Diagnosis and treatments for oropharyngeal dysphagia: effects of capsaicin evaluated by newly developed ultrasonographic method

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Abstract

Oropharyngeal dysphagia (OD) is a common symptom in the older people, and may cause fatal complications such as aspiration pneumonia. However, there is no established treatment for OD. The relationship between the transient receptor potential vanilloid 1 (TRPV1) and substance P released by activated TRPV1 was recently demonstrated. Further, there are several reports showing that capsaicin, a specific agonist of TRPV1, can improve OD. Currently, the evaluation of swallowing is mainly performed by videofluoroscopic examination. However, there are no reports on the clinical application of ultrasonography using tissue Doppler imaging. In this review, we describe the pathophysiology and treatments for OD, introduce our novel US method to evaluate cervical esophageal motility, and then outline our clinical study examining the effects of capsaicin, a specific TRPV1 agonist, in older patients with OD.

Key words: oropharyngeal dysphagia, capsaicin, substance P, transient receptor potential vanilloid 1, ultrasonographic tissue Doppler imaging

Introduction

Oropharyngeal dysphagia (OD) is a common major symptom in daily practice, and the number of patients with OD is approximately 16,500,000 in the USA (1). In our previous study targeting 6,069 Japanese patients (mean age 58.7 ± 17.9 years), the percentage of patients with dysphagia was 3.9% in enrolled outpatients (2). The prevalence of OD is higher in independently living older persons—16.6% in the 70–79 years-old group,
and 33.0% in the >80 years-old group (3, 4). OD reduces the social and psychological quality of life for both patients and caregivers, and can also cause fatal complications including malnutrition and/or dehydration, aspiration pneumonia, and asphyxia (1, 5, 6). These serious complications are reported to be closely associated with mortality in older people, because the frequency of aspiration pneumonia increases with age, and is considered an important complication of OD (4, 7, 8).

Accurate diagnosis of OD is extremely important. OD is assessed using screening, clinical signs, and instrumental methods. To date, the gold standard for OD diagnosis includes videofluoroscopic examination of swallowing (VF), and videoendoscopic evaluation of swallowing (VE) (9–11). However, existing modalities to assess oropharyngeal motility have several drawbacks such as location constraints, high costs, radiation exposure, or intricacy. VF can indicate the movement of the oral, pharyngeal, laryngeal and esophageal during swallowing, by using radiopaque contrast agents such as barium with mixed test agent like liquid or solid, under the X-ray (9, 10). It is not a direct observation of inflow of bolus into the esophagus, but an indirect observation method using X-ray. There are several limitations such as the risk of barium aspiration, the need to move X-ray equipment, and the risk of radiation exposure (9, 10). VE is a transnasal endoscopic method to evaluate the pharyngeal movement in direct observation during swallowing little amount of colored agents (11). VE can indicate the residue in pharynx, presence or absence of vocal cord paralysis. Furthermore, it is possible to perform at the bedside without radiation exposure (11). However, there might be risks of epistaxis, vasovagal response or laryngospasm, and concern associated the use of topical anesthesia. In addition, VE cannot observe the oral movement during swallowing and the bolus inflow into the esophagus due to white out (11). Although the both methods enable detailed evaluation of dysphagia, they are dynamic observation and quantitative evaluation is difficult, and they are complicated because of various evaluation factors (9–11) (Table 1). Nevertheless, ultrasonography (US) has no limitations of radiation exposure or the examination location, allows noninvasive testing, and is a useful technique for clinical practice. However, few studies have used US to evaluate oropharyngeal motility (12–15).

There is no definitive treatment for OD, and as such, most OD patients go untreated (16, 17). It was recently reported that substance P (SP) can cause swallowing and coughing reflexes of central origin via afferent stimulation of the transient receptor potential vanilloid 1 (TRPV1), which is expressed in the oral mucosa, pharyngolaryngeal mucosa, gastrointestinal tract mucosa, and airway mucosa (18). Thus, neuropeptides such as SP may be a potential target for treatment of OD.

In this review, we describe the pathophysiology and treatments for OD, introduce our novel US method to evaluate cervical esophageal motility, and then outline our clinical study examining the effects of capsaicin, a specific TRPV1 agonist, in older patients with OD.

### Table 1. The characteristics of modalities used to assess oropharyngeal dysphagia

| Evaluation of swallowing phase | Location constraint | Cost | Radiation exposure | Quantitative evaluation | Procedure complexity |
|-------------------------------|---------------------|------|-------------------|------------------------|----------------------|
| Videofluoroscopic swallowing examination | Oral, pharyngeal, and esophageal phase | Yes | High | Yes | Difficult | Intricate |
| Videoendoscopic swallowing evaluation | Pharyngeal phase | No | High | No | Difficult | Intricate |
| Tissue Doppler imaging | Pharyngeal, and esophageal phase | No | Low | No | Simple | Simple |
Figure 1 shows a summary of the important factors associated with oropharyngeal dysphagia (OD) in older patients. There are numerous factors (19, 20), which fall into two broad systems: the input system involving sensory nerves, and the output system involving various muscles and swallowing reflex (21).

**Sensory system of swallowing**

The perception of swallowing is transmitted through various nerves to the brainstem, and is collected in the solitary nucleus in the reticular formation through the fifth cranial nerve (trigeminal nerve, CN-V), the seventh cranial nerve (facial nerve, CN-VII), the ninth cranial nerve (glossopharyngeal nerve, CN-IX), and the tenth central nerve (vagal nerve, CN-X). Those signals are then transmitted to the nucleus ambiguus, which integrates motor output, and the swallowing reflex occurs by applying output stimulation to the swallow muscle through the trigeminal (CN-V), glossopharyngeal (CN-IX), vagal (CN-X), accessory (CN-XI), and hypoglossal nerves (CN-XII). The swallowing reflex is extremely reproducible, and these series of responses are controlled by a central pattern generator (CPG) in the medulla oblongata (20–23). The CPG is also regulated by upper motor neurons from the central cortex (21, 23–25).

The stimulation related to swallowing stimuli includes both chemical and mechanical stimuli. The mechanical stimuli are transmitted by myelinated fibers, while the chemical stimuli are transmitted by unmyelinated fibers (C-fibers). The TRP family plays an important role as a receptor for chemical stimulation in the pharyngeal, laryngeal, and airway regions. TRPs are six-transmembrane ion channels, with a number of subfamilies including TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), TRPP (polycystin), TRPC (canonical), and TRPN (Drosophila NOMPC) (26). TRPV1 is expressed on C-fiber terminals of afferent nerves involved in the swallowing sensation, and is a selective receptor for low pH, noxious heat (≥43 °C), and capsaicin (27–29).
Motility system of swallowing

The swallowing movement is divided into the oral, pharyngeal, and esophageal phases. After the pharyngeal phase, a swallowing reflex and involuntary movement occur via the CPG. As the bolus passes through the pharynx, the input stimulus activates the CPG, closing the vocal cords, moving the tongue backward, raising the hyoid bone, inverting the epiglottis, and raising the thyroid and cricoid cartilage. The pharyngeal constrictor muscle contracts sequentially from above for peristalsis, and the upper esophageal sphincter (UES) relaxes and opens, causing the bolus to be sent into the esophagus (21, 23). Aging causes a decrease in the muscle volume and elasticity of the tongue and masticatory muscle. Efficient pharyngeal contraction is impaired in the older people, the UES pressure at rest decreases, the UES relaxation pressure decreases, and the duration of UES opening time is prolonged (30–33). Therefore, the movement of the bolus from the oral cavity to the esophagus is disturbed, reflux from the esophagus to the pharynx occurs, and motor function decreases in all phases of swallowing (20, 30, 31, 33, 34).

Relationship between sensory and motility system

Disturbed input of the swallowing reflex causes swallowing reflex failure, while disturbed output causes motility dysfunction (35, 36). CPG impairment can cause swallowing abnormalities after the pharyngeal phase, resulting in impaired pharyngeal peristalsis and an abnormal UES opening timing (35). Although both the input and output systems are impaired in the older people, leading to aspiration, oral and pharyngeal sensitivity are considered the most important for initializing adequate UES opening.

Current treatment strategies for patients with oropharyngeal dysphagia

The primary clinical goal of OD treatment is relief of symptoms, prevention of various complications such as aspiration pneumonias, and prevention of degradation. The social and psychological quality of life should be also considered as a secondary goal. Several treatment options have been proposed to date, although without a high level of evidence.

Modification of diet and postural control

Previous studies have shown that dietary modification and postural control can improve certain aspects of swallowing (37, 38). Although these treatment methods can be performed at low cost, they are difficult to unify and reproduce, and there is only limited evidence for their efficacy at present.

Dental care and oral health

Dental care and oral health are important treatment strategies for OD. For example, Van Der Maarel-Wierink et al. showed that dental care or oral health improved the swallowing reflex and cough reflex, and decreased the amount of potential respiratory pathogens by avoiding bacterial overgrowth (39). However, there is lack of evidence from comparative studies on dental care or oral health in combination with pharmacological treatment in older patients.

Rehabilitation and training

Several studies have shown that rehabilitation and training can have significant positive effects in OD patients, and are recommended as supportive treatments (19, 20, 40). Swallowing intervention with exercise,
such as rehabilitation and swallowing training, was also reported to improve swallowing dysfunction and OD-related comorbidities (41, 42). Generally, the methods of rehabilitation for OD in older patients include training tongue pressure to improve lip muscle function, and the Shaker exercise (1, 43, 44). Although these treatments are noninvasive, there are individual differences in their effects. Expert advice or intervention is also required for a certain period. Further, several recent reports have shown that swallowing function improves more when combined with transcranial magnetic stimulation or pharyngeal electrical stimulation (neuromuscular electrical stimulation), or pyriform sinus ballooning (42, 45, 46). However, there have been no large studies examining the long-term efficacy.

Current medication therapies

As OD is often treated empirically, there are no medication therapies with a high level of evidence. Goals of medication therapy for OD are classified into preventing aspiration pneumonia, and improving sensory dysfunction of swallowing. There are two randomized controlled trials to prevent aspiration pneumonia in older patients. Nakagawa et al. reported that the newly developed pneumonia ratio was significantly lower in OD patients treated with amantadine than in those without treatment (47). Further, Yamaya et al. reported that use of cilostazol in patients with stroke reduced the risk of pneumonia by approximately 40% compared with the no-use group (48). However, although those studies showed significant benefits, there were problematic side effects including bleeding (4.4%), palpitation and/or tachycardia (4.1%), headache (0.7%), and diarrhea (0.4%).

New treatment options

Capsaicin is a specific agonist to TRPV1. As shown in Fig. 2, capsaicin, an agonist of TRPV1, can activate peripheral sensory C-fibers, leading to the release of several neuropeptides including SP (27, 28). Stimulation of the sensory C-fiber branches of the vagus in the laryngopharyngeal mucosa with capsaicin was reported to induce the swallowing reflex (29, 49). Rofes et al. also showed that stimulation of TRPV1 by capsaicinoids strongly improved the swallow response in older patients with OD (50). Further, several other studies have re-
Effects of capsaicin and US-TDI for OD

### Table 2. Previous reports examining the effects of capsaicin on swallowing

| Author (ref.) | Journal, years | Subjects (number) | Mean age (± SD, years) | Capsaicin Evaluation modality Parameter | The effect of capsaicin | Side effect |
|---------------|----------------|-------------------|------------------------|----------------------------------------|------------------------|------------|
| Ebihara et al. (51) | Lancet, 1993 | Patients with cerebral thrombosis (n=20) and age-matched controls | 76 ± 2.0 74 ± 1.0 | Bolus injection of 1 ml (10⁻¹² to 10⁻⁹ mol/ml capsaicin) into pharynx | EMG LTSR (time from injection to onset of swallowing) | LTSR was dose-dependently shorter in capsaicin group. | None |
| Ebihara et al. (52) | J Am Geriatr Soc, 2005 | Elderly in nursing home allocated into intervention group (n=32), and control group (n=32) | 81.7 ± 1.5 82.1 ± 1.2 | Capsaicin trochisci (1.5 µg/tablet) for 4 weeks | EMG LTSR | LTSR was shorter in capsaicin group after 4 weeks intervention compared with before the study. The reduction ratio of LTSR was increased in the high risk group (LTSR ≥6.0 s, n=8) than in the low risk group (LTSR <3.0 s, n=16). | NA |
| Rofes et al. (50) | Gut, 2013 | Patients with OD (n=33) | 73.9 ± 2.3 | 185.5 µg/g of capsaicin with bolus | VF Prevalence of penetration | Prevalence of penetration reduced. Prevalence of pharyngeal residue reduced. The time to UES opening was shorter. | NA |
| Kondo et al. (53) | Clin Interv Aging, 2014 | Patients with OD allocated into: outpatients (n=10; mean ESS 4.5 ± 1.4), outpatients (n=6; mean ESS 6.7 ± 0.8), and long-term inpatients (n=10; mean ESS 6.5 ± 1.6) | 79.3 ± 7.9 80.7 ± 7.4 81.3 ± 5.0 | 0.5 g of ointment (0.025% capsaicin) applied to external auditory canal | VE ESS after 5 min | ESS improved after application compared with before application in all three experimental groups. | None |
| Shin et al. (54) | Dysphagia, 2016 | Young healthy group (n=10) Older group without history of dysphagia or aspiration pneumoniae (n=16) | 21.6 ± 0.5 81.6 ± 9.4 | 10 g of pickled Napa cabbage (includes 1.5 µg capsaicin) before every meal for 20 days | EMG LSR assessed by S-SPT (time from solution injection into oropharynx with a nasoesophageal feeding tube to the onset of laryngeal movement | LSR improved on post-intervention compared with pre-intervention in both young and elderly groups. | NA |
| Our study (55) | Digestion, 2017 | Patients with OD (n=49) | 70.8 ± 11.6 | Capsaicin-containing film food (0.75 µg capsaicin per sheet) | US-TDI Improvement of symptoms CEOT (time from beginning of cervical esophageal wall opening to maximum cervical esophageal wall opening during swallowing the total test meal volume) SP level in saliva | Number of patients with improvement of symptoms by capsaicin intake was larger than with placebo. CEOT in the effective group was shorter capsaicin administration versus placebo. SP levels in saliva in the effective group increased after capsaicin administration versus placebo. Negative correlation of rate of change in CEOT with rate of change in SP in saliva. | None |

EMG: electromyography; LTSR: latency time of swallowing reflex; NA: not available; OD: oropharyngeal dysphagia; VF: videofluoroscopic examination of swallowing; UES: upper esophageal sphincter; ESS: endoscopic swallowing score; VE: videoendoscopic evaluation of swallowing; LSR: latency of swallowing response; S-SPT: simple swallowing provocation test; US-TDI: ultrasonographic examination with tissue Doppler imaging; CEOT: cervical esophageal wall opening time; SP: substance P.
ported effects of capsaicin on the swallow response in patients with OD (Table 2) (50–55). However, there are no double-blind placebo-controlled, crossover trials. Further, these reports evaluated the responsiveness of the swallowing reflex, but did not evaluate meal swallowing (successful movement of a meal into the esophagus through the pharynx), and did not measure improvement of symptoms in detail, or measure SP.

Menthol, an agonist of TPRM8, was reported to have an inhibitory effect on the cough reflex, and to reduce the latency time of the swallowing reflex via cold stimulation in the anterior facial arches (56, 57). However, there is one interesting study showing that the improvement in the swallowing response with menthol treatment was lower than that for capsaicin (58), although further studies are required.

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**The effects of capsaicin in older patients with oropharyngeal dysphagia: a double-blind, placebo-controlled, crossover study**

The detailed protocol for this study was previously described (Fig. 3) (55). The subjects of this study was 49 patients with oropharyngeal dysphagia, and the mean age was 70.8 years old. In brief, following an initial screening at visit 1, eligible patients were asked to answer a self-completion interview sheet, and collect their saliva at rest. An ultrasonographic examination with tissue Doppler imaging was then performed to evaluate cervical esophageal wall motion (59). After these examinations, patients were prescribed either capsaicin or placebo for 1 week. At visit 2, on the day when the patient had completed their 1-week capsaicin or placebo treatment, they were instructed to write a self-completion interview sheet, to collect their saliva, and to undergo an US examination as for visit 1. After these examinations, the medications were changed from capsaicin to placebo or placebo to capsaicin, and the patients were instructed to take the changed medicine for an additional week. At visit 3, the last day of the study, patients were instructed to write a self-completion interview sheet, to collect their saliva, and to undergo an US examination. Cottons were used for saliva collection based on a previous report (60), and the saliva volume, pH, and SP concentrations (enzyme immunoassay) were measured.

Capsaicin was significantly more effective (38.8%) for improving symptoms of oropharyngeal dysphagia than placebo (6.1%) in OD patients. There was also a significant increase in the change rate of salivary SP concentrations after administration of capsaicin compared with placebo only in OD patients who exhibited symptomatic improvement. Further, the duration of the cervical esophageal wall opening time evaluated by

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**Fig. 3.** The detailed protocol of our study. Taken from Nakato et al. Digestion 2017 (ref. 55).
US was significantly shorter in the capsaicin administration group compared with placebo only in OD patients who exhibited symptomatic improvement. Interestingly, there was a significant negative correlation of the change ratio of the duration of cervical esophageal wall opening time with salivary SP level (Fig. 4) (55). Thus, our study showed that elevated salivary SP concentration stimulated by capsaicin strongly improved the safety and efficacy of swallowing, and shortened the swallow response, in older patients with OD (Table 2).

**Conclusion**

Although OD is a highly prevalent disease, no diagnostic and treatment strategies are fully established. OD is an aging disease (“geriatric syndrome”) and is expected to rapidly increase in the near future with the aging society (1, 19, 20). Several modalities to assess oropharyngeal functions have been developed, although less invasive and more convenient screening methods are desirable. Our US method provides a useful tool that can overcome the disadvantages of previous modalities. Multifaceted approaches are also required for OD treatment, including tailored treatment combining swallowing training therapy and medication targeting neuropeptides such as SP. Future large-scale prospective studies are needed to evaluate the efficacy of these tailored treatments using our newly developed US method.

**Award Presentation**

This review is based on the 4th Tsumeo Shiratori Award at the 60th annual meeting of the Japan Society of Smooth Muscle Research in Tokyo, Japan.

**Conflict of Interest**

The authors declare that they have no conflict of interests.
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Effects of capsaicin and US-TDI for OD

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