Chapter 6 General discussion

6.1 EIPH: A SOUTH AFRICAN PERSPECTIVE

Exercise-induced pulmonary haemorrhage (EIPH) was first described in South Africa in 1950.[23] At that stage, flexible videoendoscopes did not exist, therefore the study had to rely on the presence or absence of epistaxis from one or both nostrils in order to detect EIPH.[23] Also, the precise aetiology was unclear, and suggestions were made that the prevalence of EIPH may be affected by genetic factors, feeding of hay, bedding on straw, or nasogastric intubation.[23] However, already in 1950, that study suggested that there may be an association between altitude and EIPH as racehorses competing at sea level had more EIPH-related epistaxis.[23] Later, more reports confirmed that a greater number of racehorses had EIPH related epistaxis at sea level.[24,32]

In South Africa, horse racing occurs at both high altitude and at sea level and horses are not allowed to race on furosemide nor use nasal dilator strips. The National Horse Racing Authority strictly controls racing, and routinely performs drug screening on urine to test for the use of prohibited medications on race day. Through creation of such an environment, this research project was able to determine the prevalence and severity of EIPH, and its association with racing performance.

The results reported here (Chapter 2) indicate that the prevalence and severity of EIPH was greater at sea level than at high altitude agreeing with previous reports.[23,24,32] However, plausible reasons do exist why EIPH may be more prevalent and more severe at altitude as racehorses often suffer from exercise-induced arterial hypoxaemia (EIAH),[3,31] develop pulmonary hypertension,[20] causing pulmonary capillary stress failure[4] and that hypoxic vasoconstriction occurs at high altitude[27] which may worsen the degree of EIAH, thereby directly causing EIPH or exacerbating pre-existing EIPH. Moreover, the overall prevalence of EIPH was 54% which indicated that the prevalence of EIPH as detected by tracheobronchoscopy was high in racehorses competing in South Africa.

In South Africa, the presence of EIPH was associated with superior racing performance in Thoroughbred racehorses not medicated with furosemide and not using nasal dilator strips. The association between racing performance and EIPH is more difficult to evaluate as numerous factors may affect a racehorse's performance on race day. Such factors may include the environment, climate (ambient temperature and humidity), genetics, training techniques, and evaluation technique. Also, factors which may be identified to affect performance at a specific geographical location may not necessarily act in a similar manner at another location. Moreover, are the criteria used to evaluate performance (distance finished behind winner, race earnings and finishing position) suitable enough to allow for accurate evaluation of racing performance?

Although not allowed on race day in South Africa, numerous racing jurisdictions (USA, Canada, Mexico, UAE, and parts of South America) currently use furosemide as prophylaxis for EIPH in the racing industry. Although the clinical efficacy of furosemide in horses with EIPH has yet to be determined under natural field conditions, extensive use of furosemide exists. As annual costs to the Thoroughbred racing industry associated with furosemide administration may be as high as $28 000 000,[14] the use of furosemide in horses with EIPH needs to be re-evaluated to determine the clinical efficacy.

6.2 RESPIRATORY TRACT DISORDERS: PREVALENCE AND ASSOCIATION WITH RACING PERFORMANCE

6.2.1 Prevalence of respiratory tract disorders

Studies reporting respiratory tract disorders in Thoroughbred racehorses have been performed in North America[22,25,30] and Australia.[5] These studies have identified asymmetry of the left arytenoid cartilage,[5,22] idiopathic laryngeal hemiplegia (ILH),[22,25,30] prosthetic laryngoplasty,[22,25] ventriculectomy,[5] right arytenoid paralysis,[22,25] arytenoid chondropathy,[5,22] ulceration of the arytenoid mucosa,[5] aryepiglottic entrapment,[5,22,25,30] pharyngeal polyps,[22] dorsal displacement of the soft palate,[5,25,30] guttural pouch discharge,[25] nasal stenosis,[25] subepiglottic cyst,[5,25] epiglottic hypoplasia,[5] epiglottic deformity[5] and tracheal mucous.[22,30]

Despite having a large population of racehorses in South Africa, the prevalence of respiratory tract disorders was historically unknown. In South African Thoroughbred racehorses, this research (Chapter 3) detected a low prevalence of left arytenoid asymmetry, idiopathic laryngeal hemiplegia (ILH), epiglottic entrapment and deformity, and dorsal displacement of the soft palate; while the prevalence of pharyngeal lymphoid hyperplasia (PLH), laryngeal and tracheal dirt, and tracheal mucous was higher. The prevalence of tracheal ring cartilage spikes was reported for the first time, and an association with sex identified as more male racehorses were affected. An association between age and PLH was found as younger racehorses had higher grades of PLH.

Considering all the respiratory tract disorders identified and reported in this research (Chapter 3), the more important disorders such as left arytenoid asymmetry, left laryngeal hemiplegia and epiglottic deformity had similar prevalence compared to elsewhere.[5,22,25,30] It seems therefore that the South African racing Thoroughbred population is comparable to other Thoroughbred racehorses competing elsewhere in terms of health. Although this research reported on other disorders too, the higher prevalence of laryngeal and tracheal dirt, and PLH should not be interpreted as a sign of ill-health.

The high prevalence of tracheal mucous is more concerning and may indicate that South African Thoroughbred racehorses suffer greater subclinical tracheobronchial inflammation. The exact cause is unclear but neutrophilic inflammation, bacteria, viruses and environmental allergens may contribute directly or indirectly to the production of tracheal mucous.[5,6]

6.2.2 Relationship with racing performance

Results of this research (Chapter 3) indicate that racing performance in South African Thoroughbred racehorses was not impaired by grade 2 arytenoid cartilage asymmetry, ILH, PLH (grade 2 and 3), epiglottic deformity and epiglottic entrapment; while superior racing performance was seen in racehorses with tracheal cartilage ring spikes and grade 3 tracheal mucous.

Similar to the results of this research (Chapter 3), previous studies have reported that racing performance was not affected by grade 2 arytenoid cartilage asymmetry, epiglottic entrapment and PLH.[5,16] However, contrary to previous reports that ILH was associated with impaired performance,[6,9,18] this report found no evidence of impaired racing performance. This finding was unexpected as studies have reported impaired gaseous exchange in affected horses.[2,6,18] This certainly does not mean that surgical correction of ILH should no longer be employed!

Although tracheal cartilage ring spikes have been reported before,[27] their significance is currently unknown. It is unclear to why this disorder may be associated with superior racing performance and occur more frequently in make racehorses. It was also surprising that racehorses with greater amounts of tracheal mucous (grade 3) had superior racing performance since tracheal mucous is associated with exercised-induced arterial hypoxaemia during a standardized treadmill test.[7,28]

Although this research reported on a wide variety of upper respiratory tract disorders, the low prevalence of certain disorders did not allow statistical analysis to determine their relationship with racing performance. Furthermore, since certain respiratory tract disorders are dynamic, such disorders could not be identified, nor could their relationship with racing performance be determined.

It should be noted that previous reports have largely been conducted on horses using high-speed treadmills[6,7,18,28] and that these studies may have either lacked adequate statistical power, random selection, and did not examine a natural population of racehorses under field conditions.

This research highlights the need for further objective research in racehorses under field conditions, as disorders that are found to impair performance in racehorses during high-speed treadmill exercise may not act in a similar manner under field conditions. Also, since reasons for impaired racing performance may be multifactorial, respiratory tract disorders should cautiously be interpreted as the sole reason for impaired racing performance.

6.3 DETECTION AND GRADING OF RESPIRATORY TRACT DISORDERS

Until endoscopy was introduced into equine medicine, horses with respiratory tract disorders could not be thoroughly examined. Although historically, rigid endoscopes provided a wealth of knowledge for internists studying equine upper airway disorders at first, these instruments were cumbersome to use, traumatized tissues easily, generated excess heat and had limited power reserves. Many of the aforementioned problems were alleviated with the advent of flexible endoscopy. Today, equine internists can evaluate the upper and lower respiratory airway and identify structural disorders at rest, while dynamic or functional disorders can be diagnosed during high-speed treadmill exercise.

Under natural field conditions, examining a large population of horses requires a diagnostic technique that can be performed quickly and safely for both personnel and horse, while yielding the maximum amount of information possible. Moreover, it should not interfere with training schedule nor be performance modifying causing disqualification of a horse participating in athletic events due to the detection of drug residues.

Following flexible videoendoscopic examinations on Thoroughbred racehorses, we used previously described grading critera[1,11,15,29] to access the presence and severity of EIPH, PLH, arytenoid cartilage movement (ACM) and tracheal mucous (TM) and established good interobserver reliability for EIPH, while moderate interobserver reliability was observed for PLH, ACM and TM. This study (Chapter 4) is in agreement with another study that also demonstrated high interobserver reliability for EIPH; however that study unfortunately did not access other disorders.[15]

Since the equine respiratory tract is an important cause of poor performance and may be examined on numerous occasions throughout the horse's lifetime, and that respiratory disorders occur worldwide, it is important to employ similar grading criteria that are reliable and reproducible by internists of varying experience.

Currently, there exists a paucity of studies documenting the prevalence of respiratory tract disorders in natural populations of Thoroughbred racehorses, making collation of data using similar grading criteria even more important. Researchers may then have the opportunity to conduct multi-centered studies at different locations throughout the world that could have a significant impact on the importance of performance-limiting disorders of the equine respiratory tract.

6.4 SYSTEMIC INFLAMMATION AND THERAPEUTIC INTERVENTIONS

Cytokines are soluble, regulatory polypeptides produced by a variety of nucleated cells of heamatopoietic and non-heamatopoietic origin. Cytokines can act locally to initiate autocrine, paracrine or endocrine effects and are critical for normal immune function.
They are involved in the regulation of growth, development and activation of the immune system, and mediation of the inflammatory response. These substances exert their effects by influencing gene activation that results in cellular activation, growth, differentiation,

functional cell molecular expression, and cellular effector function. Cytokines may therefore have a dramatic effect on immune response regulation and pathogenesis of diseases.

Pulmonary inflammation has been previously reported in racehorses with EIPH and may be due to pre-existing small airway disease[19] or intrapulmonary accumulation of blood.[21] Following autologous blood installation within the lung, there is a pulmonary neutrophilia,[21] and since neutrophils are a major source of proinflammatory cytokines,[17] it is therefore not surprising that a systemic inflammatory response was detected by this study (Chapter 5). However, as previously reported, it is still uncertain whether this inflammatory response is pre-existing or if it develops as a consequence of EIPH.

It is possible, that racehorses may have mild, undetectable episodes of EIPH repeatedly during strenuous training periods. This is exacerbated on race day, resulting in tracheobronchoscopic detection of blood. The ability to identify horses that have subclinical EIPH may be of benefit to trainers and allow earlier therapeutic intervention. Although therapeutic options for horses with EIPH have included lowering transmural pulmonary capillary pressure, relieving upper and lower airway obstruction, decreasing interstitial inflammation and bronchial angiogenesis, and treating for haemostatic dysfunction,[8] no strategies exist for combating this disorder at a molecular level. Anti-cytokine therapies exist in human medicine and include neutralizing antibodies, receptor antagonists, soluble receptors and inhibitors of proteases.[10] For instance, in models of inflammation, neutralizing antibodies to IL-8 reduces neutrophil infiltration in the lung, joint, kidney, skin, and myocardium.[13]

These results are novel and certainly interesting, and provide insight into the immunopathogenesis of EIPH at a molecular level. Further research is needed to identify whether the use of anticytokine therapy may help reduce the prevalence and severity of EIPH.

6.5 CONCLUSIONS

The research reported in this thesis has contributed substantially to the determination of the prevalence, severity and affect on racing performance of respiratory tract disorders in Thoroughbred racehorses competing in South Africa. Also, determination of an association between EIPH and systemic inflammation at a molecular level may assist future researchers in anti-cytokine therapies which may help reduce the prevalence and severity of EIPH.

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