

# GRANT EXPENDITURE RESPONSIBILITY REPORTS

MAY 2012  
USEF EQUINE HEALTH  
RESEARCH FUND

\$21,218  
FOR RESEARCH BY  
PURDUE UNIVERSITY  
COMPARING INHALED  
LEVALBUTEROL AND  
RACEMIC ALBUTEROL  
IN HORSES AFFECTED  
WITH RECURRENT  
AIRWAY OBSTRUCTION (RAO)



## Final Report for 2012 USEF funded project

# Comparison of inhaled levalbuterol and racemic albuterol in horses affected with recurrent airway obstruction (RAO)

Laurent L Couëtil, Maria Arroyo, Nora Nogradi, Muhammad Munsiff, Kathleen M. Ivester

Department of Veterinary Clinical Sciences, Purdue University College of Veterinary Medicine,

625 Harrison Street Lynn Hall, West Lafayette, IN 47907

### **Introduction:**

Inhaled bronchodilator therapy is commonly utilized in the management of chronic lower airway inflammatory diseases in horses, including recurrent airway obstruction (RAO). It allows maintenance of a good quality of life for horses suffering from these diseases, without risking the adverse effects caused by long-term systemic therapy. The most commonly used short acting beta2-agonist administered via inhalation therapy is albuterol however, duration of action in horses is short (1 hour). Albuterol is the 1:1 racemic mixture of (R) – and (S) – albuterol, with the (S) – albuterol being responsible for the side effects, while the (R) - enantiomer is responsible for the bronchodilatory and bronchoprotective properties. Levalbuterol is the (R) enantiomer. Studies in humans have shown that inhalation with levalbuterol is associated with greater bronchodilation, longer duration of action and lack of development of adverse effects when compared to albuterol in asthmatic patients.

Therefore the objectives of this study were two-fold:

1. To determine the minimal dose of inhaled levalbuterol that can cause maximal bronchodilation in horses during an acute RAO crisis.
2. To determine the duration of action of inhaled levalbuterol on clinical signs and lung mechanics and compare it to inhaled albuterol in horses during an acute RAO crisis.

### **Materials and methods:**

- Experimental design:

The study is designed as a randomized, controlled, crossover trial where each RAO susceptible horse was treated with albuterol and levalbuterol. Investigators making clinical observation or recording lung function were unaware of the drug administered to the horses.

- Animals and monitoring:

Research horses owned by Purdue University were involved in the study. Inclusion criteria were history of RAO with inducible and reversible airway obstruction. Horses also had to be free of any concurrent disease at the time of enrollment into the study, confirmed by a physical exam. Research animals were kept on pasture and fed a diet of complete pelleted feed for at least 3 months prior to the experiment to ensure remission of the disease. Horses were transported to the research barn for the experiments and exposed to a dusty environment in order to trigger active disease. They were housed in individual stalls and bedded on wood shavings. They were fed a diet of good quality grass hay and complete pelleted feed and in addition moldy hay was placed in their

stalls and shaken twice a day for 5 minutes next to the horses' nose in order to increase dust exposure.

A physical examination was performed daily. Previously adopted clinical scoring system was used to assess respiratory compromise during the moldy hay challenge (Bertin et al.). Horses remained in the dusty environment until they developed clinical signs of RAO, confirmed by a clinical score >10, at which point pulmonary function testing was performed.

- Pulmonary function testing

Lung mechanics was measured as previously described (Bertin et al.). Briefly, horses were restrained in stocks without sedation. An esophageal balloon catheter (inside diameter, 4.8 mm; outside diameter, 6.4 mm; length, 240 cm) was advanced through the nose to mid-thorax. The exact position of the catheter was recorded for each horse at baseline testing and used in subsequent measurements. A mask was placed over the nose of each horse with a pneumotachometer coupled to a differential pressure transducer that measured a signal proportional to airflow. A second catheter of same size and diameter was used to measure pressure within the mask and both catheters were connected to a differential pressure transducer. Maximum change in transpulmonary pressure ( $\Delta PL_{max}$ ) was defined as the difference between pleural and mask pressures during peak inspiratory and expiratory effort. Once a  $\Delta PL_{max} > 15 \text{ cmH}_2\text{O}$  was achieved, horses were enrolled into the treatment trial.

Lung resistance ( $R_L$ ) was measured using the isovolume 50% method. During the bronchodilation challenge,  $\Delta P_{max}$  was measured without the mask.

- Bronchodilator challenge:

Horses were administered sequential doses of albuterol or levalbuterol, delivered by an ultrasonic nebulizer (the SaHoMa™ - II). The order of bronchodilator used first was chosen at random. After the first dose was administered, the nebulization mask was removed and 5 minutes later  $\Delta P_{Lmax}$  was determined. Then, the second dose of bronchodilator was administered and  $\Delta P_{Lmax}$  was determined. Subsequent doses of bronchodilator were given until maximal bronchodilation was obtained. The dose causing maximal bronchodilation was determined by detecting two subsequent measurements of  $\Delta P_{Lmax}$  with < 10% difference. The facemask was then placed again to determine  $\Delta P_{Lmax}$  and  $R_L$  at peak effect. The same parameters were recorded 10, 20, 40, 60, 90, 120 and 180 minutes following the last dose to determine duration of action for both drugs. Horses then were returned to their stalls and maintained in the same environment for the washout period (minimum 24 hours). A second bronchodilator challenge was conducted using the other drug.

- Statistical analysis:

Clinical scores and lung mechanics data were summarized as mean  $\pm$  SD. Data were compared using one-way analysis of variance for repeated measures. (Statistica 10, Statsoft Inc. OK, USA). Post-hoc tests were conducted using Tukey HSD when

appropriate. The bronchodilator dose that resulted in a 50 % (ED50%) and maximum (EDmax) decrease in  $\Delta$ PLmax from baseline were compared between albuterol and levalbuterol using t-test. Significance level was set a  $P \leq 0.05$ .

#### Results:

##### - Duration of effect:

Administration of bronchodilator resulted in a marked reduction in  $\Delta$ PLmax 10 minutes following the challenge (49.6 % and 51.8 % for albuterol and levalbuterol, respectively). However, the magnitude of this decline was no significantly different between the two treatment groups (Fig. 1). Albuterol effect dissipated rapidly with measurements taken at least 20 min following nebulization being not significantly different from baseline whereas levalbuterol treated horses had significantly decreased  $\Delta$ PLmax between 10 and 40 min following administration.

##### - Dose effect:

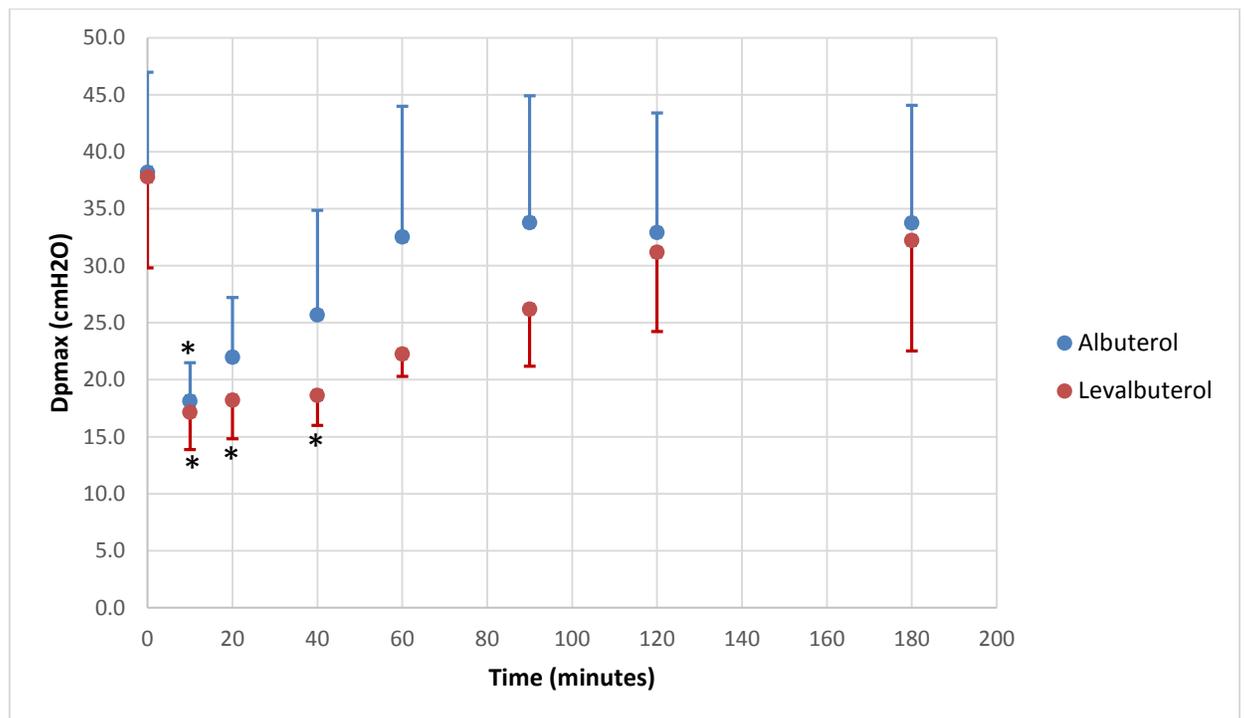
Parameters were not significantly different between albuterol (ED50% =  $46.1 \pm 22.8 \mu\text{g}$  and EDmax =  $187.6 \pm 176.7 \mu\text{g}$ ) and levalbuterol (ED50% =  $50.8 \pm 24.3 \mu\text{g}$  and EDmax =  $287.8 \pm 200.3 \mu\text{g}$ ) treated horses.

#### Conclusion:

We demonstrated that levalbuterol has a longer duration of action compared to albuterol however, the effect lasted less than 2 hours. Unlike findings in human

asthmatics, administration of levalbuterol to horses with RAO didn't result in greater bronchodilation compared to albuterol. Therefore, levalbuterol is an effective bronchodilator but the relatively short duration of action makes this drug non-practical for therapy of RAO.

Figure 1: Effect of bronchodilator administration on maximum transpulmonary pressure following albuterol and levalbuterol nebulization in horses with recurrent airway obstruction. \* Data significantly different from measurement at baseline (T = 0 min; P<0.05).



## Efficacy of Inhaled Levalbuterol Compared to Albuterol in Horses with Recurrent Airway Obstruction

M.G. Arroyo, L.L. Couëtill, N. Nogradi, M.M. Kamarudin, and K.M. Ivester

**Background:** The (R)-enantiomer of racemic albuterol (levalbuterol) has bronchodilatory properties whereas the (S)-enantiomer causes adverse effects in human airways, animal models, and isolated equine bronchi. Levalbuterol is commercially available and improves pulmonary function of asthmatic patients with a longer duration of effect than albuterol.

**Objective:** To determine the dose at which inhaled levalbuterol produces maximal bronchodilatory effect (ED<sub>max</sub>) and determine its duration of action in recurrent airway obstruction (RAO)-affected horses in comparison to racemic albuterol.

**Animals:** Nine horses with inducible and reversible RAO.

**Methods:** Randomized, crossover trial. Horses were challenged with moldy hay to induce airway obstruction. Horses were treated with nebulized albuterol or levalbuterol chosen randomly. Pulmonary function testing (PFT) was measured before and for up to 3 hours after bronchodilatation challenge. Maximum change in transpulmonary pressure (DP<sub>max</sub>) was measured to assess the dose effect and duration of action of each drug. After a 24 hours washout period, the bronchodilatation challenge was repeated with the second bronchodilator.

**Results:** The duration of effect was 60 minutes for albuterol and 120 minutes for levalbuterol. The dose of bronchodilator ED<sub>max</sub> was not significantly different between albuterol and levalbuterol (ED<sub>max</sub> = 125.0 [125–125 µg] and ED<sub>max</sub> = 188 [125–188 µg] respectively; *P* = .068). The magnitude of bronchodilatation was not significantly different between the 2 treatments (61.1 and 59.9% decrease in DP<sub>max</sub> for albuterol and levalbuterol respectively; *P* = .86).

**Conclusions and clinical importance:** Levalbuterol is as effective a bronchodilator as albuterol; although levalbuterol lasts twice as long as albuterol, its duration of action is still too short to make it practical for RAO treatment.

**Key words:** Aerosol treatment; Bronchodilator; Heaves.

Recurrent airway obstruction (RAO), also known as “heaves”, is an inducible and reversible chronic inflammatory airway disease commonly encountered in older horses in the northern hemisphere. An episode of acute RAO can be triggered by inhalation of dust from hay and the disease in horses has many similarities to asthma in humans.<sup>1,2</sup> Functional changes include increases in maximum transpulmonary pressure change (DP<sub>max</sub>) and pulmonary resistance (*R<sub>L</sub>*) and a decrease in dynamic lung compliance (*C<sub>dyn</sub>*).<sup>3</sup>

Equine RAO is a disease that cannot be cured but can be managed with medical treatment (systemic or inhaled corticosteroids and bronchodilators) and environmental changes (decreasing dust exposure by modifying housing and diet). Some horses need continuous medical management because of the challenge of achieving appropriate environmental control. Aerosol treatment is considered the best approach because of its rapid onset of action and deposition of high

### Abbreviations:

<i>C<sub>dyn</sub></i>	dynamic lung compliance
DP <sub>max</sub>	maximum change in transpulmonary pressure
ED <sub>50%</sub>	dose producing 50% decrease in DP <sub>max</sub>
ED <sub>max</sub>	dose producing maximum bronchodilatation
IL-4	interleukin-4
IQR	interquartile range
PFT	pulmonary function testing
RAO	recurrent airway obstruction
<i>R<sub>L</sub></i>	lung resistance

concentration of medication in the peripheral airways while minimizing systemic adverse effects.

Bronchodilators are used commonly in horses with acute exacerbation of RAO as a rescue medication, as treatment in combination with corticosteroids or as a diagnostic tool.<sup>4</sup> Albuterol, a short acting β<sub>2</sub>-adrenergic receptor agonist, is an effective bronchodilator that relieves acute airway obstruction by relaxing airway smooth muscle.<sup>5</sup> Within 5 minutes after administration, pulmonary function is improved maximally. The effect, however, lasts only 30–60 minutes on average, making long-term control of RAO impractical.<sup>4,5</sup> Albuterol is a racemic mixture containing equal concentrations of (R) – and (S)-enantiomers. The (R)-enantiomer, called levalbuterol, is responsible for the rapid bronchodilatory effect, decrease in wall edema, inhibition of mast cells, and decrease in eosinophilic migration to airways.<sup>6</sup> The (S)-enantiomer has been shown to have adverse effects in the human respiratory tract such as inducing airway hyper-responsiveness, increasing production of histamine and interleukin-4 (IL-4) in mast cells and promoting activation of eosinophils.<sup>6–8</sup> The (S)- enantiomer also causes airway hyper-responsiveness and

From the Veterinary Clinical Sciences, Purdue University College of Veterinary Medicine, West Lafayette, IN (Arroyo, Couëtill, Nogradi, Kamarudin, Ivester).

This work was performed at Purdue University.

Corresponding author: L. Couëtill, Purdue University College of Veterinary Medicine, 625 Harrison St, West Lafayette, IN 47906; e-mail: couetill@purdue.edu.

Submitted November 27, 2015; Revised April 25, 2016; Accepted May 10, 2016.

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DOI: 10.1111/jvim.14320

bronchoconstriction in isolated equine bronchi *in vitro*<sup>9</sup>, but, there is no report regarding the clinical effect of levalbuterol in horses. Levalbuterol is commonly used in human medicine because it improves pulmonary function and provides up to 6 hours of bronchodilatation.<sup>6,10–12</sup> However, recent evidence has shown no clinical benefit of levalbuterol versus albuterol in adult patients with asthma and chronic obstructive pulmonary disease (COPD).<sup>13</sup> The purpose of our study was to compare the bronchodilatory effect as well as the duration of action of levalbuterol and albuterol in horses with an acute episode of RAO.

## Materials and Methods

### Study Design

All methods were approved by the Purdue University Animal Care and Use Committee.

Nine horses (3 geldings, 6 mares; age range, 9–24 years) owned by Purdue University and with a history of inducible and reversible RAO were involved in this randomized, crossover trial. All of the horses remained on pasture on a complete pelleted feed for at least 2 months before the trial to achieve clinical remission. The animals were transported to the research facilities and resided there for the duration of the trial. On arrival, a physical examination and pulmonary function testing (PFT) were performed.

The horses were housed in individual stalls bedded with wood shavings and fed complete pelleted feed as well as free choice hay placed in a hay net. In addition, they were exposed to moldy hay which was shaken 2 times a day for 3 minutes next to the horse's nose to increase dust exposure.<sup>4</sup> A daily physical examination was performed, and a clinical score was assigned to every horse based on a scale that ranges from 0 to 21 as previously described.<sup>14</sup> When the clinical score reached  $\geq 10$ , PFT was performed. The horse was enrolled in the study if  $DP_{max} \geq 15$  cm H<sub>2</sub>O. The PFT was performed at baseline followed by administration of the bronchodilator challenge, randomly chosen (racemic albuterol or levalbuterol). The bronchodilator was given in a stepwise fashion until maximum dilatation was achieved. The PFT was performed 5 minutes after each dose. The horse then was returned to the stall for a washout period of at least 24 hours. The second treatment was administered the next day if the same inclusion criteria were achieved and testing was repeated.

### Pulmonary Function Test (PFT)

An esophageal balloon catheter<sup>a</sup> was placed to obtain measurements analogous to pleural pressure. The position of the catheter was estimated by measuring the distance between the horse's nostrils to mid thorax. The horse was placed in stocks with no sedation and an air-tight mask<sup>b</sup> was fitted around the horse's muzzle with the port of the mask holding the pneumotachometer<sup>c</sup> to measure airflow. Esophageal pressure and airflow output signals from both devices were recorded simultaneously by computer software<sup>d</sup> for 2 minutes to average the measurement of  $DP_{max}$  and calculation of pulmonary  $R_L$  and  $C_{dyn}$  over 10 adequate breaths.<sup>4,15</sup>

### Bronchodilator Challenge

A first dose (62.5  $\mu$ g) of albuterol sulfate<sup>e</sup> or levalbuterol hydrochloride<sup>f</sup> solution was chosen randomly by flipping a coin. This low dose corresponded to 0.15 mL of the bronchodilator solution as measured with a 1-mL syringe and given nondiluted. The bronchodilator was administered using an ultrasonic

nebulizer<sup>g</sup> and  $DP_{max}$  measured 5 minutes later. The doses were repeated and the  $DP_{max}$  was measured 5 minutes after each dose to evaluate the effects of cumulative bronchodilator administration and the dose at which maximal bronchodilatation was achieved. If the  $DP_{max}$  reached a plateau consisting of a difference  $\leq 10\%$  between 2 successive doses, the air-tight mask was repositioned and PFT repeated 10, 20, 30, 40, 60, 90, 120, 180 minutes after the last dose of bronchodilator to determine the duration of the treatment effect, as previously described.<sup>4</sup> After a washout period of 24 hours, physical examination and clinical scores were obtained to ensure that enrollment criteria were met again, and measurements were repeated after switching treatment drug.

The dose of bronchodilator that resulted in a 50% decrease in  $DP_{max}$  (ED<sub>50%</sub>) was calculated by linear interpolation and the dose resulting in maximum bronchodilatation (ED<sub>max</sub>) was determined as the first dose of the plateau effect.

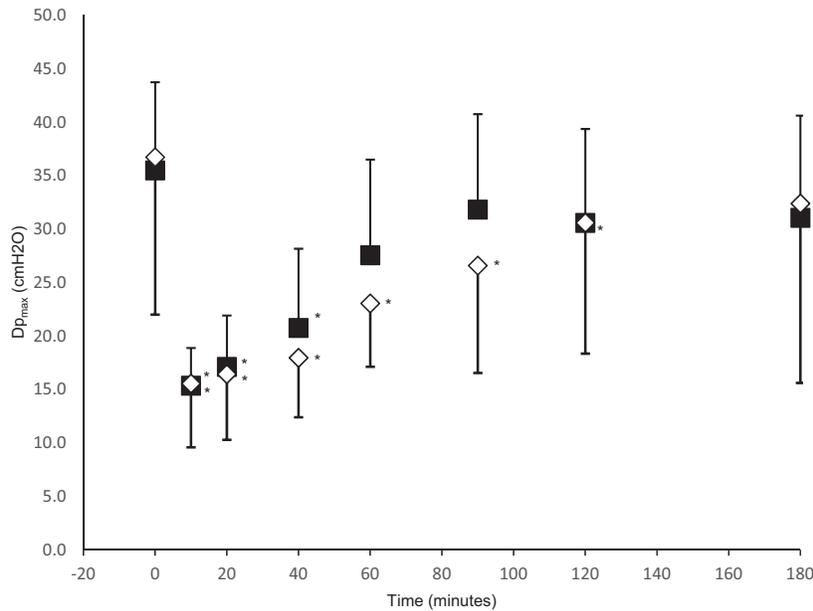
### Statistical Analysis

Clinical scores and PFT data were compared between treatments using the Wilcoxon Matched Paired Test.<sup>h</sup> The dose that resulted in a 50% and maximum decrease in  $DP_{max}$  from baseline was compared between both drugs administered. Changes in PFT variables between baseline and subsequent time points were compared using Friedman ANOVA. Post-hoc tests were conducted using Wilcoxon matched pairs test when appropriate. Association between  $DP_{max}$  at baseline and ED<sub>max</sub> was assessed by Spearman's rank correlation. Data were summarized as median and interquartile range (IQR) and significance was defined as  $P < .05$ .

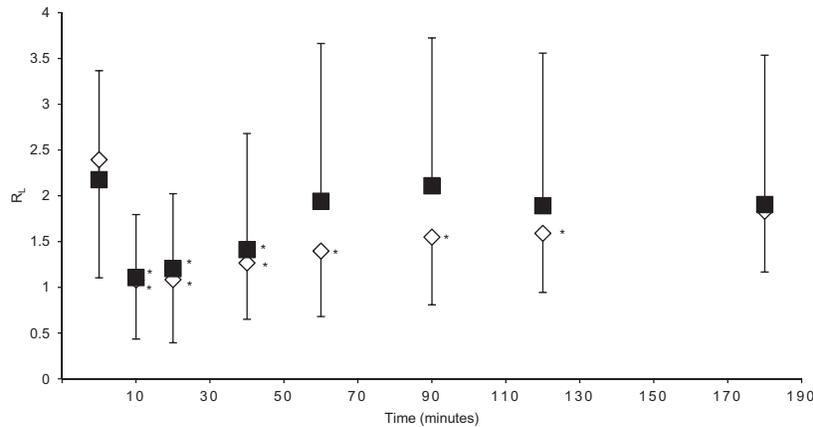
## Results

All 9 horses met the inclusion criteria and responded to the moldy hay during 2 weeks of exposure. None of them developed anorexia or clinically relevant weight loss throughout the study. Results of baseline PFT ( $DP_{max}$ ,  $R_L$  and  $C_{dyn}$ ) before administration of bronchodilators were not statistically different between the 2 treatment groups ( $P = .76$ ).

The mean duration of bronchodilator effect was 60 minutes for albuterol and 120 minutes for levalbuterol (Fig 1). A comparable response was observed with  $R_L$  data whereby albuterol effect lasted 40 minutes and levalbuterol effect was significant up to 120 minutes (Fig 2). Bronchodilator effect on  $C_{dyn}$  followed a similar trend but was only statistically significant for 10–40 minutes. Two of the 9 horses continued to experience decreased  $DP_{max}$  3 hours after levalbuterol administration. The effects on PFT were noted after the first dose (63  $\mu$ g) of either albuterol or levalbuterol and resulted in average decreases of 50 and 56% in  $DP_{max}$  respectively. The calculated ED<sub>50%</sub> and ED<sub>max</sub> of the doses were not significantly different between albuterol (ED<sub>50%</sub> = 43.6 [38.2–47.3  $\mu$ g] and ED<sub>max</sub> = 125.0 [125–125  $\mu$ g]) and levalbuterol (ED<sub>50%</sub> = 39.7 [35.0–52.5  $\mu$ g;  $P = .40$ ] and ED<sub>max</sub> = 188 [125–188  $\mu$ g;  $P = .068$ ]; Fig 3). Similarly, the relative magnitude of bronchodilatation was not significantly different between the 2 treatments (61.1 [43.1–67.9] and 59.9 [52.2–63.6] % decrease in  $DP_{max}$  for albuterol and levalbuterol respectively;  $P = .86$ ). There was no significant correlation between  $DP_{max}$  at baseline and ED<sub>max</sub>.



**Fig 1.** Mean  $\pm$  standard deviation of the maximum change in transpulmonary pressure ( $DP_{max}$ ) recorded with the mask before (0) and after completion of the bronchodilator challenge with albuterol (solid squares) and levalbuterol (open diamonds). \*: significantly different from baseline ( $P < .05$ ).



**Fig 2.** Mean  $\pm$  standard deviation of the lung resistance ( $R_L$ ) recorded with the mask before (0) and after completion of the bronchodilator challenge with albuterol (solid squares) and levalbuterol (open diamonds). \*: significantly different from baseline ( $P < .05$ ).

**Discussion**

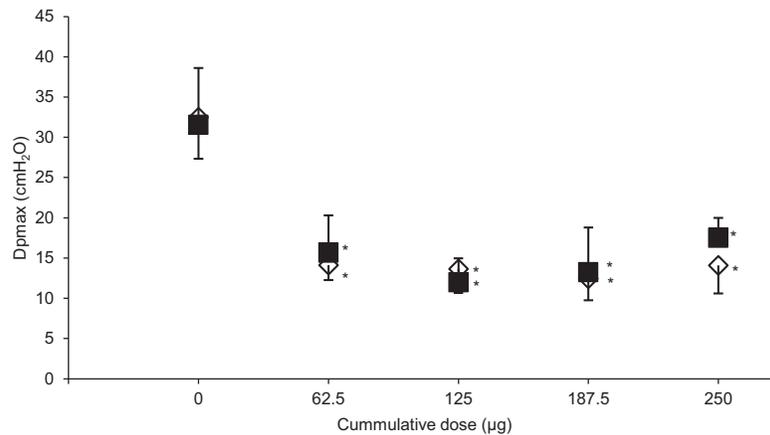
Levalbuterol, a  $\beta$ -agonist containing only the (R)-enantiomer of racemic albuterol, has been developed for human asthmatic patients to avoid the adverse effects of the (S)-enantiomer.<sup>6,11,12,16,17</sup> To our knowledge, no previous studies have compared the use of levalbuterol and racemic albuterol for the treatment of horses with an acute episode of RAO.

Our results suggest that there are no significant differences in the magnitude of improvement in pulmonary function achieved by both bronchodilators, although the effects of levalbuterol lasted twice as long as those of albuterol (2 versus 1 hour respectively). No adverse effects were noted with this single short-term treatment

with either bronchodilator, but future studies using daily treatment over several days would be needed to further assess this possibility. Despite this longer duration of action, the return of pulmonary pressures to baseline values by 180 minutes limits the use of levalbuterol to a rescue medication for horses with an acute RAO crisis or as a diagnostic method to confirm reversibility of airway obstruction.

Before the bronchodilator challenge, there was no significant difference in pulmonary function ( $DP_{max}$ ,  $R_L$ , and  $C_{dyn}$ ) between each arm of the study, demonstrating that a washout period of 24 hours was adequate, as previously reported.<sup>4</sup>

The average albuterol dose that induced a maximum bronchodilatory effect (125  $\mu$ g) is markedly lower than



**Fig 3.** Mean  $\pm$  standard deviation of the maximum change in transpulmonary pressure ( $DP_{max}$ ) recorded without the mask before (0) and following each dose of nebulized albuterol (solid squares) and levalbuterol (open diamonds). \*: significantly different from baseline ( $P < .05$ ).

the dose reported in previous studies (360–540  $\mu\text{g}$ ).<sup>4,5</sup> This difference suggests that a higher proportion of drug was deposited in the lung using the ultrasonic nebulizer, presumably because of the smaller particle size delivered with the nebulizer compared to the hand-held device used in the previous studies.<sup>4</sup> The nebulizer was easy to place and it took approximately 1 minute to administer each dose. The horses showed no adverse behavior throughout the bronchodilator challenge, similar to reports in previous studies.<sup>18</sup> Bronchodilatation was significant after the first dose (63  $\mu\text{g}$ ) of either albuterol or levalbuterol, which corresponded to 0.15 mL of solution. We did not attempt to start the bronchodilator challenge with a lower dose because of the difficulty in accurate measurement of small volumes.

The deposition of the aerosol reaching the lungs in horses with ultrasonic nebulizers ( $5.09 \pm 0.66\%$ ) is lower than the average 10% of aerosol deposition achieved in human patients.<sup>18</sup> This difference is likely attributed to horses being nasal breathers, causing higher filtration. In addition, the deposition of small-sized aerosol particles in the human lung is augmented by deep inhalation, followed by a period of breath-holding at total lung capacity. This maneuver is not possible in horses.<sup>19–21</sup> Horses experiencing an acute RAO episode tend to have rapid and shallow breaths that would be expected to decrease lung deposition of the bronchodilator. However, the doses of albuterol and levalbuterol resulting in  $ED_{max}$  in horses (125 and 188  $\mu\text{g}$ , respectively) were very small compared to  $ED_{max}$  reported in human patients with severe asthma exacerbation (7.5 and 3.25 mg respectively).<sup>22</sup> An additional effect from oral absorption of drugs deposited in the nasopharynx is unlikely because it would be expected to result in a delayed therapeutic effect, but this phenomenon was not observed in our study. Furthermore, there is evidence that oral albuterol is poorly absorbed in the horse<sup>1</sup> and a closely related compound, terbutaline, also is not bioavailable orally in horses.<sup>23</sup> Therefore, nebulized albuterol and levalbuterol are

highly potent bronchodilators in horses with acute RAO exacerbation.

The effect of levalbuterol lasted 2 hours in RAO horses compared to 6 hours in human asthmatic patients.<sup>12,24</sup> This decreased duration of action of levalbuterol in the horse is similar to that observed with another bronchodilator, salmeterol xinafoate.<sup>25</sup> Salmeterol in human asthmatic patients has a duration of action of 12 hours and only 6 hours in horses with RAO. We hypothesized that the difference might be attributed to rapid drug clearance from the lung because of enhanced alveolar and bronchial absorption secondary to increased airway epithelial permeability<sup>25</sup> or a species-specific pharmacokinetic difference in disposition of the drug. There are no validated explanations of why the duration of action of these bronchodilators is shorter in horses than in people.

Our results suggest that levalbuterol is effective to treat acute RAO in horses but, the only benefit of levalbuterol is the slightly longer duration of bronchodilatory effect compared to albuterol. There was no statistically significant difference in PFT after  $ED_{max}$  using either bronchodilator. These results suggest that both bronchodilators achieve a similar degree of bronchodilatation in horses, as opposed to humans in whom levalbuterol is more efficient at improving pulmonary function in addition to having a longer acting bronchodilatory effect than albuterol.<sup>6</sup>

In conclusion, unlike findings in human asthmatic patients, administration of levalbuterol to horses with RAO did not result in greater bronchodilatation compared to albuterol. Levalbuterol is an effective bronchodilator, but the short duration of action makes this drug nonpractical for treatment of RAO.

### Funding

The United States Equestrian Federation and the state of Indiana, the Purdue University College of Veterinary Medicine Research account funded by the Total Wager Tax.

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## Footnotes

- <sup>a</sup> Tygon lab catheter, ¼ "ID × 3/8" OD, Cole Parmer, Vernon Hills, IL
- <sup>b</sup> Equine AeroMask, Trudell Medical International, London, Ontario, Canada
- <sup>c</sup> No. 4 Fleisch, EMKA Technologies, Paris, France
- <sup>d</sup> Pulmonary mechanics analyzer, XA version, Buxco Electronics Inc, Sharon, CT
- <sup>e</sup> 1.25 mg of albuterol sulfate in 3-mL unit-dose vial, Nephron Pharmaceuticals Corporation, Orlando, FL
- <sup>f</sup> Xopenex<sup>®</sup>, 1.25 mg of levalbuterol in 3-mL unit-dose vial, Sunovion Pharmaceuticals Inc., Marlborough, MA
- <sup>g</sup> SaHoMa<sup>™</sup> – II, NEBU-TEC International, Elsenfeld, Germany
- <sup>h</sup> Statistica, Statsoft Inc., Tulsa, OK
- <sup>i</sup> Ball MA, Pharmacokinetics of orally administered albuterol in the horse. World Equine Airway Symposium proceedings, 1998
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## Acknowledgment

*Conflict of Interest Declaration:* Authors declare no conflict of interest.

*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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