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Coordination of cough and swallow: A meta-behavioral response to aspiration

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Airway protections is the prevention and/or removal of material by behaviors such as cough and swallow. We hypothesized these behaviors are coordinated to respond to aspiration. Anesthetized animals were challenged with simulated aspiration that induced both coughing and swallowing. Electromyograms of upper airway and respiratory muscles together with esophageal pressure were recorded to identify and evaluate cough and swallow. During simulated aspiration, both cough and swallow intensity increased and swallow duration decreased consistent with rapid pharyngeal clearance. Phase restriction between cough and swallow was observed; swallow was restricted to the E2 phase of cough. These results support three main conclusions: 1) the cough and swallow pattern generators are tightly coordinated so as to generate a protective meta-behavior; 2) the trachea provides feedback on swallow quality, informing the brainstem about aspiration incidences; and 3) the larynx and upper esophageal sphincter act as two separate valves controlling the direction of positive and negative pressures from the upper airway into the thorax.

1. Introduction

Airway protection is the coordination of several behaviors to prevent and/or correct the aspiration of material into the lungs. Two important behaviors in airway protection are swallow and cough. Swallowing is a coordinated behavior that is dependent upon afferent feedback for initiation and modulation. Touch, pressure, and/or liquid on the tongue, faucial pillars, soft palate, uvula, epiglottis, pharyngeal wall, and/or junction of the pharynx/esophagus can induce swallowing (Miller and Sherrington, 1916; Pommerenke, 1928; Storey, 1968; Miller, 1982). Cough is a reflex which responds to material entering the airway by producing high velocity airflows creating shearing forces in larger airways and squeezing actions in smaller airways to remove mucus and foreign matters (Ross et al., 1955; Fontana and Lavorini, 2006; Widdicombe and Chung, 2007).

Disordered airway protection, is clinically defined as intrusion of material below the level of the vocal folds during swallowing (dysphagia), (DePippo et al., 1992; Aviv et al., 1996; Rosenbek et al., 1996a; Robbins et al., 1999; McCullough et al., 2001a; Kalia, 2003; Robbins et al., 2008; Cichero and Altman, 2012), and/or an impaired/lack of cough response to aspiration (dystussia) (Muz et al., 1989; Martin et al., 1994; Smith Hammond et al., 2001; Kelly et al., 2007). Cough is the most noticeable response to aspiration; however there are a host of responses including swallowing, expiration reflex, increased mucous secretions, and/or alterations contractions of the smooth muscle lining the airway (Bolser et al., 1995; Belvisi and Bolser, 2002; Bolser and Davenport, 2007; Vovk et al., 2007). The patient may also exhibit other clinical indicators such as postural changes and changes in voice quality (McCullough et al., 2001b, 2005; Logemann et al., 2008).

Cough and swallow can both be elicited in experimental models. Cough can be initiated by mechanical stimulation of the trachea or larynx, (Bolser and DeGennaro, 1994; Bolser et al., 2006; Wang et al., 2009; Poliacek et al., 2011) or inhalation of an irritant aerosol (Bolser et al., 1995); and swallow by injection of water

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into the oropharynx, mechanical stimulation of the pharynx, and/or electrical stimulation of the superior laryngeal nerve (Miller and Sherrington, 1915). Swallow is proposed to be generated by a dorsal and ventral medullary network that may share upper airway motor outputs with that of the respiratory pattern generator (Jean, 2001). The central initiation and rhythmogenesis of swallow is thought to be restricted to the dorsal swallow group and not controlled by the ventral respiratory pattern generator (Jean, 2001). On the other hand, the available evidence supports reconfiguration of existing elements of the respiratory pattern generator in the production of coughing (Shannon et al., 1996, 1998, 2004), although some control functions for cough are mediated by brainstem systems that are not required for breathing (Bolser and Davenport, 2002). As such, preclinical data support some sharing of neural elements between the pattern generators for swallow, cough, and breathing but the core network for swallow appears to be anatomically separate within the brainstem from that for cough and breathing (Dick et al., 1993; Oku et al., 1994; Shannon et al., 1996; Baekey et al., 2001).

There are clear clinical associations between dysphagia (disordered swallow) and dystussia (disordered cough) in those with Parkinson's disease and stroke (Smith Hammond et al., 2001, 2009; Pitts et al., 2008, 2009). Training paradigms to influence or prevent episodes of aspiration have been intensely studied (Rosenbek et al., 1991, 1996a,b, 1998; Schmidt et al., 1994; Ali et al., 1996b; Aviv et al., 1997, 2002; Miller et al., 2006; Clave et al., 2008; Miller, 2008; Troche et al., 2010; Voytas and Al Rifai, 2012), however, few treatments have demonstrated therapeutic effectiveness in modifying or preventing aspiration across patient populations. This may be because the primary treatment is for dysphagia with little intervention for dystussia (Bath et al., 1999; Foley et al., 2008; Wheeler-Hegland et al., 2009).

The clinical association between dysphagia and dystussia could be explained simply by the fact that the minimal neural elements for both cough and swallow are located in the brainstem. In this scenario, disease processes such as stroke, would be expected to affect each behavior similarly because of this anatomical association. However, dystussia and dysphagia can occur in patients with neurologic diseases that do not directly affect the brainstem. Alternatively, a more complex, but not mutually exclusive, hypothesis could account for co-depression of cough and swallow in neurological diseases. A central control system could exist that that coordinates the expression of these behaviors to optimize airway protection. Additionally, the coordinated expression of several behaviors, each with unique regulation, to achieve a common goal – such as cough and swallow – is consistent with the hypothesis that response to aspiration is a "meta-behavior." This is analogous to the behavior of autonomous agents used to schedule responses when two or more components are combined to react to incoming stimuli (Guessoum and Briot, 1999). Features of the behavior include "precedence" in which the actions that have little to no central processing take precedence over actions which require additional processing, and "blocking" in which any of the components (behaviors) can block any other action until it is completed. An additional assumption is that the gain or excitability of the components (behaviors) can also be altered without sacrificing homeostasis (Fibla et al., 2010). If these hypotheses are true, this system may be affected and/or impaired by multiple neurologic disease states, which may account for the known clinical associations between disordered cough and swallow. However, the evidence for a coordinating mechanism between reflexive swallow and cough is based solely on inferences from clinical observations.

The aims of this study were to determine if the cough and swallow motor patterns are coordinated and, if so, identify operational principles which govern their interactions following an aspiration event. We hypothesized that during a simulated aspiration, there will be minimal overlap of the cough and swallow behaviors. Furthermore, we speculated that the behaviors interact spatially to optimize mechanical effectiveness during aspiration.

2. Methods

Experiments were performed on 17 spontaneously breathing adult male cats. Ethical approval of the protocol was confirmed by the University of Florida Intuitional Animal Care and Use Committee (IACUC). The animals were initially anesthetized with sodium pentobarbital (35–40 mg/kg i.v.); supplementary doses were administered as needed (1–3 mg/kg i.v.). A dose of atropine sulfate (0.1–0.2 mg/kg, i.v.) was given at the beginning of the experiment to reduce secretions from repeated tracheal stimulation. Cannulas were placed in the femoral artery, femoral vein, and trachea. An esophageal balloon was placed via an oral approach to measure pressure in the midthoracic esophagus. Arterial blood pressure and end-tidal CO_2 were continuously monitored. Body temperature was monitored and maintained at $37.5 \pm 0.5\,^{\circ}C$ using a heating lamp and pad. Arterial blood samples were periodically removed for blood gas analysis. PO_2 was maintained using air mixtures with enriched oxygen (25–60%) to maintain values above 100 mmHg.

Electromyograms (EMG) were recorded using bipolar insulated fine wire electrodes. Seven muscles were used to evaluate cough and/or swallow function: mylohyoid, geniohyoid, thyrohyoid, thyropharyngeus, thyroarytenoid, cricopharyngeus, parasternal, and rectus abdominis. The digastric muscles were dissected away from the surface of the mylohyoid and electrodes were placed on the left mylohyoid. A small horizontal incision was made at the rostral end of the right mylohyoid followed by an incision following the midline for approximately 1 cm to reveal the geniohyoid underneath. Electrodes were placed 1 cm from the caudal insertion of the geniohyoid muscle. The thyroarytenoid electrodes were inserted through the cricothyroid window into the anterior portion of the vocal folds, which were visually inspected post-mortem. Rotation of the larynx and pharynx counterclockwise revealed the superior laryngeal nerve, which facilitated placement of the thyropharyngeus muscle electrodes. The thyropharyngeus is a fan shaped muscle with the smallest portion attached to the thyroid cartilage; electrodes were placed in the ventral, caudal portion of the muscle overlaying thyroid cartilage within 5 mm of the rostral insertion of the muscle. To place the electrodes within the cricopharyngeus muscle, the larynx and pharynx were rotated counterclockwise to reveal the posterior aspect of the larynx. The tissue was palpated for the edge of the cricoid cartilage and electrodes were placed just cranial to the edge of this structure. Thyrohyoid electrodes were inserted approximately 1 cm rostral to the attachment to the thyroid cartilage; those for the parasternal muscle were placed in the third intercostal space, just adjacent to the sternum. The rectus abdominis electrodes were located approximately 2 cm caudal to the xiphoid process just medial to the margin of the rectus abdominis. The positions of all electrodes were confirmed by visual inspection and EMG activity patterns during breathing, cough and swallow.

Cough was induced by mechanical stimulation of the extra and intra-thoracic trachea using a thin polyethylene catheter (diameter 1.27 mm). The catheter was manually rotated along the length of the intra-thoracic trachea. Cough was defined as a burst of activity in the parasternal EMG, followed by (and partially overlapping) a burst in the thyroarytenoid and rectus abdominis, along with a negative to positive change in esophageal pressure. To initiate swallowing, a one-inch long, thin polyethylene catheter (diameter 2.37 mm), attached to a 6 cc syringe was placed into the oropharynx. Water was injected into the pharynx via a syringe (3 cc's). Swallowing was defined as a quiescence of the cricopharyngeus with overlapping activity in the mylohyoid, geniohyoid,