

# Review of Alternative Therapies for EIPH

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There are effective alternatives to furosemide for the prevention and treatment of exercise-induced pulmonary hemorrhage. They include the nasal strip, concentrated equine serum, and a diet rich in omega-3 fatty acids. Conjugated estrogens and antifibrinolytics may also be effective. Authors' address: College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506; e-mail: tepp@vet.k-state.edu. © 2007 AAEP. \*Presenting author.

## 1. Introduction

Exercise-induced pulmonary hemorrhage (EIPH) is a major health concern and cause of poor performance in the equine athlete.<sup>1-3</sup> Significant progress has been made in recent years to diagnose EIPH and to understand the pathogenesis, prevention, and treatment of EIPH. The development of effective therapies for EIPH has been difficult because of controversy regarding the mechanisms causing EIPH and the methods to quantify EIPH. Some alternatives to furosemide that are used to prevent and treat EIPH include nasal dilators, concentrated equine serum, nitric oxide (NO), herbal formulations, conjugated estrogens, aminocaproic acid, a diet rich in omega-3 fatty acids, and rest.

## 2. Nasal Dilators

During quiet breathing and during exercise, 40–50% of the total pulmonary resistance is located within the nasal passages.<sup>4</sup> During inspiration, the extrathoracic airways account for >90% of the total resistance. Horses are obligate nasal breathers, so nasal resistance is of much greater importance than in humans. During exercise, partial collapse of the unsupported nasal passages may oc-

cur during inspiration. A nasal strip<sup>a</sup> 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 reduce intrapleural and alveolar pressure swings that may contribute to high pulmonary capillary transmural pressures and EIPH. Holcombe et al.<sup>5</sup> conducted studies which concluded that the nasal strip tents the skin over the nasal valve and dilates this section of the nasal passage, resulting in decreased airway resistance during inspiration. In our laboratory, seven horses were evaluated during high-intensity running on the treadmill under both control conditions and wearing the nasal strip. These studies showed that the nasal strip significantly reduced oxygen uptake and CO<sub>2</sub> production, supporting a reduced work of breathing with nasal dilation.<sup>6,7</sup> Moreover, bronchoalveolar lavage showed a 33% reduction in EIPH with the nasal strip, with the largest reduction in EIPH being in those horses that bled the most.<sup>7</sup> These results have subsequently been confirmed in other studies<sup>8-11</sup> (Fig. 1) with, in each instance, substantial reductions in EIPH and one intriguing finding of increased time to fatigue.<sup>11</sup> In the field, nearly 400

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## NOTES

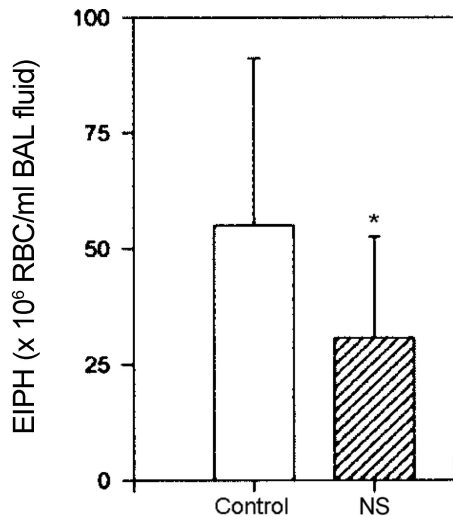


Fig. 1. EIPH incurred during near-maximal exercise was reduced significantly in five horses (\**p* < 0.05) by the nasal strip (NS).<sup>8</sup>

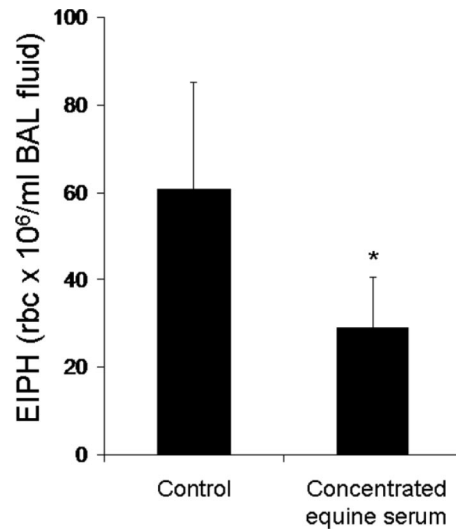


Fig. 2. Severity of EIPH was reduced by treatment with CES (\**p* < 0.05).<sup>d</sup>

horses that wore nasal strips were evaluated at the Calder Race Course in Florida in 1999–2000.<sup>b</sup> It was observed that horses with the strip had a win percentage 3.4% higher than horses that did not wear a strip. Horses wearing a nasal strip had a 15% decrease (*p* < 0.001) in the interval to the next race (23 days) compared with the race-to-race interval before wearing a nasal strip (29 days). In a study of 30 Thoroughbred racehorses at Golden Gate Fields Racetrack in California, Valdez et al.<sup>10</sup> observed a 65% reduction in the number of red blood cells in bronchoalveolar lavage fluid 12–18 h after racing in horses with severe EIPH that used a nasal strip.

### 3. Concentrated Equine Serum

Inflammatory airway disease may be an important component of EIPH.<sup>12,13</sup> A concentrated equine serum (CES) product<sup>c</sup> collected from multiple draft horse donors and containing high levels of immunoglobulins and other serum proteins has been used to treat horses with EIPH. The product is given in a series of five injections 24 h apart (20 ml intratracheal and 10 ml IV) with subsequent weekly boosters thereafter during training and performance. This treatment regimen is based on field studies completed at various racetracks over a 5-yr period where a reduction in EIPH and mucus was observed when CES was used to treat chronic bleeders on the race track. In a maximal exercise study (*n* = 6) on the treadmill,<sup>2</sup> CES resulted in a 53% decrease in the number of red blood cells (Fig. 2) and a 32% decrease in the white blood cells in the bronchoalveolar lavage fluid. CES may have immunomodulatory and anti-inflammatory effects that are beneficial in reducing small airway disease, which may be one of the mechanisms responsible for EIPH. CES may reduce EIPH through an immune-medi-

ated mechanism that may improve the healing of the lung tissue and reduce scar formation.

### 4. Nitric Oxide

Nitric oxide (NO) is a vascular smooth muscle relaxing factor that is produced by the action of NO synthase on L-arginine within vascular endothelial cells. Inhaled NO reduces pulmonary arterial pressure during exercise<sup>14,15</sup>; however, the severity of EIPH increases with NO inhalation (*n* = 5)<sup>16</sup> (Fig. 3). These findings support the notion that extremely high pulmonary artery pressures may reflect, in part, an arteriolar vasoconstriction that serves to protect at least some parts of the capillary bed from the extraordinarily high pulmonary arterial pressures during maximal exercise in the horse. These data also suggest that exogenous NO treatment during exercise in horses may not only be poor

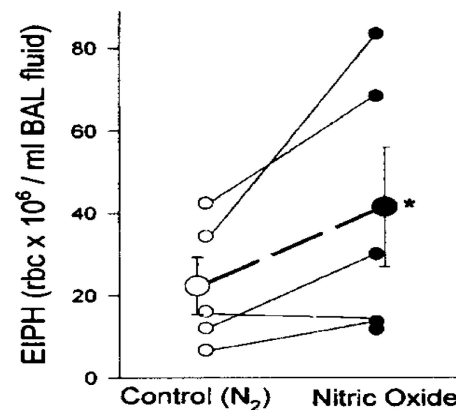


Fig. 3. Severity of EIPH was exacerbated by inhalation of NO.<sup>16</sup> Large symbols denote mean data (\**p* < 0.05).

prophylaxis but may actually exacerbate the severity of EIPH.

### 5. Herbal Formulations

Herbal formulations are used to treat horses with EIPH; however, very few scientific studies have been done to determine the effectiveness of herbal remedies. Herbal formulations are used to decrease inflammation and edema 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 have been hypothesized to contribute to EIPH. Two commonly used herbal formulations<sup>e</sup> were recently evaluated in five Thoroughbred horses but were not found to be effective, at this particular dose and duration of treatment, in reducing EIPH.<sup>17</sup>

### 6. Omega-3 Fatty Acids

Many equine supplements are high in omega-3 fatty acids, which are hypothesized to reduce EIPH through their action on the arachadonic acid cascade and consequent reduction in airway 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. Portier et al.<sup>18</sup> recently reported modulation of the decrease in erythrocyte membrane fluidity during exercise in horses fed a diet enriched with docasahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) for 4 wk. Preliminary results from a study in 10 Thoroughbred horses at Kansas State University showed a reduction in EIPH after 83 and 145 days on a diet enriched with both DHA and EPA, but not with DHA alone.<sup>f</sup> One putative mechanism for this response is that the preservation of red blood cell membrane fluidity improves pulmonary vascular hemodynamics after treatment.

### 7. Conjugated Estrogens and Anti-fibrinolytics

Hemostatic agents are often used to treat uncontrolled bleeding in patients with systemic fibrinolysis. There is no scientific evidence that horses with EIPH have increased fibrinolysis or defective coagulation.<sup>19,20</sup> However, conjugated estrogens and antifibrinolytics<sup>21</sup> are used on the race track to prevent EIPH. Heidmann et al.<sup>21</sup> recently reported that aminocaproic acid (30 and 100 mg/kg, IV) significantly modified hemostasis in resting horses, consistent with its antifibrinolytic effects. We recently studied the effects of conjugated estrogens<sup>g</sup> (25 mg) and aminocaproic acid<sup>h</sup> (5 g) given IV 2 and 4 h, respectively, before exercise in five Thoroughbred horses; preliminary results indicate a trend toward less EIPH (a decrease in EIPH of ~50% in four of five horses) with both treatments.<sup>i</sup> There was a trend to earlier fatigue with aminocaproic acid, but delayed fatigue after treatment with conjugated estrogens.<sup>i</sup>

### 8. Conclusions

In summary, there are alternatives to furosemide to reduce and treat EIPH. The nasal strip, CES, and a diet rich in omega-3 fatty acids have shown scientific efficacy at this time; conjugated estrogens and aminocaproic acid may also be beneficial. Rest and a reduced training schedule should also be a part of the treatment regimen to allow healing of traumatized lung tissue and clearance of blood from the airways.

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