Original Article

Cholinergic bronchomotor tone and airway caliber in tetraplegic patients

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Study design: Case-control study.

Objectives: To evaluate the resting airway caliber in subjects with tetraplegia; to define the participation of cholinergic innervation in this condition; and to determine if baclofen modifies this pattern.

Setting: A rehabilitation hospital, Brasília, Brazil.

Methods: We studied 18 tetraplegic patients, with complete motor loss between C4 and C8, and 18 healthy control subjects by measuring airway conductance, before and after inhaled ipratropium bromide.

Results: At baseline, the pulmonary function parameters revealed mild-to-moderate restrictive impairment in tetraplegic patients as defined by decreases in total lung capacity and predicted percent of slow vital capacity. The average baseline specific airway conductance (sGaw) was less in tetraplegic patients (0.25 ± 0.11) than in the control group (0.41 ± 0.10 l/s/cm H₂O) ($P < 0.0001$). All patients had improved postbronchodilator sGaw $\geq 40\%$ compared with only four of the 18 controls ($P < 0.001$). The average increase for tetraplegic patients was $235\% (\pm 93)$ versus $25\% (\pm 24)$ for controls ($P < 0.0001$). Analysis of variance for repeated measurements showed significant difference in sGaw between the control and spinal cord injury (SCI) groups ($P < 0.0001$) following bronchodilator challenge, but found no difference for total gas volume. No difference for mean basal sGaw and bronchodilator challenge was encountered comparing tetraplegic patients using baclofen to those not using it.

Conclusions: Cervical SCI patients have a reduced baseline conductance compared to controls. Marked improvement occurs after an inhaled anticholinergic drug. This behavior was not affected by the use of baclofen. The study adds support to the hypothesis of an increased cholinergic bronchomotor tone in tetraplegic patients.

Spinal Cord (2006) 44, 269–274. doi:10.1038/sj.sc.3101836; published online 27 September 2005

Keywords: spinal cord injury; lung function tests; anticholinergic agents; airway innervation; baclofen; respiratory mechanics

Introduction

Pulmonary dysfunction is one of the chief clinical challenges facing patients with high spinal cord lesions.^{1,2} Transection of the cervical or high thoracic spinal cord interrupts sympathetic innervation and circulating catecholamine levels fall,³ but the vagal nuclei of the brain stem remain intact.⁴ Such unopposed vagal tone might be expected to cause enhanced vagal activity to the heart and airways. Clinical examples of this imbalance are the hypotension, bradycardia and symptomatic breathlessness following exposure to hot air and passive cigarette smoke experienced by tetraplegic patients. This may suggest bronchial hyperactivity⁵ associated with cervical spinal cord injury (SCI).

Therefore, it is hypothesized that the interruption of sympathetic out flow in these patients results in an increase in bronchial tone.

It was previously suggested by spirometry that approximately 45% of subjects with chronic cervical SCI experienced significant bronchodilatation following inhalation of either beta-2 agonist (metaproterenol sulfate) or anticholinergic (ipratropium bromide),^{6,7} thereby suggesting that baseline airway caliber is decreased in at least half of subjects. Recently, it was demonstrated that conductance improves in these subjects when nebulized with metaproterenol sulfate⁸ and ipratropium bromide.⁹

The aim of the present study is to further define cholinergic bronchomotor tone in patients with cervical SCI. The use of spirometric forced expiratory flows is

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not sensitive as a marker of airway size nor for the detection of airway patency.¹⁰ Therefore, we chose plethysmography to assess airway conductance, before and after specific blockage of cholinergic receptors by ipratropium bromide. Secondly, we hoped to clarify the effect of baclofen on the airway tone of these subjects.

Materials and methods

Subjects

Following Institutional Ethics Committee review, informed consent was obtained from all participants. In all, 18 clinically stable male inpatients, mean age 25.3 ± 7.1 years ($\pm$ standard deviation (SD)) (range 18–42), with traumatic lesions of the cervical spinal cord were recruited from the Spinal Cord Service at the SARAH Rehabilitation Hospital/Brasilia during the period February, 1998 to August, 1999. The hospital has an integrated program of rehabilitation accepting clinically stable patients. Time since injury varied from 1.4 to 37.9 months. The control group consisted of 18 male able-bodied subjects, mean age 26.8 ± 5.0 years (range 16–33), studied during the same time period. All participants were screened for a history of pulmonary disease or respiratory symptoms, recent respiratory viral or bacterial infection, and asthma or seasonal allergy. None of the control group had ever been cigarette smokers, whereas three subjects in tetraplegic group were former smokers (ceased >24 months previously) and one was currently smoking. Data regarding

patient's age, level, duration of injury and smoking status, as well as medications in use, are provided in Table 1.

Procedures

First, forced spirometric measurements were obtained with the subjects seated in their wheelchairs using an automated pulmonary function laboratory (Master-Scope, Erich Jaeger GmbH). Baseline and postbronchodilator values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) were obtained for each subject according to the recommendations of the American Thoracic Society (ATS).¹¹ Baseline slow vital capacity (SVC) and other related measurements were obtained from subjects seated within the plethysmographic chamber. 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.¹² Spirometry results are expressed as absolute values and percent of predicted.¹³

Following the forced spirometry, thoracic gas volume (TGV) and airway resistance were measured by the methods of DuBois *et al*^{14,15} using a constant-volume body plethysmograph (Medgraphcs® PF/Dx 1085D). Specific airway conductance (sGaw) was calculated by dividing the airway resistance reciprocal by the TGV at which the measurements were made. At least five measurements were made per individual during each phase of the study, and the results are reported as the

Table 1 Patient characteristics and profile

Patient	Age (year)	Duration of injury (months)	Level of injury/ASIA ^a	Smoking status	Medications
1	29	21.7	C5–C6/B	Former ^b	None
2	18	15.7	C6–C7/A	Never	None
3	23	21.9	C6/A	Current	Baclofen
4	21	7.9	C7/A	Former	None
5	21	37.9	C7/B	Never	Baclofen
6	31	22.1	C5/A	Former	Baclofen
7	21	1.4	C6/A	Never	None
8	30	2.6	C7/A	Never	None
9	42	15.5	C6/B	Never	None
10	25	13.6	C6/A	Never	None
11	40	4.4	C4/A	Never	Baclofen + oxybutynin
12	21	5.4	C5/A	Never	Baclofen
13	25	2.0	C6/A	Never	None
14	30	2.9	C8/A	Never	Baclofen
15	22	15.9	C5/A	Never	None
16	18	6.4	C8/A	Never	None
17	20	22.0	C5/B	Never	Baclofen + oxybutynin
18	19	1.9	C6–C5/A	Never	None
Mean	25.3	12.3	—	—	—
$\pm$ SD	7.1	10.1	—	—	—

^aASIA = American Spinal Injury Association;³² A denotes complete motor and sensory loss; B denotes incomplete injury, only sensory is preserved at S4–S5

^bFormer = at least for 2 years

Figure 1 Subject within the closed plethysmographic chamber during an exam using nasal clip and cheek support to prevent soft tissue pressure changes during panting

mean values of the acceptable panting maneuvers. Tetraplegic patients have difficulty supporting the cheeks with their hands to prevent pressure changes induced by the mouth. Therefore, we developed a special clip for this maneuver (Figure 1). All subjects in both groups used it. The measurements began only after evidence of chamber thermal equilibrium and only when the panting frequency was approximately 1.5 Hz. The body plethysmograph results were obtained following the AARC clinical practice guidelines.¹⁶

Spirometry and plethysmography measurements were performed before and 45 min after inhalation via a spacer of four puffs of ipratropium bromide (Boehringer Ingelheim, Ridgefield, CT, USA) delivering a total dose of 72 μ g. With the lips securely around the aerosol spacer, each subject inhaled from residual volume (RV) to total lung capacity (TLC) and the researcher manually triggered the metered dose inhaler at about functional residual capacity. Each subject held his breath at TLC for 10 s and then breathed normally for 30 s before the next inhalation of drug. During spirometry, those patients classified as 'responders' achieved a bronchodilator response equal to or greater than a minimum of a 12% and 200 ml either in FEV₁ or FVC as described by the ATS.¹¹ Additionally, during plethysmography 'responders' achieved an improvement in sGaw equal to or greater than 40%.¹⁷ Those with less than these thresholds were classified as 'nonresponders'.

Statistical analysis

All data are expressed as means $\pm$ SD. An unpaired Student's *t*-test and Fisher's exact test (one-tailed) was performed to assess differences between the groups. We also performed analysis of variance (ANOVA) for repeated measurements of the sGaw and TGV results between the groups of control and tetraplegic subjects, before and after bronchodilator challenge. In addition, a

one-way ANOVA with *post hoc* analysis was conducted using Fisher's pairwise comparisons to determine whether there were differences between the control group and two subgroups of patients, one currently using and the other not using baclofen. StatView for Windows (SAS Institute Inc., version 5.0.1) was used for all statistical analysis. Statistical significance was defined as $P < 0.05$.

Results

The mean baseline values of pulmonary function parameters revealed mild-to-moderate restrictive impairment in tetraplegic patients as defined by decreases in TLC and the percentage of predicted SVC. In the tetraplegic group, all the mean percent predicted values of spirometry and lung volumes were lower than the control group ($P < 0.001$) with three exceptions. RV was greater in the tetraplegic group ($P < 0.001$), and the FEV₁/FVC ratios were equal (Table 2). At baseline, there was no difference between the TGV of controls (3.87 ± 0.82 l) and that of the tetraplegic patients (3.68 ± 0.59 l).

Five of 18 tetraplegic patients were 'responders' to bronchodilator by spirometry. No control subjects responded by spirometry ($P = 0.019$). All tetraplegic patients were 'responders' versus four of 18 controls when evaluated by sGaw ($P < 0.001$). The percentage change showed an average increase of 235% (± 93) for the tetraplegic group compared with 25% (± 24) for controls ($P < 0.0001$) (Table 3). Prebronchodilator results demonstrate that baseline average sGaw was lower in tetraplegic patients (0.25 ± 0.11) than controls (0.41 ± 0.10 l/s/cm H₂O), ($P < 0.0001$) (Table 3 and Figure 2). The specific airway resistance was 0.33 ± 0.12 l/s/cm H₂O for the tetraplegic group, and 0.24 ± 0.19 l/s/cm H₂O in the control group. No difference for mean basal sGaw and percentage difference after bronchodilator challenge was encountered in tetraplegic patients with and without baclofen. Both tetraplegic subgroups maintained the previously described significant difference when compared to controls ($P < 0.002$).

The ANOVA for repeated measurements detected changes in sGaw only in the group with tetraplegia after bronchodilator administration ($P < 0.0001$). No changes were identified by ANOVA in TGV before and after bronchodilator in either group nor was there a difference between the groups. Withdrawing the four patients with ASIA B lesions did not change these results (data not shown).

Discussion

This study shows that patients with cervical SCI have a reduced baseline conductance that improves after an inhaled anticholinergic drug. This behavior was not affected by the use of baclofen. The study adds support to the hypothesis of a reduced baseline airway caliber motivated by an unopposed parasympathetic activity secondary to the loss of sympathetic innervation of the

Table 2 Individual (for tetraplegic patients only) and mean spirometry and lung volumes parameters (percent predicted) between the two groups^a

Patient	TLC (l) (% pred)	SVC (l) (% pred)	RV (l) (% pred)	ERV (l) (% pred)	IC (l) (% pred)	FEV ₁ /FVC ratio
<i>Tetraplegic group (n = 18)</i>						
1	5.25 (101.0)	2.18 (54.2)	3.07 (260.1)	0.31 (24.2)	1.87 (68.5)	91.8
2	4.65 (76.5)	2.78 (56.5)	1.87 (161.2)	0.99 (60.4)	1.80 (54.9)	93.3
3	5.21 (82.2)	1.76 (35.1)	3.45 (259.4)	0.12 (7.2)	1.65 (49.3)	86.9
4	6.05 (87.8)	2.87 (52.7)	3.17 (220.1)	0.92 (49.5)	1.96 (54.8)	96.4
5	4.31 (72.8)	2.80 (59.8)	1.51 (121.7)	1.21 (75.6)	1.59 (51.8)	80.7
6	6.47 (84.8)	2.99 (51.6)	3.47 (188.5)	0.86 (43.7)	2.14 (56.0)	90.0
7	3.59 (49.9)	1.67 (29.4)	1.92 (125.4)	0.63 (32.1)	1.04 (28.0)	87.0
8	4.41 (71.1)	1.69 (35.4)	2.72 (190.2)	0.44 (28.8)	1.25 (38.6)	100.0
9	4.58 (72.5)	2.34 (50.8)	2.23 (131.1)	0.74 (52.5)	1.61 (50.3)	86.3
10	4.62 (93.9)	1.89 (48.7)	2.73 (262.5)	0.60 (48.4)	1.28 (48.5)	100.0
11	5.04 (94.0)	1.23 (31.1)	3.81 (270.2)	0.13 (10.7)	1.10 (40.3)	75.6
12	5.42 (79.6)	2.21 (41.0)	3.21 (226.0)	0.50 (27.2)	1.71 (48.2)	91.7
13	4.46 (63.9)	0.98 (18.1)	3.48 (225.9)	0.11 (6.0)	0.87 (24.2)	94.0
14	5.05 (82.5)	2.00 (42.5)	3.04 (215.6)	0.50 (33.3)	1.50 (46.7)	89.7
15	3.87 (63.6)	1.22 (25.2)	2.65 (213.7)	0.23 (14.5)	0.99 (30.4)	96.8
16	4.96 (71.7)	2.31 (41.8)	2.65 (190.6)	0.88 (46.1)	1.43 (39.5)	87.8
17	3.78 (54.3)	1.26 (22.8)	2.52 (175.0)	0.09 (4.7)	1.17 (32.3)	83.3
18	4.72 (79.9)	1.36 (28.9)	3.36 (277.6)	0.30 (18.5)	1.06 (34.4)	100.0
Mean	4.80 (76.8)	1.97 (40.3)	2.83 (206.4)	0.53 (32.4)	1.45 (44.3)	90.6
±SD	0.74 (13.5)	0.63 (12.6)	0.63 (49.9)	0.34 (20.4)	0.37 (11.6)	6.8
<i>Control group (n = 18)</i>						
Mean	6.58 (103.07)	4.68 (97.70)	1.74 (123.64)	1.77 (97.46)	3.42 (98.37)	85.99
±SD	0.96 (11.01)	0.88 (12.24)	0.66 (46.16)	0.77 (26.56)	0.71 (11.68)	4.95

^aExcept for FEV₁/FVC ratio, all means of percent predicted parameters were different between the groups ($P < 0.001$)**Table 3** Pre- and postbronchodilator (BD) spirometry and plethysmography assessments

Parameter	Pre-BD	Post-BD	% Change	% Responders ^a
<i>Tetraplegic patients (n = 18)</i>				
FEV ₁ (l)	2.14 ± 0.54	2.17 ± 0.63	1.73 ± 20.42	22.2 (4/18)*
FVC (l)	2.37 ± 0.58	2.43 ± 0.58	3.44 ± 14.19	16.7 (3/18) [†]
sGaw (l/s/cm H ₂ O)	0.25 ± 0.11 [‡]	0.77 ± 0.22	234.7 ± 92.64 [‡]	100.0 (18/18) [‡]
<i>Control group (n = 18)</i>				
FEV ₁ (l)	4.16 ± 0.56	4.33 ± 0.63	4.04 ± 3.97	0 (0/18)
FVC (l)	4.85 ± 0.65	4.91 ± 0.69	1.20 ± 3.61	0 (0/18)
sGaw (l/s/cm H ₂ O)	0.42 ± 0.10	0.52 ± 0.15	25.2 ± 23.87	22.2 (4/18)

^aThe ≥ 12% and 200 ml increase to FEV₁ or FVC; ≥ 40% increase in sGaw* $P = 0.02$ tetraplegic × control[†] $P = 0.11$ tetraplegic × control[‡] $P < 0.0001$ tetraplegic × control

lungs.⁴ Autonomic imbalance among subjects with tetraplegia might also be the consequence of denervation of the adrenal medulla.³

Perhaps because reduced flow rates were always felt to be in proportion to the reduction in vital capacity of tetraplegic patients, the presence of an obstructive component in the respiratory dysfunction of these patients may not have been suspected by previous investigators.¹⁸ With bronchodilator administration,

most of these patients demonstrated a disproportionate improvement in FEV₁ relative to FVC, thereby increasing the FEV₁/FVC, unmasking an associated pulmonary obstruction.¹⁸

Efferent vagal nerve fibers provide bronchoconstrictor tone to the airway, but doubt exists regarding the influence of direct adrenergic innervation of bronchial smooth muscle.⁴ Sympathetic fibers may have a counter regulatory function as suggested by anatomic studies

Figure 2 Individual sGaw responses pre- and postipratropium bromide in control (left) and tetraplegic (right) groups. Short thick black lines indicate mean values

showing intermingling of postganglionic sympathetic fibers with parasympathetic fibers in plexuses within airway walls.⁴ Other neural pathways such as the noncholinergic and nonadrenergic system may have a role in bronchomotor tone.¹⁹ Our results add supportive evidence for the participation of adrenergic system into the bronchomotor tone regulation.

To date, two studies have measured conductance in tetraplegic patients. The study of Schilero *et al*,⁸ in 2004, using metaproterenol sulfate demonstrated an average increase in conductance of 134%. A year later, using ipratropium bromide, the same research group⁹ showed an average increase of 135%. This evidence reinforces the hypothesis of vagal dominance on resting bronchomotor tone in these patients. They studied patients with average time postlesion of at least 13 years and their methodology did not use cheek support during the panting maneuvers. Our patients have a shorter time postinjury (range 1.4–37.9 months; average of 12 ± 10 months). In all three studies, the results are similar but appear greater in our patients with a shorter average time postinjury (235% improvement).

In general, spirometric values are markedly reduced, as are maximal mouth pressure in high SCI patients.^{20–22} Many studies used surrogate spirometric indexes of airway size (FEV₁ percent predicted and forced expiratory flow 25–75% vital capacity percent predicted) and airway size relative to lung size (forced expiratory flow 25–75% vital capacity/FVC ratio) in tetraplegic patients to demonstrate airway flow rate improvement by inhaled bronchodilator.^{6,7} These same spirometric techniques were used to demonstrate bronchial hyper-responsiveness following inhalation of methacholine, histamine and/or distilled water.^{6,7,10,23–29} This bronchial hyper-reactivity maybe an additional indirect evidence of pre-existing airway narrowing. Any small further reduction in caliber would produce a large increase in resistance (resistance of laminar gas flow being inversely related to the fourth power of the radius), thus leading to the clinical impression of hyper-reactivity.

Maximum expiratory flow volume curves to detect airflow obstruction in tetraplegic patients are hampered

by skeletal muscle weakness and paralysis essential for the forced expiratory maneuvers. Thus, forced lung function measurements may reflect different components of respiratory muscle strength and weakness, giving little information on the mechanical characteristics of the respiratory system.^{30,31} We feel plethysmography to estimate the airway caliber better defines the magnitude of the autonomic imbalance suggested in prior investigations in tetraplegics.

Baclofen and oxybutynin can alter airway reactivity. SCI patients frequently use both. Prior studies^{26,32} show an attenuation of bronchial hyperactivity induced by methacholine, but not that due to histamine, in tetraplegic patients using baclofen. Since we did not use bronchial provocation, our study is not directly comparable to the studies of Grimm *et al*²⁶ and Dicipinigaitis *et al*.³² We considered it important to exclude any potential confounding effect this anticholinergic medication might have had on airway caliber. No such effect was observed on our results. Smoking is known to induce a fall in respiratory conductance.³³ None of the control group had ever smoked, but the tetraplegic group contains one smoker and two former smokers, therefore we reanalyzed the data excluding these three individuals. No changes were observed in our results.

It is worth noting that the baseline sGaw in our control group is at the lower limits of normal range.³⁴ There are two possible explanations for this phenomenon. Spirometry conducted immediately prior to body plethysmography might lead to changes in airway stretch properties. The use of the special clip device to support the cheeks might have contributed to this result. We feel, however, that any artifacts that may have been produced by this methodology have been controlled by the strictly equal application of the experimental protocol in both groups.

We conclude from these findings that ipratropium bromide improves specific conductance in cervical spine lesion patients, although it does not change total gas volume. This would appear to have important implications for a group of individuals whose mortality due to pulmonary causes remains significant,³⁵ as does the frequency of their respiratory complaints.³⁶ There may be a future role for prolonged bronchodilator treatment in tetraplegic patients that needs confirmation in clinical trials. The fact that we did not observe change in TGV might imply that the elevated airway resistance in these patients does not interfere with the functional residual capacity.

References

- 1 Bergofsky EH. Mechanism for respiratory insufficiency after cervical cord injury. *Ann Intern Med* 1964; **61**: 435–447.
- 2 Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. *Am Rev Respir Dis* 1981; **124**: 41–44.

- 3 Schmid A *et al*. Catecholamines, heart rate, and oxygen uptake during exercise in persons with spinal cord injury. *J Appl Physiol* 1998; **85**: 635–641.
- 4 Barnes PJ. Neural control of human airways in health and disease. *Am Rev Respir Dis* 1986; **134**: 1289–1314.
- 5 Spungen AM *et al*. Self-reported prevalence of pulmonary symptoms in subjects with spinal cord injury. *Spinal Cord* 1997; **35**: 652–657.
- 6 Spungen AM *et al*. Pulmonary obstruction in individuals with cervical spinal cord lesions unmasked by bronchodilator administration. *Paraplegia* 1993; **31**: 404–407.
- 7 Almenoff PL *et al*. Bronchodilatory effects of ipratropium bromide in patients with tetraplegia. *Paraplegia* 1995; **33**: 274–277.
- 8 Schilero GJ *et al*. Bronchodilator responses to metaproterenol sulfate among subjects with spinal cord injury. *J Rehab Res Dev* 2004; **41**: 59–64.
- 9 Schilero GJ *et al*. Assessment of airway caliber and bronchodilator responsiveness in subjects with spinal cord injury. *Chest* 2005; **127**: 149–155.
- 10 Grimm DR *et al*. Airway hyperreactivity in subjects with tetraplegia is associated with reduced baseline airway caliber. *Chest* 2000; **118**: 1397–1404.
- 11 Standardization of Spirometry. 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; **152**: 1107–1136.
- 12 Ashba J *et al*. Spirometry – acceptability and reproducibility in spinal cord injured subjects. *J Am Paraplegia Soc* 1993; **16**: 197–203 (1167/id).
- 13 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981; **123**: 659–664 (114/id).
- 14 Dubois AB *et al*. A rapid plethysmographic method for measuring thoracic volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956; **35**: 322–326.
- 15 Dubois AB, Botelho SY, Comroe Jr JH. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J Clin Invest* 1956; **35**: 327–335.
- 16 AARC clinical practice guideline. Body plethysmography. American Association for Respiratory Care. *Respir Care* 1994; **39**: 1184–1190.
- 17 Van Noord JA *et al*. Assessment of reversibility of airflow obstruction. *Am J Respir Crit Care Med* 1994; **150**: 551–554.
- 18 Spungen AM *et al*. Pulmonary obstruction in individuals with cervical spinal cord lesions unmasked by bronchodilator administration. *Paraplegia* 1993; **31**: 404–407.
- 19 Barnes PJ. The third nervous system in the lung: physiology and clinical perspectives. *Thorax* 1984; **39**: 561–567.
- 20 Baydur A, Adkins RH, Milic-Emili J. Lung mechanics in individuals with spinal cord injury: effects of injury level and posture. *J Appl Physiol* 2001; **90**: 405–411.
- 21 Tully K *et al*. Maximal expiratory pressures in spinal cord injury using two mouthpieces. *Chest* 1997; **112**: 113–116.
- 22 Linn WS *et al*. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 2001; **39**: 263–268.
- 23 Singas E *et al*. Airway hyperresponsiveness to methacholine in subjects with spinal cord injury. *Chest* 1996; **110**: 911–915.
- 24 Singas E *et al*. Inhibition of airway hyperreactivity by oxybutynin chloride in subjects with cervical spinal cord injury. *Spinal Cord* 1999; **37**: 279–283.
- 25 Grimm DR *et al*. Airway hyperresponsiveness to ultrasonically nebulized distilled water in subjects with tetraplegia. *J Appl Physiol* 1999; **86**: 1165–1169.
- 26 Grimm DR *et al*. Effects of GABA-B agonist baclofen on bronchial hyperreactivity to inhaled histamine in subjects with cervical spinal cord injury. *Lung* 1997; **175**: 333–341.
- 27 Dicpinigaitis PV *et al*. Bronchial hyperresponsiveness after cervical spinal cord injury. *Chest* 1994; **105**: 1073–1076.
- 28 Fein ED *et al*. The effects of ipratropium bromide on histamine-induced bronchoconstriction in subjects with cervical spinal cord injury. *J Asthma* 1999; **35**: 49–55.
- 29 DeLuca RV *et al*. Effects of a B2-agonist on airway hyperreactivity in subjects with cervical spinal cord injury. *Chest* 1999; **115**: 1533–1538.
- 30 Wang AY *et al*. Cough in spinal cord injured patients: the relationship between motor level and peak expiratory flow. *Spinal Cord* 1997; **35**: 299–302.
- 31 De Troyer A. Respiration mechanics in tetraplegia. *Bull Mem Acad R Med Belg* 1997; **152**: 91–97.
- 32 Dicpinigaitis PV *et al*. Inhibition of bronchial hyperresponsiveness by the GABA-agonist baclofen. *Chest* 1994; **106**: 758–761.
- 33 Stanescu DC, Veriter C, Brasseur L. Airway conductance: the most sensitive index of abnormality in long-term smokers. *Bull Eur Physiopathol Respir* 1978; **14**: 383–399.
- 34 Watanabe S *et al*. Airway responsiveness to a bronchodilator aerosol. I. Normal human subjects. *Am Rev Respir Dis* 1974; **109**: 530–537.
- 35 Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehab* 1994; **75**: 270–275.
- 36 Spungen AM *et al*. Self-reported prevalence of pulmonary symptoms in subjects with spinal cord injury. *Spinal Cord* 1997; **35**: 652–657.