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COPD, RAO, Heaves, IAD: Sorting out the Phenotypes of Chronic Airway Disease in the Horse

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The literature on chronic airway disease in horses contains a plethora of names to describe the problem. Classically, “heaves” or “broken wind” described the respiratory cripple with severe airway obstruction that resulted in obvious respiratory distress and the classical forced exhalation. With the advent of lung function testing and methods for airway cytology, clinicians realized that the horse with heaves is only the tip of the iceberg and that many horses have airway inflammation and changes in airway function that do not result in clinically obvious respiratory distress at rest. These observations occurred at the time that human physicians were also trying to differentiate human COPD from asthma. Because the neutrophil is the predominant inflammatory cell in airway secretions of horses with heaves and humans with COPD, heaves was renamed equine COPD and this term was extended to describe any horse with signs of lower-grade airway inflammation in the absence of an infectious cause. Unfortunately, diagnostic criteria for use of the term equine COPD were never specified and, as a consequence, many research papers on COPD included poorly defined populations of horses.

At a workshop in 2000, an international group of investigators began defining the phenotypes of equine chronic airway disease. Because airway obstruction in human COPD is not easily reversible but airway obstruction in equine COPD is reversible, it was decided to eliminate the term equine COPD in favor of terms that more specifically define the equine phenotypes. Recurrent airway obstruction (RAO) was selected to describe the horse with classic heaves. RAO occurs in mature horses and is characterized by measurable airway obstruction that is induced by exposure to organic dust. The airway obstruction is reversible with a change in environment and is rapidly relieved by treatment with a bronchodilator drug. For the latter reason, the main cause of airway obstruction in RAO-affected horses is bronchospasm. Because the airway obstruction is not totally reversed by use of bronchodilator drugs, there must be other causes of airway obstruction, including accumulations of mucus and inflammatory cells in the airway lumen and structural changes in the airway wall. The principal inflammatory cell in the airway lumen of horses with heaves is the neutrophil. This same workshop grouped less severe forms of chronic airway disease under the term “inflammatory airway disease” (IAD) and clearly stated that the relationship between IAD and RAO is currently unknown.

In 2001, a second workshop tackled the definition of IAD. The general description included endoscopically visible accumulations of mucus and inflammatory cells in the airway lumen in the absence of visible respiratory distress. These criteria can be fulfilled in many other respiratory conditions so these must first be ruled out. Criteria were also established for airway cytology and included greater than 5 and 20 percent neutrophils in BALF and tracheal lavage fluid respectively. It was recognized that the term IAD was being used clinically to describe at least two widely different syndromes, one in young racehorses and the other in mature pleasure and performance horses. Several epidemiological investigations in the UK, Australia, and the USA have described a respiratory syndrome that has its highest prevalence when racehorses enter training and that becomes less prevalent the longer horses are in training. The syndrome includes endoscopically visible accumulations of mucoid secretions in the trachea that may be accompanied by cough and that causes reduced racing performance. In performance horses, similar visible accumulations of secretions in the trachea can be associated with reduced performance and sub-clinical airway obstruction that can be detected by sensitive lung-function tests. A recent epidemiological study by our group indicated that horses older than 15 years of age are at increased risk of having visible accumulations of mucoid secretions in the trachea.

Pathogenesis of Recurrent Airway Obstruction (Heaves)

Of the inflammatory airway syndromes in horses, RAO has been most extensively investigated because the affected horse is easy to identify and bouts of airway inflammation and obstruction can be readily induced by exposure of horses to organic dust either by feeding hay or by use of a hay dust suspension. A similar syndrome of summer pasture-associated airway obstructive disease is induced by organic dusts in pasture, generally in the southern USA. When an RAO-susceptible horse is exposed to organic dust, neutrophils accumulate within the lungs within 6-8 hours and can be found in the bronchoalveolar lavage fluid (BALF) shortly thereafter. Concomitantly airway obstruction and hyperresponsiveness develops, although the former
may not become clinically evident for hours to days. Mucoid secretions with decreased clearability increase in amount concomitant with airway neutrophilic inflammation. Horses also exhibit increased cough frequency. Control horses in the same environment have a significant but much lesser increase in BALF neutrophils but this is unaccompanied by measurable airway obstruction, or accumulation of mucoid secretions. However, one study reported a transient one-day increase in coughing in stabled control animals.

Cellular mechanisms responsible for the excessive inflammation in heaves include activation of NFkappaB p65 homodimer in distal airway cells, probably by increased and continued production of TNFalpha and IL-1beta, in part from granulocytes that have delayed apoptosis. Other inflammatory cytokines expressed in heaves-affected animals include interleukins-4, 8, 13, and 17, IFN-gamma, and TGF-beta. Expression of IL-8, increased production of LTB4, and expression of ICAM explain increased chemotactic activity of BALF and the exuberant neutrophilic inflammation. The roll of oxidant stress is under debate.

There is considerable debate over the immune mechanisms responsible for heaves with evidence in favor of both TH2 and TH1-type responses. Differences may reflect differences in sampling times and duration of dust exposure. The innate immune system apparently also plays a role because the severity of inflammation can be reduced when endotoxin is removed from a hay dust suspension that induces inflammation in RAO-susceptible horses. New evidence from our group indicates increased expression of Toll-like receptor-4 when RAO-susceptible but not control horses are exposed to organic dust.

What is the Characteristic Lesion of Heaves?

Heaves is classically described as a diffuse bronchiolitis with mucus plugs containing neutrophils in the airway lumen and a mixed mononuclear inflammatory response in the peribronchiolar connective tissue. Epithelial hyperplasia, mucous cell metaplasia, peribronchiolar fibrosis, smooth muscle hypertrophy and increased numbers of mast cells also are commonly described. None of the descriptive studies of the lesions of heaves includes a well-characterized control group. Other papers describe similar and other lesions in a group of horses with COPD.

We have conducted two recent investigations in which we compared and quantified lesions in RAO-affected and mature control horses that were provided with similar environmental challenges. In the first investigation, a lung pathologist blindly scored the severity of bronchiolar inflammation, epithelial hyperplasia and mucous cell metaplasia and we also quantified the amount of stored mucosubstances in goblet cells and the number of epithelial cells in the terminal airways. There were no significant differences between groups in any of the variables. However, regardless of disease group, there was a significant association between inflammation score and both mucous cell metaplasia and the amount of stored mucosubstances. In a more recent but similar study, we found no group differences in the number of mucous cells in small bronchi and no differences in the amount of Masson's trichrome staining for peribronchiolar fibrosis (unpublished data). Interestingly, in the second investigation, the amount of stored mucosubstances was negatively correlated with the number of BALF neutrophils in the RAO-affected group. These two investigations confirm that there is considerable bronchiolar inflammation in control (non-RAO-affected) horses and that, regardless of phenotypic diagnosis, inflammation has effects on the mucus apparatus—causing it to store more mucins if inflammation is not too severe and to release mucins if inflammation is severe. These findings also tend to confirm that RAO is largely a functional disease, the clinical signs of which are due to bronchospasm that may be due in part to smooth muscle hyperplasia.

Pathogenesis of Racehorse IAD

There is considerable evidence that tracheal infection with bacteria, especially Streptococcus zooepidemicus, and Staphylococcus pneumoniae is associated with racehorse IAD and that the more severe the tracheal inflammation, the more likelihood there is of isolating pathogenic bacteria. Interestingly, there is little evidence in support of an association between IAD and respiratory viral infection. Because upper airway secretions could have contaminated the tracheal samples, some skepticism remains about the importance of bacteria. Also, no evidence has been produced to demonstrate that the tracheal infection extends deeper into the lung. However, the observation that IAD bouts become less frequent as racehorses spend more time in training stables suggests the development of immunity to an infectious agent. In horses with less severe IAD, positive bacterial cultures are fewer and it is possible that other factors such as stable dust and endotoxin exposure could play a role in the syndrome. In light of this information, our group is presently doing an extensive investigation of particulate exposure of racehorses and its relationship to IAD.

Pathogenesis of Mature Horse IAD

There has been little investigation of IAD of mature horses. Sensitive lung function tests can detect measurable airway obstruction in IAD-affected horses that do not have visible respiratory distress at rest. Is this form of IAD just an earlier form of RAO? Certainly, the
risk factors for IAD in Michigan pleasure horses include eating hay and older age, also factors known to be associated with RAO. These observations point out the need for more extensive investigation of the inflammatory and immune pathways involved in mature horse IAD to determine if the latter is a precursor to RAO.

**Beware the Use of Tracheal Lavage Cytology to Diagnose IAD/RAO**

There is now ample evidence that large numbers of neutrophils can occur in tracheal lavage fluid of apparently normal horses and there is very little correlation between tracheal lavage fluid and BALF cytology. Horses with an increased percentage of neutrophils in BALF also have a high percentage in tracheal lavage fluid but many horses with a normal neutrophil percentage in BALF have a high percentage in tracheal lavage fluid. It is also true that visible accumulations of mucoid secretions in the trachea are generally accompanied by a high percentage of neutrophils but many horses with abundant neutrophils in the tracheal lavage fluid do not have increased amounts of mucoid secretions. The reason for the increased number/percentage of neutrophils is unknown but eating hay (especially from round bales), being outdoors in cold winter weather, and intense exercise such as racing are all risk factors for increased neutrophil numbers/percentage in tracheal secretions. However, in the latter investigation, BALF neutrophils were not counted. As pointed out by Malikides et al., the trachea and lower airways need to be considered somewhat independently when evaluating the causes of changes in airway cytology. Certainly, it is unwise to use a cutoff value like 20% neutrophils as a criterion for phenotype definition. About 70% of Michigan pleasure horses would have IAD if more than 20% neutrophils in tracheal secretions were the diagnostic criterion.

**References**


