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Time–frequency energy distribution of phrenic nerve discharges during aspiration reflex, cough and quiet inspiration

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ABSTRACT

Aspiration reflex (AspR) represents a specific inspiratory motor behavior expressed by short, powerful inspiratory activity without subsequent active expiration and characterized by the ability to interrupt strong tonic inspiratory activity, as well as hypoxic apnea and several other functional disorders. Multiresolution analysis-based determination of spectral features arising during AspR has not yet been satisfactorily investigated.

The time–frequency energy distribution of phrenic nerve electrical activity was compared during the AspR, inspiratory phase of tracheobronchial cough and quiet inspiration. Data obtained from 16 adult cats anesthetized with chloralose or pentobarbital were analyzed using a wavelet transformation, a sensitive method suitable for processing of the non-stationary respiratory output signal.

Phrenic nerve energy was accumulated within lower frequency bands in AspR bursts. In AspR, higher frequencies contributed less to the total power, when compared to cough inspiration. Moreover, AspR indicated a stable time–frequency energy distribution, regardless of which of the two types of anesthesia were used. Chloralose anesthesia induced a decrease of parameters in cough and quiet inspiration related to the quantity of energy.

The results indicate a specific method of information processing during generation of AspR, underlying its powerful ability to influence various severe functional disorders with potential implications for model experiments and clinical practice.

1. Introduction

The quiet respiratory rhythm is generated by a plastic neuronal network located in the rostral ventrolateral medulla [1–3] in adult mammals and affects a variety of respiratory neuronal structures. Solitary rapid and strong inspiratory effort without subsequent active expiration, known as the sniff- and gasp-like aspiration reflex (AspR), can be evoked by mechanical or electrical stimulation of the nasopharynx in cats and other mammals [4,5]. Nasopharyngeal stimulation evokes a strong pre-motor burst of electric activity in the bulbar inspiratory neurons, followed by similar motor bursts in the phrenic nerves. This short-lasting but very intense inspiratory motor activity is characterized by rapid and strong activation of the inspiratory muscles, resulting in a kind of spasmodic inspiration. Its main functional role, supported by mucociliary transport, is to remove irritants from the upper airways to the hypopharynx through aspiration and their further elimination by cough or swallowing [4,6].

Inspiratory pre-motoneurons are located within the intermedial part of the ventral respiratory group (VRG) and in the

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dorsal respiratory group (DRG) of the medulla. It has been well documented that the discharge pattern of many medullary respiratory neurons activated during quiet breathing, is also markedly altered during coughing. Thus, the respiratory pattern generating network is involved both in production of quiet breathing and coughing [7]. Subgroups of inspiratory neurons in the nucleus tractus solitarius (NTS), are believed to be the primary site of integration related to this sniff-like reflex [8]. Other investigations imply that a long loop of the medullary-pontine-mesencephalic control circuit could be involved in AspR coordination, where the neurons of the lateral medullary tegmental field and the caudal mesencephalic neurons seem to be crucial. As a result of the many similarities in character and intensity derived from the analysis of airway occlusion pressure and airflow in anesthetized cats, a common effector mechanism was suggested for AspR and gasping [9], since common brainstem areas resulting in generation of these reflexes were not directly proved.

The inspiratory effort in AspR was traditionally analyzed from airflow records [9,10]. Several results indicated comparable features of motor manifestation during AspR and gasping, differing markedly from the normal breathing pattern. The analysis of phrenic nerve activity *via* the Short Time Fourier Transform indicated similar power spectra during the AspR and gasping, differing from that found in eupnea [11]. This specification was based on the detection of characteristic spectral signs of high frequency oscillations (HFOs) which were often described as signatures of respiratory network activity [12], being specific for various respiratory efferent systems [13].

However, due to the changing degrees of stationarity in recordings of inspiratory motor outputs, use of methods involving time–frequency localization of spectral features seems to be useful [14]. Moreover, there is a lack of information regarding comparison of spectral components between AspR and other defensive airway reflexes. Thus, this comparison is necessary because the nasopharyngeal stimulation evokes high-frequency impulses in the afferent fibers of the glossopharyngeal nerve, reaching nearly 400 Hz [15] and provocation of such a powerful AspR can interrupt various severe functional disorders [4].

The sniff- and gasp-like aspiration reflex (AspR), elicited by nasopharyngeal stimulation, manifests through marked respiratory, cardiovascular, neuromuscular and bronchomotor changes [4]. AspR can be provoked in any phase of the respiratory cycle and in very deep stages of general anesthesia of different types and during hypothermia, contrary to other airway defense reflexes, such as coughing and sneezing. The powerful AspR is able to interrupt strong tonic inspiratory activity in the phrenic nerve, i.e. apneusis, as well as hypoxic apnea and several other functional disorders in model experiments in animals, similar to "autoresuscitation by gasping" in infants in danger of imminent death from sudden infant death syndrome (SIDS). Various degrees of arousal reaction and resetting of central mechanisms for several vital functions can be elicited as a result of nasopharyngeal stimulation [9,10]. Therefore, AspR provides a unique model for interruption of various functional disorders, at least in animal models. Generating mechanisms and dynamics of time–frequency varying components arising in respiratory motor outputs during AspR are, however, still not fully understood.

In this study, we analyzed the time–frequency distribution of the whole energy stored within phrenic bursts emerging during AspR, the inspiratory phase of the tracheobronchial (TB) cough and quiet inspiration. A method of wavelet analysis suitable for processing of non-stationary respiratory neural activity was used.

The aims of the study were:

1. To investigate the time–frequency energy distribution of phrenic nerve activity during AspR using wavelet transformation

Because of unique inspiratory motor behavior, specific time–frequency energy distribution of phrenic nerve activity is expected in AspR. Method of wavelet transformation, suitable for analysis of non-stationary respiratory outputs, helps to clarify the controversy presented in literature concerning spectral features of aspiration reflex.

2. To compare the properties of phrenic nerve pattern during AspR with the inspiratory phase of tracheobronchial cough and quiet inspiration

Strong AspR without subsequent active expiration probably represents basic initial burst of inspiratory activity. Creation of tracheobronchial cough pattern requires activation of additional circuits that are responsible for preparation of strong expulsive effort. Therefore, wider spectral range of phrenic activity is expected during inspiratory phase of tracheobronchial cough and quiet inspiration under comparison with aspiration reflex.

3. To assess the effect of two different types of anesthesia on the character of phrenic nerve activity during the examined respiratory behaviors

According to the ability of AspR to be elicitated in any phase of the respiratory cycle, as well as in very deep stages of general anesthesia, to interrupt hypoxic apnea and other functional disorders, it would be hypothesized that aspiration reflex presents a stable respiratory pattern, and its energetic distribution is not markedly sensitive to narcosis, contrary to cough or quiet inspiration.

2. Materials and methods

2.1. *Data recording and pre-processing*

The experiments were performed on 16 adult cats (3.0 ± 0.52) kg of both genders. Eight cats underwent pentobarbital anesthesia (PTBT; Pentobarbital, Spofa) with an initial intraperitoneal (i.p.) dose (35–40) mg kg^{-1}. Supplementary doses of anesthetic were given when required. Eight cats were anesthetized with alpha-chloralose (CH; Merck, (40–50) mg kg^{-1}) given i.p. Tracheal airflow, respiratory rate (RR), end-tidal CO_2 concentration ($ETCO_2$) and blood pressure (BP), esophageal pressure (EP) were continuously monitored. Body temperature