

# Preponderance of pulmonary aspiration episodes in diabetic neuropathy

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## Abstract

**Background:** Episodes of pulmonary aspiration during swallowing of oropharyngeal contents into the larynx is not so uncommon incidence. However, when severe, it could be an important cause of mortality and morbidity. Such episodes most commonly happen when deglutition reflexes involving closure of the epiglottis and closure of true and false vocal cords and concomitant laryngospasm, during the process of swallowing, do not occur. Coughing reflex is also an important protective reflex against pulmonary aspiration. All these reflexes are impaired or lost when sensory receptors and nerves are damaged or nonfunctioning. Uncontrolled diabetes mellitus for prolonged period leads to generalized peripheral neuropathy, and, hence, there is a possibility of impaired nerves and receptors in the areas of upper respiratory tract also. Therefore, a comparative study on episodes of pulmonary aspiration between normal persons and patients with diabetic neuropathy will not be unreasonable and is, therefore, performed in this work.

**Objective:** To study preponderance of pulmonary aspiration episodes in patients with diabetic neuropathy.

**Materials and Methods:** Thirty-seven healthy persons and 30 patients with known diabetic neuropathy of same age group but of both sexes were chosen for the study. They were then asked to note down any coughing and/or choking episodes during swallowing of food and drinks for a period of 1 week. The results of the two groups were compared and analyzed statistically using standard tests of significance.

**Results:** The results showed that, in control subjects, the fasting blood sugar (FBS) was  $85 \pm 7.12$  mg/dL and, in patients with diabetes,  $122.9 \pm 26.31$  mg/dl. The glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was  $5.1\% \pm 0.72\%$  and  $8.46\% \pm 1.06\%$ , respectively. The number of episodes of coughing and choking incidences during the swallowing of food and drinks (deglutition interruption episodes) in 1-week period was  $1.84 \pm 1.55$  in control subjects and  $7.9 \pm 2.68$  in patients with diabetes. This difference is statistically significant ( $p < 0.05$ ).

**Conclusions:** It is shown in our study that the patients with diabetic neuropathy have greater episodes of coughing/choking incidences, proving indirectly that there are more incidences of increased coughing episodes and impairment of other laryngeal airway reflexes leading to incoordination between these and the swallowing reflexes and, thereby, more pulmonary aspiration episodes in these populations. However, more elaborate studies are required to confirm these findings.

**KEY WORDS:** Pulmonary aspiration, diabetes mellitus, diabetic neuropathy

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## Introduction

For more than the last 150 years, pulmonary and respiratory tract receptors and the reflexes they produce have been studied in an elaborate way. The main interest in these extensive studies has mostly been related to the defensive reflexes such as sneeze and cough, to the physiological role of the receptors in modifying the respiratory and

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cardiovascular systems, and to their potential importance in respiratory diseases.<sup>[1]</sup> By now, we know in gross detail about the mechanisms of receptors in the larynx, lower respiratory tract, and lungs. We also know a good bit of receptors and reflexes related to the upper respiratory tract. However, our knowledge is a bit less regarding the latter, compared with the former, the reason probably being that, in experimental animals, the surgical approach to the nerves of the lungs—the vagus and the sympathetic nerves—is easier than is that to the upper respiratory tract. In addition, the importance of lung reflexes in relation to breathing has been of special interest to physiologists from even before the classical description of the Herring Breuer reflex in 1868.<sup>[2]</sup>

Inspired noxious agents are prevented from entering the lungs by the airway reflexes cough and bronchoconstriction, which are evoked both from the larynx and tracheobronchial tree and from some extrathoracic sites. Certain sites within the airways are particularly sensitive to cough stimulation (e.g., larynx and points of proximal airway branching); however, bronchoconstriction can be triggered from the whole of the tracheobronchial tree. The “irritant” receptors with myelinated afferents give rise to cough and bronchoconstriction in the larynx. Only less is known about the laryngeal nonmyelinated afferents and their reflexes. In the tracheobronchial tree and lung, slowly adapting (SARs) and rapidly adapting stretch receptors (RARs) act in opposing manner on the airway tone: the former mediates bronchodilation, while the latter bronchoconstriction. However, in the process of cough, these two receptors operate concurrently, with a mediatory role for RARs and a facilitatory role for SARs. The bronchial and pulmonary C-fiber endings lead to bronchoconstriction. Inhalation of the so-called “selective” C-fiber stimulants evokes cough; but, the excitation of RARs has not been eliminated. There is also a possibility that the cough arises secondary to other lung actions mediated by these nerve endings. Although same type of receptor mediates both cough and bronchoconstriction, they seem to have different afferent neural pathways.<sup>[3]</sup>

During swallowing, pulmonary aspiration of oropharyngeal contents into the larynx and through the tracheobronchial tree to the lungs is an important cause of deglutition disorder causing much eating discomfort, morbidity, and even occasional cases of mortality. This is all the more important in both anesthesia and critical care settings.<sup>[4]</sup> In 1848, James Simpson recognized aspiration as a cause of an anesthetic-related death.<sup>[5]</sup> Mendelson<sup>[6]</sup> reported two syndromes involving pulmonary aspiration in obstetric patients.<sup>[6]</sup> Aspiration is defined as the inhalation of material into the airway below the level of true vocal cords.<sup>[7]</sup> Normal cough reflex may or may not exist within the range of 3–8 of Glasgow coma score.<sup>[8]</sup> The four physiological laryngeal airway reflexes are described as (i) closure of both true and false vocal cord with laryngospasm; (ii) coughing reflex; (iii) expiration reflex; and (iv) spasmodic panting reflex.<sup>[9]</sup> The larynx and trachea are more sensitive than the bronchus and esophagus. As reflex sensory site,<sup>[10]</sup> reduced airway

sensitivity is reported in and around surgery, under sedative, and in elderly persons.<sup>[11,12]</sup> Diabetic neuropathy may also cause such impairment, and, therefore, a comparative study with normal persons has been ventured here.

## Materials and Methods

Subjects were divided into two groups: one group (group A) acting as controls consists of 37 healthy persons without diabetes, neurological diseases, or any notable disease including cough, aged between 18 and 60 years irrespective of sexes. The other group (group B) taken as test subjects comprised 30 persons provided each one is suffering from diabetes mellitus for a prolonged period (>2 years). The fasting blood sugar (FBS) and glycosylated HbA<sub>1c</sub> were estimated in all the persons to either accept or reject the diagnosis of diabetes mellitus. All the 67 persons (patients and healthy controls) were subjected to thorough history taking and clinical examination. Diabetic persons were further subjected to clinical neurological examinations, including 10-g monofilament sensitivity test, 128-Hz tuning fork sensitivity, ankle and knee jerks, planter reflex elicitation, biothesiometry, and nerve conduction velocity studies in both lower limbs. Only those 30 patients with diabetes were chosen as test subjects who had proven diabetic neuropathy. It was ensured that none of the subjects (test or control) had any respiratory or other illnesses, which could lead to vigorous cough.

FBS was determined by traditional GOD/POD method after taking 8 h fasting blood. Glycated HbA<sub>1c</sub> was determined using an autoanalyzer by direct enzymatic HbA<sub>1c</sub> assay taking 7.0 as cutoff point. Direct Enzymatic HbA<sub>1c</sub> test is an enzymatic assay in which lysed whole blood samples are subjected to extensive protease digestion with *Bacillus* sp. protease. This process results in release of amino acids such as glycated valines from the  $\beta$  chains of hemoglobin. These glycated valines become the substrates for specific recombinant fructosyl valine oxidase (FVO) enzyme, which is produced in *Escherichia coli*. FVO produces hydrogen peroxide by specifically cleaving the N-terminal valines, which can be measured by horseradish peroxidase (POD)-catalyzed reaction and a suitable chromagen. No need to measure total hemoglobin separately in this assay. The HbA<sub>1c</sub> concentration is expressed directly as percentage using a suitable calibration curve in which the calibrators have values for each level.

All the subjects (test and control) were then asked to lead normal regular life for 7 days and to record in a diary the number of episodes of coughing/choking during swallowing of food and drinks for a period of 1 week.

The results of the two groups were compared and analyzed using usual statistical procedures.

## Results

The results showed that, in control subjects, the FBS was  $85 \pm 7.12$  mg/dL and, in test subjects,  $122.9 \pm 26.31$  mg/dL

**Table 1:** Comparison of FBS, HbA<sub>1c</sub> & episodes of coughing and choking (per week) in Group A & B

S. No.	Parameters	Group A	Group B	t	p	Level of statistical significance
1	FBS	85 ± 7.12	122.9 ± 26.31	4.45	<0.005	Highly significant
2	HbA <sub>1c</sub>	5.1 ± 0.72	8.46 ± 1.06	4.54	<0.005	Highly significant
3	No. of episodes of coughing and choking (in 1 week)	1.84 ± 1.55	7.9 ± 2.68	1.61	<0.05	Significant

[Table 1]. The glycosylated HbA<sub>1c</sub> levels were 5.1% ± 0.72% and 8.46% ± 1.06%, respectively. The number of episodes of coughing and choking incidences during swallowing of food and drinks (deglutition interruption episodes) in the 1-week period was 1.84 ± 1.55 in control subjects and 7.9 ± 2.68 in patients with diabetes. This difference is statistically significant ( $p < 0.05$ ).

## Discussions

The results of our study show that the number of episodes of interrupted swallowing or drinking because of occurrence of cough and/or choking, shortness of breath, or respiratory distress were much more and significantly higher in persons with diabetic neuropathy compared with similar phenomenon in a week in normal and healthy control subjects ( $p < 0.05$ ). It is known that the important causes of impaired airway reflexes increased tendency to regurgitate are diabetic autonomic neuropathy and diabetic peripheral neuropathy.

It is important to note that cough and bronchoconstriction are protective reflexes, and these episodes of coughing and choking signifying sudden pulmonary aspiration are because of loss of central integration of swallow and airway protective reflexes in diabetic neuropathy. The reflex bronchoconstriction and closure of both true and false vocal cord do not occur, and instead of food being nicely channeled through the pharynx into the esophagus, it wrongly takes up the laryngeal, that is, respiratory path, leading to all these unwanted coughing and choking phenomenon.<sup>[13]</sup> The relationship between the timing of respiration and swallowing has been proven not to be random. Using pseudo-rabies virus (PRV) as a transsynaptic neural tracer, a basis for the central integration of swallowing and airway-protective reflexes can be located in the neural circuits projecting to swallowing-related muscles.<sup>[13]</sup> The premotor neurons (PMNs) that constitute the swallowing central pattern generators and the interneuronal networks able to initiate repetitive rhythmic muscle activity independent of sensory feedback and connect with multiple areas of the brain stem and other areas of the central nervous system. Those PMNs that project to muscles used in swallowing have been localized within the nucleus of the tractus solitaries (NTS) and its adjacent reticular formation, and they are synaptically linked to both peripheral afferents and cortical swallowing areas. Bertha PRV, an attenuated vaccine strain of swine alpha-herpes virus with a long postinjection survival period and

the ability to produce controlled infections in a hierarchical manner within synaptically linked neurons, can specifically label neurons projecting to PMNs of a given circuit. Thus, it has been used to isolate two neuroanatomically distinct subnetworks of PNMs involved in the buccopharyngeal and esophageal phases of swallowing. Use of PRV as a neural tracer shows that, during the buccopharyngeal phase of following, vagal afferents from the pharynx and larynx and fibers of the superior laryngeal nerve terminate in the intermediate and interstitial subnuclei of the NTS. Motor neurons projecting to the pharynx and larynx are located in the semi-compact and loose formations of the nucleus ambiguus. Through these connections, reflex activities nicely coordinate swallowing and respiratory reflexes, so that respiratory pathway from glottis onward is totally closed during the period of swallowing and airway is protected during that period. During neuropathy, this coordination is impaired.

Effects of these minor but frequent aspirations in patients with diabetic neuropathy would have far reaching consequences with both acute and delayed after effects such as loss of ciliated epithelia and subsequent regeneration with upregulation of cell adhesion molecules, which cause increased thromboxin and oxygen radical release.<sup>[14-17]</sup>

## Conclusions

In conclusion, it can be said that, within our limited setup, which includes mainly clinical criteria, the preponderance of coughing and choking occurring owing to incoordination of airway and swallowing reflexes following at least minor pulmonary aspirations during swallowing of solid and liquid substances is definitely and significantly increased in patients with diabetic neuropathy when compared with normal and healthy controls. This finding has definitely some clinical importance, in as much as this obviously gives a warning to all patients with diabetic neuropathy and autonomic neuropathy to remain aware of this problem and eat and drink carefully and without hurry, and this is also a message to the anesthetists to become even more careful while giving general anesthesia to those particular category of patients.

However, our studies have been primarily a clinical one. Therefore, more elaborate studies with more sophisticated equipments and methodology might be done to demystify the conditions further and to reach a more definitive conclusion.

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