Exercise Induced Pulmonary Hemorrhage

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Disorders of the Respiratory System are:

- The **second most common** limiting factor for the athletic performance of horses
- Often result in **major** economic losses for owners
- Many horses are lost for performance or must be retired
EIPH

- EIPH occurs in Thoroughbreds, Quarter Horses and Standardbreds
- During sprint racing
- Also observed in other high performance non-racing equine athletes e.g.
  - Barrel, Cutting, Reining, Roping
  - Polo
  - Cross-country and 3-day event
  - Show jumping and Hunter-jumper
  - Steeplechase
  - And even draft horses
Exercise Induced Pulmonary Hemorrhage

- Dr. Robinson has defined EIPH
- Explained how it occurs
- Described important pre-disposing and/or coexisting conditions
- Shared a great deal about both the underlying mechanisms responsible for the development of this problem and described how it might impact performance horses
- My task is to discuss available treatment options along with how and why these might be effective in treatment of EIPH
PREVENTION AND TREATMENT OF EIPH

• Exercise-induced pulmonary hemorrhage (EIPH) is a major health concern and cause of poor performance in the equine athlete

• Many therapeutic and management interventions have been tried, but few have proven efficacy in treating EIPH
Most Evidence for Treatment of EIPH

- **Furosemide and Flair Nasal Strip**

- Currently being used to treat EIPH based on evidence that these *decrease but do not prevent* EIPH
  
  - Sweeney et al 1984 (in *Eq Exercise Physiology*)
  - Goer et al 2001 (*Equine vet J* 33, 577-584)
  - Kindig et al 2001 (*J Appl Phys* 91, 1396-1400)
  - Zawadz kas et al 2006 (*Eq vet J supp* 36, 291-293)
  - Hinchcliff et al 2009 (*JAVMA* 235, 76-82)
Treatment of EIPH

- Furosemide, a high-loop diuretic, decreases plasma volume, cardiac output and pulmonary vascular pressures reducing EIPH up to 50% (Kindig et al. 2001a).

- The Flair nasal strip decreases EIPH a similar amount by preventing nasal passage narrowing on inspiration thereby lowering airway resistance (Poole et al. 2000; Geor et al. 2001; Kindig et al. 2001a; Holcombe et al. 2002).
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al. 2009 (JAVMA 235, 76-82)
  - Study was randomized, placebo-controlled, crossover field trial
  - Conducted in South Africa at a racing venue
  - Horses assigned to fields of 9 to 16 horses
  - Raced twice one week apart once on Lasix and once with saline control
  - Other factors were identical (surface, jockey, length, etc.)
  - After the race all horses were returned to the parade ring, tack removed and a tracheobronchoscopic examination was performed
Most Evidence for Treatment of EIPH

- **Furosemide**
  - Hinchcliff et al 2009  (JAVMA 235, 76-82)
  - A total of 328 horses were nominated
  - 193 were **enrolled** in the study by a professional handicapper
  - **155** competed in **both races**, 12 in only the 1\textsuperscript{st} race and 26 did not compete
  - Horses from **40 stables**
  - Only three horses were unable to be scoped after racing
  - Horses were scoped approximately 42 minutes after racing
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009 (JAVMA 235, 76-82)
  - Scores for endoscopic severity for EIPH were less severe after *furosemide* with no 3 or 4.
  - Scores for endoscopic severity for EIPH ranged from 1 to 4 in horses after saline.

- FOR THE 152 HORSES SCOPED AFTER BOTH RACES 57% HAD EIPH ≥ 1 WITH FUROSEMIDE AND NONE WAS A GRADE 3 TO 4 WHILE 79% HAD EIPH AFTER SALINE.
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009 (JAVMA 235, 76-82)

  - OVERALL (67.5%) OF THE HORSES THAT HAD EIPH AFTER SALINE HAD A REDUCTION OF EIPH SEVERITY SCORE OF AT LEAST 1 GRADE WHEN TREATED WITH FUROSEMICIDE
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009  (JAVMA 235, 76-82)
  - AGE, GENDER, DISTANCE RACED AND TREATMENT SEQUENCE DID NOT HAVE AN EFFECT ON EIPH
  - MEAN WEIGHT LOSS WAS 12.7 Kg +/− 0.33Kg WITH LASIX AND 5.4Kg +/− 0.28 Kg WITH SALINE
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009 (JAVMA 235, 76-82)

  - RESULTS OF THIS STUDY INDICATED THAT PRERACE ADMINISTRATION OF FUROSEMIDE **DECREASED** THE INCIDENCE AND **SEVERITY** OF EIPH IN THOROUGHBREDS RACING UNDER TYPICAL CONDITIONS IN SOUTH AFRICA
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009  *(JAVMA 235, 76-82)*

  - **Strengths of the study:**
    - Large number of horses
    - Standard race conditions
    - Horses used were in an at risk group
    - Statistical methods used made it unlikely results were due to confounding factors
Most Evidence for Treatment of EIPH

- **Furosemide** Hinchcliff et al 2009 (JAVMA 235, 76-82)

  - Some remaining questions:
    - Did not identify an association between weight lost and prevention of EIPH
    - Crossover period was adequate to find no lasix in saline group
    - Furosemide is reported to reduce mucociliary clearance in humans and bronchodilation in ponies with recurrent airway obstruction
Treatment of EIPH

- Diuretics other than Furosemide
Exercise Induced Pulmonary Hemorrhage

- Effect of furosemide and furosemide – carbazochrome combination on exercise-induced pulmonary hemorrhage in Standardbred racehorses.
Exercise Induced Pulmonary Hemorrhage

- Carbazochrome salicylate, also known as Kentucky Red
  - Classified among hemostatic drugs as a capillary stabilizer
  - It is used clinically for the treatment of hemorrhage due to capillary fragility in humans
  - The mechanism of action of carbazochrome is unknown
Exercise Induced Pulmonary Hemorrhage

- **RESULTS:**
  - **EIPH endoscopy scores were:**
    - Placebo 1.56
    - Furosemide 1.12
    - Furosemide – carbazochrome 1.0
  - **Weight loss over 4-hour period after treatment was:**
    - Placebo 9.4 kg
    - Furosemide 14.8 kg
    - Furosemide–carbazochrome 13.8 kg
Exercise Induced Pulmonary Hemorrhage

- In this study pre-exercise administration of furosemide or furosemide-carbazochrome combination did not affect the severity of pulmonary bleeding or the performance of horses that had a history of EIPH.

- Low number of Standardbred horses not under race conditions
Exercise Induced Pulmonary Hemorrhage

Effects of conjugated oestrogens and aminocaproic acid upon exercise-induced pulmonary haemorrhage (EIPH)

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5(2); 95–103
Why even try these medications?

Aminocaproic acid and Premarin

- **ACA** used in an attempt to mitigate EIPH as a result of hypothesized transient coagulation deficiencies in exercising horses
- Antifibrinolytic treatments may result in increased stability/lifespan of the clot and control of numerous causes of hemorrhage, benefiting human patients
Treatment of EIPH

Aminocaproic acid and Premarin

- Why try PREMARIN
  - Two primary mechanisms of action for conjugated estrogens are:
    - Restoration and/or strengthening of vascular integrity by strengthening collagen and eliminating endothelial discontinuity and degeneration
    - Shortening the bleeding time
Aminocaproic acid and Premarin

- There was a trend (p = 0.09) for decreased time-to-fatigue by ACA (This is a negative).
  - ACA treated horses performed at least one stage less than runs completed after PREMARIN or placebo administration.
- Time-to-fatigue was not affected by treatment with PREMARIN.
Treatment of EIPH

- The principal findings of this investigation were that neither ACA nor PRE effectively reduced EIPH.
- There was an acute decrease in pulmonary inflammation (i.e. decreased BALF [WBC]) which could be helpful.
- The decreased time to fatigue may partially explain some of the anecdotal reports by veterinarians that ACA may impair performance.
Effects of intravenous aminocaproic acid on exercise-induced pulmonary hemorrhage (EIPH) B. M. Bucholz, A Murdock, W. M. Bayly, R. H. Sides
Equine vet J 2010;42 (supp 38) 256–260

Examined erythrocyte counts in BALF of 8 Thoroughbreds following treadmill exercise at an intensity level to achieve greater than that needed to reach maximal oxygen consumption

Horses exercised to fatigue 3 times using saline placebo 2 and 7 grams ACA 4 hours before exercise
Effects of intravenous aminocaproic acid on exercise-induced pulmonary hemorrhage (EIPH) B. M. Bucholz, A Murdock, W. M. Bayly, R. H. Sides Equine vet J 2010;42 (supp 38) 256–260

RESULTS:

- Aminocaproic acid had no effect on VO₂ max, run time, or erythrocyte counts in pre or post-exercise BALF

Conclusions:

- ACA was not effective in preventing or reducing the severity of EIPH or improving performance under the exercise conditions in this study
Treatment of EIPH

- Drugs with less available data for EIPH
  - An injectable product designed to reduce airway inflammation, concentrated equine serum

- Dietary omega-3 fatty acids, may also ameliorate EIPH (Erickson and Hildreth 2004).

- Vitamin K deficiency of vitamin K is not occurring in EIPH
Treatment of EIPH

- Possibly or not effective in EIPH
  - Neither inhaled nitric oxide (irrespective of lowering pulmonary artery pressure, Kindig et al. 2001b)
  - Nor herbal formulations designed to remedy putative coagulation defects Have evidence of benefit
Treatment of EIPH: use of a proprietary Omega-3 technology

A study conducted at Kansas State University reported that feeding this proprietary Omega-3 technology, designed to provide specific dietary levels of essential fatty acids (EPA and DHA), to horses with varying degrees of EIPH appears to be helpful in managing the condition.

Levels of EPA and DHA increased in blood of horses
Ten Thoroughbred horses with a history of EIPH

Horses were subjected to a pre-treatment maximum treadmill run followed by bronchoalveolar lavage

Diets were fed for 145 days. Maximum exercise runs were performed at 83 and 145 days of feeding
Results:

- RBC in BAL fluid of control horses increased relative to the pre-treatment run (773 ± 32 %). While horses fed EPA and DHA had substantially less change (P < 0.05) in BAL RBC (186 ± 32 %).
Herbal formulations to treat EIPH but Little or No published scientific research EASTERN MEDICINE

What are these said to do:
- Decrease inflammation and edema in the lung
- Move stagnated blood out of the airways
- Address coagulation defects, such as platelet function, proposed to contribute to EIPH in horses during exercise.

Erickson et al evaluated the effects of (Yunnan Paiyao and Single Immortal) Herbal formulations were not effective in reducing EIPH severity in horses exercising on the treadmill as evaluated by BAL

However, time to fatigue was slightly, but significantly increased after treatment with Single Immortal.
To date, the authors are unaware of any experimental or clinical evidence that an aerosolized product to treat EIPH is effective or, indeed, even available.
Diseases that might be related to EIPH

- As Dr. Robinson indicated part of the mechanism for EIPH may be related to other diseases affecting small airways
  - If a horse has a bacterial infection then appropriate antibiotics could be useful in treatment of EIPH
  - If a horse had bronchconstriction as a result of inflammatory or reactive airway disease use of bronchodilators such as Clenbuterol, Albuterol or others as inhaled or systemic administration
Diseases that might be related to EIPH

Additionally, horses with inflammatory or reactive airway disease might also benefit from either inhaled or systemic corticosteroids.

- However, work in his and Dr. Fred Derksen’s laboratory have not strongly supported this conclusion.
Corticosteroids do not provide immediate improvement in pulmonary function

Aerosolized corticosteroids work best with mild exercise intolerance to moderate increases in respiratory effort

Available equine formulations:

- Fluticasone 2,000ug BID most potent and most expensive
- Beclomethasone 500-1500 ug BID
Inhalation therapy

- Treatment:
  - **Equine Aeromask** (Canadian Monaghan, Ontario, Canada)
  - Can be used for nebulization solutions, MDI devices, or dry powder inhaler get ~6% of CFC propellant and 14% of HFA propellant drugs
Inhalation therapy:

- Equine patients are ideal because of their cooperative nature
- Large tidal volume
- Obligate nasal breathing

Newer systems for delivery have made this even more effective and easy

Focus is on bronchodilators and anti-inflammatory agents
**Inhalation therapy:**

- Anti-inflammatory therapy is the **KEY** component to treatment of non-infectious respiratory disease
- **Bronchodilators** are important for **immediate** relief of symptoms
- Mast cell stabilizers sodium cromoglycate and nedocromil sodium inhibit degranulation of Mast cells
Diseases that might be related to EIPH

- Another important problem is pleuropneumonia
- In my opinion EIPH is one risk factor associated with development of this condition
- For purposes of example I have included a typical case scenario
Signalment

- 3 year Thoroughbred colt
- History: Raced on Saturday, shipped on Monday did not eat on the day of arrival
- Post race scope revealed a trail of blood in trachea
- Primary complaint dyspnea (RR 36), fever (T – 103.5 F), depression
- But often all you see is FEVER
EIPH
Normal thorax
Pleuropneumonia

- The majority of pleural effusions and septic pleuritis (pleuropneumonia) result from pneumonia or pulmonary abscesses.
- Pleuritis/pleuropneumonia is sometimes the result of thoracic trauma, esophageal rupture.
- The microorganisms most commonly isolated are aerobic or facultative anaerobic organisms which reside in the oral pharynx such as *Streptococcus* spp., *Pasteurella* spp., *Actinobacillus* spp., *E. coli*, and others.
- Anaerobic organisms are *Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, and *Clostridium*.
Pleuropneumonia

- Epidemiology
  - Factors commonly associated with the onset of pleuropneumonia in horses are
    - Transportation for long distances
    - Extreme exercise often with EIPH
    - Viral infection
    - General anesthesia
    - Systemic disease (e.g., Colitis)
  - Other factors incriminated:
    - Aspiration of microorganisms of the upper respiratory tract
    - Interference with the respiratory tracts ability to clear these organisms
Pleuropneumonia

Pathogenesis

These factors compromise the pulmonary defense mechanisms and permit bacterial contamination of the lower respiratory tract and subsequent pneumonia or formation of abscesses.
Pleuropneumonia

**Treatment**

1. Chronic Effective Drainage
2. Appropriate Antimicrobials (penicillin, gentamicin, metronidazole)
3. Anti-inflammatory medications (e.g. flunixin meglumine or phenylbutazone)
4. Nursing Care
Pleuropneumonia