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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Sympathetic skin responses in adult humans during sequential swallowing

Les réponses cutanées sympathiques chez le sujet adulte au cours des différentes phases de la déglutition

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Swallowing;
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Tachycardia;
Vegetative system

Summary
Study aims. — Autonomic changes, especially those of sympathetic skin responses (SSR), during sequential water swallowing (SWS) have not been systematically investigated. This study aims to electrophysiologically examine these autonomic changes (SSR and heart rate) that occur during 50 ml sequential water swallowing from a cup.
Materials and methods. — Fifty-eight normal healthy adults were included in the study. Their submental muscle activity, respiratory activity, heart rate changes, and sympathetic skin responses were recorded during 50 ml water swallowing. In addition, we requested subjects to imagine drinking water as they did just before. The same recordings were performed during this imagination period.
Results. — SSR appeared at the beginning and at the end of SWS in 52% of subjects. A first sympathetic skin response was evoked at the onset of SWS, and a second one appeared 8.6 ± 1.7 seconds after the first one and at the end of swallowing. Similar double SSRs were also obtained during imagination in most investigated subjects (33 out of 35 of selected subjects in a total group of 58 subjects). Swallowing tachycardia was observed during the SWS-associated apnea period, but not during the imagination period. Heart rate significantly increased during the SWS-associated apnea period.
Conclusion. — The first SSR that appeared at the onset of swallowing is likely related to arousal. The appearance of a second response is a novel finding, which is probably related to the activity

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of subtil corticosubcortical networks. While discrete/single swallows can be used to evoke SSRs, SWS is unlikely to be clinically useful in its current form. In contrast, swallowing tachycardia could be a useful tool to examine dysphagic patients.

MOTS CLÉS
Déglutition ;
Déglutition séquentielle ;
Fréquence cardiaque ;
Réponse cutanée sympathique ;
Tachycardie

Résumé

But de l'étude. — On ne dispose jusqu'à présent d'aucune étude systématique de l'influence, sur l'activité du système nerveux autonome et, plus particulièrement sur les réponses cutanées sympathiques (RCS), des mouvements séquentiels de déglutition (MSD) d'une certaine quantité d'eau. L'objectif de notre étude était ainsi d'examiner électrophysiologiquement les modifications d'activité du système nerveux végétatif induites par les MSD d'un verre de 50 mL d'eau.

Patients et méthodes. — Notre étude porte sur 58 sujets en bonne santé chez lesquels on a enregistré, au cours de la déglutition de 50 mL d'eau, l'activité du muscle sous-mentonnier, la respiration, les modifications de la fréquence cardiaque et les réponses cutanées sympathiques. Nous avons également demandé aux sujets d'imaginer qu'ils buvaient la même quantité d'eau et avons réalisé les mêmes enregistrements durant cette période d'imagination.

Résultats. — Des RCS sont apparues au début et à la fin de la période de MSD dans 52 % des cas. La première RCS est apparue en début de la déglutition. Une seconde RCS est apparue à 8.6 ± 1,7 secondes après la première, ainsi qu'à la fin de la déglutition. De la même manière, des doubles RCS ont été obtenues durant la période d'imagination chez la majorité des sujets examinés (33 sur 35 sujets choisis parmi le groupe total de 58 sujets). Une tachycardie de déglutition a été mise en évidence durant la période d'apnée associée aux MSD de 50 mL d'eau mais pas durant la période d'imagination. La fréquence cardiaque était considérablement augmentée pendant la période d'apnée associée aux MSD.

Conclusions. — La première RCS apparaissant au début de la déglutition semble être liée à une réaction d'alerte. La mise en évidence d'une seconde RCS constitue une donnée originale. Elle reflète vraisemblablement l'action de subtils circuits nerveux cortico-sous-corticaux. Alors que des déglutitions isolées peuvent être utilisées pour évoquer les RCS, nous n'avons actuellement aucun argument établissant l'utilité clinique d'une étude des MSD. En revanche, la tachycardie de la déglutition pourrait constituer une méthode utile d'évaluation des patients dysphagiques.

Introduction

Sweat glands are classified into apocrine and eccrine types. While apocrine glands are diffusely distributed, eccrine sweat glands are densely distributed over the palms of hands and soles. Two types of sweating have been recognized: thermoregulatory sweating, which depends on apocrine glands and therefore occurs over the whole body in response to changes in environment; and emotional sweating, which is confined to the hand and feet as it depends on eccrine glands [2,11,39]. Both types of sweating obey different and independent rhythmicity, due to their different central drivers [2].

Any increase in sweat secretion lowers skin resistance to electrical conduction (electrodermal activity [EDA]). An increase in EDA can follow activation of sympathetic nerve fibers by miscellaneous ''internally generated'' and/or ''externally applied'' stimuli, which increases sweat secretion (sympathetic skin response [SSR]) [11,39]. As a sensitive index of emotion- and attention-related bodily arousal [4,38], SSR has been used to assess sudomotor function in human clinical studies [20,34]. In clinical practice, SSR recording is performed from hand or foot, usually in response to electrical shocks to major peripheral nerves. SSR can also be evoked or enhanced by other types of stimuli like inspiratory gasp, cough, deep breathing, or unexpected, surprising stimuli causing arousal or emotion [10,34,39]. Moreover, in addition to sweating, both parasympathetic and sympathetic autonomic efferents also influence heart (in both terms of its absolute value and variability) and blood pressure [16,32]. In particular, heart rate modulation in the high-frequency range is due to oscillations in parasympathetic influences correlated with spontaneous breathing (respiratory variability) [16]. Thus the respiratory system is the most important bodily function related with such autonomic nervous system functions as sweating and heart rate during continuous breathing, which can be clinically investigated by electrocardiography (ECG) and SSR. Deep inspiration as well as forced-expiration stimuli can be used to elicit SSR. SSR was also described in response to brief (about 1 second) occlusions of physiological breathing, either in inspiration or expiration [15,19,23,24], but not to longer (about 10 s) occlusion periods [19].

As a single swallowing is also associated with an apnea period of about 1 second, which is actually similar to the aforementioned occlusion periods, it can be expected that such ''swallowing apnea'' would also produce SSR [24]. However, the situation is far less clear regarding sequential water swallowing (SWS), for three reasons. First, the swallowing apnea is longer (about 10—15 s during SWS of 100 ml for example) [1]. Second, a SWS-evoked SSR, if any, could also be explained by a internal modulation in sympathetic efferents due, not to apnea but to the swallowing events themselves. Third, an arousal SSR could also appear in response to the examiner's order to start SWS. In another words, an SWS-evoked SSR, if any, could be related either to internally generated stimuli (apnea and/or swallowing) or to external influences (arousal SSR). The same principles hold true for the ''swallowing tachycardia'', which was first reported in 1883 by Melzer (cited by [36]). Indeed, drinking water causes an immediate and transient increase in sympathetic activities, which gives rise to an increase in both mean arterial pressure and heart rate [8,29]. Such rapid rises in blood pressure and heart rate might also be caused by internal swallowing-induced factors or correspond to arousal responses related to central descending influences from higher brain centers [7,8,14,36].

Even if it is currently unknown to what extent the study of autonomic changes during SWS could be helpful to clinical studies, adding SSR and ECG recording to routine SWS studies could help improve diagnostic workup, especially in patients with neurogenic dysphagia. This study aims at clarifying this issue. More specifically, our objectives are threefold:

- to test our proposal that SSRs might occur immediately before and after SWS from a cup;
- to establish that the origins of both responses might be slightly different;
- to stress the importance of swallowing tachycardia in patients with dysphagia.

Methods

Fifty-eight normal healthy subjects were included in this study (21 male, 37 female). Their mean age was 48.4 ± 14.8 (range 20—83) years, including 14 elderly subjects between 60—83 years. All were voluntary participants, including hospital staff and relatives of inpatients without polyneuropathy. The ethics committee of our hospital approved this study and informed consent was obtained from each subject.

During examination each subject was instructed to sit on a chair and hold his or her head in a neutral upright position. Examinations were performed in the afternoon, at least two hours after lunch. SSRs were measured in several different oropharyngeal experiments, as described below.

Sequential water swallowing

Liquid swallows were voluntarily initiated with 50 ml tap water from a standard disposable plastic cup positioned between the lips. Swallow signals were continuously recorded following water administration. These were detected based on the submental/suprahyoid electromyography (SM-EMG) changes. The SM-EMG was recorded by bilateral silver-silver chloride cup electrodes taped under the subject's chin, over the sub-mental muscle complex (mylohyoid, geniohyoid, and anterior digastric muscles). Signals were filtered (band pass 100 Hz to 10 kHz), amplified, rectified, and integrated. Total analysis time was adjusted to 20 seconds. A Nicolet-Viking V11.0 was used.

Before the start of the experiment, subjects were instructed that upon a command they should drink water continuously, like they would do in ''their daily life''. The first few seconds of SM-EMG analysis were performed at rest, then the examiner ordered the subject to swallow. The SWS test was repeated three times in all subjects. As it was considered the most reliable part of the experiment, only the third trace was used for individual measurement. By this way, we wanted to minimize the risk of slow or too fast SWS that would be the consequence of a lack of subject's experience during the first two trials. Numbers of swallows were counted from the periodic movements of SM-EMG during SWS. The total duration of SWS was calculated from the onset of the first to the end of the last swallow burst on the SM-EMG traces in a SWS epoch.

Swallowing apnea period

In parallel with SM-EMG, a respiratory signal was obtained through a nasal cannula (Sleep-sense®) that was placed at the entrance of the nostrils and connected to an airflow sensor transducer (Sleep-sense®). Airflow direction was recorded as a negative polarity representative of inspiration, or as a positive polarity representative of expiration. Both SM-EMG and respiration phase were simultaneously recorded to determine the ''swallowing apnea'' and respiratory phase patterns before, during, and after 50 ml of sequential water drinking. Respiratory signals were also recorded at rest. A plateau in the respiratory signals along the baseline indicated the swallowing apnea period. EMG filters for respiratory channel were adjusted with band pass of 0.2 Hz to 30 Hz.

Heart rate at rest and during swallowing

Heart rate was recorded using a silver-silver chloride cup electrode. An active electrode was taped to the second left intercostal space and a passive electrode was placed on the dorsum of the left hand. Signals were filtered (band pass 0.2 Hz to 30 Hz) and amplified. Total analysis time was adjusted to 20 seconds. The heart rate was measured and recorded at rest for 20 s before the experiment as well as throughout all swallowing experiments.

Imagination of 50 ml SWS

Some subjects were instructed to think about or imagine the 50 ml SWS after the start command. Thirty-five out of the 58 subjects were selected for this experiment; all had had easily-evoked SSRs in SWS experiments. Before the start of this experiment, subjects were instructed to keep their lips, tongue, head, and face muscles as relax as possible. During the procedure, there was complete silence except for the command to ''begin to imagine swallowing 50 ml water as you did before''. The imagination tests were also repeated three times.

Sympathetic skin response measurement

The SSR was recorded from the skin of the left hand. Skin surfaces were cleaned and silver-silver chloride electrodes were placed on the skin of the palm and dorsum of the hand using electrolyte gels. Band pass was 0.2—100 Hz. Subjects were seated and relaxed and room temperature was kept at 22—25 °C. Spontaneous EDA or background fluctuations of

EDA were first recorded for 20 seconds with subjects at rest. The presence or absence of the SSR was specifically related to deglutition experiments.

During the 50 ml SWS test, the first SSR was evoked after the examiner's command. Detection of this SSR was a requirement for a subject to be included in the later ''imagine'' experiment. About 10—15 minutes separated the initial SWS test and the subsequent imagination test. In all tests, the examiner's commands triggered the first SSR, which was related to ''attention'' and labeled ''arousal SSR'' for the sake of brevity. Additionally, during all above-mentioned procedures, some subjects also exhibited a late evoked SSR near the end of SWS, which was labeled ''second SSR''. The study was not focused on spontaneous EDA. We measured the intervals between the onset of arousal SSR and second SSR were measured, which we labeled ''SSR intervals''. SSR intervals were compared with 50 ml SWS duration and swallowing apnea periods.

Statistical analyses

The mean ± SD and SEM of all measured quantities were calculated and paired *t*-test were applied for comparisons.

Pearson correlation tests were used to compare SSR intervals and swallowing apnea and oropharyngeal swallowing time. To determine individual deviations, the upper or lower limits of the normal controls were used. Chi-square analyses were used to test for differences in percentage of respiratory pattern between groups. The significance was tested at the 5% level and the statistical analysis was conducted using the Medcalc® statistical package.

Results

SSR in SWS of 50 ml

Three types of SSR patterns were observed in the 58 controls. In 26 subjects (44%), no evoked SSRs were detected, a fluctuating low-amplitude spontaneous EDA activity was continuously recorded. In two subjects (3%), only an arousal SSR was evoked. The remaining 30 subjects (52%) exhibited clear-cut, both arousal- and second SSRs (Fig. 1). For the 30 subjects who exhibited both SSRs, the SSR interval was 8.6 ± 1.7 s (mean ± SD), SWS duration 6.3 ± 2.0 s, and swallowing apnea duration 6.1 ± 1.9 s) The SSR interval was significantly correlated with both swallowing and swallowing apnea durations ($r = 0.46$, $p = 0.01$ and $r = 0.53$, $p < 0.002$, respectively). In some of the patients swallowing apnea and tachycardia were present but there were no SSRs recorded (Fig. 2).

SSR in ''imagine'' condition

The ''imagine'' test was performed in 35 normal subjects. Interestingly, 33 out of these 35 subjects displayed both arousal and second SSRs, with SSR-intervals varying from 7 to 16 s with mean values of 9.5 ± 2.2 s (Fig. 3). Table 1 presents the SSR-interval values for the two different experiments. Although the mean SSR-interval values were somewhat longer in the ''imagine'' vs. actual SWS duration, the difference did not reach statistical significance. In the real 50 ml SWS test, both swallowing and apnea durations did not significantly differ. There were no changes of respiratory rhythm during imagination process.

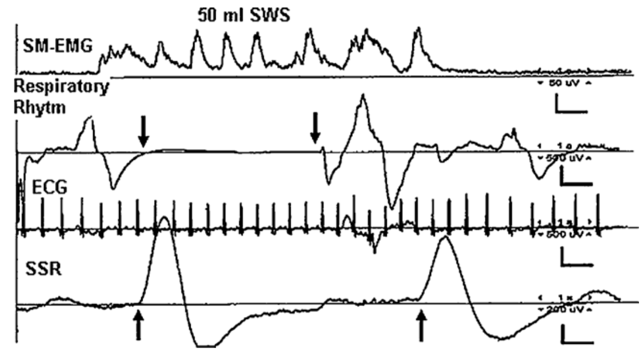

Figure 1 Sequential 50-ml water swallowing (SWS) from a cup. Each burst of sub-mental EMG (upper trace) corresponds to single swallowing. Second trace corresponds to the respiratory rhythm: the period between downward arrows defines the swallowing apnea duration. Third trace is electrocardiogram (ECG): note the increase in heart rate during the swallowing apnea period. Fourth trace corresponds to the arousal SSR (first and second SSRs are indexed by the first and second upward arrows, respectively). Amplitude calibration marks are 50, 500, 300 and 200 microvolt from top to bottom. Total analysis time: 20 seconds. Patients were instructed to swallow a few seconds after the start of recording.

Table 1 Statistics of SSR intervals and heart rate during deglutition (mean ± SD).

50 ml SWS (s)	
Swallowing duration	6.3 ± 2.0
Swallowing apnea	6.1 ± 1.9
Heart rate	
During rest	76.4 ± 11.6
During swallowing apnea 50 ml SWS	88.2 ± 12.3
During imagination	77.5 ± 11.4
SSR-interval (s)	
During 50 ml SWS	8.6 ± 1.7
During imagination	9.5 ± 2.2

Heart rate in swallowing apnea

The mean heart rate was 76.4 ± 11.6/min at rest and significantly increased during the swallowing apnea period (88.2 ± 12.4/min) ($p < 0.001$) (Table 1). In contrast, there were no changes in heart rate during the imagination process (77,5 ± 11.4/min), i.e., there was no swallowing tachycardia (compare Figs. 1 and 3).

Discussion

This study evaluated SSRs and heart rate changes during SWS. Our results can be summarized as follows:

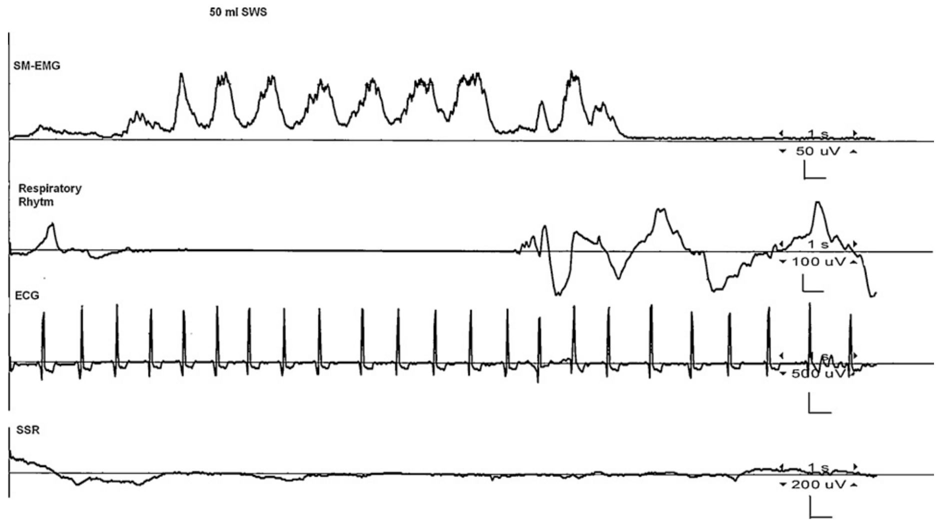

Figure 2 Sequential 50-ml water swallowing (SWS) from a cup. Swallowing apnea and tachycardia occur without SSR.

- an arousal SSR was recorded just before swallowing and after the examiner's order to swallow in 52% of subjects. Although this does not constitute an unexpected finding in normal subjects, such incidence appears lower than that to any other type of emotional arousal or peripheral-nerve stimulation;
- in most subjects (30 out of 32) in whom an arousal SSR was elicited, a second SSR was recorded at the end of the SWS. Conversely, a second SSR never occurred in the absence of an arousal SSR. This second SSR constitutes a novel finding and its genesis deserves more discussion;
- in 33 out of 35 normal subjects, SWS imagination also produced both arousal SSR and second SSRs. SSR intervals elicited in the ''imagine'' condition did not significantly differ from the ''real'' condition. This also constitutes a new finding in deglutition field of research;
- mean heart rate significantly increased during the swallowing apnea period as compared to the rest period.

This had already been reported in previous studies.

The arousal SSR most likely reflects attentional/emotional arousal that can be expected during such a task [4,38]. It was not directly related to SWS and likely depends on the degree of subject's anxiety and/or concentration. However, the incidence of the arousal SSR was lower than expected, which might be attributed to aging, insufficient concentration, or very fast habituation or insufficient augmentation. As concerns aging, although SSR is normally present in both hands and feet in normal subjects under the age of 60 years, it has been reported in only 50% of feet and 73% of hands in subjects older than 60 years [6]. The absence of SSR augmentation might be another important factor. Indeed, it was reported in a previous study that, while the first two to four electrical stimuli did not elicit any SSR, the SSR appeared and eventually augmented if the random stimuli were continued [33]. Therefore, it might be that the number of three SWS trials was not enough to evoke an arousal SSR. Unfortunately, we could not repeat our SWS trials more than three times due to long nature of test. Therefore, in some subject, absence of response could be due either to habituation or, conversely, to insufficient augmentation in skin conductance [11,33].

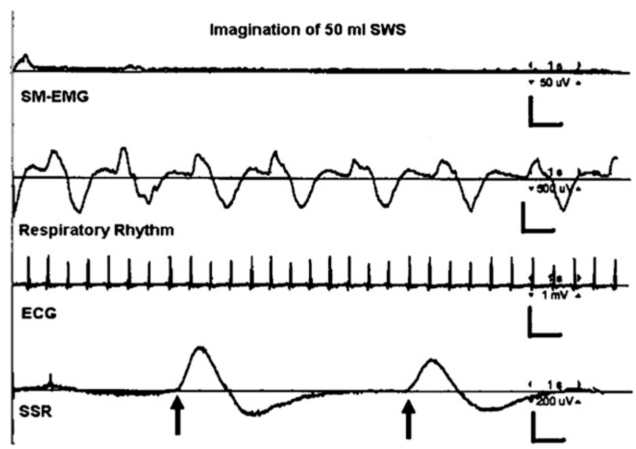

Figure 3 Imagination of 50-ml SWS. Figure design and arrangement are the same as in Fig. 1. Both the arousal and second SSRs clearly appear in spite of no swallowing movement (upper trace) and no swallowing apnea (second trace). Heart rate does not change (third trace).

After the arousal SSR, a second SSR appeared at the end of SWS and swallowing apnea. Time intervals between both SSRs were positively correlated with both swallowing and swallowing apnea SWS durations.

A first explanation of this relationship could be an influence of the swallowing apnea or other breathing-related processes. Indeed, during SWS, drinking is intermittently associated with instantaneous and repeated upper-airway opening and closure, which could have an effect on breathing, heart rate, and blood pressure. In particular, breathing was intermittently stopped albeit not to the degree of such breath holding maneuvers as forced expiration or inspiration [1,8]. As an abrupt decrease of sympathetic nerve activity and parasympathetic predominance has been observed during water drinking in humans [8,36], the hypothesis of an internally generated rebound of sympathetic activity at the end of the SWS period might be put forward. This hypothesis appears unlikely for the following reasons:

- the fact that, while all subjects actually displayed swallowing apnea, a second SSR appeared in only 52% of them;
- the absence of a one-to-one relationship between swallowing apnea and inspiratory changes;
- and the fact that a second SSR was observed in most subjects in the ''imagine'' conditions, which was not associated with any swallowing apnea or, more generally, changes in breathing.

A second hypothesis would be the influence of factors that would be directly related to swallowing. Thus, water swallowing in SWS might activate the chemoreceptors in the oropharynx with subsequent activation of these brainstem and cortical regions that are related with deglutition. An influence of direct oropharyngeal stimulation can be ruled out, given the fact that a second SSR was also observed in the ''imagine'' condition, in which, by definition, no direct oropharyngeal stimulation occurred.

A third hypothesis would be an influence of another arousal factor originating in the central nervous system. Two evidences support this hypothesis. Firstly, a second SSR was never observed in the absence of the first one that is obviously related to arousal factors. Secondly, even if it was somewhat less stable, a second SSR could also be evoked in the ''imagine'' condition in 33 of 35 investigated subjects. Recent neuroimaging studies have increased our knowledge about both the central origins of SSR and swallowing processes. On the one hand, both in single swallowing or SWS, anterior cingulate cortex (ACC) activation precedes the swallowing movement, which suggests an influence of this region on such visceromotor activities as digestive functions. It might also indicate an affective/attentive response to the challenge of safely swallowing [5,26]. Similarly, there is a clear deglutition center in and around the nucleus tractus solitarius (NTS) and nucleus ambiguus in the lower brainstem [1,9,17]. On the other hand, it was shown that neural activities from the ACC and lower-brainstem structures, including NTS, were correlated with SSR [13,21,28,31]. Such functional overlap could explain the relationship between SWS and SSR.

As SWS is a motor process that is repeated thousands of times along human life, it must be subtended by neural, cortical/subcortical networks that could easily be triggered through mental imagery [27]. As a result the mental activity related with deglutition can influence bodily states, such as increase of skin conductance of SSR, as well as real SWS [22,25,30,35].

Heart rate increased during real swallowing but not in the ''imagine'' condition. Heart rate (and blood pressure) increase during real drinking has been known from long [8,12,36,37] and labeled as swallowing tachycardia [36]. Two explanations were proposed for swallowing tachycardia, one of which is that swallowing tachycardia develops owing to inspiratory efforts [12]. In keeping with this hypothesis, Jean proposed that the neurons responsible for the motor pattern of swallowing also function as a inspiratory unit or linked with the respiratory pattern generator [17] or both. Whatever its mechanism, tachycardia as a cardiovascular consequence of swallowing has been easily reproduced with high stability, at least in normal subjects. As many patients with neurogenic dysphagia are older, it seems that swallowing tachycardia can be routinely used for electrophysiological studies related with swallowing, especially SWS. Deglutition-induced atrial tachycardia and atrial fibrillation were reported especially in patients with recent stroke and dysphagia [3,18]. In conclusion, swallowing tachycardia is a constant physiological phemenon and may be related to swallowing apnea during SWS. The arousal and second SSRs are not stable responses and may be related with central nervous system activities. Thus swallowing tachycardia and especially second SSR may not be directly related to each other.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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