

## Bronchodilator responses to metaproterenol sulfate among subjects with spinal cord injury

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**Abstract**—A previous study using spirometric methods demonstrated that 42% of subjects with tetraplegia experienced significant bronchodilation following inhalation of metaproterenol sulfate (MS). Comparative studies involving subjects with paraplegia were not performed and none has been performed in this population using body plethysmography, a more sensitive method used to assess airway responsiveness. Stable subjects with tetraplegia ( $n = 5$ ) or paraplegia ( $n = 5$ ) underwent spirometry and determination of specific airway conductance (sGaw) by body plethysmography at baseline and 30 minutes after nebulization of MS (0.3 mL of a 5% solution). Among subjects with tetraplegia, inhaled MS resulted in significant increases in spirometric indices and sGaw. Among subjects with paraplegia, only sGaw increased significantly, although this increase was considerably less than that seen in subjects with tetraplegia. Our findings indicate that subjects with tetraplegia exhibit greater bronchodilation in response to inhaled MS than do subjects with paraplegia and that sGaw measurements may confer greater sensitivity for assessing bronchodilator responsiveness in tetraplegia.

**Key words:** adrenergic beta-agonists, airway resistance, bronchodilator agents, paraplegia, spinal cord diseases, spirometry, tetraplegia, whole-body plethysmography.

### INTRODUCTION

It was previously observed that significant bronchodilator responsiveness to inhaled metaproterenol sulfate

(MS), as defined by at least a 12 percent increase in the forced expiratory volume in 1 s ( $FEV_1$ ), occurred among 42 percent of spontaneously breathing subjects with chronic cervical spinal cord injury (SCI) [1]. In theory, increased responsiveness to a beta-2 agonist in tetraplegia could be secondary to baseline bronchoconstriction caused by overriding cholinergic activity on airway caliber. Amplified cholinergic activity could result from the interruption of sympathetic innervation arising from the upper six thoracic segments of the spinal cord, and/or from low circulating catecholamine levels as a consequence of adrenal gland denervation [2]. Therefore, inhalation and binding of MS to beta-2 adrenergic receptors on airway smooth muscle cells would be expected to exert comparatively greater bronchodilation among subjects with tetraplegia as compared with those with low

**Abbreviations:** FEF = forced expiratory flow,  $FEV_1$  = forced expiratory volume in 1 s, FVC = forced vital capacity, Gaw = airway conductance, MS = metaproterenol sulfate, Raw = airway resistance, SCI = spinal cord injury, sGaw = specific airway conductance, Vtg = thoracic gas volume.

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paraplegia, who have intact innervation of the airways and adrenals. The clinical implications of bronchodilator responsiveness among subjects with tetraplegia are unknown, although increase in airway patency would presumably help promote clearance of airway mucus and reduce the incidence of atelectasis and pulmonary infections, which account for appreciable morbidity and mortality in this population [3,4].

The use of spirometric measurements to assess airway dynamics in tetraplegia is potentially limited if fatigue resulting from repeated expiratory maneuvers leads to suboptimal efforts in which flow limitation is not reached. Also, FEV<sub>1</sub> is complex physiologically and cannot be analyzed simply in terms of changing airway caliber [5]. Measurement of specific airway conductance (sGaw) by use of whole body plethysmography offers an alternative method for assessing bronchodilator responsiveness [6]. sGaw, the reciprocal of airway resistance corrected for the lung volume, is a more sensitive parameter than spirometric determinations, because resistance to airflow varies inversely with the fourth power of the airway radius [7]. Accordingly, with narrowed airways, a given degree of pharmacologically induced bronchodilation will be associated with greater apparent decrease in resistance than that appreciated with normal airways. The primary aim of this study was to assess bronchodilator response to aerosolized MS among subjects with tetraplegia and paraplegia by use of standard spirometric criteria and sGaw.

## METHODS

Ten clinically stable outpatients, five with chronic cervical SCI (tetraplegia, injury C4–C7) and five with chronic thoracolumbar SCI (paraplegia, injury below T5) participated in this study. None of the participants were receiving medications known to alter airway caliber. We selected subjects who reported no prior history of pulmonary disease, atopy, or asthma, and all denied recent or active pulmonary infections. Study participants were recruited from individuals followed by the SCI Service at the Bronx Department of Veterans Affairs (VA) Medical Center. The Institutional Review Board approved the study, and informed consent was obtained before the investigation.

We performed pulmonary function tests usually during morning hours. Airway resistance (Raw) and thoracic gas volume (Vtg) were obtained while subjects were

seated in a variable-pressure, constant-volume, whole-body plethysmograph (Vmax/6200 Body Plethysmograph, SensorMedics, Inc., Yorba Linda, California), according to methods originally described by Dubois et al. [8]. After subjects were seated in the body box chamber, a few minutes were required for thermal stabilization of the cabin as determined internally by the Vmax system. With a mouthpiece and nose clip attached, each subject was subsequently instructed to begin a period of baseline tidal breathing until a stable breathing pattern was established. Subjects were also instructed to minimize use of their cheek muscles and to maintain an open airway while performing rapid and shallow panting maneuvers at a frequency of approximately 2 c/s (60–180 breaths a minute) at or near functional residual capacity. The panting maneuvers were executed first with the automated breathing shutter open for determining Raw and then closed for determining Vtg; these were followed by a slow vital capacity maneuver. We determined thoracic gas volume and Raw by calculating the ratio of closed and open shutter tangents, respectively, from graphs plotting simultaneous changes in mouth pressure (for Vtg determination) and flow (for Raw determination) against changes in body box pressure, averaged from two to five separate and acceptable maneuvers [9]. We converted airway resistance to conductance (Gaw) by taking its reciprocal; we corrected Gaw for Vtg to determine sGaw.

While subjects remained seated in the body plethysmograph, standard spirometry with maximal forced expiratory maneuvers was performed according to American Thoracic Society standards [10]. Accordingly, we obtained the best forced vital capacity (FVC) and corresponding FEV<sub>1</sub> values from three reproducible FVC maneuvers ( $\pm 5\%$ ). In some individuals, reproducible efforts were deemed acceptable despite back extrapolated volumes in excess of standard limits and/or despite forced expiratory times lasting less than 6 s, as previously validated among subjects with cervical SCI [11]. Study subjects were then administered 0.3 mL of a 5 percent solution of MS via a Salter 8900 nebulizer, followed 30 minutes later by repeat sGaw measurements and spirometry. Spirometric parameters were expressed as absolute and percent-predicted values based on the prediction equations of Morris et al. [12]. The study was completed over approximately 6 months.

All data are expressed as mean  $\pm$  standard deviation (SD). We used an unpaired Student's t-test to compare differences between study subjects with paraplegia and

tetraplegia. We used a paired t-test within each group to assess mean changes in spirometric parameters and sGaw following administration of MS. To compare bronchodilator responsiveness across all subjects, we used simple linear regression as assessed by relative percentage changes in sGaw and spirometric parameters. Statistical significance for these analyses was established at a *p* value less than 0.05.

## RESULTS

Baseline characteristics are shown in **Table 1**. The two groups were well matched with regard to age, height, weight, completeness of injury, duration of injury, and smoking status.

Responses to MS are shown in **Table 2**. Among subjects with tetraplegia, the FEV<sub>1</sub> and forced expiratory flow (FEF) across the middle 50 percent of the vital capacity (FEF 25%–75%) increased significantly following inhalation of MS. Specifically, FEV<sub>1</sub> increased by 170 mL (8%) and FEF 25–75 percent by 0.36 L/s (18%). In contrast, among subjects with paraplegia, no significant changes were found in spirometric parameters in response to MS; bronchodilator responses were roughly one-half of those observed among subjects with tetraplegia. Specific airway conductance increased significantly following inhalation of MS among subjects with tetraplegia (0.17 cmH<sub>2</sub>O<sup>-1</sup>s<sup>-1</sup> [134%]) and paraplegia (0.05 cmH<sub>2</sub>O<sup>-1</sup>s<sup>-1</sup> [17%]), although the magnitude of this increase was significantly greater among subjects

with tetraplegia. By simple linear regression analysis across all study subjects, there was no significant correlation between relative percentage changes in sGaw and any spirometric parameter.

## DISCUSSION

Pulmonary function studies of subjects with cervical SCI have characteristically demonstrated restrictive ventilatory impairment correlating with the level of injury [13]. An obstructive component was unmasked among 14 of 34 subjects (42%) who exhibited significant increases in FEV<sub>1</sub> (>12%) following inhalation of a beta-2 adrenergic receptor agonist [1]. This response occurred independently of smoking status and suggested a physiology unique to subjects with tetraplegia. Injury to the cervical spinal cord, by interrupting sympathetic innervation to the lungs arising from the upper six thoracic nerve roots, may lead to an imbalance, favoring vagally mediated parasympathetic (cholinergic, bronchoconstrictive) over sympathetic (adrenergic, bronchodilatory) control of airway caliber and tone. Although cholinergic transmission is felt to be the principal determinant of resting airway tone, sympathetic fibers may have a counterregulatory function as suggested by anatomic studies showing intermingling of postganglionic sympathetic fibers with parasympathetic fibers in plexuses within airway walls [14]. Autonomic imbalance among subjects with tetraplegia might also be the consequence of denervation of the adrenal medulla, thereby leading to decreased circulating epinephrine levels [2]. In this paper, the first to compare responses with an inhaled beta-2 adrenergic agonist between subjects with tetraplegia and paraplegia, significant increases in spirometric parameters (FEV<sub>1</sub>, FEF 25–75%) among subjects with tetraplegia, but not those with low paraplegia (below T5), support the autonomic imbalance hypothesis.

Although subjects with tetraplegia as a group had a significant increase in FEV<sub>1</sub> and FEF 25–75 percent following inhalation of MS, only one of five subjects (**Table 2**) exhibited significant responsiveness as defined by current American Thoracic Society standards (minimum of a 12% and 200 mL increase in FEV<sub>1</sub> or FVC) [15]. Discriminatory power, although possibly affected by the small number of study participants, was more likely hampered by lack of sensitivity of spirometry for assessing bronchodilator responsiveness in subjects with SCI.

**Table 1.**  
Subject characteristics.

| Parameters              | Paraplegia<br>(n = 5) | Tetraplegia<br>(n = 5) |
|-------------------------|-----------------------|------------------------|
| Age (yr)                | 40 ± 9                | 45 ± 16                |
| Height (m)              | 1.78 ± 0.06           | 1.78 ± 0.10            |
| Weight (kg)             | 78 ± 16               | 74 ± 22                |
| Duration of Injury (yr) | 19 ± 10               | 17 ± 8                 |
| Complete Injury (%)     | 2/5 (40)              | 2/5 (40)               |
| Smoking Status          |                       |                        |
| Never                   | 1                     | 0                      |
| Former                  | 3                     | 3                      |
| Current                 | 1                     | 2                      |

Note: Data shown as mean ± standard deviation.

**Table 2.**  
Results of bronchodilator responses.

| Subject     | FVC (L)     |             |          | FEV <sub>1</sub> (L) |              |          | FEF 25–75% (L/s) |              |          | sGaw (cmH <sub>2</sub> O <sup>-1</sup> s <sup>-1</sup> ) |              |           |
|-------------|-------------|-------------|----------|----------------------|--------------|----------|------------------|--------------|----------|--|--------------|-----------|
|             | Pre-MS      | Post-MS     | % Change | Pre-MS               | Post-MS      | % Change | Pre-MS           | Post-MS      | % Change | Pre-MS   | Post-MS      | % Change  |
| Tetraplegia |             |             |          |                      |              |          |                  |              |          |  |              |           |
| 1           | 2.28        | 2.37        | 4        | 1.98                 | 2.09         | 6        | 2.25             | 2.98         | 32       | 0.21   | 0.51         | 143       |
| 2           | 2.47        | 2.73        | 11       | 1.64                 | 1.98         | 21       | 1.13             | 1.48         | 31       | 0.06   | 0.14         | 133       |
| 3           | 2.74        | 2.62        | -4       | 2.13                 | 2.22         | 4        | 2.13             | 2.55         | 20       | 0.16   | 0.41         | 156       |
| 4           | 4.56        | 4.80        | 5        | 3.42                 | 3.70         | 8        | 2.87             | 3.49         | 22       | 0.12   | 0.23         | 92        |
| 5           | 5.78        | 2.85        | 3        | 2.21                 | 2.26         | 2        | 2.10             | 2.19         | 4        | 0.09   | 0.23         | 156       |
| Mean (SD)   | 2.97 (0.91) | 3.07 (0.98) | 4 (5)    | 2.28 (0.68)          | 2.45 (0.71)* | 8 (7)    | 2.10 (0.62)      | 2.46 (0.73)† | 18 (10)  | 0.13 (0.06)  | 0.30 (0.15)† | 134 (25)‡ |
| Paraplegia  |             |             |          |                      |              |          |                  |              |          |  |              |           |
| 1           | 4.79        | 4.57        | -5       | 3.89                 | 3.90         | 0        | 4.01             | 4.57         | 14       | 0.3  | 0.40         | 33        |
| 2           | 4.59        | 4.82        | 5        | 3.55                 | 3.76         | 6        | 3.29             | 3.65         | 11       | 0.27   | 0.29         | 7         |
| 3           | 4.07        | 4.06        | 0        | 3.37                 | 3.39         | 1        | 3.37             | 3.91         | 16       | 0.4  | 0.44         | 10        |
| 4           | 4.30        | 4.38        | 2        | 4.03                 | 4.08         | 1        | 6.23             | 6.48         | 4        | 0.32   | 0.34         | 6         |
| 5           | 3.56        | 3.75        | 5        | 2.67                 | 2.85         | 7        | 2.15             | 2.48         | 15       | 0.22   | 0.28         | 27        |
| Mean (SD)   | 4.26 (0.48) | 4.32 (0.42) | 1 (4)    | 3.50 (0.53)          | 3.60 (0.49)  | 3 (3)    | 4.0 (1.82)       | 4.09 (1.47)  | 9 (10)   | 0.3 (0.07)   | 0.35 (0.07)* | 17 (13)   |

\*Significantly greater than prebronchodilator values at  $p < 0.05$ .

†Significantly greater than prebronchodilator values at  $p = 0.01$ .

‡Significantly greater percentage increase for subjects with tetraplegia compared to subjects with paraplegia at  $p < 0.001$ .

Pre-MS = baseline values prior to inhalation of metaproterenol sulfate.

Post-MS = values after inhalation of metaproterenol sulfate.

% Change = percentage change in pulmonary function parameter after inhalation of metaproterenol sulfate.

Repeated forced expiratory maneuvers in those with paralysis of respiratory muscles could result in suboptimal spirometric efforts in which flow limitation is not reached, thereby dampening otherwise apparent bronchodilator responses. Smaller responses that are reproducible, however, may have relevance for individual subjects.

Among able-bodied subjects, sGaw has been shown to increase more in response to bronchodilator regimens of increasing potency than spirometric parameters, although FEV<sub>1</sub> and FVC had greater discriminatory power for discerning bronchodilator responses after variability in measurements were considered [7]. This may not be the case, however, among subjects with SCI for whom avoidance of effort-dependent techniques might prove advantageous. The findings in this study, in which we use sGaw measurements for the first time to assess bronchodilator responses among subjects with SCI, attest to the sensitivity of this technique. The consistently observed increases in sGaw among all five subjects with tetraplegia (92% to 156%) following inhalation of MS greatly exceeded the 40 percent threshold that defines significant bronchodilator responsiveness [16]. Finally, the marked increase in sGaw among subjects with tetraplegia

as compared to subjects with paraplegia following inhalation of MS further supports the theory that subjects with chronic cervical SCI have baseline bronchoconstriction.

Pulmonary dysfunction is a major cause of significant morbidity and mortality among subjects with SCI [3]. The spectrum of pulmonary complications encountered includes atelectasis, pneumonia, recurrent aspiration, and late-onset respiratory failure requiring long-term mechanical ventilation [17]. Because subjects with tetraplegia are at greatest risk for developing pulmonary complications, they may achieve the most benefit from interventions designed to help promote clearance of respiratory secretions and to decrease the incidence of pulmonary infections.

The chronic use of inhaled beta-2 adrenergic agonists, such as the MS used in this study, has not been systematically evaluated among subjects with SCI. Among subjects with tetraplegia, clinical studies including the present one have shown that these medications elicit bronchodilation [1]. Pretreatment with a beta-2 adrenergic receptor agonist has also been found to block non-specific airway hyperreactivity, which is prevalent among subjects with tetraplegia [18]. In addition to direct

bronchodilatory effects, these agents enhance mucociliary clearance, inhibit cholinergic neurotransmission, and inhibit mediator release from inflammatory cells [19]. Whether these effects would translate into salutary long-term outcomes in SCI is unknown. Although usually well tolerated, chronic use of beta-2 agonists must be weighed against the potential for unwanted side effects, such as tremor, tachycardia, cough suppression, prolongation of the QT<sub>c</sub> interval of the electrocardiogram, hyperglycemia, hypokalemia, and peripheral vasodilation [19,20]. Long-term clinical studies are needed to clarify these issues.

## CONCLUSION

In subjects with tetraplegia and paraplegia, bronchodilator responses to inhaled MS, a beta-2 adrenergic receptor agonist, were assessed by use of standard spirometric techniques and by whole-body plethysmography. Subjects with tetraplegia exhibited significant increases in spirometric parameters and sGaw consistent with bronchodilation. Measurement of sGaw by body plethysmography was found to be a more sensitive method for detecting bronchodilation; it may prove superior to spirometry for assessing bronchodilator responsiveness among subjects with tetraplegia. Bronchodilator administration to subjects with SCI has unclear benefits, but given the high prevalence of serious pulmonary complications in this population, it warrants further study.

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