CEREBRAL INFARCT SITE AND AFFECTED VASCULAR TERRITORY AS FACTORS IN BREATHING WEAKNESS IN PATIENTS WITH SUBACUTE STROKE

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Objective: A better understanding of factors influencing breathing weakness in stroke survivors would help in planning rehabilitation therapies. The main objective of this study was to determine whether the location of cerebral infarct is associated with breathing weakness in patients with subacute stroke.

Design: Cross-sectional analysis of a prospective cohort.

Patients: Consecutive patients admitted to a neurology rehabilitation unit with first-time ischaemic stroke (n = 170).

Methods: Breathing weakness was defined as >70% reduction in maximal inspiratory and expiratory pressures (PImax and PEmax, respectively) compared with reference values. Computed tomography and magnetic resonance imaging were used to locate stroke lesions, which were classified as cortical, subcortical, cortico-subcortical, brainstem, or cerebellum. The affected cerebrovascular territory was identified to classify stroke subtype. The association between maximal respiratory pressure and affected brain area was studied using median regression analysis.

Results: Breathing weakness was detected in 151 (88.8%) patients. Those with cortical and cortico-subcortical stroke location had the lowest PImax and PEmax values (median 33 cmH2O). This value differed significantly from maximal respiratory pressures of patients with strokes located in the brainstem and the cerebellum, with PImax median differences (β) of 16 cmH2O (95% confidence interval (95% CI) 4.1–27.9) and 27 cmH2O (95% CI 7.8–46.2), respectively, and PEmax median differences of 27 cmH2O (95% CI 11.4–42.7) and 49 cmH2O (95% CI 23.7–74.3), respectively, both of which remained significant after adjustments.

Conclusion: The prevalence of breathing weakness was very high in stroke patients admitted to a neurorehabilitation ward, being more severe in cortical or cortico-subcortical stroke.

Key words: breathing weakness; stroke assessment; stroke subtype; rehabilitation.

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Muscle weakness in stroke survivors affects both peripheral muscles and those of the respiratory system (1). Maximal voluntary respiratory strength values in stroke are less than half those expected in healthy adults (2). Nonetheless, respiratory muscle function is not included in routine assessment guidelines at stroke rehabilitation facilities; interventions mainly focus on physical and cognitive functions (3).

Although the exact mechanisms setting respiration rhythm remain unknown, neural control depends on a central drive to the respiratory muscles, modulated by chemical and mechanical inputs. Lesions affecting the brainstem, corticobulbar, and/or corticospinal tracts may disrupt breathing (4). Breathing weakness in stroke is related to decreased cortico-respiratory outflow from the damaged cortex, rather than intrinsic strength reductions (5). Hemispheric lesions can also cause contralateral reductions in chest wall movements and diaphragmatic excursion in the paralysed side (6). In stroke, attributing
respiratory function to localized anatomical substrates is difficult; lesions are rarely circumscribed in a single well-defined area, and comorbidities associated with breathing weakness are often present (7). A better understanding of factors (such as stroke location) that may influence breathing weakness in stroke survivors, could help to explain the mechanisms and abnormalities of this relatively unstudied topic.

The association between respiratory muscle weakness in stroke and respiratory complications is not well established. However, it has been suggested that impaired respiratory muscle function, ineffective cough, and difficulty swallowing may increase aspiration risk and incidence of bronchopneumonia (8, 9). A longitudinal association between respiratory muscle strength and cough capacity has been reported in other neurological conditions (e.g. spinal cord injuries) (10). In clinical practice, early assessment of breathing weakness may help to detect patients who are at risk of complications, and to individualize treatment and rehabilitation strategies (9).

This study aimed to determine whether a specific hemisphere, anatomical location, and cerebrovascular territory are associated with breathing weakness in patients with subacute stroke. If a locational effect were confirmed, individuals with acute infarction involving specific brain regions could be referred for respiratory assessment and treatment.

### METHODS

#### Study design

This study was a cross-sectional, observational analysis of a prospective cohort, reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (11). The cohort was part of the RETORNUS study (NCT 02125760, clinicaltrials.gov).

#### Participants

From March 2011 to November 2014, the RETORNUS study recruited 202 consecutive patients with ischaemic stroke admitted to in-patient rehabilitation at a university hospital in Barcelona (Catalonia, Spain). Inclusion criteria were age >18 years, first-ever ischaemic stroke, time since stroke onset <3 weeks, and upper or lower limb hemiparesis. Exclusion criteria were: chronic heart failure, chronic pulmonary diseases, neurological condition other than stroke, medical treatments with potential effect on muscle structure and function, and inability to conduct study procedures.

#### Study variables

The study evaluated 3 main variables: respiratory muscle strength, stroke location, and stroke subtypes according to affected cerebrovascular territory.

Respiratory muscle strength, defined as the ability to make a brief maximal effort, was assessed through maximal inspiratory and expiratory pressures (PImax and PEmax, respectively) measured at the mouth throughout a volitional manoeuvre, using a respiratory pressure meter (MicroRPM, Micro Medical/CareFusion, Kent, UK), as described previously (9). Patients were urged to perform a maximum inspiration from residual volume against an occluded airway and a maximum expiratory effort from total lung capacity. The highest value of 3 reproducible manoeuvres (<10% variability) was used for analysis. All assessments were performed by the same expert therapist. Respiratory pressures <70% of reference values (9, 13) for a Mediterranean population (12) were considered as decreased.

Stroke location was obtained from computer tomography or magnetic resonance imaging scan reports by a consultant neuroradiologist blinded to respiratory muscle assessments. Lesions were

### Table I. Baseline demographic and clinical characteristics of the sample

| Characteristics | Total sample (n=170) |
|-----------------|---------------------|
| Age, years, mean (SD) | 66.4 (10.6) |
| Sex, men, n (%) | 102 (59.6) |
| Body mass index, kg/m², mean (SD) | 26.2 (4.3) |
| Smoking history, n (%) | 55 (32.4) |
| Current smoker | 36 (21.1) |
| Former smoker | 79 (46.5) |
| Never smoked | 11.8 (7.8) |
| Charlson Index (median, P25–75) | 77.1 (19.0) |
| Right | 93 (54.7) |
| Left | 77 (45.3) |
| Stroke aetiology, n (%) | 39 (22.9) |
| Large-artery atherosclerosis | 34 (20.1) |
| Lacunar or small vessel disease | 34 (20.1) |
| Other determined aetiology | 34 (20.1) |
| Modified Rankin Scale | 3.4 (1.0) |
| Barthel Index, admission | 48.8 (15.9) |
| Barthel Index, discharge | 77.1 (19.0) |
| Stroke hemisphere, n (%) | 93 (54.7) |
| Total anterior circulation infarction | 39 (22.9) |
| Partial anterior circulation infarction | 34 (20.1) |
| Posterior circulation infarction | 34 (20.1) |
| Lacunar anterior circulation infarction | 34 (20.1) |
| Unknown data | 34 (20.1) |
| Supratentorial | 126 (74.1) |
| Infratentorial | 41 (24.1) |
| Undetectable by imaging tests | 3 (1.8) |
| Respiratory muscles | 44.3 (23.0) |
| PImax, cmH2O, mean (SD) | 42.7 (20.4) |
| PEmax, cmH2O, mean (SD) | 66.9 (32.8) |
| PEmax, %pred, mean (SD) | 43.0 (20.2) |
| Peripheral muscles, kg, mean (SD) | 6.8 (8.6) |
| Handgrip strength, affected side | 22.3 (9.2) |
| Quadriiceps strength, affected side | 11.8 (7.8) |
| Quadriiceps strength, non-affected side | 18.7 (8.4) |

NIHSS: National Institutes of Health Stroke Scale; PImax: maximal inspiratory pressure; PEmax: maximal expiratory pressure; SD: standard deviation.
localized according to affected hemisphere and classified as cortical, subcortical, cortico-subcortical, brainstem, or cerebellum.

Stroke subtypes according to affected cerebrovascular territory were classified as total or partial anterior circulation infarct (TACI or PACI), posterior circulation infarct (POCI), or lacunar infarct (LACI). This classification, from the Oxford Community Stroke Project (OCSP), primarily relies on neuroimaging and initial symptomatology (14).

Six additional variables were collected:

- Severity, according to the National Institutes of Health Stroke Scale (NIHSS).
- Aetiology, using the Trial of Org 10172 in Acute Stroke (TOAST) classification (large-artery atherosclerosis, cardioaortic embolism, small-vessel occlusion, and stroke of other or undetermined aetiology).
- Disability, according to modified Rankin Scale.
- Peripheral muscle strength, estimated by maximal voluntary contraction of hand flexor and quadriceps muscles.
- Functional status, assessed with the Barthel Index.
- Comorbidity, according to the Charlson index.

Demographic data, smoking history, general health, and other stroke characteristics were collected from medical records. All assessments were performed at admission to the in-patient stroke rehabilitation facility.

Ethics

Written informed consent to participate was obtained. This research was approved by the Institutional Clinical Ethics Committee as part of the RETORNUS study. National and international research ethics guidelines were followed, including the Deontological Code of Ethics, Declaration of Helsinki, and Spain’s confidentiality law concerning personal data (Ley Orgánica 3/2018, Protección de Datos de Carácter Personal).

Statistical analysis

Percentages and frequencies were used to describe categorical variables. Quantitative variables were reported as mean and standard deviation (SD) or median with 25th and 75th percentiles. Assumption of normality was analysed using normality charts and the Kolmogorov-Smirnov test corrected with the Lilliefors test. χ², Student’s t-test for independent samples, and Mann–Whitney test were used for bivariate analyses, as appropriate. In a median regression analysis, unstandardized beta coefficient (β) was used to check respiratory pressure differences according to stroke subtype and location; median PImax and PEmax were dependent variables. Independent variables were stroke location, Oxford Topographic Classification, stroke hemisphere, NIHSS, TOAST, Charlson Index, Barthel Index at admission, and age. Significance was set at p < 0.05.

Of 202 eligible patients admitted to the stroke rehabilitation unit during the study period, 32 were excluded for inability to perform the volitional manoeuvres. The final sample was 170 individuals (mean age 66.4 years (SD 10.6), 59.6% men). Clinical and demographic characteristics are described in Table I. Prevalence of inspiratory and/or expiratory muscle weakness was 88.8%. Patients without breathing weakness had better NIHSS scores (mean difference 2.0 (95% confidence interval (95% CI) 1.1–2.9, p < 0.001)) and Barthel index scores at admission (mean difference 9.2 (95% CI 1.6–16.7, p = 0.018)) and at discharge (mean difference 11.5 (95% CI 4.3–18.7, p = 0.030)). Although breathing weakness was not associated with handgrip strength, its presence was related to decreased quadriceps strength in the non-affected side (mean difference 6.8 kg (95% CI 1.9–11.8, p = 0.007)).

Table II shows maximal respiratory muscle pressures according to stroke hemisphere, supra- or infratentorial position, anatomical area, and affected cerebrovascular territory. Student’s t-test analysis detected differences between supra- and infratentorial strokes, a mean of 46.8 cmH₂O (95% CI 38.4–55.4, p = 0.007) for PImax and 37.9 cmH₂O (95% CI 23.2–52.6, p = 0.007) for PEmax.

In median regression analysis, respiratory muscle strength differed according to the brain area affected

![Table II. Maximal respiratory muscle pressures according to stroke hemisphere, supra- or infratentorial position, anatomical area location, and affected cerebrovascular territory](image)

*Student’s t-test was statistically significant. SD: standard deviation.
Patients with cortical and cortico-subcortical strokes had the lowest inspiratory muscle strength (median $P_{\text{Imax}} = 33 \text{ cmH}_2\text{O}$). The $\beta$ coefficient indicates deviation from the lowest median value (cortical and cortico-subcortical strokes): $\beta$ of 16 $\text{ cmH}_2\text{O}$ (95% CI 4.1–27.9, $p = 0.009$) for the brainstem, and 27 $\text{ cmH}_2\text{O}$ (95% CI 7.8–46.2, $p = 0.006$) for the cerebellum. In multivariate analysis, these differences persisted after adjusting for confounding factors: $\beta$ of 17 $\text{ cmH}_2\text{O}$ (95% CI 5.8–28.2, $p = 0.003$) for strokes located in the brainstem, and 27.8 $\text{ cmH}_2\text{O}$ (95% CI 8.9–46.7, $p = 0.004$) for those in the cerebellum. Patients with cortical and cortico-subcortical strokes also had the lowest expiratory muscle strength (median $P_{\text{Emax}} = 51.5 \text{ cmH}_2\text{O}$).

### Table III. Univariate and multivariate median regression analysis for maximal inspiratory and expiratory pressures ($P_{\text{Imax}}$ and $P_{\text{Emax}}$, respectively) according to cerebral infarct site and affected vascular territory

| Cerebral infarct site                          | Median $P_{\text{Imax}}$ (cmH$_2$O) | $\beta$ | SE | 95% CI | $p$-value | Cerebral infarct site                          | Median $P_{\text{Emax}}$ (cmH$_2$O) | $\beta$ | SE | 95% CI | $p$-value |
|-----------------------------------------------|-------------------------------------|--------|----|--------|-----------|-----------------------------------------------|-------------------------------------|--------|----|--------|-----------|
| Cortical and cortico-subcortical              | 33                                 | 0      | -  | -      | -         | Subcortical                                   | 61                                 | 0      | -  | -      | -         |
| Subcortical                                   | 37.5                               | 4      | 4.9| -5.6 to 13.6 | 0.412     | Brainstem                                     | 50.5                               | 16     | 6.0| 4.1 to 27.9 | 0.009     |
| Brainstem                                     | 57.2                               | 7      | 6.0| 9.3 to 12.9  | 0.001     | Cerebellum                                    | 61                                 | 27     | 9.7| 7.8 to 46.2  | 0.006     |
| Age                                           | -0.4                               | 0.19   | 0.08 to -0.06 | 0.025     | Charison Index                                | 0.02                               | 1.8    | -3.4 to 3.5 | 0.993     |
| NIHSS                                         | -0.003                             | 0.002  | -0.008 to 0.02 | 0.212     | Barthel Index                                 | 0.003                              | 0.002  | -0.002 to 0.009 | 0.070   |
| Stroke hemisphere: left                       | -0.4                               | 4.04   | -8.4 to 7.6  | 0.917     | Stroke hemisphere: left                        | -2.3                               | 5.3    | -12.7 to 8.1 | 0.659     |

| OCSP classification                           | Median $P_{\text{Imax}}$ (cmH$_2$O) | $\beta$ | SE | 95% CI | $p$-value | OCSP classification                           | Median $P_{\text{Emax}}$ (cmH$_2$O) | $\beta$ | SE | 95% CI | $p$-value |
|-----------------------------------------------|-------------------------------------|--------|----|--------|-----------|-----------------------------------------------|-------------------------------------|--------|----|--------|-----------|
| Total anterior circulation infarcts            | 28                                 | 0      | -  | -      | -         | Total anterior circulation infarcts            | 48                                 | 0      | -  | -      | -         |
| Partial anterior circulation infarcts          | 33.5                               | 7      | 5.9| -4.8 to 18.8 | 0.241     | Partial anterior circulation infarcts          | 46                                 | 10.0   | 10.0| -22.8 to 16.8 | 0.765     |
| Posterior circulation infarcts                 | 51                                 | 23     | 6.4| 10.3 to 35.7 | <0.001    | Posterior circulation infarcts                 | 79                                 | 10.8   | 10.8| 8.7 to 51.3  | 0.006     |
| Lacunar anterior circulation infarcts          | 50                                 | 22     | 5.6| 10.8 to 33.2 | <0.001    | Lacunar anterior circulation infarcts          | 75                                 | 9.5    | 9.5| 7.2 to 44.8  | 0.007     |
| Age                                           | -0.4                               | 0.19   | 0.08 to -0.06 | 0.025     | Charison Comorbidity Index                     | 0.5                                | 1.7    | -2.8 to 3.8  | 0.756     |
| NIHSS                                         | -0.001                             | 0.002  | -0.006 to 0.003 | 0.573     | Barthel Index                                 | 0.002                              | 0.002  | -0.001 to 0.005 | 0.184   |
| Stroke hemisphere: left                        | -2.7                               | 3.9    | -10.4 to 4.9 | 0.483     | Stroke hemisphere: left                        | -4.4                               | 5.9    | -16.0 to 7.3 | 0.461     |

*NIHSS: National Institutes of Health Stroke Scale; OCSP: Oxford Community Stroke Project; $P_{\text{Imax}}$: maximal inspiratory muscle pressure; $P_{\text{Emax}}$: maximal expiratory muscle pressure; $\beta$: non-standardized beta coefficient; SE: standard error; CI: confidence interval.
Breathing weakness and stroke location

This study explored the association of breathing weakness with the affected brain area in stroke survivors. Respiratory muscle impairment after stroke has received minimal attention despite its high prevalence. Although one would expect increased respiratory weakness in both cortical and brainstem strokes (4), the current univariate and multivariate median regression found significantly higher median maximal respiratory pressures in brainstem stroke, compared with cortical locations. Selective interruption of voluntary pathways (corticospinal and corticobulbar) would impair types of voluntary respiration (e.g., volitional maneuvers to determine respiratory pressures).

Brain lesions in one hemisphere result in contralateral dysfunction of ventilatory muscles (6). Although reductions in chest wall and diaphragm movements correlate well with localization of the cortical diaphragm, shown by transcranial magnetic stimulation and positron emission tomography scanning (7), there is no clear evidence of cerebral dominance for diaphragm function. The diaphragm has a contralateral cortical representation in the primary motor cortex, usually quite small in size and near the hip area (15). Therefore, patients with cortical stroke could experience greater impairment of respiratory muscle function. Moreover, impaired reflex and voluntary cough seem to be cortically modulated by an ineffective coordination of different muscle groups after cerebral injury, resulting in impaired lung clearance and greater risk of bronchoaspiration (16).

Anatomical classification of ischaemic strokes follows the architecture of arteries that irrigate the brain, brainstem, and cerebellum, defining 2 vascular territories (anterior and posterior circulation). Thus, when stroke is located in the vertebrobasilar area and affects the brainstem, the basic respiratory rhythm generated in the respiratory neurone network of the lower brainstem may be compromised. Furthermore, selective interruption of corticospinal and corticobulbar tracts would impair any type of voluntary respiration. In the current study, mean Plmax and PEmax were 44.3 cmH2O (SD 23.0) and 66.9 cmH2O (SD 32.8) in effort-dependent maneuvers; these values are slightly higher than other reports (6, 16, 17).

Anatomical and physiological mechanisms underlying the generation and regulation of respiratory rhythm share characteristics with regulation of swallowing. Respiratory centers localized in the brainstem interact with neuronal networks of the hypothalamus and primary motor cortex to mediate automatic respiratory control mechanisms. This complex physiology is best explained graphically (Fig. 1). Although respiratory pathways are largely independent above the segmental level, both anatomically and functionally, increasing evidence supports some extent of interaction between them (18). Occurrence of respiratory “apraxia” might have special interest in brainstem strokes, where interruption of the bulboospinal pathway combined with swallowing disorders and impaired cough reflex could increase bronchoaspiration risk (7).

Establishing a relationship between breathing weakness and increased risk of medical complications is difficult, due to the lack of prospective cohort studies of respiratory muscle function in stroke. To our knowledge, no previous studies have directly associated breathing weakness with respiratory complications. Although our sample size was not powered to detect differences in the incidence of respiratory complications, a post-hoc analysis of the cohort showed that 46 (95.8%) of the 48 patients with respiratory infections during the one-year follow-up had expiratory muscle dysfunction (Fisher exact test p = 0.065). Results of a previous randomized clinical trial by our group suggest a decreased incidence of respiratory complications after respiratory muscle training (RMT) in patients with subacute stroke (9); this was corroborated in stroke patients with dysphagia, with improved deglutition security following RMT (19). Other authors report no relationship between improved respiratory pressures after RMT and respiratory infections (20). A more recent meta-analysis concludes that RMT may reduce lung infections after stroke, but given that this finding was based in just 2 clinical trials, with small-to-medium sample sizes and some losses to follow-up, the authors noted that stronger evidence of this association is required (21).

DISCUSSION

deviation in median difference from cortical and corticobasal cortical strokes was observed between patients with strokes located in the brainstem and cerebellum: β of 27 cmH2O (95% CI 11.4–42.7, p = 0.001) and 49 cmH2O (95% CI 23.7–74.3, p = 0.001), respectively. Again these differences persisted in the multivariate analysis after adjustments for confounding factors. The same analysis was used to assess differences in respiratory muscle function according to vascular territory. The lowest Plmax values were observed in the TACI groups (median Plmax = 28 cmH2O), and differed significantly from inspiratory muscle strength in patients with POCI and LACI: β of 23 cmH2O (95% CI 10.3–35.7, p < 0.001), and 22 cmH2O (95% CI 10.8–33.2, p < 0.001), respectively. Finally, expiratory muscle strength was lowest in patients with TACI strokes (median PEmax = 49 cmH2O). In comparison, POCI and LACI groups had higher median values for PEmax: β of 30 cmH2O (95% CI 8.7–51.3, p = 0.006) and 26 cmH2O (95% CI 7.2–44.8, p = 0.007), respectively. All these differences persisted after adjusting for confounders.
Study strengths and limitations

This study described stroke location from information available in clinical rehabilitation settings; this bedside-to-bench approach is, in our opinion, a strength of the study. Several limitations also must be considered. The appropriateness of studying a volitional manoeuvre in all stroke types regardless of location is the most important question to be resolved, as volition might be influenced by awareness level, mood, and cognition. Facial hemiparesis can complicate PExmax assessment. Infratentorial stroke might be expected to yield more accurate measurements, compared with supratentorial stroke. Lower incidence of respiratory complications following inspiratory and expiratory muscle training regardless of stroke location (9) suggests an effect related to clinical status.

Other study limitations include the characteristic bias in rehabilitation samples, as patients are preselected for capacity to follow a therapeutic programme. Patients with haemorrhagic strokes, who experience more severe impairments and different recovery periods, were excluded. Although tobacco-induced oxidative changes in muscle proteins might contribute to muscle dysfunction (22), excluding patients with a smoking history (53.5% in our sample) would have made the study population less representative. Moreover, stratification by smoking history did not detect differences in respiratory muscle function in the current study sample. Baseline assessment did not include diaphragm movement, which could provide valuable information. Finally, defining the brain infarct site according to the OCSP classification is unlikely to be specific to a particular stroke aetiology. Previous studies have found that differentiation to stroke subtypes by OCSP does not always show precise results (23), and its use to investigate risk factors or causes of stroke is not recommended (24). Nonetheless, the OCSP classification is useful to classify patients into groups based on symptoms and neuroimaging, and to predict safety and efficacy of thrombolysis (25).

The findings of the current study suggest a very high prevalence of breathing weakness in patients with subacute stroke, being more severe in cortical or cortico-subcortical strokes. Despite the prognostic implications of respiratory issues, the study of potential associations of stroke location and respiratory
Breathing weakness and stroke location

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The authors have no conflicts of interest to declare.

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