The Effect of an Oral Beta-2 Agonist on Respiratory Muscle Strength in SCI

Background and Significance:

With an estimated 12,000 incident cases per year, spinal cord injury (SCI) now affects over 300,000 Americans, approximately 52% of whom have injury at the cervical level (tetraplegia) [1]. Although the past 40 years has witnessed a substantial improvement in the acute and chronic management of persons with SCI, mortality remains high during the first year post-injury, and pulmonary complications including pneumonia, lung collapse (atelectasis), respiratory failure, and thromboembolism are the predominant cause [2,3]. History has also seen a shift in the principal cause of mortality during the chronic phase of SCI (> 1 year post-injury); mortality related to urosepsis and renal failure has now been supplanted by pulmonary complications, particularly pneumonia [2]. Thus, pulmonary complications are now the primary cause for premature mortality in the SCI population regardless of time post-injury [2,3].

The propensity for pulmonary complications among subjects with SCI stems from paralysis of respiratory muscles. Injury to the cervical and upper thoracic cord significantly compromises function of the diaphragm, intercostal muscles, accessory respiratory muscles, and abdominal muscles. Respiratory muscle dysfunction is manifest as diminution in lung volumes, reduction in maximal static inspiratory and expiratory mouth pressures (MIP and MEP, respectively), and reduction in peak cough pressure and flow [4]. In a cross sectional analysis of two large outpatient populations with SCI, the forced vital capacity (FVC), or the volume of air forcibly exhaled during a maximal expiratory maneuver, varied inversely with level of lesion; injury levels T6 and above were associated with FVC values below the predicted limits of normal, falling to approximately 50% of predicted at the highest injury levels [5]. Reduced volume and ineffective cough predispose to airway closure and atelectasis, secretion retention, and pneumonia. Residual function of the diaphragm, the principal muscle of inspiration innervated by phrenic nerve roots C3 to C5, is required for unassisted breathing. Excluding C1 and C2 motor complete injuries, most subjects with tetraplegia achieve spontaneous ventilation due to a functioning diaphragm despite intercostal and abdominal muscle paralysis. However, muscle paralysis impairs integrated thoracic expansion during inspiration via alterations in the mechanical properties of the lungs and chest wall, specifically paradoxical downward displacement of the upper rib cage during inspiration [6] and reduced lung and chest wall compliance [7]. These changes in turn are associated with reduction in lung volumes [8,9] and in maximal static mouth pressures (MIP and MEP) [6,7]. Reduced inspiratory capacity directly affects expulsive cough pressure generation and may limit the ability to sigh deeply, both of which may predispose to retained secretions, atelectasis, and increased pneumonia risk [4,10].

Expiratory muscle function is more severely compromised than inspiratory muscle function with higher level SCI given more widespread paralysis of expiratory muscles, principally the expiratory intercostals and abdominal musculature. Residual expiratory muscle function required for forceful expiration (as during exercise) and for effective cough has been attributed to the clavicular portion of the *m. pectoralis major* innervated by nerve fibers originating in the fifth through seventh cervical segments [11] and to the *m. latissimus dorsi* [12]. In patients with neuromuscular disease, conditions often associated with chronic disease progression, diaphragmatic function as reflected by MIP is usually well maintained until late in the disease course, which explains why reduction in MEP compared to MIP has been found to be a more sensitive indicator of progressive respiratory impairment [13]. However, in traumatic cervical SCI, characterized by simultaneous disruption of inspiratory and expiratory muscle function at time of injury, assessment of MIP may confer greater predictive value. Kang et al. found among subjects with tetraplegia that MIP correlated better than MEP with pulmonary function parameters requiring active expiratory effort such as FVC and peak cough flow [14]. Thus, significant decreases in MIP as compared to MEP might better identify individuals with tetraplegia and high paraplegia who are at highest risk for pulmonary complications; impaired inspiratory muscle strength results in further impairment of already significantly compromised expiratory muscle function and cough effectiveness. Indeed, deeper inspiration (greater inspiratory capacity) accompanied by higher MIP is associated with expansion of more distal airways (preventing atelectasis), improvement in expiratory muscle function (better length-tension relationships), and increases in lung elastic recoil pressure [15-17]. Further, in our experience, subjects with high level SCI generally have comparatively lower percent predicted MEP as compared to MIP, again suggesting that deterioration in MIP has greater discriminatory power than subtler decreases in an already depressed MEP for identifying individuals at greatest risk for future pulmonary complications.

Respiratory muscle atrophy and subsequent impaired function are not only the result of muscle paralysis, but also stem from inactivity and deconditioning of residual and neurologically intact respiratory

muscles. Numerous interventional studies in persons with tetraplegia have investigated whether inspiratory and expiratory resistive or threshold training, involving relatively inexpensive portable devices, are effective for improving respiratory muscle strength. Most studies have been uncontrolled and not comparable due to diverse protocols, heterogeneity of subject characteristics, or differences in training techniques [18, 19]. Since 2006, there have been three systematic reviews of respiratory muscle training (RMT) in persons with SCI, and similar conclusions have been drawn; although there is a suggestion that RMT can result in increases in vital capacity and static mouth pressures, the effect size is small, and the data inconclusive[18-20]. Further, there is no evidence of carryover beyond the training period [21]. Insufficient data exists to make conclusions regarding the effects of RMT upon endurance, quality of life, exercise performance, or pulmonary complications [18, 19]. In two of the better designed trials, repetitive training of the clavicular portion of the pectoralis major via isometric exercise for 6 weeks among subjects with tetraplegia resulted in improvements in expiratory muscle strength [22], and a novel approach using non-resistive normocapnic hyperpnea training resulted in significant improvement in respiratory muscle strength and endurance [23]. A systematic review and meta-analysis found a lack of sufficient evidence to either support or discourage use of an abdominal binder to improve respiratory function in SCI [24]. Lastly, interventions to improve inspiratory muscle function via diaphragmatic or phrenic nerve stimulation, or to improve expiratory muscle function and cough strength via magnetic or electrical stimulation can prove highly efficacious, but are often invasive and reserved for highly selected individuals [25].

Pharmacologic interventions to improve respiratory muscle strength have received little attention in the SCI population. A randomized trial with crossover demonstrated that oral theophylline for 6 weeks did not improve pulmonary function in persons with SCI [26]. Studies involving oral beta-2 adrenergic agonists, however, which have been shown to elicit anabolic effects on skeletal muscle in young men [27] and an increase in muscle strength among patients with facioscapulohumeral muscular dystrophy [28], have also demonstrated salutary effects in persons with SCI. One small study showed that administration of an oral beta-2 agonist to subjects with tetraplegia amplified total work output during functional electronic stimulation of leg muscles [29]. In a separate study, it was demonstrated that administration of an oral beta-2 agonist in persons with tetraplegia improved forearm muscle size and strength [30]. On the basis of these reports, we performed preliminary experiments and now have compelling data that lends support to the efficacy of beta-2 agonists for improving respiratory muscle strength in persons with SCI. Salmeterol (Serevent ©) is a long-acting inhaled beta-2 adrenergic agonist approved as a bronchodilator for maintenance management of obstructive lung disease; this agent also exhibits systemic absorption following inhalation [31]. We performed a randomized, double-blind, placebo-controlled, crossover trial of inhaled salmeterol in eleven persons with chronic stable tetraplegia, and found significant improvements compared to matching placebo in lung volumes [FVC, FEV_1, expiratory reserve volume (ERV)] and static mouth pressures (MIP and MEP) after 4 weeks of twice daily administration suggesting improvement in lung function and respiratory muscle strength (see Table in Preliminary Studies section) [32]. The medication was well tolerated, and no adverse events were reported. As a follow-up, we recently completed a randomized, double-blind, placebo-controlled, parallel group trial in 30 persons with tetraplegia and high paraplegia (15 subjects each in the active drug and placebo groups) who were administered an oral beta-2 agonist (albuterol repetabs 4 mg twice daily) versus matching placebo over 12 weeks (data not published). Significant improvements were noted in MIP among subjects who received active drug compared to placebo, and improvements in MEP trended toward significance. Also, it was noted that the greatest increases in MIP were in subjects with the lowest MIP at baseline, suggesting that the weakest individuals targeted by a baseline MIP of < 90 cmH2O would stand to derive the greatest benefit in terms of improvement in respiratory muscle strength and potentially reduction in pulmonary complications.

There are many foreseeable advantages of a pharmacologic approach to improve respiratory muscle strength in persons with SCI. For instance, RMT can be physically demanding and time consuming, compliance can be an issue, and sustainable improvements have not been realized [21, 23]. Perhaps more importantly, in our experience the weakest individuals with SCI who are at greatest risk for recurrent pulmonary complications are the least likely to engage in effort-related protocols. Indeed, our research subjects are often more independent and generally healthier and more willing to engage in research than their weaker counterparts. If we witness what we have documented thus far, we anticipate that most of these issues will be of limited concern given the ease of implementation of this oral medication, the minimal side effects encountered, the minimal time commitment or need for ancillary assistance, and the potential for sustainable effects on respiratory muscle function. Further, it is foreseeable that combination modalities (i.e. pharmacologic and respiratory muscle training regimens) would be possible in motivated individuals. The

ultimate challenge, which remains to be investigated, is whether improvement in respiratory muscle strength and cough effectiveness translates to a decrease in respiratory complications.

Our intent in the present proposal is to enroll a targeted cohort of 24 comparatively weaker subjects with tetraplegia and high paraplegia in a randomized, double-blind, placebo-controlled, parallel group trial to assess the effects of an oral beta-2 agonist upon respiratory muscle strength and cough effectiveness. Based upon the findings from our recent study (please see "Preliminary Studies"), we have chosen a MIP of < 90 cmH2O as a criterion for study inclusion. Use of MIP as the preferred surrogate of underlying respiratory muscle strength in persons with SCI has been previously reported [14]. Individuals will be randomized equally (12 in each group) to receive oral albuterol versus matching placebo for 16 weeks (initial 4 weeks at previous dose of 4 mg twice daily, then in the absence of significant side effects, increased to 8 mg twice daily for the final 12 weeks). If we identify as we anticipate significant improvements in indices of respiratory muscle strength in the active study group after 16 weeks, we intend to repeat testing two weeks later to see if improvements are sustainable. Positive results would dictate the need to pursue a multicenter trial to see if pulmonary complications are reduced, thus making a significant impact on the welfare of this at risk population.

B. Preliminary Studies

Independent of effects upon respiratory muscle strength, we found that administration of the inhaled beta-2 adrenergic agonist, metaproterenol sulfate, to subjects with chronic stable tetraplegia resulted in a significant increase (>12% and 200 ml) in the forced expiratory volume in one second (FEV_1) in 14 of 34 (41%) subjects [33]. We hypothesized that the previously unrecognized airflow obstruction unmasked by bronchodilator administration among subjects with tetraplegia was due to autonomic imbalance; sympathetic (bronchodilating) innervation to the lungs is interrupted, whereas parasympathetic (bronchoconstrictive) neurotransmission carried by vagal nerve fibers remains intact. Support came from a subsequent investigation that employed body plethysmography to measure specific airway conductance (sGAW), a more sensitive indicator of airway caliber and bronchodilation than the FEV_1, among subjects with tetraplegia and low paraplegia (injury below T5) [34]. In subjects with tetraplegia but not paraplegia, we found baseline sGAW to be reduced consistent with resting airway narrowing, and witnessed significant increases in sGAW consistent with bronchodilation following inhalation of metaproterenol sulfate. These findings are important to the present proposal insofar as bronchodilation induced by beta-2 agonists can help prevent atelectasis and enhance lung volumes independent of anabolic effects, thereby potentially conferring added benefits.

We performed a preliminary study to evaluate the potential role of a long-acting beta-2 agonist in tetraplegia [32]. Eleven subjects with tetraplegia completed a randomized, double blind, placebo-controlled crossover study. All received placebo or the long-acting beta-2 agonist salmeterol (50ug twice a day from a Diskus inhaler) for 4 weeks with a 4-week washout period. Salmeterol is known to be rapidly absorbed into the systemic circulation following inhalation [31]. Results obtained during the 4th week of salmeterol or placebo administration, regardless of the order of administration, are shown in the following table:

Table 1	Baseline	Placebo	Salmeterol
Total lung capacity (TLC) (L)	5.20±0.47	5.11±0.48	5.32±0.32
Force vital capacity (FVC) (L)	3.11±0.38	3.22±0.41	3.36±0.52*§
Forced expiratory volume in 1 sec (FEV_1) (L)	2.40±0.51	2.52±0.49	2.74±0.52*§
Expiratory reserve volume (ERV) (L)	0.51±0.20	0.55±0.17	0.60±0.20●
Residual volume (RV) (L)	2.11±0.45	.89±0.41	1.98±0.44
Maximum inspiratory pressure (MIP) (cmH_20)	72.50±18.6	73.9±21.5	81.6±20.8*§
Maximum expiratory pressure (MEP)(cmH_20)	40.9±16.6	45.9±19.2	51.3±20.0*§

*data are mean±SD; *p<0.01 versus baseline; §p<0.05 versus placebo; ●p<0.05 versus baseline; L=liters*

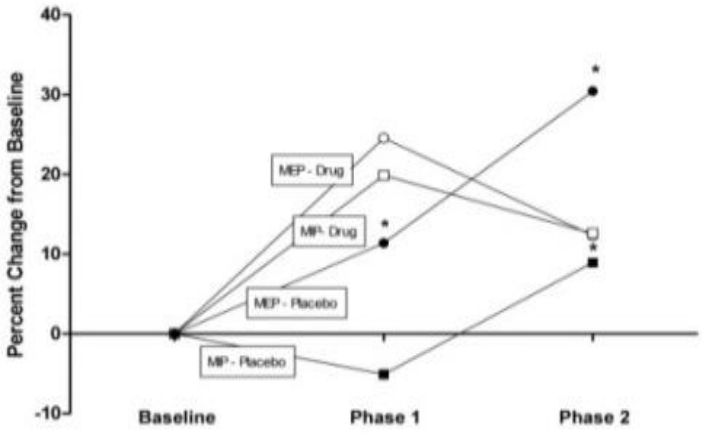
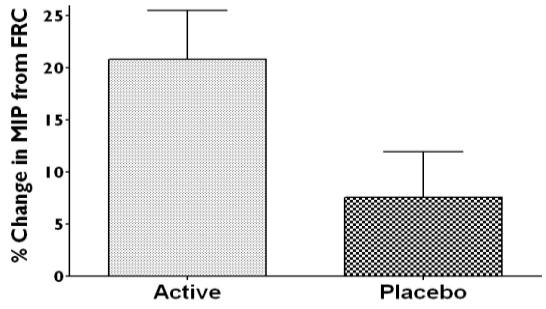


Figure 1: Percent change from baseline in MIP and MEP during phase 1 and phase 2. *p <0.05 for percent change from baseline.

Patients receiving salmeterol had significant improvement in FVC, FEV_1, MIP, and MEP compared to placebo and baseline. Expiratory reserve volume improved during administration of salmeterol compared to baseline (Table 1, Figure 1). Because spirometric parameters improved consistent with bronchodilation, it cannot be stated for certain that improvement in MIP and MEP represented an increase in respiratory muscle strength because both parameters are highly dependent upon the lung volume at which they are measured. However, by considering MIP and MEP values in relationship to whether salmeterol was given first or second, it appeared that improvement in MIP and MEP among those given salmeterol first was sustained through the washout period and into the placebo period (Figure 1), suggesting that sustained increase in MIP and MEP was due to improvement in respiratory muscle strength. Also, a significant increase in the ERV suggested that salmeterol improved expiratory muscle strength (Table 1) [33].

To pursue this question further, we recently completed a randomized, double-blind, placebo-controlled, parallel group trial in 30 persons with tetraplegia and high paraplegia (injury T6 and above). Fifteen subjects each in the active drug and placebo arms were randomized to receive an oral beta-2 agonist (albuterol repetabs 4 mg twice daily) versus matching placebo across 12 weeks (data not published). For post-intervention testing, we waited the equivalent of 5 half-lives of the drug to eliminate acute bronchodilator effects; any improvements in pulmonary function were therefore deemed secondary to increases in respiratory muscle strength. We found a statistically significant increase in MIP among subjects who received active drug versus placebo (%change = 22.7 ± 19.6 vs. 7.5 ± 17.0; p=0.03). The corresponding change in MEP (active drug versus placebo) trended toward significance (%change= 18.5 ± 29.1 vs. -0.2 ±19.8; p=0.06) [Figures 2a and 2b]. In the subset of individuals who received active drug (n=15), a statistically significant inverse correlation was found between baseline MIP and change in MIP (r^2= -0.326; p=0.03), with a trend toward an inverse correlation between baseline MEP and change in MEP [(r^2= 0.181; p=0.11) [Figures 2c & 2d]. These findings suggest that those with the lowest baseline mouth pressures tended to have the greatest improvement in respiratory muscle strength after receiving oral albuterol (see shaded boxes, Figures 2c & 2d). Thus, administration of an oral beta-2 agonist appeared to elicit the greatest effect on respiratory muscle strength in the weakest individuals, thereby targeting those persons who conceivably stand to derive the greatest benefit. Upon further inspection, a cutoff baseline MIP value of 90 cmH2O identified subjects below which appeared to have the greatest responses to administration of active drug, while those with more “normal” MIP values above this threshold exhibited little improvement. Similar findings were noted with regard to MEP, but did not reach statistical significance. Albuterol was also very well tolerated with minimal side effects; one subject in the active drug group withdrew because of jitteriness.

a)



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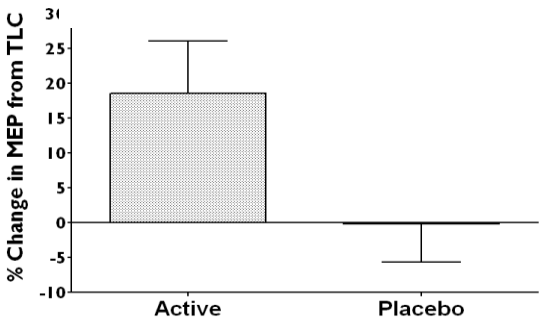

c)

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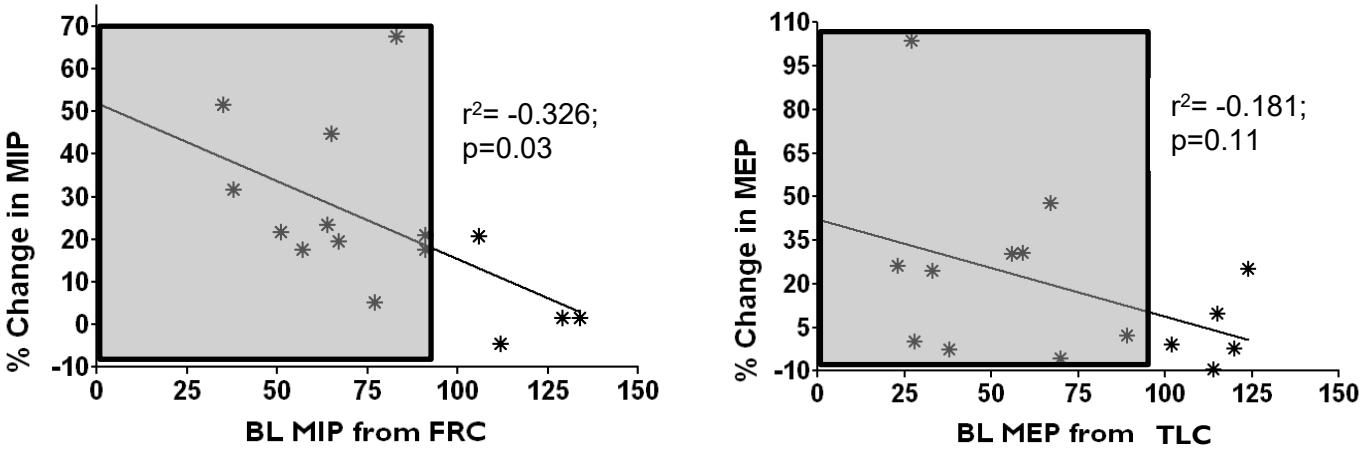

Figure 2: Oral Beta-2 versus Placebo for a) % change in MIP from FRC, b) % change in MEP from TLC, c) % change versus baseline MIP in active; and d) % change versus baseline MEP in active.

C. Research Design and Methods:

PROPOSED STUDY: This prospective interventional study will be performed at the National Center of Excellence for Medical Consequences of Spinal Cord Injury located at James J. Peters Veterans Affairs Medical Center (JJPVAMC), Bronx, NY. Prior to patient recruitment, approval by the local Institutional Review Board and Research and Development Committee will be obtained. Written informed consent will be obtained from all participants prior to the screening. An oral beta-2 agonist, or placebo, will be administered to subjects with tetraplegia and high paraplegia; the study will be prospective, double-blind with placebo. Subjects will be selected who have no history of asthma, allergies, hypertension or cardiovascular disease. Also excluded will be those already using beta-2 adrenergic agonists, corticosteroids, or antidepressants. Twenty-four patients with tetraplegia (C3-C8) and high paraplegia (T1-T6) who have baseline MIP < 90 cmH2O if male or MIP < 65 cmH2O if female, will be studied. Participants with SCI will be selected from the approximately 120 individuals with SCI who undergo annual pulmonary function testing at our facility. These tests are routinely performed in our pulmonary function lab and interpreted by the principal investigator (~ 120 per year). We estimate that 65% of these subjects will have tetraplegia or high paraplegia (~ 78 subjects), and of these ~ 50% will have a MIP < 90 and 65 cmH2O leaving 39 subjects for enrollment; assuming an attrition rate of 30%, this leaves 27 subjects, more than the 24 anticipated, to complete the trial. Based on power analysis (provided below), we need 12 subjects in each group (albuterol vs. placebo) to have a power of 81% at the alpha of 5%. Subjects will be divided into two groups of twelve, randomized equally to receive sustained-release albuterol repetabs versus matching placebo over a 16 week period. For the first week, the dosage of albuterol shall be 4 mg every 12 hours as in the previous trial, then in the absence of untoward side effects, increased to 8 mg every 12 hours for the remaining 15 weeks. The study drug/placebo will be dispensed by the VA Research Pharmacy on the subject's first visit and provided at no cost; both study investigators and subjects will be blinded as to study drug. Spirometric parameters, lung volume parameters, diaphragmatic thickness, maximal mouth inspiratory and expiratory pressures (MIP and MEP, respectively), simultaneously obtained esophageal pressure measurements (E-MIP, E-MEP), cough esophageal pressures (C-ESO) will be measured as described below at baseline, after 16 weeks and again at 18 weeks. The flow chart below highlights the test schedule:

Table 2: Procedures To Be Performed.	**Baseline**	**Drug or Placebo**	**Post**	**Residual**
	Week: 0	**Week: 1-16**	**Week: 16**	**Week: 18**
Pulmonary Function Test and Lung Volumes	**X**		**X**	**X**
Respiratory Muscle Strength Testing	**X**		**X**	**X**
Diaphragmatic Ultrasound	**X**		**X**	**X**
Pulmonary Questionnaire	**X**		**X**	**X**
Take Daily Medication		**X**		

Weekly Home Pulmonary Function Test		**X**		
Weekly Self-Symptom Survey		**X**		
Bi-Weekly Phone Interview		**X**		

Pulmonary Function Testing and Lung Volumes:

Pulmonary Function Test: While seated in the chair and after a mouth piece and nose clip are applied, the subject will be asked to breathe normally for 3 to 6 breaths. They will then be instructed to forcibly inhale until their lungs are filled. After a brief pause, they will then be instructed to forcibly exhale the air in their lungs and hold the maneuver for approximately 6 seconds. After a brief rest, the maneuver will be repeated a minimum of three times to ensure reliability.

Static Lung Volumes**:** The volume of air in the lungs will be assessed using the nitrogen washout technique. The nitrogen washout technique, which takes about five minutes to perform, will begin while a subject is seated in his/her wheelchair and after a mouth piece and nose-clips have been applied. The subject will then be asked to breathe room air into and out of the mouthpiece for 3-6 breaths. The air exhaled, which normally contains mostly nitrogen, will be collected and analyzed by a machine called a metabolic cart. Once a subject has completed the 3-6 breaths, he/she will be asked to take a slow deep breath in and to exhale until he/she feels that the lungs are empty, after which the subject returns to a normal breathing pattern. Following an additional 3-6 regular breaths, the metabolic cart will begin delivering 100% oxygen through the mouthpiece. The subject will continue to inhale 100% oxygen while taking normal breaths until oxygen is the only gas measurable in his/her exhaled air. After a brief rest, the maneuver will be repeated a minimum of two times to ensure reliability.

Respiratory Muscle Strength Testing*:* Maximal inspiratory pressure (MIP) from functional residual capacity (FRC), and maximal expiratory pressure (MEP) from TLC will be performed with a flanged mouthpiece according to established protocols using a modification of the Black and Hyatt technique [36]. For simultaneous measurement of transesophageal pressures, subjects will be asked to swallow a small balloon-tipped catheter connected to a computer. The balloon will be inserted into one nostril and into the esophagus after numbing medicine (4% lidocaine) has been applied to the nasal passages, throat, and to the tube itself in order to make swallowing the balloon easier. Then, pressures at the mouth and at the balloon will be recorded simultaneously by having the subject blow in and out as strongly as possible through a mouthpiece connected to a recording device. The subject will repeat these maneuvers a maximum of five times, and then be asked to perform 5 to 10 cough maneuvers of varying intensities while pressure at the esophageal balloon is recorded. The principal investigator's team has ample experience in esophageal manometry.

Diaphragmatic Ultrasound**:** A 7.5 MHz ultrasound (Acuson 128 XP/10, Mount View, Ca) linear transducer probe will be used to obtain 2D images (cross sectional view of the structure) of the diaphragm at the zone of apposition (ZOA) of the right hemithorax. All subjects will be seated comfortably in their wheel chairs during imaging. The diaphragm will be visualized in the right mid-axillary line at the levels of 8th or 9th intercostal space depending on a clarity and parallelism of visualized structures (pleura, diaphragm muscle and peritoneum). The diaphragm muscle in the ZOA is represented as a non-echogenic central structure bordered by two echogenic lines representing pleural and peritoneal membranes. Subjects will be asked to perform breathing through a flow volume meter (Carefusion, Yorba Linda, Ca) and to perform maneuvers of maximal inspiration and expiration. They will be asked to maintain an active respiratory effort in maximal inspiration and expiration for 1-2 seconds to prevent closure of the glottis and relaxation of the diaphragm and to provide a better visualization of the diaphragm in those positions. Continuous recording of the images will be obtained through at least 5 breathing cycles (maximal expiration to maximal inspiration). Simultaneous recording of time points and lung volumes will be obtained. All recordings will be done by the single experienced investigator. Retrograde analysis of the recordings will be done and freeze frame control will be used during replay alongside time records to precisely determine the end inspiration and end expiration. Diaphragm thickness (Tdi) will be measured as a distance between the midpoints of the pleural and peritoneal membranes at the end of inspiratory volume (EIV) and end of expiratory volume (EEV). The diaphragm thickness will be reported to the nearest 0.1mm which is within the range of accuracy of the transducer. The change in transdiaphragmatic index (Tdi) during inspiration (shortening of diaphragm), will be calculated and reported as the difference between Tdi at EEV and EIV, respectively.

Randomization: An independent investigator (unaffiliated with the pulmonary program and the present study) will generate a counter-balanced randomization table for enrolled participants. The randomization table will

account for equal sample sizes in the placebo and active drug group, and will be forwarded to the research pharmacy wherein the appropriate allocation of placebo/active drug will be dispensed and serve as the official study record.

Weekly Home Pulmonary Function Assessment: As a part of monitoring respiratory function, all subjects will be asked to perform weekly spirometry measurements using a portable spirometer [Microlife Digital Peak Flow & FEV1 Meter (Micorlife Corporation, Dunedin, FL)]. This device will allow subjects to check and record peak flow and other relevant parameters of a forced expiration. Subjects will be given detailed instructions and a demonstration on a first visit to ensure their understanding of the device and the maneuvers they will need to perform. Upon turning on the device, subjects will be prompted to take a maximal breath in and then to exhale forcefully through a mouthpiece. Subjects will be instructed to close their lips around the mouthpiece to prevent air leak that could affect the measurement. The device will automatically record the results, and the dates and times of recording. All participants will be asked to perform three consecutive maneuvers preferably upon awakening in the morning.

Weekly Self-symptom Survey: Subjects will be asked to fill out a questionnaire [37] regarding their symptoms on a weekly basis, the responses for which will be entered into a master database on each visit.

Bi-weekly phone interview: A member of the investigative team will contact the subject over the phone on a biweekly basis to speak about any symptoms or changes in lung function that the subject may be experiencing or have experienced since a previous discussion. The phone interview will only last a few minutes. The subject will be reminded that they are allowed to contact a member of the study team at any point should they have a question or emergency.

D. Data and Statistical Analysis*:* The study design consists of two between factors (Treatment and SCI groups) and two within factors (Time). A mixed ANOVA will be used to determine main and interaction effects. Analyses will permit us to determine the effect of the drug treatment alone. We are expecting large effect sizes (*d* >0.80) for percentage increases in MIP among subjects receiving active drug versus placebo (see preliminary data above), therefore, the power is greater than 0.95 at *alpha* <0.05. Allowing for a 12 subject dropout, our power is still better than 0.85.

E. Expected Results and Benefits*:* We anticipate that administration of a beta-2 adrenergic agonist to a targeted cohort of individuals with tetraplegia and high paraplegia who have significantly reduced MIP at baseline shall result in significant improvements in surrogate indices of respiratory muscle strength and decreased work of breathing. It is also possible that anabolic effects might be sustained on follow-up testing 2 weeks after stopping test medication. Findings that a beta-2 adrenergic agonist improves inspiratory and expiratory muscle strength would have significant therapeutic implications by increasing cough effectiveness to help prevent mucus retention and atelectasis. Salutary effects would provide a rationale for a larger scale multicenter trial to assess if administration of beta-2 agonists is associated with a reduction in pulmonary complications, a major cause of morbidity and mortality in this population.

Human Subjects Involvement and Characteristics

Subjects will be enrolled at the James J. Peters VA Medical Center for both the screening phase and the intervention phase. We estimate that a total of approximately 40 subjects will be recruited for the screening phase with about 24-27 meeting inclusion criteria and completing the study. All subjects will be studied at the James J Peters VA Medical Center within the Center of Excellence for the Medical Consequences of SCI. Subjects will be recruited from individuals that undergo annual pulmonary function testing within our Center (approximately 120 annually), of whom ~ 65% are anticipated to have cervical or high thoracic injury, and 50% of these also with reduced MIP (< 90 cmH_2O).

Identify the criteria for inclusion or exclusion of any subpopulation.

Subjects with Spinal Cord Injury will be recruited according to the following:

Inclusion criteria:

1. Chronological age between 18-80 years,
2. Subjects with Tetraplegia (Level of SCI C3-8); All ASIA Levels
3. Subjects with High Paraplegia (Level of SCI T1-T6); All ASIA Levels
4. Duration of injury ≥ 1 year,
5. Maximal inspiratory pressure < 90 cmH_2O (Men)
6. Maximal inspiratory pressure <65 cmH_2O (Women)

Exclusion criteria:

1. Smoking, active or history of smoking within the past year
2. Ventilator dependence
3. Any history of blast injuries to the chest,
4. Active respiratory disease or recent (within 3 months) respiratory infections
5. Use of medications known to alter airway caliber (i.e. beta 2 agonists or anticholinergic agents)
6. Pregnancy
7. Lack of mental capacity to give informed consent
8. Use of oral or inhaled corticosteroid agents
9. History of epilepsy or seizure disorder
10. Subjects already using beta-2 adrenergic agonists
11. Hypertension or cardiovascular disease
12. History of asthma or significant extrinsic allergies
13. MAOI use in prior 14 days
14. Hypersensitivity to albuterol or any of its constituents
15. Antidepressant use

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