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Treatment of Left Laryngeal Hemiplegia Using a Nerve Muscle Pedicle Graft

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ABSTRACT. The efficacy of a nerve muscle pedicle graft (NMP) for treatment of induced left laryngeal hemiplegia (LLH) was evaluated in exercising horses by measuring variables of upper airway function, including peak inspiratory and expiratory airflow ($\dot{V}_{IMAX}$ and $\dot{V}_{EMAX}$), transupper airway pressure (P_{UI} and P_{UE}), and impedance (Z_I and Z_E). Measurements were recorded before left recurrent laryngeal neurectomy (baseline); 4 weeks following left recurrent laryngeal neurectomy; and 12, 24, and 52 weeks after NMP graft or sham operation. Following left recurrent laryngeal neurectomy, abnormal findings were present only in horses exercising at 7.0 m s^{-1}. The P_{UI} and Z_I were increased, whereas $\dot{V}_{IMAX}$ was decreased. The sham operation did not improve airway function. Fifty-two weeks after NMP graft, P_{UI} remained elevated, but $\dot{V}_{IMAX}$ and Z_I were no longer significantly different from baseline values. We conclude that the NMP graft restores upper airway impedance within 52 weeks in horses with induced LLH.

Key words: Horses; laryngeal hemiplegia; reinnervation; nerve muscle pedicle graft.

INTRODUCTION

Left laryngeal hemiplegia (LLH) is one of the most serious respiratory conditions affecting horses and it has been estimated that between 2.6[21] and 8.3%[17] of all Thoroughbreds develop the condition. The disease prevalence is greatest in the 2 to 7 year age group, when affected horses are at the peak of their athletic performance, but it is also a common respiratory unsoundness of Thoroughbred yearlings presented for sale.[19] Left laryngeal hemiplegia, which causes significant exercise intolerance and noise production on inhalation,[15] results from decreased motor activity of the intrinsic muscles of the larynx, innervated by the left recurrent laryngeal nerve.[11] In the majority of cases, paralysis of these muscles is associated with a left recurrent laryngeal neuropathy, which has been defined as a distal axonopathy.[3]

While the search for a cause of LLH continues, treatment of clinically affected horses has been necessary to allow these horses to pursue their athletic endeavors. Surgical treatments used in cases of LLH include ventriculectomy,[18] prosthetic laryngoplasty,[20] arytenoidectomy,[16] and tracheostomy.[4] Until recently the success or failure of surgical techniques for the treatment of equine LLH was based on subjective findings, including a decreased noise production on inhalation during exercise,[1] or improved athletic performance.[23] Recently, evaluation of upper airway function in exercising horses demonstrated the efficacy of prosthetic laryngoplasty in improving upper airway flow mechanics in horses with LLH.[5] Similarly, evaluation of the efficacy of ventriculectomy[22] and subtotal arytenoidectomy[2] in the treatment of this disease proved the ineffectiveness of these techniques. Although prosthetic laryngoplasty is an efficacious treatment for horses with LLH, a number of complications have been reported, including nasal discharge of food, chronic coughing, and prosthesis failure.[15,24] These complications have stimulated investigations into new treatments for LLH using a nerve muscle pedicle graft.

In 1976, Tucker described a neuromuscular pedicle graft technique for treatment of laryngeal paralysis in humans.[25] A neuromuscular pedicle created from the ansa hypoglossus nerve and omohyoideus muscle was implanted into the affected M. cricoarytenoideus dorsalis, resulting in reinnervation of this muscle. In the horse, histological evidence of reinnervation of the M. cricoarytenoideus dorsalis (i.e. the major abductor muscle of the arytenoid cartilage) has been reported following a nerve muscle pedicle (NMP) graft created from the second cervical nerve and omohyoideus muscle, but arytenoid abduction was only observed in 1 of 4 ponies.[8-10] In that study horses were not evaluated during exercise. The purpose of the present study was to evaluate the efficacy of a NMP graft for the treatment of LLH in exercising horses.

MATERIALS AND METHODS

Horses

Seven adult Standardbred horses (4.4 ± 0.64 years old, weighing 380 ± 8.3 kg) were used in this study. The horses were vaccinated against tetanus, equine influenza, and rhinopneumonitis. The endoscopic appearance of their upper airway, including the cervical trachea, was normal prior to any surgical procedures. The horses were trained to exercise on a treadmill (Jetline, Desales Inc., Sand Lake, MI) (6.38° incline) while wearing a fiberglass face mask that covered the nostrils and mouth. Horses were kept at pasture between surgical procedures and measurement protocols.

Measurement techniques

Measurement of upper airway function has been previously described.[5,22] Briefly, a fiberglass face mask with attached pneumotachograph (Merriam Instruments, Grand Rapids, MI) was placed over the nostrils and mouth. The mask allowed complete dilation of the nostrils and was sealed against the face using a rubber shroud and adhesive tape. A wire mesh (Mesh SS Screen, McMaster Carr, Chicago, IL) was present between the nostrils and pneumotachograph. The resistance of the pneumotachograph was 0.04 cm $H_2O\ l^{-1}s^{-1}$ up to an airflow rate of 90 $l\ s^{-1}$. Pressure changes across the pneumotachograph were measured using a differential pressure transducer (Model DP-45-22, Validyne Sales, Northbridge, CA), which produced a signal proportional to airflow. The flow signal was integrated to give tidal volume (V_T). The pneumotachograph was calibrated before each measurement protocol using a rotameter flowmeter (Model FP-2-37-P10/77, Fischer and Porter Co., Warminster, PA) capable of measuring rates up to 90 $l\ s^{-1}$. Although flow was measured continuously, only peak flows are reported in this study.

Transupper airway pressure (P_U) was defined as the pressure difference between a lateral tracheal catheter[5] and lateral mask catheter positioned just cranial to the nostrils. The P_U was measured using a differential pressure transducer (Model DP45-22, Validyne Sales, Northbridge, CA) calibrated using a water manometer prior to each protocol. All signals were recorded on a physiograph (Model 8188, Gould, Inc, Madison Heights, MI). Inspiratory and expiratory impedance (Z_I and Z_E) were calculated as the ratio of peak P_U and peak airflow during inspiration and expiration, respectively, averaged over 10 breaths. Pressure and flow catheter systems were evaluated for phase differences as previously described.[6] Phase differences were not detected up to a frequency of 10 Hz. Heart rate (HR) was recorded on a heart rate computer (Equistat, Biomechanics and Exercise, Unionville, PA). Respiratory rate (f) was calculated from the physiograph recording and minute ventilation ($\dot{V}_E$) was calculated as the product of f and V_T.

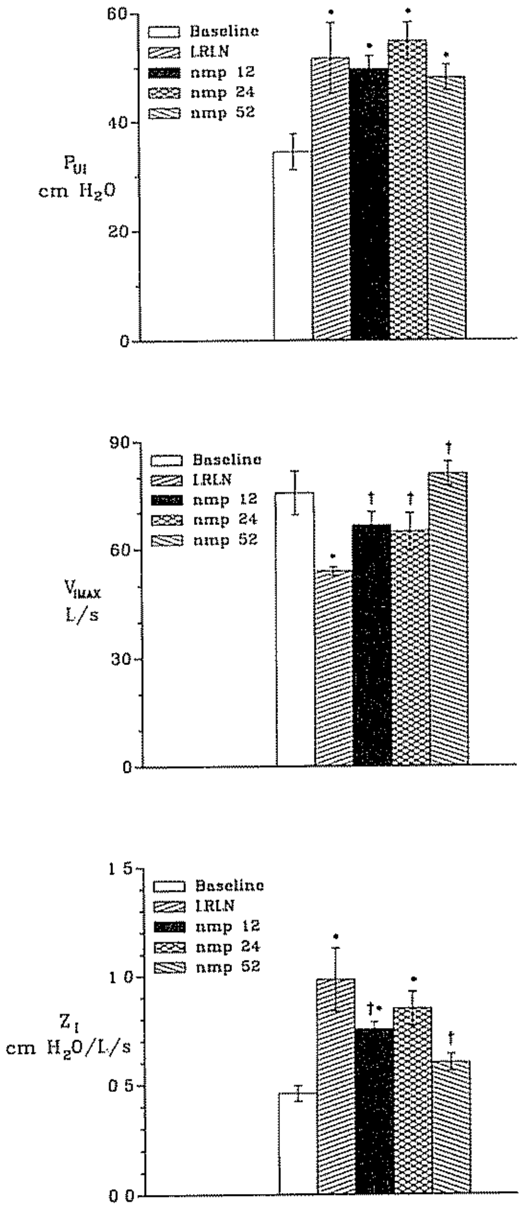

Fig. 1 Peak inspiratory pressure (P_{UI}); inspiratory airflow ($\dot{V}_{IMAX}$) and inspiratory impedance (Z_I) before and after all surgical procedures with horses exercising at 7.0 m s^{-1} ($n=5$). Baseline=before surgical intervention. LRLN=left recurrent laryngeal neurectomy. nmp 12=12 weeks following nerve muscle predicle graft. nmp 24=24 weeks following nerve muscle pedicle graft. nmp 52=52 weeks following nerve muscle pedicle graft. *=significantly different from baseline value ($p<0.05$). †=significantly different from LRLN value ($p<0.05$).

Experimental design

Measurements of upper airway function were made while the horses were resting and during exercise on a 6.38° inclined treadmill at 4.2 m s^{-1} for 2 min and 7.0 m s^{-1} for 4 min. A 2 min rest was allowed between exercise periods. Baseline measurements were made before left recurrent laryngeal neurectomy, 28 days after left recurrent laryngeal neurectomy to ensure atrophy of the M. cricoarytenoideus dorsalis, and then at 12, 24, and 52 weeks after NMP graft.

Surgical procedures

Anesthesia for all surgical procedures was induced in the horses with glycerol guaiacolate (Guaiacol glycerol ether, USP, Aceto Chemical Co., Flushing, NY) and thiamylal sodium (Biotal, Boehringer Ingelheim Animal Health, Inc., St. Joseph, MO), then maintained with halothane (Fluorothane, Ayerst Laboratories, Inc., New York, NY) in oxygen via an endotracheal tube and semiclosed anesthetic system. Left recurrent laryngeal neurectomy was performed in the mid-cervical area. After a 3 cm long segment of the recurrent laryngeal nerve was removed, the proximal and distal ends of the nerve were folded over and ligated with 3-0 polydioxanone suture (Ethicon Inc., Sommerville, NJ). Subcutaneous tissues and skin were closed in a routine manner.

The NMP graft was performed as described by Ducharme,[8] except that the first rather than the second cervical nerve was used. Two horses designated as controls had the same surgical procedure performed, but, in addition, a 5 cm section of the first cervical nerve was removed after the NMP had been sutured into the M. cricoarytenoideus dorsalis. All horses were treated with procaine penicillin (25000 iu kg^{-1}) 2 hours prior to surgery and twice post-operatively at 12 hour intervals.

Statistical analysis

A three factorial analysis of variance was used according to the model $Y_{ijk} = \mu + A_i +$

Table 1. *Effect of exercise on the measured variables in the five principal horses before left recurrent laryngeal neurectomy*

HR = heart rate, f = respiratory frequency, V_T = tidal volume, $\dot{V}_E$ = minute ventilation, P_{UI} = inspiratory pressure, P_{UE} = expiratory pressure, $\dot{V}_{Imax}$ = peak inspiratory flow, $\dot{V}_{Emax}$ = peak expiratory flow, Z_I = inspiratory impedance, Z_E = expiratory impedance

	Exercise level		
Variable	Rest	4 2 m s^{-1}	7.0 m s^{-1}
HR (beats min^{-1})	39 6±2 24	176.4±2 29[a]	201.6±2.25[ab]
f (breaths min^{-1})	17 4±1.33	69 3±3.67[a]	86±2.92[ab]
V_T (l)	7 87±0.97	13.94±1.45[a]	17.76±1.44[ab]
$\dot{V}_E$ (l min^{-1})	133.2±10.18	968±128[a]	1 518±148[ab]
P_{UI} (cm H_2O)	2 22±0.193	20.66±2.31[a]	34.42±3.35[ab]
P_{UE} (cm H_2O)	1.29±0.315	10 71±2.20[a]	13.03±2.49[a]
$\dot{V}_{Imax}$(l s^{-1})	5.78±0.79	47.59±6.40[a]	75.46±6 21[ab]
$\dot{V}_{Emax}$ (l s^{-1})	6.52±0.91	46.09±3.67[a]	66.94±5.87[ab]
Z_I (cmH_2O l^{-1} s^{-1})	0.399±0.04	0.454±0.069	0.459±0.037
Z_E (cmH_2O l^{-1} s^{-1})	0.198±0.03	0 289±0.094	0.211±0.058

[a] Data significantly different ($p<0.05$) from the same measurement at rest.
[b] Data significantly different ($p<0.05$) from the same measurement at 4.2 m s^{-1}.

$B_j+AB_{ij}+C_k+AC_{ik}+BC_{jk}+$ error[13]; where A_i was the fixed effect of exercise (3 levels), B_j was the fixed effect of surgical procedure (5 levels), and C_k the random effect of the 5 horses. Where F values were significant at $p<0.05$, treatment means were compared using the Tukeys test.

RESULTS

Before surgical intervention, increasing exercise in the principal horses, from rest to 4.2 and then to 7.0 m s^{-1}, significantly ($p<0.05$) increased heart rate (HR), respiratory frequency (f), maximal inspiratory ($\dot{V}_{IMAX}$) and expiratory flow ($\dot{V}_{EMAX}$), peak inspiratory (P_{UI}) and expiratory pressure (P_{UE}), tidal volume (V_T), and minute ventilation ($\dot{V}_E$). For each of the two increments in exercise intensity, the inspiratory and expiratory impedance (Z_I and Z_E) did not change significantly (Table 1). Similar baseline values were recorded in the 2 control horses.

Following left recurrent laryngeal neurectomy and before NMP graft, the only significant ($p<0.05$) changes were recorded in horses exercising at 7.0 m s^{-1}. The $\dot{V}_{IMAX}$ decreased and P_{UI} and Z_I increased, compared to baseline values (Fig. 1).

Twelve weeks after the NMP graft, with principal horses exercising at 7.0 m s^{-1}, P_{UI} and Z_I remained significantly greater than baseline values at the same speed, but Z_I was significantly less than the value after left recurrent laryngeal neurectomy (Fig. 1). The $\dot{V}_{IMAX}$ had increased significantly compared to the left recurrent laryngeal neurectomy value. The reversal of improvement in Z_I at 24 weeks after the nerve muscle pedicle graft was primarily because of an increased Z_I in one horse. Fifty-two weeks after the MNP graft, with horses exercising at 7.0 m s^{-1}, P_{UI} was still significantly greater than baseline values, but Z_I and $\dot{V}_{IMAX}$ were no longer significantly different from baseline values (Fig. 1).

The sham operation had no effect on any of the variables at any measurement period, when compared to the left recurrent laryngeal neurectomy values.

DISCUSSION

As reported in previous studies, increasing levels of exercise increased HR, f, V_T, $\dot{V}_E$, peak P_{UI}, $\dot{V}_{IMAX}$ and V_{EMAX} while Z_I and Z_E remained unchanged.[2,22] The left recurrent laryngeal neurectomy resulted in a significant increase in Z_I when horses exercised at 7.0 m s^{-1}. This was caused by a dramatic increase in P_{UI}, whereas peak $\dot{V}_{IMAX}$ decreased. These changes are caused by dynamic collapse of unsupported structures (arytenoid cartilage) into the airway lumen during inhalation. Dynamic collapse occurs because on inhalation a negative pressure exists within the airway relative to atmospheric pressure.[7] Negative pressures in the upper airway on inhalation are greatest during exercise, which explains why an increase in Z_I was most apparent while horses exercised at 7.0 m s^{-1}. Dynamic collapse of the arytenoid cartilages in exercising horses with LLH has been documented with videoendoscopy during exercise.[7]

The prosthetic laryngoplasty has been demonstrated to decrease Z_I and P_{UI} and increase $\dot{V}_{IMAX}$ in horses with induced LLH[5]. However, in clinical cases treated with laryngoplasty, a number of post-operative complications have been reported. These include failure of the prosthetic suture to maintain abduction, wound dehiscence, infection of the tissue around the suture, and chronic suture sinus tract associated with the prosthesis. Coughing, aspiration of feed into the trachea, pneumonia, chondritis, cartilage ossification, and laryngeal granulomas have also been reported.[24] These complications have led to the suggestion that the ideal treatment for LLH in horses would be reinnervation of the M. cricoarytenoideus dorsalis.[24]

In 1976 Tucker et al. described a nerve muscle pedicle graft as a treatment of laryngeal paralysis in humans.[25] Since that time this technique has been used in dogs[14] and extensively in humans.[12] Excellent return of muscle function and minimal complications have been reported.[12]

In the present study, we evaluated the NMP graft technique in exercising horses. The NMP was created from an accessory muscle of respiration, the omohyoideus muscle. The omohyoideus is quiescent at rest and is activated during inspiration only during exercise.[8] Thus in treated horses, arytenoid cartilage abduction is only expected during exercise. Twelve weeks following the NMP graft and with horses exercising at 7.0 m s^{-1}, the Z_I in 3 out of 5 horses had decreased when compared to values obtained after left recurrent laryngeal neurectomy. This decrease in Z_I had resulted mainly from a significant rise in $\dot{V}_{IMAX}$. Return of function of reinnervated laryngeal muscle is seen at 6 to 12 weeks in humans.[12] The rapid reinnervation of laryngeal muscle is thought to be due to transplantation of motor endplates allowing conduction of impulses to the muscle fibers once the pedicle has healed to the recipient muscle.

Fifty-two weeks after the NMP graft procedure, in all horses, Z_I had returned toward baseline values. The return of Z_I to baseline values after the NMP graft procedure indicates that in these horses the airway caliber had returned to normal. At this time horses selected a respiratory pattern that included a high $\dot{V}_{IMAX}$ and a high P_{UI}. The reason for this is presently unclear.

A study in dogs has reported a similar trend following NMP graft transplantation into the M. cricoarytenoideus dorsalis, where there was partial improvement at 19 weeks after surgery and further improvement by 36 to 44 weeks.[14] Slow return of function following surgery is thought to be due to transplantation of few motor endplates, along with transected nerve fibers in the pedicle, increasing the time necessary for complete reinnervation to occur.

The lack of serious post-operative complications makes the NMP graft an inviting surgical technique. Rapid reinnervation (i.e. 12 weeks after surgery) is possible but not consistent, as 52 weeks was necessary to observe improvement in respiratory function of all principal horses. At present, the NMP graft cannot be recommended as a routine treatment for LLH in athletic horses, because the convalescent period is too long. However, with improvement of the surgical technique, the NMP graft may become a suitable treatment for LLH in horses.

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