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Ventilatory responses to chemosensory stimuli in quadriplegic subjects

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ABSTRACT: We tested the hypothesis that interruption of motor traffic running down the spinal cord to respiratory muscle motoneurons suppresses the ventilatory response to increased chemical drive. We compared the hypoxic (HVR) and hypercapnic (HCVR) ventilatory responses, based on the rebreathing technique, before and during inspiratory flow-resistive loading in 17 quadriplegic patients with low cervical spinal cord transection and in 17 normal subjects. The ventilatory response was evaluated from minute ventilation ($\dot{V}_E$) and mouth occlusion pressure ($P_{0.2}$) slopes on arterial oxygen saturation (Sao_2) or on end-tidal P_{CO_2} (P_{ACO_2}), and from absolute $\dot{V}_E$ values at Sao_2 80% or at P_{ACO_2} 55 mmHg. We found no difference in the unloaded HVR or HCVR between the quadriplegic and normal subjects. In the loaded HVR, the $\Delta\dot{V}_E/\Delta Sao_2$ slope tended to decrease similarly in both groups of subjects. The $\Delta P_{0.2}/\Delta Sao_2$ slope was shifted upwards in normal subjects, yielding a significantly higher $P_{0.2}$ at a given Sao_2. In contrast, this rise in the $P_{0.2}$ level during loaded HVR was absent in quadriplegics. Loaded HCVR yielded qualitatively similar results in both groups of subjects; $\Delta\dot{V}_E/\Delta P_{ACO_2}$ decreased and $\Delta P_{0.2}/\Delta P_{ACO_2}$ increased significantly. The results show that the ventilatory chemosensory responses were unsuppressed in quadriplegics, although they displayed a disturbance in load-compensation, as reflected by occlusion pressure, in hypoxia. We conclude that the descending drive to respiratory muscle motoneurons is not germane to the operation of the chemosensory reflexes.
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Low cervical spinal cord transection entails paralysis of the respiratory muscles of the rib cage and abdomen, which are a major part of the effector in the respiratory control system. Muscle paralysis underlies an impairment of pulmonary function [1] and disordered motion of the chest [2] in quadriplegic patients.

We hypothesized that if the respiratory muscles are paralysed, *i.e.* if motor traffic descending along the bulbospinal respiratory neuron axons to the intercostal and abdominal spinal motoneurons is interrupted by a spinal cord lesion, stimulatory ventilatory responses, requiring enhanced respiratory pump muscle activity, would be suppressed. This suppression might be accentuated during the ventilatory response to increased chemical drive, since both O_2 and CO_2 chemoreflexes have been implicated, *via* an effect on the central respiratory controller, in the facilitatory modulation of the descending drive to the respiratory muscle motoneurons [3–5]. The suppression might be further potentiated during ventilatory loading, since load-compensating reflexes amplify inspiratory effort of the respiratory muscles [6].

Previous evidence suggests that quadriplegics can increase respiratory motor output to the diaphragm in response to a variety of graded elastic and resistive inspiratory loads [7, 8] or negative pressure applied through a cuirass placed around the torso [9]. KELLING *et al.* [10] reported a reduced hypercapnic ventilatory response with no added load but a similar-to-normal response during resistive loading. It does not seem certain, however, whether factors other than the load-compensating mechanisms *per se*, like the inevitably increased chemical drive due to loading [7, 8] or central hyperoxia [10], contributed to the ventilatory adjustment. We therefore thought it worthwhile to re-evaluate the ventilatory responses to hypoxia and hypercapnia before and during inspiratory flow-resistive loading in the same quadriplegic patients and to compare these responses with those in normal subjects. The progressive hypoxic and hypercapnic tests used ensured control of

changes in chemical drive due to ventilatory loading. In general, quadriplegics had the chemosensory responses strikingly well preserved.

Methods

Subjects

The study was carried out on 17 healthy volunteers aged 23–60 years and on 17 patients with chronic, traumatic C_4-C_7 spinal cord transection aged 16–62 years. The mean post-injury time was 39.1±9.6 months (range 4–108 months). All subjects consented to study procedures approved by an ethical board for human research. They were all Japanese except for 3 control subjects who were Caucasian. Anthropometric data are set out in table 1. The patients were under usual care. They had no overt respiratory ailment at the time of the study. All subjects were studied in the supine posture after at least a 2 h fast.

Instrumentation

A scheme of the experimental set-up is depicted in fig 1. Subjects with a mouthpiece and noseclip breathed through a one-way valve (Lloyd valve) from which end-tidal O_2 (P_{AO_2}) and CO_2 (P_{ACO_2}) tensions were measured with a rapidly responding O_2 and CO_2 analyser (San-ei IH21). Breath-by-breath expired airflow was measured with a hot wire flowmeter (Minato RF-H) inserted between the mouthpiece and the respiratory valve. The flowmeter was calibrated against a 2 *l* piston and the gas analyser with mixtures of known gas concentrations. Tidal volume (V_T) was integrated electrically from the flow signal, from which also inspiratory (t_I) and expiratory (t_E) times were computed by an analogue calculator. Mouth occlusion pressure at 0.2 s from onset of inspiratory

Table 1. – Anthropometric, pulmonary function, and arterial blood gas content data under the control conditions

	Quadriplegic	Normal
Sex M/F	17/0	13/4
Age years	39.6±4.2	33.9±2.6
Wt kg	54.8±2.2†	65.2±2.3
Ht cm	166.2±1.7	169.5±1.6
BSA m^2	1.60±0.03†	1.75±0.04
FVC *l*	2.15±0.1†	4.05±0.2
% pred.	55.6±3.9†	99.2±2.9
FEV_1 *l*	1.69±0.1†	3.33±0.2
FEV_1/FVC %	79.0±1.7	82.5±1.7
V_D ml	270±10†	243±8
V_D/V_T	0.50±0.03†	0.44±0.01
$P_{I_{MAX}}$ kPa	11±1.4†	16±1.4
$P_{E_{MAX}}$ kPa	11±1.7†	16±0.9
SaO_2 %	96.3±0.2†	97.8±0.3
pHa	7.422±0.01	-
Pao_2 kPa	11.1±0.3	-
$Paco_2$ kPa	5.0±0.12	-
HCO_3 mM	24.8±0.4	-
Hb $g \cdot dl^{-1}$	13.8±0.3	-

Values are mean±SEM. Standard abbreviations are presented. For further details see text. †: $P<0.05$ for comparisons between the two groups of subjects.

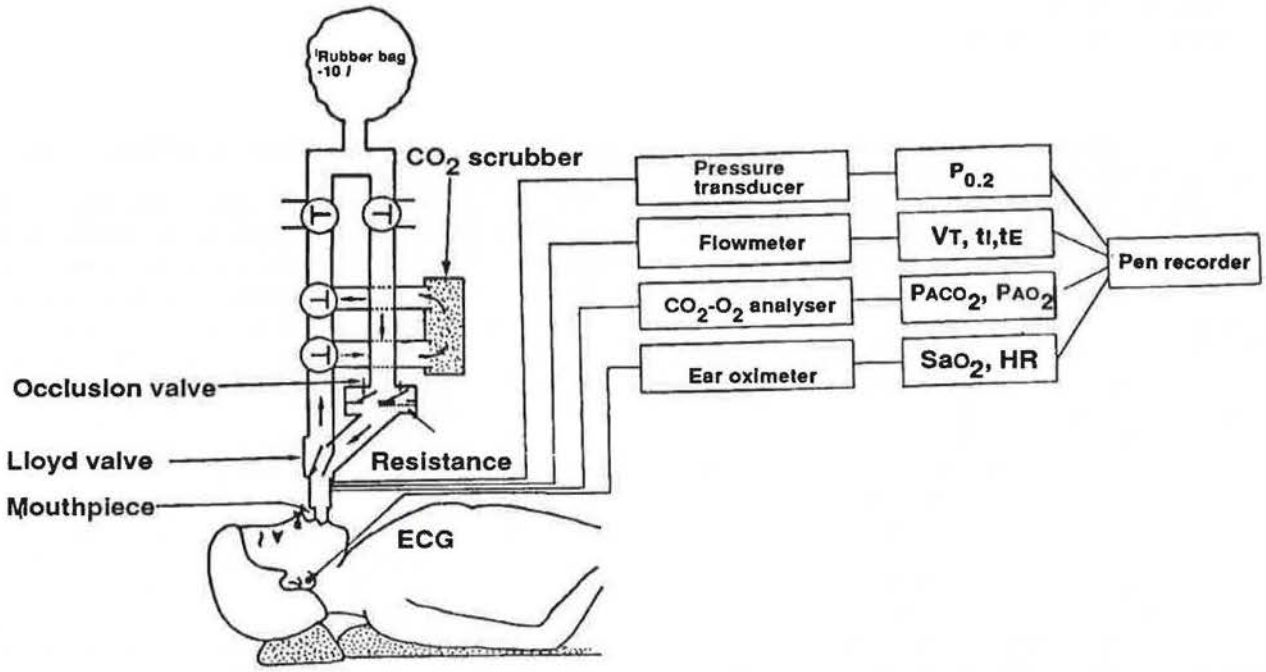

Fig. 1. – Schematic diagram of the experimental set-up.

effort ($P_{0.2}$) was measured with differential pressure transducer (Toyo Boldwin LPU-01). Arterial O_2 saturation (Sao_2) and heart rate were measured with an ear oximeter (Ohmeda, Biox III). All these variables were recorded continuously on a multi-channel strip-chart pen oscillograph (San-ei Instruments). From the variables recorded, breath frequency (f), minute ventilation ($\dot{V}_E$; the product of V_T and f), mean inspiratory flow (V_T/t_I), and inspiratory time as a fraction of total respiratory cycle time (t_I/t_{tot}) were computed.

Study protocol and measurements

A familiarization period of about 7 min breathing room air while connected to the breathing circuit preceded the start of the experiment. The protocol consisted of two hypoxic and two hypercapnic tests one each before and during inspiratory flow-resistive loading. The tests were always done in the foregoing sequence. The loading was achieved by interposing a porous disc of a resistance 1 $kPa \cdot l^{-1} \cdot s$ at a flow rate of 1 $l \cdot s^{-1}$ in the inspiratory limb of the breathing circuit.

The progressive hypoxic test was a modification of that of WEIL *et al.* [11]. The subject breathed room air initially for about 5 min until a steady level of resting ventilation was achieved. During this control time, expired gas was collected for the calculation of O_2 consumption ($\dot{V}O_2$, STPD) and CO_2 production ($\dot{V}CO_2$, STPD) from the gas volume and O_2 and CO_2 fractional concentrations measured by a San-ei analyser. On the basis of expired CO_2, alveolar ventilation ($\dot{V}_A$), which is more relevant than minute ventilation to gas exchange in the lung, was calculated; $\dot{V}CO_2$ was converted to BTPS. To determine the ventilatory response to acute hypoxia, the subject started rebreathing through the closed circuit from a bag filled with 5–7 *l* of room air (fig. 1). A resting $PACO_2$ was maintained within 0.13 kPa (1 mmHg) throughout the test by adjusting the volume of exhaled air flowing through the CO_2 scrubber. The test end point was an Sao_2 of 70–75%, which corresponded to a $PACO_2$ of 4.6–5.9 kPa (35-45 mmHg).

The progressive hypercapnic test was done with a rebreathing method similar to that of READ [12]. After a control period, the subjects rebreathed through a closed circuit from a bag containing a mixture of 7–8% CO_2 and 92–93% O_2 with a volume slightly exceeding vital capacity. The test end-point was a $PACO_2$ of 7.2–7.8 kPa (55–60 mmHg).

The mean duration of the hypoxic test was 7.9±0.3 min and that of the hypercapnic test 4.2±0.2 min. A 10 min rest was allowed between each test. Since each patient was subjected to four consecutive tests, for obvious ethical reasons the chemical stimuli used were of moderate intensity.

Ventilation may not accurately reflect respiratory neural output during ventilatory loading or in quadriplegia, since it may be influenced by the changes in chest mechanics independent of respiratory centre output. We therefore used the $P_{0.2}$ measurement [13] as an index of respiratory neural drive. The $P_{0.2}$ was measured by intermittently and randomly closing the occlusion valve 8–18 times at end-expiration during each test, so that the following inspiration would be made against the occluded valve.

To ascertain the validity of the $P_{0.2}$ measurement in quadriplegics, we conducted 3 test trials on 3 patients both with and without added load, relating $P_{0.2}$, $\dot{V}_E$, and peak diaphragmatic electromyographic activity (EMG) recorded with bipolar surface electrodes and processed to yield a moving-time average. All the interrelationships of the variables were linear and allowed us to draw two interferences. Firstly, since $P_{0.2}$ corresponded closely to $\dot{V}_E$ in the unloaded state (r=0.89) and to EMG in the loaded state (r=0.82), its difference between the two states could be taken as a measure of ventilatory compensation for the imposed load. Secondly, $P_{0.2}$ seemed to be a reasonably good approximation of neural drive. Since occlusion pressure also correlates well with EMG in normal subjects during loaded breathing [14], comparison of the $P_{0.2}$ measurement between the quadriplegic and normal subjects seems justifiable.

The HVR and HCVR were evaluated by relating $\dot{V}_E$ and $P_{0.2}$ to Sao_2 and to $PACO_2$, respectively. These relationships are linear and were analysed by a least squares regression. The equation y=A(x-B) was used, where A is the slope ($\Delta\dot{V}_E/\Delta Sao_2$ and $\Delta\dot{V}E/\Delta PACO_2$ slopes are measures of hypoxic and hypercapnic sensitivities) and B is the extrapolated x-intercept. For the HVR, Sao_2 values were scaled from high to low on the abscissa, yielding the slope with a positive sign. Additionally, the absolute changes in $\dot{V}_E$ and $P_{0.2}$ at the fixed levels of Sao_2 and $PACO_2$ of 80% and 7.2 kPa (55 mmHg) were evaluated by interpolation.

Arterial blood samples were withdrawn from a femoral artery in each patient before the start of the experiment for blood gas measurements (Radiometer ABL3 assembly). Forced vital capacity (FVC), forced expired volume in one second (FEV_1), and the fraction of FVC expired in the first second ($FEV_1/FVC\%$) were measured in all subjects with a hot wire flowmeter, and maximal inspiratory (P_{IMAX}) and expiratory (P_{EMAX}) pressures at the functional residual capacity level with a mercury manometer at the end of the experiment. Physiological deadspace (V_D) was computed from the Bohr equation.

Data collection and analysis

All data were collected from the strip-chart recording. 3–5 complete breath cycles were analysed at the time of each occlusion pressure measurement, from which individual variables were retrieved, averaged, and when required expressed per min. Data were further processed by a microcomputer (NEC PC-9801) to yield the HVR and HCVR response lines, which were averaged for each group.

Values are presented as mean±SEM. Statistical analysis was made with a two-tailed paired t-test for comparison within a group, and an unpaired t-test for comparison between corresponding conditions of the two groups. $P<0.05$ was considered significant.

Results

Characterization of subjects and breathing patterns

Quadriplegic and normal subjects were matched for age and height (table 1). The quadriplegics were significantly lighter than the normal subjects; the likely reason being chronic muscle wasting. Consequently their body surface area was smaller. As expected, their pulmonary function was severely impaired. The FVC and FEV_1 were almost halved, and the levels of maximal inspiratory and expiratory pressures were significantly depressed. The fraction of FVC expired in 1 s was comparable with that in the normal subjects, pointing to a restrictive pattern of impairment. Their arterial gas content and acid-base status were within normal limits, although a slightly reduced Sao_2 was noted.

Seven out of the 17 quadriplegics displayed a paradoxical inward motion of the chest on inspiration. Since such a motion might be disadvantageous for ventilation and a potential source of error in estimation of the ventilatory response, we compared the basic ventilatory data for patients with paradoxically and nonparadoxically moving chests. This comparison is shown in table 2. No appreciable differences were noted between the two subgroups of quadriplegics. Therefore, data for all quadriplegics were pooled together for further analysis.

Table 2. – Basic ventilatory data for quadriplegics with paradoxical (n=7) and nonparadoxical (n=10) motion of the rib cage under the control condition and during HVR

	No load		Load	
	Paradox.	Nonparadox.	Paradox.	Nonparadox.
$\dot{V}_E$ *l* BTPS·min^{-1}	8.0±0.3	9.5±0.4	9.3±0.9	8.8±0.3
$P_{0.2}$ kPa	0.24±0.01	0.28±0.02	0.38±0.05	0.32±0.03
V_T/V_T	0.53±0.03	0.48±0.04	0.49±0.03	0.50±0.04
$\Delta\dot{V}_E/\Delta Sao_2$ *l*·min^{-1}·%$^{-1}$	0.49±0.12	0.34±0.12	0.26±0.08	0.23±0.07
$\dot{V}_E$ at Sao_2 80% *l*·min^{-1}	16.5±2.3	15.1±2.1	13.9±1.6	12.5±1.3
$\Delta P_{0.2}/\Delta Sao_2$ kPa·%$^{-1}$	0.017±0.005	0.015±0.007	0.01±0.003	0.01±0.005
$P_{0.2}$ at Sao_2 80% kPa	0.52±0.08	0.57±0.13	0.57±0.08	0.55±0.08

Values are mean±SEM. Standard abbreviations are presented. Data for the two subgroups of patients did not differ significantly.

Table 3. – Steady-state ventilatory measurements before and during ventilatory loading under the control conditions

	Quadriplegic		Normal	
	No load	Load	No load	Load
$\dot{V}_E$ *l* BTPS·min^{-1}	8.9±0.4†	9.0±0.6	7.7±0.3	7.8±0.7
V_T ml BTPS	581±50	613±64	562±27	568±40
f breaths·min^{-1}	16.6±1.3	16.1±1.3	14.1±0.8	14.2±1.3
t_I s	1.59±0.1	1.77±0.2	1.82±0.1	1.95±0.1
t_E s	2.29±0.2	2.35±0.3	2.62±0.2	2.66±0.2
V_T/t_I ml·s^{-1}	375±23†	347±18	317±16	307±27
t_I/t_{tot}	0.41±0.01	0.43±0.02	0.41±0.01	0.42±0.01
$P_{0.2}$ kPa	0.26±0.02†	0.34±0.04*†	0.34±0.03	0.48±0.06*
P_{AO_2} kPa	14.2±0.21	14.0±0.25	13.9±0.36	13.7±0.36
P_{ACO_2} kPa	4.6±0.10†	4.6±0.14	5.0±0.10	4.9±0.17
$\dot{V}O_2$ ml STDP·min^{-1}	221±11	230±12	227±8	232±9
$\dot{V}CO_2$ ml STDP·min^{-1}	183±12	181±12	196±8	188±15
$\dot{V}_A$ *l* BTPS·min^{-1}	4.5±0.4	4.6±0.5	4.4±0.2	4.6±0.6
Heart rate beats·min^{-1}	68±3†	66±3†	58±3	57±2

Values are mean±SEM. Standard abbreviations are presented. For further details see text. *:$p<0.05$ for comparisons between unloaded and loaded states within a group. †:$p<0.05$ for comparisons between the corresponding conditions of the two groups of subjects.

Steady-state eupnoeic ventilatory measurements delineating the breathing pattern in both groups of subjects before and during inspiratory flow-resistive loading are set out in table 3. In the unloaded state the quadriplegics had a slightly but significantly higher $\dot{V}_E$ than the normal subjects with consequent alveolar hypocapnia. The increase in $\dot{V}_E$ could not be related to any specific changes in V_T or f, nor could it be a result of increased metabolic rate, as there were no appreciable changes in O_2 consumption or CO_2 production. The t_I and t_E were proportionately, although not significantly, shorter, which did not alter the t_I/t_{tot}, indicating an unchanged central respiratory timing. The higher $\dot{V}_E$ in quadriplegics was due to compensation for increased dead-space, since the values of $\dot{V}_A$ were almost equal, and due in part to anxiety associated with connecting the subjects to the circuit. The latter mechanism is supported by the arterial Pco_2 being in the normal range, measured before putting the patient on the circuit (table 1), and by the lack of consistently higher ventilation in the control period of the loaded state later in the course of the experimental procedure (table 3). The ventilatory effect of conscious cortical influences may have been different in severely diseased patients from that in healthy subjects.

Resistive loading, as a rule, increased variability of respiratory indices. The only significant differences between the loaded and unloaded states in both groups of subjects was the increase in $P_{0.2}$ (table 3).

Comparison of the $P_{0.2}$ responses in the quadriplegic and normal subjects during eupnoeic ventilation is shown in figure 2. The $P_{0.2}$ was significantly higher in the loaded state in both groups, although its initial unloaded level was lower in the quadriplegics. The magnitude of the $P_{0.2}$ increase (fig. 2 inset) did not differ significantly between the two groups, indicating an intact compensation for the load in the quadriplegics.

Responses to hypoxia

In the unloaded state, as oxygenation fell $\dot{V}_E$ increased in 14 normal subjects, remained nearly unchanged in 2, and decreased in 1. The range of $\Delta\dot{V}_E/\Delta Sao_2$ was from +1.86 to -0.11 $l \cdot min^{-1} \cdot \%^{-1}$ Sao_2 (mean 0.39±0.12). These values fall within the published range of the hypoxic response at eucapnic Pco_2 [15]. In the quadriplegic patients, $\Delta\dot{V}_E/\Delta Sao_2$ increased in 13 cases, remained flat in 2, and decreased in 2. The slope ranged from +1.26 to -0.15 $l \cdot min^{-1} \cdot \%^{-1}$ Sao_2 (mean 0.40±0.12). Numerical data for the mean $\dot{V}_E$ and $P_{0.2}$ responses to progressive hypoxia for the normal and quadriplegic subjects are set out in table 4(I). In the unloaded state, the quadriplegics' $\Delta\dot{V}_E/\Delta Sao_2$ and $\Delta P_{0.2}/\Delta Sao_2$ and the absolute values of $\dot{V}_E$ and $P_{0.2}$ at an Sao_2 of 80% were no different from those in the normal subjects. In the loaded state the $\dot{V}_E$ slope and $\dot{V}_E$ absolute level decreased by nearly the same magnitude in both groups of subjects, the decrease being insignificant.

The effect of ventilatory loading on the mean $P_{0.2}$ responses to progressive hypoxia is illustrated in figure 3. In both normal (fig. 3A) and quadriplegic (fig. 3B) subjects the slope of the $P_{0.2}$ response was not changed compared with the unloaded value. In the normal subjects however loading shifted the $P_{0.2}$ response line upward, yielding a significant increase in the absolute $P_{0.2}$ level at an Sao_2 of 80%. This increase was absent in the quadriplegics.

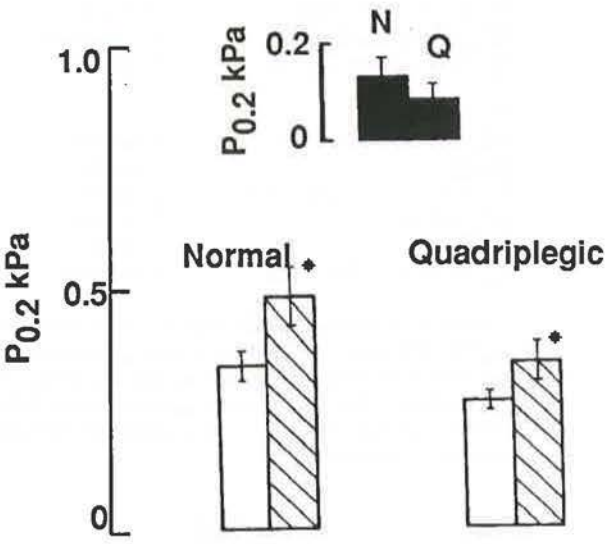

Fig. 2. – Average (mean±SE) mouth occlusion pressure responses to inspiratory flow-resistive loading in the quadriplegic and normal subjects in eupnoea. Inset, increases of occlusion pressure due to loading in normal (N) and quadriplegic (Q) subjects. Loading increased occlusion pressure significantly in each group, the increases (inset) being not appreciably different. □ :No load; ▨ Load.

The pattern of breathing during the ventilatory response to hypoxia was assessed by plotting the V_T-$\dot{V}_E$ relationship. An illustration of this relationship constructed from the mean V_T and $\dot{V}_E$ values at the mean control Sao_2 of 97.1±0.1% and fixed hypoxic Sao_2 of 80% for the normal and quadriplegic subjects with no added ventilatory load is shown in fig 4A. The quadriplegics met the increased $\dot{V}_E$ due to hypoxia of the normal subjects with a smaller increase in V_T and a greater increase in f. These changes in the pattern of breathing, which did not assume statistical significance, had a similar character during ventilatory loading.

Respiratory timing changes at the hypoxic Sao_2 of 80% before and during ventilatory loading in the normal and quadriplegic subjects are shown in table 5(I). The t_I and t_I/t_{tot} increased significantly in response to loading in each group of subjects, and there were no appreciable differences in either index between the two groups during unloaded or loaded breathing.

Responses to hypercapnia

The $\dot{V}_E$ was invariably increased as $PACO_2$ increased. Data for the $\dot{V}_E$ and $P_{0.2}$ responses to progressive hypercapnia are set out in table 4(II). In the unloaded

Table 4. – Hypoxic and hypercapnic ventilatory responses

	Quadriplegic		Normal	
	No load	Load	No load	Load
I-HVR				
$\Delta\dot{V}_E/\Delta Sao_2$ $l\cdot min^{-1}\cdot\%^{-1}$	0.40±0.12	0.24±0.07	0.39±0.12	0.28±0.06
$\dot{V}_E$ at Sao_2 80% $l\cdot min^{-1}$	15.7±2.1	13.1±1.4	14.9±1.7	13.1±1.0
$\Delta P_{0.2}/\Delta Sao_2$ $cmH_2O\cdot\%^{-1}$	0.016±0.006	0.010±0.004	0.014±0.004	0.014±0.004
$P_{0.2}$ at Sao_2 80% cmH_2O	0.56±0.11	0.56±0.08	0.56±0.07	0.73±0.09*
II - HCVR				
$\Delta\dot{V}_E/\Delta PACO_2$ $l\cdot min^{-1}\cdot kPa^{-1}$	8.54±0.92	7.46±0.77*	11.15±1.00	8.62±0.85*
B kPa	3.8±0.21	3.4±0.31*	4.2±0.29	3.8±0.29*
$\dot{V}_E$ at $PACO_2$ 7.2 kPa $l\cdot min^{-1}$	27.2±2.7	25.3±2.1	30.5±2.8	26.6±2.1*
$\Delta P_{0.2}/\Delta PACO_2$	0.33±0.05	0.50±0.07*	0.32±0.03	0.49±0.05*
B kPa	4.1±0.22	4.2±0.22	3.8±0.44	3.9±0.38
$P_{0.2}$ at $PACO_2$ 7.2kPa kPa	0.94±0.10	1.35±0.17*	0.99±0.11	1.44±0.16*

Values are mean±SEM. HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response. HVR and HCVR were analysed by a least squares regression. Slopes and x-intercepts (B) of the responses are presented. Absolute values for $\dot{V}_E$ and $P_{0.2}$ at Sao_2 80% and $PACO_2$ 7.2 kPa (55 mmHg) were obtained by interpolation. For further detail see text. *:$p<0.05$ for comparisons between unloaded and loaded conditions within a group. There were no significant differences between the corresponding conditions of the two groups of subjects.

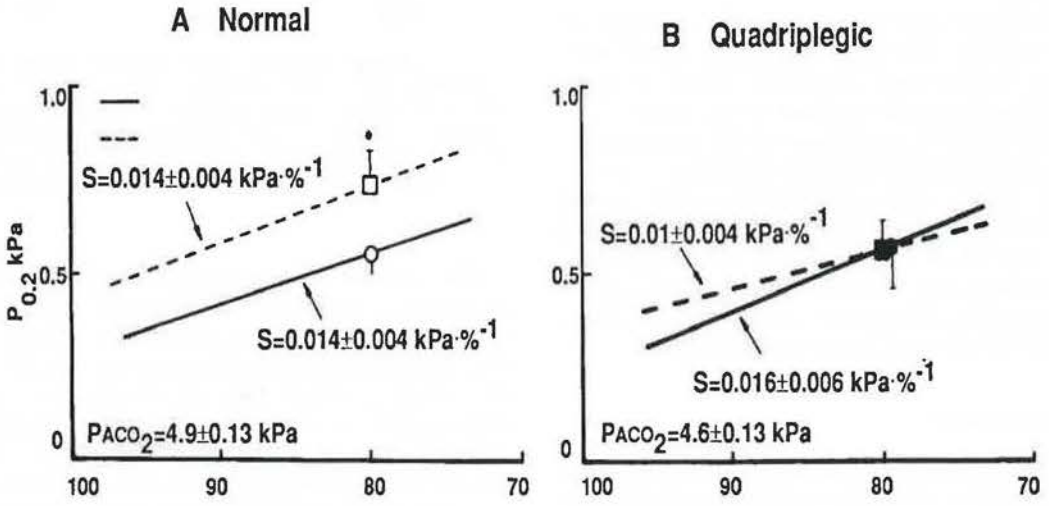

Fig. 3. – Unloaded and loaded mouth occlusion pressure responses to progressive isocapnic hypoxia in normal (Panel A) and quadriplegic (Panel B) subjects. Lines are mean linear regression slopes of occlusion pressure on arterial saturation; symbols denote mean (SE) occlusion pressure at SaO_2 80%. ——: no load; -----: load.

state the quadriplegics had a slightly lower $\Delta\dot{V}_E/\Delta PACO_2$ slope compared with that in the normal subjects, the difference being insignificant. In the loaded condition, $\Delta\dot{V}_E/\Delta PACO_2$ was decreased significantly in both groups of subjects by about the same magnitude. Resistive loading significantly decreased the absolute level of $\dot{V}_E$ at a $PACO_2$ of 7.3 kPa (55 mmHg) in the normal subjects but less so in the quadriplegics. Loading also significantly decreased the apnoeic $PACO_2$ level, as reflected by the extrapolated x-intercept, in both groups of subjects.

In contrast to $\dot{V}_E$, both the slope of the $P_{0.2}$ response, $\Delta P_{0.2}/\Delta PACO_2$, and the absolute $P_{0.2}$ level at a $PACO_2$ of 7.3 kPa (55 mmHg) were uniformly and significantly increased ($p<0.05$) in both groups of subjects during loading. Comparison of the unloaded or loaded state between the normal and quadriplegic subjects showed no discernible differences (table 4(II)).

A graphical illustration of the V_T-$\dot{V}_E$ relationship during HCVR is shown in figure 4B. The symbols represent the mean values of V_T and $\dot{V}_E$ at the mean control $PACO_2$ of 4.7±0.13 kPa (36±1 mmHg) and fixed hypercapnic $PACO_2$ of 7.3 kPa (55 mmHg) with no added load in the normal and quadriplegic subjects. The pattern of breathing and its changes during HCVR were qualitatively the same as those during HVR.

Table 5 – Respiratory timing during hypoxic and hypercapnic ventilatory responses

	Quadriplegic		Normal	
	No load	Load	No load	Load
I - HVR				
Sa_{O_2} %	80		80	
P_{ACO_2} kPa	4.6±0.07		5.0±0.08	
t_I s	1.40±0.13	1.72±0.14*	1.64±0.11	1.98±0.16*
t_I/t_{tot}	0.44±0.01	0.48±0.02*	0.42±0.01	0.47±0.01*
I - HCVR				
Sa_{O_2} %	100		100	
P_{ACO_2} kPa	7.2		7.2	
t_I s	1.25±0.08†	1.78±0.16*	1.64±0.13	2.02±0.16*
t_I/t_{tot}	0.45±0.01	0.55±0.02*	0.45±0.01	0.54±0.01*

Values are mean±SEM. HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response. For abbreviations and detail see text. *:$p<0.05$ for comparisons between unloaded and loaded states within a group. †: $p<0.05$ for comparisons between the corresponding conditions of the two groups of subjects.

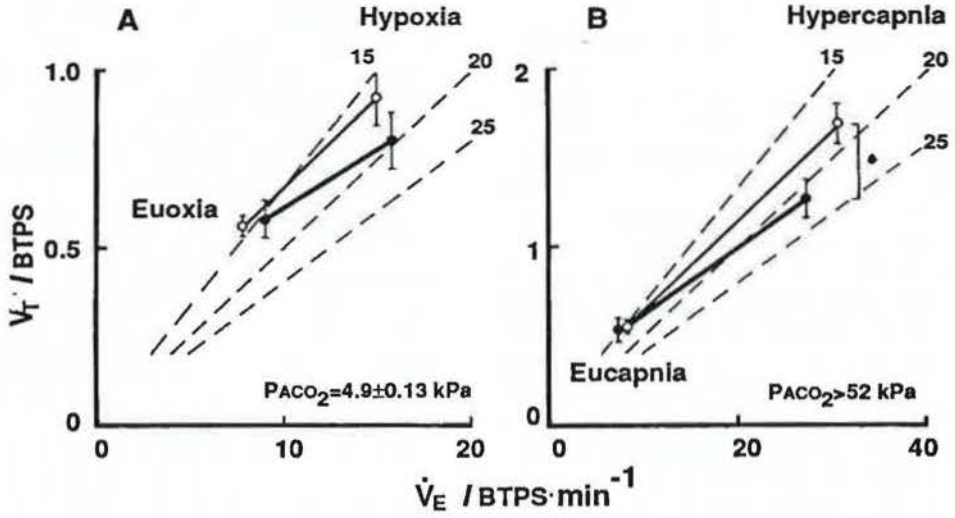

Fig. 4. – V_T-$\dot{V}_E$ relationship during progressive hypoxia (Panel A) and hypercapnia (Panel B) in normal and quadriplegic subjects. Dashed lines are respiratory rate isopleths. Mean (SE) V_T is given for each level of O_2 and CO_2. ○ :normal; ● :quadriplegic.

In the quadriplegics the increased $\dot{V}_E$ in response to hypercapnia was achieved by a significantly smaller increase in V_T and a greater increase in f. The increase in f fell short of matching the level of ventilation achieved by the normal subjects. Ventilatory loading did not influence the changes in the V_T-$\dot{V}_E$ relationship.

Respiratory timing (table 5(II)) also exhibited changes qualitatively similar to those during HVR. The t_I and t_I/t_{tot} were prolonged significantly by hypercapnia during loading in both normal and quadriplegic subjects. Whereas no differences were noted in t_I and t_I/t_{tot} between the two groups of subjects in the loaded state, t_I was significantly shorter in the unloaded quadriplegics.

Discussion

This study demonstrates that respiratory muscle paralysis by low cervical spinal cord transection left the ventilatory chemosensory responses unimpaired both before and during ventilatory loading. The ability of the quadriplegic patients to compensate for the load, assessed by mouth occlusion pressure, was however curtailed by hypoxia.

The finding of the unchanged ventilatory responses was rather unexpected in view of the massive respiratory pump muscle paralysis. This pump must clearly be less efficient at a time when demands on it are great due to increased chemical drive and mechani-cal load. This finding partly differs from the only other study to date

[10], which found quadriplegics to have a reduced ventilatory response to hypercapnia in the unloaded but not in the loaded state. The cause of the difference might lie in the lower slope of the CO_2 response achieved by both normal and quadriplegic subjects in our study, which indicates different characteristics of the kinetic CO_2 changes during rebreathing, yielding moderate intensity of the chemical stimulus. Possibly, had the patients been stressed to the limits of respiratory control they would have shown reduced responses.

That the ventilatory response to chemical stimuli is no less in quadriplegics is further unexpected, given the possible respiration facilitating effects of chemoreceptors on the descending drive to respiratory muscle motoneurons. Hypoxic stimulation of carotid body (CB) afferents increases bioelectrical activity of both phrenic nerve and external intercostal muscles [5]. Investigations on the effect of hypoxia on internal intercostal muscle activity (IIMA) yielded conflicting results. MATSUMOTO [4] has reported that stimulation of CB afferents by NaCN excited the IIMA, the effect disappearing after sinus nerve section. Others observed a reduction of IIMA during hypoxia [5, 16]. FREGOSI *et al.* [3] reported an acute excitatory effect of hypoxia on abdominal expiratory nerve activity (AENA), although the opposite effect was suggested for long-lasting CB stimulation. LEDLIE *et al.* [17] have implicated CB afferents in hypoxia-induced stimulation of AENA. Likewise, the effect of hypercapnia on respiratory muscle activity is unsettled. Most investigators report a stimulatory effect of hypercapnia on IIMA and AENA [3, 17, 18], but a lack of effect [19] has also been reported. Assuming that the predominant effect of chemical stimuli would be one of augmentation, an increase in expiratory flow and facilitation of inspiration might be expected. The corollary is that muscle paralysis due to a spinal cord lesion might diminish ventilatory responses to hypoxia and hypercapnia, since the descending drive could not breach the lesion. We found no evidence to this end in the present study, which calls into question any major role of the descending drive in shaping the ventilatory response to chemical stimuli.

There is no perfect noninvasive method of assessing inspiratory neural output in quadriplegics. The method of occlusion pressure in this study was selected to avoid interferences of the mechanical properties of the respiratory system, uncontrolled by respiratory centres, and to enhance comparability with normal subjects, whose diaphragmatic EMG, if recorded in lieu of $P_{0.2}$, might be distorted by signals from the chest and abdominal wall muscles. The contribution of these muscles increases more than that of the diaphragm with increasing respiratory drive [20]. The EMG is also hampered by the great and unpredictable difference between normal and quadriplegic subjects of the ever-changing distance from the surface electrodes to the diaphragm as lung volume changes. Although the reliability of the $P_{0.2}$ measurement in quadriplegics has by no means been established, the close relationship between $P_{0.2}$ and EMG suggests that $P_{0.2}$ is an adequate method for assessing neural drive. Physical principles of the occlusion pressure method clearly indicate that it reflects instantly the driving power of inspiratory muscles during zero airflow, *i.e.* inspiratory neural drive, and is independent of respiratory system resistance and compliance [13]. Possible paradoxical inward motion of the chest, or any other motion for that matter, is thus unlikely to influence the level of occlusion pressure, the more so that any detectable isotonic muscle movement occurs long after the time of occlusion pressure measurement. Some driving pressure may however be used for distortion of the chest early in inspiration and lost in terms of producing effective tidal volume. Quadriplegics are apparently able to offset this loss by increasing respiratory rate.

Disruption of the descending spinal pathways did not affect the augmentation of neural drive, as assessed by the occlusion pressure slope on oxygen saturation, $\Delta P_{0.2}/\Delta Sao_2$, either during hypoxia or hypercapnia in the loaded state. It interfered, however, with the compensatory rise of the baseline $P_{0.2}$ level during loaded response to hypoxia (fig. 3), which meant that quadriplegics had a higher ventilation at a given $P_{0.2}$ than normal subjects. The same trend was also apparent in eupnoeic breathing. Mechanisms of the high $\dot{V}_E/P_{0.2}$ ratio in quadriplegics are not easy to explain. Several speculative explanations could be offered. Higher than hypoxic or euoxic functional state of the central nervous system may be required for full operation of the neural load-compensating mechanisms. Load compensation is abolished in brain hypoxia [21] or under anaesthesia [22]. Bronchorelaxing effects of the adrenergic system and possibly altered action of local neuromodulators might ease airways impedance to flow and increase the peripheral effectiveness of a given central inspiratory output. Adrenergic hyperreflexia is noted in quadriplegia [23], and its expression in the present study could be a relatively higher heart rate (table 3). The diaphragm seems to be at a mechanical advantage in quadriplegia stemming from a longer resting muscle length due to a small lung volume, so that for a given neural drive more force is developed. Finally, the increased V_D/V_T in quadriplegics may signify maldistribution of ventilation-to-perfusion in the lung. To compensate for increased deadspace, minute ventilation must be higher. This is achieved by increased frequency rather than tidal component.

There are a few hypothetical reasons which call for prudence in interpreting the occlusion pressure in quadriplegics. To aid the respiratory pump, some accessory muscles may be activated that do not normally contribute to $P_{0.2}$ generation. The $P_{0.2}$ may not reflect the actual neural drive, if the pattern of respiratory muscle activation or pressure generation is different in quadriplegics. Quadriplegics might exert a smaller fraction of total muscular pressure during the first 0.2 s of inspiration than normal subjects do. Since any of these mechanisms would be common to both unloaded and loaded states, they are unlikely to have been

responsible for the disappearance of the compensatory $P_{0.2}$ increase in the loaded quadriplegics during hypoxia in this study.

We did not correct for the abdominal expiratory muscle activity in normal subjects, another potentially confounding factor. Activation of these muscles, shrinking the end-expiratory abdominal volume, and subsequent relaxation early in inspiration might add to the occlusion pressure level an extraneuronal fraction depending on recoil of the respiratory system, leading to overestimation of $P_{0.2}$. This mechanism is however operative chiefly in the sitting as opposed to the supine position [24].

Ventilatory loading alters the pattern of the respiratory cycle. A prolongation of t_I is typically observed during resistive loading in conscious healthy humans [8, 10]. AXEN [7] has studied episodes of 10 consecutive inspirations against graded elastic and resistive loads in quadriplegics and reported a progressively longer t_I on repeated exposures to resistive loads. t_I prolongation was however absent in another study of AXEN and HAAS [8]. KELLING *et al.* [10] in a study methodologically similar to ours reported the inability of quadriplegics to appreciably extend their t_I during loaded ventilatory responses to hypercapnia, suggesting that thoracic afferents could modulate the compensatory increase in inspiratory duration. Our results are different, as we showed equally prolonged t_I coupled with increased t_I/t_{tot} in response to loading in both normal and quadriplegic subjects during HVR and HCVR. A likely explanation of the discrepancy relies on labile conscious mechanisms perceiving the added load, which are known to modify respiratory timing [25]. That conscious mechanisms were more active in our quadriplegics than in those studied by KELLING *et al.* [10] might be inferred from the greater frequency response.

In summary, this study showed that quadriplegics had strikingly little changes in their pattern of breathing and ventilatory chemosensory responses, despite drastic impairments in pulmonary function caused by interruption of the spinal neural pathways passing from and to the chest and abdominal respiratory muscles. Their respiratory motor drive was able to meet the hypoxic or hypercapnic challenges ensuring a stable chemoreflex control and maintaining an adequate pulmonary ventilation.

We conclude that the hypoxic and hypercapnic chemoreflexes are operative in generating increased respiratory activity in the absence of the descending drive to the intercostal and abdominal muscles as a sequel to cervical spinal cord transection.

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Réponses ventilatoires aux stimuli chemo-sensitifs chez les patients quadriplégiques. M. Pokorski, T. Morikawa, S. Takaishi, A. Masuda, B. Ahn, Y. Honda.

RÉSUMÉ: Nous avons testé l'hypothèse selon laquelle l'interruption du trafic moteur allant de la moelle épinière aux moto-neurones des muscles resporatoires supprime la réponse ventilatoire à un stimulus chimique accru. Nous avons comparé, par la technique de rebreathing, la réponse hypoxique (HVR) et hypercapnique (HCVR) avant et pendant une surcharge résistive au flux cours de l'inspiration cheez 17 patients quadriplégiques avec section médullaire cervicale basse, et chez 17 sujets normaux. La réponse ventilatoire a été évaluée à partir des courbes de ventilation minute (V_E) et de pression d'occlusion buccale ($P_{0.2}$) sur la saturation artérielle en oxygéne (Sao_2), ou encore sur la Pco_2 en fin d'expiration calme ($PACO_2$), ainsi qu'à partir des valeurs absolues de V_E à une saturation de 80% ou à une $PACO_2$ de 55 mmHg. Nours n'avons pas trouvé de différence dans HVR ou HCVR sans résistance entre les patients normaux et quadriplégiques. En cas de HVR avec résistance, la courbe $\Delta V_E/\Delta Sao_2$ tend à dimineur de façon similaire dans les deux groupes de sujets. La courbe $\Delta P_{0.2}/\Delta Sao_2$ est décalée vers le haut chez les sujets normaux, ce qui entraîne une $P_{0.2}$ significativement plus élevée à une Sao_2 determinée. Par contre, cette augmentation dans le niveau de $P_{0.2}$ au cours d'une HVR avec résistance, etait absente chez les quadriplégiques. HCVR avec résistance entraîne des résultats qualitativement similaires dans les deux groupes de sujets; $\dot{V}_E/PACO_2$ diminue, et ΔPaco2 augmente de façon significative. Ces résultats montrent que les réponses ventilatoires à un stimulus chimique ne sont pas supprimées chez les quadriplégiques, quoiqu'elles démontrent un trouble dans la compensation en cas de surcharge, comme cela apparaît par la pression d'occlusion en cas d'hypoxie. Nous concluons que le stimulus descendant aux moto-neurones des muscles respiratoires est sans relation avec le fonctionnement des réflexes chemo-sensibles.
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