A correlational study of cough sensitivity to citric acid and radiographic features of airway compromise

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ABSTRACT

Patients with an impaired reflexive cough response are at increased risk of pneumonia. This study examined the correlation between cough sensitivity to citric acid and radiographic features of airway compromise. Eighty patients referred for a radiographic assessment of swallowing at an acute hospital over an 8-month period participated in the study. Nebulised citric acid diluted in 0.9% sodium chloride was inhaled through a facemask at four concentrations to assess cough sensitivity. These data were then compared to Penetration Aspiration Scale scores based on radiographic swallowing studies. There was a statistically significant correlation between cough response/lack of response and the radiographic features of airway compromise; that is, patients who had a weak or absent response to inhalation of citric acid were also likely to aspirate silently during radiographic assessment. Sensitivity for identifying absent cough was found to be high at all 4 concentrations (0.750, 0.833, 0.941, 1.000), however specificity was consistently quite low (0.344, 0.456, 0.238, 0.078).

The significant findings of this research suggest that clinicians adopting cough reflex testing into their clinical practice will have a reliable screen for silent aspiration at bedside. Clinicians will be able to identify patients who require instrumental assessment and are at high risk of pneumonia. This will likely, in turn, decrease length and cost of hospital admissions as well as decrease aspiration pneumonia related morbidities.

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CHAPTER 1

Introduction

The term dysphagia refers to disordered swallowing. This often originates from neurological impairment, but can also be the result of structural changes due to injury or cancer and developmental issues. Aspiration is the passage of material into the respiratory tract, below the level of the vocal folds.

In the healthy population, the laryngeal cough reflex protects the respiratory system from aspiration of food or fluids (Addington, Stephens, Widdicombe & Rekab, 2005). In patients with dysphagia, the cough reflex can be impaired or even absent. Consequently, this population can be without vital means of airway protection. This can result in silent aspiration which refers to aspiration that occurs without immediate signs or symptoms (Addington, Stephens & Gilliland, 1999; Addington et al., 2005; Nakajoh, Nakagawa, Sekizawa K, Matsui, Arai & Sasaki, 2000). The standard clinical assessment of swallowing consists of subjective analysis of behavioural features, and this can not reliably identify reduced laryngeal sensation. Research demonstrates that subjective assessments of dysphagia do not detect silent aspiration (Splaingard, Hutchins, Sulton & Chaudhuri, 1988). As a result, this population has an increased risk of developing aspiration-related pneumonia (Splaingard et al., 1988).

This thesis examines the relationship between cough sensitivity to citric acid and levels of airway invasion seen on videofluoroscopic swallowing study (VFSS).

CHAPTER 2

Literature Review

2.1 What is cough?

Cough is a vagally mediated, defensive airway reflex. It consists of a modified respiratory act aimed primarily at generating high flow velocities required for removal of mucus or any other foreign body from the lower respiratory tract (Fontana & Lavorini, 2006). Fontana (2008) defines cough as a three-phase expulsive motor act beginning with an inspiratory effort (inspiratory phase), followed by a forced expiratory effort initially against a closed glottis (compressive phase) and concluding with active glottal opening and rapid expiratory flow (expulsive phase). The inspiratory phase of the cough is important as it differentiates the cough from another airway protective reflex, the expiration reflex (Fontana, 2008). This reflex is comprised of glottal closure and forced expiration followed by glottal opening and expulsive airflow but does not include an initial inspiratory effort. The differences between cough and expiration reflex imply activation of different neural mechanisms (Fontana, 2008) and subsequently serve different functions. Cough will clear the lower airway of debris, including mucus. The expiration reflex will prevent aspiration of material into the lungs (Fontana, 2008). Clinically, it is a combination of coughs (preceded by inspiration) and expiratory reflexes that act to shelter the lower airway and lungs (Fontana, 2008).

Four types of cough, the voluntary cough, reflexive cough, laryngeal expiration cough and cough on swallow, have been described (Widdicombe, Addington, Fontana & Stephens, 2011). The voluntary (volitional) cough has inspiratory, compressive and expulsive phases, as stated in the above paragraph. It originates in the cerebral cortex and is preceded by an intention to cough. The reflexive cough is the cough associated with airway annoyance. The reflexive cough too has inspiratory, compressive and expulsive phases. However, the design and purpose of the reflexive cough is clear: it will expel material that reaches the lower airways, which may block or agitate them. After the initial inspiration that may draw the material into the airways, the reflexive cough will provide a sizeable surge and volume of air that should then eject it. The laryngeal expiration reflex begins with expiration, and is said to be 'anti-aspiration' in nature. The laryngeal expiration reflex involves closure of the glottis, together with a strong reflex expiratory effort forcing the glottis to reopen and expel air from the lungs. Cough on swallowing can be tested only by direct observation of aspiration (during instrumental assessment).

In populations affected by central nervous disorders, like stroke, cough may occur during the clinical swallowing examination. This examination usually involves swallowing a water and/or other bolus; it is presumed that cough on swallowing occurs when the bolus enters the glottis and produces cough as an outward sign. The paradox of this is when the bolus enters the glottis and no cough is triggered. This is silent aspiration (Widdicombe et al., 2011).

2.2 Neurophysiology of Cough

In all species, including humans, the cough reflex follows a fairly straightforward reflex arc (Canning, 2008) (see Figure 1). Chemical or mechanical irritants in the larynx, trachea and large bronchi activate vagal sensory nerves (cough receptors) to discharge an action potential. This potential is then transmitted via sensory afferent fibres of the vagus nerves to the brainstem for processing (Canning, 2008). If the specificity and intensity of afferent nerve signal is sufficient, the cough reflex will be activated (Chang, Phelan, Sawyer, Del Brocco, & Robertson., 1999).

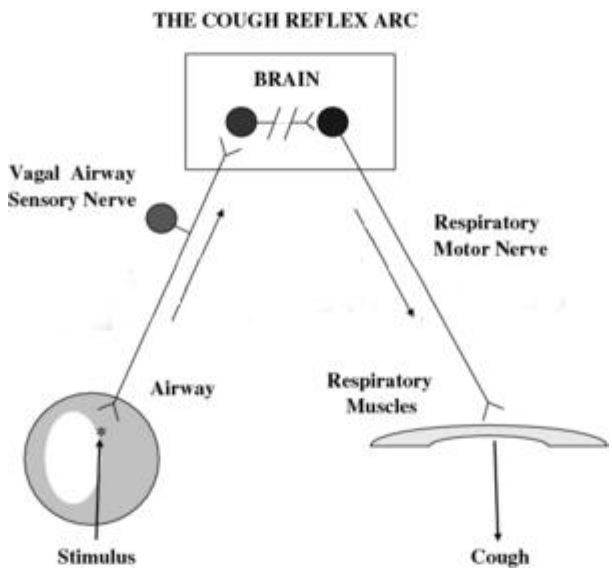

Figure 1.

The Cough Reflex Arc. Irritants in the larynx, trachea and large bronchi activate vagal sensory nerves (cough receptors). The sensory afferent nerves then discharge an action potential, which are transmitted via the vagus nerves to the brainstem for processing (Canning, 2008).

Moving beyond the well-known cough reflex arc, several researchers have evaluated the specific neural mechanisms of cough (Fontana & Lavorini, 2006; Pantaleo, Bongianni & Mutolo, 2002; Shannon, Backey, Morris, Nuding, Segers & Lindsey, 2004; Widdicombe, 1998). The prime stimulatory regions for the cough reflex are dispersed throughout the larynx and tracheobronchial tree (Fontana & Lavorini, 2006). The superior laryngeal nerve carries sensory information from afferent receptors in the larynx (Widdicombe, 1998). The pulmonary branch of vagus serves receptors that are distributed lower down in the tracheobronchial tree and pleural areas (Widdicombe, 1998)

2.3 Volitional and reflexive cough

Cough can be initiated volitionally and reflexively (Widdicombe et al., 2011). Additionally, humans have the ability to both voluntarily induce the cough and suppress it (Hutchings, Morris, Eccles & Jawad, 1993; Lee, Cotterill-Jones & Eccles, 2002; Shannon et al., 2004). These acts differ in the organisation of the motor activity involved (Lasserson, Mills, Arunachalam, Polkey, Moxham & Kaira, 2006). Studies of reflexive coughing triggered by a tussive agent (tartaric acid) consist of early and simultaneous activation of accessory and respiratory muscles. The volitional cough, in comparison, was characterised by sequential activation of muscle groups (Lasserson et al., 2006). Widdicombe et al. (2006) suggested that there is a cortical component to cough, as humans can induce and inhibit the voluntary force. This study went on to detail that stroke patients often have an impaired reflexive and volitional cough, in the absence of brainstem injury (Widdicombe et al., 2006).

In alert individuals, the cough engages a complex integration of brainstem reflex mechanisms and voluntary cortical control (Lee et al., 2002). When volitional initiation of cough occurs, sensory afferents relay in the respiratory area of the brainstem, (the medulla oblongata), then pass to the cerebral cortex (the primary sensory cortex) where sensation is mediated (Lee et al., 2002). It is proposed that the cerebral cortex might initiate cough by acting centrally on the medulla oblongata responsible for respiration, or at the spinal level (Lee et al., 2002). This cough, which has been initiated from the cerebral cortex, may be affected by inhibition within the cortex that suppresses the ‘‘urge to cough’’ (Lee et al., 2002). In turn, this suppression may increase the threshold for the reflexive cough via cough control regions in the brainstem. This cortical inhibition of cough can be overridden when afferent input from peripheral cough receptors cause cough threshold to be surpassed, despite cortical suppression (Lee et al., 2002). This produces the reflexive cough. It is thought this reflex is generated when irritation of the airway receptors reach a reflexive threshold that is then communicated via the reflex pathway of the brainstem (Lee et al., 2002). Research has revealed the brainstem networks that generate and modulate breathing are also involved in producing the motor patterns of the reflexive cough and other airway defense reflexes (e.g. sneeze, expiration reflex) (Shannon et al., 2004).

Although it is apparent that there are cortical components to the cough, presently little is known about the neural pathways involved (Mazzone, 2005). A recent fMRI study was used to evaluate the supramedullary pathways involved in cough (Mazzone, McGovern, Koo & Farrel, 2008). The study found activation in the cerebellum and primary motor cortex. Despite this result, the authors concluded that these findings do not explain the way that supramedullary regions interact with the brainstem neuronal network to generate voluntary or reflexive coughing. This leads to the conclusion that there are likely multiple primary and secondary sensory pathways involved (Mazzone et al., 2008). The precise way in which cortical pathways are implicated remains unknown.

2.4 Suppressed cough

To better understand the volitional and reflexive cough, the inhibited cough must also be investigated. Leow, Huckabee and Anderson (2006) demonstrated higher cough thresholds when participants (healthy controls and patients with Parkinson’s disease) suppressed cough. Cough initiated in the cerebral cortex may be reduced or abolished by inhibition, suppressing the ‘’urge to cough’’ (Lee et al., 2002). This suppression will often depend upon the patients’ mood and other psychological factors such as obsessional symptoms (Hutchings et al, 1993). This raises the issue of the placebo effect. Patients with the ‘‘common cold’’ experienced a 50% reduction in cough frequency when administered a placebo treatment (Lee et al., 2002). This supports findings that the extent cough could be suppressed was largely voluntary (Lee et al., 2002). Research states that 85% of the effectiveness of the majority of ‘‘over-the-counter’’ cough medicines is due to placebo action (Schroeder & Fahey, 2002; Widdicombe et al., 2006). These effects are based upon psychological factors, such as the patients’ attitude to health care professionals and their beliefs in the efficacy of treatment (Lee et al., 2002; Eccles, 2006). Based on the above studies it is thought areas in or near the cerebral cortex contribute to the suppression of cough and the success of the placebo effect (Widdicombe et al., 2006). Capsaicin evoked cough, which triggers chemoreceptors, has been found to be able to be voluntarily suppressed (Hutchings et al., 1993). This led Widdicombe et al. (2006) to postulate that any cough provoked by chemosensory mediated stimulants may not be a true reflexive cough. It has been suggested that chemoreceptor elicited cough is distinct from coughing triggered by direct stimulation of mechanoreceptors (Mazzone, 2005), questioning if ability exists to suppress cough triggered by actual aspiration. Citric acid is known to trigger both chemoreceptors and mechanoreceptors (Tanaka & Maruyama, 2005) (see section 2.5) and is thus likely to give a true result. If the subject inhaling nebulised citric acid is able to suppress their cough, it is likely that their airway protection mechanism is impaired.

2.5 Cough receptors and tussive agents

Two main types of cough receptors are found in the respiratory system: mechanoreceptors and chemoreceptors (Mokry & Nosalova, 2007). Mechanoreceptors originate in the nodose ganglia and terminate in the intrapulmonary airways and lung parenchyma (Mazzone, 2005). Mechanical stimuli (lung inflation and light touch) activate mechanoreceptors, which do not usually exhibit a response to chemical stimuli (Mazzone, 2005). An exception to this rule occurs if the action of the chemical stimuli results in a mechanical distortion of the nerve terminal (Widdicombe, 2001). Another exception occurs with citric acid, a chemical stimuli that will also activate mechanoreceptors (Mazzone, 2005; Tanaka et al., 2005). Conversely, chemoreceptors are activated by chemical stimulus including capsaicin, bradykinin and citric acid. Chemoreceptors are relatively insensitive to mechanical stimuli (Ho, Gu. Lin & Lee, 1993. Pecova, Javorkova, Kudlicka & Tatar, 2007). They are dispersed throughout the airway and lungs (Mazzone, 2005) and are inactive in the non-agitated airways; they recruit during airway irritation. The more proximal airways (larynx and trachea) are sensitive to mechanical stimulus, while the more distal airways are more chemosensitive and less sensitive to mechano-stimulation (Chang, 1999).

Inducing cough experimentally was first trialled over 50 years ago using citric acid (Bickerman, Barach, Itkin and Drimmer, 1954). Since this time, a wide range of tussive agents have been investigated, including cigarette smoke, ammonia and sulphur dioxide (Gravenstein, Devloo & Beecher, 1954). However, the most commonly evaluated include tartaric acid, capsaicin and citric acid (Morice, Kastelik & Thompson, 2001). Although distinctive in their composition, capsaicin and citric acid have demonstrated greater reproducibility (Morice et al., 2001). Combining this information with the previous findings from Mazzone (2005) and Tanaka et al (2005) that documented activation of both chemoreceptors and mechanoreceptors by citric acid, its use in both research and clinical application is therefore justified.

2.6 Methods of cough challenge

There are two primary methods used to deliver tussive agent cough tests: ‘single dose’ or ‘dose response’ (Morice et al., 2001). Single dose requires subjects be administered just one concentration of acid. The single dose method has been associated with lower propensity for tachyphylaxis (Morice et al., 2001). Tachyphylaxis is the rapid desensitisation to a pharmacologically or physiologically active substance (Morice, Fontana, Belvisi, Birring, Chung, Dicpinigaitis, Kastelik, McGarveye, Smith, Tatar, & Widdicombe, 2007). Tachyphylaxis can however be controlled for as reported in the European Respiratory Society Guidelines on the Assessment of Cough (Morice et al., 2007). The dose response method consists of inhalation of incremental concentrations of tussive agents, interspersed with placebo (Morice et al., 2001). Dose response can be further classified into ‘‘single-breath’’ or ‘‘fixed-time’’ inhalation challenges (Morice et al., 2001). Single-breath method involves one inhalation of each incremental dose of tussive agent, with non-acid agent inhalation interspersed between trials. Fixed-time inhalation challenge usually last between 15 – 60 seconds. The disadvantage of the fixed-time method is that it requires long inhalation times (up to one minute), decreasing the accuracy of delivery, however this is largely due to the variation in dose delivered from nebulisers. Ultrasonic nebuliser output is conducive to prolonged use and is not recommended for reproducible bursts as required for tussive agent tests (Morice et al., 2007). Jet nebulisers produce low volume; they are designed to be activated for short periods of time. They are the recommended system when nebulisation is for a timed burst of gas (Morice et al., 2001). It is of note that while the output can be accurately calibrated, participant compliance varies greatly, in terms of velocity and depth of inspiration (Morice et al., 2001). A comparison of the tidal breathing and dosimeter methods of cough challenge demonstrated both to be reproducible, with good agreement between the two methods (Nejla, Fujiura & Kamio, 2000). The reproducibility of the citric acid challenge has also been demonstrated recently (Wright, Jackson, Thompson & Morice, 2007).

2.7 Significance of cough

In the normal population, the cough reflex shields the supraglottic larynx from aspiration of fluids or food (Addington, 2005). In the presence of neurological disorders or stroke, humans with a compromised cough reflex are susceptible to aspiration and pneumonia (Canning, 2008). Clinically, the consequences of poor cough are severe. Nakajoh et al. (2000) demonstrated an inverse relationship between strength of cough reflex and the incidence of pneumonia in the post stroke population.

2.8 Impaired cough reflex

Cough can be impaired or absent after a stroke or other neurological illness (Addington et al., 1999) resulting in the phenomena of silent aspiration. Silent aspiration is defined as “the occurrence of aspiration before, during or after swallowing in the absence of cough” (Smith-Hammond, 2008 p 157S). One challenge in the diagnosis and management of dysphagia is the reliable detection of silent aspiration. The laryngeal cough reflex can be diminished or absent for up to four weeks (or permanently) in the stroke population (Kobayashi et al., 1994). Building on this research, Addington (2005) introduced the concept of ‘‘brainstem shock’’ which refers to a “global neurological condition involving a transient or permanent impairment of one or more of the following vital functions: the reticular activating system, respiratory drive or the laryngeal cough reflex” (Addington et al., 2005, p.7). It was then suggested that the mechanism of neurological suppression is physiologically important as coughing increases cerebrospinal fluid pressure, and this may exacerbate the brain injury (Widdicombe, Eccles & Fontana, 2006).

2.9 Adaptations in cough

The literature has consistently verified that there is minimal influence of age on natural cough (Katsuma, Sekizawa, Ebihara & Sasaki, 1995; Sams, Truncale & Brooks, 2005; Chang & Widdicombe, 2007; Leow et al., 2006; Monroe et al., 2010). However, a recent study demonstrated that normal youngers (< 60 years of age) can suppress the cough longer than normal elders (Monroe et al., 2010). Studies examining the potential gender difference in cough sensitivity have demonstrated that women have greater sensitivity when compared to men (Dicpinigaitis & Rauf., 1998; Kastelik, Thompson, Aziz, Ojoo, Redington & Morice., 2002).

The literature also reports many contributing factors that modify cough. Factors that diminish cough include central nervous system disorders such as stroke (Addington et al., 2005), spinal cord injuries (Lin, Lai, Wu, Wang, & Wang, 1999), sleep and general anaesthesia (Widdicombe et al., 2006 Nichino et al., 1996), pneumonia, gastro-oesophageal reflux, allergic rhinitis, atopic dermatitis (Percova et al., 2007) and diabetes with autonomic neuropathy (Vianna, Gilbey, Barnes, Guy, & Gray, 1988). Conversely, acute and viral upper respiratory tract infections induce transient hyper-responsiveness of cough receptors (O’Connell, Thomas, Studham, Pride & Fuller, 1996). Angiotensin-converting enzyme inhibitors (ACE inhibitors) too increase cough sensitivity (Yamaya, Yanai, Ohrui, Arai & Sasaki, 2001).

Another reported adaptation of cough is smoking; however, the way in which it alters cough remains somewhat unclear. It is likely due to chronic, cigarette smoke-induced desensitisation of the cough receptors (Dicpinigaitis, 2003). Conversely, in the initial fortnight of smoking cessation, cough reflex sensitivity is enhanced (Sitkauskine, Stravinskaite, Sakalauskas & Dicpinigaitis, 2007).

Interestingly, when the relationship of cough sensitivity and intensive daily oral care and hygiene was examined in elderly residents in nursing homes, cough improved significantly with better oral care (Wantando et al., 2004). Langmore, Terpenning, Schork, Chen, Murray, Lopatin and Loesche (1998) showed that the primary factors that contribute to pneumonia include poor oral hygiene and dependence for oral care. These findings together suggest that if oral hygiene was maintained, the cough reflex would be stronger. Consequently, the likelihood of developing pneumonia would reduce.

2.10 Normative data

Monroe and Huckabee (2010) evaluated 80 age and gender matched subjects to establish a normative citric acid inhalation challenge data set. A range of concentrations of citric acid diluted in sodium chloride, from 0.8M to 2.6M were trialled and the facemask method was employed. Subjects inhaled nebulised citric acid passively (for up to 15 seconds), with a 30 second interval between trials to prevent tachphylaxis (Morice, 1996). Cough was deemed present with the occurrence of two successive coughs with no respiration between. This criterion was achieved on two of a potential three trials. Suppressed cough thresholds were also tested. Monroe et al. (2010) found the majority (92.5%) of subjects triggered natural cough threshold at 0.8M. Suppressed cough threshold was triggered by 70% of the cohort at 0.8M. A limitation of this study was a significant flooring effect; including lower concentrations would have been beneficial. This study also had extensive subject exclusion criteria in an attempt to control for influence on cough sensitivity; however, the typical patient will likely have at least one-exclusion condition (e.g. gastro-oesophageal reflux disease, codeine based-drugs, asthma, smoking). This study also introduced the concentrations of citric acid incrementally; randomization may have made for a more robust method for gathering normative levels.

The work of Manco, Bennett and Huckabee (2011) addressed many of the limitations of Monroe et al. (2010) by lowering the threshold levels and presenting concentrations in a randomised order. Citric acid was randomly administered ranging in concentrations from 0.1M-1.2M. Manco et al. (2011) found that natural cough threshold was reached by 83.8% of subjects at 0.8M. Suppressed cough threshold was reached by 91.9% of subjects at 0.9M citric acid. This study was limited by its sample size. There was a spread of responses across the threshold levels; representation would have improved with greater numbers of participants.

2.11 Cough reflex testing

Addington et al., (1999) sought to evaluate the efficacy of testing the laryngeal cough reflex in identifying pneumonia risk in acute stroke patients. A prospective study of 400 stroke patients was conducted using a single dose cough reflex test. This study administered tartaric acid via a mouthpiece and employed the exhalation-inhalation method. A normal response to the cough reflex test was presumed to indicate a neurologically intact laryngeal cough reflex and a protected airway. It was inferred that these patients were at low risk of developing aspiration pneumonia with oral feeding. An abnormal response was classified as an absent or weak response to the cough test. It was inferred that these patients were at high risk of significant aspiration based pneumonia. Decisions on whether the patient was fed or not was based on the outcome of the cough test (i.e. abnormal: nil by mouth; normal: proceed with routine bedside assessment). The outcome of pneumonia from this group was contrasted with a control group of 204 stroke patients who were examined without the cough reflex test. They established that 1.25% of the patients who received the cough test developed pneumonia, compared to 13% of the patients who did not receive the cough test. This study was flawed in various ways. For example, it did not control for site of lesion and there was no consistency in the use of instrumental assessment as it was only completed when staff believed it to be clinically indicated. The patients' swallowing was therefore not consistently assessed to establish pathophysiology. It is likely that this led to patients being tube fed unnecessarily.

A subsequent study was conducted which examined pneumonia risk in 818 acute stroke patients. This study considered site of the lesion and laryngeal cough reflex status (Addington et al., 2005). Tartaric acid was administered via mouthpiece and exhalation-inhalation method was employed. A normal cough was found when "an immediate series of forceful coughs" (p.2.) occurred. Abnormal was defined as "an absence of coughing, a diminished cough or coughing not immediately after administration of the test stimulus" (p.2). Of the 818 patients, 35 (4.3%) developed pneumonia. Of the 736 (90%) patients who had a normal cough response, 26 (3.5%) developed pneumonia. Of the 82 (10%)

patients with an abnormal/diminished cough response, 9 (11%) developed pneumonia despite preventative interventions. They concluded that the “reflexive cough test acted as a reflex hammer or percussor of the laryngeal cough reflex and neurological airway protection and indicated pneumonia risk” (p.1.). This study was not necessarily looking specifically at aspiration pneumonia risk. It was also correlating site of lesion and pneumonia risks, so may not have been trying to separate dysphagia related pneumonia. This would have been easily clarified with a clear descriptive of their pneumonia criteria.

These two studies were notably flawed in a number of ways. For example, they utilised tartaric acid that has been shown to activate only chemoceptors (Morice et al., 2007), is not reproducible across time and is not reliable for clinical use. The single dose method was used to deliver the cough test but they failed to detail the concentration of acid used and how they decided on this measure. Moreover, the interpretation of cough testing allowed only for binary decisions. The measure of cough was subjective in nature and had poorly defined variables considering factors such as the number of coughs elicited and what defined a ‘diminished cough’ for example. The expiratory-inspiratory method with a mouthpiece ruled out many patients who could not perform an adequate lip seal. It is likely that this created an inclusion bias and altered the results. As mentioned above, the researchers did not define the specific diagnostic criteria of pneumonia. This means that it is unclear whether patients developed aspiration-related or non-aspiration related pneumonia. As detailed previously, the use of instrumental assessment of swallowing following absent cough result was not consistent; this was only conducted when staff deemed it necessary. All of these factors make it challenging to draw firm conclusions from these studies about the effectiveness of the cough test in detecting those patients at risk of developing aspiration pneumonia.

The work of Miles, McLauchlan and Huckabee (2011) addressed many of the limitations of Addington et al. (1999, 2005). They conducted a randomised controlled trial to examine cough reflex testing with stroke patients across four large urban hospitals. Three hundred and twelve acute stroke patients referred for swallowing assessment were assigned to either the control group (standard clinical assessment), or the experimental group (standard assessment with the inclusion of the cough test). Guided by normative data (Monroe et al., 2010), 0.8M and 1.2M citric acid was administered via facemask method. Natural cough threshold and suppressed cough threshold were tested. Each participant's suppressed cough response was classified as pass, weak or fail. A cough was considered present when two coughs occurred with no breath between. Unlike the Addington et al. (1999) study, in which management was dictated solely by cough test results, these researchers allowed clinicians greater flexibility in clinical decision making. The primary outcome measure for this study was the pneumonia rate within three months of inclusion in the study. Pneumonia was clearly defined by the criteria published by Mann, Hankey and Cameron (1999).

Miles et al. found that 21% of the participants in the control group and 26% of the participants in the experimental group developed pneumonia, with 38% of those who failed a cough reflex test developing pneumonia. This revealed that those patients who received the cough reflex test still had a high rate of pneumonia within the three-month period. The strengths of this study included the use of the facemask method with the stroke population. The use of facemask allowed for a higher subject inclusion rate that previously discussed studies did not possess. This study was also guided by the normative data, and justified the decision regarding concentration of citric acid utilised. The variable clinical pathway limited this study; as in Addington et al (1999, 2005) individual patient management was based on the therapists' clinical decision making.

It would be beneficial for future studies to integrate a management protocol for patients who have an abnormal result on the cough reflex test to undergo instrumental assessment.

The clinical use of citric acid cough reflex testing to identify patients at risk of pneumonia requires validation against instrumental assessment. Wakasugi, Tohara, Hattori, Motohashi, Nakana and Goto (2008) utilised the citric acid cough reflex test via mouth-mask, together with the modified water-swallowing test. The researchers aimed to create an accurate screening system for silent aspiration. The screen was administered to suspected dysphagic patients. Patients breathed passively during the presentation of citric acid (1.0w/v% in concentration) for one minute. Five coughs were considered normal and less than four coughs were considered abnormal. The findings of the cough test were then compared with VFSS or videoendoscopy.

Of the 204 patients, 97 presented with no aspiration, 84 of which were 'normal' on the cough test. Silent aspiration was demonstrated by 52 patients, 45 of whom had an 'abnormal' response to the cough test. Eighteen patients presented with 'silent aspiration by little aspiration'. These patients coughed when larger amounts were aspirated. In this group two patients had an 'abnormal' cough test. These researchers concluded that the cough test is a useful screening test for silent aspiration. Sensitivity was reported at 0.67 and specificity was 0.90. None of the above-mentioned studies justified the concentration of acid. This limits the clinical application of the reported findings. Wakasugi et al.'s

(2008) study also indicated inconsistencies with the timing of cough test and instrumental assessment. The cough test was conducted on the day prior, the same day or the subsequent day after the instrumental assessment.

2.12 Summary of limitations

Considering the insensitivity of the traditional bedside swallowing assessment (Splaingard, 1988), the use of citric acid cough testing may have potential in identifying patients who are at risk of silent aspiration, however current research is conflicting. The facemask method—utilised in the recent normative data collection studies—appears to be the most appropriate for use with the dysphagic population. This is because the potential of facial weakness and poor lip seal are probable. Previous studies have examined the relationship between aspiration, pneumonia and cough reflex testing; however, they have not specified dose/concentration of acid and have had inconsistent timing between cough testing and instrumental assessment. Before cough reflex testing can be incorporated into the bedside assessment of dysphagia, a proven correlation between cough sensitivity to citric acid and radiographic features of airway compromise is required.

2.13 Aim of this study

The aim of this project was to investigate the relationship between the citric acid cough reflex test findings and the radiographic features of airway compromise, in persons with dysphagia.

Although the natural and suppressed cough thresholds were both tested, we have analysed only the suppressed cough result (unless the participant had an absent response to the highest concentration of citric acid during the natural cough test).

The following hypotheses were also tested:

1. There will be a significant relationship between patients who pass the cough reflex test and those who have a weak or absent response
2. The participants who have an absent or weak response to citric acid during the cough reflex test will consequently have a higher score on the Penetration-Aspiration Scale
3. The mean threshold level that participants have their suppressed cough triggered at will be established

CHAPTER 3

Methodology

3.1 Participants

Eighty patients of mixed aetiology (See Appendix 1) were recruited from a large acute urban hospital. All participants were referred for a VFSS as part of their standard inpatient or outpatient dysphagia management. The participants ranged in age from 22-100 years, with a mean age of 66.84 years. Exclusion criteria included the presence of a tracheostomy tube, oxygen support for respiration and/or spinal injuries. Ethical approval was obtained from the Upper South B Regional Ethics Committee of the Ministry of Health in Christchurch, New Zealand.

3.2 Procedure

To obtain four different concentrations 0.4M, 0.6M, 0.8M and 1.2M, citric acid was diluted in 0.9% sodium chloride. The concentrations were prepared by the hospital pharmacy each week. The concentrations were selected based on Manco, et al. (2011). This study demonstrated that natural cough threshold was reached by 83.8% of subjects at 0.8M. Suppressed cough threshold was reached by 91.9% of subjects at 0.9M citric acid.

Upon arrival at the radiology wing for their swallowing study, participants provided informed consent. Proxy consent was obtained as appropriate. Participants then underwent VFSS led by the clinician responsible for their care, according to usual practice. The fluoroscopic study was recorded at a rate of 30 frames/second onto an analogue Video Home System (VHS). The researcher who conducted the cough testing was blind to the VFSS and its findings. Immediately after completion of the VFSS the researcher commenced the cough testing procedure.

The nebuliser used in this study was a De Velbiss Pulmomate with a constant flow rate of 8L/minute. Citric acid was delivered via a facemask. Participants were instructed to place the mask over their nose and mouth, and to breathe normally. To acquaint them with the procedure, participants were then coached on a placebo solution of 0.9% sodium chloride. The citric acid was then presented in incremental concentrations; each concentration was administered up to three times for a maximum of 15 seconds for every administration. To prevent tachyphylaxis, a 30 second interval was placed between each exposure (Morice, 1996). Both natural and suppressed cough thresholds were tested. To test the natural cough threshold, participants were instructed to “breathe normally and cough if you feel the need to; do not cough if you do not need to”. The natural cough threshold was judged present when two successive coughs (with no respiration between) were observed on at least 2 out of 3 presentations, within the 15-second timeframe. If there was no response at the highest dose of citric acid on 2 out of 3 presentations, the test was concluded, and suppressed cough was not trialled for these participants. The continuing participants were then told the test would carry on, but with different instructions.

To test the suppressed cough threshold, participants were told to “breathe normally; this time try to suppress the cough to the best of your ability”. The suppressed cough threshold was deemed present when two successive coughs (with no respiration between) were observed on at least 2 out of 3 presentations, within the 15-second timeframe. For each cough reflex test response, the researcher gave a subjective grade of pass (strong cough), weak (audibly reduced strength) or absent.

The VFSS recordings were played back on a video cassette recorder (VCR) in both real time and reduced rate play back. Recordings were then independently rated using the Penetration-Aspiration Scale (Rosenbek, Robbins, Roecker, Coyle & Wood, 1996) by the researcher and a clinician with similar work experience in speech pathology and dysphagia. The clinician was blind to the cough test result. The ratings took place one month after the participants' procedures and cough test results were not revealed until rating was determined. This penetration-aspiration scale (see Appendix 2) is a standardised 8-point equal appearing interval scale that describes penetration and aspiration events. The score is determined by how far the material invades the airway, and whether or not it is expelled.

3.3 Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences Inc (SPSS) version 19.0.0. A p-value <.05 was considered to be statistically significant. To investigate the inter-rater reliability, two clinicians with similar work experience in speech pathology and dysphagia independently assessed the VFSS recordings and rated the level of airway invasion on the Penetration-Aspiration Scale (Rosenbek et al., 1996). The two ratings were then compared to compute the intraclass correlation coefficient.

Prior to data analyses, the researcher who was blind to results of the VFSS coded participants' cough test results: 0 absent/fail, 1 weak, or 2 pass. This coded response was the independent variable. To investigate how the cough reflex test result was related to the penetration- aspiration scale (Rosenbek et al., 1996) a correlational analysis was conducted. The cough reflex test data was coded (i.e., ordinal) we therefore used the Spearman’s rho to analyse this correlation. Spearman’s rho is the most suitable correlational analyses for nonparametric data. Subsequently a one-way ANOVA was also used to investigate how this independent variable influenced the outcome variable (level of airway invasion). A between-subjects t-test was used to test whether participants who coughed or did not cough in response to citric acid (independent variable) recorded different penetration-aspiration scale scores (dependent variable). Sensitivity and specificity were calculated for each threshold level.

CHAPTER 4

Results

The categories were coded based on threshold testing; the concentration the cough was triggered at is detailed in Table 1. Four levels of citric acid were used in this study: 0.4M, 0.6M, 0.8M and 1.2M. The percentage of participants who had a pass, weak and absent/fail result is shown in Figure 2.

Table 1. Participants' threshold level results of the cough reflex test (i.e. the concentration the cough was triggered).

	Pass (cough)	Weak (cough)	Fail (no cough)	Number
0.4M	16	10	0	26
0.6M	9	8	0	17
0.8M	5	6	0	11
1.2M	0	6	20	26

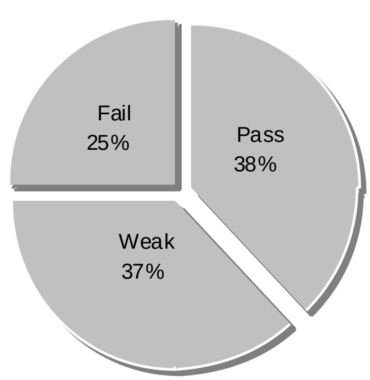

Figure 2. *Response to citric acid cough reflex testing: pass, weak or fail/absent.*

Sensitivity and specificity were calculated for each threshold level. Table 2 presents a breakdown of these contingency tables, demonstrating the presence of cough group (pass/weak) and the absence of cough group (absent/fail) and their corresponding sensitivity and specificity. The odds ratio at each threshold level is also detailed.

Table 2. Sensitivity and specificity and subsequent odds ratio calculated for each threshold level. Presence of cough (pass/weak) Vs Absence of cough (absent/fail).

	Sensitivity	Specificity	Odds ratio
0.4M	0.750	0.344	1.571
0.6M	0.833	0.456	4.189
0.8M	0.941	0.238	5.000
1.2M	1.000	0.078	-

Correlational analysis showed a significant negative correlation (Spearman's rho = -.48, $p < .001$) between scores on the penetration-aspiration scale and the citric acid cough reflex test result (pass, weak or absent/fail). As previously noted, two independent clinicians rated participants on the Penetration-Aspiration Scale (Rosenbek et al., 2006). There was a strong level of inter-rater reliability (0.998) between the two clinicians.

A one way ANOVA revealed that participants' penetration-aspiration scale score differed significantly depending upon the result on the cough reflex test; that is, pass, weak or absent [$F(2,77) = 9.15$, $p < .001$]. Tukey post-hoc analysis showed that participants who had an absent/fail ($p < .001$) or a weak ($p = .04$) response to the cough reflex test had a significantly higher score on the penetration-aspiration scale than participants who passed the cough reflex test (see Table 3). However, there was no significant difference ($p = .12$) between participants' penetration-aspiration scale scores who had an absent or weak response to the cough reflex test.

Table 3. Participants' cough response to citric acid and penetration-aspiration scale scores (ANOVA)

	Mean	Standard Deviation	Number
Fail/Absent	5.15	3.15	20
Weak	3.70	2.65	30
Pass	2.07	1.86	30

To investigate whether participants' scores on the penetration-aspiration scale differed depending upon the presence (pass/weak) or absence (absent/fail) of a cough response to citric acid, a between subjects t-test was conducted. Given that the Levene's test for Equality of Variances was violated ($F = 11.43$, $p = .001$), the adjusted t-test was interpreted (i.e. equal variances not assumed). This t-test explained [$t(26.84)=2.94$, $p < .01$] that participants who coughed had a lower penetration-aspiration scale score than participants who did not cough (see Table 4). The median dose at which participants passed the cough reflex test was 0.6M (see Figure 3 for illustration).

Table 4. Participants Penetration-Aspiration Scores (t-test)

	Mean	Standard Deviation	Number
Cough	2.88	2.42	60
No cough	5.15	3.15	20

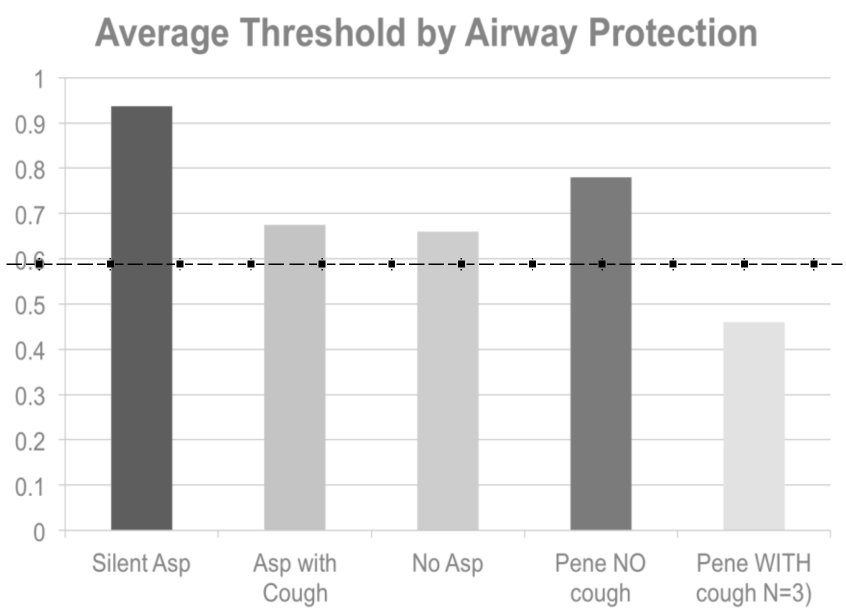

Figure 3. *Median threshold (concentration) of citric acid and airway reaction. The dotted line indicates median level.*

CHAPTER 5

Discussion

We hypothesised that participants who penetrated or aspirated during VFSS would have a weak or absent response to the citric acid cough reflex across the threshold levels. Indeed, the results demonstrated that participants who had a higher score on the penetration-aspiration scale (Rosenbek et al., 1996) exhibited a weak or absent response to the citric acid cough reflex test across the threshold levels. In turn, participants with a lower score on the penetration-aspiration scale were more likely to pass the citric acid test. Combining the ‘‘weak’’ and ‘‘fail’’ groups corroborates the work done by Addington et al. (2005) that rated coughing as ‘‘normal’’ or ‘‘abnormal’’ when ‘‘abnormal’’ is described as ‘‘an absent or diminished cough’’. This supports our hypothesis, as there was not a significant difference between participants who had a weak response to the cough test and those who failed the cough test. Addington et al (2005) considered both features as irregular and identifies those at high risk of aspiration.

Our results supported previous research (Splaingard, 1988). Splaingard (1988) found that 70% of patients with dysphagia who were aspirating during bedside clinical exam were not diagnosed. Similarly, our data revealed that 62% of the cohort had a weak or absent response to the cough reflex test, as detailed in our results. These subjects received a higher score on the penetration-aspiration scale, indicating airway invasion.

Statistical evaluation revealed Cohen’s d (effect size) is approaching large (d=.50) (Cohen, 1992). This indicates that this correlation was highly significant within the sample group. Sensitivity and specificity testing for each threshold revealed that concentration level 0.8M had the highest odds ratio (5.000). Patients who fail screening at this concentration are five times more likely to be identified as being at risk of silent aspiration. Although the sensitivity of the citric acid was high, the specificity was low. The implications of this are significant in clinical practice. The clinician employing the citric acid cough reflex test is likely to identify patients at risk of silent aspiration; however, there is also a high chance that patients who are not silently aspirating will be identified as ‘‘at risk’’. Clinically, this may lead to patients being kept nil by mouth unnecessarily and may expose patients to unnecessary instrumental assessments.

The present study used a robust testing procedure with regard to timing and consistency of VFSS and immediate cough reflex testing. This differs from the previous study (Wakasugi et al., 2008) that tested participants’ cough reflex on the day prior to, the same day as or the subsequent day after the instrumental assessment. However, this study does support Wakasugi et al.’s (2008) statement that the cough test is a useful screening test for silent aspiration.

One key difference between this study and Addington et al.’s studies (1999, 2005) is the administration of the tussive agent. A facemask method was used rather than a mouthpiece. This facemask method allows participants to breathe passively. This means that participants with facial weakness, motor planning deficits and other relevant ailments can have their cough reflex assessed. Another distinction between the present study and that of Addington et al. (1999, 2005) is the choice of tussive agent. Addington et al. (1999, 2000) utilised tartaric acid that has been shown to activate only chemoreceptors, is not reproducible across time and is not recommended for clinical use (Morice et al., 2007). The present study, however, like those of Wakasugi et al. (2008) and Miles et al. (2011) utilised citric acid. This is the only tussigenic agent that has been shown to stimulate both chemo and mechanoreceptors (Tanaka et al., 2005). This reinforces our results and emphasises the relevance of the present validation study.

5.1 Threshold testing

We also investigated four citric acid threshold levels. The recent normative data (Monroe et al., 2010; Manco et al., 2011) guided these choices. Previous researchers (Addington et al., 1999; Addington et al., 2005; Wakasugi et al., 2008) had not justified the level of acid selected for their clinical research. It was consequently difficult to understand how their findings were substantiated. Manco et al. (2011) found that natural cough threshold was reached by 83.8% of subjects at 0.8M citric acid. Suppressed cough threshold was reached by 91.9% of subjects at 0.9M. Similarly, the median concentration level of this study that triggered participants' cough was 0.6M. This indicates that if a patient fails to respond at this concentration, this is likely to be an abnormal response. This suggests an impaired cough reflex and reduced airway protection. A challenging issue with threshold levels is striking a balance between sensitivity and specificity. This study found that the trialled threshold levels were highly sensitive but had poor specificity. As demonstrated in the results, 0.6M was found to have 0.83 specificity and 0.46 specificity. This was the strongest in terms of synchronization between the two measures, however further demonstrates the potential for over-identification of patients at risk of silent aspiration.

5.2 Implications for the clinician

The present study will enhance the clinician's understanding of the cough reflex in the dysphagic population. This study demonstrates that there is a correlation between failed cough reflex test and silent aspiration. The cough reflex test highlights those at risk patients who require instrumental assessment. This is a significant finding and will enable clinicians to refer patients for instrumental assessment prior to the prescription of food, fluids and oral medications. This will reduce the high number of patients with dysphagia who are fed inappropriately and unsafely.

5.3 Strengths and weaknesses

Although the findings of this study were significant, there are several limitations. For example, a small number of patients failed the cough reflex test and did not aspirate during VFSS. On reviewing the VFSS recordings, we found that the clinicians conducted the studies differently. A range of bolus sizes were administered, but regularly participants were not suitably challenged during VFSS (ASHA, 2004). Therefore, when their oropharyngeal systems were not being pressured, airway invasion often did not occur, where it may have done if guidelines had been followed. This study would have been strengthened with a VFSS procedure protocol. Future studies should stipulate how the VFSS must be conducted, including bolus sizes, rate of intake and quantities to be trialled during VFSS. Conversely, there were a small number (n=6) of patients who passed the cough reflex test, and silently aspirated during VFSS. Five of those six participants had a weak cough during the citric acid test. This adds to the ongoing discussion around the diminished cough representing a high risk of silent aspiration. The significant findings of this study demonstrate that the majority of participants who were at risk of silent aspiration were identified by the cough reflex test.

This study could have used placebo presentations of sodium chloride to further combat potential tachphylaxis, as recommended by Morice et al. (2007). A further limitation of this study was the rating of cough strength. The researcher independently rated the cough strength of each participant; this would have been strengthened by an inter-rater.

Another consideration of this study was the variety of clinical presentations of the participant cohort. Both acutely unwell patients and stable patients from the community setting were included. The broad range of participants may indeed reflect the general medicine population. However, future researchers may refine our study by focusing on a single population group, for example, stroke patients.

5.4 Future directions

5.4.1 Placebo effect

The cough reflex provides crucial information about the integrity of the vagus nerve. Different branches of the vagus nerve innervate chemo and mechanoreceptors; the cough reflex test allows for stimulation of these. However, the cough reflex is highly vulnerable to the placebo effect, and it is documented that the mechanism through which suppression of the cough occurs is similar to this (Hutching et al., 1993). It is challenging to evaluate the cough reflex, whilst minimizing placebo-type effects. This is because the word “cough” is mentioned numerous times in the tests’ instructions, potentially priming the participants to cough (Wegner, 1994). It would be valuable to investigate cough reflex testing using a blind study design. This would rule out the potential impact of the cortical component of the cough reflex.

5.4.2 Oral hygiene

Cough sensitivity improves with oral hygiene and oral care (Watando, Ebihara, Ebihara, Okazaki, Takahashi, Asada & Sasaki, 2004). Improved oral care reduces the risk of pneumonia (Langmore et al., 1998). Given the incidence of dysphagia in stroke (Daniels, Brailey, Priestly, Herrington, Weisberg, Foundas, 1998) it would be valuable to conduct research that examines oral hygiene, cough reflex sensitivity and the impact on pneumonia rates. However, presently the measure of cough strength remains subjective; there is no published inter-rater reliability information. This would be another relevant piece of work for future researchers.

5.4.3 Rehabilitation

Rehabilitation of the cough reflex should be researched. Presently, there is no documented method of rehabilitation for the airway protection mechanism. Research into this area may produce significant information for those patients who do not experience natural recovery. Researchers might evaluate whether the laryngeal reflex can be primed to protect the airway during deglutition. One could consider whether the stimulation of the sensory system with high doses of citric acid might prime this reflex.

ACE inhibitors typically used with hypertensive patients increase cough sensitivity. It has been established (Arai, Sekizawa, Ohrui, Fujiwara, Yoshima, Matsuoko, and Sasaki, 2005) that patients who are prescribed ACE inhibitors have a reduced pneumonia rate. This research could be applied to the rehabilitation of cough work. Although these are only suppositions, these would be rewarding areas of research that would translate into the realm of patient care.

CONCLUSIONS

Using VFSS, we have validated citric acid cough reflex testing with the facemask method. The research gives clinicians information that can easily be utilised in hospital and community settings. This will assist clinicians to identify patients who are at risk of silent aspiration. Additionally, it will enable clinicians to refer patients for instrumental assessment prior to the prescription of food, fluids and oral medications. This will reduce the high number of patients with dysphagia who are fed inappropriately and unsafely. Therefore, it is reasonable to assume this tool will contribute to the reduction of pneumonia rates and in turn, lengths of hospital stay, costs and morbidity associated with aspiration pneumonia. This is a stimulating new area of research in the field of dysphagia. Although this study is preliminary and future research is required, we have provided a good basis on which to build.

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Appendix 1.
Participants' range of aetiologies

- Myotonic muscular dystrophy
- Renal cell carcinoma
- Neurofibromatosis type 2
- Chronic obstructive pulmonary disease
- Multiple sclerosis
- Adenocarcinoma left parotid gland
- Mandibulectomy
- Parkinson's disease
- Atrophied larynx
- Squamous cell carcinoma of right oropharynx
- Dermatomyositis
- Cerebral palsy
- Post-pharyngoplasty
- Large B cell lymphoma of the thyroid gland
- Right subdural haemorrhage
- Right parietotemporal bleed
- Pneumonia
- Right middle cerebral artery infarct
- Supraglottic squamous cell carcinoma
- Right cerebrovascular accident
- Right cerebellar haemorrhage
- Thoracic aortic aneurysm
- Vertigo
- Oesophagitis
- Hydrocephalus
- Left middle cerebral artery infarct
- Seizures
- Oesophageal diverticulum
- Sjogren's syndrome
- Transection of pharynx, bilateral laryngeal nerve resection
- Huntington's chorea
- Globus
- Meningitis
- Pleural effusion
- Posterior fossa bleed

Appendix 2.
Penetration-Aspiration Scale
Rosenbek et al., 2006

The 8-Point Penetration-Aspiration Scale

1. Material does not enter the airway
2. Material enters the airway, remains above the vocal folds, and is ejected from the airway
3. Material enters the airway, remains above the vocal colds, and is not ejected from the airway
4. Material enters the airway, contacts the vocal folds, and is ejected from the airway
5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway
6. Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway
7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort
8. Material enters the airway, passes below the vocal folds, and no effort is made to eject