Effects of capsaicin on older patients with oropharyngeal dysphagia : A double-blind, placebo-controlled, crossover study

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Short running head: Oropharyngeal dysphagia and capsaicin

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Keywords: capsaicin; oropharyngeal dysphagia; ultrasonographic tissue Doppler imaging; substance P; saliva

Abstract

Background/Aims: The standard of care for older patients with oropharyngeal dysphagia (OD) is poor. Stimulation of transient receptor potential vanilloid 1 might become a pharmacological strategy for these patients. This study aimed to compare the therapeutic effect of film food containing 0.75 μg of capsaicin in these patients.

Methods: In a crossover, randomized trial, 49 patients with OD were provided capsaicin or identical placebo at least 7 days apart. Patients' reported symptoms during repeated swallowing, the volume, pH and substance P (SP) concentrations in saliva, and cervical esophageal wall motion evaluated by ultrasonographic tissue Doppler imaging were obtained before and after capsaicin or placebo administration.

Results: Significantly more patients with OD who took capsaicin experienced improvement in symptoms than those who took placebo. Salivary SP levels were significantly increased after capsaicin administration compared with placebo in effective group. The duration of cervical esophageal wall opening was significantly shorter in capsaicin administration in effective group. Furthermore, a significant negative correlation was found between the duration of cervical esophageal wall opening and salivary SP levels.

Conclusion: Elevated salivary SP concentrations stimulated by capsaicin greatly improve safety and efficacy of swallowing, and shorten the swallow response in older patients with OD.

Introduction

Oropharyngeal dysphagia (OD) is a common major complaint in daily medical practice, occurring in 20–23% of older persons who live an independent life [1,2]. This condition is considered to be an important causative factor of aspiration pneumonia [3]. Aspiration pneumonia is reportedly present in 93.5% of inpatients who are admitted for pneumonia [4]. OD is an important clinical issue because Japan, as well as Western countries, is facing a super-aging society in future years [5, 6].

OD begins with minor symptoms, such as laryngopharyngeal dysesthesia or a strange sensation during swallowing, which later causes various complications, leading to a decreased quality of life (QOL) [7,8]. In older persons in particular, OD may cause fatal complications, such as aspiration pneumonia and suffocation, or lead to undernutrition due to decreased oral intake or decreased mental activity [9,10]. Therefore, caution in the early phase of OD is required in older patients.

Pathological conditions of swallowing can be divided into three phases: the oral phase, pharyngeal phase, and esophageal phase. Except for the oral phase, swallowing movements are involuntary, and the swallowing reflex is important. There are many factors involved in the pathophysiology of OD. While most diseases leading to OD are increasingly prevalent with advancing age, the physiological changes of aging are also linked to the risk of OD [11-13]. Loss of muscle thickness and function, a reduction in tissue elasticity, changes in the cervical spine, reduction of saliva production, impaired dental status, reduced oral and pharyngeal sensitivity, reduced olfactory and gustatory function, and reduced compensatory capacity of the aging brain increase the susceptibility to OD and may act as precipitating factors [14]. Among

them, an overall decrease in the sensitivity of the pharyngeal and supraglottic areas might play an important role in older patients with OD [15,16]. Recent studies have shown that afferent myelinated nerve fibers in the superior laryngeal nerve decrease with age and may be the cause of age-related sensory dysfunction of the oropharynx [17]. With regard to oropharyngeal motility, investigators have found that older people with impaired oropharyngeal sensitivity swallow more slowly because of delayed laryngeal vestibule closure, maximal hyolaryngeal excursion, and upper esophageal sphincter opening [18,19].

Substance P (SP) causes swallowing and cough reflexes of central origin by providing afferent stimulation of the vagus and pharyngeal nerves. SP is released by activation of transient receptor potential vanilloid 1 (TRPV1), which is expressed in the oral mucosa, gastrointestinal (GI) tract mucosa, and airway mucosa [20]. TRPV1 is considered to be a therapeutic target of OD [21]. Capsaicin is a specific agonist to TRPV1, and it has occasionally been reported that administration of capsaicin improves OD [22-25]. However, there are no randomized, double-blind, placebo-controlled trials on the effect of capsaicin on OD to date.

In this study, the effects of capsaicin plus®, a capsaicin-containing supplement, on symptoms and swallowing function in patients with OD were examined. This study aimed to compare the effects of capsaicin plus® and placebo in older patients complaining of OD, and to determine its mechanism of action. Additionally, correlations between evaluation of esophageal motor function by tissue Doppler imaging (TDI) and evaluation items of improvement in swallowing function were determined.

Methods

Subjects

A total of 51 consecutive patients who complained of the sensation of OD visited the outpatient clinic of our hospital between April 2014 and January 2016. Inclusion criteria were age ≥55 years, no known disease affecting swallowing, and written informed consent to participate. Exclusion criteria were as follows: presence of disease affecting swallowing; a history of surgery or radiotherapy involving the upper airways; neurological diseases, such as Parkinson's disease or multiple sclerosis; and psychiatric disorders and otorhinolaryngological diseases, such as Zenker's diverticulum and laryngeal palsy affecting swallowing. All of the patients answered our previously validated questionnaire about GI symptoms [26,27] and their scores of symptoms regarding OD were 4 points or more (0=none, 1=extremely rare, 3=rare, 4=sometimes, 5=often, 6=always) on a seven-grade Likert scale. Eosinophilic esophagitis was also excluded by biopsy during the upper GI endoscopic examination.

Study design

This study was a double-blind, placebo-controlled, crossover study (Figure 1). The enrolled patients were randomly allocated into two groups: patients were provided capsaicin or placebo. The test agent was provided for 1 week, and subjective and objective symptoms were evaluated. The test agent was then changed to the other agent in a crossover manner, and symptoms were evaluated. For double-blinding, an information manager who had no direct connection with this study allocated the enrolled patients to either the active agent group or the placebo group, using a random number table. For administration of the active agent, capsaicin plus® (Sanwa Kagaku Kenkyusho Co., Ltd. Nagoya, Japan), a capsaicin-containing film food that is commercially available in Japan, was used. Capsaicin plus® is a thin film food measuring 2 × 3 cm composed of gelatin and starch as major ingredients, and contains 0.75 μg capsaicin per sheet. This film

dissolves within several seconds when administered in the oral cavity. One or two sheets of this product are usually administered to the oral cavity, and a meal should be taken after the film is dissolved completely. This product contains 24 sheets of film per case and is good for 18 months after being manufactured. Placebo was made to be identical to capsaicin plus®, except for containing capsaicin, and was provided for free from Sanwa Kagaku Kenkyusho Co. The test meal used was Weider in Jelly® (Moringa & Co., Ltd. Tokyo, Japan), which is commercially available in Japan. One sheet of the test agent was orally administered just before examination. Initially, no test agent (either active agents or placebo) was used, and subjective symptoms were assessed by a questionnaire. After collecting saliva, cervical esophageal motility was evaluated by ultrasound examination using TDI. The test agent was used for 1 week and a follow-up visit was made 1 week later. At the follow-up visit, the same test agent was administered, and collection of saliva and evaluation of cervical esophageal motility by TDI were conducted again. The degree of improvement in subjective symptoms was determined by the self-administered visual analogue scale (VAS). Subsequently, a crossover was made with the other test agent, and observation and evaluation were conducted in the same manner. After both test agents were evaluated similarly, whether the patient desired to continue use of the agent was determined by a self-administered questionnaire.

Saliva test

SP in saliva was measured as described previously [28]. Specifically, saliva samples were collected in a Salivette (Sarstedt, Nümbrecht, Germany). After centrifugation (1000 × g for 2 min, 4°C), the supernatant was stored at −80°C. The samples were purified as follows. Each frozen sample was diluted by adding an equal volume of 1% trifluoroacetic acid (TFA) and was centrifuged at 4°C at 17,000 × g for 15 min. After adding 1 ml of acetonitrile and 15 ml of 1%

TFA to a 200-mg Strata C18 Sep column (Cat # 8B-S001-FCH; Phenomenex, CA), the supernatant was added to a Sep-Pak column and washed with 15 ml of 1% TFA. The sample was then extracted by slowly adding 3 ml of a 6:4 mixture of acetonitrile and 1% TFA. The sample was dried in a CC-105 (Tomy Seiko Co., Ltd. Tokyo, Japan) and stored at −20°C. SP concentrations were measured by enzyme-linked immunosorbent assay using the Correlate-EIA, Substance P ELISA Kit (Cat #ADI-901-018; Assay Designs, Inc., Ann Arbor, MI). Absorbance was measured immediately at 405 nm and corrected at 570 nm with a microplate reader (Varioskan Flash; Thermo Scientific Co., Ltd., Waltham, MA). SP in saliva was examined in terms of the rate of change during the use of placebo [(SP during placebo administration − SP before use of test agent)/SP before use of test agent] and the rate of change during the use of the active agent [(SP during use of the active agent − SP before use of the test agent)/SP before use of the test agent].

Evaluation of cervical esophageal motility by TDI

Observation of the cervical esophagus using TDI was performed as previously reported [29]. Although pretreatment was not particularly instructed, the test was conducted with the subject in the sitting upright position for longer than 30 min after taking a meal to prevent vomiting. The apparatus used was the Aplio XG (Toshiba Medical Systems Co., Ltd., Tochigi, Japan) with a 12.0-MHz linear-type probe. For visualization of the cervical esophagus, the cricopharyngeal muscle was identified on the left side of the cervical midline. The short axis view of the cervical esophagus was obtained at a site 1 cm caudal to the cricopharyngeal muscle. While the short axis view of the cervical esophagus was visualized, a single empty swallowing was initially instructed to confirm that the patient was able to perform swallowing. After 5 ml of Weider in Jelly® was administered into the oral cavity of the subject, swallowing of the total

volume of the jelly was instructed and observed during real-time observation of the cervical esophagus. When using the test agent, one sheet of film was orally provided before administration of the jelly. After dissolution of the test agent was self-reported by the subject, swallowing motion was observed 5 times, and moving images from each observation were saved as raw data. The images were captured at a speed of 45 frames per second, which is fast enough to analyze the velocity of cervical esophageal wall movements [24].

For evaluation of cervical esophageal motility, the cervical esophageal wall opening time (CEOT) was measured. This evaluation was based on previous studies, which showed that older people with impaired oropharyngeal sensitivity swallow more slowly because of delayed laryngeal vestibule closure, maximal hyolaryngeal excursion, and upper esophageal sphincter opening [18,19]. The CEOT was defined as the time from the beginning of cervical esophageal wall opening to the maximum cervical esophageal wall opening during swallowing of the total volume of the test meal (Figure 2). When multiple swallowing movements were required to swallow the test meal, CEOT was defined as the time between the beginning of cervical esophageal wall opening and the maximum opening during one swallowing. The CEOT was determined for 5 swallowing movements before and after the use of the test agent. Their mean values were obtained using the incorporated analysis software TDI-Q for saved data of moving images obtained in the examination. The CEOT was examined by using mean values of CEOT for obtaining the rate of change during the use of placebo [(CEOT during placebo administration − CEOT before use of the test agent)/CEOT before use of the test agent] and the rate of change during use of the active agent [(CEOT during administration of the active agent − CEOT before use of the test agent)/CEOT before use of the test agent]. These procedures were performed by three doctors registered as accredited specialists of the Japan Society of

Ultrasonic Medicine, each with more than 10 years of experience with ultrasonic examination.

Primary endpoints

Differences in the rate of improvement in subjective symptoms between the active agent and placebo were analyzed. Subjective symptoms were evaluated using self-administered questionnaires (eating assessment tool [EAT-10] [30,31], medical outcome study 8-item short-form health survey [SF-8] [32], and frequency scale for the symptoms of gastroesophageal reflux disease [FSSG] [33]) and the self-administered VAS. VAS evaluation covered the degree of improvement in seven items (1, increased saliva; 2, stimulation to the larynx; 3, strange sensation in the oral cavity; 4, change in taste; 5, change in sensation of warmth in the throat; 6, improvement of swallowing; 7, degree of satisfaction). Patients with a good response were defined as those who had improvement in swallowing by the VAS after use of the test agent and the degree of satisfaction was improved by ≥20% from baseline.

Secondary endpoints

Patients' characteristics, subjective symptoms examined by questionnaire (EAT-10, SF-8, FSSG, and the VAS), and GI series (GIS) findings were examined for differences between patients with and without a good response to capsaicin (the effective and ineffective groups). These groups were also compared regarding changes in salivary components (salivary pH, amount of saliva, amount of SP in saliva) and changes in CEOT as determined by TDI before and after use of capsaicin and placebo. Correlations among subjective symptoms, salivary components (salivary pH, amount of saliva, and amount of SP in saliva), and CEOT determined by TDI were also examined.

Patients' characteristics included age, sex, body mass index (BMI), smoking rate, drinking rate, disease duration, and oral medicine. With regard to GIS findings, the presence/absence of reflux esophagitis of grade A or higher in the Los Angeles classification [34] and the presence/absence of esophageal hiatus hernia of grade I or higher in the Hill classification [35] were compared.

Statistical analysis

Estimated values and theoretical values were compared by 2 × 2 chi-squared test. For comparison of the two groups, the Wilcoxon t-test was used for paired comparisons and the Mann–Whitney U-test was used for unpaired comparisons. Spearman's correlation was used for correlation and regression analyses. Differences were regarded as statistically significant at $p<0.05$ for any comparison. Statistical processing was conducted using the statistical analysis software SPSS statistical package release 17.0 (SPSS Inc., Chicago, IL).

Results

Of the 51 enrolled patients, two were excluded from the study because they used placebo alone. TDI was performed in all of the remaining 49 patients. They received both placebo and the active agent, did not have any adverse reactions, and completed the study.

Primary endpoints

Efficacy of capsaicin

As shown in Figure 3, among the 49 patients, the active agent was effective in a significantly higher number of patients (n=19, 38.8%) than those who took placebo, (n=3, 6.1%, $p<0.001$). The active agent was also effective in the three patients who responded to placebo.

Secondary endpoints

Comparison of patients' characteristics in relation to the level of efficacy of capsaicin

There was no difference in sex or age between the two groups (Table 1). BMI values in both groups were similar to the mean BMI value for the Japanese population (21.5–24.9 kg/m^2 for persons in their 70s or older) [36], with no significant difference between the groups.

EAT-10 scores of subjective symptoms were significantly higher in the effective group than in the ineffective group (p=0.01). When health-related QOL was evaluated by the SF-8, there was no significant difference in the physical component summary or mental component summary between the effective and ineffective groups. However, these values were lower than mean values for Japanese (physical component summary: 48.60, mental component summary: 49.44) [33]. The FSSG also showed no significant difference between the two groups. Patients completed the VAS after using the capsaicin or placebo in this study, not at baseline. We found differences in VAS scores for several questions between responders and non-responders after capsaicin administration, but not after placebo (Table 2).

Analysis of GIS findings showed that there was no significant intergroup difference (p=1.0) regarding patients with reflux esophagitis (Los Angeles classification [34] grade A or higher). Additionally, there was no significant difference in the incidence of concomitant esophageal hiatus hernia between the groups (Hill classification [35] I or higher) (p=0.33).

Salivary findings

There was no significant difference in the rate of change in the amount of saliva before and after administration of placebo or the active agent in either the effective or ineffective groups

(p=0.50). Similarly, there was no significant difference in the rate of change in the pH of saliva in the effective or ineffective groups (p=0.56). The amount of SP in saliva was significantly increased in the effective group after administration of the active agent compared with before administration (p=0.047) (Figure 4). However, there was no significant difference in the rate of change in SP between administration of placebo and the active agent in the ineffective group.

Items evaluated by TDI

CEOT before and after administration of the active agent was no different in overall patients (n=49) (data not shown). However, CEOT after administration of the active agent was significantly shortened in the effective group (n=19), but not in the ineffective group (n=30) (Figure 5).

Correlation between the rate of change in CEOT and the rate of change in SP

There was a significant negative correlation between the rate of change in CEOT and the rate of change in SP (n=34, p=0.001, r=0.53; Figure 6). However, there were no significant correlations between CEOT and other salivary components, such as salivary pH and amount of saliva.

Discussion

The present study demonstrated that the active agent containing capsaicin was significantly more effective for OD than placebo. In effective cases, administration of capsaicin caused a reduction in CEOT along with an increase in SP in saliva. This finding indicates that capsaicin plus® might serve as a therapeutic option for treatment of OD.

In this study, we used capsaicin plus®, which is commercially available in Japan. The use of this agent allowed us to maintain a constant amount of capsaicin. Capsaicin, a natural red pepper component, can be used without causing any distinct adverse reactions. No serious adverse reactions occurred in the 49 patients who used the active agent in our study. The active agent had a low content of capsaicin (0.75 μg) and was difficult to distinguish from placebo because the taste was the same. Therefore, we considered that this agent was appropriate for placebo-controlled studies.

As to the study design, crossover testing was performed, even though this was a double-blind, randomized study. The efficacy of capsaicin was primarily evaluated based on patients' self-reported symptomatic response, which leads to variation among subjects. Therefore, to minimize variation as much as possible, we used a crossover study design. As for the possibility of carry-over effects, the period of efficacy of capsaicin was considered to be less than 90 minutes [36]. Therefore, there was no possibility of carry-over effects in this study.

Maintaining a sufficient amount of saliva is effective for preventing dental caries and improvement of oral symptoms in gastroesophageal reflux disease (GERD) [37]. However, the present study showed no significant difference in the rate of change in the amount of saliva or in the rate of change in salivary pH before and after the use of the active agent between patients who responded and those who did not respond to the agent. The scarcity of patients with GERD in this study might have affected our results. However, the use of saliva-increasing agents in patients with OD without careful consideration might result in mis-swallowing. Considering the fact that decreased oral sensation is involved in OD in older patients, improvement of sensory perception may be a more suitable treatment for this pathological condition.

One of the core findings of our study is that patients with the longest cervical esophageal opening time at baseline had the best response to capsaicin. These findings indicate that capsaicin may normalize abnormal esophageal opening in patients, but may not change opening time if already within normal limits. There are many causes for the symptoms of OD. Among these, an overall decrease in the sensitivity of the pharyngeal and supraglottic areas might play an important role, especially in older OD patients. Decreased sensitivity in the pharyngeal and supraglottic areas might lead to abnormal bolus transit of jelly, which might cause delayed cervical esophageal opening. Because capsaicin is a specific agonist for TRPV1, we think that capsaicin may be especially effective for OD patients with decreased sensitivity in the pharyngeal and supraglottic areas, although further studies will be necessary to confirm these points.

Our study showed that EAT-10 scores were significantly higher in the effective group than in the ineffective group. Our previous study on the efficacy of proton pump inhibitors in patients with globus sensation also showed that proton pump inhibitors were more effective in patients with higher heartburn scores [26]. These findings indicate that patients who have more severe target symptoms respond better to treatment, suggesting that the EAT-10 score may serve as a predictive factor for the efficacy of capsaicin. A recent paper showed that there are many factors associated with OD, including age-related decreases in muscle function, tissue elasticity, and cortical plasticity, as well as skeletal changes [14]. Patients who did not respond to capsaicin administration had significantly lower EAT-10 scores than responders, indicating that they had significantly fewer symptoms of OD, and suggesting that OD in these patients was caused by these age-related factors rather than by decreased sensitivity. However, the number of patients

in our study is insufficient for conclusion. Further investigation of this issue is required.

Although a few studies have evaluated swallowing function by ultrasonography [38-40], they mostly used the moving distance of bone [39] or lingual movement [38] for indirect evaluation of swallowing function. These studies did not provide direct observation of swallowing movement. In contrast, the present study allowed real-time observation of the passage of bolus through the opened cervical esophagus by external ultrasonographic observation of the cervical esophagus, achieving direct evaluation of swallowing movement. Because ultrasonography has no limitations of radiation exposure or the examination site, and allows noninvasive testing, it is a useful technique for clinical practice. However, ultrasonography has the disadvantage that quantitative evaluation is difficult. In a previous ultrasonographic study, quantification was attempted by immobilizing the head [38]. In this study, we used TDI for evaluation. Quantitative evaluation of myocardial motion by TDI is a useful method for evaluating myocardial function [41, 42]. TDI enables evaluation of muscular movement simply and quantitatively in detail. Although the gold standard of evaluation of swallowing function is VF [43], VF requires X-ray exposure [44] and a specific facility for examination, causing a limitation in the location. Our study demonstrated, for the first time, that evaluation of cervical esophageal motility by TDI reflected swallowing function, and showed a correlation between cervical esophageal motility and SP in saliva. Whether all swallowing stages can be evaluated by TDI in the same manner as VF may be controversial. However, ultrasonic evaluation of swallowing function may be applicable for screening of OD, considering the disadvantages of VF, such as radiation exposure and limitation of the facility.

In the present study, differences in the effect of capsaicin in relation to its dose and changes in

the efficacy during prolonged use were not examined. However, this study used a general dose of capsaicin plus®, and we found no attenuation of the effect when the efficacy was evaluated in 1 week (data not shown). However, treatment of patients with OD will inevitably be prolonged. Therefore, we intend to conduct additional studies to determine the presence/absence of desensitization of the TRPV1 receptor and changes in the therapeutic effect during prolonged administration. The goal of treatment for patients with OD is to inhibit the onset of aspiration pneumonia and to improve nutritional status through medication. We are planning to conduct a placebo-controlled study using capsaicin plus® in the future.

In the present study, effective cases were defined as not all patients who showed improvement of swallowing by the use of the agent, but those who showed such improvement and ≥20% improvement from baseline in the degree of satisfaction with the use of the agent. Because effective cases were restricted to those who agreed with these two requirements, symptoms of patients were better reflected. The value of 20% was derived from the fact that all patients who desired continuous use of the agent on the subsequent questionnaire survey showed a degree of satisfaction of ≥20%. However, what percentage is suitable for the criterion of efficacy remains to be determined in the future. The follow-up period was 1 week in this study. Therefore, a questionnaire at the time of enrollment was not used. We plan to conduct evaluation by the VAS and questionnaires in future studies concerning improvement of subjective symptoms by setting a longer follow-up period.

Because the upper esophageal sphincter, that is, the cricopharyngeal muscle, moves orally during deglutition, TDI analysis may not be suitable for evaluating movement in this area. In the present study, however, we did not use the cricopharyngeal muscle to monitor cervical

esophageal motility, but instead evaluated the cervical esophagus at a site 1 cm below the cricopharyngeal muscle. Because the cervical esophagus at this site does not move orally during deglutition, we think that TDI measurements of the velocity of the cervical esophagus at this site are worth analyzing.

We did not evaluate cervical esophageal motility by high resolution manometry (HRM) before and after capsaicin administration. However, in a previous report, we showed that upper esophageal sphincter relaxation observed by HRM was closely correlated with CEOT as determined by TDI in healthy subjects [29]. We consider that evaluation by TDI parallels evaluation by HRM. The chemical cascade of the TRPV1 receptor affects GI peristalsis via the GI sensory nerve [45, 46]. This mechanism is expected to be applied to treatment of GI tract of functional disorders, such as irritable bowel syndrome [45, 46]. Therefore, there might have been some changes in esophageal peristalsis before and after capsaicin administration in patients who responded to capsaicin. Consequently, we also intend to conduct evaluation by HRM before and after administration of this agent in the future.

Inter-observer agreement was not assessed in this study. However, the cervical esophagus can be detected close to the body surface, and it is considered that there may be no difference in visualization by the examiners. Further studies will be necessary to confirm this matter.

In conclusion, elevated salivary SP concentrations stimulated by capsaicin plus® improve opening time of the cervical esophageal wall. This may prevent complications caused by OD.

Acknowledgements: The authors thank Mrs. Yayoi Mori for her assistance in the measurement

of SP level. This study was supported in part by a Research Project Grant #27G-003 from Kawasaki Medical School, The KAWASAKI Foundation for Medical Science & Medical Welfare, and The Japanese Society of Gastroenterology; Support for Young Gastroenterologists Attending International Gastroenterology Meetings.

Conflict-of-interest statement: None declared.

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Table 1. Patients' background

	Effective（N=19）	Not effective（N=30）	*P*-value
Gender M/F	11/8	15/15	0.589
Age (SD) ys	70.4±13.7	71.1±10.4	0.525
BMI(SD) kg/m^2	23.3±4.9	22.1±3.4	0.512
Smoking (%)	22.2	7.7	0.167
Drinking (%)	50.0	19.2	0.068
During time(range) ys	3.6±2.3(1-8)	2.6±2.0(0.5-8)	0.111
PPI (%)	57.9	63.3	0.703
EAT10(SD)	13.6(12.8)	5.7(7.4)	0.010*
FSSG (SD)	11.1(8.4)	8.8(8.0)	0.252
SF8 (PCS)	46.0±9.6	45.4±7.7	0.508
SF8 (MCS)	46.8±8.0	45.5±7.5	0.510
Reflux esophagitis† (%)	12.5	10.3	1
Hiatus hernia‡ (%)	18.8	6.9	0.512

SD: standard deviation, BMI: body mass index, PPI: proton pump inhibitor, PCS: physical component summary, MCS: mental component summary, FSSG: frequency scale for symptoms of GERD. *Significant difference, †Los Angeles classification >A, ‡Hill classification >I.

Table 2. Differences in VAS score in the seven items between the two groups

VAS question	placebo/ capsaicin	Responders Mean (25%–75%)	Non-responders Mean (25%–75%)	*P* value
Q1. Did you have increased saliva production?	placebo	13.3 (0–19.5)	5.6 (0–0)	N.S.
	capsaicin	26.7 (0–44.2)	22.9 (0–38.6)	N.S.
Q2. Did you feel more stimulation in the larynx?	placebo	1.7 (0–0)	4.8 (0–0)	N.S.
	capsaicin	16.1 (0–33.8)	13.0 (0–16.9)	N.S.
Q3. Did you experience more strange sensations in the oral cavity?	placebo	2.7 (0–0)	4.0 (0–0)	N.S.
	capsaicin	11.1 (0–13.6)	11.9 (0–18.2)	N.S.
Q4. Did you experience a change in taste?	placebo	1.1 (0–0)	0.2 (0–0)	N.S.
	capsaicin	1.9 (0–0)	2.9 (0–0)	N.S.
Q5. Did you experience a change in the sensation of warmth in the throat?	placebo	0 (0–0)	0.3 (0–0)	N.S.
	capsaicin	3.3 (0–0)	0.9 (0–0)	N.S.
Q6. Did you have improved swallowing?	placebo	4.4 (0–0)	0 (0–0)	N.S.
	capsaicin	41.8 (24.7–50.0)	3.9 (0–0)	<0.01
Q7. Are you satisfied with this treatment?	placebo	4.2 (0–0)	0.4 (0–0)	N.S.
	capsaicin	33.4 (20.8–39.0)	3.3 (0–0)	<0.01

Values shown are means with interquartile ranges. VAS: self-administered visual analogue scale.

Figure Legends

Figure 1. Study design.

US-TDI: ultrasonographic examination with tissue Doppler imaging (TDI).

Figure 2. Typical time–velocity curve of cervical esophageal wall motion after analysis by using TDI-Q.

Five images (i, ii, iii) in the upper panels show cervical esophageal wall movement i) before swallowing, ii) during swallowing (jelly showing high echoic fluid passing through the esophagus), and iii) after swallowing. Each ultrasound image matches the time phase indicated by the red circle on the time–velocity curve. E, B, T, and A indicate the esophagus, bronchus, thyroid gland, and carotid artery, respectively. The outer line of the cervical esophagus is indicated by a dotted line. E, B, T, and A indicate the esophagus, bronchus, thyroid gland, and carotid artery, respectively. The parameter shown in this figure indicates the cervical esophageal wall opening time (CEOT).

Figure 3. Efficacy of capsaicin.

The efficacy rate was significantly higher in patients who were provided capsaicin than in those who were provided placebo.

Figure 4. Change in the ratio of salivary substance P.

A significant increase in the change in ratio of salivary substance P was only detected in patients who responded to capsaicin.

Figure 5. Change in duration of the cervical esophageal wall opening time.

A significant decrease in the duration of the cervical esophageal wall opening time was only detected in patients who responded to capsaicin.

Figure 6. Correlation between the duration of the rate of change in the cervical esophageal wall opening time and the rate of change in salivary substance P.

There was a significant negative correlation between the rate of change in the cervical esophageal wall opening time and the rate of change in substance P.

Erratum

In the article by Nakato et al., entitled “Effects of Capsaicin on Older Patients with Oropharyngeal Dysphagia: A Double-Blind, Placebo-Controlled, Crossover Study” [Digestion 2017;95:210–220, DOI: 10.1159/000463382], the Disclosure Statement should read as follows:

Ken Haruma received honoraria from Abbott Japan Co., Ltd., Astellas Pharma Inc., AstraZeneca plc, Daiichi Sankyo Company, Ltd., Deep Impact Co., Ltd., EA Pharma Co., Ltd., Kyorin Pharmaceutical Company, Ltd., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Research Organization for GastroEnterological Disease Treatment, Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Company Ltd., Tsumura & Co., Zeria Pharmaceutical Co., Ltd. Jiro Hata received honoraria from AstraZeneca plc, EA Pharma Co., Ltd., Toshiba Medical Systems Co., Tsumura & Co. Akiko Shiotani received honoraria from AbbVie GK, Astellas Pharma Inc., AstraZeneca plc, Daiichi Sankyo Company, Ltd., EA Pharma Co., Ltd., Medtronic Japan Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Research Organization for GastroEnterological Disease Treatment, Takeda Pharmaceutical Company Ltd., Tsumura & Co., Zeria Pharmaceutical Co., Ltd. Noriaki Manabe received honoraria from Abbott Japan Co., Ltd., AstraZeneca plc, Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Company Ltd.

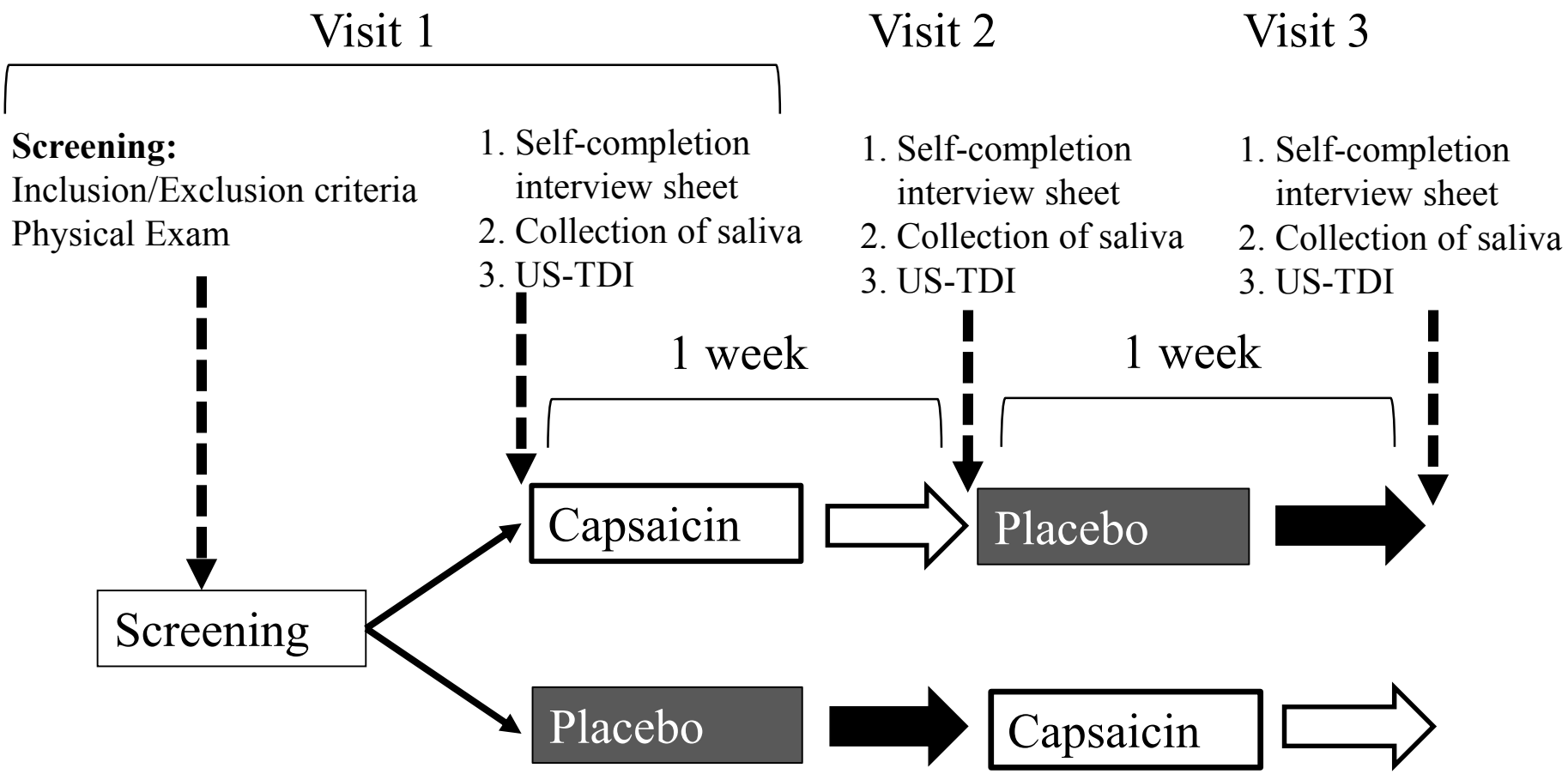
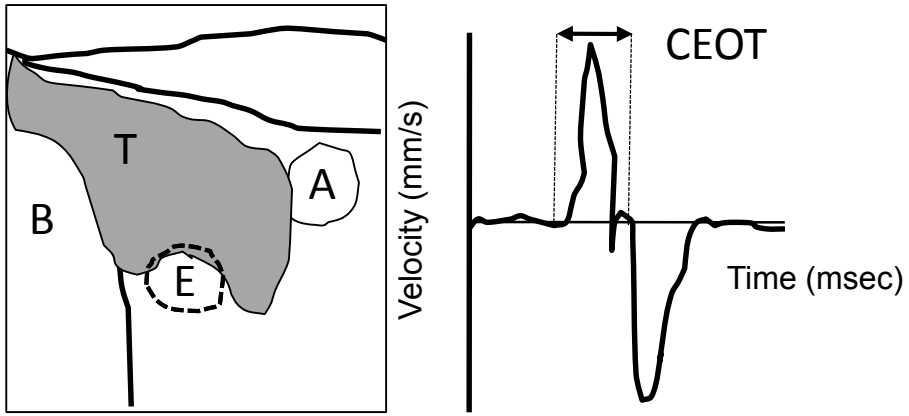
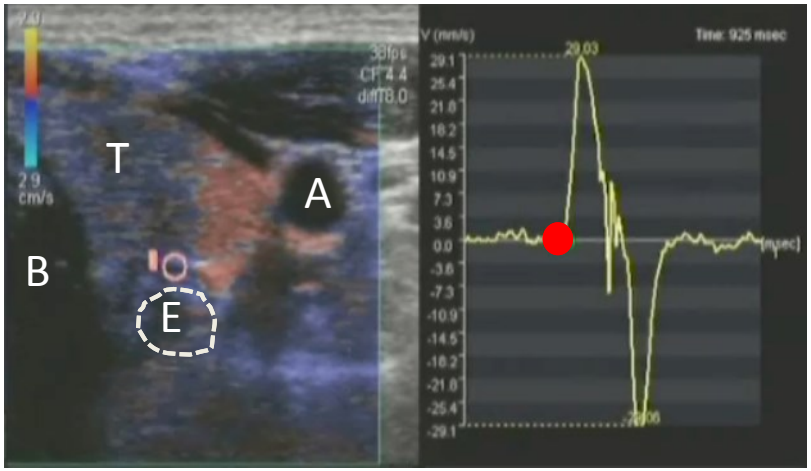

Visit 1
Visit 2
Visit 3
Screening:
Inclusion/Exclusion criteria
Physical Exam
1. Self-completion interview sheet
2. Collection of saliva
3. US-TDI
1. Self-completion interview sheet
2. Collection of saliva
3. US-TDI
1. Self-completion interview sheet
2. Collection of saliva
3. US-TDI
1 week
1 week
Screening
Capsaicin
Placebo
Placebo
Capsaicin

Figure 1.



(i)



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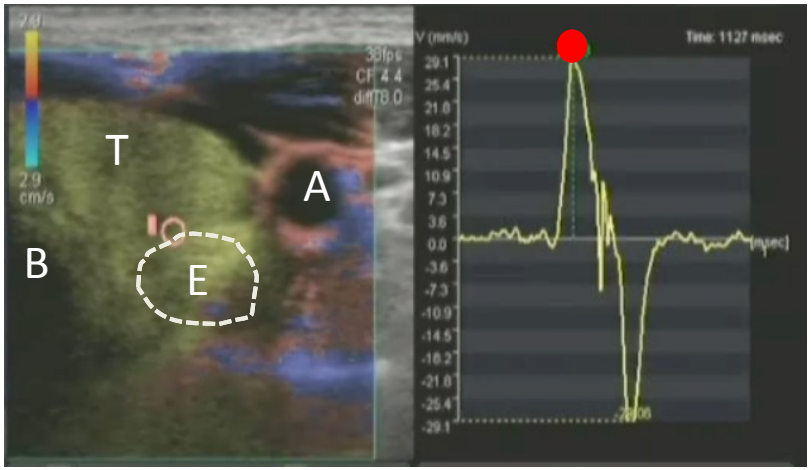

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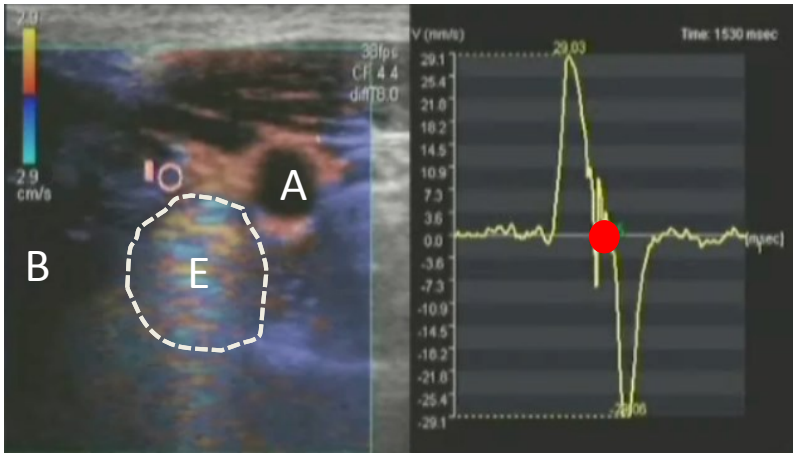

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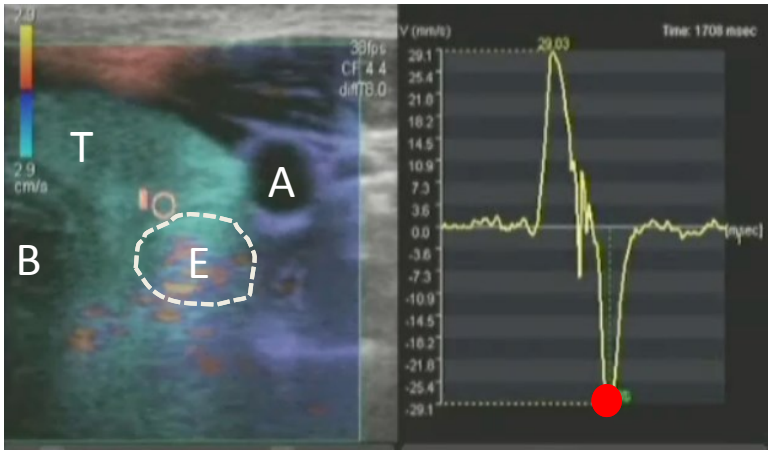

(iii)

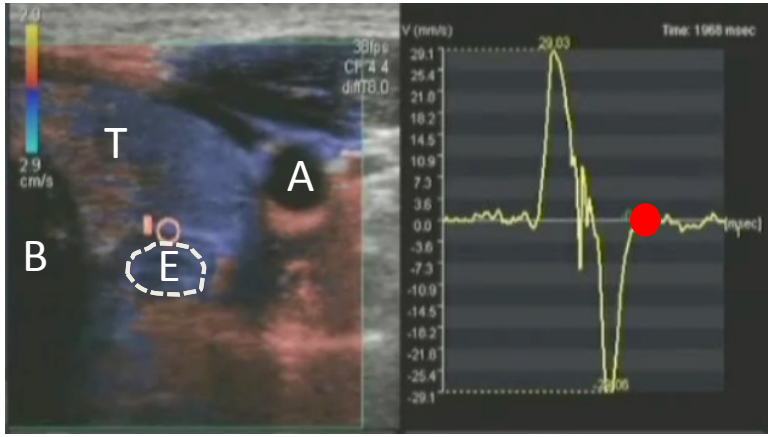

Figure 2.

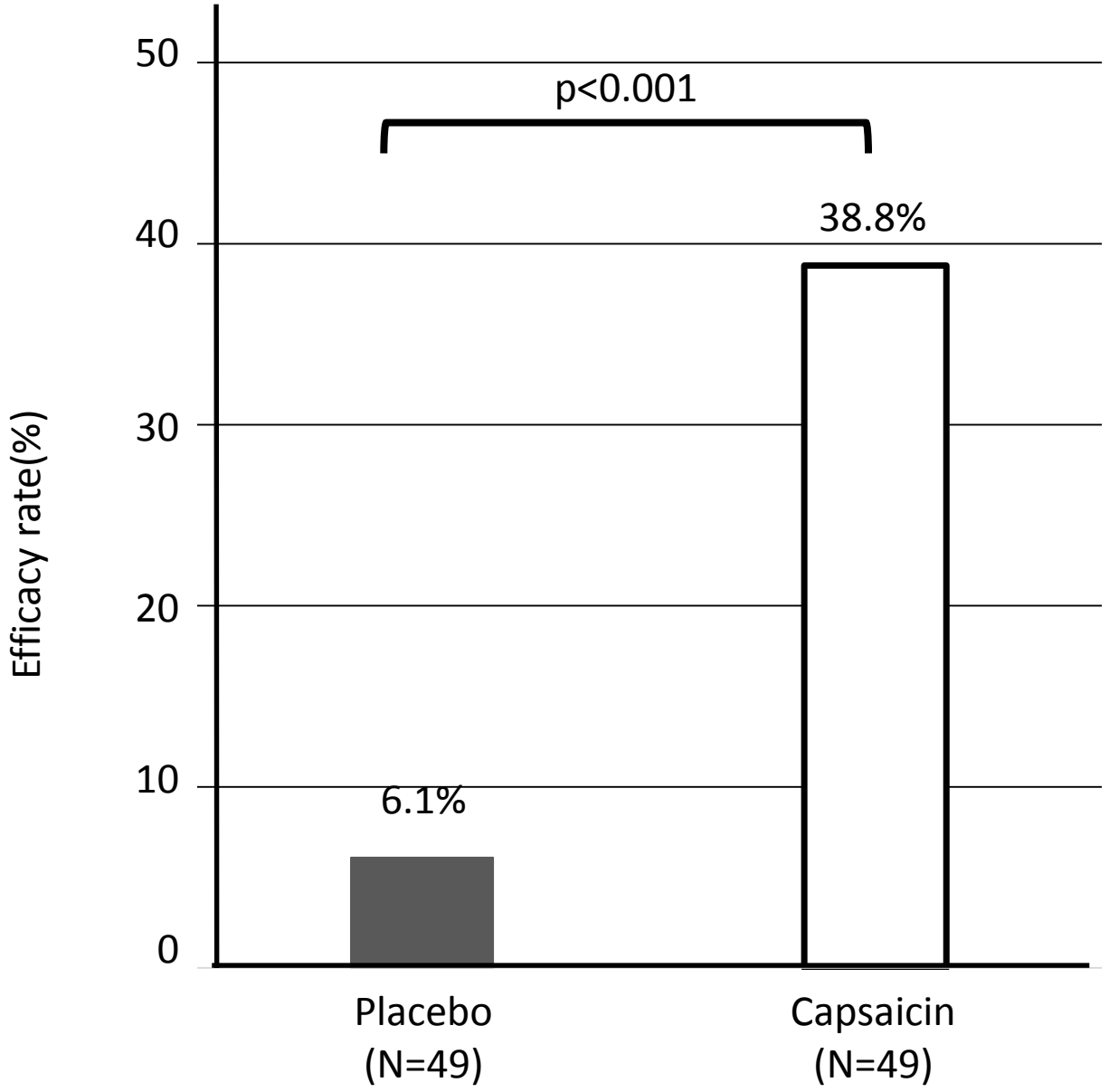
50
40
30
20
10
0
Efficacy rate(%)
p<0.001
38.8%
6.1%
Placebo
(N=49)
Capsaicin
(N=49)

Figure 3.

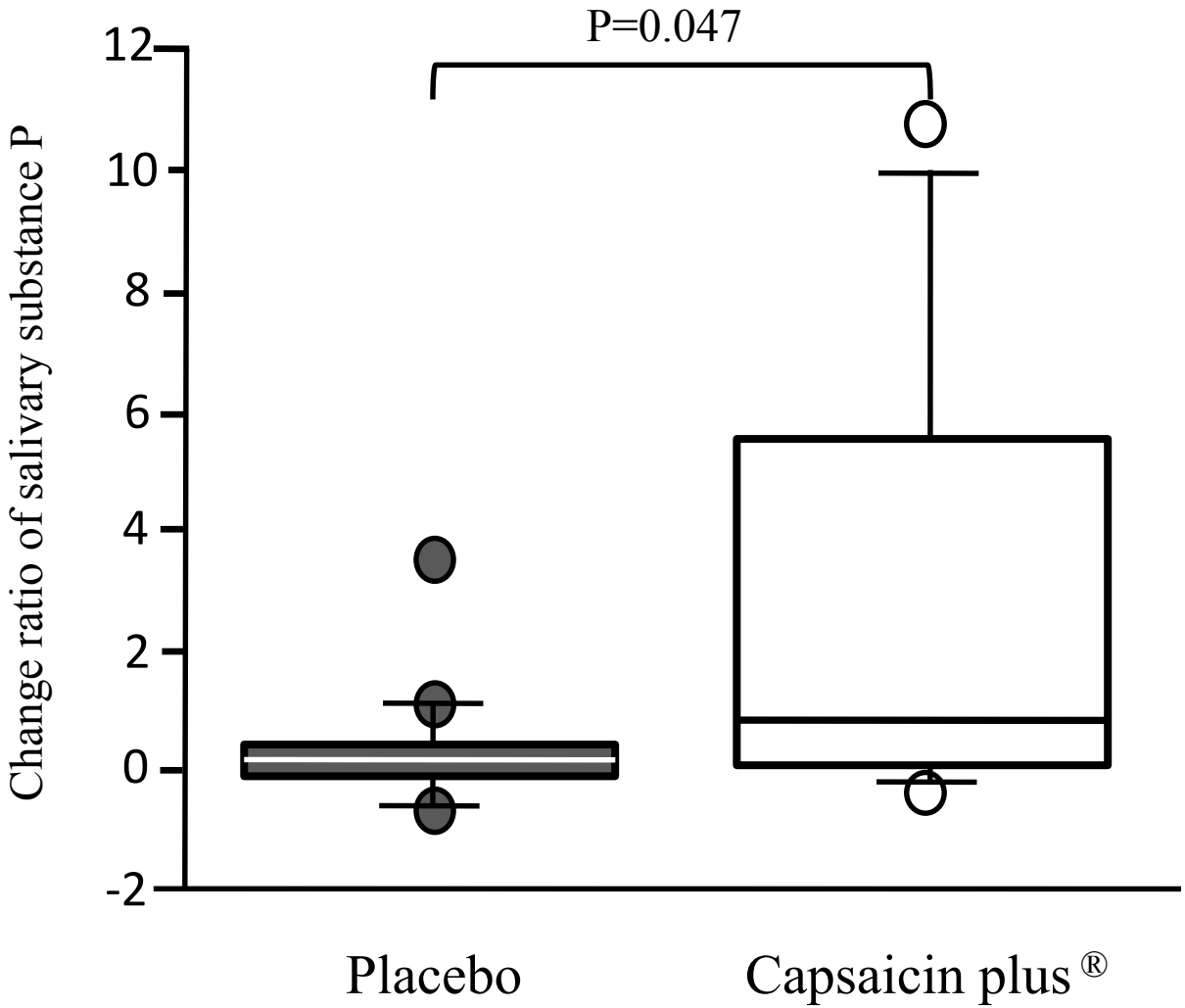
P=0.047
12
10
8
6
4
2
0
-2
Change ratio of salivary substance P
Placebo
Capsaicin plus ®

Figure 4.

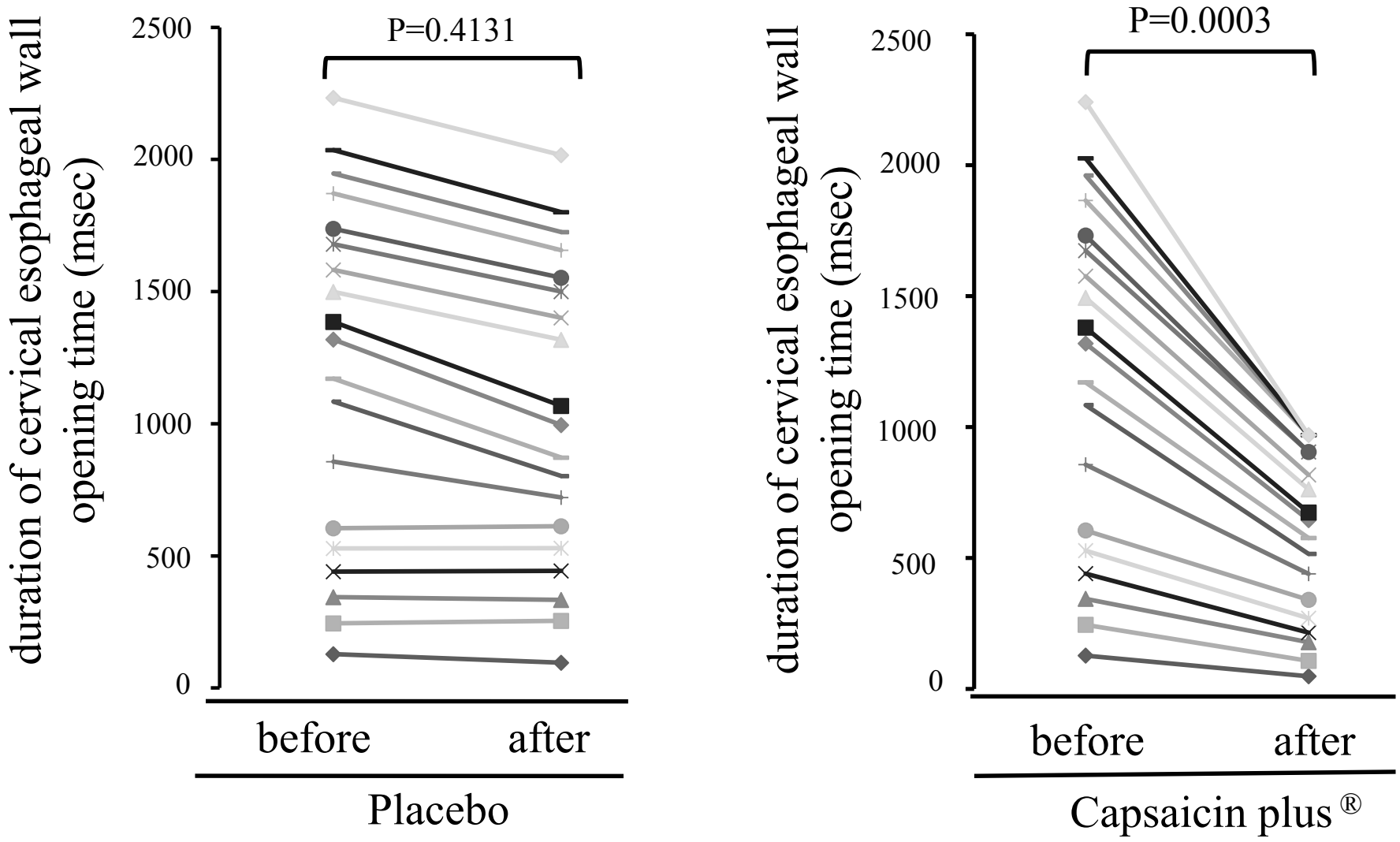
P=0.4131
duration of cervical esophageal wall opening time (msec)
2500
2000
1500
1000
500
0
before
after
Placebo
P=0.0003
duration of cervical esophageal wall opening time (msec)
2500
2000
1500
1000
500
0
before
after
Capsaicin plus ®

Figure 5.

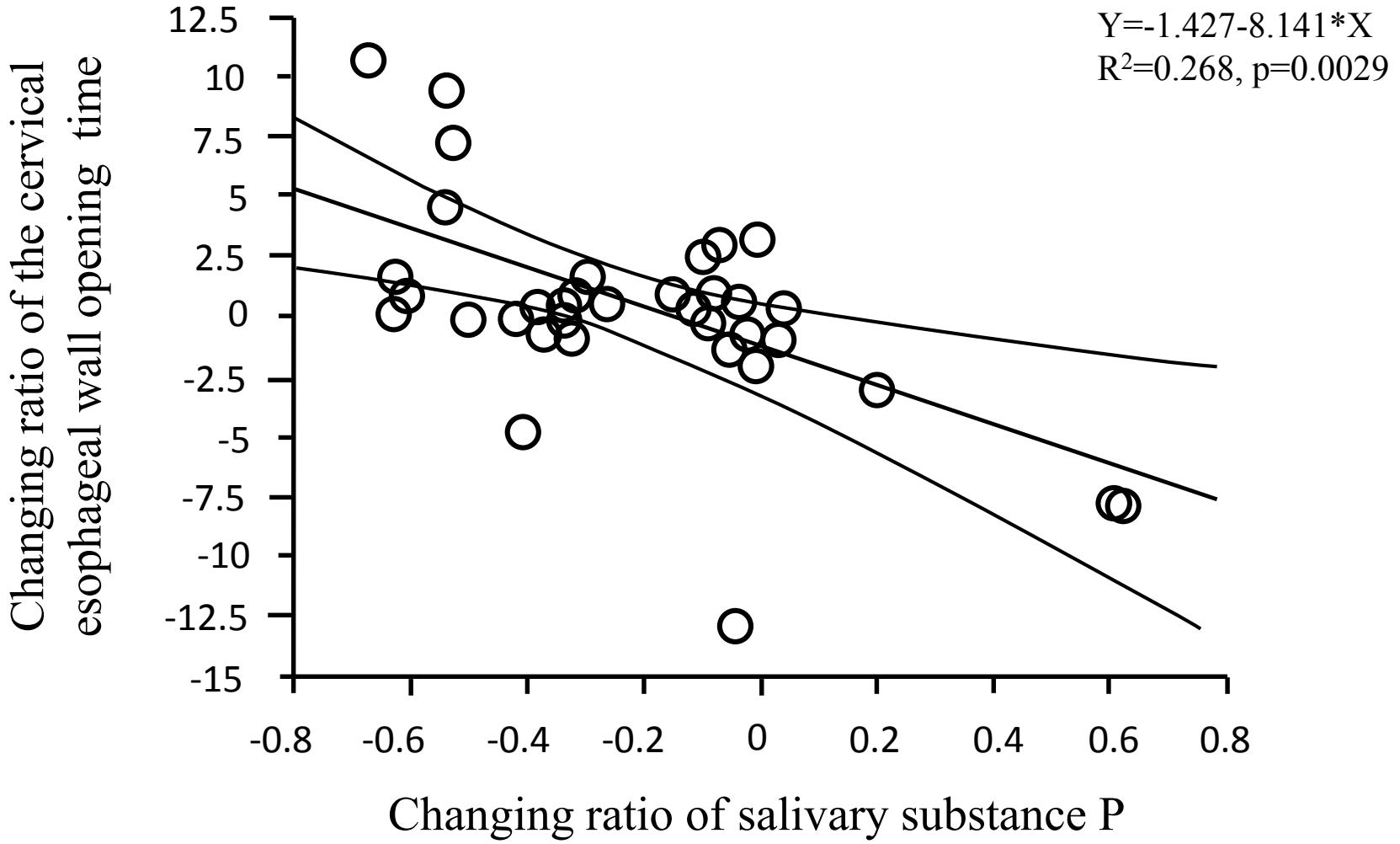
Y=-1.427-8.141*X
R2=0.268, p=0.0029
Changing ratio of the cervical esophageal wall opening time
12.5
10
7.5
5
2.5
0
-2.5
-5
-7.5
-10
-12.5
-15
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
Changing ratio of salivary substance P

Figure 6.