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Acute ischaemic hemispheric stroke is associated with impairment of reflex in addition to voluntary cough

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ABSTRACT: Cough function is impaired after stroke; this may be important for protection against chest infection. Reflex cough (RC) intensity indices have not been described after stroke. RC, voluntary cough (VC) and respiratory muscle strength were studied in patients within 2 weeks of hemispheric infarct. The null hypotheses were that patients with cortical hemisphere stroke would show the same results as healthy controls on: 1) objective indices of RC and VC intensity; and 2) respiratory muscle strength tests.

Peak cough flow rate (PCFR) and gastric pressure (P_{ga}) were measured during maximum VC and RC. Participants also underwent volitional and nonvolitional respiratory muscle testing. Nonvolitional expiratory muscle strength was assessed by measuring P_{ga} increase after magnetic stimulation over the T_{10} nerve roots (twitch T_{10} P_{ga}). Stroke severity was scored using the National Institutes of Health Stroke Scale (NIHSS; maximum=31).

18 patients (mean±SD age 62±15 yrs and NIHSS score 14±8) and 20 controls (56±16 yrs) participated. VC intensity was impaired in patients (PCFR 287±171 *versus* 497±122 L·min^{-1}) as was VC P_{ga} (98.5±61.6 *versus* 208.5±61.3 cmH_2O; $p<0.001$ for both). RC PCFR was reduced in patients (204±111 *versus* 379±110 L·min^{-1}; $p<0.001$), but RC P_{ga} was not significantly different from that of controls (179.0±78.0 *versus* 208.0±77.4 cmH_2O; $p=0.266$). Patients exhibited impaired volitional respiratory muscle tests, but twitch T_{10} P_{ga} was normal.

VC and RC are both impaired in hemispheric stroke patients, despite preserved expiratory muscle strength. Cough coordination is probably cortically modulated and affected by hemispheric stroke.

KEYWORDS: Abdominal muscles, cerebral infarction, cough, respiratory muscles, stroke

Stroke accounts for >5 million deaths annually worldwide [1]. Most stroke deaths are caused by complications, of which chest infections are the most important. One large study showed that 30% of acute stroke patients diagnosed with pneumonia had died before hospital discharge [2]. Aspiration is common after stroke, and is associated with an 11-fold increase in the risk of chest infections [3].

Cough is important for clearing the lungs of aspirated material. This is demonstrated by studies showing a higher incidence of aspiration and chest infections in stroke patients with a weak voluntary cough (VC) [4, 5], and a significant association between absent cough reflex in acute stroke patients and subsequent development of pneumonia [6]. A strong cough, whether VC or reflex cough (RC), requires powerful coordinated contraction of expiratory (abdominal) muscles, along with adequate inspiration prior to cough, low upper airways resistance, adequate duration of glottis closure, fast and complete glottis opening, and the ability to keep small airways patent during sudden rises in intrathoracic pressure [7]. That some of these abilities are impaired after stroke is suggested by studies of stroke patients showing asymmetry of ventilation, reduced movement of the diaphragm and chest on the hemiparetic side, poor performance on volitional respiratory muscle tests, and reduced VC flow rates and sound [8–10]. As might be expected, more recent studies suggest cortical involvement in cough production. Cortical activation during VC has been demonstrated in healthy volunteers in functional magnetic

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resonance imaging studies [11, 12]. Using transcranial magnetic stimulation, increased latency and decreased amplitude of the motor-evoked potentials from the abdominal (expiratory) muscles, and reduction of the evoked rise in gastric pressure (P_{ga}), have recently been shown in acute stroke patients compared with controls, suggesting impaired cortical control of the abdominal muscles after stroke [13]. However, RC may be more important than VC in ensuring adequate airway protection and clearance after acute stroke [6, 14]. RC is thought to originate primarily in the brainstem, but previous studies have noted cortical stroke patients with absence of RC in response to food swallowing [6] or an inhaled noxious substance [15]. However, these studies did not describe intensity measures (flow, pressure or sound) for any RC produced. Therefore, we considered further evaluation of RC in hemispheric stroke to be worthwhile. The null hypothesis was that patients with cortical hemisphere stroke would show the same results as a group of age-matched nonstroke controls on objective indices of both RC and VC intensity. As a secondary hypothesis, it was sought to confirm the prior observation [13] that stroke patients showed no evidence of abdominal muscle weakness, as judged by peripheral nerve stimulation, but did when assessed by voluntary tests of abdominal muscle strength. It was anticipated that both of the null hypotheses would be refuted, as previous studies suggested that an intact cerebral cortex is required for effective VC and RC. The primary outcome measure of cough intensity was cough flow rate for both VC and RC.

MATERIALS AND METHODS

Study subjects

45 consecutive patients admitted to the stroke unit of King's College Hospital (London, UK) within 2 weeks of a first-ever middle cerebral artery territory ischaemic stroke were screened. Six patients were excluded, as they did not wish to take part. Six patients with lacunar infarcts were excluded and 15 were unsuitable due to diabetes, excess alcohol consumption, respiratory or neurological disease other than stroke, or inability to follow commands. 18 adults (seven females) were studied. 20 healthy controls (five females) were recruited from a volunteer database and studied. The mean age and the proportion of female subjects were not significantly different between groups. Institutional ethical approval was obtained (LREC 02-120), and the subjects gave written informed consent.

Baseline assessments

Smoking history, alcohol and angiotensin-converting enzyme (ACE) inhibitor use, height and weight were documented for all subjects. For patients, stroke diagnosis and location were confirmed by brain computed tomography. Stroke severity on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. NIHSS score is a clinical stroke assessment tool for the evaluation of neurological status in acute stroke patients. The maximum score is 31, reflecting the most severe impairment [16]. Patients had a bedside swallowing assessment within 24 h of admission, using radio-opaque contrast to detect aspiration [17]. A hand-held spirometer (Jaeger SpiroPro; Erich Jaeger, Hoechberg, Germany) was used to measure forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), which were expressed as percentage of that predicted for age, sex and height [18]. Oxygen saturations were measured with subjects at rest, and breathing room air (Ohmeda Biox 3740 Pulse Oximeter; BOC Healthcare, Manchester, UK). Radiologists' reports of chest radiography examinations (for patients only) were acquired from the hospital records.

Respiratory muscle strength measurements

Measurements were made under controlled laboratory conditions with subjects on a bed, with the back rest at 45°, but otherwise in accordance with the American Thoracic Society/European Respiratory Society statement [19]. This ensured that patients had the head end of the bed raised at an angle of >30°, recommended to prevent aspiration and enabling inclusion of subjects unable to sit upright. P_{ga} and oesophageal pressure (P_{oes}) were measured using balloon catheters (CooperSurgical, Trumbull, CT, USA) inserted nasally. The catheters and a pneumotachograph were attached to individual pressure transducers (MP45; Validyne, Northridge, CA, USA). The transducer signals were amplified (CD-280 amplifier; Validyne) and acquired at 2 kHz using an analogue-to-digital converter (Powerlab; ADinstruments, Chalgrove, UK) and a computer running Chart 5 software (ADinstruments). Transdiaphragmatic pressure (P_{di}) was obtained by online subtraction of P_{oes} from P_{ga}.

Respiratory muscle strength was assessed volitionally by measuring maximum static expiratory mouth pressure ($P_{E,max}$), maximum static inspiratory mouth pressure ($P_{I,max}$) and sniff pressures. The subjects made strong expiratory efforts from total lung capacity (for $P_{E,max}$) or inspiratory efforts from functional residual capacity (for $P_{I,max}$) against a closed shutter. The maximum (for $P_{E,max}$) or minimum (for $P_{I,max}$) mean pressure over 1 s was recorded. The maximum nasal, oesophageal (sniff P_{oes}) and transdiaphragmatic (sniff P_{di}) pressure changes achieved during a sniff from functional residual capacity were also measured. Volitional respiratory muscle tests were performed at least three times until consistency was achieved. Nonvolitional assessment of expiratory (abdominal) muscle strength was made using magnetic stimulation over the spine at the level of the 10th thoracic nerve roots (T_{10}) [19]. A magnetic stimulator (MagStim 200; Magstim Co., Whitland, UK) set to 100% output and a 90-mm diameter circular coil were used. Subjects rested for 20 min before stimulation to minimise twitch potentiation. A minimum of three stimulations were performed and the evoked rise in P_{ga} above baseline (twitch T_{10} P_{ga}) measured. The mean of three reproducible twitch responses was calculated.

VC and RC tests

Airflow rates before, during and after cough were measured with subjects wearing a face mask (Hans-Rudolf, Shawnee, KS, USA) connected to a pneumotachograph (Fleisch; Phipps and Bird, Richmond, VA, USA). Cough inspiratory and expiratory volumes were calculated online by integration of the flow signal (fig. 1). VC was assessed before RC in order to avoid any effect of tartaric acid on VC. Subjects were told to inhale maximally and produce the biggest VC possible until five consistent readings of maximum cough P_{ga} were achieved. RC was induced by nebulising escalating doses of 5, 10, 15 and 20% weight/volume L-tartaric acid solution. L-tartaric acid is thought to act on airway C-fibres to precipitate cough [14]. The

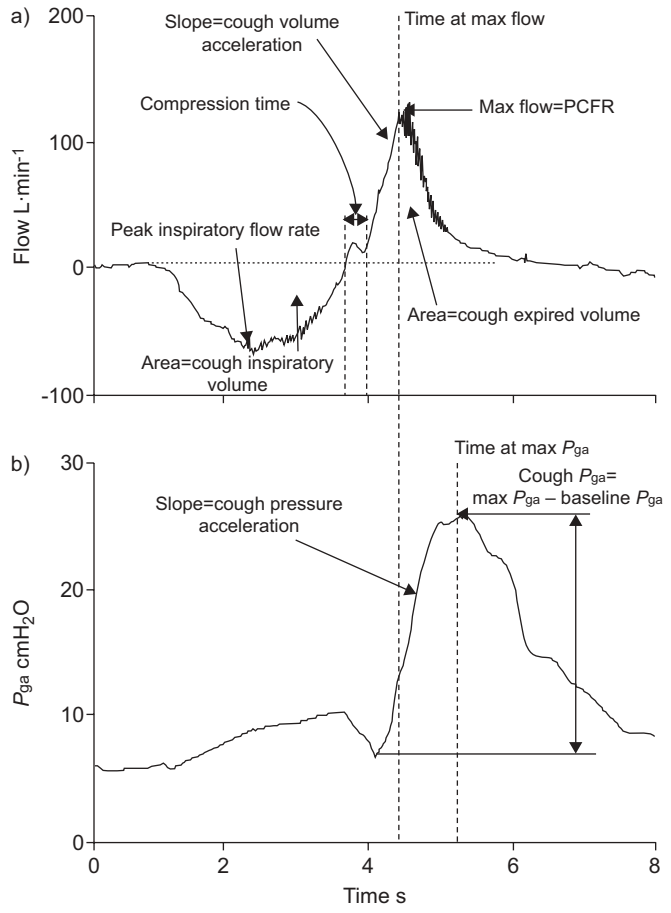

FIGURE 1. Voluntary cough trace for a stroke patient with a guide to the measurements made: a) flow and b) gastric pressure (P_{ga}). max: maximum; PCFR: peak cough flow rate.

L-tartaric acid was administered using a Porta-Neb® compressor and Sidestream® nebuliser (Philips Respironics, Chichester, UK) attached to the pneumotachograph and face-mask *via* a T-piece connector. The data sheet for the nebuliser states that 80% of the particles delivered are $\leqslant$0.5 μm in diameter. Solutions were administered for 1 min during normal breathing. Dose escalation was undertaken until five or more coughs were produced; if a subject failed to respond to 20% tartaric acid, no further solutions were administered. Corresponding cough spikes on the flow and P_{ga} traces were counted as coughs; all cough spikes within a cough bout were counted.

Peak cough flow rate (PCFR) was the maximum expiratory flow achieved during cough. PCFR was recorded, and expressed as a percentage of peak expiratory flow rate, to correct for a difference in height between the groups. Cough inspiratory volume and cough expiratory volume (fig. 1) were expressed as a percentage of the predicted FVC [18]. Cough P_{ga} was the maximum rise in P_{ga} during cough (fig. 1).

For each subject, the five coughs (VC and RC) with the biggest PCFRs were averaged and the following derived measures determined (fig. 1). 1) Compression time: duration of zero airflow from the time cough P_{ga} started to rise to the onset of expiratory flow; this is likely to represent the glottis closure period. 2) Cough pressure acceleration: the maximum cough P_{ga} divided by the time taken to reach maximum, starting from the onset of expiratory flow. 3) Cough volume acceleration: PCFR divided by the time taken to reach maximum flow.

Sample size and data analysis

The primary outcome measure was cough flow rate, for both VC and RC. In a previous study with similar methods, healthy subjects had a mean$\pm$SD VC PCFR of 351$\pm$112 L·min^{-1}, which was 200 L·min^{-1} greater than that of the stroke group [13]. Using these data and G*Power v3.0.8 software (created by F. Faul, University of Kiel, Kiel, Germany); it was calculated that 13 subjects in each group were required for an 85% chance of detecting a 150 L·min^{-1} difference in PCFR between groups, at a significance level of 5%. Statistical analyses were performed using Prism 5.00 (GraphPad, La Jolla, CA, USA), Confidence Interval Analysis 2.2.0 [20] and SPSS 16.0.1 (SPSS, Inc., Chicago, IL, USA). $p<0.05$ was considered significant. Data were tested for normality using the D'Agostino and Pearson omnibus method; unpaired t-tests or Mann–Whitney U-tests for two independent groups were used for comparisons [20].

Univariate and multiple linear regression was used to investigate possible causes of impaired VC and RC flow rates. Patients and controls were analysed together, with controls being assigned a stroke severity score (NIHSS score) of zero for the purposes of these analyses. Cough flow rate, for both VC and RC, was the dependent variable and stroke severity (NIHSS score), height and FEV1/FVC ratio were entered as independent predictors. All models included a constant.

RESULTS

Participants

The baseline characteristics of participants are given in table 1. Acute hemispheric infarction was present in the left hemisphere in nine patients and the right hemisphere in nine patients. Of the left infarcts, three were frontal, one was frontoparietal, one was temporofrontoparietal and four were capsulostriate. Of the right infarcts, three were frontal, one was frontoparietal, four were temporofrontoparietal and one was capsulostriate. Six out of 18 patients had been treated with thrombolysis.

Pulmonary function and respiratory muscle tests

Results are given in table 2. Patients showed significant impairments on spirometry and volitional respiratory muscle tests. There was no difference between the patient and control groups on the nonvolitional expiratory muscle strength test for twitch T_{10} P_{ga}. The patients' mean$\pm$SD twitch T_{10} P_{ga} of 26.4$\pm$6.6 cmH_2O was well above the published normal minimum value of 16 cmH_2O, indicating that the expiratory muscles themselves were not weak but that the stroke patients could not fully recruit them volitionally.

Patients' oxygen saturations were lower than those of controls and their respiratory frequencies were higher (table 2). Nurses measured patients' oxygen saturations hourly for the first 48 h after stroke and then every 4 h subsequently. No patient had an oxygen saturation recording of <92% at any time.

Reports of chest radiographs taken during the admission for stroke were available for 14 out of 18 patients. For 10 patients,

TABLE 1 Baseline characteristics

	Stroke	Control	Δ (95% CI)	p-value
Subjects	18	29		
Age yrs	62±15	56±16	6 (-3–17)	0.183
Sex				
Males	11	15		
Females	7	5		
Proportion male	0.61	0.75	-0.14 (-0.40–0.15)	0.489#
Height cm	166±7	176±9	-10 (-4– -14)	0.001
BMI kg·m^{-2}	24 (21–17)	24 (23–28)	-1 (-4–2)	0.538
Smoking pack-yrs	35 (14–53)	0 (0–5)	30 (10–45)	0.003
Time from stroke onset days	6±3			
NIHSS score	14±8			
Dysphagia				
Subjects	4			
Proportion	0.22			
Taking ACE inhibitor				
Subjects	9	0		
Proportion	0.50	0		

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. Δ: difference; BMI: body mass index; NIHSS: National Institutes of Health Stroke Scale; ACE: angiotensin-converting enzyme. #: Fisher's exact test.

the radiologist reported the lung fields and pleura to be clear. For two patients, chest radiographs were reported as showing signs of chronic obstructive pulmonary disease (COPD), although these patients had not been diagnosed with COPD previously. One radiograph showed interstitial pulmonary oedema, but, as the relevant patient was unable to perform spirometry or cough, this did not affect group results for these tests. One radiograph showed a small left pleural effusion.

Voluntary cough

VC was significantly impaired in patients (table 3; fig 2). Two patients were unable to produce any VC manoeuvres and so were excluded from the cough intensity analysis. The patients' mean cough P_{ga} of 98.5 cmH_2O was well below the cut-off value of 130 cmH_2O used to aid diagnosis of expiratory muscle weakness [21].

Reflex cough

Results for RC are given in table 4. Traces of RC for a control participant and a severely affected stroke patient are given in figure 3. The median concentration of L-tartaric acid solution required to produce five coughs was 10% for both patients and controls. One patient and two controls found L-tartaric acid inhalation intolerable and so the RC test was not performed. Three (17.6%) of the remaining 17 patients had no reflex cough response to 20% tartaric acid; all 18 normal subjects produced a cough response (0% nonresponders).

The subjects who did not cough were not included in the cough intensity analysis. The patients' mean RC P_{ga} of 179.0 cmH_2O was well above the normal cut-off value of 130 cmH_2O for VC P_{ga} [21].

Predictors of VC and RC flow rate

The results of univariate linear regression with PCFR as the dependent variable and stroke severity as the predictor are shown in figure 4, for both VC and RC. VC flow rate was predicted by a model including NIHSS score, height and FEV1/FVC ratio (adjusted $r^2=0.653$; $p<0.001$). Stroke severity (NIHSS score) had the greatest and most significant effect

TABLE 2 Lung function and respiratory muscle tests

	Male norm [21]	Stroke#	Control	Mean Δ (95% CI)	p-value
Subjects n		18	20		
Resting f_R breaths·min^{-1}		19±5	13±2	6 (3–8)	<0.001
FEV_1 % pred		60±22	102±23	-42 (-59– -24)	<0.001
FVC % pred		73±22	108±23	-35 (-52– -17)	<0.001
FEV_1/FVC¶ %		71 (55–76)	77 (73–80)	-7 (-17– -1)	0.019
O_2 saturation¶ %		96 (92–98)	98 (97–100)	-2 (-4– -1)	0.014
$P_{E,max}$#,¶ cmH_2O	>80	50.5 (39.5–69.5)	106.0 (82.9–140.0)	-55.7 (-74.3– -31.7)	<0.001
Twitch T_{10} P_{ga} cmH_2O	>16	26.4±6.6	32.0±14.1	-5.6 (-15.0–4.0)	0.258
$P_{I,max}$# cmH_2O	>45	38.9±25.1	95.1±33.0	-56.2 (-77.7– -34.7)	<0.001
Sniff P_n# cmH_2O	>50	40.7±25.8	92.7±25.9	-52.0 (-70.2– -33.8)	<0.001
Sniff P_{oes}# cmH_2O	>55	57.7±36.7	109.3±28.7	-51.7 (-76.1– -27.3)	<0.001
Sniff P_{di}# cmH_2O	>100	63.2±40.6	121.1±38.7	-58.0 (-88.4– -27.4)	0.001

Data are presented as mean±SD, unless otherwise stated. p-values are from unpaired t-tests except for skewed data where p-values are calculated using the Mann–Whitney U-test. Δ: difference; f_R; respiratory frequency; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $P_{E,max}$: maximal expiratory pressure; T_{10}: 10th thoracic nerve roots; P_{ga}: gastric pressure; $P_{I,max}$: maximal inspiratory pressure; P_n: nasal pressure; P_{oes}: oesophageal pressure; P_{di}: transdiaphragmatic pressure. #: n=15 in stroke group, as three patients were unable to perform spirometry, $P_{E,max}$, $P_{I,max}$ and sniff tests; ¶: data are skewed and are presented as median (interquartile range) and median Δ (95% CI).

TABLE 3 Maximum voluntary cough

	Stroke	Control	Mean Δ (95% CI)	p-value
Subjects n	16	20		
PCFR L·min^{-1}	287±171	497±122	-210 (-314– -106)	<0.001
PCFR % pred PEFR	70±43	102±19	-32 (-55– -10)	0.005
Cough V_E mL	1170±755	2100±864	-930 (-1541– -319)	0.004
Cough V_E % pred FVC	33±21	47±16	-14 (-28– -1)	0.041
PIFR$^{\#}$ L·min^{-1}	112 (80–164)	213 (157–256)	-88 (-136– -42)	<0.001
Cough V_I mL	1519±546	2710±818	-1191 (-1773– -609)	0.003
Cough V_I % pred FVC	43±21	62±18	-19 (-34– -3)	0.020
Cough P_{ga} cmH_2O	98.5±61.6	208.5±61.3	-110.0 (-152.4– -67.6)	<0.001
Cough pressure acceleration cmH_2O·s^{-1}	583±512	927±303	-344 (-644– -45)	0.026
Compression time ms	212±105	261±127	-49 (-138– -40)	0.265
Cough volume acceleration L·s^{-2}	83±57	200±70	118 (-165– -70)	<0.001

Data are presented as mean±SD, unless otherwise stated. p-values obtained from unpaired t-tests. Δ: difference; PCFR: peak cough flow rate; % pred: % predicted; PEFR: peak expiratory flow rate; V_E: expiratory volume; FVC: forced vital capacity; PIFR: peak inspiratory flow rate; V_I: inspiratory volume; P_{ga}: gastric pressue. $^{\#}$: data are skewed and are presented as median (interquartile range) and median difference (95% CI), and p-values are from the Mann–Whitney U-test.

(regression coefficient -12.6 L·min^{-1} per point of NIHSS score, 95% CI -19.2– -6.1; p<0.001). Further details of the linear regression model are given in the online supplementary material (table S1). The only significant predictor of RC flow rate was NIHSS score; details are given in figure 4. ACE inhibitor use was tried as a predictor for both VC and RC, but did not exert a statistically significant effect.

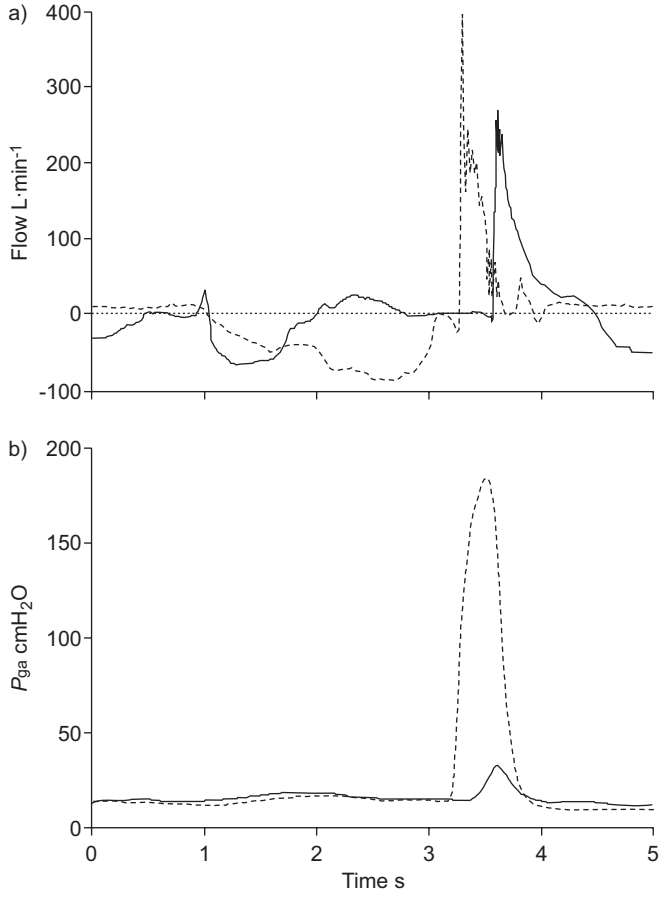

FIGURE 2. Voluntary cough in normal subject (-----) compared to stroke patient (——): a) flow; b) gastric pressure (P_{ga}). ·····: zero flow.

DISCUSSION

The present study shows that VC and RC are both impaired after acute hemispheric infarction. Impairments of respiratory muscle function measured by volitional tests, and reductions in VC flows and P_{ga} in stroke patients have been described previously [4, 5, 13, 22], but RC may be considered more important for airway protection and clearance [23]. The novel and important finding of the present study is that, despite patients achieving normal RC P_{ga}, flow rates and expiratory volumes for RC are both decreased.

Critique of the method

The differences in RC flow rate, RC expired air volume and RC volume acceleration between patients and controls could not be attributed to differences in air volume inspired prior to cough, concentration of L-tartaric acid solution required to produce five or more coughs, duration of glottis closure, peripheral nerve conduction or expiratory muscle strength. Higher stroke severity score predicted impairment of both VC and RC flow rates, suggesting a physiological basis for impaired cough in acute stroke.

Spirometry, respiratory muscle strength and VC are measured by volitional tests, in the sense that they require a patient to make a maximal effort and their interpretation depends on the vigour of that effort being maximal. Stroke patients may theoretically perform badly, because the tests depend upon subject understanding and effort [19], although the more obvious manifestations of stroke concern motor skills. Even so, these factors would not affect RC, where any impairment observed is likely to be due to nonvolitional factors. P_{ga} and glottis closure times in patients were no different to controls. RC inspired air volume tended to be smaller for patients, but this did not reach statistical significance.

TABLE 4 Maximum reflex cough response to L-tartaric acid

	Stroke	Control	Mean Δ (95% CI)	p-value
Subjects n	14	18		
[TA] giving ⩾5 coughs in 1 min# %	10 (5–10)	10 (10–20)	0 (-5–0)	0.610
Coughs in 1 min with suprathreshold TA stimulus n	11.4±5.0	12.3±7.6	0.9 (-3.9–5.7)	0.705
PCFR L·min^{-1}	204±111	379±110	-175 (-253– -96)	<0.001
PCFR % pred PEFR	43±34	77±20	34 (-54– -15)	<0.001
Cough *V*E mL	478±203	1269±1119	791 (-1412– -169)	0.015
Cough *V*E % pred FVC	13±5	27±25	-14 (-29– -0.3)	0.046
Cough *V*I mL	763±406	1172±699	-410 (-893– -74)	0.093
Cough *V*I % pred FVC	22±13	26±15	-4 (-15–7)	0.479
Cough P_{ga} cmH_2O	179.0±78.0	208.2±77.4	-29.3 (-81.9–23.4)	0.266
Cough pressure acceleration cmH_2O·s^{-1}	788±297	947±216	-159 (-393–75)	0.171
Compression time# ms	280 (236–383)	270 (197–325)	23 (-52–99)	0.661
Cough volume acceleration L·s^{-2}	99±58	179±64	-80 (-129– -31)	0.003

Data are presented as mean±SD, unless otherwise stated. Δ: difference; TA: L-tartaric acid; PCFR: peak cough flow rate; % pred: % predicted; PEFR: peak expiratory flow rate; *V*E: expiratory volume; FVC: forced vital capacity; *V*I: inspiratory volume; P_{ga}: gastric pressure. #: TA strength data are ordinal and compression time data are skewed, and are presented as median (interquartile range) and median difference (95% CI), and p-values calculated using Mann–Whitney U-tests.

It is possible that reduced functional residual capacity (FRC) in patients may have contributed to reduced cough flow rates, as a lower starting lung volume results in higher airway resistance and reduced flow rates. Little is known about FRC in stroke patients at rest (and none at all during cough), but one small study showed normal FRC in moderately severe

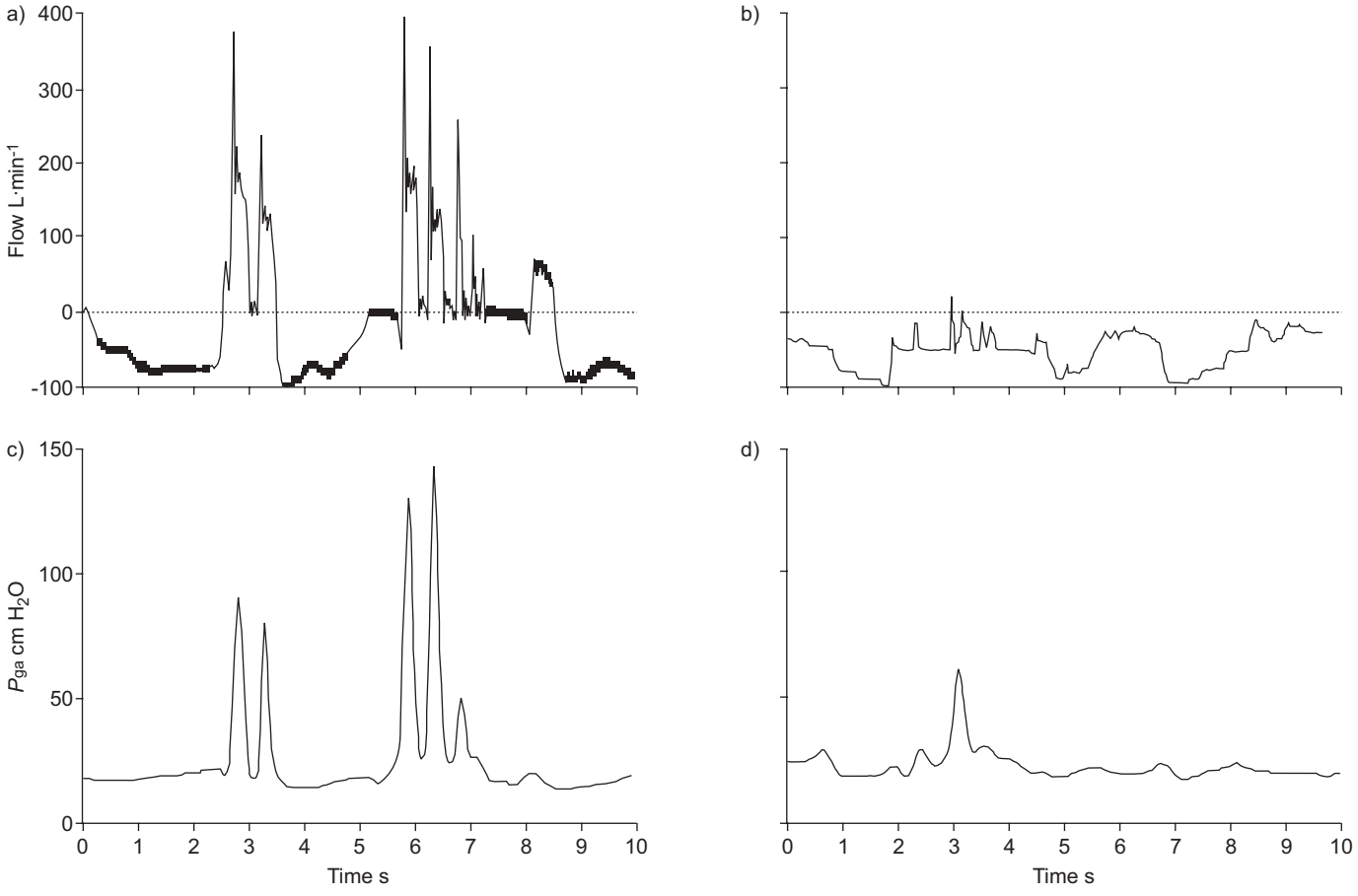

FIGURE 3. 10-s trace of a, b) flow and c, d) gastric pressure (P_{ga}) in a, c) a healthy control subject and b, d) a severely affected patient. ·····: zero flow.

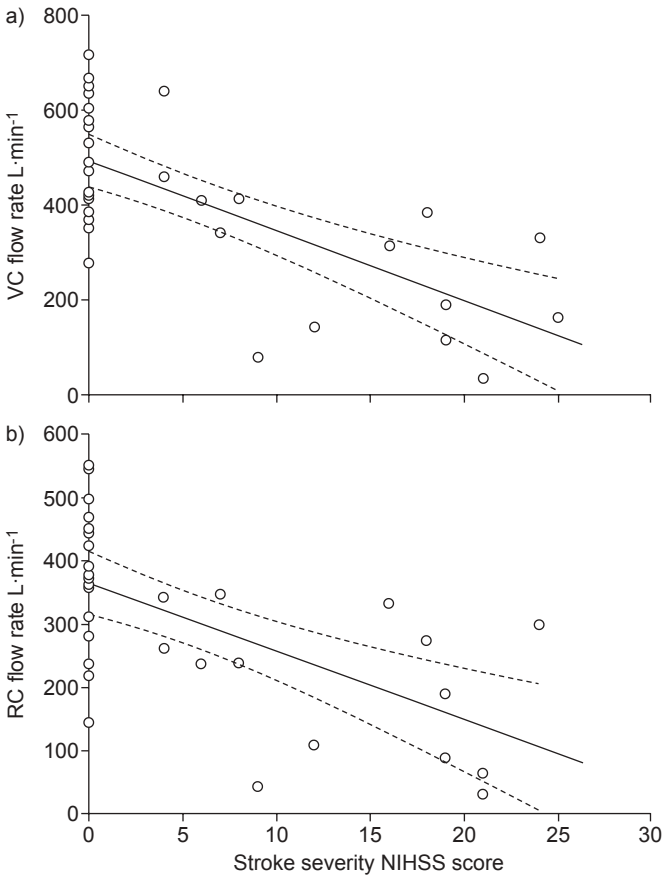

FIGURE 4. Univariate linear regression. Regression line (——) and 95% mean prediction interval (-----) drawn on a scatter diagram relating: a) voluntary cough (VC) flow rate in 36 subjects able to produce a VC; and b) reflex cough (RC) flow rate in 32 subjects able to produce a RC and stroke severity. The regression slope is: a) -15 L·min^{-1} per point of National Institutes of Health Stroke Scale (NIHSS) score (95% CI -20– -9 L·min^{-1}; $p<0.001$; adjusted $r^2=0.465$); and b) -11 L·min^{-1} per one point of NIHSS score (95% CI -16– -6 L·min^{-1}; $p<0.001$; adjusted $r^2=0.367$).

patients at 2–4 weeks after onset [9]. Patients had more airway obstruction than controls (significantly reduced FEV1 and FEV1/FVC ratio). Airway obstruction would be expected to lead to a reduced VC flow rate, although, from the regression models, the influence of FEV1/FVC ratio on VC flow rates was smaller and less significant than the effect of stroke severity. Neither FEV1 nor FEV1/FVC ratio were significant predictors of RC flow rate.

Previous studies have separately described intra-abdominal pressure changes during RC and VC in normal subjects [23], but this is the first study to describe PCFRs, volumes and pressures during RC and VC in an homogeneous sample of stroke patients and controls. One merit of the present study is that subjects with diabetes or previous heavy alcohol use were excluded, because these may affect cough [24, 25]. Similarly, application of lidocaine to the pharynx (to allow passage of pressure catheters) can alter cough [26]; therefore, cough tests were performed $\geqslant$90 min after administration. Finally, although ACE inhibitor use was recorded because of the previously described effect on cough [27], it was not found to be a significant independent predictor of cough flow rate in the present study.

Significance of the findings

The rapid rise in P_{ga} but not expiratory flow during RC suggests that the sensory pathways are intact, since abdominal muscles must be recruited to generate a positive P_{ga}. However, the slower rise in expiratory flow suggests an additional flow limitation as a manifestation of ischaemic cortical injury. We suspect that this injury may affect the coordinated activation of the upper airway muscles with the abdominal and thoracic muscles used for cough production [7]. Cortical involvement in RC and VC is supported by studies showing voluntary suppression of capsaicin-induced RC in healthy volunteers [28], absent or delayed conduction in corticorespiratory tracts on stimulating the affected hemisphere of stroke patients [13] and cortical modulation of pharyngeal coordination in stroke [29].

This study is of modest size, but the sample appears representative and shows baseline characteristics similar to those in other studies. The patients' mean VC PCFR was similar to that found 6 days after stroke onset in a recent study of 96 patients (261 ± 188 L·min^{-1}) [23]. As the definition of effective cough remains elusive [14], it is impossible to know whether the reduction in patients' cough flows are clinically meaningful. One method would be to correlate cough impairments with incidence of chest infections, but the number of events in the present study (n=2) precludes such analysis. RC produced in the laboratory does not accurately replicate the response to aspirated fluid or food, which cannot easily be studied for safety reasons. Although desirable, measurements and imaging of the upper airways during cough could not be performed because of logistical and patient discomfort considerations.

The present study shows that acute stroke patients have impaired VC and RC; this may result in impaired lung clearance. The data suggest that impairment may be, in part, due to ineffective coordination of different muscle groups following cerebral injury. Further studies are required into the mechanisms that may underlie RC and VC impairment, and to test interventions that may improve cough function, in order to try and reduce the incidence and consequences of aspiration after stroke.

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STATEMENT OF INTEREST

None declared.

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