study, horses diagnosed with EIPH grade 4 were diagnosed with EIPH grade 0 (11.1%), grade 1 (33.3%), grade 2 (27.8%), grade 3 (2.2%) and grade 4 (5.6%) at their next observation. Whereas, the majority (59%) of horses graded EIPH 0 remained EIPH grade 0 at the next observation.

Factors associated with movement in EIPH score from one race start to another have been recently identified by the author. Increasing the number of days between races is associated with a transition from a higher to a lower grade of EIPH at the next observation; racing in cooler weather was associated with a transition from a lower to a higher EIPH grade at the next observation. There are also likely to be other unmeasured intra-horse and race factors that could also account for the variation in EIPH scores from one race start to another.
RISK FACTORS FOR EIPH

Ambient temperature

A Canadian study of Standardbreds was the first to highlight worsening of EIPH in colder weather[18].

This was followed by a Melbourne study of Thoroughbreds that reported that horses that raced at temperatures less than 20°C were 1.8-2 times more likely to have EIPH, and to have more severe EIPH than horses racing at temperatures above 20°C[19].

Our study of WA Thoroughbreds also identified that cold weather on race day increased the chances of diagnosing EIPH and increased the chances of diagnosing more severe grades of EIPH[20]. Furthermore, for horses that previously had no or only mild (grade 1) EIPH, racing in colder weather was more likely to be associated with a worsening of EIPH grade at the next observation[8]. Cold weather was also associated with disease progression modelling.

The reason that EIPH worsens with cold weather is unknown. The response could be mimicking other species that experience a cold-induced pulmonary hypertension[21], which plausibly would worsen EIPH severity by increasing pulmonary blood pressure. These findings may reflect the ambient temperature during training rather than specifically on race day.

Avoiding cold weather during training (fast work) or racing may reduce the risk of EIPH in horses with a history of moderate to severe EIPH.

Cumulative exposure to racing

Early studies reported age to be a risk factor for EIPH; the older the horse, the more likely to have EIPH. But as studies explored risk factors further, age was superseded by lifetime starts as a stronger predictor of EIPH[19]. Our research expanded on this further. Although lifetime starts was a strong predictor for EIPH risk it was superseded by the number of races in a current racing preparation[8]. The ‘number of races in a current preparation’ was directly associated with the EIPH score and disease progression modelling, reflecting a straightforward, short-term cumulative association between EIPH and racing. Trainers frequently recognise that horses with EIPH perform well ‘fresh’, meaning that they perform at their best early in a racing preparation. This finding supports this trainer sentiment based on the association between EIPH and race day performance.

From a management point of view, limiting the number of races in a racing preparation for horses with EIPH is a viable and practical solution for trainers to implement, which could reduce EIPH severity.

Did you know?
That Australian veterinarian Dr John Pascoe was the lead author in the first article published that described EIPH? Am J Vet Res. 1981 May;42(5):703-7.
Timing of endoscopy examination
The time interval between racing and endoscopy is a risk factor for EIPH as it pertains to diagnosis. The movement of blood from the caudo-dorsal lung to the trachea is a time and volume dependent process. Examinations conducted too soon after racing reduce the likelihood of detecting blood and underestimate the severity of disease\[19\]. Examinations should not be conducted earlier than 30 minutes post-race, trial or gallop. Lower grades of EIPH are also susceptible to misclassification as the blood is only transiently present in the trachea.

Bar shoes
Our group also identified that the application of one or more bar shoes increases the risk of EIPH and severity\[20\]. The reason for this is unknown but was speculated that subclinical hoof pain experienced during racing could increase cardiovascular pressures during racing.

On a side note, performance analysis of horses wearing bar shoes identified that they were less likely to collect prize money, collected less prize money and finished further behind the winner than horses racing in standard plates\[9\].

Trainers and vets should reconsider or delay racing a horse that requires a bar shoe for a short-term foot issue.

Prosthetic laryngoplasty and ventriculocordectomy
A small study examining a group of Thoroughbreds returning to racing after prosthetic laryngoplasty and ventriculocordectomy to treat recurrent laryngeal neuropathy identified increased risk of post-race epistaxis compared to the general racing population (36% vs 7%)\[22\]. There was an increased trend to EIPH post-surgery but this was not statistically significant (68% vs 43%).

It is advised to closely monitor horses returning to racing following this surgery for evidence of EIPH.

Other factors that have been investigated such as track firmness and race distance have mixed results in the literature with no definitive associations established.

TREATMENT OF EIPH
There are numerous treatments proposed for EIPH; which ultimately suggests that no single treatment is universally successful or accepted. Treatments are often empirical, and like many things in racing are propagated by successful performances rather than demonstrated efficacy under racing conditions.

Furosemide (FUR) / Lasix
FUR is a fast acting, potent loop diuretic peaking at 15-30 minutes after intravenous injection and producing a 40-fold increase in urine production. FUR produces potent cardiovascular effects, likely due to the diuresis and reduction in plasma volume. This acts to dampen the increase in pulmonary artery pressure that occurs with exercise. It is via this mechanism that amelioration or elimination of EIPH occurs. In a randomised, placebo-controlled trial that simulated race conditions in South Africa, FUR was shown to lower the chance of developing EIPH, and significantly lower the odds of developing moderate or severe EIPH (grade ≥2)\[23\].

Chronic use of loop diuretics in people and dogs leads to diuretic resistance, whereby the diuretic effect is diminished with continual use. This phenomenon has recently been described (published abstract) in resting horses receiving a standard dose of FUR weekly for seven weeks\[24\]. This weekly dosing regimen would be similar to that received by many racehorses in training, with use extending well beyond 7 weeks in many cases.

Other medications used to treat pulmonary hypertension in people have been trialed without success in horses with EIPH. Fundamental differences between pathological pulmonary hypertension in people, and
exercise-associated hypertension in horses likely underlie the inabilities of these medications to work.

**Treatments to reduce pulmonary inflammation**

There was a long-held perception that EIPH was unlikely to occur in “healthy lungs” and it was caused by a pre-existing respiratory disease. It is controversial if pulmonary inflammation (Inflammatory Airway Disease or Equine Asthma) plays a role in EIPH. Some investigators have reported no association between haemosiderophages and neutrophil counts in BAL fluid or tracheal aspirates, and no association between EIPH and clinical signs of inflammatory airway disease, such as coughing or tracheal mucus.\(^a\),\(^b\),\(^c\)

Certainly, it appears prudent to alleviate any infectious or non-infectious airway disease to maintain lung health, but widespread treatment with inhaled or systemic anti-inflammatories/corticosteroids has become habitual in racing stables despite no studies examining the efficacy of these treatments on naturally occurring EIPH. And unfortunately, many of the studies involve only small sample sizes, which can affect the reliability of their conclusions.

**Clenbuterol** causes bronchodilation and transient pulmonary and systemic vasodilation. Clinical trials were unable to show any change in pulmonary vascular pressure after administration\(^d\). \(^e\). \(^f\). \(^g\). \(^h\)\(^i\). \(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\)\(^A\)\(^B\)\(^C\)\(^D\)\(^E\)\(^F\)\(^G\)\(^H\)\(^I\)\(^J\)\(^K\)\(^L\)\(^M\)\(^N\)\(^O\)\(^P\)\(^Q\)\(^R\)\(^S\)\(^T\)\(^U\)\(^V\)\(^W\)\(^X\)\(^Y\)\(^Z\)

**Corticosteroids** (inhaled beclomethasone or oral prednisolone) have been recommended to reduce the number of RBC retrieved in BAL fluid on day 3 after blood was instilled in the airway, suggesting this treatment may help with blood clearance.\(^d\)\(^e\)\(^f\)\(^g\)\(^h\)\(^i\)\(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\)\(^A\)\(^B\)\(^C\)\(^D\)\(^E\)\(^F\)\(^G\)\(^H\)\(^I\)\(^J\)\(^K\)\(^L\)\(^M\)\(^N\)\(^O\)\(^P\)\(^Q\)\(^R\)\(^S\)\(^T\)\(^U\)\(^V\)\(^W\)\(^X\)\(^Y\)\(^Z\)

**Antibiotics**

While it may be tempting to treat horses that experience an episode of EIPH with antibiotics, there is no evidence that horses with EIPH are at an increased risk of respiratory infection. If we consider the statistics; the prevalence of EIPH is 55% and horses that race more than 7 times are likely to have blood in the airway at least once, yet the incidence of pneumonia in racehorses remains incredibly small. The use of antibiotics to treat horses after an episode of EIPH is generally not indicated and it contravenes appropriate antimicrobial stewardship.

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Commonly Used Grading System for EIPH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clean</td>
</tr>
<tr>
<td>1</td>
<td>Flecks of blood in trachea</td>
</tr>
<tr>
<td>2</td>
<td>Long stream of blood or 2 short streams occupying &lt;33% tracheal circumference</td>
</tr>
<tr>
<td>3</td>
<td>Multiple streams of blood covering &gt;33% tracheal circumference</td>
</tr>
<tr>
<td>4</td>
<td>Blood pools at thoracic inlet, extending up to 90% of tracheal surface</td>
</tr>
</tbody>
</table>

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Randlab’s Respiratory Range

**Airway Gel**
Clenbuterol Hydrochloride 41μg/mL
An aid in the treatment of respiratory conditions where bronchodilators or clearance of excess mucus or respiratory secretions would be beneficial. Useful in the treatment of conditions such as Equine Asthma, Inflammatory Airway Disease, EIPH, Recurrent Airway Obstruction and Bronchopneumonia.

**AirwayTmps**
Clenbuterol Hydrochloride 21.44 μg/g
Sulfadiazine 335 mg/g
Trimethoprim 67 mg/g
For the treatment of respiratory disease in horses caused by organisms susceptible to an antibiotic trimethoprim/sulfadiazine combination. Treatment of respiratory conditions characterised by restriction of the airways, including bronchospasm and obstruction resulting from bacterial and viral infection, bronchitis and bronchopneumonia. Indicated where bronchodilation and antibacterial protection is desirable.

**BromoTmps**
Sulfadimidine 430 mg/g
Trimethoprim 86 mg/g
Bromhexine Hydrochloride 8.6 mg/g
For the treatment of respiratory infections in horses due to organisms susceptible to the combination of sulfadimidine and trimethoprim and where mucolytic activity is desirable.