Incidence and predictive factors of diaphragmatic dysfunction in acute stroke.

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Abstract

Background: The most characteristic clinical signs of stroke are motor and/or sensory involvement of one hemibody. Respiratory involvement has also been described, which could be related to diaphragmatic dysfunction contralateral to the brain injury. Our objective is to establish the incidence of diaphragmatic dysfunction in ischaemic stroke and analyse the relationship between this and the main prognostic markers.

Methods : Patients with supratentorial ischaemic stroke were selected in the first 48 hours of admission for 6 months. Ultrasonography of the diaphragm was performed on each hemithorax to obtain the thickening fraction applying the formula $[(\text{inspiratory thickness} - \text{expiratory thickness}) / \text{expiratory thickness}]$. Forced breathing was then requested to them and the examination was performed again. Diaphragmatic dysfunction was considered as a thickening fraction lower than 20%. The statistical relationship with the vascular territory involved, the NIHSS scale, the hemiparesis degree and the success of reperfusion techniques were examined.

Results : An incidence of diaphragmatic dysfunction of 51.7% was observed on the contralateral side and of 1.7% on the ipsilateral side. A reduction of up to 11.7% was seen in the incidence of dysfunction on the contralateral side upon breathing forcedly. All patients with NIHSS above 6 had diaphragmatic dysfunction on the contralateral side ($p < 0.001$). They also had lower degrees of muscle strength ($p < 0.001$).

Conclusions : There is a high incidence of diaphragmatic dysfunction in patients with supratentorial ischaemic stroke. An estimation of the diaphragmatic function can be obtained using the thickening fraction.

Background

Acute stroke is the third cause of death and first cause of disability in Western countries^{1,2}. However, in recent years a reduction has been seen both in the incidence and mortality due to the improved preventive and therapeutic measures taken³.

The motor and/or sensory involvement of a hemibody is the prevalent clinical sign, though there are also respiratory disorders which for the moment are poorly characterised in the literature. These depend on the location and extent of the neurological injury⁴. They can be due to involvement of the respiratory mechanics due to involvement of the respiratory control centres or weakness of respiratory muscles⁴. They usually occur as respiratory failure, atelectasis, lung infections or sleep disturbances⁵⁻⁷. Diaphragmatic dysfunction is another potential mechanism of respiratory impairment in stroke⁸.

The diaphragm is responsible for performing from 60% to 80% of the inspiratory effort^{5,9,10}. It shows bilateral innervation from the cervical plexus through two phrenic nerves that are formed from C3 to C5

roots (C4 probably to a higher extent)^{11,12}. Involvement of diaphragmatic muscles or the phrenic nerve can cause diaphragmatic dysfunction¹³. This dysfunction ranges from a partial loss of the ability to generate pressure due to muscle weakness to a full loss of diaphragmatic function due to palsy thereof¹⁴. Unilateral involvement of this muscle is usually paucisymptomatic¹⁵, and may be an underdiagnosed cause of dyspnoea. On the contrary, the bilateral lesion leads to significant dyspnoea at rest, in particular in a lying-down-on-the-back position¹⁶⁻¹⁸.

Involvement of the diaphragm in ischaemic stroke has been generally described as a palsy contralateral to the lesion in patients with hemiparesis^{1,5,6}. A bilateral mobility reduction has been also seen, with no direct diaphragmatic dysfunction, that can contribute to reducing respiratory function in these patients^{19,20}. This diaphragmatic dysfunction could contribute to the appearance of respiratory failure⁵ or other complications such as respiratory infections¹.

The ultrasonographic study of the diaphragm has been developed in recent years to evaluate the function of this muscle²¹. This technique means a non-invasive method, independent of the effort of the patient, and allows to view images in real time^{17,22,23}.

The objective of our study is to establish the incidence of diaphragmatic dysfunction measured by ultrasonography in a number of patients with acute ischaemic stroke. We also have analysed the relationship of this diaphragmatic dysfunction with the main prognostic markers of stroke: vascular territory, clinical severity, degree of hemiparesis and administration of reperfusion treatments.

Methods

An observational, prospective study in a cohort of cases diagnosed with acute ischaemic stroke. Patients diagnosed with supratentorial ischaemic stroke in the first 48 hours of hospital admission to a stroke unit or critical care unit were selected from the period between 1 November 2017 and 1 May 2018.

The exclusion criteria were: infratentorial ischaemic stroke, patients not collaborating for the diaphragmatic ultrasonography, non-evaluable study of the thickening fraction, use of maintained assisted ventilation in the first 48 hours of hospital stay, and patients with a medical history that could interfere with diaphragmatic mobility, such as known previous diaphragmatic dysfunction, history of chest and upper abdominal surgery, previous chest injury and previous hemiparesis leading to significant functional limitation, defined by the mRs scale (*Modified Rankin Scale*) as 3 or higher.

In our site, patients are evaluated initially by a neurologist on duty and a baseline computerised tomography (CT) is performed, administering thrombolytic treatment (alteplase) for up to 4.5 hours, following the recommended guidelines of the Spanish Society of Neurology of 2014²⁴. In the cases where primary or rescue mechanical thrombectomy (MT) is considered, perfusion CT and angioCT of supra-aortic trunks and brain are performed previously. Imaging tests were performed in a Philips 64-detector multi-slice CT, Brilance model (*Koninklijke Philips Electronics N.V., Amsterdam, Netherlands*).

The images are analysed by a neuroradiologist, considering MT in patients with large vessel occlusion (M1, M2, ICA, intracranial or in tandem, A1, P1, basilar) and time from onset of 8 hours or less. Those with an indeterminate time from onset (for instance, stroke on awakening) are considered candidate to MT if they show a perfusion deficit consistent with mismatch of 30% or higher, measured by perfusion CT. Patients undergoing MT are treated with general anaesthesia and are extubated systematically after the procedure. They are subsequently admitted to the Critical Care Unit and, if there are no incidents, they are referred to the Stroke Unit at 24 hours of the MT. The rest of the patients with acute stroke, including those treated with alteplase, are admitted to the Stroke Unit in the first 24-72 hours.

Data were collected from the medical records, including demographics, history of the patients: cardiovascular risk factors, functional class according to the NYHA scale (New York Heart Association) and history of respiratory diseases [chronic obstructive pulmonary disease (COPD) or sleep apnoea-hypopnoea syndrome (SAHS)]. Clinical data were collected: aetiology of the stroke, vascular territory affected, NIHSS (National institute of Health Stroke Scale), severe sensory aphasia defined as not understanding instructions, degree of hemiparesis (MRC scale, Medical Research Council), application of reperfusion therapies and their success measured by the TICl scale (Thrombolysis in cerebral infarction) or the TIBI scale (Thrombolysis in Brain Ischemia), as applicable.

Ultrasound images were obtained with a portable Mindray TE7 ultrasound machine (*Mindray, Shenzhen, P. R. China*), with probe of 12 mHz of frequency. For performing the diaphragmatic ultrasonography the patient was placed in a supine position. The ultrasound probe was placed in the axillary midline from T4 and was guided to caudal to identify the three lines corresponding to the diaphragm. After they were located, a section was made in mode M and the maximum thickness and minimum thickness of this muscle were measured. Once the measures were obtained, the thickening fraction was calculated using the formula described in previous studies: $[(\text{inspiratory thickness} - \text{expiratory thickness}) / \text{expiratory thickness}]^{16,21}$. A bilateral ultrasonography of the diaphragm was performed, studying the thickening fraction in both sides. Diaphragmatic dysfunction was considered as thickening fraction of less than 20%^{16,21,25}. The thickening fraction was measured both under normal breathing and under forced breathing and the same two measurements were performed in both hemidiaphragms.

A descriptive study of the variables was performed by calculating the central tendency and dispersion measures for the quantitative variables and the exact calculation and the percentage for the qualitative variables. The comparison between patients with diaphragmatic dysfunction and no diaphragmatic dysfunction was performed using the Wilcoxon rank test. The comparison of the categorical variables between two or more subgroups was performed using the Pearson's chi-squared test or, if appropriate, the exact Fisher test. A value of $p \leq 0.05$ was considered significant throughout the study. All the results were analysed with the IBM SPSS Statistics® software Version 19 (*SPSS, Chicago, IL, US*).

Ethics

It is an observational, non-interventional study, the ultrasonographic data obtained were not used for modification of the standard treatment regimens. The authors of the research asked all patients to sign an informed consent prior to undergoing the diaphragmatic ultrasonography. The good clinical practice guidelines and the declaration of Helsinki were followed. Confidentiality of the data obtained was kept and they were only used for the study purposes. Our clinical research was reviewed and approved by the Clinical Research Ethics committee of the University Hospital Complex of Albacete, and was approved on 17 October 2017 with act number 09/2017.

Results

During the study period a total of 160 patients with diagnosis of stroke were admitted, including ischaemic, haemorrhagic and vertebrobasilar stroke. The study subjects were recruited consecutively to reach a total of 72 patients. The final cohort comprises 60 patients, as 12 patients were rejected for not meeting accurately the inclusion criteria. The demographic data and the history of the patient are given in Table 1.

Table 1: Demographic data and the history of the patient.

Age	69.30 years $\pm$ 9.66 years
Sex	51.7% (n = 31) male
Arterial hypertension	63.3% (n = 38)
Dyslipemia	46.7% (n = 28)
Diabetes mellitus	30% (n = 18)
Smoking	66.7% (n = 40) no smoking 16.7% (n = 10) former smoker
COPD	6.7% (n = 4)
SAHS	10% (n = 6)
Dyspnea	84.7% (n = 50) Grade 0 10.2% (n = 6) Grade 1
NYHA scale	60% (n = 36) Class 1 35% (n = 21) Class 2
Vascular territory affected	Pequeño vaso 19 (31.7%) ACA 4 (6.66%) MCA 32 (53.33%) PCA 4 (6.66%) Carotid 1 (1.66%)
NIHSS	3 (2 - 6)
Reperfusion therapies	58.3% (n = 35) No therapy 20% (n = 12) Thrombolysis 18.3% (n = 11) Thrombectomy 3.3% (n = 2) Both therapies

ACA: Anterior cerebral artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery.

The overall incidence of diaphragmatic dysfunction in acute ischaemic stroke in the first 48 hours following admission was 51.7%. An incidence of diaphragmatic dysfunction of 51.7% was seen under normal breathing and of 11.5% under forced breathing, with a statistically significant difference ($p < 0.0001$). Figure 1 details the differences between basal breathing and forced breathing.

Diaphragmatic dysfunction under basal breathing

Diaphragmatic dysfunction was seen on the side contralateral to the lesion in 51.7% (n = 31) vs 1.7% (n = 1) on the ipsilateral side ($p < 0.0001$). The median thickening fraction was 19% [12% - 43%] on the contralateral side vs 37% [33% - 51%] on the ipsilateral side ($p < 0.0001$).

Diaphragmatic dysfunction under forced breathing

Diaphragmatic dysfunction was seen on the side contralateral to the lesion in 11.5% (n = 6), while on the ipsilateral side no dysfunction was seen in any patient (p = 0.014). The median thickening fraction was 38% [27% – 72%] on the contralateral side vs 75% [55% – 85%] on the ipsilateral side (p < 0.,0001).

It was seen that 42.1% of the subjects with small vessel involvement had diaphragmatic dysfunction. Of the patients with large artery involvement, 62.5% of those with the middle cerebral artery (MCA) involved had diaphragmatic dysfunction. These data are given in Table 2.

Table 2: Vascular territory affected and diaphragmatic dysfunction.

Artery	Dysfunction		No dysfunction	Total*
Small vessel	8	(42.1%)	11 (57.9%)	19
ACA	1	(25%)	3 (75%)	4
MCA	20	(62.5%)	12 (37.5%)	32
PCA	1	(25%)	3 (75%)	4
Carotid	1	(100%)	0	1
Total	23		18	41

p = 0.313, Chi-squared test. ACA: Anterior cerebral artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery.

The median in the NIHSS scale was 2 (1 – 3) in patients without diaphragmatic dysfunction and 6 (4 – 15) in patients with diaphragmatic dysfunction. The NIHSS scale was divided into 3 subgroups²⁵ and it was seen that all patients with NIHSS above 6 had diaphragmatic dysfunction on the contralateral side. Of the six patients under forced breathing with NIHSS within 7-15, five had diaphragmatic dysfunction. Significant differences were reached in both cases (p < 0.001). The data are given in Table 3.

Table 3: Diaphragmatic dysfunction and NIHSS in subgroups.

	Basal breathing*		Forced breathing**	
	Dysfunction	No dysfunction	Dysfunction	No dysfunction
NIHSS 0 - 6	17 (44.7%)	21 (55.2%)	1 (2.3%)	42 (97.6%)
NIHSS 7 - 15	7 (100%)	0	5 (83.3%)	1 (16.6%)
NIHSS ≥ 16	7 (100%)	0	0	3 (100%)

* Chi-squared test, $p < 0.001$ ** Chi-squared test, $p = 0.002$.

With regard to the relationship between the degree of hemiparesis and diaphragmatic dysfunction it is seen that both under normal breathing and forced breathing patients with dysfunction had lower degrees of muscle strength in the scale as compared to patients without dysfunction, on a statistically significant basis ($p < 0.001$). The data are given in Table 4.

Table 4: Scale of hemiparesis and its relationship with diaphragmatic dysfunction.

	Basal breathing*		Forced breathing**	
	Dysfunction	No dysfunction	Dysfunction	No dysfunction
0	0	0	0	0
1	6 (100%)	0	1 (50%)	1 (50%)
2	6 (100%)	0	3 (50%)	3 (50%)
3	10 (100%)	0	2 (20%)	8 (80%)
4	6 (54.5%)	5 (45.4%)	0	11 (100%)
5	3 (11.1%)	24 (88.2%)	0	23 (100%)

Representation of the scale of hemiparesis and its relationship with diaphragmatic dysfunction in the different moments and forms measured. * $p < 0.001$. ** $p = 0.002$.

The relationship between the reperfusion techniques and the diaphragmatic dysfunction under normal breathing and under forced breathing did not show any statistically significant data. The data are summarised in Table 5. Similarly, effective reperfusion did not provide statistically significant data either, as shown in Table 6.

Table 5: Reperfusion techniques and the diaphragmatic dysfunction under normal breathing and under forced breathing.

	Basal breathing*		Forced breathing**	
	Dysfunction	No dysfunction	Dysfunction	No dysfunction
No therapy	17 (48.6%)	18 (51.4%)	3 (9.7%)	28 (90.3%)
Thrombolysis	6 (50%)	6 (50%)	2 (20%)	8 (80%)
Thrombectomy	8 (72.7%)	3 (27.3%)	1 (11.1%)	8 (88.9%)
Both therapies	0	2 (100%)	0	2 (100%)

*p=0.237. **p=0.785.

Table 6: Effective reperfusion and diaphragmatic dysfunction.

	Basal breathing		Forced breathing	
	Dysfunction	No dysfunction	Dysfunction	No dysfunction
TIBI 2	2 (100%)	0	1 (100%)	0
TIBI 3	1 (25%)	3 (75%)	1 (25%)	3 (75%)
TIBI 4	1 (100%)	0	0	0
TIBI 5	2 (40%)	3 (60%)	0	5 (100%)
TICI 2b2	2 (66.7%)	1 (33.3%)	1 (50%)	1 (50%)
TICI 3	6 (60%)	4 (40%)	0	9 (100%)

Discussion

This is the first study to evaluate the incidence of diaphragmatic dysfunction in acute supratentorial stroke, obtaining an overall incidence of 51.7%. This diaphragmatic dysfunction is seen mainly on the side contralateral to the brain injury, where dysfunction is seen in 51.7% of the cases vs 1.7%, where it is seen on the ipsilateral side. Under forced breathing, the increased inspiratory effort reduced the incidence of diaphragmatic dysfunction to 11.5%. The previous studies evaluating diaphragmatic dysfunction in stroke were performed in patients with hemiparesis and none early after the diagnosis^{1,27}. In 1988, Santamaría and Ruiz²⁸ observed diaphragmatic dysfunction in 62 patients with recent hemiparesis due to supratentorial stroke after comparing the chest X-rays of these patients to those of subjects with brain diseases. Subsequently, in 1994, Cohen et al²⁹ reported similar results in patients with hemiparesis between 9 days and 14 months before.

The relationship existing between diaphragmatic dysfunction and ischaemic stroke can be explained both by the change in the voluntary function of the diaphragm due to a lesion in the corticospinal tract and by the lack of automatic control through the bulbospinal tract^{5,6}. However, other studies have suggested that the involvement of the diaphragm in stroke may be due to a disorder in the corticodiaphragmatic pathways³⁰. Using magnetic stimulation techniques, it has been seen that the response of the diaphragm to stimulation of a single brain hemisphere is mainly contralateral, and there

is a lower response in the ipsilateral side³¹. This response in the ipsilateral side is explained by the presence of small cross connections between the two phrenic nerves, originating bilateral innervation of the diaphragm³⁰. These connections were also studied in patients with unilateral diaphragmatic dysfunction that show dyspnoea, where an impairment is seen in the pressure generated by the theoretically healthy diaphragm³².

Diaphragmatic dysfunction is not a disease commonly diagnosed, in particular in the case of an unilateral injury³³. In our study we used ultrasonography to make the diagnosis of diaphragmatic dysfunction, through the analysis of the thickening fraction. The study of lung and diaphragmatic function by ultrasonography was characterised by Khedr et al in 2000⁵ and Jung et al in 2014⁶ who observed a correlation between clinical motor deficit in patients with hemiparesis and the hemidiaphragmatic excursion on the side ipsilateral to the hemiparesis. Ultrasonography is a technique with advantages derived from its non-invasive nature, at the bedside of the patient³⁴ and with no radiation²². In addition, it allows to view images in real time and analyse the muscle independently from the effort of the patient^{16,17,23}. Using this technique, the diaphragm can be seen as two hyperechogenic layers corresponding to the peritoneal wall and the pleural wall together with an intermediate hypoechoic line corresponding to the muscle itself¹⁶.

Upon breathing, the diaphragm contracts and this results in a muscle thickening proportional to contraction³⁵. Therefore, diaphragmatic function can be evaluated by the analysis of thickening of the diaphragm during its contraction, which corresponds to the thickening fraction¹⁶. Although other studies previously measured the diaphragmatic excursion^{5,6}, in our case we have studied the thickening fraction due to the difficult evaluation of the left window that is obtained with the low-frequency probe necessary for the excursion^{9,33,36}. In addition, the diaphragmatic excursion reflects the inspiratory volume that may be influenced by participation of the accessory muscles, responsible for 20% of the respiratory effort^{5,9,10}.

In our sample, we have seen that the highest percentage of patients with diaphragmatic dysfunction is seen in those affected by stroke in the MCA territory. The relationship of diaphragmatic dysfunction with involvement of the vascular territory of the MCA has been previously described in the literature^{1,5,27}, explained by the motor involvement secondary to the injury in the corticospinal tracts³⁷.

The relationship between clinical severity measured by the NIHSS scale and the diaphragmatic dysfunction has provided clinically and statistically significant data. In line with previous studies²⁶, we have found a close relationship between a score above 6 points in the NIHSS scale and diaphragmatic dysfunction, both under normal breathing and forced breathing. Similarly, we have observed a statistically significant association between the degree of hemiparesis and diaphragmatic dysfunction. However, 23% of the patients with diaphragmatic dysfunction do not experience muscle weakness. This can be because the site of the stroke can affect differently some corticospinal tracts or others, and cases with exclusive involvement of the lower extremity are seen³⁸. Even so, more studies are required designed

to evaluate adequately the association between diaphragmatic dysfunction and the severity of stroke and the degree of hemiparesis.

With regard to the treatment of ischaemic stroke, in our study we have not found any significant relationship between the administration of reperfusion treatment and the development of diaphragmatic dysfunction. Patients undergoing MT had proportionally higher diaphragmatic dysfunction rates (72.7%), possibly because they were patients in a worse clinical condition. However, analysing the degree of reperfusion using the TICl scale, it must be noted that 66.6% of the patients with TICl 2b had diaphragmatic dysfunction as compared to patients with complete recanalisation (TICl 3. 0 patients). There is a similar relationship with the patients treated with alteplase iv, where it is seen that both patients (100%) with TIBI 2 show diaphragmatic dysfunction as compared to 40% of the patients with TIBI 5.

The evaluation of the diaphragmatic function after an ischaemic stroke could have potential clinical consequences. Development of respiratory failure, atelectasis and respiratory infections has been described, as well as a reduction in the cough reflex in these patients³⁹. In addition, the early diagnosis of this dysfunction could reinforce rehabilitation treatment for the purpose of improving recovery of respiratory function in these patients.

Our study sample comprised 60 patients. As it is a pilot study, the sample has been sufficient to obtain the incidence of diaphragmatic dysfunction. However, when dividing the sample into subgroups we found limitations in some comparisons and could not achieve statistical significance, despite noticing a clinical tendency to the differences observed between subgroups. In addition, the limitation for performing deep breathing in some patients has made the sample to decrease even further in this group. A limitation common in many of the studies is the subsequent reproducibility and the within-observer variability that can exist in the same test. It must be noted that within-observer variability, despite being limited in the thickening fraction⁴⁰, has been removed in our case as all ultrasonographies were performed by the same observer.

Conclusions

The incidence of diaphragmatic dysfunction in patients with supratentorial ischaemic stroke in the first 48 hours is high (51.7%). Considering its potential clinical implications, studies are required to evaluate the incidence of respiratory complications in these patients, as well as the impact of respiratory rehabilitation in the clinical prognosis. A fast, simple estimation of diaphragmatic function can be obtained by ultrasonography from the analysis of the thickening fraction.

List Of Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; CT: Computerised Tomography; MRC: Medical Research Council; MT: Mechanical Thrombectomy; NIHSS: National institute of Health Stroke Scale; NYHA: New

York Heart Association; SAHS: Sleep Apnoea-Hypopnoea Syndrome; TIBI: Thrombolysis in Brain Ischemia; TICI: Thrombolysis in cerebral infarction.

Declarations

Ethics approval and consent to participate: Our clinical research was reviewed and approved by the Clinical Research Ethics committee of the University Hospital Complex of Albacete, and was approved on 17 October 2017 with act number 09/2017. We obtained patients' written consents for their clinical information and diaphragmatic exploration.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests: The authors declare that they have no competing interests.

Authors' contributions: JVC carried out the diaphragmatic exploration, interpreted the patient data and was a major contributor in writing the manuscript. JAM supervised the data collection and review the manuscript. FH was responsible for the diagnosis and neurological management of the patients and review the manuscript. All authors read and approved the final manuscript.

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