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Circadian Changes of Influence of Swallowing on Heart Rate Variability with Respiratory-phase Domain Analysis*

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Abstract— **Respiratory sinus arrhythmia (RSA) is known as an index of cardiac vagal activity and useful to evaluate the response of the cardiovascular system to external stimuli. As an external stimulation, swallowing is known to strongly affect the cardiovascular system. However, the influence of swallowing and its relation with the autonomic nervous system remain incompletely understood. In this study, since autonomic nervous control of the cardiovascular system has a circadian rhythm, we evaluated circadian changes of influence of swallowing on RSA. Measurements were conducted on healthy humans with periodic swallowing in the morning, afternoon, and evening. RSA waveforms were extracted from an instantaneous R-R Interval (RRI) as functions of the respiratory phase and the data were divided into three subsets with respiration with swallowing, one respiration after the swallowing, and normal respiration. As a result, the RSA amplitude during respiration with swallowing was larger in the morning than in the evening. In addition, the minimum RRI during respiration with swallowing was larger in the morning than in the afternoon and evening. Thus, circadian changes of influence of swallowing on the RSA amplitude are extracted and swallowing-induced tachycardia is different with different states of autonomic nervous activity. Therefore, vagal activity should largely contribute to tachycardia induced by swallowing and evaluation of circadian changes of influences of external stimuli would be useful to investigate the mechanisms of response of the cardiovascular system to external stimuli.**

I. Introduction

The autonomic nervous system controls the cardiovascular system in order to maintain physiological homeostasis, allowing the cardiovascular system to respond to external stimuli and then recover to its previous state. Therefore, it is important to extract and evaluate the cardiovascular response to external stimuli for the clarification of the mechanism and control dynamics to maintain homeostasis. As a cardiovascular response, it is useful to investigate the external stimuli on heart rate variability (HRV) and extracted respiratory sinus arrhythmia (RSA). The amplitude of RSA, which is the HRV evoked by respiration activity, is known to be a useful index to estimate parasympathetic activity [1] and previous studies proposed methods to extract RSA as a waveform in the respiratory-phase domain [2].

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In regard to external stimuli, some stimuli are known to strongly affect the cardiovascular system. Especially, swallowing strongly affects the cardiovascular system [3]-[4]. Swallowing sometimes leads to fatal disease presentations such as atrial tachyarrhythmia and atrial fibrillation [5]. In spite of these clinical and physiological importances, swallowing effects and its relation with the autonomic nervous system are poorly understood. To clarify the mechanism of the influence of swallowing on cardiovascular system, it is effective to evaluate the influence of swallowing with different states of autonomic nervous activity. However, the interaction between the influences of autonomic nervous activity and swallowing on cardiovascular system has been only examined with pharmacological effects [4] or physical activity such as postural changes [4], and it has not studied whether RSA waveform would change by the influence of swallowing without pharmacological intervention or physical activity.

In regard to the autonomic nervous activity, autonomic nervous control of the cardiovascular system has a circadian rhythm, and heart rate and RSA are fluctuated in a day [6]-[7]. Thus, heartbeat and RSA are known to be different in the morning, afternoon, and evening. Therefore, it should be useful to evaluate the circadian changes as the different states of autonomic nervous activity.

In this study, we evaluated circadian changes of influence of swallowing on RSA with respiratory-phase domain analysis. We then evaluated the physiological mechanisms underlying swallowing effects on the cardiovascular system.

II. Methods

A. Experimental Procedures

Nine healthy males (with ages ranging from 22 to 28 years) were tested in the sitting position while in a state of rest. The experimental protocol is shown in Fig.1. Subjects were tested three times in a day. The first experiment was conducted between 08:30 and 09:30 a.m. in the morning, the second was conducted between 2:30 to 3:30 p.m. in the afternoon, and the last was conducted between 8:30 to 9:30 p.m. in the evening. In each experiment, 13 swallows were performed intentionally, once every 30 s between expiration and inspiration. Swallows in the experiments were performed under free-breathing conditions because paced respiration may result in unnatural hyperventilation or an alteration in the autonomic balance [8]. This study was approved by the Ethics Committee of the Graduate School of Frontier Sciences (The University of Tokyo). All of the participants gave informed consent after being given a full description of the study.

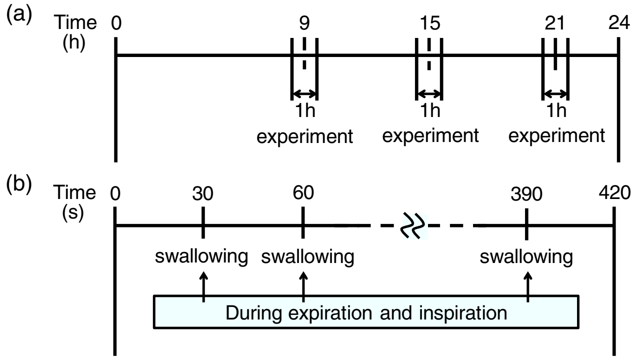

Fig. 1. Experimental protocol. (a) Time table of three experiments in the day. (b) Time table of each experiment.

During the experiments, continuous recordings were made of electrocardiographic R-R intervals (RRI) (AC-601G, Nihon-Koden), instantaneous lung volume (ILV) by means of inductive plethysmograph (standard type Respitrace, A.M.I), and the motion of the laryngeal prominence by means of two accelerometers (8305A2M4 and 8305B2M4, Kistler). To detect the time of swallowing, one accelerometer was positioned on the top of the laryngeal prominence, and the other was positioned on the bottom of the laryngeal prominence. The electrocardiogram and acceleration were digitized at a sampling frequency of 1,000 Hz, and ILV was digitized at a sampling frequency of 100 Hz.

In addition, tympanic temperature was measured by thermometer (MC-510, Omron) in each experiment. Tympanic temperature is one of the core temperatures and it is known as a useful index to estimate circadian rhythm [9]. Therefore, tympanic temperature was measured in order to estimate circadian rhythm of heartbeat and RSA.

B. Signal Processing

A schematic diagram of the signal-processing algorithm of extraction of RSA waveform in this study is shown in Fig.2. The algorithm for extracting RSA waveform is the same algorithm used in a previous study [3]. The method of signal-processing regarding each box in the diagram is described below.

In the box labeled *BPF* and *Hilbert transform*, an instantaneous respiratory phase was estimated by analytic signal using a Hilbert transform [2] after filtering ILV. ILV data were filtered by a band-pass filter of 0.1-10Hz and data from the first and last 20 s were eliminated by the filter because the order of the band-pass filter was 4000. Thus, data between 20 s and 400 s were analyzed.

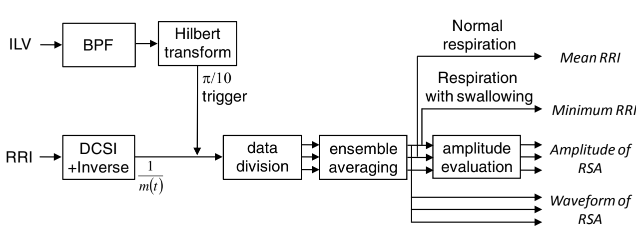

Fig. 2. Schematic diagram of the signal-processing method for extracting the RSA waveform using the respiratory-phase domain analysis.

In the box labeled *DCSI* + *Inverse*, discrete RRI data were first converted to a continuous time series by the method of derivative of cubic spline interpolation (DCSI) [2]. The DCSI method, which is based on a model of sinus node activity, is expressed by

$$M(t_k) = \int_0^{t_k} m(t)dt = kT, \qquad (1)$$

where t_k (k = 1, 2, …, n) are times at which heartbeats were observed, and $m(t)$ is the instantaneous HR obtained from first derivative of the interpolated $M(t_k)$ using a cubic spline function. Then the instantaneous RRI is calculated as $1/m(t)$. Thus, instantaneous RRI was resampled in each π/10 rad of the respiratory phase.

In the box labeled *data division*, the data were divided into three patterns of respiration in which swallowing occurred, one respiration after the swallowing, and normal respiration.

In the box *ensemble averaging*, mean values of equi-sampled RRI in the same phase were averaged and stable waveforms of RSA were extracted. In addition, the mean value of RRI during normal respiration and the minimum value of RRI during respiration with swallowing were calculated. The mean RRI was derived to evaluate the circadian rhythm of HR, and the minimum RRI was derived to evaluate whether the tachycardia by swallowing is same under different states of HR or not.

In the box labeled *amplitude evaluation*, the amplitude of RSA was derived by the difference between the maximum and the minimum value of the RSA waveform to evaluate the circadian rhythm of RSA and circadian changes of influences of swallowing on RSA quantitatively.

C. Statistical Analysis

For the statistical analysis, the statistical differences of tympanic temperature, the mean RRI, the RSA amplitudes of three patterns in the morning, afternoon, and evening, and the minimum RRI during respiration with swallowing were tested by the one-way repeated measures analysis of variance (ANOVA) with post hoc tests. We controlled for multiple testing by estimating the false discovery rate [10]. In this study, we evaluated the influences of circadian rhythm and swallowing on RRI and RSA, and then circadian changes of influence of swallowing. Detailed explanation is described below.

First, we compared the tympanic temperature, the mean RRI, and the RSA amplitudes during normal respiration in the morning, afternoon, and evening, to evaluate the circadian rhythm of HR and RSA. Second, we compared the RSA amplitude among normal respiration, respiration with swallowing, and one respiration after swallowing, to evaluate whether the influence of swallowing would be extracted accurately. Therefore, each RSA amplitude was derived by the average of all data in the morning, afternoon, and evening. Finally, we compared the RSA amplitudes during respiration with swallowing and one respiration after swallowing and the minimum RRI during respiration with swallowing, in the morning, afternoon, and evening, to evaluate the circadian changes of influence of swallowing.

III. Results

A. Influence of Circadian Rhythm

Fig.3 shows the comparison of the tympanic temperature (Fig.3a), the mean RRI (Fig.3b), the RSA waveforms (Fig.3c) and the RSA amplitudes (Fig.3d) during normal respiration in the morning, afternoon, and evening. As a result, the values of tympanic temperature and mean RRI were significantly larger in the morning than in the afternoon and evening. In addition, the RSA amplitude was larger in the morning than in the afternoon ($p < 0.01$).

B. Influence of Swallowing

Fig.4 shows the comparison of the RSA waveform (Fig.4a) and RSA amplitude (Fig.4b) among normal respiration, respiration with swallowing, and one respiration after swallowing. By RSA waveform, it can be seen that swallowing induced tachycardia and that respiration after swallowing had almost the same waveform as normal respiration. In addition, the RSA amplitude during respiration with swallowing was larger than those of during normal respiration and one respiration after swallowing ($p < 0.01$).

C. Circadian Changes of Influence of Swallowing

Fig.5 shows the comparison of RSA waveforms (Fig.5a), RSA amplitudes (Fig.5b) and the minimum RRI during respiration with swallowing (Fig.5c), in the morning, afternoon, and evening. As a result, it can be seen that swallowing induced tachycardia all the time (Fig.5a). The RSA amplitude was larger in the morning than in the evening ($p < 0.05$). In addition, the value of the minimum RRI was larger in the morning than in the afternoon ($p < 0.01$) and evening ($p < 0.05$).

In addition, Fig.6 shows the comparison of RSA waveforms (Fig.6a) and RSA amplitudes (Fig.6b) during one respiration after swallowing. As a result, RSA amplitudes showed significantly difference among morning, afternoon, and evening by ANOVA ($p < 0.05$).

IV. Discussion

A. Influence of Circadian Rhythm

In this study, the value of tympanic temperature was high in the morning and low in the afternoon and evening while the mean RRI and RSA amplitude was large in the morning and

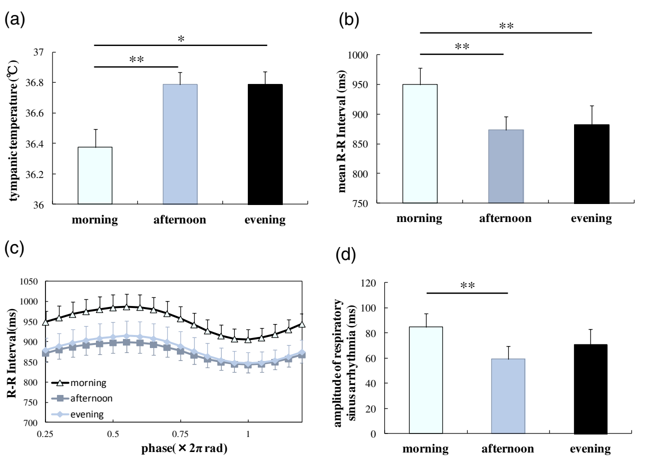

Fig. 3. Comparison of tympanic temperature, RRI and RSA during normal respiration in the morning, afternoon, and evening. (a) tympanic temperature, (b) mean RRIs, (c) RSA waveforms, and (d) RSA amplitudes. ** indicates P < 0.01, * indicates P < 0.05 and vertical bars represent SE.

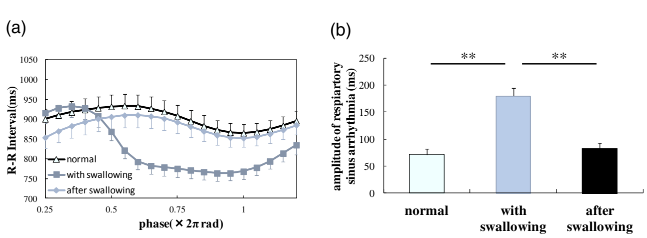

Fig. 4. Comparison of RSA waveforms and RSA amplitudes among normal respiration (normal), respiration with swallowing (with swallowing), and one respiration after swallowing (after swallowing). (a) RSA waveforms and (b) RSA amplitudes. **indicates P < 0.01 and vertical bars represent SE.

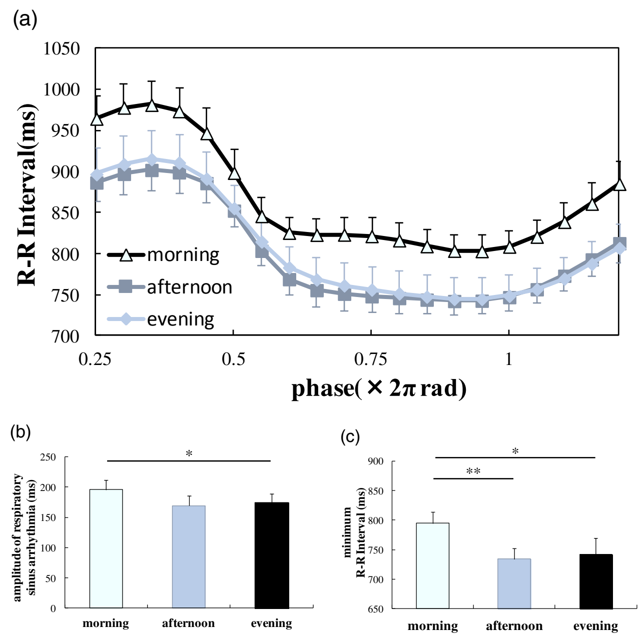

Fig. 5. Comparison of RSA waveforms, RSA amplitudes and the minimum RRI during respiration with swallowing in the morning, afternoon, and evening. (a) RSA waveforms, (b) RSA amplitudes, and (c) the minimum RRIs. ** indicates P < 0.01, * indicates P < 0.05 and vertical bars represent SE.

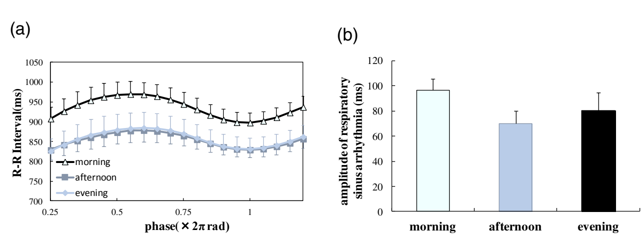

Fig. 6. Comparison of the RSA waveform and RSA amplitude during one respiration after swallowing in the morning, afternoon, and evening. (a) RSA waveforms and (b) RSA amplitudes of all subjects. ** indicates P < 0.01, * indicates P < 0.05 and vertical bars represent SE.

small in the afternoon and evening. These results are same as previous studies that circadian rhythms of core temperature and heart rate and RSA are negative correlated, and circadian rhythm of RSA is observed with a maximum occurring early in the morning, reflecting high vagal tone at that time [6]-[7]. Therefore, the circadian rhythm of heartbeat and RSA should be extracted by signal processing with respiratory-phase domain analysis in this study and parasympathetic nervous activity should be predominant in the morning and inhibited in the afternoon and evening.

B. *Influence of Swallowing*

As shown in Fig.4, swallowing-induced tachycardia is observed and this tachycardia recovers within one respiration. These results are same as the previous study [3], therefore the influences of swallowing on RSA are extracted indeed.

Thus, the influence of swallowing with different state of autonomic nervous activity could be evaluated by the interaction between circadian rhythm and influence of swallowing on RSA.

C. *Circadian Changes of Influence of Swallowing*

As shown in Fig.5, the RSA amplitudes during respiration with swallowing are significantly different between morning and evening. In addition, the minimum RRIs are significantly different between morning and afternoon, and between morning and evening. Therefore, swallowing leads to the different state of RRI and swallowing-induced tachycardia is different with different states of autonomic nervous activity.

In regard to tachycardia by swallowing with healthy humans, there are two possible physiological factors, which are changes in intrathoracic pressure and autonomic nerve activity [3]-[4]. If change in intrathoracic pressure is the main factor that induces tachycardia, the degree of tachycardia should be the same with different states of autonomic nervous activity such as influence by circadian rhythm, because the same intensity of stimulation occurs. However, in this study, circadian changes of influence of swallowing are observed. Therefore, change in intrathoracic pressure is unlikely the main factor underlying tachycardia induced by swallowing, and the change in autonomic nerve activity is a more probable causative factor. Thus, it is revealed that vagal activity largely contributes to swallowing-induced tachycardia by the evaluation of circadian changes of influence of swallowing with respiratory-phase domain analysis.

The evaluation of circadian changes with respiratory-phase domain analysis in this study can also reveal the effect of swallowing with disease presentations and the mechanism of atrial tachyarrhythmia and atrial fibrillation induced by swallowing. Although the paths of swallowing in healthy humans appear to differ from those of swallowing with disease presentations [5], the interaction between the influences of swallowing and autonomic nervous activity can be extracted to elucidate the mechanism of swallowing with disease presentations. In addition, evaluation of circadian changes could be applied to investigate the mechanisms of other external stimuli and wide ranges of applications including clinical testing are possible because of no necessity of pharmacological intervention or physical activity. For example, postural change modulates the circulatory dynamics and the circulatory control dynamics by the autonomic nervous system [11]. Therefore, the evaluation of circadian changes of the circulatory response to postural change would be useful to reveal the circulatory control dynamics by autonomic nervous activity. Thus, the method in this study would be useful to evaluate circadian changes of influences of external stimuli on HRV for understanding the mechanisms of response of the cardiovascular system.

V. Conclusion

In this study, we investigated the circadian changes of influence of swallowing on HRV using respiratory-phase domain analysis. The results show that circadian changes of influence of swallowing on RSA amplitude are extracted and swallowing-induced tachycardia is different because of different autonomic nervous activity without pharmacological intervention or physical activity.

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