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Detection of airway protective level of the cough reflex in acute stroke patients

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Abstract

Background: The most common respiratory complications in cerebrovascular strokes were respiratory infection, pulmonary edema, acute lung injury (ALI) acute respiratory distress syndrome (ARDS) and pulmonary embolism (PE). The inhalation cough challenge facilitates the quantification of cough.

Objectives: To detect the level of cough reflex that is enough to protect against respiratory infection in stroke patients, and to identify predictors of post-stroke respiratory infection.

Patients and methods: One hundred and one of cerebrovascular stroke patients were assessed in the first week of symptoms by National Institutes of Health Stroke Scale (NIHSS) Arabic version, Mann Assessment of Swallowing Ability (MASA), cough challenge test, cough flow meter, and A2DS2 score. Then, follow up after 1 week.

Results: Post-stroke respiratory infection was higher in older patients and those who were not working. Respiratory infection was significantly associated with high A2DS2 and NIHSS score (p value < 0.001). A highly significant increase in the levels of the inflammatory markers was detected in patients with a respiratory infection. Eighty percent of stroke patients with no cough developed a respiratory infection. The Mann total scores and the peak cough flow were lower in patients who had a respiratory infection.

Conclusion: Preserved cough reflex is essential in preventing aspirations and consequent respiratory infections.

Keywords: Post-strokes respiratory complications, Cough reflex, Mann Assessment of Swallowing Ability

Introduction

Respiratory infection is the second most common cause of death in acute stroke, and stroke patient may develop any type of pneumonia: hospital-acquired, community-acquired, or aspiration pneumonia [1]. Cough reflex plays a very important role in airway protection, the site of aspiration into the lung is the larynx, there are two main types of laryngeal mechanism that prevent aspiration: those that close the glottis and those that expel material that might be inhaled into the lung [2]. Both voluntary and reflex cough decrease after acute hemispheric infarction so cough challenge test has been shown to be a reliable method for predicting post-stroke pneumonia, additionally citric acid is the only one that has been found to stimulate mechanoreceptors and chemoceptors [3]. Stroke guidelines require that a trained clinician screen individuals admitted with stroke for dysphagia with standardized tools. Those patients with a positive dysphagia screen result should be kept "nil by mouth" (NBM) and a full assessment of swallowing within 24 h should be carried out [4]. The aims of this article are to detect the level of cough reflex that is enough to protect against respiratory infection, to identify risk factors for post-stroke chest infection, and to assess swallowing ability in patients with post-stroke respiratory infection.

Patients and methods

This is an observational prospective study, conducted on 101 consecutive patients with recent cerebrovascular stroke (recruited within the first week of stroke) both ischemic and hemorrhagic types, whether first stroke or recurrent stroke if the previous strokes were not known to affect the swallowing ability or cough reflex. We excluded mechanically ventilated patients, asthmatic patients or have a known medical condition—other than stroke—affecting swallowing or cough uncooperative patients due to disturbance in the conscious level and stroke patients who were treated

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with thrombolysis and showed rapid change in NIHSS. Patients were selected from the intermediate and intensive care unit, Kasr Al Aini Hospitals, Department of Neurology, between September 2016 and April 2018. The sample size was calculated using the Medcalc program, setting the type-1 error (α) at 0.05 and power at 80%. The result from a pilot study conducted on a sample of acute stroke patients showed that using ROC curve analysis, cough threshold could be used to discriminate cases with aspiration pneumonia (area under curve = 0.663), with a 40% prevalence of aspiration pneumonia. Calculation according to these values produced a minimal sample size of 100 stroke cases

The procedures and aim of the study were explained to every participant and informed consent was obtained before being enrolled in the study. The study was approved by the ethical committee of Faculty of Medicine, Cairo University. The inpatient general health services was equal to all patients according to The Guidelines for Infection Prevention and Control Protocol in hospital.

Within the first week of the onset of stroke all the patients were subjected to (a) assessment of stroke severity: using the Arabic version of the NIHSS (arNIHSS)

to quantify the neurological deficit in acute stroke [5]. (b) Mann Assessment of

Swallowing Ability (MASA) with a score of 178 is considered to be the cut-off for the absence of dysphagia, and 170 is for the absence of aspiration risk [6]. (c) A2DS2 score: it is a 10-point score [age ≥ 75 years = 1, atrial fibrillation = 1, dysphagia = 2, male sex = 1, stroke severity, National Institutes of Health Stroke Scale 0–4 = 0, 5, 15 = 3, ≥ 16 = 5; A(2)DS(2)] [7]. (d) Cough challenge test using citric acid: to stimulate both chemosensitive C-fibres and mechanosensitive A-fibres [8]. It was used to assess the cough threshold, latency, number of coughs after stimulation, and the cough peak flow. Citric acid was diluted in 0.9% sodium chloride, to obtain 10 different concentrations, ranging from 0.8 to 2.6, increasing in increments of 0.2 [9].. These included a lower dose of 0.8 mol/L at which 92.5% of healthy individuals produced a natural cough (an evoked, cortically modulated cough) and a higher dose of 1.2 mol/L at which 80% of healthy individuals were no longer able to suppress a cough (a true reflex cough). "Single breath" method of administration was used. The delivery of citric acid was via the facemask method. Each dose was administered 3 times, with the nebulizer running for 15 s each trial. There was a 30-s interval between each inhalation to prevent tachyphylaxis, which was based on the protocol proposed by Morice and co-workers [10]. The cough threshold is determined when the patient is able to cough at a certain concentration on at least two trials of the three. If the patient did the cough test, patients were judged whether the cough response was strong or weak subjectively. Absence of a natural cough at 0.8 mol/L or the ability to suppress a cough at the higher dose was considered a failed test and cough latency is the period between the start of citric acid inhalation and the onset of cough, it is measured in seconds. Cough flow meter is a small portable device used to measure the peak cough flow. It is important to clarify that no patient had citric acid induced bronchoconstriction or other side effects. (e) Radiological workup; chest X-ray and CT or MRI brain, (f) laboratory work; total leucocytic count (TLC), erythrocyte sedimentation ratio (ESR), C-reactive protein (CRP).

After 1 week, the patients were divided into two groups, those who did not developed respiratory infection (as a control group) and those who suffered from post-stroke respiratory infection confirmed by clinical assessment including fever (> 38 °C), purulent sputum, tachypnea (> 22/min), inspiratory crackles and bronchial breathing, tachycardia, abnormal chest X-ray or CT chest and elevated TLC, ESR, CRP, and organism isolation in case of aspiration pneumonia.

Statistical analysis

Data were coded and entered using the statistical package SPSS, version 25; SPSS Inc., Chicago, IL, USA. Data was summarized using mean and standard deviation for quantitative variables, median and interquartile range for non-parametric numerical data, and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Student's t test was used for comparing two groups. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test or unpaired test in normally distributed quantitative variables while non-parametric Kruskal–Wallis test and Mann–Whitney test were used for non-normally distributed quantitative variables. For comparing categorical data, chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than five. Correlations between quantitative variables were done using the Spearman correlation coefficient. The sensitivity and specificity for quantitative diagnostic measures were calculated by using the ROC curve (receiver operating characteristic). p values less than 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

Demographic and clinical data at presentation are represented in Table 1. The patients' examination on admission revealed that most of them (72.3%) had clear chest, and about 74.3% had normal chest X-ray, these percentages changed after 1 week of admission as 44% developed signs and symptoms of chest infection, and 46%

Table 1 Demographic and clinical data characteristics for all patients

Demographic and clinical data characteristics		
Age in years (mean ± SD)		59.59 ± 13.12
A2DS2 (mean ± SD)		4.26 ± 1.62
NIHSS(mean ± SD)		10.83 ± 5.53
MANN total (mean ± SD)		154.59 ± 43.66
Sex (no (%))	Male	60 (59.4%)
	Female	41 (40.6%)
Habits (no (%))	No	64 (63.4%)
	Smoking	35(34.7%)
	Other drug abuse	2 (2.0%)
Occupation (no (%))	Not working	63 (62.4%)
Handedness (no (%))	Right	98 (97.0%)
	Left	3 (3.0%)
Medical history (no (%))	Medical problem (DM, HTN, IHD, AF, and MI)	61 (60.4%)
	Neurological problem	2 (2.0%)
	Medical and neurological problem (epilepsy, TIA, and migraine)	21(20.8%)
Medication (no (%))	Drug affecting cough (ACE inhibitors)	23 (22.8%)
	Drug not affecting cough	41 (40.6%)
CVS TYPE (no (%))	Arterial ischemic	87 (86.1%)
	Arterial hemorrhagic	11 (10.9%)
	Venous ischemic	2 (2.0%)
	Venous hemorrhagic	1(1.0%)
CVS location (no (%))	Right anterior circulation	42 (41.6%)
	Left anterior circulation	39 (38.6%)
	Right posterior circulation	9 (8.9%)
	Left posterior circulation	11(10.9%)

AF atrial fibrillations, *ACE* inhibitors angiotensin-converting enzyme inhibitor, *DM* diabetes mellitus, *HTN* hypertension, *MI* myocardial infarction, *TIA* transient ischemic attack

had findings in their chest X-ray that suggested respiratory infection.

The mean TLC on admission was 9.06*103 with a shift to the left 2.28, raised after 1 week to be 10.49*103 and 4.08, respectively. Other inflammatory markers were high; the mean ESR level on admission was 20/45 compared to its levels after 1 week, 5/46. The mean CRP level on admission was around 75 then became about 83.12 after 1 week. Sputum samples obtained from only 41 patients who were having a productive cough. The microbiological organism growth mainly Klebsiella (8%) whether alone or with other organisms and aerobic and with lesser extent acinetobacter was found with a percentage of 4% MRSA and E. coli (2%). Forty patients developed a respiratory infection, 35 of them fulfilled the criteria for aspiration pneumonia and 5 were diagnosed with bronchitis.

The stimulated cough was positive in 91 patients who were able to cough on stimulation with citric acid while the rest had a negative cough challenge test (at citric acid concentration 2.6 M they either could not cough at all or had a cough in only one of the three trials) (Table 2).

Descriptive statistics and comparison according to the occurrence of respiratory complications

Older patients tended to have respiratory complications (63.4 ± 10.27). The higher the scores on A2DS2 score (5.5 ± 1.26) and 15 (10.5–17.5) NIHSS score the higher the possibility to develop a chest infection. While Mann scores (180.17 ± 20.92) showed that the scores were higher in patients who had no infection by the end of the study with statistically significant, on the other hand, there was no significant difference between both groups as regard gender, smoking, and handedness. Moreover, the peak cough flow was significantly lower in patients with respiratory infection with a p value < 0.001, and patients with no cough recorded the highest mean value on A2DS2 and NIHSS with $p = 0.001$ (Table 3).

All the inflammatory markers increased in the respiratory infection group but decreased in the non-infection group (p value < 0.001).

Descriptive analysis and comparison according to the cough challenge test

Patients with no cough recorded the highest mean value on A2DS2 and NIHSS 5.6 ± 1.26 and 14.5 ± 4.88, respectively, followed by patients with a weak threshold 4.94 ± 1.7 and 12.03 ± 6.65 with the least value 3.61 ± 1.31 and 8.67 ± 4.12 in patients with normal cough threshold. With a significant difference between the 3 groups $p = 0.00$ and $p = 0.001$, respectively.

Respiratory infections were detected in 80% of patients with absent cough, in comparison to 50% of patients with a weak threshold and 26.3% of patients with a normal cough threshold of $p = 0.002$.

Detect cut-off points

We found the cut-off point of the cough threshold for chest infection incidence at concentration > 1 ml of the citric acid test, with a significant p value and the

Table 2 Cough challenge for the whole group

Cough challenge: No = 91(%) = 90.1%	Mean	SD	Median (IQR)
Threshold (mol/L)	1.08	0.49	0.8 (0.8–1.2)
Number of coughs	2.67	1.07	3 (2–3)
Peak flow (L/min)	128.57	88.54	100 (70–150)
Latency (s)	6.87	3.49	6 (4–10)

Table 3 Descriptive statistics and comparison according to the occurrence of respiratory infection

Variables		Respiratory infection		Fisher's exact test	
		No	Yes		
		Mean ± SD	Mean ± SD	*p* value	Sig
Age		57.1 ± 14.23	63.4 ± 10.27	0.011[(T)]	S
A2DS2		3.44 ± 1.28	5.5 ± 1.26	<0.001	S
MANN total		180.17 ± 20.92	116.23 ± 40.76	<0.001	S
		No. (%)	No. (%)	*p* value	Sig
Sex	Male	36 (59.02%)	24 (60%)	0.922[(C)]	NS
	Female	25 (40.98%)	16 (40%)		
Habits	No	35 (57.38%)	29 (72.5%)	0.114	NS
	Smoking (Cig., hash, shisha)	25 (40.98%)	10 (25%)		
	other drug abuse	1 (1.64%)	0 (0%)		
	Smoke + other drug	0 (0%)	1 (2.5%)		
Occupation	Not working	31 (50.82%)	32 (80%)	0.003[(C)]	S
	Working	30 (49.18%)	8 (20%)		
Handedness	Right	59 (96.72%)	39 (97.5%)	1.00	NS
	Left	2 (3.28%)	1 (2.5%)		
		Median (IQR)	Median(IQR)		
NIHSS		7 (6–10)	15 (10.5–17.5)	<0.001[(M)]	S
Cough challenge	Threshold (mol/L)	0.8 (0.8–1)	1 (0.8–1.7)	0.013	S
	Number of coughs	3 (2–3)	2 (2–3)	0.289	NS
	Peak flow (L/min)	140 (90–200)	70 (55–100)	<0.001	S
	Latency (s)	6 (4–8)	7 (4.5–10)	0.146	NS

Significance level $P < 0.05$, *S* = significant, *NS* = non-significant
[(C)]Chi-square test of significance
[(M)]Mann-Whitney test of significance
[(T)]Student's *t* test of significance

correlation between the peak cough flow and the incidence of post-stroke pneumonia was significant, the cut-off point of the peak flow was found to be <= 100 with a *p* value < 0.001 (Table 4).

Discussion

Predictors of post-stroke respiratory infection and the level of cough reflex that is enough to protect against respiratory infection remains a challenge. So far, clinical predictors and tests have offered prognostic values [9]. We included acute stroke patients whether they had dysphagia or not, and the citric acid used in titrating concentrations from 0.8 to 2.6, and the follow-up was only for 1 week. The goal of this work is to administer the swallowing ability test and cough reflex challenge to all stroke patients to predict post-stroke aspiration pneumonia.

In this observational prospective study, the mean age of stroke patient was around 60 years old, males more than females, most of our stroke patients were unemployed and 60.4% had previous positive medical problems such as DM, our results were nearly the same as reported by Thrift and colleagues 2017 [11].

In the current study, stroke patients who were older ages and unemployed had significantly higher rates of developing respiratory infections than those who did not. High NIHSS score exposes stroke patients to a higher risk of post-stroke pneumonia. Sellars and colleagues [12] found that NIHSS score more than 6 is predictive of post-stroke pneumonia. Also, these findings were consistent with the study carried out by Westendrop and colleagues [13].

No statistically significant difference was found between males and females as regards developing chest infection,

Table 4 ROC curve for threshold and peak flow of cough challenge

	AUC	95% CI	*p* value	Sig.	Cut-off point	Sensitivity	Specificity	PPV	NPV
Cough threshold	0.638	0.530 to 0.736	0.0148	S	> 1	43.75	83.05	58.3	73.1
Cough peak flow	0.797	0.700 to 0.874	<0.001	S	<= 100	84.37	62.71	55.1	88.1

AUC = area under curve, *CI* = confidence interval, *NPV* = negative predictive value, *PPV* = positive predictive value, *S* = significant

so was smoking. Also, stroke location either anterior or posterior circulation, type, past medical history, and medications did not show a significant difference between patients with and without post-stroke chest infection.

All our stroke patients had a significantly higher cough threshold level (1.08 mol/L) than the normal value (0.8 mol/L); this is consistent with the results of [14] who studied the cough reflex in post-stroke patients and found that its mean values were higher than the values of the healthy volunteers, in common we both found that stroke patients needed higher citric acid concentrations than healthy individuals.

It is worth the attention that impairment of swallowing is associated with an increased risk of aspiration. In our study, the difference in the total MANN score between the patients that developed respiratory infection was significantly higher than that those did not have any respiratory complications, this is consistent with the results of Vilardell and colleagues [15] who stated that incidence of post-stroke pneumonia has been found to be significantly increased with both impaired swallowing and cough responses.

Moreover, regarding the level of cough reflex and incidence of respiratory infections, chest infection occurs in 80% of our stroke patients with absent cough, in comparison to 50% in stroke patients with a weak cough. Our results were consistent with the results from Field and colleagues [16] who found higher aspiration pneumonia rates in patients with absent cough (25%) than those with weak cough (7.7%) and the least found in patients with strong cough (0%). These findings interpreted in the context that the absence of a protective cough reflex exposes stroke patients to one of the most post-stroke morbidities which is pneumonia. Although our results were inconsistent with those found by Miles and colleagues [17].

In the present study, we found significant negative correlation between the NIHSS score and cough reflex levels, as patients with no cough had the highest mean NIHSS then weak then normal cough group who had the lowest NIHSS mean score; this result is consistent with Vilardell and colleagues [18] that stated that incidence of post-stroke pneumonia has been found to be significantly increased with both impaired swallowing and cough responses.

Stroke patients with absent cough reflex had the highest score of A2DS2 followed by those with weak cough, and the least score was found in patients with normal cough threshold; the difference was significant between the three groups as the higher the patient score A2DS2, the higher the possibility to develop a chest infection. These results were supported by a previous study by Zapata-Arriaza and colleagues [19] that stated that the A2DS2 score is a valid tool to predict aspiration pneumonia. In our study, it correlated significantly with the cough threshold, PCF, and no. of coughs. Unfortunately, we did not find a study that made such a correlation before, but the cough threshold and peak flow were correlated with the risk of pneumonia in many studies.

We found that dysphagia correlated significantly with weak voluntary cough ability in acute stroke patients as the MASA scores correlated significantly with all the items of the cough challenge test. These results matched with another important study by Ward and colleagues [3] that assessed VC and RC by measurements of airflow and gastric pressure.

The present study revealed that inflammatory markers ESR and CRP showed non-significant between the three groups on admission, but after 1 week the CRP showed significant difference unlike the ESR that the difference remained nonsignificant, this goes in accordance with Zapata-Arriaza and colleagues [19] who stated that CRP more sensitive and responds more quickly to changes in the clinical situation. To the best of our knowledge, this study is the first to highlights this correlation.

In the current study, cut-off values showed that the citric acid threshold was > 1 mol/L. Nakajoh and colleagues [20] documented swallowing latency of response longer than 5 s and a cough threshold higher than a concentration of 1.35 mol/L. We, thus, recommend that every institution must have its own reference cut-off value.

We detected the cut-off value for the peak cough flow in post-stroke respiratory infection to be <= 100 L/min. Bianchi and colleagues, 2012 reported a cough peak flow of lower than 242 L/min predicting the development of pneumonia [21] while Sohn and colleagues, 2018 found that cut-off flow of 59 L/min diagnosed dysphagia attributable to cerebrovascular disease and the incidence of aspiration pneumonia in 6 months and the citric acid concentration used was 0.28 mol/L [22], this is different than our methodology. Regarding the cough latency and number of coughs after stimulation, their cut-off values were non-significant.

We should address that our study is limited by a small number of participants and a short follow-up duration.

Conclusion

From all previous results, cough challenge test is a predictive tool to assess the level of cough reflex that is needed to protect the airway against aspiration in acute stroke patients, and we recommend cough reflex challenge to all stroke patients to anticipate aspiration pneumonia. Moreover, it could be concluded that elders, non-workers, and high NIHSS scores all are risk factors for developing a post-stroke respiratory infection. Positive correlation between A2DS2 scale and post-stroke chest infection while a negative correlation between MASA scores and occurrence of post-stroke chest infection.

Abbreviations
ACE inhibitors: Angiotensin-converting enzyme inhibitor; ALI: Acute lung injury; ANOVA: Analysis of variance; ARDS: Acute respiratory distress syndrome; arNIHSS: Arabic version of the NIHSS; CRP: C-reactive protein; CT: Computerized tomography; E. coli: Escherichia coli; ESR: Erythrocyte sedimentation ratio; MASA: Mann Assessment of Swallowing Ability; MRI: Magnetic resonance imaging; MRSA: Methicillin-resistant Staphylococcus aureus; NBM: Nil by mouth; NIHSS: National Institutes of Health Stroke Scale; PE: Pulmonary embolism; TIA: Transient ischemic attack; TLC: Total leucocytic count

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Authors' contributions
ESB participated in the concept and the study design, applying the inclusion and exclusion criteria and drafting the manuscript. SSA participated in the concept and design of the study and is responsible for the laboratory handling, preparation, and analysis of the blood sample. AMA corresponding author and participated in the design of the study and analysis of data, helped in the clinical examination, helped in applying the inclusion and exclusion criteria, and performed the statistical analysis AMH participated in the concept and design of the study, is responsible for the coordination and recruitment of participants, and helped in the clinical examination and data analysis. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to the current Cairo University regulations and Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

Ethics approval and consent to participate
Informed written consent was taken from each patient. All data obtained from every patient were confidential and were not used outside the study. The patients have the right to withdraw from the study at any time without giving any reason. All the cost of the investigations was afforded by the researcher. Our study was approved by the ethical committee of the Department of Neurology, Faculty of Medicine, Cairo University, on the 6th of July 2017, but Cairo University does not provide the approval reference number.

Consent for publication
Not applicable.

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

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