New Strategies for Aspiration Pneumonia

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Aspiration pneumonia is associated with decreases in both swallowing and cough reflexes and is the most common cause of death in the elderly. Basal ganglia strokes might predispose these patients to develop pneumonia owing to reductions of both reflexes, resulting in frequent aspiration during sleep. An impairment of dopamine metabolism in the basal ganglia is observed in these patients and levodopa administration improves the impaired swallowing reflex. Both swallowing and cough reflexes are mediated by endogenous substance P (SP) released from vagal sensory nerves in the pharynx and upper airways. The addition of a low dose of capsaicin to liquid or food, which stimulates the release of SP, may help prevent aspiration pneumonia. Angiotensin-converting enzyme inhibitor decreases SP catabolism resulting in improvements in both reflexes. Oral care and the sitting position after meals may decrease aspiration pneumonia in the elderly.

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Introduction

Pneumonia is not only a common infection in the elderly, it is also the most common cause of death from nosocomial infection in this population (1). Both the increased incidence of pneumonia and the high mortality are a consequence of a number of age-related factors, including coexisting illnesses, therapeutic intervention, and the aging process itself (2). These factors combine to adversely affect upper and lower respiratory tract host defenses against invading pathogens (3).

Silent aspiration of oropharynx bacterial pathogens to the lower respiratory tract is an important risk factor for nosocomial pneumonia (4). The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration (5). Disorders of the central nervous system are more likely to develop in the elderly, and pneumonia has been estimated to occur in about one-third of patients with stroke (6).

However, the role of silent aspiration in the patients with pneumonia in the elderly is not proved. It is unclear if there is an association between the location of a cerebral stroke and the occurrence of pneumonia in the elderly. What are the defense mechanisms of aspiration in the elderly? We investigated therapeutic methods to improve impaired defense mechanisms resulting in the prevention of aspiration pneumonia in these patients.

Silent Aspiration in Elderly Patients

Silent aspiration of oropharynx bacterial pathogens to the lower respiratory tract is an important risk factor for nosocomial pneumonia (4). However, the role of silent aspiration in community-acquired pneumonia is not known. Kikuchi et al (7) examined the incidence of silent aspiration during sleep in elderly patients with community-acquired pneumonia using a new technique employing indium111 chloride. One mCi of indium111 chloride stirred with a paste was fixed to the subject’s teeth before sleep. The paste melted in the mouth during sleep. The next morning scanning of the thorax was performed with a Gamma camera, and 71% of patients with community-acquired pneumonia had positive scans, that is the tracer was detected within the thorax lateral to the midline. However, among control age-matched subjects, a positive scan was observed in only 10% (7). Although examination of aspiration was limited to one night, Kikuchi et al (7) have demonstrated that aspiration occurred more frequently in patients with an acute episode of pneumonia than in control subjects. These observations suggest that elderly people frequently aspirate during sleep and the development of pneumonia may occur when normal pulmonary defense mechanisms are overwhelmed. Thus, silent aspiration may be an important risk factor for community-acquired pneumonia as well as nosocomial pneumonia in the elderly.

A number of studies have pointed out several risk factors that predispose to pneumonia. These include aspiration (particularly when defense mechanisms are bypassed by intubation) (8), increased age (9), severity of illness (10), decreased levels
of consciousness (11), and immunosuppressive states (12). Tracy and coworkers (13) studied the effects of age on oropharyngeal deglutition in normal subjects without a history of structural damage on the head or neck, neurological damage, gastrointestinal disorders, or dysphagia. The study suggests that oropharyngeal deglutition is impaired with age, probably because of increased neural processing time and diminished oral control (13). Therefore, aging itself might be the cause of oropharyngeal dysfunction.

Defense Systems of Silent Aspiration

Adequate protective reflexes in the airway are important and the depression or absence of these reflexes has been suggested as leading to aspiration pneumonia (14). To see if aspiration pneumonia is associated with decreases in swallowing reflex and cough reflex, Sekizawa et al (15) and Nakazawa et al (16) studied both reflexes and determined the critical levels of depression in the defense systems that lead to aspiration pneumonia. Cough reflex was measured during tidally breathing a nebulized citric acid delivered by an ultrasonic nebulizer. The cough threshold was defined as the concentration at which the patient coughed at least five times. The swallowing reflex was induced by a bolus injection of 1 ml of distilled water into the pharynx through a nasal catheter, as described by Nishino et al (17). The swallowing action was identified by visual observation and submental electromyographic activity. The swallowing reflex was evaluated by the latency of response, which was timed from the injection to the onset of swallowing (17). The latent time of swallowing was 1.2 ± 0.1 (SE)s and the threshold concentration of citric acid was 2.6 ± 0.4 (SE) mg/ml in the controls. All of the patients with aspiration pneumonia had a latent time of swallowing longer than 11s and a threshold concentration of citric acid higher than 180 mg/ml. Patients above these thresholds of both reflexes may be vulnerable to the development of aspiration pneumonia (15, 16).

The elderly are more likely to develop disorders of the central nervous system and aspiration is more commonly associated with debilitation, dementia, and depression than specific neuromuscular disorders (18). In healthy people, the frequency of swallowing during sleep is slightly less than when awake (19). However, the influence of sleep on the swallowing reflex has not been studied in elderly patients at risk of aspiration. Pinto et al (20) examined the swallowing reflex during day and night in elderly patients with cerebral thrombi or dementia due to cerebral arterial sclerosis, and compared the results with those in age-matched healthy controls. Severely delayed of the swallowing response in the night compared with that in the day was observed in patients with multiple lacunar infarctions in bilateral basal ganglia lesions. It is suggested that nighttime might be an important risk factor in the development of aspiration pneumonia in elderly patients with cerebrovascular disease (20).

Mechanisms of Swallowing and Cough Reflexes

In order to investigate therapeutic intervention to silent aspiration, mechanisms of both swallowing and cough reflexes should be investigated. Because pharyngolaryngeal mucosa receives innovation of nonmyelinated C-fibers (21), and these nerves contain neuropeptides having a variety of biologic activities including pain transmission (21), nonmyelinated C-fibers may play an important role in both reflexes. Jin et al (22) studied the swallowing reflex elicited by injections of distilled water into the pharynx of guinea pigs treated with and without systemic capsaicin, which is known to selectively act on nonmyelinated C-fibers (23). They found that nonmyelinated C-fibers regulate the swallowing reflex through the release of substance P (SP) in response to stimulation. Ujiie et al (24) studied the mechanisms of cough reflex using guinea pigs in the same manner as that used to study the swallowing reflex and found that SP released from sensory nerves in the airway may be an endogenous substance causing cough.

Since there are marked depressions of both swallowing and cough reflexes in patients with aspiration pneumonia, depletion of SP in the pharynx, larynx and tracheobronchial tree causes impairment of both reflexes. Nakagawa et al (25) measured SP concentration in hypersonic saline-induced sputum (26) and found that a reduced SP concentration in sputum may be a marker for increased risk of aspiration pneumonia in the elderly.

Stroke is one of the major causes of aspiration pneumonia (27). Kobayashi et al (28) showed the combined depression of the swallowing and cough reflexes during the first 2 weeks after the onset of stroke. However, it was unclear if there is an association between the location of an infarct and the occurrence of pneumonia in the elderly. Nakagawa et al (29) have shown that the risk of pneumonia in patients followed up for a 2-year period in a long-term care facility was significantly higher in patients with basal ganglia infarcts than in patients with or without cerebral hemispheric strokes in other locations. They also found that multiple episodes of pneumonia occurred only in patients with bilateral basal ganglia infarcts and that there was a higher mortality rate associated with pneumonia in these patients.

Simultaneously, Ito et al (30, 31) observed that central dopamine metabolism is gradually impaired in the progression of dementia patients with multiple cerebral infarction as well as in Alzheimer’s disease. Dopamine metabolism became more disturbed in vascular type dementia than in Alzheimer’s disease. Multiple cerebral infarctions were primarily involved by basal ganglia infarcts. It is well known that dopamine agonist treatments in the rat bring about a heightened striosomal expression of SP and both dopamine D1 and D2 antagonists decrease SP (32). Mice lacking the dopamine D1 receptor and those treated with dopamine D1 receptor antagonist showed abnormal motor activities and feeding problems (33). Then, the mechanisms of silent aspiration may be speculated as follows. Patients with basal ganglion infarcts may suffer reduced
New Strategies for Aspiration Pneumonia

dopamine metabolism, which decreases SP in the vagal sensory nerves. Depression of SP concentration in these nerves impairs both swallowing and cough reflexes which increases the frequency of silent aspiration. Because the act of swallowing and coughing is a fundamental defense mechanism against aspiration of oropharyngeal contents into the respiratory tract, impairment of both reflexes is one of the major reasons for the development of aspiration pneumonia (34).

Prevention of Aspiration Pneumonia

Delayed triggering of the swallowing reflex occurs in patients with infarctions in the basal ganglia (20), and an impairment of dopamine metabolism in the basal ganglia is observed in these patients (30, 31). Kobayashi et al (35) investigated whether levodopa improves the swallowing reflex in patients with basal ganglia infarctions who had a history of aspiration pneumonia. The subjects were given an intravenous drip infusion of levodopa (50 mg in 20 ml saline) or an infusion of 20 ml of saline identical in appearance for 30 minutes. They found that administration of levodopa improved the impaired swallowing reflex in patients with cerebral infarctions (Fig. 1). Levodopa administration may help to prevent aspiration pneumonia in these patients.

Because SP is a neurotransmitter of swallowing reflex and SP is depleted in patients with aspiration pneumonia, capsaicin, the pungent substance in red peppers that stimulates sensory nerves, may improve the swallowing reflex in the elderly. Ebihara et al (36) measured the swallowing reflex with a bolus injection of 1 ml solution into the pharynx through a nasal catheter and measured the dose-response effects of capsaicin on the swallowing reflex. Patients received either vehicle or capsaicin (10⁻¹² to 10⁻⁹ mol/ml). The effect of capsaicin was dose dependent. They concluded that the addition of a low dose of capsaicin to liquid or food may stimulate the swallowing reflex and help prevent aspiration pneumonia in the elderly. An adverse effect observed during angiotensin converting enzyme (ACE) inhibitor therapy is a dry cough (37). SP is degraded by ACE (38), and its action is potentiated by ACE inhibitors (39, 40). Therefore, SP might accumulate in the upper respiratory tract by impairment of ACE activity and diffuse to rapidly adapting receptors, thereby causing an increase in the sensitivity of the cough reflex (41, 42). In a similar way, like the cough reflex, ACE inhibitor improved the swallowing reflex in the elderly (unpublished observation). ACE inhibitor may reduce occurrence of aspiration pneumonia in the elderly.

Aspiration pneumonia is thought to be due to organisms that inhabit the pharynx and aspiration of pharyngeal contents has been suggested as the mechanism by which these bacteria reach the lower respiratory tract (43). Johanson and Harris (44) speculated that the pulmonary infections caused by bacteria following the introduction of pathogenic organisms by aspiration of oropharyngeal contents is one of the major reasons for pneumonia in the elderly. Elderly patients in nursing homes are commonly characterized by recurrent infections manifested by fever. Although fever was not necessarily observed, which may underestimate the infectious signs, fever is often the only symptom of infection in non-communicative patients (45). Yoneyama et al (46) provided oral care to these patients in order to minimize respiratory infections, possibly caused by silent aspiration. The oral care consisted of daily care of the teeth and gingiva and cleaning the mouth after each meal. This oral care may prevent bacterial respiratory infections due to pharyngeal aspiration. During oral treatment for 6 months, febrile days did not improve but degradation of febrile days were prevented by oral care in a limited number of patients. They suggest that oral care may be useful to some extent in elderly patients to prevent respiratory infections (46).

It has also been estimated that more than one-third of the elderly population have intermittent symptoms of gastroesophageal reflex (47). Treatment of gastroesophageal reflux has been studied using drugs (48) and bed elevation for at least 2 hours after each meal (49). They observed that these treatments minimized respiratory infections in bed-bound eld-
elderly patients.

Wynne et al (50) suggested that gastric contents caused marked damage to the tracheal mucosa even when the amount of aspirated gastric juice was too small to cause clinically significant pneumonia. Damage is more severe when the pH of the gastric contents is low and gastric juice may contain substances that delay healing. Gastric juice causes epithelial damage probably through the additive effects of gastric acid, pepsin activity, and lower osmolarity (51). Therefore, counteraction of only gastric acid by histamine 2 receptor antagonist may not improve epithelial damage caused by gastric juice. Mays et al (52) suggested that repeated, long periods of aspiration of gastric juice may cause interstitial pulmonary fibrosis. Use of bactericidal clothes for bed-bound elderly patients for prevention of aspiration pneumonia has been proposed (53).

**Aging Effects on Aspiration Pneumonia**

It has been suggested that the progressive loss of protective reflexes (eg, swallowing and cough reflexes) with age is one of the reasons for aspiration pneumonia, which is often seen in older people (14). However, the effects of age on both reflexes have not been studied. Both reflexes were studied in relation to age in healthy subjects, and the results were compared with those in age-matched patients with aspiration pneumonia (54, 55). They observed that both reflexes did not decrease with the advance of age (54, 55). Therefore, a pronounced decrease in both reflexes observed in patients suffering from aspiration pneumonia may not be explained by aging effects on these reflexes.

In order to prevent aspiration pneumonia, immune function should be considered in these patients. Animal and human studies have shown that stress can affect many features of cellular immune function, including cytokine production (56). Kiecolt-Glaser et al (57) investigated the effects of stress, caused by caring for a relative with Alzheimer’s disease, on wound healing. They found that wound healing took significantly longer in caregivers than in controls. Stress-related defects in wound repair could have important clinical implications, for instance for occurrence of silent aspiration.

In Japan, increasing medical fees for older people, a growing elderly population, care systems and health problems themselves may cause psychological social stress for the elderly. One of the main issues of the Welfare Ministry of Japan is the means by which to reduce medical costs for older people (58, 59). In contrast, other reports support the opinion that medical costs for older people are not unfairly spent (60, 61) and that the growing older population will not disturb Japanese productivity in the future (62, 63). These positive thoughts toward longevity may encourage the elderly with psychological social stress and may improve immune systems.

Is pneumonia “the old man’s friend” (64) – a terminal event for patients who will otherwise die so soon of an underlying chronic disease? If so, chronological age might influence treatment policy. Brancati et al (65) investigated the predictors of 2-year mortality after patients admission to hospital for community-acquired pneumonia, and focused on the predictive value of age. They found that patients 75 years of age and older were more likely to die in the 2 years after discharge than patients between 18 and 44 years of age, but this difference did not reach statistical significance. These results suggest that underlying health is much more important than age in determining prognosis after hospital care with community-acquired pneumonia. Old age should not be a sole criterion for withholding aggressive treatment of community-acquired pneumonia.

**References**

New Strategies for Aspiration Pneumonia


