Doctoral Dissertation

Relation between short- and very short-term blood pressure variability

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August, 2022
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A Doctoral Dissertation
submitted to Graduate of Science and Technology,
Nara Institute of Science and Technology
In partial fulfillment of the requirements for the degree of
Doctor of ENGINEERING

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Abstract

Blood pressure variability (BPV) is an essential indicator for risk stratification of hypertension. Among the 24-hour BPV assessed by ambulatory blood pressure monitoring (ABPM), systolic BPV at night has been suggested to predict cardiovascular risks. However, the physical burden of ABPM on patients has hindered its widespread clinical use. Various mechanisms regulate blood pressure (BP) within a specific operating frequency, including baroreflex, which controls it predominantly within 24 hours. Since the baroreflex can be considered a first-order lag system with a cutoff frequency of about 0.1 Hz, we focused on predicting 24-hour BPV from very short-term BPV. In particular, we hypothesized that very short-term BPV at rest correlates well with nocturnal BPV. Preliminary validation in rats (male Wister-Kyoto, N=10) compared 30-minute and 12-hour BPV during resting and active periods. BPV correlations were highest in the resting (resting vs. resting $r=0.973$, $p<0.01$; active vs. active $r=0.875$, $p<0.01$). In the clinical settings, 30 adults took 30-minute continuous beat-by-beat BP recordings in the supine, followed by 24-hour ABPM. The relation between very short-term BPV (standard deviation (SD), coefficient of variation (CV)) and daytime and nocturnal BPV (SD, CV, average real variability (ARV), and standardized ARV (CV-ARV)) was assessed with Pearson's correlation coefficients. Very short-term BPV correlated significantly with nocturnal BPV (ARV, $r=0.604$, $p<0.01$) but not with daytime BPV. The increasing data length of continuous BP recording pronounced these trends. Using a data segment from the last 10 minutes of a 30-minute continuous beat-by-beat BP recording resulted in a stronger correlation between very short-term BPV and nocturnal BPV than earlier segments. The findings of this study suggest that very short-term BPV in the supine position at rest may predict nocturnal BPV, which in turn, very short-term BPV has the potential to develop a novel index of BPV.

Keywords:

Blood pressure variability, Hypertension, Sympathetic nervous system, Baroreflex, Risk stratification

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* Doctoral Dissertation, Graduate of Science and Technology, Nara Institute of Science and Technology, August, 2022

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1. Introduction

1.1 Blood pressure variability

Hypertension is the most common and important risk factor for many cardiovascular diseases, and blood pressure (BP) levels are strongly associated with the risk of cardiovascular disease[1, 2]. Recent studies have reported that the progression of hypertensive organ disorders and the onset of cardiovascular events are associated with increased BPV independent of the absolute BP level[3–6]. Blood pressure variability (BPV) is also well known to be an important indicator in the risk stratification of hypertension.

Parati et al.[7] classified BPV based on the timescale of BP fluctuation: beat-by-beat (very short-term; such as continuous beat-by-beat BP recording for 30 min), daily (short-term; such as intermittent BP recording for 12-24 h), day-to-day (mid-term), and visit-to-visit (long-term). From here on, we follow the definition of Parati et al. and describe "very short-term BPV" as BPV for a very short period, about 30 minutes, assessed on a beat-by-beat basis. Likewise, BPV variability within a few hours to 24 hours is described as "short-term BPV". Among various methods of measuring BPV, daily systolic BPV assessed using a 24-hour ambulatory BP monitor is an established method for stratifying cardiovascular risk in hypertensive patients[8]. Pringle et al.[9] reported an association between nocturnal systolic BPV and an increased risk of stroke. In meta-analysis, Palatini et al.[10] reported that nocturnal systolic BPV was a predictor of all-cause mortality, cardiovascular mortality, and cardiovascular events, whereas daytime systolic BPV was not. Available evidence indicates that the assessment of nocturnal systolic BPV by 24-hour ambulatory blood pressure monitoring (ABPM) may help manage hypertensive patients. However, several issues, such as a high physical burden on patients and poor reproducibility due to decreased sleep quality and physical activity level, hinder its widespread use in clinical practice[11, 12]. Therefore, BPV evaluation by ABPM has not become a routine clinical test, and although a substantial amount of clinical evidence has been accumulated, it has not reached guideline recommendations[13, 14, 15]. In other words, developing a less intrusive method of BPV analysis is an unmet need in BP assessment and would improve the quality of hypertension management and risk prediction. The recent development of BP measurements allows the assessment of very short-term BPV derived from continuous beat-by-beat BP recording over short durations such as 30 min, which involves much less burden on the patients than 24-hour ABPM[16]. Wei et al. reported that 10-minute very short-term BPV was more strongly associated with

increased left ventricular mass index (LVMI) than short-term BPV, suggesting that very short-term BPV is a promising cardiovascular risk indicator[17]. With the trend of technological innovation in beat-by-beat BP monitoring, very short-term BPV will be actively evaluated in the future. In order to involve relevant academic societies in the social implementation of new BPV indicators in the future, a clear evidence strategy is needed, along with practical evaluation methods. Therefore, evaluating how very short-term BPV relates to short-term BPV, mainly nocturnal BPV, which is known to be strongly associated with cardiovascular disease, would help understand the clinical significance of very short-term BPV.

1.2 The influence of the baroreflex on the diurnal BPV

Returning to the mechanism of BPV within 24 h, various factors, including mental stress, behavior, environmental temperature, and food/drink intake, may lead to fluctuations in BP. The living body is constantly exposed to hemodynamic changes due to ever-changing disturbances. A typical example of such disturbance is a change in body position. A change in body position from supine to upright causes a decrease in venous return to the heart, leading to a decrease in cardiac output and, eventually, a decrease in BP. Therefore, the nocturnal BPV is lower than the daytime BPV because of lower physical activity levels. In the living body, changes in BP are immediately buffered and stabilized by the arterial baroreflex through changes in autonomic nervous activity. The arterial baroreflex transmits information from arterial baroreceptors in the carotid sinus and aortic arch to the vasomotor center via afferent nerves according to the degree of blood vessel stretching caused by blood pressure changes. The vasomotor center alters sympathetic and vagal activity. In the short term, such autonomic activity stabilizes BP by altering the properties of the effector organs, the heart, and blood vessels. It is well known that the BPV within 24 hours is mainly regulated by the sympathetic baroreflex[18]. This result indicated that the BPV regulatory system overlapped between very short-term BPV and daily BPV. From a control engineering point of view, animal experiments suggested that the baroreflex open-loop characteristic is a first-order lag system with a cutoff frequency of around 0.1 Hz [19, 20, 21, 22]. This feature means that in an actual closed-loop feedback operation, the system behaves as a low-cut filter with a cutoff frequency of around 0.1 Hz against BP fluctuation. In other words, BP is regulated by a simple first-order delay system, from fluctuations of a few seconds to intraday fluctuation. Considering these facts, we hypothesized that very short-term BPV measured in the resting supine position minimizes physical activity, and nocturnal BPV would show a correlation because of the shared BP regulatory system.

Casali et al. demonstrated that daytime BPV was associated with BPV during an orthostatic challenge while less associated with nocturnal BPV [23]. We speculated that sympathetic activation in the standing position alters BPV characteristics from resting positions. Therefore, we hypothesized that the resting supine position, which minimizes external stimuli, would have a higher association with nocturnal BPV. In the present study, we examined the relationship between very short-term BPV and daily BPV. Establishing this relationship could optimize the management of hypertensive patients using a less burdensome BPV measurement method.

1.3 Outlines

This paper discusses the relationship between very short-term BPV and intraday BPV variability. Chapter 2 is a preliminary validation of the extrapolation of the diurnal BPV validation in rats to clinical practice. Here, we discuss the similarity of the dynamic characteristics of baroreflex function between rats and humans based on frequency analysis of short-time BP recordings. Chapter 3 evaluates the association between very short-term BPV variability and diurnal BPV variability in model animals during active and inactive periods. This preparation is a preliminary evaluation under a controlled situation to minimize external stimuli. We compare the correlations between very short-term BPV and short-term BPV for each active and inactive period. Chapter 4 discusses the relationship between very short-term BPV and diurnal BPV in the clinical setting. 24-hour BPV is assessed separately during the daytime and nighttime and is compared to very short-term BPV under resting conditions. Finally, Chapter 5 summarizes this study and discusses its prospects.

2. Similarity in frequency characteristics of arterial baroreflex in rats and humans

2.1 Introduction

Various factors cause daily BP variations. These include mental stress, postural changes, hormonal changes, and autonomic reflexes. Among them, arterial baroreflex, a negative feedback system, plays a pivotal role in BP homeostasis [18, 24]. Parati et al. demonstrated that the spectrum analysis of BP showed 1/f characteristics[25]. It has been well established that baroreflex failure induced by sinoaortic denervation (SAD) strikingly increased BP variability [26]. An open-loop transfer function analysis of arterial baroreflex indicated that the baroreflex operating frequency range is 0.01-0.1Hz (baro-frequency) in rats [19]. This baro-frequency is the frequency range where SAD markedly increased the power spectral density (PSD) of BP in rats [27]. In a human case report, the slope of PSD in the baro-frequency range steepened after brain stem death[28]. Thus, the changes in baroreflex-dependent PSD parallel BP variability [26, 27, 28, 29]. Laitinen et al. reported that aging impairs the baroreflex function via changing the deterioration of cardiovascular function and autonomic nervous system [30]. In this study, we will evaluate the similarity of baro-frequency by comparing PSD changes before and after SAD in rats and PSD differences between young and elderly humans. We will examine whether the association between very short-term BPV and diurnal BPV in rats can be extrapolated to clinical interpretation.

2.2 Materials and Methods

For the animal study, experiments and animal care were approved by the Committee on Ethics of Animal Experiment, Kyushu University Graduate School of Medical Sciences, and performed in strict accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. The clinical study was approved by the Institutional Review Board (IRB) of Morinomiya University of Medical Sciences, Japan.

We used a nonparametric PSD estimation method based on Fast Fourier Transform (FFT) as described in the data analysis section. In protocol 1, we estimated PSD from 12-hour BP recordings in a light phase. In protocol 2, we obtained PSD from short-term tonometric BP recordings of human participants and compared their characteristics with rats. We also examine whether aging affects PSD in human participants.

Experimental study in rats (Protocol 1)

We used nine-week-old Wister-Kyoto male rats (N=5). As shown in Figure 1A, we implanted a telemetry system (TA11PA-C40, DSI, MN, USA) and inserted the pressure sensing catheter in the abdominal aorta to record BP continuously. One week after the implantation, we performed sinoaortic denervation (SAD) [31] to create baroreflex failure. All the rats, after surgery, were housed in a cage and maintained a light/dark cycle (12-hour each, 9:00-21:00 is the light period). We recorded BP for 24 hours at 200 Hz sampling rate before (Pre-SAD) and one week after SAD (Post-SAD). Previous works have demonstrated that rats spend most of the light period sleeping and most of the dark period awake. Spontaneous locomotion has been reported to be greater during dark periods than during light periods[32, 33].

Clinical study (Protocol 2)

We recruited a group of 12 healthy young adults (Young; 10 male, two female, 20 to 39 years old) and 8 healthy elderly adults (Elderly; eight female, 81 to 94 years old). As shown in Figure 1B, participants rested for 5-15 min in a supine position during preparation. We attached a continuous tonometric BP monitor under development at OMRON Healthcare to the left wrist and recorded BP for 30 min. We digitized continuous BP recordings at 125 Hz. We also measured BP by using a cuff oscillometry (HEM-7252G, OMRON Healthcare Co., Ltd, Kyoto, Japan) before and after the tonometric BP recordings.

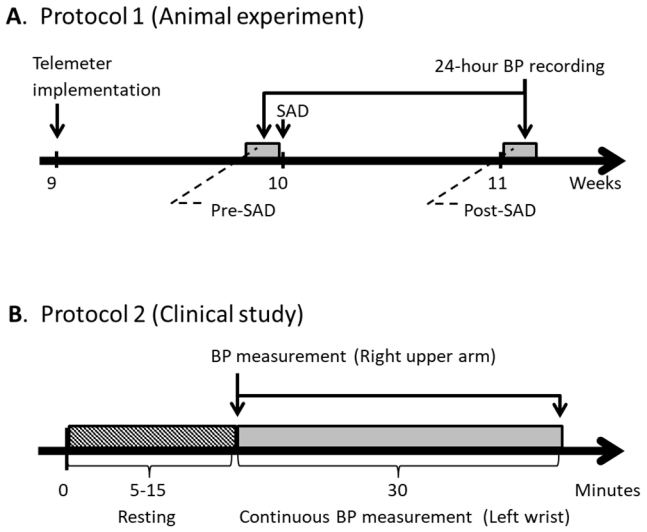

Figure 1. Protocol of the continuous BP measurement

(A) Protocol 1, (B) Protocol 2

Data analysis

In Protocol 1, we used continuous BP recordings from the 12-hour light period in the 24-hour recordings for analysis. After down-sampling the BP recordings at 1 Hz, we estimated PSD by Welch's periodogram [34]. We used the fixed segment length of 200 sec (sample points) for FFT with the 50% overlapping. We removed the linear trend in each segment and applied the Hanning window.

To define the BP variations in the baro-frequency range, we estimated the PSD difference (ΔPSD) between 0.01Hz and 0.1Hz, where the former is the lowest, and the latter is the highest baro-frequency range as:

$$\Delta PSD = PSD_{0.01\mathrm{Hz}} - PSD_{0.1\mathrm{Hz}} \qquad \text{(Eq1)}$$

where subscripts indicate frequencies of interest. We compared PSD and ΔPSD before and after SAD in rats (pre- and post-SAD). We also compared characteristics of PSD between rats and humans. Finally, we examined how aging affects PSD

in human participants (young and elderly) to explore its clinical applicability.

2.3 Results

The representative examples of 12-hour BP recordings of pre-SAD and post-SAD are shown in Figure 2. Figure 3 shows the mean and standard deviation (SD), the gold standard of daily BP variations, of 12-hour BP in all rats. SAD nearly tripled the SD of BP while maintaining mean BP. Figures 4A and 4B show the PSD estimated from the 12-hour BP recordings. Compared to pre-SAD, SAD increased the PSD in the baro-frequency range, reflecting the increased BP variations. The slope of PSD in the baro-frequency range was higher in post-SAD than that in pre-SAD. SAD significantly increased ΔPSD (Figure 4C), reflecting the high SD of BP obtained from 12-hour BP recordings (Figure 3B).

Table 1 shows the characteristics of participants enrolled in the human study. The PSDs estimated from 30-minute BP recordings in the young, and the elderly are shown in Figures. 4D and 4E, respectively. There were no significant differences in systolic or diastolic BP between the two groups. In the young, PSD decreased with increasing frequency and inflected at around 0.1Hz. These characteristics were similar to those in pre-SAD rats. In contrast, there was no distinct inflection point in PSD in elderly or post-SAD rats. As a result, ΔPSD in the elderly was significantly higher than in the young (Figure 4F).

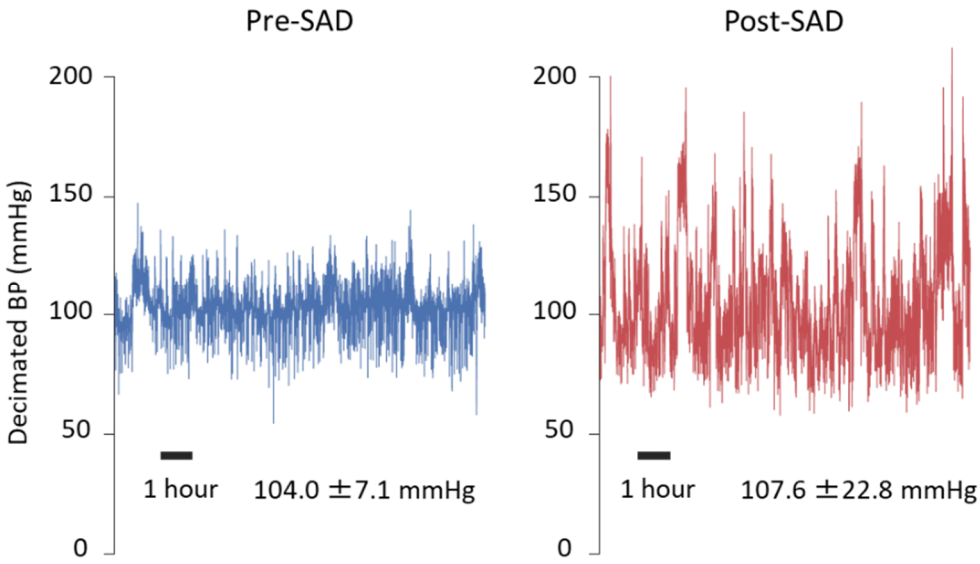

Figure 2. Representative 12-hour BP recordings in a rat

Displayed BP was decimated to 1 Hz under Pre-SAD and Post-SAD.

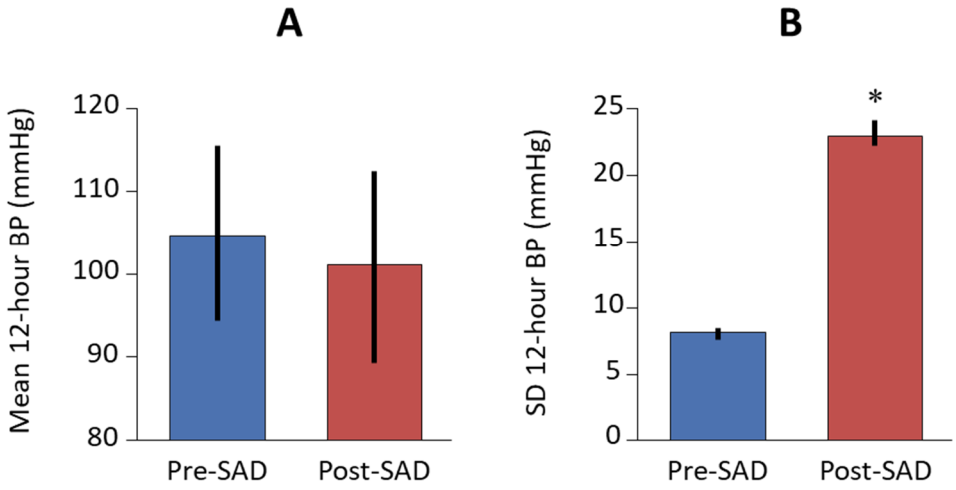

Figure 3. Impact of SAD on 12-hour BP.

(A) mean of the respective mean of 5 rats, (B) mean of the respective SD of 5 rats, Data are expressed as mean±SD

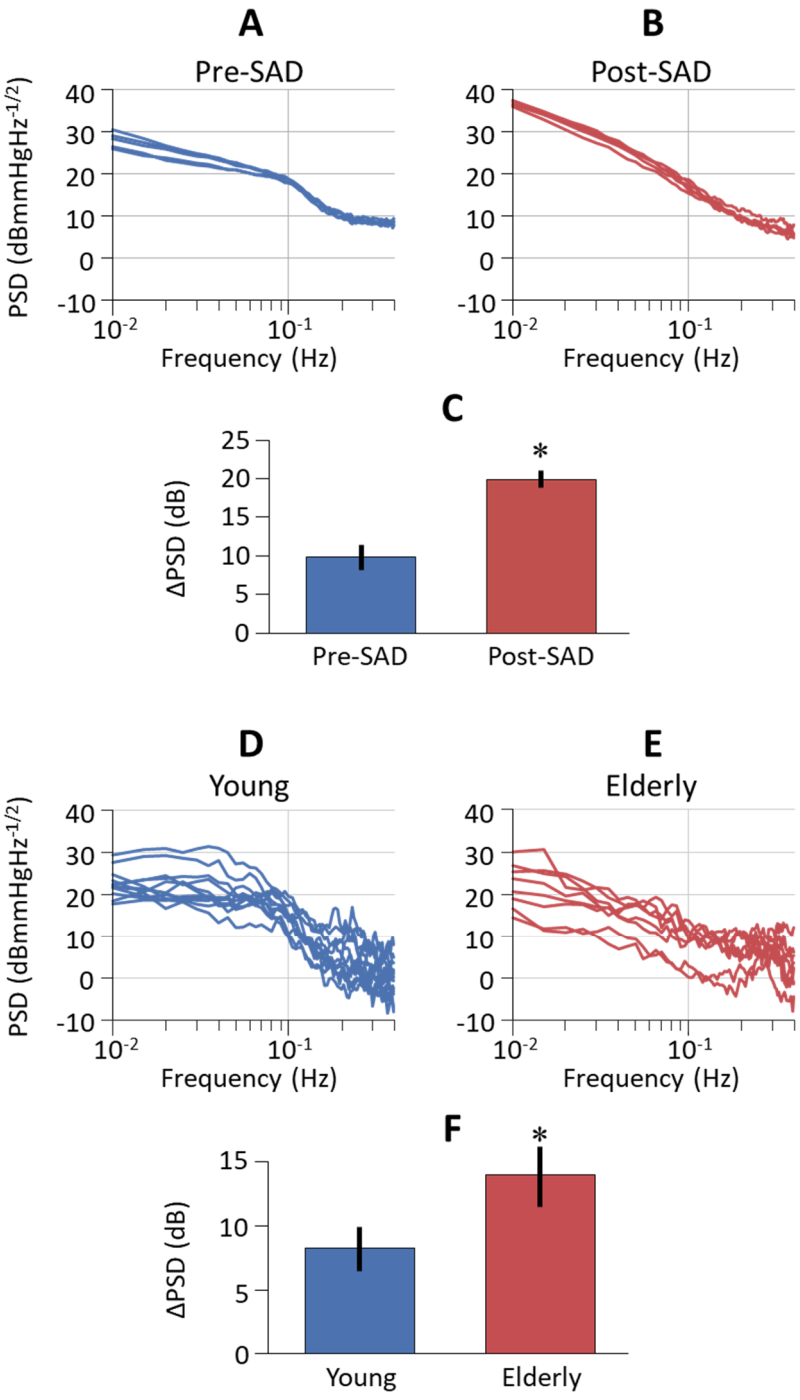

Figure 4. PSD and ΔPSD in rats and human.

(A) PSD in pre-SAD rats. (B) PSD in post-SAD rats. (C) Comparison of ΔPSD between pre-SAD and post-SAD rats. (D) PSD in young participants. (E) PSD in elderly participants. (F) Comparison of ΔPSD between young and elderly participants. Data are expressed as mean±SD in (C) and (F). * $p<0.01$, Student's paired t-test on (A) and Welch's t-test on (B)

Table 1. Baseline characteristics of participants analyzed (N=20).

	Young (N=12)	Elderly (N=8)
Male (%)	10 (83.3)	0 (0)
Age, y.o.	24.3 ± 1.6	85.5 ± 4.7
Systolic BP, mmHg	118.2 ± 2.3	119.9 ± 2.4
Diastolic BP, mmHg	67.8 ± 2.8	70.3 ± 1.5

Systolic and diastolic BP was measured by cuff BP monitor before continuous BP measurement

2.4 Discussion

Parati et al. demonstrated that the spectrum analysis of BP showed 1/f characteristics. They also reported that the slope of PSD in the baro-frequency range is significantly higher in SAD model cats than in normal cats [20]. In a human case report, the slope of PSD in the baro-frequency range steepened after brain stem death [28]. These observations support the notion that the baroreflex suppressed the slope of PSD in the baro-frequency range.

In this study, we demonstrated that PSD increased in the baro-frequency range in both rats and elderly participants. The fact that the slope of PSD in the baro-frequency range in the elderly steepened may indicate that the baro-frequency significantly overlapped between rats and humans, and the elderly may have baroreflex dysfunction (Figure 5)[30]. However, there are several limitations, such as a limited number of participants and the presence of confounding factors, e.g., antihypertensive medication in the elderly. Thus, further investigations are needed to develop a reliable method for assessing the daily BP variations in humans. Despite certain limitations, this similarity between rats and humans in the frequency response of baroreflex dysfunction suggests that analysis of 24-hour BPV in model rats may contribute to extrapolation to clinical interpretation.

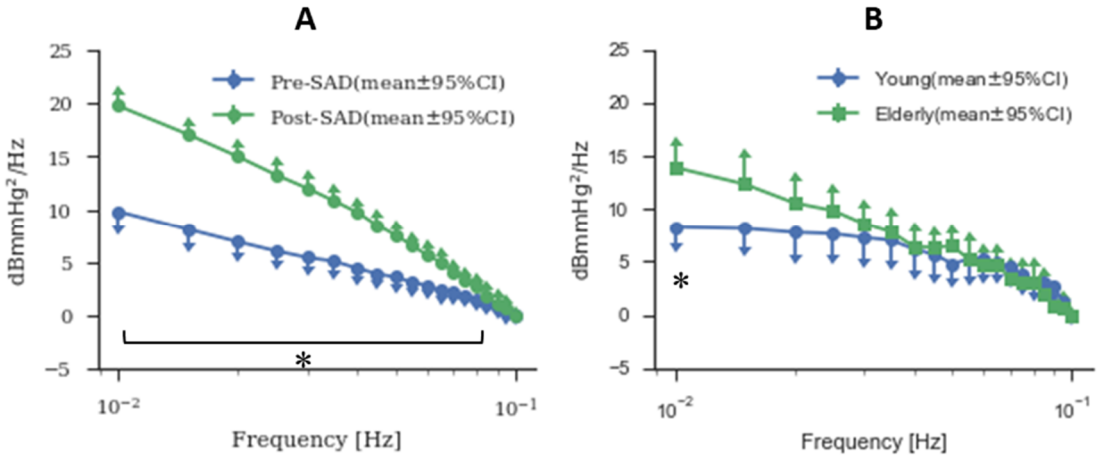

Figure 5. PSD comparison in baro-frequency

(A) Pre-SAD vs. Post-SAD in rats, (B) Young subjects vs. elderly subjects. PSDs are normalized at 0.1Hz. Data are expressed as mean±95%CI (confidence interval). * $p < 0.01$, Student's paired t-test on (A) and Welch's t-test on (B)

3. Association between very short-term BPV and short-term BPV variability in rats

3.1 Introduction

Chapter 2 discussed the similarity of the frequency characteristics of baroreflex-mediated diurnal BPV in rats and humans. Clinical evaluation of the association between very short-term BPV and diurnal BPV requires large data sets due to many confounding factors in ambulatory settings. Hence, we will conduct preliminary validation in rat models where the measurement environment can be strictly controlled.

As described in Chapter 2, freely behaving rats' dark and light phases are considered active and resting, respectively. Correlation analysis for each combination of the active and resting phases evaluates the association between very short-term BPV variability and diurnal BPV variability.

3.2 Materials and Methods

The data set consisted of Wister-Kyoto male rats (N=10) before and after SAD. The preparation of the experiments was the same as described in Chapter 2. Pearson's correlation coefficient evaluated the correlation between short-term and very short-term BPVs. The statistical significance level was set at $p < 0.05$. Statistical analysis was performed with R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Preprocessing

The systolic phase in the arterial pressure was detected beat-by-beat basis from the BP recordings. Systolic BP (SBP) was extracted as peak pressure in the systolic phase for each cardiac cycle. Afterward, the SBP series was resampled into 10 Hz.

Very short-term BPV

Standard deviation (SD) of resampled SBP series from 0 to 30 minutes every hour was calculated. The minimum value of SDs in resampled SBP for each light and dark period was adopted as the basal level for the very short-term BPV.

Short-term BPV

An ABPM measures BP with the oscillometric method, which presses the upper arm with a cuff sufficiently above SBP before gradually releasing it. In other words,

oscillometry estimates the averaged instantaneous BP value for 30-60 seconds. Therefore, one-minute averages of beat-by-beat BP were aggregated every 30 minutes to simulate a 30-minute-interval SBP series by ABPM. In this simulation, start points were shifted every minute from 0 to 29 minutes per hour. The minimum SD of the light and dark phases of this 30-minute-interval SBP series was defined as the basal level of short-term blood pressure variability during each activity phase.

3.3 Results

Figure 6 shows the mean and standard deviation of beat-to-beat SBP before and after SAD; SAD markedly increased BPV variability while maintaining the BPV mean. Figure 7 shows the correlation between very short-term BPV and intraday BPV variability in the basal state. The correlation coefficient for each activity cycle combination was highest at rest vs. resting ($r=0.973$, $p<0.01$). On the other hand, the correlation coefficient was lowest for the active period vs. the active period ($r=0.875$, $p<0.01$).

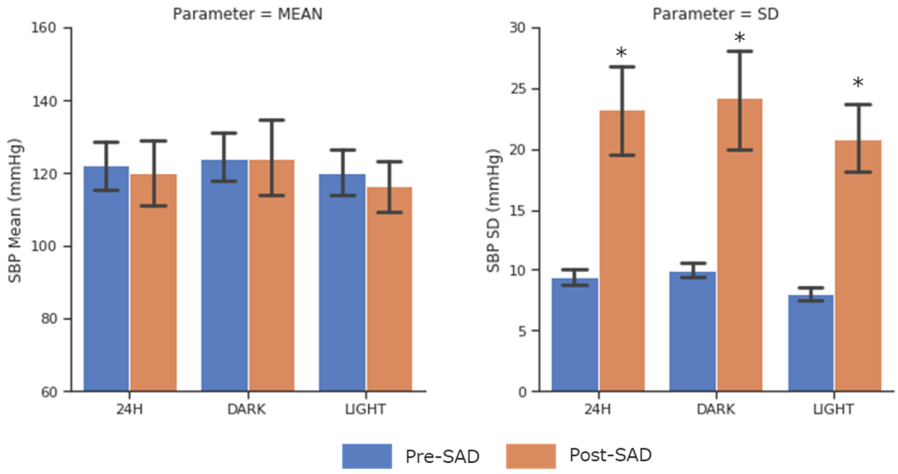

Figure 6. Mean and SD of SBP before and after SAD.

Data are expressed as mean±SD. * $p<0.01$, Student's paired t-test.

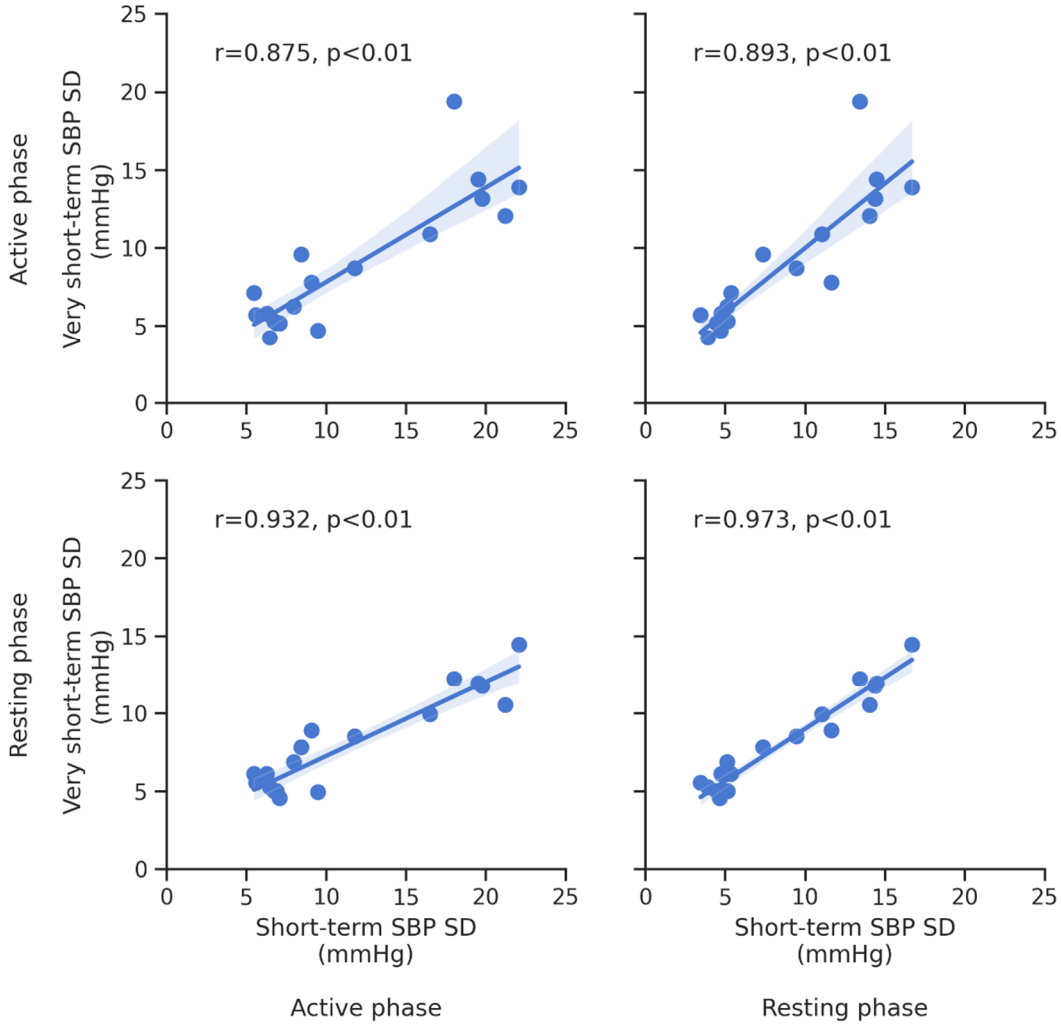

Figure 7. Scatter plots of 30-minute and 12-hour BPV variability in the basal state. The vertical axis shows 30-minute BPV in the active and resting phases in the upper and lower panels, respectively. The horizontal axis shows 12-hour BPV in the active and resting phases in the left and right panels, respectively. The shaded band indicates the 95% confidence interval for the regression estimate.

3.4 Discussion

According to Guyton et al., the primary regulator of diurnal BPV variability is the arterial baroreflex function, which has the most significant control gain in the operating band within 24 hours, except for control for emergencies such as central nervous ischemia[18]. Under resting basal conditions, disturbances to the hemodynamics are minimized, and BPV is limited to endogenous fluctuations[35]. Therefore, 30-minute and 12-hour BP are regulated by a common control factor and correlate well. In contrast, numerous factors such as physical activity, drinking water, and eating disturb hemodynamics under free-ranging conditions. Since these disturbances vary in intensity and duration, the disturbance components differ depending on the time of day. This inconsistent disturbance may be one factor that reduces the correlation between very short-term BPV and short-term BPV.

4. Association between very short-term BPV and short-term BPV variability in humans

4.1 Introduction

Chapter 3 examined the correlation between 30-minute BPV and 12-hour BPV in rats; the correlation between 30-minute BPV and 12-hour BPV is highest in the basal state without physical activity, suggesting that brief, continuous BPV measurements at rest may be able to predict nocturnal BPV. This result suggests that continuous BP measurements at rest may predict nocturnal BPV. This chapter evaluates the relationship between resting very short-term BPV and nocturnal BPV variability in the clinical setting.

4.2 Materials and Methods

A total of 63 volunteers (age 22–78 years; male, N=33; female, N=30) were recruited between November 2018 and December 2019. The inclusion criterion was age over 20 years. The exclusion criteria were antihypertensive treatment, arrhythmias, epilepsy, pregnancy, and the presence of a pacemaker. Each participant's self-report was used to determine the status of treatment. This study was approved by the ethics review committee of Omron Healthcare Co., Ltd. (Kyoto, Japan). All participants provided written informed consent to participate. All participants underwent noninvasive continuous beat-by-beat BP recording in a resting supine position for 30 min, followed by 24-hour ambulatory BP measurement. The protocol is shown schematically in Figure 8.

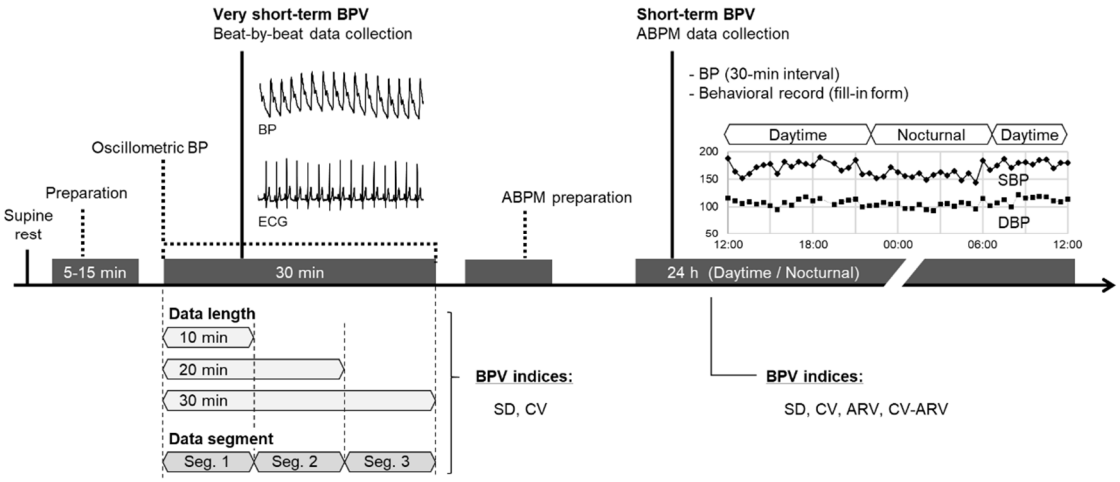

Figure 8. Schematic representation of the study protocol.

A participant first undergoes continuous beat-by-beat BP recording for 30 min in a resting supine position and thereafter undergoes ABPM for 24 h. BP, blood pressure; BPV, blood pressure variability; ABPM, ambulatory blood pressure monitoring.

Noninvasive continuous beat-by-beat BP recording

A participant rested in a supine position for 5-15 min and then underwent continuous BP measurement for 30 min. For this measurement, a wearable continuous tonometric BP monitor developed by Omron Healthcare Co., Ltd. was attached to the left wrist[36, 37, 38]. A patient monitor (Moneo BP-A308, Omron Healthcare Co., Ltd., Kyoto, Japan) was used to simultaneously record the lead II electrocardiogram.

Before and after the continuous BP recording, we measured oscillometric BP with a cuff wrapped around the right upper arm. The oscillometric BP before the continuous recording was regarded as the reference BP for each participant. The time of measurement varied from participant to participant. All signals were recorded on a computer with a 16-bit analog-to-digital converter (PowerLab PL3508, ADInstruments, Sydney, Australia) at a sampling rate of 1 kHz. Systolic BP (SBP) and diastolic BP (DBP) were extracted for each cardiac cycle corresponding to the detected R wave. We performed linear calibration such that the mean SBP and DBP of each beat measured by the tonometry method for 30 s immediately after the first oscillometric BP measurement were the same as the reference SBP and DBP, respectively.

We have previously reported that very short-term BPV can be assessed stably using 30-min continuous beat-by-beat BP recording data[38]Using the 30-min beat-by-beat BP, we determined the BPV of SBP and DBP by calculating the standard deviation (SD) and

coefficient of variation (CV) of the two BPs.

ABPM

After the 30-min continuous beat-by-beat BP recording was completed, we attached the ambulatory BP monitor (TM-2441, A&D, Tokyo, Japan) to a participant's upper left arm to measure ambulatory BP for 24 h according to the Japan Circulation Society Joint Working Group guideline[13]. BP was measured at 30-min intervals over 24 h. The cuff size was chosen according to the participant's arm circumference. The participant was instructed not to move during measurement and was asked to record their activity immediately before each measurement, as well as their bedtime and wake-up time, on a behavioral record sheet. After completing the operational checks of the ambulatory BP monitor, BP monitoring was started. The participant was instructed to return to normal activities and to remove the device after 24 h and end the BP recording.

From the recording, we excluded abnormal BPs or pulse pressures as invalid data[13]. By referring to the behavioral record, we excluded measurements recorded during conversation or immediately after physical activity, which were regarded as deviations from the resting state. We derived nocturnal BPV from the data recorded during the period between the self-recorded bedtime and wake-up time. We calculated the SD, average real variability (ARV), CV and standardized ARV (CV-ARV) for daytime and nocturnal SBP and DBP. ARV is the average of the absolute differences of consecutive BP measurements[39]. CV-ARV is the ARV divided by the averaged BP. It is well known that BPV is affected by the absolute value of BP. We normalized the ARV by the averaged BP to assess the association of BPVs adjusted for absolute values, as with SD to CV. Thus, the CV-ARV characterizes the variation ratio that considers both the time order and average values. These parameters were used as daytime and nocturnal BPV indices.

$$ARV = \frac{1}{N}\sum_{k=1}^{N-1}|BP_{k+1} - BP_k| \quad \text{(Eq 2)}$$

$$CV\text{-}ARV = ARV/mean(BP) \quad \text{(Eq 3)}$$

Association between short-term BPV and very short-term BPV

We evaluated the association between very short-term (beat-by-beat) BPV and short-term (daily) BPV by analyzing the correlation between the SD of very short-term BP and the SD or ARV of ABPM data. The association between very short-term and daily BPV standardized by the absolute BP level was evaluated by the correlation between the CV of very short-term BP and the CV or CV-ARV of ABPM data.

We also examined whether the data length and data segment of very short-term BPV affected the correlation of very short-term BPV with daytime or nocturnal BPV. The data length used for calculating very short-term BPV was configured at 10, 20 and 30 min from the start of the 30-min continuous beat-by-beat BP recording. In addition, the data segment used for calculating very short-term BPV was derived from the first (Seg. 1, 0 to 10 min), middle (Seg. 2, >10 to 20 min) or last (Seg. 3, >20 to 30 min) 10-min data segment of the 30-min continuous beat-by-beat BP recording.

Association between heart rate variability (HRV) and BPV

We performed an HRV analysis on ECG simultaneously recorded with the 30-min continuous beat-by-beat BP recording. SDNN (standard deviation of all normal-to-normal (NN) RR intervals in milliseconds) and pNN50 (percentage of adjacent NN intervals that differ by more than 50ms) were derived as time-domain measures[40]. Spectral analysis on the series of RR intervals based on Fourier transform derived LF/HF (ratio of power in low frequency (LF, 0.04-0.15Hz) and high frequency (HF, 0.15-0.4Hz) bands) as a frequency-domain measure[40]. SDNN estimates global HRV. pNN50 and LF/HF reflect parasympathetic activity and autonomic (sympatho-vagal) balance, respectively. By analyzing the Pearson's correlation coefficient between each parameter of HRV and SDs of 30-min and nocturnal SBP, we assessed whether BPV and HRV are related. The statistical significance level was set at $p < 0.05$

Statistical analysis

Before data analysis, participants meeting the following criteria were excluded (Figure 9): participants on antihypertensive medication (N=9), participants who were unable to maintain continuous beat-by-beat BP recording for 30 min (N=5), participants whose difference in one-min averaged beat-by-beat SBP before and after body movement was 15 mmHg or more due to the displacement of the tonometric sensor (N=3), participants with a difference of 30 mmHg or more between beat-by-beat BP and oscillometric BP at the end of continuous beat-by-beat BP recording (N=5), and participants with less than 70% of the expected number of valid measurements on the 24-hour ABPM recording (N=11) [14]. Finally, we studied the remaining 30 participants.

Differences in baseline characteristics among groups were analyzed using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Kruskal–Wallis test for nonnormally distributed variables. Categorical variables were analyzed using the chi-square test. One-way repeated-measures ANOVA was performed to examine the differences in BPV among various time periods of interest. Bonferroni

correction was used in post hoc analyses where appropriate. The correlation between short-term and very short-term BPVs was evaluated using Pearson's correlation coefficient. The statistical significance level was set at $P < 0.05$. Statistical analysis was performed with R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

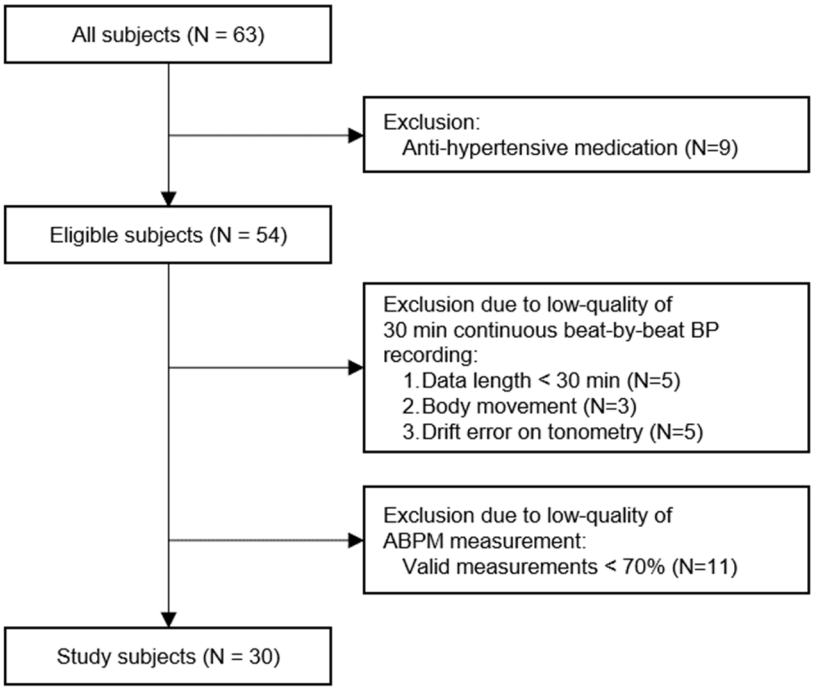

Figure 9. Flow diagram of participants included in the study

4.3 Result

Table 2 shows the baseline characteristics of the participants. Based on the reference oscillometric BP, 10 had normal BP, 8 had high normal BP or elevated BP, and 12 had hypertension according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019)[15]. Age, sex, BMI, and pulse rate were not significantly different among the groups.

Table 2. Baseline characteristics of participants analyzed (N=30).

	Normal (N=10)	High normal or Elevated (N=8)	Hypertension (N=12)	p
Age (years)	45.9 ± 17.7	59.9 ± 15.3	57.8 ± 11.0	0.10
Male	4 (40%)	6 (75%)	6 (50%)	0.32
BMI (kg/m^2)	23.1 ± 4.1	24.0 ± 1.5	25.0 ± 4.5	0.49
SBP (mmHg)				
Reference	111.5 (105.5–114.9)	131 (128.9–133.5)	144.3 (139.5–148.9)	<0.01
Daytime mean	121.8 ± 16.5	140.5 ± 16.9	150.3 ± 17.7	<0.01
Nocturnal mean	102.7 ± 13.2	125.2 ± 15.7	127.7 ± 18.9	<0.01
DBP (mmHg)				
Reference	71.0 (62.9–73.5)	87.5 (81.5–88.6)	91.5 (89.4–97.6)	<0.01
Daytime mean	78.0 ± 7.6	93.6 ± 10.0	97.3 ± 8.4	<0.01
Nocturnal mean	64.7 ± 8.5	82.8 ± 11.3	82.1 ± 11.7	<0.01
Pulse rate (bpm)				
Reference	65.7 ± 7.9	65.6 ± 9.2	71.8 ± 11.6	0.27
Daytime mean	79.0 ± 6.8	72.6 ± 6.4	81.0 ± 10.0	0.09
Nocturnal mean	61.5 (56.9–68.5)	58.0 (56.6–65.1)	69.3 (62.9–76.4)	0.08

Categorical variables are presented in number (%). Continuous variables are presented in mean ± standard deviation if normally distributed and median (interquartile range) otherwise. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute. The oscillometric BP before continuous BP recording was regarded as the “Reference” BP.

Very short-term BPV and its correlation with short-term BPV

The upper portion of Table 3 shows the mean BP and the BPV (the SD and CV of BP) when analyzing 10-, 20- and 30-minute data lengths of continuous beat-by-beat BP recordings. The mean SBP was constant regardless of data length, whereas systolic BPV increased in a data length-dependent manner. DBP decreased with increasing data length; conversely, diastolic BPV increased as data length increased.

The lower portion of Table 3 shows the mean BP and the BPV (the SD and CV of BP) when analyzing the first (Seg. 1), middle (Seg. 2) and last (Seg. 3) data segment of continuous beat-by-beat BP recording. The mean DBP decreased significantly in the order of Seg. 1, Seg. 2 and Seg. 3, but no significant differences were observed in any other parameters.

Figure 10 shows the individual plots of the relationship between very short-term BPV (30 min) and daytime or nocturnal BPV. Very short-term BPV apparently shows a higher correlation with nocturnal BPV, especially in systolic BP analyses (Figure 10A). No correlation was found between very short-term BPV and daytime BPV for either systolic or diastolic BP (not significant for either SD or CV). In contrast, a significant correlation was observed between very short-term BPV and nocturnal BPV for systolic BP (SD: $r = 0.526$, $p = 0.003$, ARV: $r = 0.604$, $p < 0.001$, CV: $r = 0.430$, $p = 0.018$, CV-ARV: $r = 0.517$, $p = 0.003$) and for diastolic BP (SD: $r = 0.386$, $p = 0.035$, ARV: $r = 0.482$, $p = 0.007$, CV: $r = 0.264$, not significant, CV-ARV: $r = 0.360$, not significant). Correlation coefficients were higher with systolic BPV than with diastolic BPV.

We further examined the impact of the data length (Figure 11) and data segment (Figure 12) used to calculate very short-term BPV on the correlation between very short-term BPV and daytime or nocturnal BPV. Individual plots and detailed statistical analyses are shown in Figures 13-14 and Table 5. As the data length increased, there was a progressive increase in the correlation coefficient between very short-term BPV and nocturnal BPV, and the increases were significant for systolic BP. On the other hand, using a long data length (30 min) yielded a markedly low correlation between very short-term BPV and daytime systolic BPV, while data length apparently had no effect on daytime diastolic BPV. Compared to the SD, the ARV of daytime or nocturnal BPV correlated more strongly with the SD of very short-term BPV.

As shown in Figure 12, analyses using the first (Seg. 1), middle (Seg. 2), and last (Seg. 3) 10-minute data segment of the 30-minute BP recording all gave a reasonable correlation between very short-term BPV and nocturnal BPV. In particular, Seg. 2 and Seg. 3 yielded a significant and the highest correlation between the very short-term BPV and the ARV of nocturnal systolic BPV. On the other hand, analysis using Seg. 1 showed

a significant correlation between the very short-term BPV and the ARV of daytime systolic BPV.

Table 3. Effects of data length and data segment on the parameters of very short-term blood pressure variability (BPV).

	Data length		
	10-minute	20-minute	30-minute
SBP			
Mean (mmHg)	130.4 ± 18.1	130.3 ± 17.8	130.0 ± 18.1
SD (mmHg)	4.13 ± 1.44	4.71 ± 1.53*	5.22 ± 1.68†‡
CV	3.16 ± 0.97	3.61 ± 1.08*	4.03 ± 1.23†‡
DBP			
Mean (mmHg)	83.0 ± 13.0	82.3 ± 12.4	81.6 ± 12.3†‡
SD (mmHg)	3.18 ± 1.26	3.68 ± 1.37*	4.07 ± 1.58†‡
CV	3.86 ± 1.41	4.48 ± 1.48*	5.01 ± 1.80†‡
HR			
Mean (bpm)	68.8 ± 9.2	68.2 ± 9.1*	67.7 ± 9.0†‡
	Data segment		
	Seg. 1	Seg. 2	Seg. 3
SBP			
Mean (mmHg)	130.4 ± 18.1	130.2 ± 17.8	129.3 ± 19.3
SD (mmHg)	4.13 ± 1.44	4.23 ± 1.49	4.30 ± 1.43
CV	3.16 ± 0.97	3.25 ± 1.04	3.36 ± 1.11
DBP			
Mean (mmHg)	83.0 ± 13.0	81.7 ± 12.1	80.1 ± 12.5††‡‡
SD (mmHg)	3.18 ± 1.26	3.41 ± 1.26	3.41 ± 1.17
CV	3.86 ± 1.41	4.20 ± 1.37	4.34 ± 1.51
HR			
Mean (bpm)	68.8 ± 9.2	67.6 ± 9.1**	66.5 ± 8.9††‡‡

Data are expressed as mean ± SD. SD, standard deviation; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. 10-minute, 20-minute and 30-minute denote data length of 10, 20 and 30 min, respectively, from the start of the 30-minute continuous BP measurement. Seg. 1, Seg. 2 and Seg. 3 denote the first (0 to 10 min), middle (>10 to 20 min), and last

(>20 to 30 min) 10-minute data segments, respectively, of the 30-minute continuous BP recording. * $p < 0.05$; 10-minute vs. 20-minute. † $p < 0.05$; 10-minute vs. 30-minute. ‡ $p < 0.05$; 20-minute vs. 30-minute. ** $p < 0.05$; Seg. 1 vs. Seg. 2. †† $p < 0.05$; Seg. 1 vs. Seg. 3. ‡‡ $p < 0.05$; Seg. 2 vs. Seg. 3.

Table 4. Short-term BPV

	Daytime	Nocturnal	p
SBP			
Mean (mmHg)	138.2 ± 20.7	118.7 ± 19.6	<0.01
SD (mmHg)	14.24 ± 4.70	11.33 ± 4.49	0.01
ARV (mmHg)	11.93 ± 3.86	11.80 ± 4.83	0.90
CV	10.39 ± 3.32	9.49 ± 3.18	0.27
CV-ARV	8.62 ± 2.39	9.88 ± 3.47	0.11
DBP			
Mean (mmHg)	89.9 ± 12.0	76.5 ± 13.3	<0.01
SD (mmHg)	10.00 ± 2.73	8.27 ± 3.31	<0.01
ARV (mmHg)	9.20 ± 2.86	8.61 ± 3.64	0.38
CV	11.30 ± 3.23	10.85 ± 3.76	0.52
CV-ARV	10.34 ± 3.15	11.28 ± 4.02	0.21
Pulse rate			
Mean (bpm)	78.1 ± 8.6	65.0 ± 8.4	<0.01

Data are expressed as mean ± SD. SD, standard deviation; ARV, averaged real variability; CV, coefficient of variation; CV-ARV, ARV divided by averaged BP; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute;

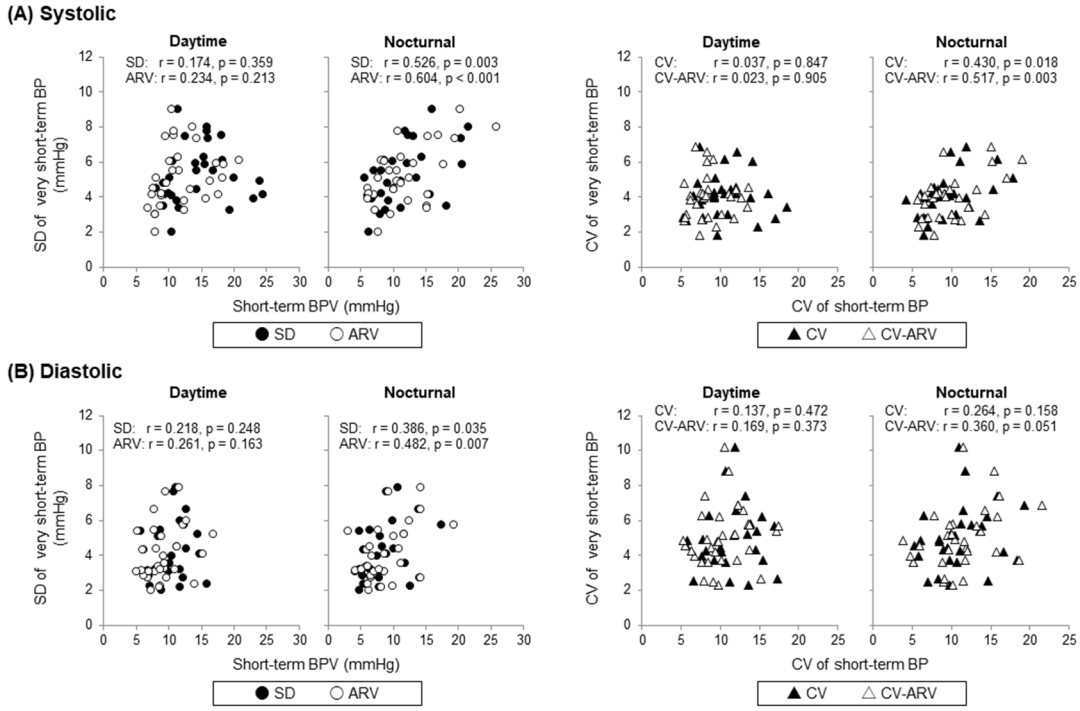

Figure 10. Scatter plot of 30-minute vs 12-hour BPVs

Correlation between very short-term (beat-by-beat, 30 min) systolic (A) and diastolic (B) blood pressure variability (BPV) and daily (divided into daytime and nocturnal) BPV. The BPV indices compared were standard deviation (SD), average real variability (ARV), coefficient of variation (CV) and standardized ARV (CV-ARV; ARV divided by averaged BP). The relationship between the SD of very short-term BP and the SD (closed circle) or ARV (open circle) of daytime or nocturnal ABPM data (left four panels), as well as the relationship between the CV of very short-term BP and the CV (closed triangle) or CV-ARV (open triangle) of daytime or nocturnal ABPM data (right four panels), are shown. The correlation coefficient (r) and statistical significance (p) obtained by Pearson's test are displayed in each panel.

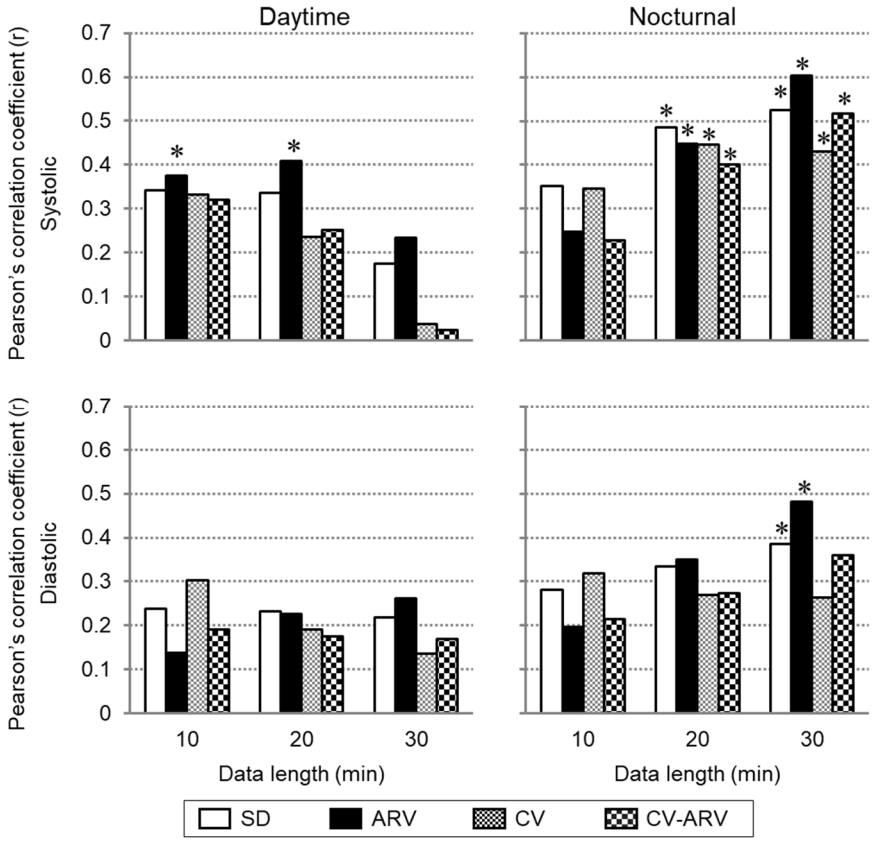

Figure 11. Comparison of correlation coefficients for short-term BPV variability by very short-term BP data length

Impact of the data length used to analyze very short-term BPV on the association between very short-term BPV and short-term BPV. Data lengths of 10, 20, and 30 min from the start of the 30-minute recording were used to calculate very short-term BPV. Bar graphs show Pearson's correlation coefficients (r) for the following relationships: open and solid bars indicate r values for the SD of very short-term BPV vs. the SD and ARV, respectively, of daytime or nocturnal BPV; shaded and checked bars indicate r values for the CV of very short-term BPV vs. the CV and CV-ARV, respectively, of daytime or nocturnal BPV. *$p < 0.05$ denotes statistical significance (Pearson's correlation test). SD, standard deviation; CV, coefficient of variation; ARV, averaged real variability; CV-ARV, ARV divided by averaged BP.

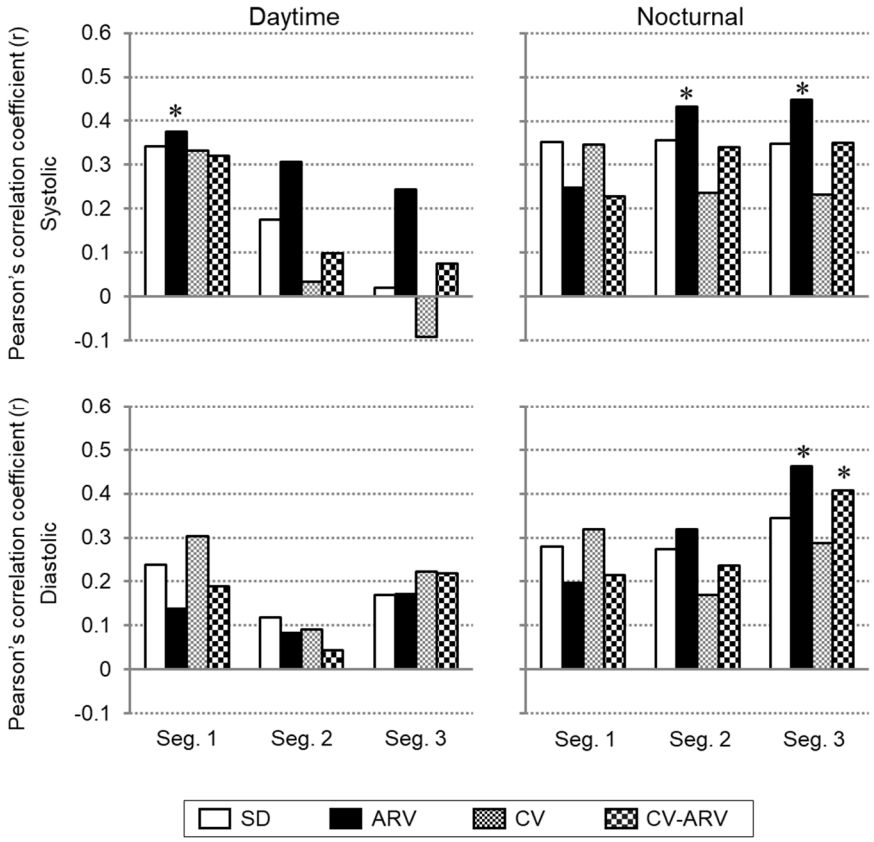

Figure 12. Comparison of correlation coefficients for short-term BPV variability by very short-term BP data segment

Impact of the data segment used to analyze very short-term BPV on the association between very short-term BPV and daily BPV. Seg. 1, Seg. 2 and Seg. 3 denote the first (0 to 10 min), middle (>10 to 20 min) and last (>20 to 30 min) 10-minute data segments, respectively, of the 30-minute continuous BP recording. Bar graphs show Pearson's correlation coefficients (r) for the following relationships: open and solid bars indicate r values for the SD of very short-term BPV vs. the SD and ARV, respectively, of daytime or nocturnal BPVs; shaded and checked bars indicate r values for the CV of very short-term BPV vs. the CV and CV-ARV, respectively, of daytime or nocturnal BPV. *$p < 0.05$ denotes statistical significance (Pearson's correlation test). SD, standard deviation; CV, coefficient of variation; ARV, averaged real variability; CV-ARV, ARV divided by averaged BP.

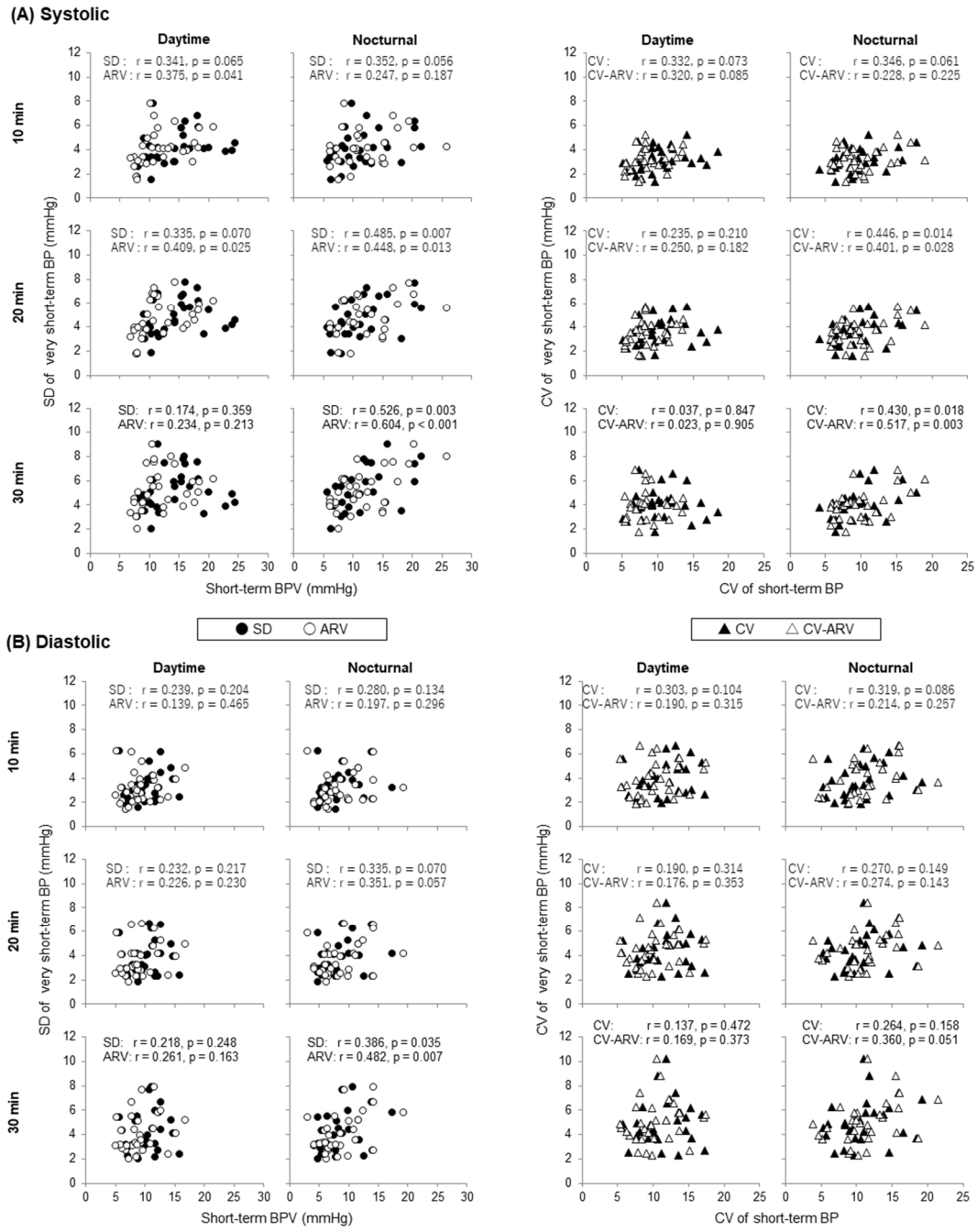

Figure 13. Individual scatter plots of correlation coefficients illustrated in Figure 11
Correlation between very short-term (beat-by-beat, 10, 20, 30 min) systolic (A) and diastolic (B) blood pressure variability (BPV) and daily (divided into daytime and nocturnal) BPV. The figure format and abbreviation are the same as Supplementary Figure 10. Correlation coefficient (r) and statistical significance (p) obtained by Pearson's test are displayed in each panel.

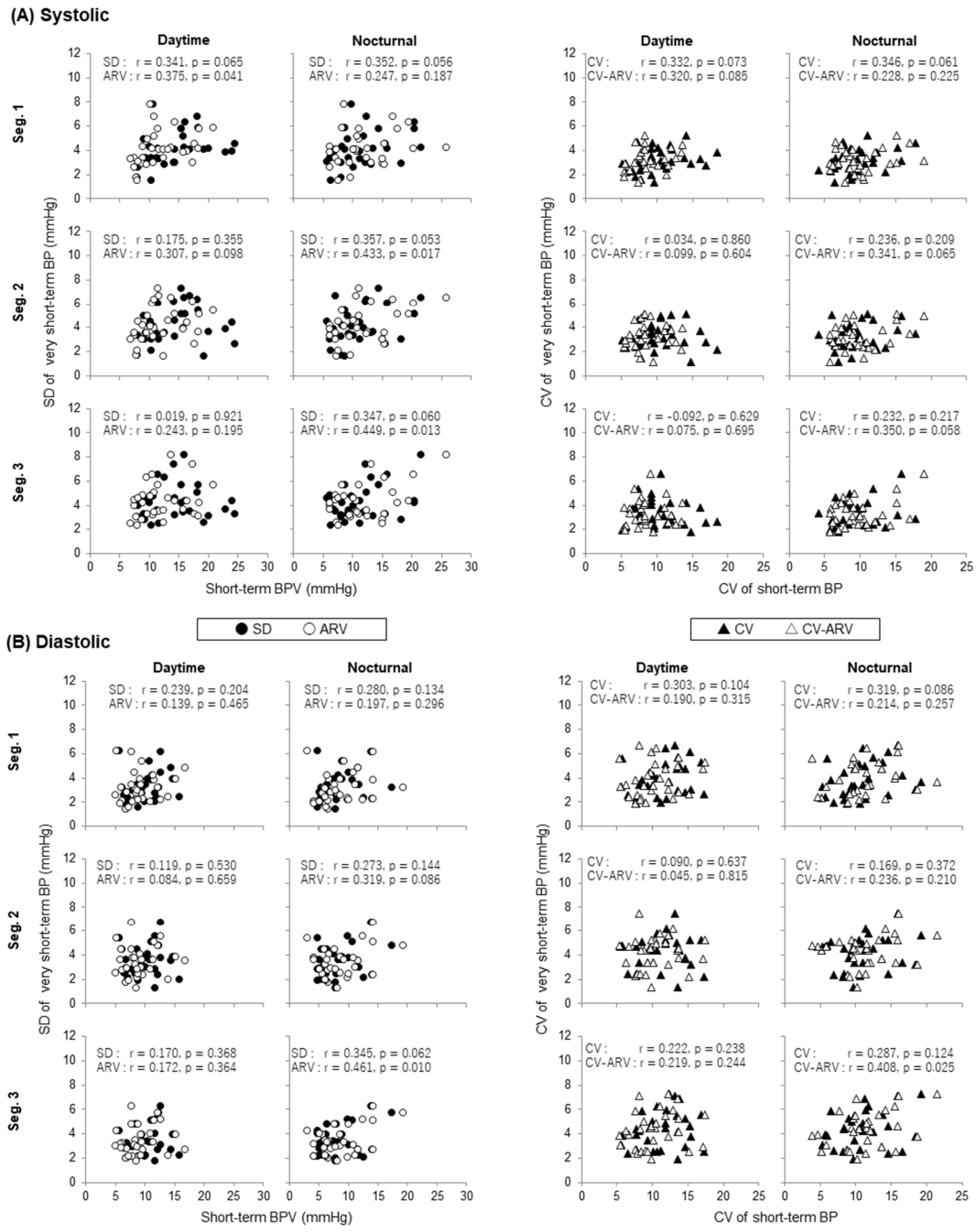

Figure 14. Individual scatter plots of correlation coefficients illustrated in Figure 12
Correlation between very short-term (beat-by-beat, Seg1, Seg2, Seg3) systolic (A) and diastolic (B) blood pressure variability (BPV) and daily (divided into daytime and nocturnal) BPV. The figure format and abbreviation are the same as Supplementary Figure 10. Correlation coefficient (r) and statistical significance (p) obtained by Pearson's test are displayed in each panel.

4.4 Discussion

In this study, we examined the relationship between the very short-term BPV assessed by 30-minute continuous beat-by-beat BP recording in a resting supine position and the short-term (divided into nocturnal and daytime) BPV calculated from 24-hour ABPM. The major findings of this study are as follows: (1) the very short-term BPV correlated significantly and most strongly with nocturnal BPV but did not correlate with daytime BPV; (2) an increase in the data length of very short-term BPV strengthened the correlation between very short-term BPV and nocturnal BPV; and (3) using the first 10-minute data segment of the 30-minute continuous beat-by-beat BP recording yielded a stronger correlation between very short-term BPV and daytime BPV than using later segments, while using the last 10-minute data segment gave a stronger correlation between very short-term BPV and nocturnal BPV than earlier segments.

Criteria for evaluating the correlation

There is no clear numerical standard for the appropriateness of correlation coefficients between clinical indicators, but they are determined individually for each intended use case of an indicator. For example, a correlation coefficient of 0.8 or higher is required empirically for a surrogate indicator of a gold standard. The estimation of the visceral fat area by abdominal bioimpedance measurement developed by Omron Healthcare Co., Ltd. has been approved as a medical device with a correlation coefficient of 0.89 against the visceral fat area from CT scan images, the gold standard [41].

Estimating of 24-hour urinary sodium excretion from spot urine samples, the gold standard for sodium intake, has a correlation coefficient of 0.54[42]. This surrogate index is a widely cited estimator that has been regarded to correlate well enough for comparisons of populational averages in epidemiological studies. Nevertheless, it is suitable for the comparative evaluation of populations as a cross-sectional assessment but not for adoption in individual diagnosis [42].

As a first step, the correlation assessment of BPV between different timescales in this study aims to identify its relevance in a cross-sectional assessment. Therefore, it is reasonable to consider a correlation coefficient of 0.5 or higher to be sufficiently relevant.

Relationship between very short-term BPV and daily BPV

In ABPM, BP is measured intermittently at 15- to 30-minute intervals over 24 or 48 h. A typical method of calculating short-term (daily) BPV from ABPM data is the SD of BP over 24 h, including daytime and nocturnal recording[15]. Thus, the physiological

circadian rhythm in BP markedly affects the BPV assessed by the SD of 24-hour BP. To overcome this issue, ARV, which averages the absolute differences between consecutive BP measurements, has been proposed. Mena et al.[39] suggested that ARV correlated well with cardiovascular risks and was superior to SD in predicting prognosis. Several investigations divided 24-hour BPV into daytime and nocturnal periods. Fan et al.[43] reported that daytime BPV was strongly associated with cerebral microvascular disease. Palatini et al.[10] reported that cardiovascular risk was more strongly associated with nocturnal BPV than with daytime BPV. Therefore, it is essential to examine the daytime and nocturnal BPV separately.

In our study, we examined the relationship of very short-term BPV with nocturnal and daytime BP and found that very short-term BPV correlated moderately with nocturnal BPV but not with daytime BPV (Figures 10 and 11). In addition, compared to the SD, the ARV of daytime or nocturnal BPV correlated more strongly with the SD of very short-term BPV. The same trend was also observed when comparing the correlation between the CV of very short-term BPV and the CV or CV-ARV of daytime or nocturnal BPV. These data indicate an improved correlation between very short-term BPV and nocturnal BPV after subtracting the effect of absolute BP.

Daytime BPV did not correlate with very short-term BPV for either systolic or diastolic BP. In addition, the longer data length used to calculate very short-term BPV significantly reduced the correlation with daytime BPV (Figure 11). We speculate that the difference in physical activity during measurements of daytime BPV and very short-term BPV may strongly affect these results. As we stated in the introduction, various physical activities, such as behavior, mental stress, environmental temperature, and food/drink intake, contribute to BPV[44, 45]. The BP data for calculating very short-term BPV were recorded under resting conditions, which minimized such physical activities. Thus, the duration of the resting period would greatly influence the correlation between very short-term BPV and nocturnal BPV. As shown in Figure 12, the very short-term BPV obtained from the first 10-minute data segment (Seg. 1) yielded a stronger association with daytime BPV than the later data segments, while the very short-term BPV obtained from the middle and last 10-minute data segments (Seg. 2 and Seg. 3) showed a stronger association with nocturnal BPV than the earlier data segment. Thus, the level of rest may strongly affect BPV assessments. These data indicate that very short-term BPV has the potential to be developed as an index to estimate nocturnal BPV, which is known to be associated with cardiovascular risks.

It should be noted that several participants showed discrepancies in the correlation analysis between very short-term and nocturnal BPV. We focused on the data outside the

95% prediction interval in the correlation analysis between very short-term and nocturnal SBP-SD. Even though the 30-minute SBP-SD was low, physiological BP changes, such as nocturnal dipping, increased BPV (Figure 15A). Due to the nature of BPV analysis, very short-term BPV cannot capture long-term fluctuations exceeding the segment length of very short-term BP recording (Figure 15B). We need to interpret very short-term BPV by considering this limitation.

We also need to consider baroreflex regulation in those windows of BPV assessment. The baroreflex is a robust negative feedback system that stabilizes daily BPV through sympathetic modulation. Guyton et al. reported that the baroreflex is a dominant regulatory system of BP over seconds to hours. They demonstrated that baroreflex dysfunction caused by sinoaortic denervation (SAD) in dogs increased the 24-hour BPV. Sakamoto et al.[46] also showed that SAD in rats increased the 24-hour BPV. Moreover, several animal and human studies have shown that the baroreflex has low-pass filter characteristics with a cutoff frequency at approximately 0.05 Hz[20, 21, 33]. Considering this evidence, the overlap of sympathetic baroreflex BP control of BPV from 30 min to 12 h may be one of the reasons for the association between the very short-term BPV and the nocturnal BPV from ABPM.

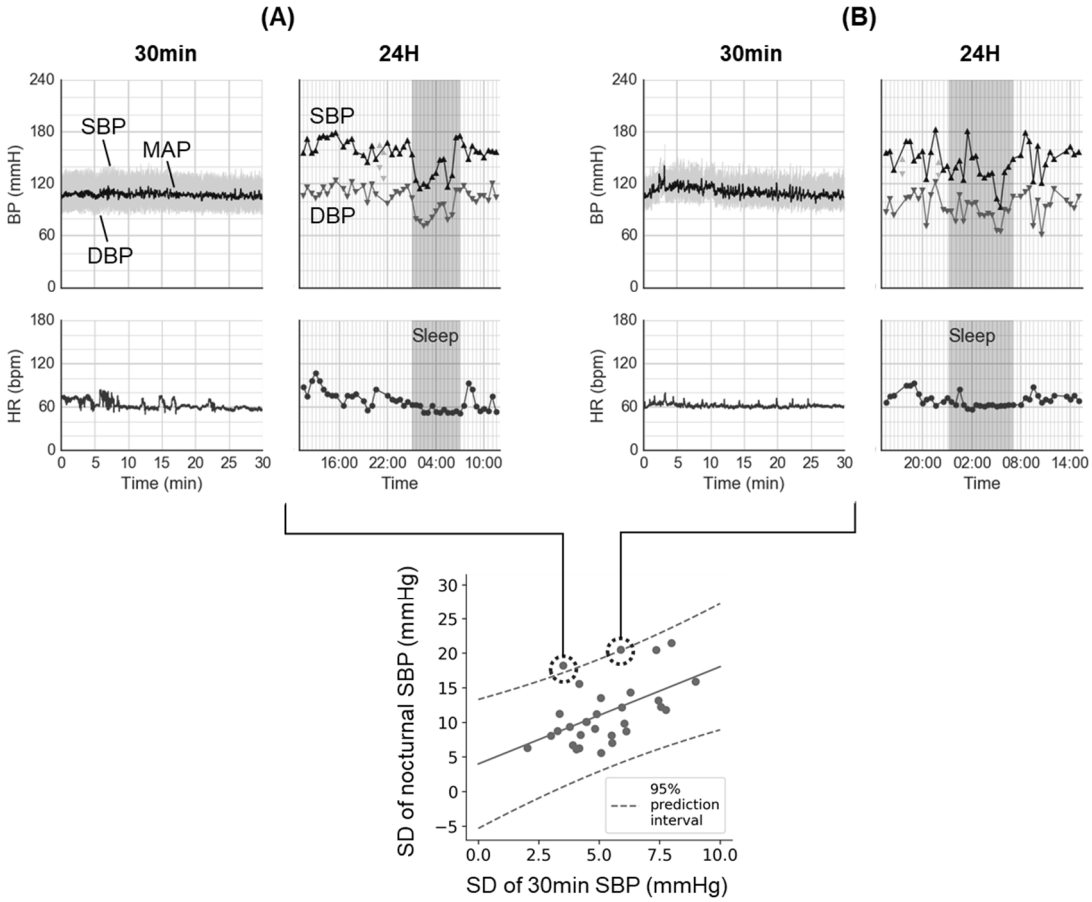

Figure 15. Sub-analysis of outliers

Two cases exceeded the 95% prediction interval in the correlation analysis of 30-minute SBP SD and nocturnal SBP SD; (A) considerable nighttime BP dipping, (B) data with a large amount of low-frequency BPV. BP trends in 30-minute and 24-hour are plotted individually. The shaded area in the 24-hour BP chart is self-reported sleep time. BP, blood pressure; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; SD, standard deviation.

The lack of evidence of individual baroreflex function was a limitation of this study. Mannoji et al.[47] demonstrated that the baroreflex pressure buffering function could be estimated from the BPV in 30-minute and 24-hour continuous BP recordings by frequency analysis in rats. Since continuous BP can be obtained by a noninvasive method, such analysis has the potential to estimate baroreflex function in the clinic. We need to evaluate the feasibility of spectral analysis of BP for baroreflex assessment in human participants. Previous studies have indicated that the decrease in baroreflex sensitivity

occurs in parallel with the decrease in heart rate variability (HRV) [48, 49]. Since HRV from ECG data could be estimated in this study, we also assessed HRV as a surrogate indicator of autonomic balance in our cohort. However, there was no clear association between BPV and HRV (Table 5, and Figure 16). Further investigation might be needed to clarify the mechanism of BPV and the relationship between baroreflex function and HRV in relatively healthy participants.

Table 5. HRV characteristics of participants analyzed (N=30).

	Normal (N=10)	High normal or Elevated (N=8)	Hypertension (N=12)	p
Mean HR (bpm)	65.9 ± 7.7	64.6 ± 7	71.2 ± 10.5	0.21
SDNN (ms)	49.5 (41.7–55.0)	50.8 (43.8–65.7)	41.1 (36.1–50.3)	0.17
pNN50	7.0 (3.2–15.7)	4.3 (1.3–15.6)	0.9 (0.3–6.4)	0.29
LF/HF	1.6 (0.9–2.5)	1.2 (0.8–2.6)	2.3 (1.3–4.1)	0.37

Continuous variables are presented in mean ± standard deviation if normally distributed and median (interquartile range) otherwise. HR, heart rate; SDNN, standard deviation of normal-to-normal (NN) R-R intervals; pNN50, proportion of NN50 divided by the total number of NN intervals; NN50: The number of pairs of successive NN intervals that differ by more than 50ms; LF/HF, ratio of the power of low frequency (LF, 0.04-0.15Hz) to high frequency (HF, 0.15-0.4Hz) bands.; bpm, beats per minute.

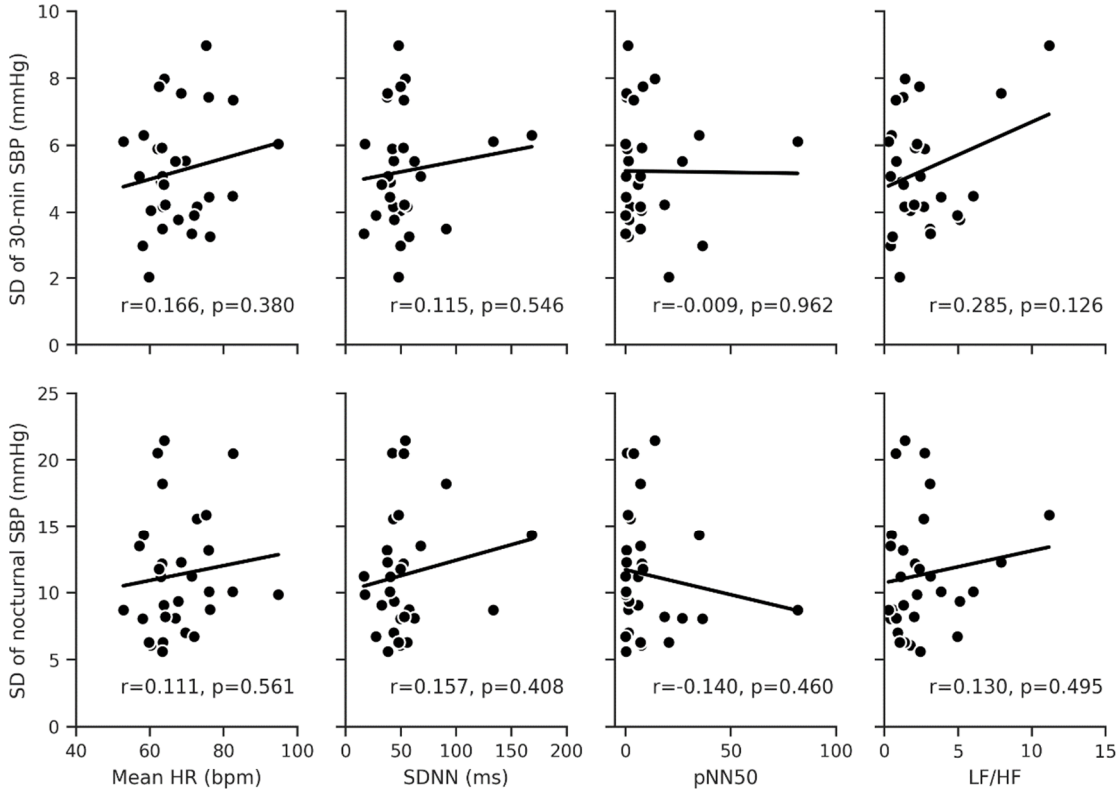

Figure 16. Correlation of HRV with very short-term and short-term BPV

Scatter plots illustrating correlations between two BPVs and four HRVs: the four columns from left to right correspond to mean HR, SDNN, pNN50, and LF/HF. The BPV in the upper and lower panels is the SD of 30-minute SBP and SD of nocturnal SBP, respectively. The solid line within each scatter plot represents the line of best fit. BPV, blood pressure variability; HRV, heart rate variability, HR, heart rate; SDNN, standard deviation of normal-to-normal (NN) R-R intervals; pNN50, proportion of NN50 divided by the total number of NN intervals; NN50: The number of pairs of successive NN intervals that differ by more than 50ms; LF/HF, ratio of the power of low frequency (LF, 0.04-0.15Hz) to high frequency (HF, 0.15-0.4Hz) bands. SDNN estimates global HRV. pNN50 and LF/HF reflect parasympathetic activity and autonomic (sympatho-vagal) balance, respectively.

Clinical implications

Our study suggests that very short-term BPV at rest may predict daily BPV. Casali et al.[23] demonstrated that very short-term BPVs during sitting and orthostatic load correlated with daytime and 24-hour BPVs. Their findings and our data indicate that both daytime and nocturnal BPV can be predicted by analyzing a shorter period of BP recording. Other studies have suggested that very short-term BPV may have potential value beyond predicting daily BPV. Manios et al.[50] and Wei et al.[17] reported that the very short-term BPV derived from beat-by-beat BP showed higher associations with common carotid intima-media thickness and left ventricular mass index than the BPV assessed by ABPM. Berry et al.[51] demonstrated that in heart failure patients with systolic dysfunction, a decrease in the very short-term BPV paradoxically increased cardiovascular events. Considering these reports, exploring the optimal method to measure very short-term BPV, including device and protocol, is a prerequisite for expanding this field.

To develop a very short-term BPV measurement as a useful clinical examination, it is essential to shorten the measurement time. As shown in Figure 12, the association of nocturnal BPV with very short-term BPV obtained from the middle (Seg. 2) or last (Seg. 3) 10-minute data segment was stronger than that derived from the first data segment. Taken together with the heart rate trend shown in Table 2, the degree and duration of resting have a significant impact on BPV. This result suggests that the establishment of an optimal resting condition for continuous beat-by-beat BP recording would improve the correlation with nocturnal BPV. At this stage, we assume that at least 10 min of BP recording after a 10-minute resting period provides an accurate estimation of nocturnal BPV.

The lack of a device to record beat-by-beat BP in the past limited the clinical research of very short-term BPV. Recently, continuous beat-by-beat BP monitoring devices based on tonometry or the volume clamp method have been developed and used in both laboratory and clinical settings. On the other hand, there are still many issues with the reproducibility and accuracy of continuous beat-by-beat BP recording, and the current development has not reached a level suitable for wide clinical use. Further device development may be needed.

Limitations

There are several limitations to this study. First, since the activities during ABPM were assessed only with a self-report form, we did not evaluate the physical activity quantitatively. Thus, we could not evaluate the impact of physical activity on daytime and

nocturnal BPV. Second, the current method of continuous beat-by-beat BP recording is susceptible to the movements and anatomical features of the participant. In the tonometric BP measurement, the sensor applies pressure through the subcutaneous tissue, compressing the radial artery against the radial bone. Thus, the optimal pressing force is essential to measure intraluminal arterial pressure. In this study, body movements that caused sensor misalignment occurred in three participants, and pressure drift occurred in five participants. Since those recording errors tended to occur in the late phase of 30-minute BP recording, we need to develop a shorter examination method for clinical application, as well as device development. Further development of device and analysis methods is needed for further clinical research. Third, the ultimate goal of this study is to improve the risk stratification for cardiovascular disease by including BPV as one of the factors. In the next step, we need to assess the very short-term BPV in a larger number of patients with cardiovascular diseases and evaluate the relationship between very short-term BPV and clinical outcome.

5. Concluding remarks

In recent years, BPV has been attracting attention as a risk stratification indicator for cardiovascular disease. Among short-term BPV, nocturnal BPV has been reported to affect cardiovascular disease events strongly. However, 24-hour BPV is time-costly, cannot be evaluated routinely, and has low reproducibility due to uncontrollable physical activities.

In this paper, we focused on very short-term BPV in resting conditions as a novel BPV marker that addresses these issues and, for the first time, evaluates its relationship with short-term BPV, which is known to be associated with cardiovascular risk. We confirmed that the very short-term beat-by-beat BPV in the supine position at rest correlates well with the nocturnal BPV assessed by ABPM. The preliminary evaluation in animal models supported these clinical results from the physiological mechanisms of BP regulation. Since very short-term continuous beat-by-beat BP recording is a less intrusive clinical examination, it may further optimize the management of hypertensive patients. Little evidence links very short-term BPV to clinical outcomes due to the lack of widely available beat-by-beat BP monitors in current situations. However, several exploratory studies suggest that very short-term BPV is more strongly associated with cardiovascular risk than short-term BPV. Meanwhile, short-term nocturnal BPV has been reported to be more strongly associated with risk than diurnal BPV.

The results of this paper provide insight into the similarity of the properties of resting BPV variability at these different timescales. Findings in this paper could also contribute significantly to deepening the understanding of very short-term BP characteristics in humans and developing a novel method of the stratification of BPV, which reflects nocturnal BPV by ABPM. Lastly, continuous beat-by-beat BP measurement is a technology that has not yet been established. Larger-scale clinical trials are required for further validation.

Research achievement

- ✓ The contents of chapter 2 were presented as: Hiroyuki Kinoshita, Hiroshi Mannoji, Keita Saku, Jumpei Mano, Tadayoshi Miyamoto, Koji Todaka, Takuya Kishi, Shigehiko Kanaya, Kenji Sunagawa. Power Spectral Analysis of Short-Term Blood Pressure Recordings for Assessing Daily Variations of Blood Pressure in Human. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference, 2018;1-4. doi: 10.1109/EMBC.2018.8513040.
- ✓ The contents of chapter 4 were published as: Hiroyuki Kinoshita, Keita Saku, Jumpei Mano, Hiroshi Mannoji, Shigehiko Kanaya, Kenji Sunagawa. Very short-term beat-by-beat blood pressure variability in the supine position at rest correlates well with the nocturnal blood pressure variability assessed by ambulatory blood pressure monitoring. Hypertension research, 2022;45(6):1008-1017. doi:10.1038/s41440-022-00911-6

Acknowledgement

I would like to express my deepest gratitude to my supervisor, Professor Kanaya, for his patience, guidance, and support. I am incredibly grateful that he took me on as a student and continued to have faith in me over the years.

I also thank the co-supervisors, Professor Yoshinobu Sato, Associate Professor Md. Altaf-Ul-Amin, Associate Professor Naoaki Ono, and Assistant Professor Alex Ming Huang generously took time out of their schedules to participate in my research and make this project possible.

This work would not have been possible without the constant support, guidance, and assistance of my major advisors, Dr. Kenji Sunagawa from the Circulatory System Research Foundation and Dr. Keita Saku from the National Cerebral and Cardiovascular Center Research Institute. They allowed me to access the research facilities and laboratory and to become part of their team.

My special thanks go to Dr. Hiroshi Mannoji of Kyushu University for providing valuable data in conducting this study.

I would like to express my deep gratitude to Dr. Toshikazu Shiga and Mr. Noboru Shinomiya from Omron Healthcare Co., Ltd for allowing me to do this research. I sincerely thank Dr. Jumpei Mano for giving the encouragement and sharing insightful suggestions and technical support for the clinical study.

References

1. Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, et al. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. Hypertens Res. 2012; 35: 947-53.
2. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiol. 2017; 2: 775-81.
3. Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. Hypertens Res. 2016; 39: 171-7.
4. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017; 6: e006895
5. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ. 2016; 354: i4098.
6. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castañé X, et al. Short-Term Blood Pressure Variability Relates to the Presence of Subclinical Brain Small Vessel Disease in Primary Hypertension. Hypertension. 2015; 66: 634–40.
7. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013; 10: 143-55.
8. Chadachan VM, Ye MT, Tay JC, Subramaniam K, Setia S. Understanding short-term blood-pressure-variability phenotypes: from concept to clinical practice. Int J Gen Med. 2018; 11: 241-54.
9. Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens. 2003; 21: 2251-7.
10. Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, Imai Y, et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study. Hypertension. 2014; 64: 487-93.
11. Viera AJ, Lingley K, Hinderliter AL. Tolerability of the Oscar 2 ambulatory

blood pressure monitor among research participants: a cross-sectional repeated measures study. BMC Med Res Methodol. 2011; 11: 59.
12. van der Steen MS, Lenders JW, Graafsma SJ, den Arend J, Thien T. Reproducibility of ambulatory blood pressure monitoring in daily practice. J Hum Hypertens. 1999; 13: 303-8.
13. JCS Joint Working Group. Guidelines for the clinical use of 24 hour ambulatory blood pressure monitoring (ABPM) (JCS 2010): – digest version –. Circ J. 2012; 76: 508-19.
14. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-3104.
15. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res. 2019; 42: 1235-1481.
16. Solà, J., & Delgado-Gonzalo, R. The Handbook of Cuffless Blood Pressure Monitoring. Cham: Springer. 2019.
17. Wei FF, Li Y, Zhang L, Xu TY, Ding FH, Wang JG, et al. Beat-to-beat, reading-to-reading, and day-to-day blood pressure variability in relation to organ damage in untreated Chinese. Hypertension. 2014; 63: 790-6.
18. Hall JE, Guyton AC. Role of the Kidneys in Long-Term Control of Arterial Pressure and in Hypertension. In Hall JE, Guyton AC, Guyton and Hall Textbook of Medical Physiology, 11th edn. Philadelphia, PA: Saunders Elsevier 2011, 216-31.
19. Kawada T, Sugimachi M. Open-loop static and dynamic characteristics of the arterial baroreflex system in rabbits and rats. J Physiol Sci. 2016 Jan;66(1):15-41.
20. Dworkin BR, Tang X, Snyder AJ, Dworkin S. Carotid and aortic baroreflexes of the rat: II. Open-loop frequency response and the blood pressure spectrum. Am J Physiol Regul Integr Comp Physiol. 2000; 279: R1922-33.
21. Kawada T, Shimizu S, Kamiya A, Sata Y, Uemura K, Sugimachi M. Dynamic characteristics of baroreflex neural and peripheral arcs are preserved in spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol. 2011; 300: R155-65.
22. Kamiya A, Kawada T, Sugimachi M. Systems physiology of the baroreflex during orthostatic stress: from animals to humans. Front Physiol. 2014; 5: 256. doi: 10.3389/fphys.2014.00256.

23. Casali KR, Schaan BD, Montano N, Massierer D, M F Neto F, Teló GH, et al. Correlation between Very Short and Short-Term Blood Pressure Variability in Diabetic-Hypertensive and Healthy Subjects. Arq Bras Cardiol. 2018; 110: 157-65.
24. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol. 2002 Oct;283(4):R815-26
25. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension. 1995 Jun;25(6):1276-86.
26. Cowley AW Jr, Liard JF, Guyton AC. Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res. 1973 May;32(5):564-76.
27. Chapuis B, Vidal-Petiot E, Oréa V, Barrès C, Julien C. Linear modelling analysis of baroreflex control of arterial pressure variability in rats. J Physiol. 2004 Sep 1;559(Pt 2):639-49.
28. Conci F, Di Rienzo M, Castiglioni P. Blood pressure and heart rate variability and baroreflex sensitivity before and after brain death. J Neurol Neurosurg Psychiatry. 2001 Nov;71(5):621-31
29. Omboni S, Parati G, Di Rienzo M, Wieling W, Mancia G. Blood pressure and heart rate variability in autonomic disorders: a critical review. Clin Auton Res. 1996 Jun;6(3):171-82.
30. Laitinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, Länsimies E. Age and gender dependency of baroreflex sensitivity in healthy subjects. J Appl Physiol (1985). 1998 Feb;84(2):576-83.
31. Krieger EM. Neurogenic Hypertension in the Rat. Circ Res. 1964 Dec;15:511-21.
32. Sudo A, Arito H, Fukuda K. Effects of swimming exercise on circadian sleep-waking rhythms and brain serotonin metabolism in rats. Ind Health 1984; 22: 153-61.
33. Honma K, Honma S, Hiroshige T. Response curve, free-running period, and activity time in circadian locomotor rhythm of rats. Jpn J Physiol 1985; 35: 643-58.
34. Welch PD. The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. IEEE Trans. Audio and electroacoustic. 1967; 15; 70–73.

35. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213(4504):220-222.
36. Kario K. Evidence and Perspectives on the 24-hour Management of Hypertension: Hemodynamic Biomarker-Initiated 'Anticipation Medicine' for Zero Cardiovascular Event. Prog Cardiovasc Dis. 2016; 59: 262-81.
37. Kokubo A, Kuwabara M, Nakajima H, Tomitani N, Yamashita S, Shiga T, et al. Automatic detection algorithm for establishing standard to identify "surge blood pressure". Med Biol Eng Comput. 2020; 58: 1393-1404.
38. Mano J, Saku K, Kinoshita H, Mannoji H, Kanaya S, Sunagawa K. Aging steepens the slope of power spectrum density of 30-minute continuous blood pressure recording in healthy human subjects. PLoS One. 2021; 16: e0248428. doi: 10.1371/journal.pone.0248428.
39. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005; 23: 505-11.
40. Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart Rate Variability Standards of Measurement, Physiological Interpretation, and Clinical Use. Circulation. 1996; 93: 1043–1065.
41. Shiga T, Hamaguchi T, Oshima Y, Kanai H, Hirata M, Hosoda K, et al., A new simple measurement system of visceral fat accumulation by bioelectrical impedance analysis, World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany. IFMBE Proceedings, vol 25/7. Springer, Berlin, Heidelberg.
42. Tanaka T, Okamura T, Miura K, et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. J Hum Hypertens. 2002;16(2):97-103.
43. Fan Y, Hou C, Peng L, Gao X, Xu Y. Twenty-Four-Hour Ambulatory Blood Pressure Variability Associated With Cerebral Small Vessel Disease MRI Burden and Its Progression in Inpatients With Cerebrovascular Disease. Front Neurol. 2020; 11: 513067. doi: 10.3389/fneur.2020.513067.
44. Peixoto AJ, White WB. Circadian blood pressure: clinical implications based on the pathophysiology of its variability. Kidney Int. 2007; 71: 855-60.
45. Smolensky MH, Hermida RC, Portaluppi F. Circadian mechanisms of 24-hour blood pressure regulation and patterning. Sleep Med Rev. 2017; 33: 4-16.
46. Sakamoto K, Hosokawa K, Saku K, Sakamoto T, Tobushi T, Oga Y, et al.

Baroreflex failure increases the risk of pulmonary edema in conscious rats with normal left ventricular function. Am J Physiol Heart Circ Physiol. 2016; 310(2): H199-205.

47. Mannoji H, Saku K, Nishikawa T, Tohyama T, Kamada K, Abe K, et al. Estimation of the baroreflex total loop gain by the power spectral analysis of continuous arterial pressure recordings. Am J Physiol Heart Circ Physiol. 2019; 316(4): H828-H839.
48. Ruiz J, Monbaron D, Parati G, Perret S, Haesler E, Danzeisen C, et al. Diabetic neuropathy is a more important determinant of baroreflex sensitivity than carotid elasticity in type 2 diabetes. Hypertension. 2005; 46(1): 162-167.
49. Wensel R, Jilek C, Dörr M, Francis DP, Stadler H, Lange T, et al. Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension. Eur Respir J. 2009; 34(4): 895-901.
50. Manios E, Michas F, Stamatelopoulos K, Barlas G, Koroboki E, Tsouma I, et al. Short-term beat-to-beat but not ambulatory blood pressure variability is correlated to carotid intima-media thickness. Blood Press Monit. 2014; 19: 288-93.
51. Berry M, Lairez O, Fourcade J, Roncalli J, Carrié D, Pathak A, et al. Prognostic value of systolic short-term blood pressure variability in systolic heart failure. Clin Hypertens. 2016; 22: 16.