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Association between Heart Rate Variability, Blood Pressure and Autonomic Activity in Cyclic Alternating Pattern during Sleep

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Study Objectives: Cyclic alternating pattern (CAP) is frequently followed by changes in heart rate (HR) and blood pressure (BP), but the sequential associations between CAP and autonomic nerve activity have not been studied. The study aimed to reveal the precise changes in heart rate variability (HRV) during phase A of the CAP cycle.

Design: Polysomnography was recorded according to the CAP Atlas (Terzano, 2002), and BP and electrocardiogram were simultaneously recorded. The complex demodulation method was used for analysis of HRV and evaluation of autonomic nerve activity.

Setting: Academic sleep laboratory.

Participants: Ten healthy males.

Measurements and Results: The increase in HR (median [first quartile – third quartile]) for each subtype was as follows: A1, 0.64 (-0.30 to 1.69), A2, 1.44 (0.02 to 3.79), and A3, 6.24 (2.53 to 10.76) bpm (A1 vs. A2 P < 0.001, A1 vs. A3 P < 0.001, A2 vs. A3 P < 0.001). The increase in BP for each subtype was as follows: A1, 1.23 (-2.04 to 5.75), A2, 1.76 (-1.46 to 9.32), and A3, 12.51 (4.75 to 19.94) mm Hg (A1 vs. A2 P = 0.249, A1 vs. A3 P < 0.001, A2 vs. A3 P < 0.001). In all of phase A, the peak values for HR and BP appeared at 4.2 (3.5 to 5.4) and 8.4 (7.0 to 10.3) seconds, respectively, after the onset of phase A. The area under the curve for low-frequency and high-frequency amplitude significantly increased after the onset of CAP phase A (P < 0.001) and was higher in the order of subtype A3, A2, and A1 (P < 0.001).

Conclusions: All phase A subtypes were accompanied with increased heart rate variability, and the largest heart rate variability was seen in subtype A3, while a tendency for less heart rate variability was seen in subtype A1.

Keywords: Cyclic alternating pattern, heart rate variability, blood pressure, complex demodulation method, autonomic nerve activation

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INTRODUCTION

Arousal reactions are important for clarifying the physiological and pathological mechanisms of natural sleep and sleep disorders. After a report published in 1992 by the ASDA (American Sleep Disorders Association) on EEG arousals, EEG arousals have been used as a marker of sleep fragmentation.[1] According to the ASDA report, an EEG arousal is an abrupt shift in EEG frequency, which may include theta, alpha, and/or EEG frequencies greater than 16 Hz. Asynchronous waves maintained for 3 seconds were defined as arousals, but high-amplitude slow waves, such as K complexes (KC) and delta bursts, were not counted as arousals. On the other hand, high-amplitude slow waves are often observed before the appearance of the asynchronous low-voltage mixed waves in NREM sleep. These periodic EEG complexes were defined as cyclic alternating patterns (CAP) by Terzano in the 1980s.[2]

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CAP is considered a marker of sleep instability and has been used for the evaluation of sleep in various sleep disorders and sleep changes with hypnotics.[3-16] A CAP cycle, which is the minimum unit of CAP, consists of two phases: phase A and B. During phase A, high voltage waves appear and diminish synchronously. The period following phase A, in which low amplitude EEG is present, is defined as phase B. Phase A is scored within a CAP sequence only if it preceded and/or follows another phase A within the 2-60 seconds temporal range. In addition, phase A is divided into three subtypes (A1, A2, A3) on the basis of the ratio of the synchronous high-amplitude slow wave period to the whole duration of phase A (A1: > 80%, A2: 50% to 80%, A3: < 50%).[2,17] Subtype A1 is frequently observed in the first part of the sleep cycle, in slow wave sleep, and subtypes A2 and A3 appear before the onset of REM sleep in healthy volunteers.

The components of arousal reactions include not only the changes in EEG frequency but also autonomic nerve activity involved with HR, BP, and skeletal muscle tension.[18] In NREM sleep, external stimuli induce not only high-amplitude slow wave components in EEG (e.g., K complexes [KC]), but also autonomic nerve reactions, such as the increase of HR and BP.[19,20] These autonomic nerve activities are also observed in the occurrences of KC and delta bursts with no external stimuli.[19,21-23] EEG shifts followed by autonomic nerve activity also appear before or simultaneously with leg movements in periodic leg movements (PLM).[3,24-27] Thus, EEG shifts,

Table 1—Demographic data (n = 10)

	Median	IQR
Age, y	21.0	4.0
Height, cm	175.0	7.4
Weight, kg	66.4	10.8
BMI, kg/m^2	21.5	2.5
PSQI GS	3.5	2.0
ESS	4.5	4.0

IQR, interquartile range; BMI, body mass index; PSQI GS, Pittsburgh Sleep Quality Index Global Score; ESS, Epworth Sleepiness Scale

including both synchronous high-amplitude slow wave and asynchronous components, are considered to have significant associations with the autonomic nerve and skeletal muscle activities in physiological and pathological conditions.

Heart rate variability (HRV) is often used for evaluating autonomic nerve activity.[28] There are a number of reports that have previously analyzed HRV in CAP using frequency analysis.[29,30] According to these reports, the balance of autonomic nerve activity is important, and the results indicate sympathetic nerve dominance during CAP sequences versus non-CAP sequences, even for the same sleep stages. However, detailed analysis of the autonomic nerve activity involved with the increased heart rate in KC and delta bursts has not been reported. Furthermore, the duration of phase A including KC and delta bursts typically lasts for 2 to 10 seconds. However, the frequency analysis logically needs data from at least 40 seconds.[28] Thus, it is impossible to assess the short, rapid autonomic nervous reactions by the standard frequency analysis. Therefore, we continuously measured both HR and BP using nocturnal polysomnography, and applied the complex demodulation method (CDM) for sequential analysis of HRV.[31,32] The CDM makes it possible to analyze the time course of amplitude in a specific frequency band and to evaluate the autonomic nerve activity with high time resolution.

This study aims to reveal the relationship between CAP and the time course of HRV, and study the physiological significance of CAP.

METHODS

Subjects

We evaluated 10 healthy males with a median age (IQR; interquartile range) of 21.0 (4.0) years. Exclusion criteria included the following: habitual drinker, habitual smoker, having physical or psychiatric diseases. Habitual sleep state was evaluated by the Pittsburgh Sleep Quality Index (PSQI).[33,34] For the PSQI, the median (IQR) global score was 3.5 (2) points, which matched the average global score of the general Japanese population.[35] Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS).[36] The median (IQR) of ESS was 4.5 (4.0) points, which was equivalent to that of healthy Japanese volunteers (Table 1).

All subjects gave written informed consent, which was conducted with the approval of the Ethics Committee of Akita University School of Medicine.

Polysomnography

Polysomnography was conducted for 8 h, in accordance with the habitual sleep time of each subject. To determine the sleep stages and the CAP parameters, both unipolar induction electrodes (C3-A2, C4-A1, O1-A2, O2-A1) and bipolar induction electrodes (Fp1-F3, F3-C3, C3-P3, P3-O1, Fp2-F4, F4-C4, C4-P4, and P4-O2) were attached to each subject. Electrodes were also attached to obtain electromyograms of the chin and anterior tibialis muscles, electroculograms, and ECGs. To measure the flow of air, airflow sensors were attached to the nose and mouth using the thermocouple method. To record breathing movements, respiratory effort sensors were attached to the chest and abdomen using the piezoelectric method. Body position sensors, snore sensors, and pulse oximeters were attached to record body position, snoring, and arterial oxygen saturation, respectively, of each subject.

The Neurofax EEG-1524 (Nihon Kohden Corporation, Tokyo, Japan) was used to record digital electroencephalographs. The data obtained were then imported and recorded on a computer using the BioSignal Acquisition System (NoruPro Light Systems, Tokyo, Japan). The sampling rates for recording were as follows: EEG, 1000 Hz; electromyograms, 200 Hz; snore sensors, 200 Hz; ECG, 1000 Hz; breathing movements, body position sensors, pulse oximeters, and pressure sensors, 100 Hz.

NightOwl Professional (NoruPro Light Systems) was used for throughout the analysis of sleep stages; 1 epoch was defined as 30 seconds. All evaluations were based on the criteria by Rechtschaffen and Kales.[37] EEG arousals and periodic limb movements were scored according to the AASM Scoring Manual.[38]

Blood Pressure Measurement

Portapres Model-2 (Finapres Medical Systems BV, Amsterdam, Netherlands) was used for consecutive blood pressure measuring, using plethysmography. Cuffs were fixed on the first and second fingers of the left hand, and BP measurement was alternated between the 2 fingers every hour. Pressure wave data obtained were imported by analog output with a sampling rate of 100 Hz and were recorded on an electroencephalograph by digital input.

CAP, Heart Rate, and Blood Pressure Analysis

For the evaluation of CAP, PSG data were visually scored by T.Y., A.K., and H.K., based on the scoring rules written by Terzano,[2] with the aid of CAP analysis software (NoruPro Light Systems). CAP analysis was also used for analyzing variations in heart rate and systolic pressure for each CAP subtype.

RR intervals were calculated in accordance with the peaks of R waves in lead II of the electrocardiogram. RR intervals < 300 ms or > 1700 ms were excluded in order to eliminate the influence of artifacts. In regards to BP, systolic blood pressure was detected by the peaks of pulse waves based on intermittent automatic calibration waves of a sphygmomanometer for 3 s with 90 s intervals. The BP data obtained during calibration were excluded for analysis.

The variations in heart rate and blood pressure were analyzed from 15 s before to 60 s after the onset of phase A. The moving averages were calculated using datum points with 0.1 second intervals; average values between 1.5 s before to

Table 2—Polysomnography findings

	Median	IQR
Total recording time, min	481.3	11.9
Total sleep time, min	456.8	37.9
Sleep efficiency, %	94.9	6.9
WASO , min	9.8	18.4
Sleep latency, min	4.5	10.3
Time in each stage, min		
REM	71.3	38.5
Stage 1	60.3	28.0
Stage 2	241.0	29.4
Slow wave sleep	56.3	34.1
Movements	6.3	2.9
Percent of TST, %		
REM	16.1	7.0
Stage 1	13.1	6.4
Stage 2	54.0	2.6
Slow wave sleep	12.2	8.2
Movements	1.4	0.6
REM latency, min	73.8	24.3
AHI , n/h	0.1	0.3
Arousal index, n/h	15.7	8.0
PLMS index, n/h	1.2	4.0

IQR, interquartile range; WASO, wake after sleep onset; TST, total sleep time; Movements, major body movements; AHI, apnea-hypopnea index; PLMS, periodic limb movements of sleep.

Table 3—CAP parameters

	Median	IQR
CAP Rate, %	36.4	21.6
CAP Time, min	140.4	82.1
CAP Cycle, n	334.0	212.3
A1, n	218.5	92.5
Ratio, %	73.2	23.3
CAP index, n/h	35.8	14.7
A2, n	62.0	77.8
Ratio, %	18.2	11.2
CAP index, n/h	10.0	12.8
A3, n	36.0	38.8
Ratio, %	11.0	12.2
CAP index, n/h	5.7	6.2

IQR, interquartile range; CAP, cyclic alternating pattern; CAP Rate was calculated as the ratio of total CAP sequence time to whole non-REM sleep time; CAP Time was calculated as total CAP sequence time; CAP Cycle indicates total CAP cycle counts; CAP Ratio represents the percentage of the number of CAP cycle counts for each subtype; CAP index represents the number of CAP cycle counts for each subtype per hour of NREM.

1.5 s after the datum points were calculated, and the amount of change was analyzed on the basis of the average 5 s prior to the onset of phase A.

HRV Analysis

We applied the CDM[31,32] for sequential analysis of autonomic nerve activity. Hayano proposed and established the use CDM for assessment of frequency shifts in HR and BP variability.[32] CDM is suited for continuous assessment of time-dependent changes in amplitude in the rhythmic components of predefined frequency bands. The RR intervals of the ECG were analyzed from 15 s before to 60 s after the onset of phase A using the CDM. The amplitude values for the low-frequency content (LF: 0.04 to 0.15 Hz) and the high-frequency content (HF: 0.15 to 0.4 Hz) were calculated continuously.

The amplitude value for the HF content is considered an indicator of parasympathetic nerve activity, while the amplitude value for the LF content reflects both sympathetic and parasympathetic nerve activity.[28] The area under the curve (AUC) of the LF and HF amplitude values was calculated for the first 20 s of CAP. In order to compare the changes before and after the CAP, the AUC for the 5 seconds leading to the CAP onset were quadrupled and compared with that of values for the 20 s after the CAP onset.

Statistics

PASW Statistics version 17.02 for Windows (SPSS Japan Inc., Tokyo, Japan) was used for statistical processing. Most data sets in this study did not indicate normal distribution. The data of HRV in subtype A3 indicated logarithmic normal distribution, but the others did not. Thus, data were shown as median (IQR) or median (first quartile – third quartile), and nonparametric statistics were applied: Kruskal-Wallis H statistic was used for comparisons among the 3 groups in CAP subtypes. Scheffe test was used for multiple comparisons. Wilcoxson signed rank test was used for comparing the AUC of the LF and HF amplitude values before and after the CAP onset. The level of significance was set at 0.05 for each test.

RESULTS

According to the sleep parameters, the sleep structures of our subjects were considered normal, and sleep related respiratory disorders and/or periodic limb movement disorders were not found (Table 2).

CAP parameters (Table 3) had large individual variations; the median CAP rate (IQR) was 36.4% (21.6%) and the median CAP cycle counts was 334.0 (212.3). Some subjects have higher CAP rates than those reported in healthy subjects from a similar age group.[39] Three of the 10 subjects had a CAP > 50%, and in 2 of the 3 subjects, the percentage of the number of subtype A2 and A3 was > 50%. The higher CAP values in this study might be due to influences on the sleep quality by the attachments of cuffs on fingers and a monitor device on the arm.

The number of phase As totaled 3527 in 10 subjects. R waves of ECG were well detected, and HRV could be calculated in 3262 of the phase As. Changes in BP could be evaluated without the influence of finger change and/or intermittent automatic calibration in 2474 of the phase As.

HR increased immediately after the beginning of CAP. The increase in HR for each subtype was as follows: A1, 0.64 (-0.30 to 1.69); A2, 1.44 (0.02 to 3.79); and A3, 6.24 (2.53 to 10.76) bpm ($H = 516.9$, $df = 2$, $P < 0.001$, A1 *vs*. A2 $P < 0.001$,

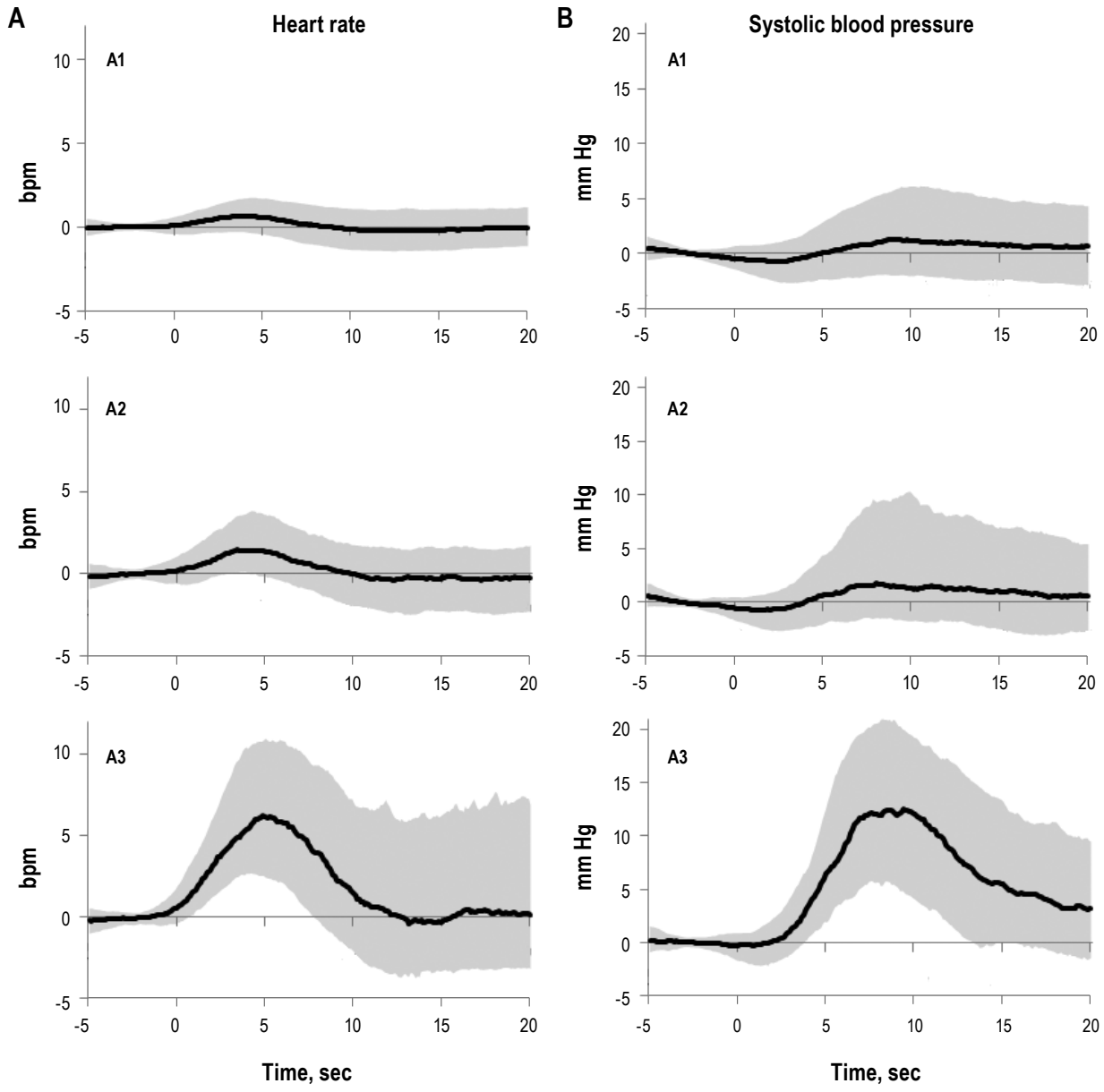

Figure 1—The time course of heart rate and systolic blood pressure changes before and after the onset of CAP. The median value (black line) of each CAP subtype was calculated **(A, B)** and graphed. Gray shadows indicate interquartile range of heart rate and systolic blood pressure. Zero seconds indicates the onset of CAP. The peak time of systolic blood pressure is delayed by approximately 4 seconds compared with that of heart rate. The increase in both heart rate and systolic pressure is higher in the order of subtype A3, A2, and A1.

A1 *vs*. A3 P < 0.001, A2 *vs*. A3 P < 0.001). In all of phase A, the peak values for HR appeared at 4.2 (3.5 to 5.4) s after the onset of phase A (Figure 1A).

BP transiently decreased after the onset of phase A, and then gradually increased. The decrease in BP for each subtype was as follows: A1, -1.40 (-3.10 to -0.07); A2, -1.44 (-3.15 to -0.24); A3, -0.89 (-2.82 to 0.46) mm Hg (H = 11.1, df = 2, P = 0.004, A1 *vs*. A2 P = 0.719, A1 *vs*. A3 P = 0.294, A2 *vs*. A3 P = 0.162). The nadir values for BP appeared at 1.5 (0.0 to 2.8) sec after the onset of phase A. The increase in BP for each subtype was as follows: A1, 1.23 (-2.04 to 5.75); A2, 1.76 (-1.46 to 9.32); and A3, 12.51 (4.75 to 19.94) mm Hg (H = 201.7, df = 2, P < 0.001, A1 *vs*. A2 P = 0.249, A1 *vs*. A3 P < 0.001, A2 *vs*. A3 P < 0.001). The time courses in all subtypes of CAP were similarly observed. Concerning the variations in HR and BP, the magnitude of subtype A3 was the largest, and the magnitude of subtype A1 was the smallest among the 3 CAP subtypes. In all subtypes of phase A, the peak values for BP appeared at 8.4 (7.0 to 10.3) s after the onset of phase A (Figure 1B).

As a result of evaluation of autonomic nerve activity using the CDM, we observed that the amplitude of LF had 2 peaks within 10 s after the onset of phase A. The AUC of LF for the 20 s after the onset of phase A was significantly higher than before the onset of phase A in all CAP subtypes. As for the AUC for LF amplitude before *vs* after the onset of phase A for each subtype, A1 was 491.3 (318.4 to 759.4) *vs*. 559.0 (387.9 to

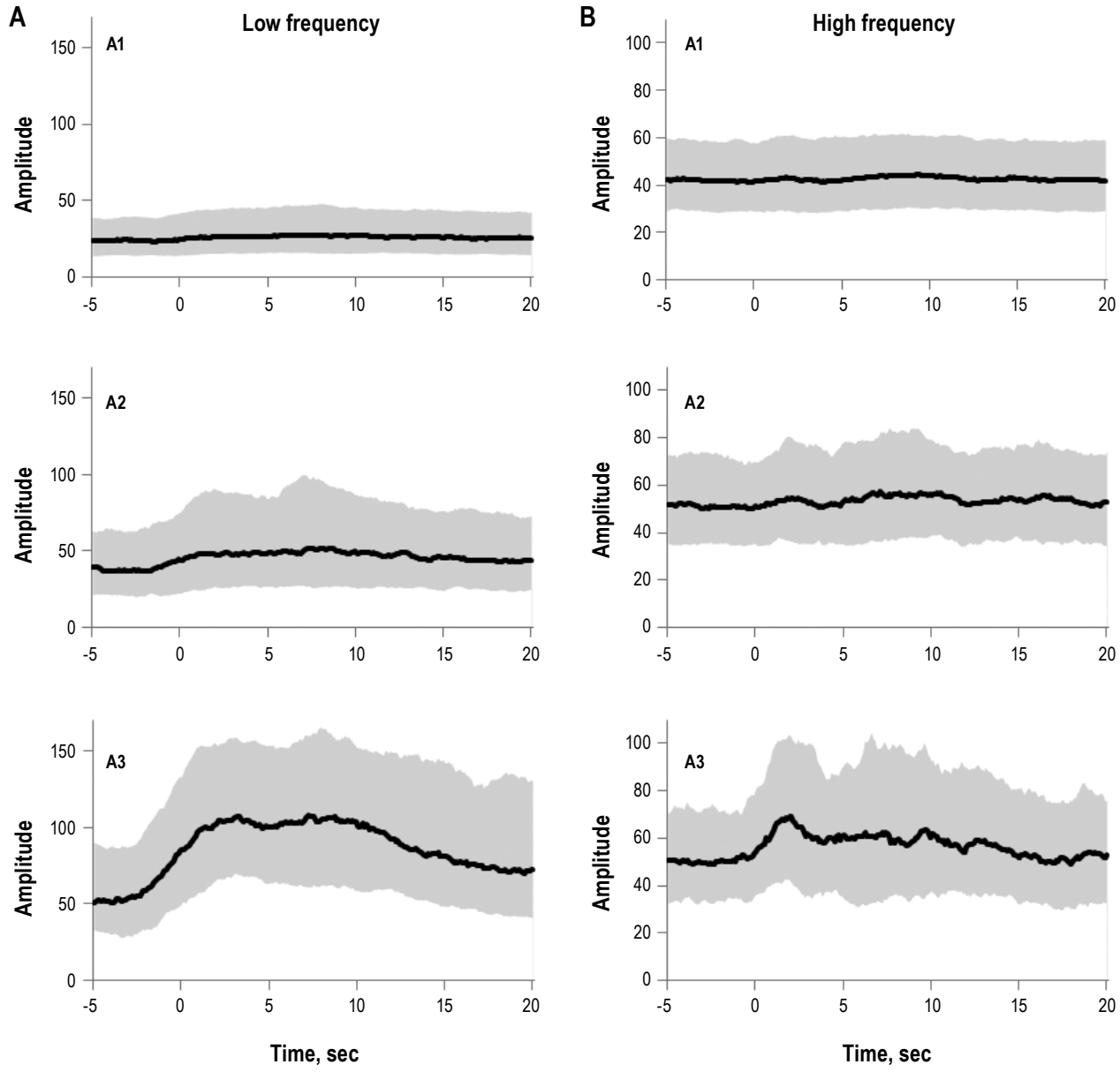

Figure 2—Comparison of time course in heart rate variability before and after the onset of CAP phase A. The median value (black line) of each CAP subtype was calculated **(A, B)** and graphed. Gray shadows indicate interquartile range of low frequency (LF: 0.04 to 0.15 Hz) and high frequency (HF: 0.15 to 0.4 Hz). Zero seconds indicates the onset of phase A. The amplitude of LF was the highest in subtype A3, followed by subtypes A2 and A1.

878.1) ($P < 0.001$); A2 was 787.1 (502.1 to 1299.1) *vs*. 1044.0 (644.3 to 1688.2) ($P < 0.001$); and A3 was 1226.9 (772.5 to 1903.9) *vs*. 2087.1 (1373.1 to 2744.0) ($P < 0.001$). The AUC for LF amplitude before the onset of phase A had significant differences among the 3 subtypes ($H = 548.3$, $df = 2$, $P < 0.001$, A1 *vs*. A2 $P < 0.001$, A1 *vs*. A3 $P < 0.001$, A2 *vs*. A3 $P < 0.001$); it was the highest in A3 and the lowest in A1. Similarly, the AUC for LF amplitude after the onset of phase A had significant differences among the 3 subtypes; it was higher in the order of A3, A2, and A1 ($H = 895.7$, $df = 2$, $P < 0.001$, A1 *vs*. A2 $P < 0.001$, A1 *vs*. A3 $P < 0.001$, A2 *vs*. A3 $P < 0.001$; Figure 2A).

The HF amplitude values changed more smoothly than those for LF. The HF amplitude values in every CAP subtype were significantly higher than those before the onset of phase A for the first 20 s after the onset of phase A. The AUC for HF amplitude before *vs* after the onset of phase A for each subtype was as follows: A1, 872.6 (631.2 to 1146.7) *vs*. 924.0 (679.4 to 1175.3) ($P < 0.001$); A2, 1054.7 (779.6 to 1401.2) *vs*. 1186.1 (910.2 to 1466.3) ($P < 0.001$); A3, 1037.5 (778.6 to 1443.5) *vs*. 1367.0 (1032.1 to 1672.4) ($P < 0.001$). The AUC for HF amplitude value had significant differences before the onset of phase A among the 3 CAP subtypes ($H = 136.1$, $df = 2$, $P < 0.001$), but the value of A3 was not significantly different to that of A2 (A1 *vs*. A2 $P < 0.001$, A1 *vs*. A3 $P < 0.001$, A2 *vs*. A3 $P = 0.999$). Concerning the AUC for HF amplitude after the onset of phase A, it was higher in the order of A3, A2, and A1 ($H = 398.9$, $df = 2$, $P < 0.001$, A1 *vs*. A2 $P < 0.001$, A1 *vs*. A3 $P < 0.001$, A2 *vs*. A3 $P < 0.001$) (Figure 2B).

DISCUSSION

Time Course of Heart Rate, Blood Pressure, And Heart Rate Variability after the Onset of CAP

To our knowledge, this is the first manuscript that analyzes the time course of HRV for each CAP subtype using a high time resolution CDM. In healthy male subjects, the HR started to increase at the onset of CAP. BP transiently decreased after the onset of phase A, and then gradually increased. The result of HRV analysis using the CDM indicates that the amplitude of LF was larger than that of HF, and its time course showed two peaks, with the latter peak corresponding to the peak time of blood pressure. Although time courses of increases in HR, BP, and HRV are similar among the three CAP subtypes, the magnitudes of the variations were larger in the order of subtype A3, A2, and A1, demonstrating that the degree of HR, BP, and HRV varied among subtypes of CAP, and that A3 induced the most prominent effects followed by A2. We thus attempted to interpret and discuss the data in detail.

Why Does Blood Pressure Increase Later than Heart Rate after the Onset of CAP?

Concerning the responsiveness of HR and BP (i.e., the time until HR and BP peaked), our findings coincided with previous reports of K complex (KC), HR, and BP changes. HR began to increase at the appearance of KC, and reached the peak value on the third beat, whereas BP increase was relatively delayed and reached the peak value on the sixth beat.[19,21]

The reaction time is determined by the network conduction velocity of the autonomic nervous system and the responsiveness of the end effectors. The reaction time is considered the same between individuals. It can explain why the BP increased later than the peak HR, based on the differences between the reaction times of the end effectors. The parasympathetic nerve activity has a rapid reaction time system (approximately 10^{-3} seconds) by the ion-channel type reaction. On the other hand, the cardiac sympathetic nerve activity has a slower reaction time system (from 10^{-1} to 10^{0} seconds) and is characterized by long reaction time duration, which is due to a series of reactions induced by the intracellular second messengers occurring through G protein-coupled receptors. The rise of blood pressure is affected by the increase of HR, the heightened vascular resistance due to the arteriole shrinking, and the cardiac contractile force. Thus, it may take approximately 8 seconds to reach the peak blood pressure as a consequence all of these vital reactions.

Muscle sympathetic nerve activity (MSNA) is a sympathetic impulse activity, which induces vascular shrinking by controlling the vascular smooth muscle in skeletal muscle and also contributes to the regulation of blood pressure. Previous studies using microneurography reported that MSNA started to rise at the second beat (approximately 1.2 s after the appearance of KC).[20] The time lapse of MSNA from KC may partly explaine the decrease of BP after the onset of phase A.

Comparison of this Study with the Time Course of Autonomic Nerve Activity Induced by PLM

Although our study reports the time course of HRV for each CAP subtype for the first time, sequential measuring of HRV to clarify of the autonomic nerve activity in PLM has been previously reported.[27] In a report by Guggisberg, the time course of LF showed two peaks at 2 and 6 seconds after the onset of PLM, and the power of LF was higher in the latter peak.[27] Interestingly, the delta power of EEG started to increase approximately 2 seconds before the onset of PLM. Sforza also reported a similar increase of delta power of EEG.[26] Moreover, reports showed CAP subtypes A2 and A3 were frequently observed in patients with PLM, and the delta power of EEG appeared prior to or in concurrence with the emergence of PLM.[11,25] Considering the time difference (2 s) between the emergences of PLM and the slow wave, the estimated time peak of LF will be 4 and 8 seconds after the occurrence of slow wave; these values coincided with our findings.

It was not clear why the time course of LF had two peaks and reached the maximum level at 8 seconds after the onset of CAP. Previous studies reported that MSNA showed a transient activation at 1.2 seconds after KC appearance.[20] This transient activation is considered the first peak of LF after the onset of CAP in our study. It was reported that MSNA was activated transiently after the onset of KC, then returned to baseline, and was suppressed at the sixth beat where the BP reached a peak.[21] However, our data and those of Guggisberg showed that the power/amplitude values for LF represented the latter peaks in these periods where MSNA were suppressed. Therefore, it is uncertain whether the latter peak of LF really reflected the sympathetic nerve activity. Baroreceptor reflex leads to the increase of the cardiac parasympathetic nerve activity. In this period, the power/amplitude values for HF actually rose. As the parasympathetic nerve activity is also reflected in the power of LF, the increase of LF power after the onset of CAP, especially in the latter peak, may represent the parasympathetic nerve activity rather than the sympathetic nerve activity.

On the other hand, the amplitude of HF increased approximately 8 seconds after the onset of phase A. Guggisberg reported that the power of HF slightly increased for a little while after the emergence of PLM, and peaked at about 6 seconds after the emergence of PLM (approximately 8 s after the occurrence of delta power of EEG).[27] It is believed that these results reflect the increase of the cardiac parasympathetic nerve activity induced by the baroreceptor reflex.

In our study, the amplitude increase of HF was observed approximately 3 seconds after the onset of phase A. The same amplitude of HF was not observed in Guggisberg's report. This may be due to the difference in the CAP occurrences; we analyzed spontaneous CAP, while Guggisberg specifically analyzed CAP induced by PLM. Further studies will be needed to clarify the difference between CAP induced spontaneously and secondarily.

Study Limitations

Although the CDM has a higher time resolution than frequency domain analysis, the amplitude values for LF are influenced by the ± 8 seconds of the evaluation point; those for HF are also influenced by the ± 3 seconds around the point. Thus, the transient changes in LF before the onset of phase A could be affected by the subsequent changes.

The power/amplitude value for HF indicates parasympathetic nerve activity, and the power/amplitude value for LF reflects both sympathetic nerve activity and parasympathetic nerve

activity. There are some studies evaluating the predominant state of sympathetic nerve using the ratio of HF to LF power/amplitude value. But these procedures are often controversial, because the time range required for measuring is different between the amplitude values for LF and HF. Thus, we should note that HRV analysis is an indirect assessment method of autonomic nerve activity.

Moreover, it should be noted that parasympathetic nerve activity is reflected not only in the HF region. Parasympathetic nerve activity reflects respiratory sinus arrhythmia (RSA). If respiratory frequency is more than 9/min, RSA is recognized in the HF region. If respiratory frequency decreases below 9/min, RSA is recognized in the LF region. The minimum of respiratory frequency was 10.8/min in this study. Thus, we believe that we could successfully assess the RSA reflected in the HF region.

As for statistical analysis, the values of measurements almost represented nonparametric distributions despite logarithmic transformation. Thus, we could not employ a suitable analysis method taking sleep stages, sleep cycles, and factors between individuals into consideration, because of use of nonparametric analysis. In this study CAP parameters had large individual differences. Therefore, more subjects with enough CAP events are needed to assess HRV that takes the influences of sleep stages and sleep cycles into consideration.

Relationship between the Autonomic Network and CAP

In regard to the amplitude before the onset of phase A, HF was similar among the three CAP subtypes. In terms of LF, subtype A3 was the largest, and subtype A1 was the smallest. In the study using the low resolution brain electromagnetic tomography (LORETA), Ferri revealed the distinct difference in the areas of the cortical generators between subtype A1 and A3; subtype A1, anterior frontal regions; A3, the parietal-occipital areas.[40] It was also reported that the amount of CAP subtype A2 and A3 was highly correlated to the arousal index.[39] However, that of subtype A1 was not. Subtype A1 instead correlated positively with the percentages of slow wave sleep, in which a tendency of parasympathetic nerve activity dominancy was frequently observed.

Our results suggest the functional interaction between the central autonomic network and the thalamo-cortical network,[41] which is related to the occurrence of high-amplitude slow waves. The central autonomic network[42] includes the limbic system and the area from the hypothalamus to the medulla oblongata and the midbrain, which regulates autonomic nerve activity. Future studies that anatomically clarify the connections between the central autonomic network and the thalamo-cortical system are needed, as well as studies that more directly evaluate the autonomic nerve activity in the occurrence of CAP, such as by MSNA measuring.

In conclusion, this is the first report that describes the sequential time course of HRV around the occurrence of CAP. We simultaneously observed rapid and transient HRV and CAP, and the largest HRV was seen in subtype A3. Since the sleep-wake controlling system has a high association with the regulation of autonomic nerve activity and is responsible for the maintenance of this behavioral state, further clarification of functional significances of the findings is warranted to understand the physiological significance of sleep and the pathological mechanisms of sleep related disorders.

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