



Havemeyer Foundation Workshop

**EXERCISE-INDUCED PULMONARY
HAEMORRHAGE: STATE OF CURRENT
KNOWLEDGE**

9th – 12th March 2006

Granville Island Hotel, Vancouver, Canada

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PREFACE

This is the first Havemeyer Workshop on exercise-induced pulmonary haemorrhage and we express our appreciation to Gene Pranzo and the Havemeyer Foundation for providing us with the opportunity to have the world's authorities on this disorder assemble for a detailed discussion of recent advances, and future directions. This Workshop is an opportunity to gather an international group of experts involved in EIPH research and to hear from those authorities involved with the condition as a regulatory or health and welfare issue.

Exercise-induced pulmonary haemorrhage is a pervasive and important problem of athletic horses, particularly racehorses. Recognising the need for further research into this important problem, the Havemeyer Foundation has sponsored this Workshop as a forum to review current knowledge of EIPH and, perhaps more importantly, to identify areas of future investigation, including definition of specific research problems and approaches to addressing these issues. Input from researchers, regulators, attending veterinarians and funding bodies is an important feature of this Workshop.

The primary objectives of the meeting are to:

- Provide a thorough review of all issues relating to EIPH in the sport horse and racehorse.
- Clarify the current scientific literature and understanding of EIPH.
- Identify future opportunities for co-ordinated international research targeted at increasing our understanding of the aetiology of EIPH and therapeutic or management opportunities that can be used to reduce its severity.
- Produce a published monograph containing a comprehensive review of EIPH.

The specific topic areas of workshop are:

- the epidemiological information currently available on EIPH
- the pathological features of EIPH
- the theories of causation and aetiology of EIPH
- evidence for effects of EIPH on pulmonary function and performance
- the efficacy of treatments or management systems to reduce EIPH
- the scale of EIPH and management and regulatory procedures in major world racing jurisdictions

The aim of these reviews will be identification of specific deficits in current knowledge and understanding of EIPH. The importance of these deficits will be assessed and ranked and a prioritised list of research needs developed with the aim, *inter alia*, of assisting acquisition of research funding so that these important questions can be answered. Success will be defined as an improvement in the well being of athletic horses.

David Marlin and Ken Hinchcliff
Havemeyer Workshop Organisers

PROGRAMME

EXERCISE-INDUCED PULMONARY HAEMORRHAGE: STATE OF CURRENT KNOWLEDGE

Granville Island Hotel, Vancouver, Canada 9th – 12th March 2006

THURSDAY 9TH MARCH

19.00-20.30 Welcome Reception (drinks and canapés)

FRIDAY 10TH MARCH

- 8.00-8.15 Introduction
G. Pranzo and D. J. Marlin
- 8.15-8.30 Meeting aims and objectives
K. W. Hinchcliff and D. J. Marlin
- 8.30-9.00 Diagnosis, detection and quantification of EIPH
D. J. Marlin
- 9.00-9.30 Epidemiology of EIPH
J. R. Newton
- 9.30-10.00 Association of EIPH and performance
K. W. Hinchcliff
- 10.00-10.30 Pathology of EIPH
R. Slocombe
- 10.30-11.00 Coffee**
- 11.00-11.30 Imaging haemorrhage and lung remodelling in EIPH using scintigraphy and radiographs
D. M. Votion^{}, D. Serteyn and P. M. Lekeux*
- 11.30-12.00 Role of airways in EIPH
F. J. Derksen
- 12.00-1.30 Lunch**
- 1.30-2.00 Inflammatory airway disease and EIPH
L. Couëtil
- 2.00-2.30 EIPH as a cause of airway inflammation and remodelling
S. McKane

**Presenting author*

- 2.30-3.00 Cardiac disease and EIPH
L. E. Young
- 3.00-3.30 Tea**
- 3.30-4.00 Effects of limb loading and retraction on thoracic shape during gait
*G. R. Colbourne**, *D. J. Marlin* and *S. H. Franklin*
- 4.00-4.30 Metabolic, cardiovascular and respiratory responses to swimming in horses
*J. H. Jones** and *A. Hiraga*
- 4.40-5.00 Summary

SATURDAY 11TH MARCH

- 8.00-8.30 Alternative therapies for EIPH
H. H. Erickson
- 8.30-9.00 Novel therapies for EIPH
E. K. Birks
- 9.00-9.30 Furosemide and EIPH
K. W. Hinchcliff
- 9.30-10.00 Regulatory issues regarding drug treatment of EIPH
R. Sams
- 10.00-10.30 Coffee**
- 10.30-11.00 EIPH and horseracing in the USA - scale of problem, management, regulation and unique aspects
S. A. Waterman
- 11.00-11.30 EIPH and horseracing in Hong Kong - scale of problem, management, regulation and unique aspects
K. L. Watkins
- 11.30-12.00 EIPH and horseracing in Australia - scale of problem, management, regulation and unique aspects
J. P. McCaffrey
- 12.00-12.30 EIPH and horseracing in South Africa - scale of problem, management, regulation and unique aspects
A. Guthrie
- 12.30-1.00 Discussion
- 1.00-2.30 Lunch**

**Presenting author*

2.30-3.30 Break out groups

3.30-4.00 Coffee

4.00-5.30 Break out groups

7.30 Workshop dinner

SUNDAY 12TH MARCH

9.00-10.00 Discussion of recommendations of break out groups. Prioritisation of research topics and development of recommendations for future research.

10.00-10.30 Coffee

10.30-12.00 Discussion

12.00-1.00 Lunch

DIAGNOSIS, DETECTION AND QUANTIFICATION OF EIPH

D. J. Marlin

1 The Millers, Ashley, Newmarket, Suffolk, UK

Abstract not available at time of going to press.

NOTES

EPIDEMIOLOGY OF EIPH

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Despite exercise-induced pulmonary haemorrhage (EIPH) being recognised by equine veterinary science for several decades, the epidemiology of the condition has only very recently been studied in detail. In epidemiological studies sufficiently large to detect statistically meaningful results, risk factors for EIPH are identified and the strengths of their associations with the condition are determined. Application of appropriate statistical methods allow the simultaneous effects of multiple factors to be accounted for and the potentially important influence of repeated observations in individual animals to be dealt with. In order to minimise the damaging effects of misclassification bias, epidemiological studies require robust and easily applied case and control definitions. In relation to EIPH, this has resulted in most studies to date looking at epistaxis (blood at the nostrils) rather than the more prevalent definition of endoscopically visible blood. However, studies of respiratory disease in racehorses in training in the UK have allowed the epidemiology of EIPH defined by visible tracheal bleeding or large proportions of haemosiderophages in tracheal lavages to be evaluated.

Risk factors for epistaxis were investigated among Thoroughbred and Anglo-Arab horses racing in Japan between 1992 and 1997. Results showed that epistaxis was more prevalent following steeplechase than flat races, in older horses than 2 year olds, among races $\leq 1,600$ m long than in races between 1,601–2,000 m in length and in females than sexually intact males. A survey of epistaxis among Thoroughbred racehorses in Korea found increased prevalence of the condition in older horses, females, horses originating from England or Ireland,

higher grade performers, heavier horses and those carrying heavier weight, those in middle or longer distances, handicap racers and during the spring season. Several horse- and race-level risk factors for epistaxis among all UK race starts between 1996–1998 have recently been investigated. Risk of epistaxis was significantly increased for hurdle and chase race types compared to both Flat and National Hunt flat races. There was a significant biological trend for increasing risk of epistaxis with increasing ground hardness ('going') and accumulated years spent racing. Findings were considered consistent with the theory that locomotory impact induced trauma contributes to exercise induced epistaxis.

In a study of EIPH in young Thoroughbreds in training in the UK in which 148 horses contributed 1,614 horse-months of data, there were 64 (4%) episodes of endoscopically visible tracheal bleeding and 824 (51%) episodes of increased haemosiderophages in tracheal washes. There were increases in prevalence and risk of EIPH by both definitions with age from ≤ 2 years to ≥ 4 years, season of sampling from winter (Nov–Jan) to autumn (Aug–Oct) and several different measures of airway inflammation, including tracheal mucus, neutrophil proportion, inflammation score and fungal material in tracheal washes. Although there was no evidence that EIPH was associated with bacterial infection of the airways, EIPH in the preceding month significantly increased the risk of the condition the following month and there was considerable variability in the prevalence of EIPH between trainers. Analyses of data from a similar study in National Hunt (jumps) racehorses are currently underway.

NOTES

ASSOCIATION OF EIPH AND PERFORMANCE

K.W. Hinchcliff

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Failure of racehorses to perform to the expected standard (poor performance) is often, accurately or not, attributed to EIPH. Many horses with poor performance have cytologic evidence of EIPH on microscopic examination of tracheobronchial aspirates or bronchoalveolar lavage fluid or have blood evident on endoscopic examination of the tracheobronchial tree performed 30–90 min after strenuous exercise or racing. However, it is important to recognise that EIPH is very common in racehorses and it should be considered the cause of poor performance only after other causes have been eliminated. Severe EIPH undoubtedly results in poor performance and, on rare occasions, death of Thoroughbred racehorses. Thoroughbred horses with EIPH racing in Victoria, Australia have impaired performance compared to unaffected horses. Affected horses are 4 times less likely to win, 2 times less likely to finish in the first 3 places, 3 times less likely to be elite

money earners, and finish further behind the winner than unaffected horses.

Results of studies in Standardbred racehorses indicate either a lack of effect of EIPH on performance or an association between EIPH and superior performance. There was not a relationship between presence of EIPH and finishing position in 29 Standardbred racehorses with intermittent EIPH examined on at least 2 occasions nor in 92 Standardbred racehorses examined on one occasion. However, of 965 Standardbred racehorses examined after racing, those finishing 1st or 2nd were 1.4 times more likely (95% CI 0.9–2.2) to have evidence of EIPH on tracheobronchoscopic examination than were horses that finished in 7th or 8th position.

These results demonstrate that EIPH adversely affects performance of both Thoroughbred and Standardbred racehorses.

NOTES

PATHOLOGY OF EIPH

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When US Secretary of Defense Rumsfeld reflected on the failures in intelligence that influenced policy regarding military action in Iraq, he concluded that there were known knowns, known unknowns and unknown unknowns. There appear to be similar failures in pathologic intelligence surrounding the lesions of exercise-induced pulmonary haemorrhage (EIPH).

KNOWN KNOWNS

The chronic lesions of severe EIPH are well understood, with axial regions of dorsal, caudal lung affected by subpleural, interstitial and septal fibrosis, siderosis of collagen, accumulation of macrophages containing iron pigments in perivascular, peribronchiolar and alveolar spaces, and variable proliferation of alveolar epithelial cells. The most advanced lesions are typically seen in older horses with histories consistent with repetitive bouts of EIPH. Neovascularisation of the peripheral bronchial circulation is described and increased risk of EIPH is associated with peripheral airway disease. The acute lesions of EIPH are striking grossly with raised, discoloured regions of lung tissue caused by subpleural, alveolar, interstitial and airway petechial to suffuse haemorrhages that may become confluent. Despite such obvious gross changes, histologic lesions are surprising bland, with blood (usually unclotted) present in lung tissue without any light microscopic evidence for pulmonary capillary endothelial injury. Recently we reported a significant proportion of acute racetrack fatalities with EIPH had concurrent severe pulmonary oedema, consistent with microvascular injury of variable severity.

KNOWN UNKNOWNNS

Our racetrack mortality study has given an excellent opportunity to study acute EIPH. Horses with severe acute EIPH often have extensive haemorrhages in the parietal pleura adjacent to regions of affected lung. Some of these cases also have extensive haemorrhage into the dorsal diaphragmatic musculature and a few also bleed into the capsule of the spleen opposing the dorsal diaphragm. Current theories of the pathogenesis of EIPH do not account for these extrapulmonary lesions. There has been no systematic review of the extrapulmonary lesions of horses with EIPH, although many have speculated on the potential role for either functional or structural abnormalities in the upper airways. We do not know the relationship between the volume of blood and the cytologic appearance of lavages or the evolution of this

relationship over time as blood is progressively removed. We do not know what factors trigger processes to remove haemorrhage, induce tissue siderosis, chronic inflammation, vascular remodelling or perhaps even repair and complete resolution in some cases.

UNKNOWN UNKNOWNNS

Recently Derksen and Robinson repeated blood inoculation studies in horses similar to those performed by McKane in my laboratory. Results from these studies seem to differ greatly from ours, and as yet we have no explanation. It seems that intrapulmonary blood inoculation as a model for EIPH needs careful re-examination. We have no way of quantitating the distribution and volume of haemorrhage after strenuous exercise unless horses are dead, and even then quantitation is difficult. Finding the point source(s) of haemorrhage after severe EIPH is problematic so that pulmonary abnormalities seen with EIPH may have little to do with the immediate episode. Haemorrhage does not seem to occur within chronically scarred areas of lung so is scarring protective or detrimental? Is there a cohort of horses that develops subclinical lesions of EIPH early in their racing careers and then completely resolve or is any EIPH lesion permanent and progressive? Do continuing bouts of exercise influence the progression of lesions once they become established? Is there a correlation between accumulation of iron pigments in tissues, tissue fibrosis and the total volume of blood lost into lung tissue? Is evidence of upper or lower airway disease, or haemorrhage in other tissues simply epi-phenomena or are they central to an understanding of the lesions of EIPH?

SUMMARY

By applying Rumsfeld 'logic' to the pathology of EIPH, the 'unknowns' seem to outweigh the 'knowns'. Understanding the clinical relevance of particular lesions found in EIPH will probably require the combination of complex epidemiologic and pathologic studies, and both standardisation and quantitation of methods to assess pulmonary pathology.

ACKNOWLEDGEMENTS

Racing Victoria, RIRDC and veterinary pathologists, Jennifer Charles, Peter Finnin, Jeanine Sandy and Lisa Boden.

NOTES

IMAGING HAEMORRHAGE AND LUNG REMODELLING IN EIPH USING SCINTIGRAPHY AND RADIOGRAPHY

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At present, the relative severity of the bleeding in exercise-induced pulmonary haemorrhage (EIPH) is better evaluated using scoring methods based on tracheobronchoscopic assessment of bleeding or red blood cells (RBCs) count in bronchoalveolar lavage (BAL). However, misinterpretation might occur with tracheobronchoscopic examination when the haemorrhage is tiny or with RBC count in BAL when the bronchi sampled are not representative of the bleeding site. Quantifying EIPH accurately would be of great interest to define the relationship between bleeding and performance as well as to assess efficacy of treatments or prophylactic measures. Several studies have attempted to determine whether lung imaging could be of value in EIPH detection and quantification.

Radiographic findings when present consist of interstitial opacities limited to the caudodorsal regions of the lungs. Resolution of opacity may last from several days to several months. Interpretation of chest radiographs has been found to be of poor value for diagnosing and for quantifying EIPH and lung remodelling.

Scintigraphy has been investigated as a mean of studying EIPH. Ventilation/perfusion (V/Q) scans show variable reduction of ventilation and a loss of perfusion in the caudodorsal fields but the relationship between V/Q mismatches and EIPH quantification

seems hazardous. The exercise-induced pulmonary perfusion redistribution may be visualised and quantified with labelled radiotracers entrapped in the pulmonary capillaries following their intravenous injection in exercising horses. This technique may not detect EIPH because scanning does not distinguish between tracer collected in alveoli (ie resulting from bleeding) and that trapped in the capillaries. The same is true with the use of labelled-RBCs; circulating tracer impedes visualisation of bleeding. To visualise the bleeding site, radioactivity of the vascular blood pool should be removed. A preliminary study indicated that this background might be removed using a double isotope scintigraphy. In fact, the horse would be first injected at exercise with RBCs labeled with 111-Indium (111In-RBCs). In bleeders, a scan taken at the end of exercise would include the haemorrhage hidden by the blood pool. As EIPH is presumed to resolve with exercise cessation due to immediate decrease in pulmonary artery pressure, a second injection of RBCs labelled with another radiotracer (99 m-technetium; 99 mTc-RBCs) would enable acquisition of the sole blood pool knowing that 99 mTc and 111 activities may be recorded on 2 different channels. Then, the computerised removal of background vascular radioactivity should enable us to visualise the bleeding site and possibly to quantify the amount of extravasated blood.

NOTES

ROLE OF AIRWAYS IN EIPH

F. J. Derksen

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While several mechanisms may be involved in pulmonary bleeding during exercise in horses, evidence is accumulating that pulmonary capillary wall stress failure is important in the pathogenesis of the condition. Capillary wall stress failure occurs when the capillary transmural pressure, the difference between intraluminal and extraluminal capillary pressures exceed capillary wall strength. Much attention has been paid to the high intravascular pressures in the equine pulmonary circulation during intense exercise as the cause of exercise-induced pulmonary haemorrhage (EIPH), but changes in extraluminal capillary pressures could also be important in the pathogenesis of this disease. The pressure outside of the pulmonary capillary, in the alveolar interstitium, is determined in part by the alveolar pressure. Circumstantial evidence suggests that in exercising horses during inhalation, negative airway pressures contribute to EIPH. Most important is a series of studies demonstrating that use of a nasal strip decreases the number of red cells in bronchoalveolar lavage (BAL) fluid after exercise. In horses, the majority of inspiratory resistance to airflow is located in the upper airway. The nasal valve region, located just cranial to the nasoincisive notch is a high resistance region, not supported by bone or cartilage. These characteristics make this region

particularly susceptible to collapse during inhalation. Application of the nasal strip to this region prevents nasal collapse, and decreases upper airway resistance during exercise. This in turn is expected to reduce negative alveolar pressure during inhalation, and decrease transmural capillary pressures.

Furosemide, like the nasal strip, decreases the number of red cells in BAL fluid collected after exercise. Furosemide's ability to decrease calculated pulmonary capillary pressure in exercising horses is most likely in part responsible for this beneficial effect. However, furosemide is also a potent bronchodilator in horses with recurrent airway obstruction. This effect is mediated via bronchodilator prostenoids. In normal resting horses, bronchodilators have no measurable effects on pulmonary function, suggesting that airways are fully dilated. Little is known about airway caliber in exercising horses, but in people, exercise-induced bronchospasm is common, particularly in dry and cold conditions. If this is true in horses, the beneficial effect of furosemide on EIPH may be explained in part by its ability to dilate airways, and decrease alveolar pressure swings and pulmonary capillary transmural pressures during exercise. Together these data demonstrate that airway caliber has an important influence on EIPH.

NOTES

INFLAMMATORY AIRWAY DISEASE AND EIPH

L. Couëtill

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Inflammatory airway disease (IAD) is a mild form of lower airway disease commonly encountered in racehorses that has been recognised recently as a separate entity from recurrent airway obstruction (RAO) and other pulmonary diseases. Clinical signs of IAD are subtle and include chronic cough, excess mucus in the trachea, and poor performance, otherwise horses have a normal attitude and appetite, are not febrile and do not exhibit increased respiratory effort at rest.

The prevalence of IAD in racehorses varies between 10% and 80% with the highest values present in yearlings and 2-year-old horses and in horses examined after exercise. Isolation of bacteria from tracheal wash samples collected from racehorses in training is more common in young animals entering training (1–2-years-old) and is associated with the degree of neutrophilic inflammation. No infectious aetiology is evident in 27–90% of horses with IAD. Exposure to inhaled dust, endotoxin and other airway irritants appears to play a role in IAD pathophysiology as well. Viral infections are rarely associated with IAD.

Horses with IAD exhibit various degrees of bronchiolitis resulting in mild peripheral airway obstruction. Airway obstruction may be detected using sensitive tests of lung function or by measuring blood gas exchange during exercise which provides a physiological explanation to the adverse effect of IAD on performance.

The possible role of small airway obstruction in the pathophysiology of exercise-induced pulmonary haemorrhage (EIPH) has been hypothesised. However, scientific evidence is conflicting. The arguments in favour of an association between IAD and EIPH include clinical, experimental and epidemiological data. However, other clinical and epidemiological studies have not found such a link.

The discrepancy probably originates from differences between study methodologies, case definitions and heterogeneity of the IAD phenotype. The definition and characterisation of IAD phenotypes are critical to the success of future studies of equine pulmonary diseases.

NOTES

EIPH AS A CAUSE OF AIRWAY INFLAMMATION AND REMODELLING

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In 1974, Cook theorised that racehorses displaying epistaxis, resulting from exercise-induced pulmonary haemorrhage (EIPH), had pre-disposing pulmonary inflammatory disease. Both acute viral disease and chronic bronchiolitis have been implicated in a number of studies over the past 30 years. Histological evaluation of racehorse lungs demonstrated that haemorrhagic lesions in the caudal lung lobes were associated with chronic peribronchial fibrosis and mononuclear cell infiltrates. Both of these studies suggested that the inflammation preceded EIPH; however, no evidence of causality was presented. Recent epidemiological studies confirmed an association but not a causal link between EIPH and pulmonary inflammation in racehorses. Given that almost every Thoroughbred racehorse suffers at least mild EIPH, the theory that acute inflammation precedes all EIPH infers a massive prevalence of undiagnosed respiratory disease. An alternative hypothesis is that blood induces airway inflammation and that this leads to the observed peribronchial fibrosis and mononuclear cell infiltrates. Two studies demonstrated that autologous blood inoculated into the airways was removed quite slowly and that by 3 days modest airway inflammation developed, that persisted for as long as 21 days. Initially this response was neutrophil dominated, but then a more chronic and persistent phase occurred that was characterised by increased

macrophage numbers and morphological signs of marked macrophage activation and erythrophagocytosis. Morphometric analysis of histological sections was used to quantify the effects of this macrophage activity during erythrophagocytosis, on alveolar cell populations and the physical structure of the alveolar walls. Signs of chronic inflammation and peribronchial fibrotic remodelling, in response to the presence of blood in the airways, included increased macrophage activity and erythrophagocytosis, increased alveolar macrophage numbers ($10,688 \pm 1,708$ cells/ μm^3 to $30,957 \pm 6,831$ cells/ μm), increased septal thickness (4.1 ± 0.4 μm to 6.1 ± 0.5 μm) and an increased alveolar septal collagen content ($6.6 \pm 0.5\%$ to $27.5 \pm 3.3\%$). These results confirmed that intrapulmonary blood was capable of inducing a prolonged macrophage dominated inflammatory response, which resulted in increased alveolar septal thickening and the development of alveolar fibrosis. These changes are the likely cause of the observed alveolar fibrosis and bronchiolitis that was once suspected to be the originating cause of EIPH. This does not however preclude a role for inflammation in the aetiology of some cases of EIPH, since it is possible that airway inflammation and remodelling may alter pulmonary mechanics and predispose the lung to more severe haemorrhage than would otherwise occur.

NOTES

CARDIAC DISEASE AND EIPH

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Exercise-induced pulmonary haemorrhage (EIPH) and tricuspid (TR) and mitral valve (MR) regurgitation occur frequently in conditioned performance horses and the prevalence of all 3 conditions increases with time in intensive training. Although the precise pathogenesis of EIPH remains elusive and the condition is generally considered to be multifactorial, all available evidence nevertheless points to stress failure of pulmonary capillaries, caused by high transmural pressures, being pivotal in its aetiology. The left atrium can also exert independent influences on pulmonary capillary and thence trans-mural pressure: the positive association of EIPH and atrial fibrillation, a condition that independently increases left atrial pressure is well-recognised in equine athletes. However, atrial fibrillation is not the only commonly occurring cardiac condition able to elevate left atrial, thence pulmonary venous pressures. Once left atrial compliance has been exceeded, MR also causes pulmonary venous hypertension; indeed this is the underlying pathogenesis of the pulmonary oedema that occurs in congestive heart failure.

The horse's ability to generate a cardiac output in excess of 250 L/min at maximum exercise and the resultant increases in pulmonary vascular and left atrial pressures also create a unique set of loading conditions and stresses for the equine right ventricle compared to other mammals. In all species, the RV is a structurally complex chamber with an elongated irregular crescent-like configuration that endows a very large surface area relative to its intracavitary size; though difficult to measure accurately using ultrasound, it is nevertheless, ideally adapted to efficiently discharge a large volume of blood into the normally low resistance pulmonary circulation. Its anatomical position, wrapped around the cranial surface of the left ventricle facilitates this 'bellows-like' action; only minimal myocardial fibre shortening being needed to cause sufficient axial excursion of the RV free wall towards the interventricular septum and displace the

stroke volume. In comparison to the left ventricle, the structural and functional responses of the equine RV to high intensity exercise and training has not been well explored. Yet the uniqueness of the Thoroughbred's pulmonary circulation during high-speed exercise make the adaptations of the equine RV particularly intriguing. Recent data have shown that the equine right ventricle undergoes significant change in chamber size in response to exercise and training and that its internal dimensions in systole and diastole are positively associated with the presence of TR assessed by colour flow Doppler echocardiography. As TR is a sequel to athletic training in racehorses and as RV adaptations to exercise will be influenced by the loading conditions imposed by the pulmonary circulation, which might in turn be modified by EIPH, we performed a series of studies to examine the adaptive responses of the RV to athletic training and to explore possible associations between EIPH and valve regurgitation. We also explored whether EIPH had independent effects upon RV chamber size.

ACKNOWLEDGEMENTS

The veterinary examinations and EIPH classifications in our studies were performed by Mr Charlie Schreiber MRCVS of Donnington Grove Veterinary Hospital, Newbury, Berkshire and Mr Liam Kearns MRCVS of Three Counties Equine Hospital, Tewkesbury, Gloucestershire. We must also thank the following racehorse trainers for their help with this study: Miss Venetia Williams, Mr Mark Pitman and Mr Graham McCourt. Dr James Wood, MRCVS of the University of Cambridge, UK and Miss Katherine Rogers of the Animal Health Trust, Newmarket, performed all of the statistical analyses for this study. The study was part of a programme of work funded by a Project grant from the Horserace Betting Levy Board.

NOTES

EFFECTS OF LIMB LOADING AND RETRACTION ON THORACIC SHAPE DURING GAIT

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Loading of the chest by the forelimbs during locomotion is assumed to result in compression, and a model of chest-forelimb interactions during early stance has indicated the potential for high frequency waves to disrupt the lung parenchyma in the dorsocaudal lung. Advancement of these models will depend on knowledge of the dynamic changes occurring to thoracic geometry during stance. We have recorded the changes in shape of the equine thorax using an infrared camera system to detect the 3-D motion of reflective markers mounted on the horse's dorsal midline and around the thoracic circumference. Our first study employed a bilateral camera configuration to measure transverse changes in thoracic diameter and ultrasonic airflow transducers to record ventilatory airflow in two horses exercising on a high-speed treadmill. At trot, the ventilatory cycle was marked by an asymmetric biphasic change in transverse diameter of the thorax. Forelimb stance on one side occurred coincident with expiration and a larger amplitude (3 cm) change in transverse diameter, while stance on the other side occurred during inspiration and resulted in a smaller (1.5 cm) change in diameter ($P < .01$). At canter and gallop, transverse expansion of the chest was partly out of phase with airflow. The transverse chest diameter increased rapidly shortly after the onset of inspiration and during expiration

there was a more gradual decrease in diameter which persisted into the next inspiratory phase. On the side of the trailing forelimb the change in thoracic transverse hemidiameter (as measured by the horizontal distance between the dorsal midline markers and the lateral chest markers) was approximately double the amplitude of change on the leading side ($P < .01$). The profile of hemi-thorax motion on the side of the trailing forelimb was more closely aligned with changes in total thoracic diameter and ventilatory cycle, while the movement of the hemi-thorax on the leading side demonstrated higher frequency reversals in motion. In our second study we used a larger marker array around the thoracic circumference to measure changes in both transverse and dorso-ventral diameter in 4 horses. We also varied treadmill slope and speed, and evaluated the effect of leading limb at canter. There was a negative correlation between changes in transverse hemidiameter and dorso-ventral diameter, the strength of which increased on the trailing side. Treadmill slope resulted in larger amplitude motions on the trailing side, but only when the horses were on the right lead ($P < .01$) indicating a lead interaction. Changes in thoracic shape are probably due to locomotor forces, and may contribute asymmetrically to lung ventilation.

NOTES

METABOLIC, CARDIOVASCULAR AND RESPIRATORY RESPONSES TO SWIMMING IN HORSES

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Swimming is heavy exercise for horses requiring significant increases in aerobic power and O₂ delivery. No investigators have reported a maximal rate of O₂ consumption (VO₂max) during swimming in horses. The highest specific VO₂ reported for swimming horses (2.0 ml O₂ (STPD)/s/kg) are approximately 70–80% the expected aerobic capacity of a trained horse. These workloads elicit plasma lactate accumulation rates (<3 mM/min) and heart rates (200/min) that both indicate metabolic power is submaximally aerobic. Mean blood pressures in the carotid artery (250 torr), pulmonary artery (105 torr) and right atrium (55 torr) during swimming are similar to those of horses exercising at VO₂max on a treadmill when exercise-induced pulmonary

haemorrhage (EIPH) can occur during terrestrial exercise. Ventilation during swimming differs from that during galloping being slower (0.5 Hz vs 2.2 Hz) and deeper with higher expiratory intrapleural pressure (100 cm H₂O vs 35 cm H₂O) and with reduced magnitude in subatmospheric inspiratory pressure (-21 cm H₂O vs -35 cm H₂O). During swimming, horses maintain ventilatory duty cycle (inspiratory time : expiratory time) near 1:1 as when galloping; however, nearly 2/3 of the ventilatory cycle is apnoea at full inspiratory volume with a closed glottis. We know of no documented evidence that EIPH occurs in conjunction with swimming in horses despite the similarity in cardiovascular pressures with those experienced during galloping.

NOTES

ALTERNATIVE THERAPIES FOR EIPH

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Exercise-induced pulmonary hemorrhage (EIPH) is a major health concern and cause of poor performance in the equine athlete. Significant progress has been made in recent years to diagnose EIPH and to understand its pathogenesis, prevention and treatment. The development of effective therapy for EIPH has been difficult due to controversy regarding the causal mechanisms and the ability to quantify EIPH. Some alternatives to furosemide that are used to prevent and treat EIPH include nasal dilators, concentrated equine serum, nitric oxide, herbal formulations, conjugated estrogens, a diet rich in omega-3 fatty acids and rest.

NASAL DILATORS

During quiet breathing and during exercise, 40–50% of the total pulmonary resistance is located within the nasal passages. The FLAIRTTM nasal strip has been developed for horses to prevent or reduce the collapse of the nasal passages, to decrease upper airway resistance, particularly nasal resistance and to prevent intrapleural and alveolar pressure swings that may contribute to high pulmonary capillary transmural pressures and EIPH.

CONCENTRATED EQUINE SERUM

Inflammatory airway disease may be an important component of EIPH. Seramune, a concentrated equine serum (CES), containing immunoglobins, is used to treat chronic bleeders on the racetrack and reduces EIPH. CES may have immunomodulatory and anti-inflammatory effects that are beneficial in reducing small airway disease which may be one of the mechanisms of EIPH.

NITRIC OXIDE

Nitric oxide is a vascular smooth muscle relaxing factor. Inhaled nitric oxide reduces the pulmonary arterial pressure during exercise; however, the severity of EIPH increases.

HERBAL FORMULATIONS

Herbal formulations are used to treat horses with EIPH because they may decrease inflammation and oedema in the lung and move stagnated blood out of the airways.

Herbal formulations have also been designed to address coagulation defects, such as platelet function, that may contribute to EIPH.

CONJUGATED ESTROGENS AND ANTIFIBRINOLYTICS

Conjugated estrogens (ie Premarin) and antifibrinolytics (ie aminocaproic acid) are used on the race track, but have not been examined scientifically in clinical trials for evidence of efficacy against EIPH.

OMEGA-3 FATTY ACIDS

Many equine supplements are high in omega-3 fatty acids that are metabolised to substances that are reported to reduce inflammation. Because inflammatory airway disease may be an important component of EIPH, a diet rich in omega-3 fatty acids may prevent and reduce EIPH.

NOTES

NOVEL THERAPIES FOR EIPH

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A number of therapeutic modalities are used in attempts to prevent/limit exercise-induced pulmonary haemorrhage (EIPH). Treatments fall into several discrete categories with specific proposed etiologies and varying degrees of efficacy. These treatments include, but are in no way limited to: 1) reducing pulmonary disease; 2) correcting airway obstructions or other excessive resistance to ventilatory airflow; 3) reducing pulmonary vascular pressures; and 4) modulation of coagulation pathways. Recently, a hypothesis has been proposed that involves locomotory-impact as another possible aetiology of EIPH. Selected aspects of therapies in these categories will be briefly discussed. Epidemiological studies have shown that EIPH can exist even in the absence of specific pulmonary disease or airway obstructions. While there may be multifactorial influences acting in individual horses, it appears that reducing pulmonary vascular pressures may provide the best option for limiting EIPH in normal, healthy athletic horses.

The most commonly utilised 'treatment' for EIPH in racehorses has been the loop diuretic furosemide (eg Lasix/Salix). Although most studies have demonstrated a reduction in pulmonary vascular pressures following furosemide administration, reports on its efficacy in preventing/reducing EIPH are somewhat equivocal.

A novel approach to EIPH has been adapted from research into treatments for cardiac angina in human patients. Nitric oxide

donor therapies (eg nitroglycerine, nitroprusside) have been shown to treat angina effectively. Research into the mechanisms related to these actions led to the discovery of organ-specific compounds with vasodilatory properties, most notably Type V phosphodiesterase inhibitors such as sildenafil, vardenafil, tadalafil, and zaprinast. Some of these also have pulmonary actions, with sildenafil recently being approved by the US-FDA to treat human pulmonary hypertension.

Reduced pulmonary vascular pressures have been reported in horses breathing nitric oxide mixtures. Because of an extremely short biological half-life, nitric oxide must either be continuously inhaled or its effects prolonged. Continuous inhalation is impractical during competitions, but prolonging vasodilatory actions is possible with certain Type V phosphodiesterase inhibitors. Significant reductions in pulmonary arterial pressures have been observed during exercise in horses given the lung-directed inhibitor, E4021, followed by brief inhalation of nitric oxide, on treadmills and at racetracks. Significant reductions in EIPH compared to controls (visual endoscopic as well BALF RBC numbers) were also seen following the treatment. This effect has been observed during exercise up to 2 h following treatment. These studies suggest that selective pulmonary vasodilation during intense exercise may prove to be an effective treatment for EIPH in equine athletes.

NOTES

FUROSEMIDE AND EIPH

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Furosemide is administered to the majority of Thoroughbred horses racing in the USA. Recent studies demonstrate that the proportion of Thoroughbred horses administered with furosemide before racing has risen to over 92%. Rates of administration of furosemide to Standardbred racehorses, while varying regionally throughout the USA, are 50–70%. Furosemide is a diuretic and the diuresis induced by furosemide results in a reduction in body weight of 1–2% (10–20 lb per 1,000 lb horse) and, importantly, attenuation of the exercise-induced increases in pulmonary artery pressure that persist 4 h

after dosing. It has been suggested that attenuation of exercise-induced increases in pulmonary artery pressure by furosemide reduces the incidence or severity of EIPH by reducing the risk of pulmonary capillary rupture. Indeed, furosemide does reduce the red cell count in bronchoalveolar lavage fluid obtained from horses within hours of strenuous exercise on a treadmill. However, the relevance of these findings to horses racing against competition over ground is questionable and the effect of furosemide on incidence or severity of EIPH in racehorses has not been determined.

NOTES

REGULATORY ISSUES REGARDING DRUG TREATMENT OF EIPH

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Furosemide is the drug most commonly used in the treatment of EIPH with approximately 70–80% of Thoroughbred horses in some US racing jurisdictions receiving pre-race injections of this drug. Furosemide is a high-ceiling loop diuretic that increases urine flow soon after intravenous administration with urine production reaching values that are as much as 40–50 times the normal rate. Diuresis persists for approximately 3 h with the rate of urine production returning to near or below normal values. The increased rate of urine production causes the urinary concentrations of substances that are not normally reabsorbed in the renal tubules to decrease and thereby interferes with methods to detect them. Analysts recognised this diluting effect of furosemide soon after its introduction and called for restrictions on the time of its administration so that post race urine samples would not be diluted. Regulators responded in 1983 by limiting the dose of furosemide to no more than 250 mg, requiring that it be administered iv, and prohibiting its administration within 4 h of the scheduled post time of the race in which the horse was entered. Various regulatory measures were taken to ensure that these requirements were followed. These measures have included a requirement for furosemide to be administered in secure areas

by regulatory veterinarians and by imposition of regulatory thresholds for furosemide in plasma. Use of secure areas has been abandoned by most regulatory bodies because of the expense of maintaining the areas. Most regulators now rely on the use of regulatory thresholds and a requirement that the urine specific gravity exceed some limit. The RMCI and the ARCI recommended regulations establishing a urine specific gravity less than 1.010 as a violation of the rules of racing if the corresponding plasma (serum) concentration is greater than 100 nanograms per milliliter. These limits have been challenged by some investigators. One group has demonstrated that urine specific gravity is a poor predictor of time since dose administration and hence is not useful in detecting administration of furosemide within 4 h of race time. Others have pointed out that the purpose of measuring specific gravity is not to detect administration within 4 h of race time but to detect administration that results in collection of a dilute sample. Others have suggested that a plasma concentration in excess of 100 nanograms per milliliter is too high and that plasma concentrations 4 h after administration are substantially lower.

NOTES

EIPH AND HORSERACING IN THE USA — SCALE OF PROBLEM, MANAGEMENT, REGULATION AND UNIQUE ASPECTS

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In the USA, racing is regulated by those states which conduct pari-mutuel wagering. Because of this, there is no central rule making authority and the regulations differ sometimes substantially when state lines are crossed. The closest the USA has had to a uniform rule since the early 1990s, however, is the legal raceday administration of furosemide to assist in managing exercise induced pulmonary haemorrhage. All 38 racing jurisdictions currently permit the administration of furosemide although there are many state-to-state differences in terms of withdrawal time before a race, maximum and minimum dosages and route of administration. In addition several jurisdictions have recently allowed the raceday administration of so called 'adjunct' bleeder medications in response to veterinary and horsemen association pressure. The most common adjunct medications allowed are aminocaproic acid, carbazochrome, tranexamic acid and the conjugated estrogens. This serves to highlight the general feeling among horsemen and veterinarians that exercise induced pulmonary haemorrhage is indeed a significant problem in the USA and has a serious impact in terms of performance on the track. As a result, EIPH is an economic burden to owners both

from direct monetary loss due to high veterinary bills to lost opportunities at purse monies.

The Racing Medication and Testing Consortium was formed in 2001 to address some of the inconsistencies in rules between states by providing model rules for adoption. The RMTC is a broad based coalition of racing industry stakeholder groups and has achieved remarkable success given the fractious political nature of racing in the USA. As a result, some of the state-to-state differences regarding furosemide administration have been resolved and true uniformity as it relates to the regulation and management of EIPH will be achieved in the near future. In addition, the RMTC has taken a strong stance regarding the use of adjunct bleeder medications by requiring scientific proof that these medication are efficacious and not a threat to the integrity of the race before condoning them as raceday medications. Ultimately it is the hope of the RMTC that a more effective medication for controlling EIPH can be developed to replace furosemide due to the negative perception of the drug among segments of the scientific community and racing stakeholders and fans.

NOTES

EIPH AND HORSERACING IN HONG KONG – SCALE OF PROBLEM, MANAGEMENT, REGULATION AND UNIQUE ASPECTS

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During the 2004/05 Hong Kong horseracing season which ran from early September to early July, 0.55% of the 9,153 starters 'bled' which represented 50 'bleeding' incidents and 49 individual horses. These Thoroughbreds were competing on the flat during 78 race meetings in 710 races over distances varying from 1,000–2,400 m, 89.4% of which were on sand-mesh turf and 10.6% on all-weather dirt tracks.

In the same season, of the population of 1,358 horses (which were imported mainly from Australia, New Zealand and Europe and stabled with 25 trainers), there were 5 horse (0.37%) 'bleeding' records during barrier trials and 23 records (1.69%) during track work. Therefore in training and racing combined, there was a total of 78 (5.74%) 'bleeding' records.

In recent years 'bleeding' as a percentage of starters during racing has fluctuated between a low of 0.46% (41/8,844 starters) in 2000/01 and a high of 0.79% (68/8,653 starters) in 1999/00 (ie 4.6 to 7.9 'bleeds' per 1,000 starts, respectively).

For the 12-year period from the 1993/94 to the 2004/05 racing seasons, there were a total of 798 'bleeding' records (combined training and racing). On average almost a third (30.6%) of horses, which 'bled' the first time (611 records), had a second 'bleeding' incident (187 records).

Five and 6-year-old horses appeared to be at the highest risk with a 'bleeding' incidence rate of 7.2 and 7.4 per 1,000 starts as recorded over 4 racing seasons (2001/02 to 2004/05 season), whereas 4- and 7-year-olds were 5.9 and 5.1 respectively and 3- and 8-year-olds were 3.3 and 2.3.

There appears also to be a seasonal trend with an apparent higher incidence of 'bleeders' from October to April, which are generally the cooler, drier and less humid months in Hong Kong.

The Hong Kong Jockey Club (HKJC) Rules of Racing define a 'bleeder' as a horse, which exhibits blood at one or both nostrils, which has originated from the lungs. On the first occasion a horse 'bleeds' it will be barred from racing for a period of 3 months and on the second occasion the horse will be permanently barred from any further racing.

However if the haemorrhage in a first time 'bleeder' is particularly severe and/or the horse pulls up severely distressed or collapsing, then a recommendation may be made for either a prolongation of the rest period or, more usually, compulsory retirement of the horse in the interests of race track safety and horse welfare.

Although not required under the rules, horses with unilateral epistaxis are invariably subjected to an endoscopic examination of their respiratory tracts to confirm that the blood originated from the lungs and if it did not, then the horse is not confirmed as an official 'bleeder'. Such horses usually have an immediate history of suffering head trauma eg rearing and hitting their heads in the Starting Stalls, causing bleeding from the nasal passages and/or sinuses.

Hong Kong conducts 'prohibited substances free racing' and in addition horses do not train on frusemide or equivalent diuretics.

NOTES

EIPH AND HORSERACING IN AUSTRALIA – SCALE OF PROBLEM, MANAGEMENT, REGULATION AND UNIQUE ASPECTS

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Detailed records have been kept since 1969 in relation to horses identified as 'bleeders' on Victorian racetracks. Despite this, specific measures to regulate horses suffering from this condition were not introduced until 1972, except for the refusal of nominations of horses which had bled three times. Subsequent to 1972, the Rules specified the embargoes to be placed on horses which had 'bled' and the conditions under which they could return to racing. At that time, bleeding was defined as the appearance of blood at one or both nostrils at any time. In the early 1980s, various studies demonstrated unequivocally that exercise induced epistaxis was generally pulmonary in origin, not nasal as had been previously presumed. These studies also indicated that the incidence of this condition in the racing horse was far higher than is evidenced by the appearance of blood at one or both nostrils after exercise.

Whilst a system of regulation based on this measure can quite reasonably be open to question (and has been over the years), the Rules introduced represented the only practical form of control given the circumstances under which Australian racing is conducted.

Since then, these Rules have been modified to define 'bleeders' more narrowly and to account for cases of haemorrhage specifically demonstrated to be of a nasal origin. Notwithstanding

this, they still rely on the identification of bilateral epistaxis as the primary predictor of exercise-induced pulmonary haemorrhage (EIPH) for regulatory purposes. Horses which bleed a second time in Australia are banned from racing completely.

This paper examines the statistics relative to the existing Australian Rules of Racing from both historical and contemporary perspectives. It will identify their impact on Australian racing and whether advances in the veterinary management of EIPH have had any effect on its prevalence over the last 20 years. In an effort to investigate the incidence, severity and effects on performance of this condition, RVL co-funded and participated recently in an endoscopic study of a cohort of horses in the immediate post race period (generally within 2 h of racing). The results of this study will be discussed. It is hoped that a parallel consideration of these 2 groups of statistics will provide a sound scientific platform on which the industry's current regulation and control of EIPH, both nationally and internationally, can be critically examined. The need to continually review the effectiveness and relevance of the regulation, control and general management of conditions such as EIPH in racing horses is essential in maintaining the health and welfare of not only the horses, but of their riders, the industry and the confidence of the community more widely in the propriety of Thoroughbred horseracing.

NOTES

EIPH AND HORSERACING IN SOUTH AFRICA - SCALE OF PROBLEM, MANAGEMENT, REGULATION AND UNIQUE ASPECTS

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Horseracing in South Africa is limited to flat racing of Thoroughbred horses. There are approximately 10,000 horses in training and approximately 45,000 starters per annum. Racing takes place year-round at 12 race courses and under various environmental and climatic conditions.

A number of studies have quantified the prevalence of epistaxis in Thoroughbred horses in South Africa. The prevalence of exercise-induced pulmonary haemorrhage (EIPH)-related epistaxis was reported as 1.2% (1948–1949), 2.41% (1976) and 0.165% (1986–2001). The prevalence of epistaxis was also reported to be higher in horses racing at sea level than at an altitude of greater than 1,500 m.

The rules of racing in South Africa stipulate that horses are suspended from racing for a period of 3 months following the first occurrence of epistaxis, 6 months following the second

occurrence and indefinitely following the third episode. Race day medication, including the use of furosemide, is prohibited in South Africa. The National Horse Racing Authority enforces this policy strictly through stringent drug testing. However, furosemide is widely used in horses in South Africa during training for racing.

A study has recently been performed where tracheobronchoscopic examinations were performed on over 1,000 Thoroughbred racehorses within 2 h of racing at 5 different racetracks in 28 race meets. The overall severity of EIPH was: Grade 0 (44.8%), Grade 1 (31.6%), Grade 2 (11.4%), Grade 3 (8.7%) and Grade 4 (3.4%). Preliminary analysis of the data indicates that the prevalence and severity of EIPH may be higher at sea level than at higher altitudes. The possible causes of this warrants further investigation.

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