Dissociation between respiratory effort and dyspnoea in a subset of patients with stroke

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ABSTRACT
Dyspnoea is not a prominent complaint of resting patients with recent hemispheric stroke (RHS). We hypothesized that, in patients with RHS presenting abnormalities in respiratory mechanics, increased respiratory motor output could translate into an increased perception of dyspnoea. We studied eight wheelchair-bound patients with RHS (mean age 62.4 years), previously evaluated by computerized tomography scanning, and a control group of normal subjects, matched for age and sex. We assessed routine spirometry, inspiratory and expiratory muscle pressures, breathing pattern and dyspnoea using a modified Borg scale. In six patients, we also measured oesophageal pressure during the maximal sniff manoeuvre and tidal inspiratory swing, and mechanical characteristics of the lung in terms of dynamic elastance during both quiet breathing and a hypercapnic/hyperoxic rebreathing test. During room air breathing, ventilation and tidal volume were similar in patients and controls, while tidal inspiratory swings of oesophageal pressure, an index of inspiratory motor output, were greater in patients \( P_{\text{fl}} < 0.005 \). Patients also exhibited a greater dynamic elastance \( P = 0.013 \). During rebreathing, dynamic elastance remained higher \( P = 0.01 \) and a greater than normal inspiratory motor output was found \( P = 0.03 \). Responses of ventilation and tidal volume to carbon dioxide tension were normal, and in all patients but one a lower Borg score for the unit change in carbon dioxide tension and ventilation was found. In conclusion, a higher than normal inspiratory motor output was unexpectedly associated with a blunted perception of dyspnoea in this subset of RHS patients. This is likely to be due to the modulation of the integration process of respiratory sensation.

INTRODUCTION
A recent hypothesis emphasizes the role of central mismatching between respiratory muscle effort and instantaneous feedback from sensory receptors throughout the respiratory system in the perception of dyspnoea. This hypothesis has its mechanical basis in the disparity between respiratory motor output and the mechanical response of the system [1–3].

The perception of dyspnoea occurs in many situations, and varies according to the clinical setting [3]. In patients with recent hemispheric stroke (RHS), dyspnoea is not a prominent complaint; a likely reason is that, being unable to exercise enough, these patients cannot increase their ventilation to the point where dyspnoea would occur. However, high levels of elastic and non-elastic respiratory work along with high inspiratory muscle output have been reported during \( \text{CO}_2 \) stimulation 11 days after the cerebrovascular episode [4]. These data suggest that a greater than normal inspiratory motor output (IMO) could increase the perception of dyspnoea during stimulated breathing associated with increased mechanical

Key words: dyspnoea, inspiratory motor output, pulmonary mechanics, respiratory muscles, stroke.
Abbreviations: CT, computerized tomography; El\text{dyn}, dynamic elastance; IMO, inspiratory motor output; \( P_{\text{co}} \), carbon dioxide tension; \( P_{\text{oes}} \), oesophageal pressure; \( P_{\text{oes-sn}} \), oesophageal pressure during maximal sniff manoeuvre; \( P_{\text{oes-sw}} \), tidal inspiratory swing of oesophageal pressure; RHS, recent hemispheric stroke; \( V_{\text{E}} \), minute ventilation; \( V_T \), tidal volume.
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loading of the respiratory system in patients with RHS.

We hypothesized that, in patients with RHS presenting anomalies in respiratory mechanics, an increased IMO could translate into an increased perception of dyspnoea. We therefore studied eight RHS patients at a time when diagnosis and treatment of the respiratory complications that may take place in severely affected patients rely on the perception of the symptoms, namely dyspnoea.

**MATERIALS AND METHODS**

**Subjects**

We studied eight patients admitted to a rehabilitation programme after an episode of RHS. The group comprised five men and three women with a mean age of 62.5 ± 15.8 years (range 29–77 years), and were studied, on average, 26.5 days (range 14–55 days) after the onset of symptoms. CT (computerized tomography) scanning showed an ischaemic or a haemorrhagic subcortical lesion in the area of the middle cerebral artery (right or left) in six and two patients respectively. The lesions affected the basal ganglia and the substantia alba. CT scanning does not define exactly the extent of the lesions, but generally the clinical effects are proportional to the magnitude of the damage. For this reason the SSS clinical score [5] was chosen to recruit patients classified as moderately affected. The major neurological fault was a right (two cases) or left (six cases) hemiplegia; five patients presented mild distal hypoesthesia of the lower limbs to the knee, and three showed no sensory faults. All the patients were fully vigilant, conscious and able to understand and carry out verbal orders. Neurocognitive and logopaedic evaluation showed a mild hemineglect in three left-hemiplegic patients and amnestic aphasia in two right-hemiplegic patients. Two patients were current mild smokers (< 5 pack years). No patient was overweight (body mass index < 28 kg/m²). None had scoliosis or any other abnormalities of the vertebral column.

Six normal subjects matched for age (range 39–78 years; mean age 55 years) and sex (five men) were studied as a control group. The study was approved by the local ethics committee, and subjects gave their informed consent.

**Functional evaluation**

Routine spirometry, performed with the patient seated in a comfortable armchair, was measured as previously described [6–8]. Functional residual capacity was measured by the helium dilution technique. The normal values for lung volumes were those of the European Community for Coal and Steel [9]. Arterial blood gas tensions were measured with an IL-1650 instrument (Instrumentation Laboratory, Milan, Italy).

Maximum static inspiratory and expiratory pressures at functional residual capacity, measured against an obstructed mouthpiece with a small leak to minimize oral pressure artifacts, were recorded using a differential pressure transducer (Valdyine, Northridge, CA, U.S.A.). The subjects were seated comfortably, wearing a nose-clip, and performed maximal inspiratory efforts, maintaining maximal pressures for at least 1 s. The manoeuvres were repeated until three measurements with < 5% variability were recorded, and the highest value obtained was used for analysis.

For mechanical studies, an oesophageal latex balloon (length 10 cm; air volume 0.5 ml) was introduced via the nose. A marker was placed on the polyethylene tubing 40 cm from the balloon tip [10]. The catheter was connected to a differential pressure transducer (Validyne). Total lung resistance and lung dynamic elastance (El dyn) were measured during resting breathing. Total lung resistance was obtained using the isovolume method [11]. El dyn was determined by dividing the difference in pleural pressure between points of zero flow by tidal volume (V T).

The highest (most negative in sign) pleural pressure, assessed as oesophageal pressure (P en), was evaluated at functional residual capacity during a maximal sniff manoeuvre (P en-sn) [12], which was repeated until three measurements with < 5% variability were recorded. The highest value of P en-sn was used for subsequent analysis.

After baseline routine testing, the ventilatory pattern and P en were evaluated with subjects sitting comfortably in an armchair during room-air breathing. In the apparatus we used, the inspiratory line was separated from the expiratory line by a one-way valve (Hans-Rudolph) connected to a Fleisch type 3 pneumotachograph. The flow signal was integrated into volume. From the spirogram we derived the total time of the respiratory cycle, V T, respiratory frequency (1/total time × 60) and minute ventilation (V E = V T × respiratory frequency). Expired CO₂ was sampled continuously at the mouth by an IR CO₂ meter (Normocap 200; Datex, Helsinki, Finland) in order to measure CO₂ tension (P CO₂). The values for dead space and the resistance of the system up to a flow of 4 litres were 201 ml and 0.94 cmH₂O·litre⁻¹·s⁻¹ respectively.

The output of the CO₂ meter, flow signal, integrated flow signal and pressure were recorded on a PC hard disk using an eight-channel A/D board at a 50 Hz sampling rate. After a 10-min adaptation period, evaluation began. Signals were recorded over a 10-min period. Average values for each subject are presented.

**Hypercapnic/hypoxic rebreathing tests**

A hypercapnic/hypoxic rebreathing test was performed using the procedure recommended by Read [13].
Table 1  Clinical characteristics and functional data of the patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Clinical data</th>
<th>CT scan findings</th>
<th>$\text{PaO}_2$ (mmHg)</th>
<th>$\text{PaCO}_2$ (mmHg)</th>
<th>TLC (v/l)</th>
<th>VC (v/l)</th>
<th>FRC (v/l)</th>
<th>FEV$_1$/VC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>Upper limb plegia, lower limb paresis,</td>
<td>Right subcortical and basal ganglia ischaemia</td>
<td>78*</td>
<td>25.3</td>
<td>124</td>
<td>114</td>
<td>113</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>69/M</td>
<td>Left hemiparesis</td>
<td>Right talamo-capsular ischaemia</td>
<td>84</td>
<td>35.4</td>
<td>97</td>
<td>103</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>77/F</td>
<td>Left hemiparesis</td>
<td>Right basal ganglia ischaemia</td>
<td>80</td>
<td>36.3</td>
<td>80</td>
<td>90</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>54/M</td>
<td>Left hemiplegia hemineglect</td>
<td>Right talamo-capsular ischaemia</td>
<td>82</td>
<td>39.4</td>
<td>106</td>
<td>82</td>
<td>126</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>69/M</td>
<td>Left hemiparesis, hemineglect</td>
<td>Right temporo-parietal haemorrhagia</td>
<td>90</td>
<td>36</td>
<td>92</td>
<td>85</td>
<td>102</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>29/M</td>
<td>Upper limb plegia, lower limb paresis</td>
<td>Right talamo-capsular ischaemia</td>
<td>77*</td>
<td>34.1</td>
<td>116</td>
<td>112</td>
<td>122</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>72/F</td>
<td>Right hemiparesis</td>
<td>Left basal ganglia ischaemia</td>
<td>94</td>
<td>40.6</td>
<td>102</td>
<td>83</td>
<td>125</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>73/F</td>
<td>Upper limb plegia, lower limb paresis,</td>
<td>Left talamo-capsular haemorrhagia</td>
<td>72*</td>
<td>46.2</td>
<td>69*</td>
<td>55*</td>
<td>77*</td>
<td>69*</td>
</tr>
</tbody>
</table>

Mean: 83.1 36.6 99.5 89.5 106 83.1
S.D.: 7.3 5.9 16.9 19.5 18.3 9.4

Rebreathing was terminated when the $P_{\text{CO}_2}$ reached 72–74 mmHg. Changes in $P_{\text{CO}_2}$, volume and time components of breathing pattern and in the tidal inspiratory swing of oesophageal pressure ($P_{es-sw}$) were recorded continuously. Details of the procedures have been described elsewhere [6–8].

Assessment of dyspnoea

Under control conditions and every 30 s during rebreathing tests, subjects were asked to quantify the sensation of dyspnoea, which was described to the subjects as a non-specific discomfort associated with the act of breathing [14]. Patients quantified dyspnoea by pointing to a score on a large Borg scale, from 0 (none) to 10 (maximal) [15]. Specifically, the subjects were asked to quantify the intensity of the symptoms by relating it to their common experience. The scale is a continuous vertical linear display, associated with ten verbal descriptors of the extent of the symptoms, corresponding to the 10-point Borg category scale. The subjects were instructed to indicate with a hand-controlled potentiometer how dyspnoeic they felt.

Protocol

All subjects were tested in the morning, and before the experiment were well acquainted with the laboratory and equipment. Six patients volunteered to swallow the oesophageal latex balloon. Arterial blood samples were obtained, and lung function and respiratory muscle strength tests were performed. Following these, changes in volume, flow and $P_{es}$ were recorded during quiet breathing and during hypercapnic/hyperoxic stimulation.

Data analysis

$P_{es-sw}$ was defined as the difference between pressure at end-expiration and that at end-inspiration, and was expressed both as an absolute value (cmH$_2$O) and as a percentage of $P_{es-sw} (%P_{es-sw})$ represents the force required for breathing relative to the maximal inspiratory force available, and is henceforth referred to as inspiratory muscle effort. Volume and time components of the respiratory cycle, total lung resistance and $E_{dyn}$ were averaged in each patient over 30 consecutive breaths.

Statistics

Values are means ± S.D. A non-parametric statistical procedure was used to test differences: the Wilcoxon test for paired samples, and the Mann–Whitney test for unpaired samples. Regression analysis was performed using Pearson’s correlation coefficient. The level of significance was set at $P < 0.05$. All statistical procedures were carried out using the Statgraphics Plus 3.1 statistical package (Manugistics, Rockville, MD, U.S.A.).

RESULTS

The respiratory function data of the patients are shown in Table 1. One patient (no. 8) showed a decrease in lung volume, with slight airway obstruction as assessed in terms of (forced expiratory volume in 1 s)/(vital capacity). Partial arterial $O_2$ pressure was mildly reduced in patient nos. 1, 6 and 8, and a low value for the partial arterial $CO_2$ pressure was found in all patients except three (nos. 4, 7 and 8). Maximal inspiratory pressure $(51.2 ± 27.2 \text{ cmH}_2\text{O})$, maximal expiratory pressure $(70.7 ± 44.5 \text{ cmH}_2\text{O})$ and $P_{es-sw}$ $(68 ± 18 \text{ cmH}_2\text{O})$ were
significantly lower than predicted [14] in all patients except two (nos. 1 and 6). $P_{es-sw}(\% P_{es-sn})$ (mean 11.4 ± 8.2%) was significantly related to maximal inspiratory pressure ($P = 0.02; r^2 = 0.87; y = a + b/x$), i.e. the weaker the inspiratory muscles, the greater the inspiratory output.

Compared with the controls, the patients exhibited a greater $E_{l,dyn}$ ($P = 0.013$), similar total lung resistance (patients, 3.7 ± 1.31 cmH$_2$O · litre$^{-1}$ · s$^{-1}$; controls, 2.25 ± 0.58 cmH$_2$O · litre$^{-1}$ · s$^{-1}$) (Figure 1, upper panels), and an increase in $P_{es-sw}(\% P_{es-sn})$ ($P = 0.005$), indicating a greater inspiratory effort (Figure 1, lower right panel).

During both room-air breathing and the hypercapnic/hyperoxic rebreathing test, $\Delta V_u/\Delta P_{CO_2}$ and $\Delta V_T/\Delta P_{CO_2}$ were similar in patients and controls (Table 2). However, patients had greater values of $\Delta P_{es-sw}(\% P_{es-sw})/\Delta P_{CO_2}$ and $\Delta E_{l,dyn}/\Delta P_{CO_2}$ (Table 2), and
Table 2 Ventilatory response, inspiratory effort and $E_l$ dyn during hypercapnic/hyperoxic rebreathing

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$\Delta V_j/\Delta P_{CO_2}$ (litres min$^{-1}$ mmHg$^{-1}$)</th>
<th>$\Delta V_j/\Delta P_{CO_2}$ (litres/mmHg)</th>
<th>$\Delta P_{esw}/\Delta P_{CO_2}$ (%P_{esw}/mmHg)</th>
<th>$\Delta E_l/\Delta P_{CO_2}$ (cmH$_2$O litres$^{-1}$ mmHg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.03</td>
<td>0.06</td>
<td>1.52</td>
<td>4.75</td>
</tr>
<tr>
<td>2</td>
<td>1.63</td>
<td>0.06</td>
<td>0.72</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>1.09</td>
<td>0.03</td>
<td>1.28</td>
<td>0.50</td>
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<tr>
<td>4</td>
<td>2.50</td>
<td>0.07</td>
<td>2.15</td>
<td>3.00</td>
</tr>
<tr>
<td>5</td>
<td>3.20</td>
<td>0.08</td>
<td>1.04</td>
<td>0.22</td>
</tr>
<tr>
<td>6</td>
<td>2.07</td>
<td>0.04</td>
<td>4.16</td>
<td>2.49</td>
</tr>
<tr>
<td>7</td>
<td>3.12</td>
<td>0.05</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>2.70</td>
<td>0.03</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean</td>
<td>2.42</td>
<td>0.05</td>
<td>1.81</td>
<td>1.99</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.76</td>
<td>0.02</td>
<td>1.24</td>
<td>1.74</td>
</tr>
<tr>
<td>Controls</td>
<td>Mean</td>
<td>1.94</td>
<td>0.06</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>0.12</td>
<td>0.02</td>
<td>0.32</td>
</tr>
<tr>
<td>$P$</td>
<td>$&gt;0.05$</td>
<td>$&gt;0.05$</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DISCUSSION

In the present study we report on decreased respiratory muscle strength in patients with RHS. As a result, these patients exhibited a greater than normal IMO associated with a normal $V_j$ during both quiet breathing and chemical stimulation of ventilation. The greater IMO apparently depended on the increased mechanical characteristics of the lung ($E_l$ dyn). Despite IMO, a lower Borg score per unit change in both $P_{CO_2}$ and $V_j$ was found. As an index of IMO we used the oesophageal (pleural) pressure swing with correction for oesophageal sniff. We chose pleural pressure rather than transdiaphragmatic pressure because the former is the sum of all inspiratory muscle force production, while the latter is a measure of diaphragm strength.

A concern with the present study is the small number of patients recruited and the heterogeneous lesions present in the patients. However, we need to underline the extreme difficulty we found in selecting patients with all of the following characteristics: (i) presence of hemiplegia without impairment of comprehension; (ii)
ability to maintain the sitting position and to use the mouthpiece correctly; (iii) absence of respiratory disease; (iv) availability to undergo invasive assessment of different respiratory muscle functions (activation and output) by swallowing oesophageal leads during different experimental conditions; (v) ability to provide reproducible manoeuvres and pressure responses. The need to include all these requirements resulted in the selection of patients with heterogeneous lesions. Results in haemorrhagic patients did not differ from those in the other ischaemic patients. This is in line with previous studies showing no correlation between respiratory pattern and site of lesion, clinical assessment or presence of blood in the cerebrospinal fluid [16,17].

Hemispheric stroke may affect respiratory system function [4,17–22] in terms of abnormalities in breathing pattern and arterial blood gases [17,19], lung mechanics and respiratory muscles [4,20–22]. Rib cage abnormalities associated with muscle weakness [23] or reduced chest wall movement [21] were likely causes of the mechanical abnormalities we found in the patients. Considering also the possibility of subclinical pulmonary congestion [4], we reviewed the patients’ chest X-rays. Evidence of a mild degree of pulmonary congestion, which was found in some patients, could easily have been overlooked in the X-rays of the remaining patients.

Some of the present results are in agreement with the data obtained some years ago by McMahon and Heyman [4]. In that study, patients with hemispheric stroke exhibited a normal ventilatory response to hypercapnia and, because of the greater than normal mechanical load, also exhibited a greater than normal ‘inspiratory power output’ in order to maintain normal ventilation. Current hypotheses on the origin of dyspnoea emphasize the importance of a disparity between respiratory motor output and the mechanical response of the system [1–3].

On the basis of this theory, validated in patients with chronic obstructive pulmonary disease [2] or some neuromuscular diseases [24], a greater perception of dyspnoea was expected in the RHS patients of the present study than in the controls. However, the presence of neuroventilatory discoupling, i.e. normal ventilation associated with an increased IMO [4], was not associated with an increase in the perception of dyspnoea. Thus the present results do not support the hypothesis that neuromuscular uncoupling increases dyspnoea in hemiplegic patients.

In fact, a lower Borg score per unit change in both $P_{CO_2}$ and $P_{O_2}$ was found in all patients but one, compared with controls. Although the reasons for this are likely to be complex, the following must be considered. Dyspnoea is a general term which both normal subjects and patients may describe as a sense of effort [3,25,26]. Although the mechanism of this sensation has not been completely clarified, it is considered to be determined chiefly by outgoing motor command signals with various modulations from chemoreceptors and mechanoreceptors [3,25,27]. The sensation is finally perceived after the signals in the higher brain have been processed. The sense of muscle effort refers to the conscious awareness of the voluntary activation of skeletal muscles [1,3,25]. A corollary discharge sent from the motor cortex to the sensory cortex at the same time as the outgoing motor command is sent to the contracting muscles [1] is involved in the perception of muscle activation as effort. In this regard, our data clearly show that an increased respiratory elastic load was translated into an increased IMO. However, if the respiratory motor output does not transmit the corollary discharge to the sensory centre, an unchanged perception of dyspnoea may result. Might this be due to functional abnormalities of the sensory cortex? In this regard, Pfeiffer et al. [28] performed a functional imaging study by PET (positron-emission tomography) to assess brain activation associated with an important component of dyspnoea respiratory discomfort during loaded breathing in healthy volunteers. They found that highly loaded breathing was associated with neural activation of a distinct brain region, and identified areas where regional blood flow was related to the mean amplitude of mouth pressure swings, and an area where neural activation was specifically associated with perceived intensity of respiratory discomfort that was not related to mouth pressure swings. Pfeiffer et al. [28] speculated that the main activation areas are part of a neural network involved in the process of two parallel integrations: the genesis and perception of respiratory discomfort, and the modulation of perceived intensity, presumably including emotional processing of this sensory experience. In turn, the hypothesis that damage to the sensory cortex, attenuating the effect of the corollary discharge, could influence a patient’s ability to perceive dyspnoea, cannot be excluded.

In conclusion, contrary to our initial hypothesis, the perception of breathlessness in hemiplegic patients is likely to be blunted because of an abnormality in the mechanisms of the process of integration of the afferent sensation.

REFERENCES


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