Doctoral Dissertation

A new index for stratification of blood pressure variability by frequency analysis of very short-term continuous blood pressure recording

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Abstract

Background: The increase of blood pressure (BP) variability (BPV) is recognized as an important additional cardiovascular risk factor. Aging-induced atherosclerosis and autonomic dysfunction impair the baroreflex and, in turn, intensify 24-hour BPV. In animal experiments, impaired baroreflex steepens the slope of the power spectrum density (PSD) of continuous BP in the frequency range of 0.01 to 0.1 Hz. Although the repeated oscillometric BP recording over 24 hours or longer is a prerequisite to quantify BPV in humans, how the very short-term continuous BP recording reflects BPV remains unknown. This study aimed to evaluate the impact of aging on the PSD characteristics by frequency analysis of the very short-term (30-min) BP recording. The PSD characteristics were evaluated the difference from other indices by frequency analysis of biological data.

Methods: 30-min continuous BP was tonometrically recorded in 56 healthy subjects. Considering the baroreflex frequency range, the PSD of BP in the frequency range of 0.01 to 0.1 Hz was calculated. The characteristics of PSD were compared among four age groups (26-40, 41-55, 56-70 and 71-85 years) and investigated the relationship with other induces (baroreflex sensitivity (BRS) and heart rate variability (HRV)).

Results: The slope of PSD between 0.01 and 0.1 Hz was steeper in older subjects (71 years or older) than in younger subjects (55 years or younger) ($p < 0.05$). The slope of PSD did not significantly correlate with BRS and HRV.

Conclusions: Aging steepened the slope of PSD of BP between 0.01 and 0.1 Hz. This phenomenon may partly be related to the deterioration of the baroreflex in older subjects. Our proposed method may contribute to the stratification of BPV differently from other indices.

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Abbreviations

BP = blood pressure

BPV = blood pressure variability

SD = standard deviation

ABPM = ambulatory blood pressure monitoring

HR = heart rate

BRS = baroreflex sensitivity

SBP = systolic blood pressure

ECG = electrocardiogram

LF = low-frequency

PSD = power spectrum density

HRV = heart rate variability

HF = high-frequency

RESP = respiratory signal

DBP = diastolic blood pressure

FFT = Fast Fourier Transform

ANOVA = analysis of variance

BMI = body mass index

NS = not significant

M = male

F = female

RAAS = renin-angiotensin-aldosterone system

1. Introduction

1.1 Issues in the management of hypertension

The leading cause of death in Japanese is cancer, the second is cardiovascular disease, and the third is cerebrovascular disease (stroke, etc.). The combined deaths from cardiovascular disease and cerebrovascular disease (cerebro-cardiovascular disease) amount to about 23% [46]. Hypertension is the largest factor to death from these disease, and proper management of hypertension is important to preventing the events (Fig 1-1) [47].

Blood pressure (BP) in Japanese is decreasing year by year (Fig 1-2) [47]. However, the number of people dying from cerebro-cardiovascular disease has not decreased (Fig 1-3) [46]. Therefore, it is considered that the current management of hypertension is insufficient.

Two issues have been pointed out in the current management of hypertension. The first is the large number of poorly managed people [47]. The number of hypertensives in Japan is estimated to be 43 million as of 2017. Of these individuals, 31 million are estimated to be poorly controlled (140/90 mmHg or higher), 14 million of these 31 million individuals are estimated to be unaware of hypertension, 4.5 million are estimated to remain untreated despite awareness of the disease and 12.5 million are estimated to be poorly controlled despite ongoing treatment (Fig 1-4) [47]. In order to reduce these poorly managed people, taking health checkups and measuring BP at home have been promoted. [47].

Second, more than half of high blood pressure-related excessive cerebro-cardiovascular disease mortality/morbidity events occurred in people with mildly high blood pressure (grade I hypertension or lower (under 160/100 mmHg)) [47].

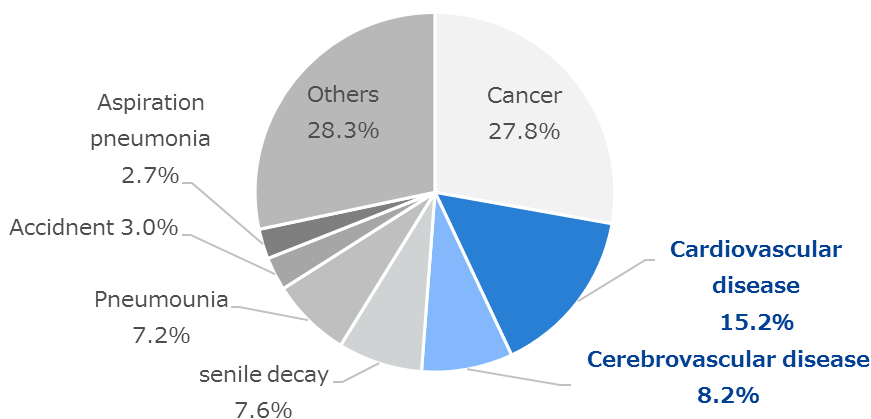

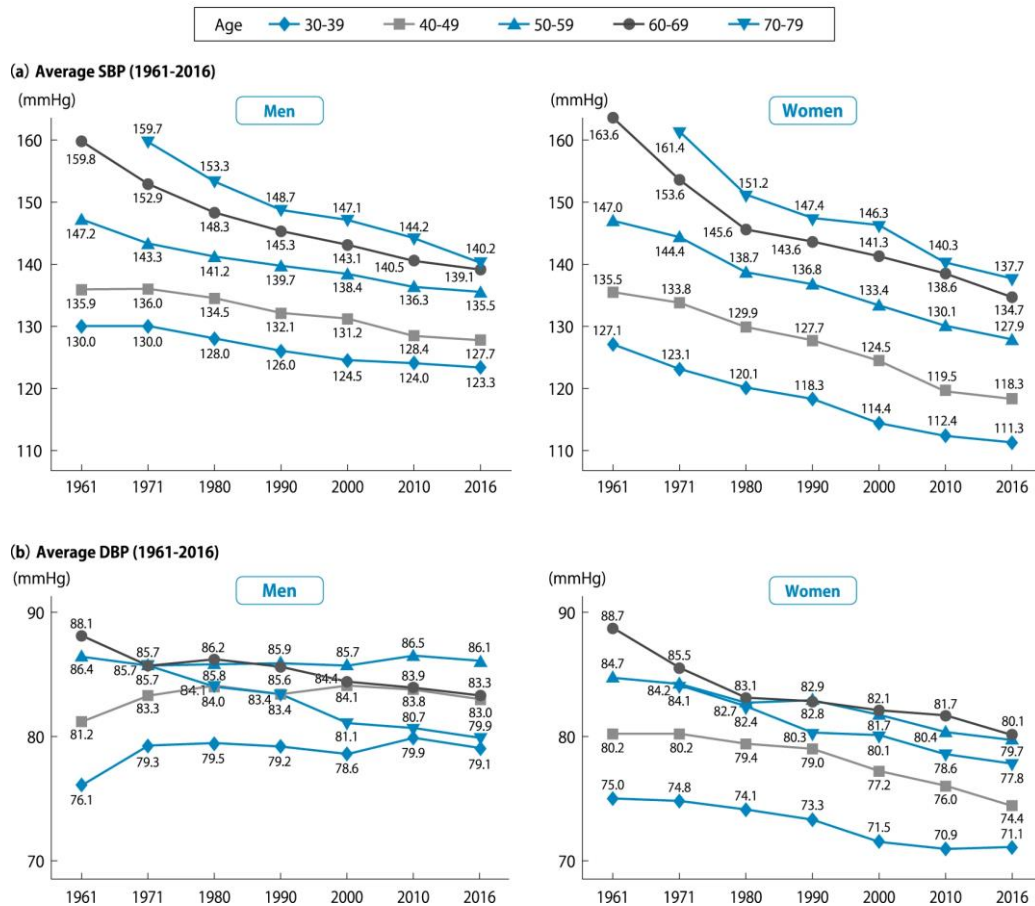**Fig 1 - 1. Percentage of deaths by major cause of death (2017) [46]**

Fig 1 - 2. Annual changes in average blood pressure by sex and age group [47]
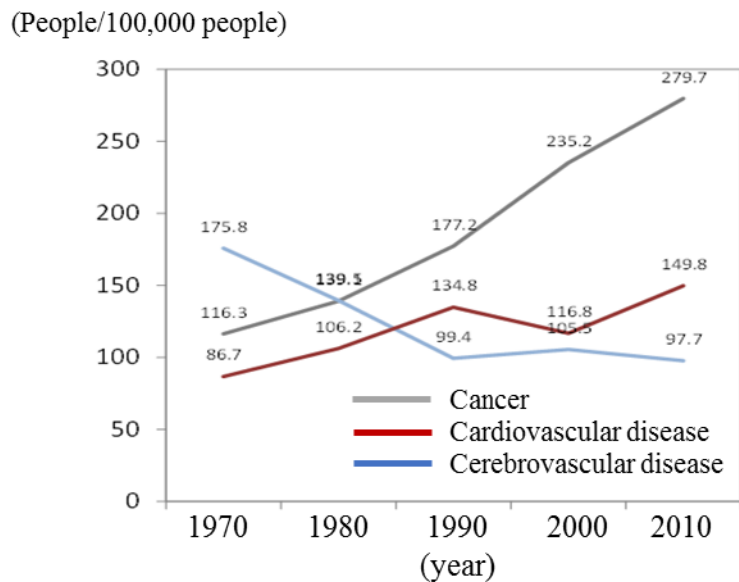

Fig 1 - 3. Annual changes in number of deaths for each cause of death in Japan [46]

Individuals with hypertension **43 million**
Individuals with blood pressure≥140/90 mmHg **31 million**

Untreated &
unaware
33%
14 million

Treated &
well controlled
27%
12 million

Untreated &
aware
11%
4.5 million

Treated &
poorly controlled
29%
12.5 million
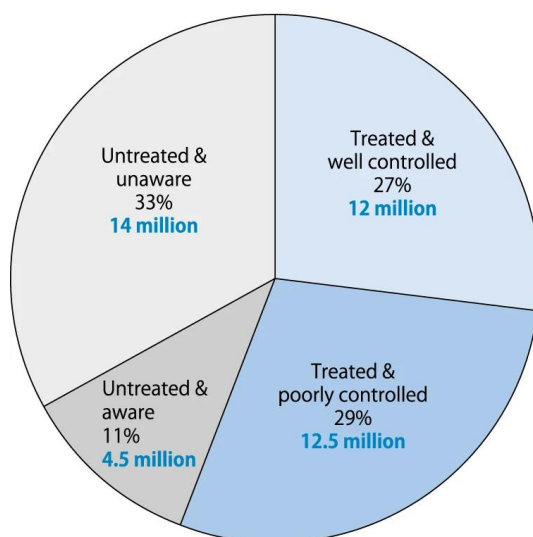
Prevalence, treatment rate and control rate are derived from the National Health and Nutrition Survey (2016) data. Population is the estimate in 2017. Awareness rate is estimated at 67% from NIPPON DATA 2010. Hypertensives are those with blood pressure 140/90 mmHg or using antihypertensive drugs. "Well controlled" means blood pressure <140/90 mmHg.

Fig 1 - 4. Estimated number of hypertensives, hypertensives receiving antihypertensive drug therapy and poorly controlled hypertensives in Japan (2017) [47]

1.2 Blood pressure variability

Recently, BP variability (BPV) has been recognized as an independent predictor of cardiovascular mortality in both normotensive subjects and hypertensive patients [2-9]. Kawai et al. [3] reported that the visit-to-visit BPV using office BP measurement correlated significantly with the incidence of cardiovascular disease. Kikuya et al. [7] also reported that daily BPV assessed by standard deviation (SD) of 24-h ambulatory BP monitoring (ABPM) every 30 min was an independent predictor of cardiovascular mortality in the general population. Furthermore, Mena et al. [9] reported that high daily BPV assessed by average real variability index of ABPM associated with the presence and progression of subclinical organ damage, as well as the incidence of cardiovascular events. Therefore, in addition to absolute BP, BPV contributes to better BP management and risk stratification.

The very short-term BPV is even shorter than daily BPV and identifiable in the beat-to-beat variations. Although the very short-term BPV analysis has the potential for stratifying the cardiovascular risk as shown by several animal studies, the predictive power is not so high as daily BPV assessed by 24-h ABPM. The major reason for the lower predicted power in the very short-term BPV may be the lack of clinical evidence, since the very short-term BPV analysis requires continuous BP measurement devices [41, 42].

Visit-to-visit BPV and daily BPV require long-term device attachment (at least during the night) or a prolonged period of observation (at least three visits), which pose a burden on patients. Since very short-term BPV can be measured in a short time, it is less burdensome for both medical staff and patients and have great clinical value.

1.3 Baroreflex function

The baroreflex is one of the body's homeostatic mechanisms that helps to maintain BP at nearly constant levels. BP is not always constant, and fluctuates due to various factors, including mental stress, behavior, environmental temperature, and food/drink intake [10]. The baroreflex is a robust negative feedback system that stabilizes daily BPV through sympathetic modulation [11, 48]. BPV are detected by pressure sensor called baroreceptor in the carotid artery and aorta. Neural impulses associated with their activation/deactivation, as occurs during transient changes in BP, transmit to the central nervous system. The neural signals systemically via the sympathetic and parasympathetic branches of the autonomic nervous system. In response to the signal via, the key determinants of BP, such as heart rate (HR), cardiac chronotropy, vascular resistance and stressed blood volume, are modified to maintain BP homeostasis [48].

BP is regulated via the interaction of various local, humoral, and neural factors. Baroreflex is the major neural function for acute BP regulation [48]. Guyton [18] reported that the baroreflex is a dominant regulatory system of BPV from seconds to hours. Studies in various animal species also have demonstrated that the baroreflex has a higher gain in the low-frequency range (low-pass characteristics) with the cutoff frequency at around 0.05 Hz [19, 20]. Thus, baroreflex dysfunction increases BPV in the low-frequency range.

1.4 Baroreflex dysfunction and the treatment

Baroreflex dysfunction increases very short-term BPV. As mentioned above, although there is less evidence than BPV over 24 hours or longer, it has been reported that large very short-term BPV assessed by SD of continuous BP is associated with organ damage [49, 50]. In addition, sharp BP rise (the BP surge) would be considered an acute risk factor which triggers cardiovascular disease events by a mechanical stress-induced plaque rupture [10].

Furthermore, baroreflex dysfunction cause not only sharp BP rise but also decline. Hypotension, such as orthostatic hypotension and postprandial hypotension, is one of the pathophysiology [51]. Falling down by hypotension is a major cause of fractures leading to long-term care.

The relationship between baroreflex dysfunction and hypertension has also attracted attention recently. Baroreflex activation therapy was reported to show long term benefit in BP reduction in resistant hypertension patients [52]. In the future, the baroreflex may be a target for the treatment of hypertension.

Research is underway on methods using invasive devices as a treatment for deteriorated baroreflex [53, 54]. However, there is currently no established treatment to cure baroreflex dysfunction. It is necessary to avoid behaviors that cause sharp BPV such as stress, sudden changes in posture and temperature.

1.5 Index for baroreflex function

Baroreflex sensitivity (BRS) is an index associated with baroreflex function and has been extensively used in clinical settings [25, 26]. BRS is a HR response to BP change in the closed-loop condition. There are phenylephrine bolus technique, spontaneous sequence analysis, cross spectral techniques for measuring BRS [27].

Phenylephrine bolus technique calculates BRS from a progressive increase in BP and a reflex slowing of HR in response to a bolus injection of phenylephrine. Generally, BRS is calculated from the mean of three such acceptable regression slopes obtained by bolus phenylephrine injections approximately five minutes apart, and is expressed in msec/mmHg [27].

Spontaneous sequence analysis examines the gain of the cardiac baroreflex during spontaneous variations in BP rather than in response to drug induced changes in BP. BRS was calculated from the slope of linear regression plots of systolic BP (SBP) against RR interval on spontaneous sequences in which SBP and RR interval concurrently increase (up sequences) or decrease (down sequences) for three or more consecutive beats [27].

Cross spectral techniques do not need drug induction as with spontaneous sequence analysis. Non-invasive beat by beat BP and electrocardiogram (ECG) are recorded for about 10 minutes during controlled breathing. After power spectral analysis of both BP and RR interval are performed, coherence analysis is used to assess the correlation among oscillations in RR interval and SBP. High squared coherence values between variations in SBP and RR interval in the low frequency (LF) band reflect an intact baroreflex control of heart period. BRS calculated by using the α index, which is the square root of the ratio of RR interval power to SBP power from 0.07 to 0.14 Hz with coherence greater than 0.5 [27].

BRS is a HR response to BP change in the closed-loop condition. BP is regulated not only by HR but also by vascular resistance, stressed blood volume and cardiac chronotropy. Therefore, it partially reflects the cardiac vagal baroreflex and is no more than an indirect index of baroreflex pressure-stabilizing capacity [21]. Recent study has shown that the slope of power spectral density (PSD) of BP in the frequency range of 0.01 to 0.1 Hz increases with the decrease in the baroreflex gain in rats [21]. Baroreflex has low-pass characteristics with the cutoff frequency at around 0.05 Hz [19, 20] and attenuates the PSD of BP, which reflect BPV, in the baroreflex functioning frequency range. The baroreflex could not operate above 0.1 Hz and fully operates at 0.01 Hz, thereby the baroreflex strongly attenuates BPV at around 0.01 Hz. Therefore, the PSD analysis of BP in the baroreflex frequency range would reflect the baroreflex modulated BPV.

1.6 Frequency analysis of biological data

The usefulness of frequency analysis of biological data for the stratification of cardiovascular patients is well known. HR variability (HRV) is most common in clinical. The high-frequency (HF) component of HRV (0.15 - 0.4 Hz) reflects the vagal nerve modulated HR change by respiratory fluctuation [12]. On the other hand, the LF component of HRV (0.04 - 0.15 Hz) is reported to indicate concomitant activity of sympathetic and vagal nerve. In addition, the LF/HF ratio reflects sympatho-vagal balance or the activation of sympathetic nervous system [12]. The frequency analysis focusing on continuous BP recording is also developed by using the data of standard catheter-manometer systems or noninvasive plethysmographic devices. The LF component (0.04-0.15 Hz) of SBP is also known as an index of sympathetic modulation directed to the vessels [13]. Thus, the LF of SBP has been reported to increase during tilt [14, 15], mental stress [15], and even several cardiovascular diseases [16, 17].

1.7 Continuous blood pressure monitors

Krotkoff method, which doctors measure the BP by listening to the sound of blood vessels with a stethoscope, and oscillometric method, which is adopted in an electronic BP monitor, are general BP measurement methods. These methods can not measure continuous BP because they require a flow pressurizing the upper arm using a cuff to block blood flow and then open it. Therefore, very short-term BPV and BRS can not be assessed by these methods.

Arterial tonometry method and volume clamp method have been used for non-invasive recording continuous BP in clinical settings. Arterial tonometry method records BP by mounting the pressure sensor directly onto the skin above a radial artery (JENTOW, Colin Electronics, Komaki, Japan) [58]. The volume clamp method records BP waveform at the finger by an inflatable cuff combined with a photodiode capturing the diameter of the artery (FMS-Finapres Medical System, Arnhem, the Netherlands; CNSystems Medizintechnik AG, Graz, Austria) [44].

Recently, cuffless continuous noninvasive BP monitors have been developed due to the increasing demand for accurate and unobtrusive devices that will permit continuous blood pressure monitoring for a wide variety of patients, allowing them to perform their daily activities without any disturbance [43]. As for cuffless continuous noninvasive BP monitors, the Visi Mobile System (Sotera Wireless, CA, USA) based on the pulse transit time method has been shown to provide acceptable BP recording during the long-term attachment [45]. Similar wearable devices such as Caretaker (Caretaker Medical LLC, VA, USA) and BB-613 (Biobeat Technologies LTD, Israel) have been approved as medical devices in the U.S

1.8   Constructs of this paper

Our goal is to derive new indices to evaluate the BPV from very short-term continuous BP recording. This study aims to investigate BPV by frequency analysis focusing on the baroreflex operating frequency range between 0.01 and 0.1 Hz.

In chapter 2, I analyze the PSD of very short-term continuous BP recordings obtained from healthy adults in various age groups. Furthermore, I will investigate the impact of aging on the characteristics of the PSD. In chapter 3, I compare the related existing indices to our proposed method. In chapter 4, I will discuss the result of my study. In chapter 5, I will show the limitation of this study. In chapter 6, I will show future work. Finally, I will show the conclusion of my study.

2. Relationships between aging and characteristics of PSD of continuous BP in healthy human subjects

2.1 Introduction

In previous animal study, the slope of PSD of BP in the baroreflex operating frequency range (0.01 to 0.1 Hz) was suggested to evaluate baroreflex function, which regulate BPV over 24 hrs [21]. In human, it is difficult to assess baroreflex function by the direct invasive measurement. Since aging is known to worsen the baroreflex function [10, 22], I hypothesized that aging steepens the slope of PSD of BP in the baroreflex operating frequency range. I evaluated the impact of aging on PSD characteristics including the slope.

2.2 Materials and Methods

Subjects

Between December 2017 and April 2018, I recruited 80 healthy volunteers of various age groups (41 women and 39 men; mean age 57.4, range 28–85 years), who were not prescribed antihypertensive drugs or

cardiovascular drugs. I excluded the volunteers who were prescribed drugs for dyslipidemia and diabetes mellitus, because these diseases may affect the circulatory regulation via autonomic or baroreflex dysfunction. None of the subjects presented clinical signs of neurological and autonomic dysfunction or received prescriptions for neurological diseases. Omron Expert Link Co., Ltd. (Kyoto, Japan) was entrusted with recruitment of volunteers. The institutional review board of Omron Healthcare Co., Ltd. (Kyoto, Japan) approved this study, and all participants provided written informed consent to participate.

Devices

Omron Healthcare Co., Ltd. (Kyoto, Japan), which I work for, developed institutionally approved wearable wrist-type tonometric BP monitor for noninvasive continuous BP recording [10, 23]. I was in charge of developing the tonometric sensor for that device.

I used the the tonometric BP monitor for noninvasive continuous BP recording. I simultaneously recorded ECG and respiratory signal (RESP) from thoracic impedance (BP-A308; Omron Healthcare Co., Ltd., Kyoto, Japan). I also measured oscillometric BP in the upper arm (BP-203RPEIII; Omron Healthcare Co., Ltd., Kyoto, Japan).

Protocol

I attached the wearable tonometric BP monitor to the wrist and the oscillometric BP monitor to the ipsilateral upper arm. I placed three electrodes for ECG and RESP on the chest. After the preparation, I waited for 5-15 min until all signals were stabilized. I then recorded continuous BP, ECG and RESP for 30 min with the subject resting in a supine position. I measured the oscillometric BP before and after the continuous BP recordings (Fig 2-1).

Data Analysis

I recruited 80 subjects. Subjects were excluded from analysis if they met any of the following exclusion criteria:

·   Subject who showed SBP ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg (averaged value of oscillometric BP measurements during the protocol).
·   Subject who could not complete the stable continuous BP recording for 30 min because of motion, respiration noise and recording failure.
·   Subject who had irregular beats more than 10 times during the 30-min recording.

Finally, I excluded 24 subjects from analysis, and studied the remaining 56 subjects.

Continuous BP Analysis

I digitized continuous BP at 1.0 kHz using a 16-bit analog-to-digital converter (Power Lab 8/35; AD Instruments, Sydney, Australia). I derived SBP (maximum BP), mean BP, DBP (minimum BP) and HR in every beat. I estimated BPV and HRV in the time domain as the SD of beat-by-beat BP (SBP, mean BP and DBP) and HR, respectively, for 30 min.

For frequency analysis of continuous BP, I resampled the mean BP time series at 5 Hz and divided them into 200-second segments with 50% overlap. In each segment, after removing a linear trend, I applied the Hanning window. I applied the fast Fourier transform (FFT) using the Welch's periodogram [24] and estimated PSD in the frequency range of 0.01 to 0.1 Hz. The integrated PSD area reflects BPV in the frequency range.

I chose this frequency range because previous studies in various animal species indicate that the baroreflex function approximates distinctive low-pass filter characteristics [19, 20]. The baroreflex cannot operate above 0.1 Hz and fully operates at 0.01 Hz; hence the baroreflex strongly attenuates BPV at around 0.01 Hz. To quantify the impact of baroreflex on PSD, I characterized PSD at 0.01 Hz ($PSD_{0.01Hz}$) and 0.1 Hz ($PSD_{0.1Hz}$) and derived the slope of PSD (Fig 2-2).

Statistical Analysis

I performed statistical analyses using commercially available software (BellCurve for Excel version 3.21, Social Survey Research Information Co., Ltd., Tokyo, Japan). I used Pearson correlation coefficients to assess the relationship between age and each measurement variable for all age groups. I divided the subjects into four age groups: 26-40, 41-55, 56-70 and 71-85 years. I compared all age groups by one-way factorial analysis of variance (ANOVA) followed by the Tukey-Kramer test. I considered differences to be statistically significant at $p < 0.05$.
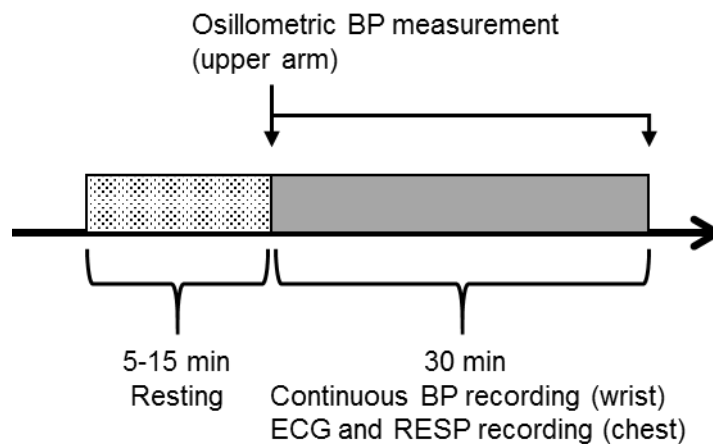

Fig 2 - 1. Protocol of this study.

After waiting for 5-15 min until all signals were stabilized, continuous BP, ECG and RESP were recorded for 30 min with the subject resting in a supine position. The oscillometric BP was measured before and after the continuous BP recording.

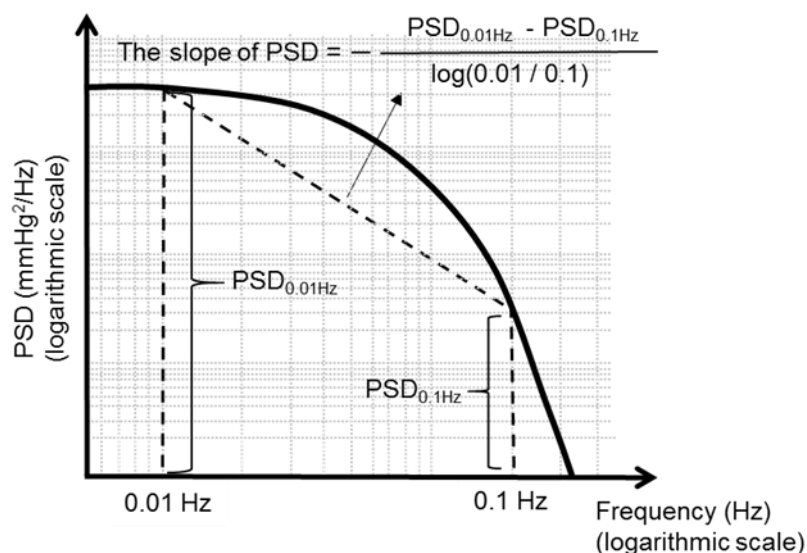BP, blood pressure; ECG, electrocardiogram; RESP, respiratory signal.

The slope of PSD $= -\dfrac{PSD_{0.01Hz} - PSD_{0.1Hz}}{\log(0.01 / 0.1)}$

Fig 2 - 2. The PSD characteristics evaluated in this study.

To characterize PSD, I focused on the three parameters. $PSD_{0.01Hz}$ is the log base 10 of PSD at 0.01 Hz, and $PSD_{0.1Hz}$ is that at 0.1 Hz. We also calculated the slope of PSD between 0.01 Hz and 0.1 Hz on a double logarithmic scale.

PSD, power spectrum density.

2.3 Results

Baseline characteristics

  Table 2-1 shows the baseline characteristics. The proportion of males was relatively low in the 26-40 age group. Body mass index (BMI) did not differ among age groups. In this cohort, SBP and DBP increased slightly with age (Fig 2-3).

Impact of aging on BP and BPV from continuous BP recordings

  Shown in Fig. 2-4 is a representative time series of continuous tonometric BP recording for 30 min. Both SBP and DBP fluctuated continuously without a large change in mean BP. Averaged BP and HR did not differ among the four age groups (Table 2-2). SBP increased slightly with age (Fig 2-5).

  Figure 2-6 demonstrates the relationship of age with BPVs and HRV in the time domain expressed by SD. The upper panels show the scatter plots of individual data between age and BPVs or HRV. While BPVs did not correlate significantly with age, HRV correlated weakly with age and tended to decrease with aging. The lower panels compare the BPVs and HRV among four age groups. The were no significant differences in BPVs and HRV among the four groups.

Impact of aging on characteristics of PSD of BP

  Figure 2-7 shows the individual and group PSD estimated from 30-min continuous BP recordings. Both PSD and frequency axes are logarithmically scaled. In all age groups, PSD was relatively flat around 0.01 Hz and decreased as the frequency increased. As shown in Fig. 2-7E, the slope of PSD between 0.01 and 0.1 Hz in the 71-85 age group was steeper than that in the 26-40 age group.

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Figure 2-8 demonstrates the relationship of age with PSD characteristics. The upper panels show scatter plots of individual data between age and PSD characteristics. The lower panels compare PSD characteristics among the four age groups. $PSD_{0.01Hz}$ did not correlate with age in individual data (Fig 2-8A) or the group data (Fig 2-8D). On the other hand, $PSD_{0.1Hz}$ correlated significantly with age and tended to decrease as age increased (Fig 2-8B). As a result, the slope of PSD between 0.01 and 0.1 Hz correlated significantly with age and tended to increase as age increased (Fig 2-8C). The slope of PSD between 0.01 and 0.1 Hz was significantly larger in the 71-85 age group than in the 26-40 and 41-55 age groups (Fig 2-8F).

The PSD characteristics between males and females in each age group was also compared. Although the sample size was small, the slope of PSD within the same age group did not differ significantly between males and females. The general trend of age-related alteration in the slope of PSD was also the same between males and females (Fig 2-9, Table 2-3 and Fig 2-10).

Table 2 - 1. Baseline characteristics and BP stratified by age group.

	Total	Age groups (years)				p value
		26-40	41-55	56-70	71-85	
No. of subject	56	14	15	17	10	-
Age (years)	54.3±16.9	32.9±3.93	47.7±3.96	62.6±4.70	80.0±3.71	-
Male sex (%)	48.2	35.7	46.7	58.8	50.0	NS
BMI (kg/m^2)	21.1±3.23	20.0±3.40	20.6±3.31	22.0±3.24	22.1±2.54	NS
SBP (mmHg)	111.7±12.6	102.1±8.61	110.8±10.2	113.1±13.3	124.4±8.22	p < 0.01
DBP (mmHg)	66.6±9.24	59.9±4.21	67.5±9.41	68.0±10.4	72.2±7.46	p < 0.01

SBP and DBP were measured by an oscillometric BP monitor. The SBP and DBP values were obtained by averaging oscillometric BP before and after the 30-min continuous BP recording. Values are expressed as mean ± SD. One-way factorial ANOVA (BMI, SBP and DBP) and Pearson's χ^2 test (percent males) were used for comparison among four groups.

BP, blood pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; SD, standard deviation; ANOVA, analysis of variance.
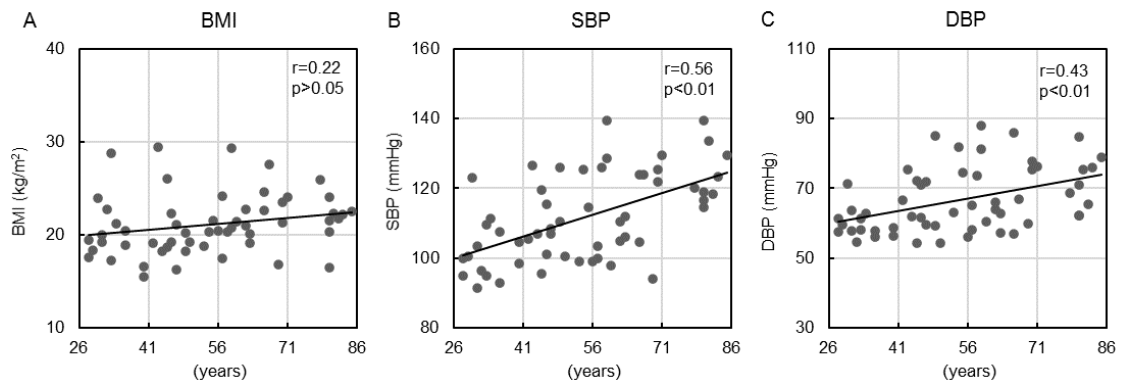
Fig 2 - 3. Impact of aging on baseline characteristics and BP.

Scatter plots of individual data for the relationship of age versus BMI, SBP and DBP analyzed by Pearson's correlation coefficient (r). Straight lines indicate linear regression lines. SBP and DBP were measured by an oscillometric BP monitor. The SBP and DBP values were obtained by averaging oscillometric BP before and after the 30-min continuous BP recording.

BP, blood pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
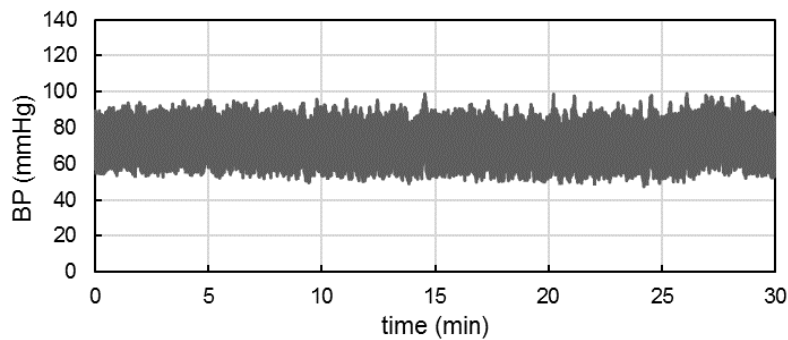

Fig 2 - 4. Representative blood pressure (BP) time series of 30-min continuous tonometric BP recording

Time series of 30-min continuous tonometric blood pressure (BP) recording.

Table 2 - 2. Averaged BP and HR obtained from 30-min continuous BP recordings.

	Total	Age groups (years)				p value
		26-40	41-55	56-70	71-85	
No. of subject	56	14	15	17	10	
SBP (mmHg)	107.1±14.7	100.8±11.8	106.7±12.9	109.4±17.3	112.5±14.9	NS
mean BP (mmHg)	78.4±11.7	74.8±7.88	78.4±12.1	81.1±14.6	78.8±10.6	NS
DBP (mmHg)	61.0±10.9	60.4±6.87	61.3±12.1	62.9±13.1	57.9±10.7	NS
HR (bpm)	63.4±10.6	62.5±9.94	64.2±13.5	60.5±8.65	68.7±8.63	NS

Continuous BP was recorded by a wearable tonometric BP monitor and HR by a 3-electrode biological monitor for 30 min. After deriving SBP (maximum BP), mean BP, DBP (minimum BP) and HR in every beat, means of

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beat-by-beat BP (SBP, mean BP and DBP) and HR for 30 min were estimated. Values are expressed as mean ± SD. One-way factorial ANOVA was used for comparison among four groups.

BP, blood pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; SD, standard deviation; ANOVA, analysis of variance.
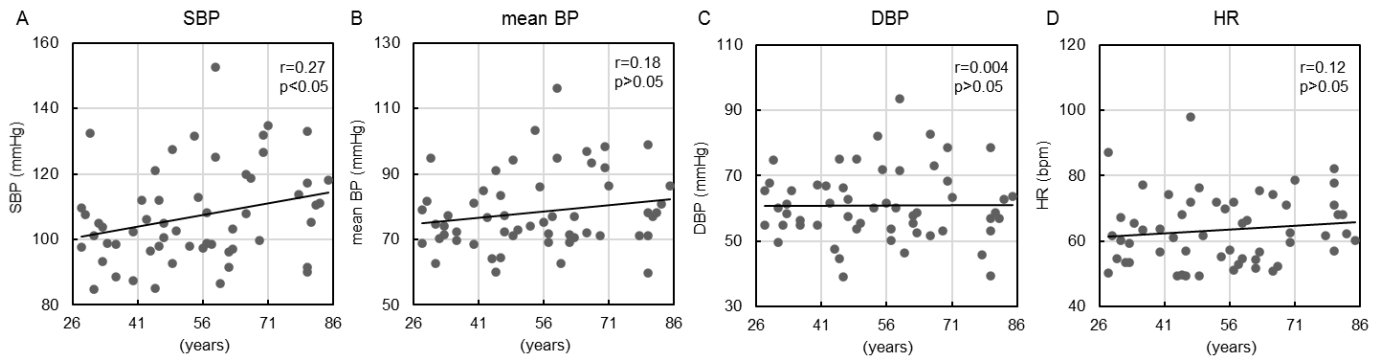

Fig 2 - 5. Impact of aging on averaged BP and HR from 30-min continuous recordings

Impact of aging on averaged BP and HR obtained from 30-min continuous recordings.

Scatter plots of individual data for the relationship of age versus SBP, mean BP, DBP and HR analyzed by Pearson's correlation coefficient (r). Straight lines indicate linear regression lines. Continuous BP was recorded by a wearable tonometric BP monitor and HR by a 3-electrode biological monitor for 30 min. After deriving SBP (maximum BP), mean BP, DBP (minimum BP) and HR in every beat, means of beat-by-beat BP (SBP, mean BP, and DBP) and HR were estimated for 30 min.

BP, blood pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
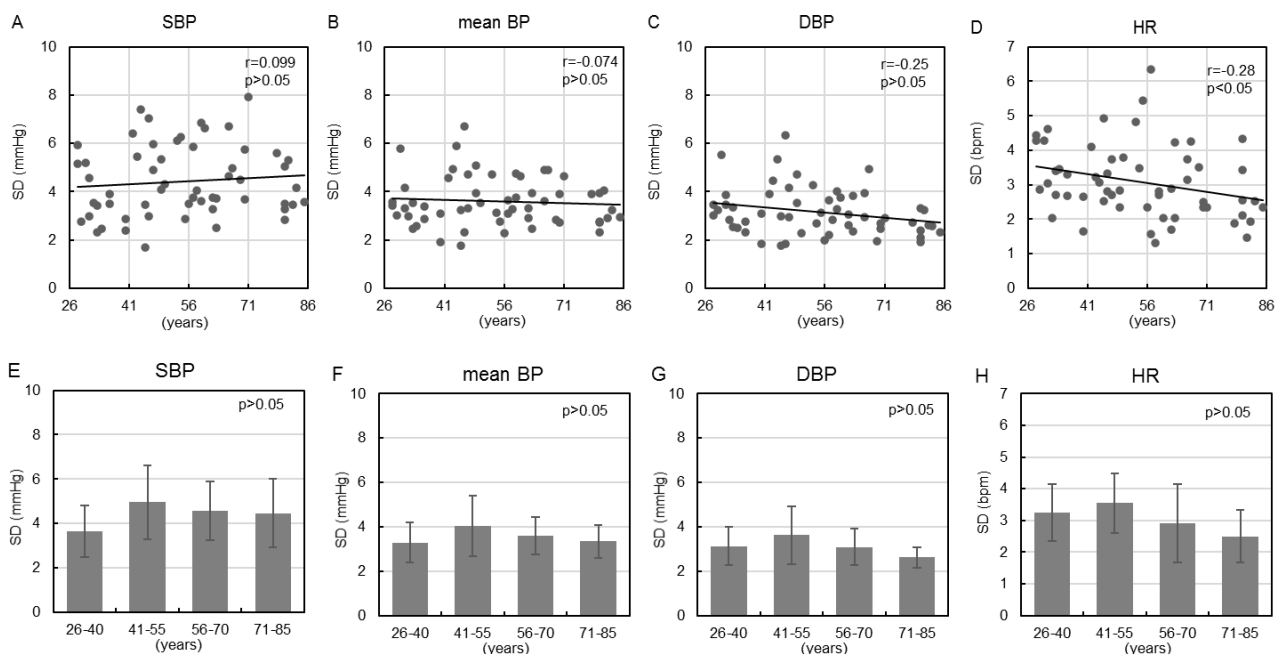

Fig 2 - 6. Impact of aging on BPV and HRV in the time domain expressed by SD.

The relationship between age and BPVs or HRV in the time domain expressed by SD. Individual data (A-D) and group data (E-H). I calculated SDs of beat-by-beat SBP, mean BP, DBP, and HR. Upper panels represent the

individual plot of the relationship between age and BPV and HRV analyzing by Pearson's correlation coefficient (r). Straight lines indicate linear regression lines. Lower panels represent the comparison of BPV and HRV among four age groups analyzing by the one-way factorial ANOVA.

BPV, blood pressure variability; HRV, heart rate variability; SBP, systolic blood pressure; BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SD, standard deviations; ANOVA, analysis of variance.

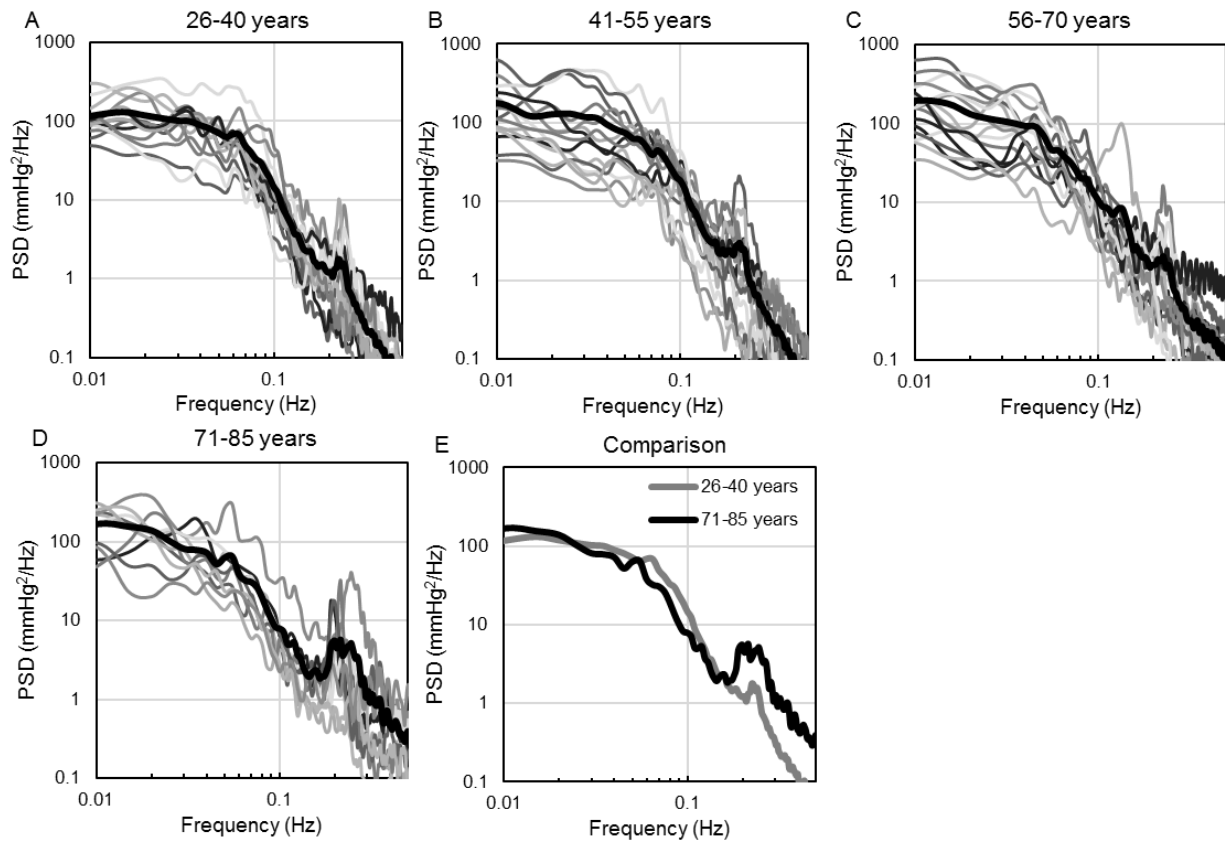**Fig 2 - 7. The PSD estimated from 30-min tonometric continuous BP recordings in each age group.**

(A-D): Individual (fine lines) and mean PSD (bold line) estimated from 30-min continuous BP recordings. (E): Comparison of mean PSD between the 26-40 and 71-85 age groups. The slope of PSD between 0.01 and 0.1 Hz was steeper in the 71-85 age group than in the 26-40 age group.

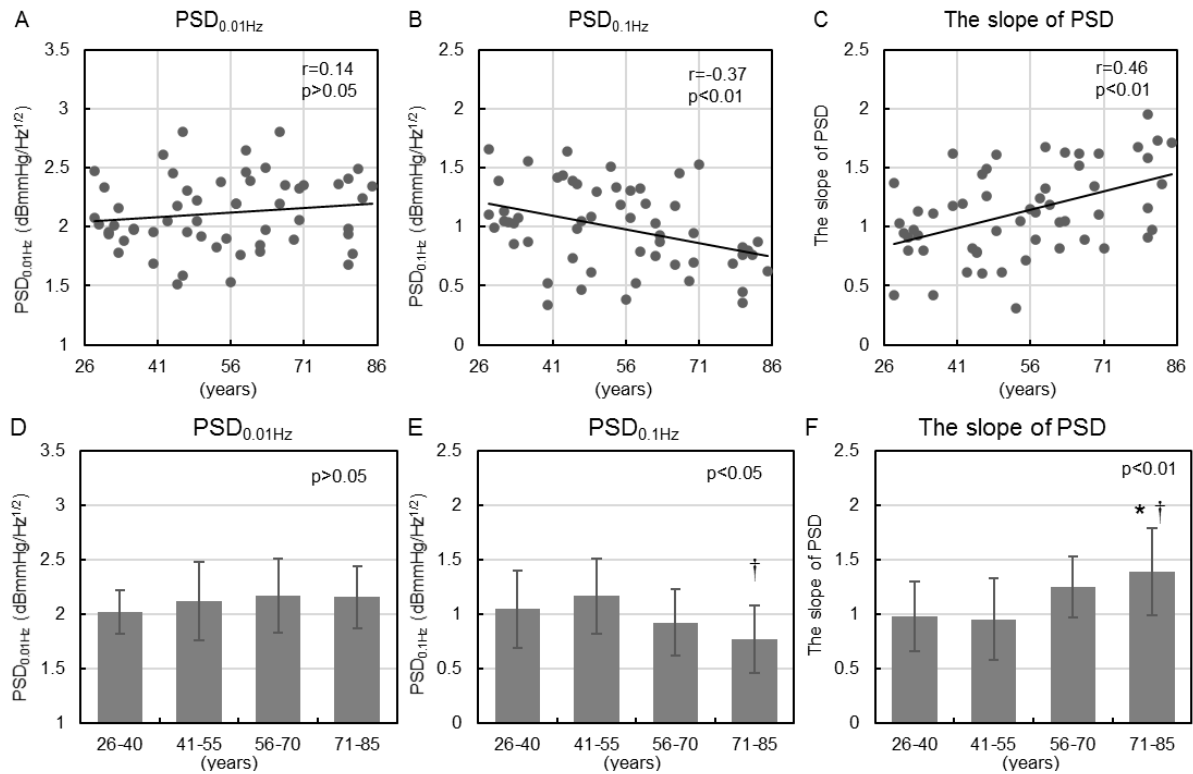PSD, power spectrum density; BP, blood pressure.

Fig 2 - 8. Relationship of age with PSD characteristics.

(A-C): Scatter plots of individual data for the relationship between age and PSD characteristics. Straight lines indicate linear regression lines. Pearson correlation coefficient (r) was used to assess the goodness of fit of the linear regression. (D-F): Age group comparison of PSD characteristics. One-way factorial ANOVA followed by the Tukey-Kramer test was used to compare the relationship among four age groups. Data are shown as mean ± SD. The slope of PSD between 0.01 to 0.1 Hz correlated significantly with age. *p < 0.05 versus 26-40 age group. †p < 0.05 versus 41-55 age group.

PSD, power spectrum density; ANOVA, analysis of variance; SD, standard deviations.

Table 2 - 3. Impact of gender on baseline characteristics and BP.

	Total	Age groups (years)											
		26-40			41-55			56-70			71-85		
		M	F	p	M	F	p	M	F	p	M	F	p
No. of subject	56	5	9	-	7	8	-	10	7	-	5	5	-
Age (years)	54.3 ±16.9	30.6 ±2.79	34.2 ±3.99	p< 0.05	48.0 ±4.58	47.4 ±3.62	NS	62.7 ±5.10	62.4 ±4.47	NS	78.8 ±4.76	81.2 ±2.17	NS
BMI (kg/m²)	21.1 ±3.23	22.2 ±4.32	18.8 ±2.19	p< 0.05	21.5 ±4.65	19.8 ±1.33	NS	23.1 ±2.65	20.4 ±3.54	p< 0.05	23.6 ±1.66	20.6 ±2.49	p< 0.05
SBP (mmHg)	111.7 ±12.6	107.8 ±10.9	98.9 ±5.47	p< 0.05	114.4 ±10.3	107.6 ±9.53	NS	116.2 ±13.5	108.6 ±12.6	NS	126.2 ±8.56	122.6 ±8.40	NS
DBP	66.6	62.9	58.2	p<	72.0	63.6	p<	71.7	62.8	p<	74.3	70.0	NS

| (mmHg) | ±9.24 | ±5.10 | ±2.60 | 0.05 | ±7.76 | ±9.35 | 0.05 | ±11.6 | ±5.78 | 0.05 | ±7.51 | ±7.57 | |

Values are expressed as mean ± SD. Student's t-test were used to compare between males and females in each age group. BMI, SBP and DBP in males of 26-40 age group were significantly higher than those in females of the corresponding age groups.

M, male; F, female; BP, blood pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; SD, standard deviation.
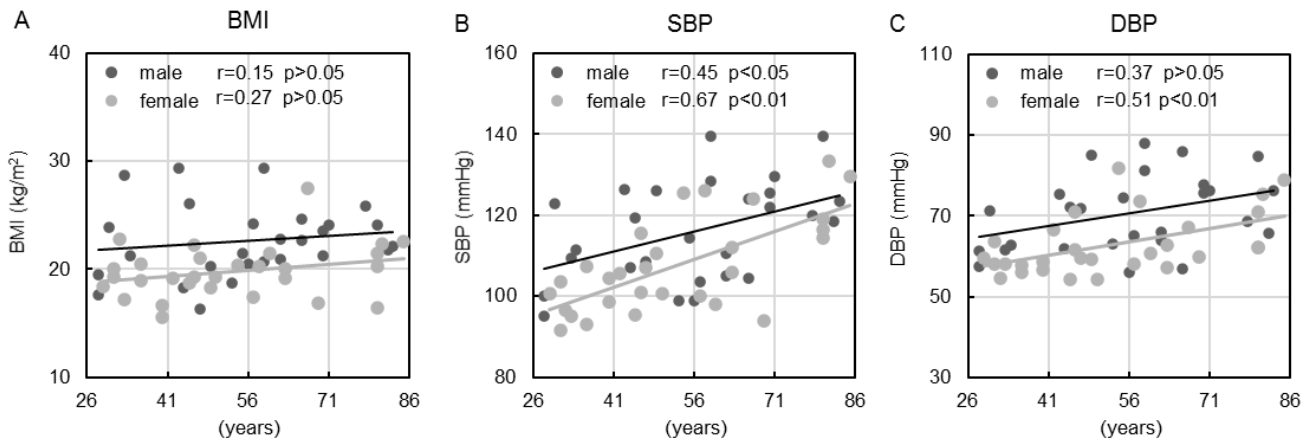
Fig 2 - 9. Impact of gender on baseline characteristics and BP.

Scatter plots of individual data for the relationship of age versus BMI, SBP and DBP analyzed by Pearson's correlation coefficient (r) for males and females. Straight lines indicate linear regression lines. SBP and DBP were measured by an oscillometric BP monitor. The SBP and DBP values were obtained by averaging oscillometric BP before and after the 30-min continuous BP recording.

BP, blood pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
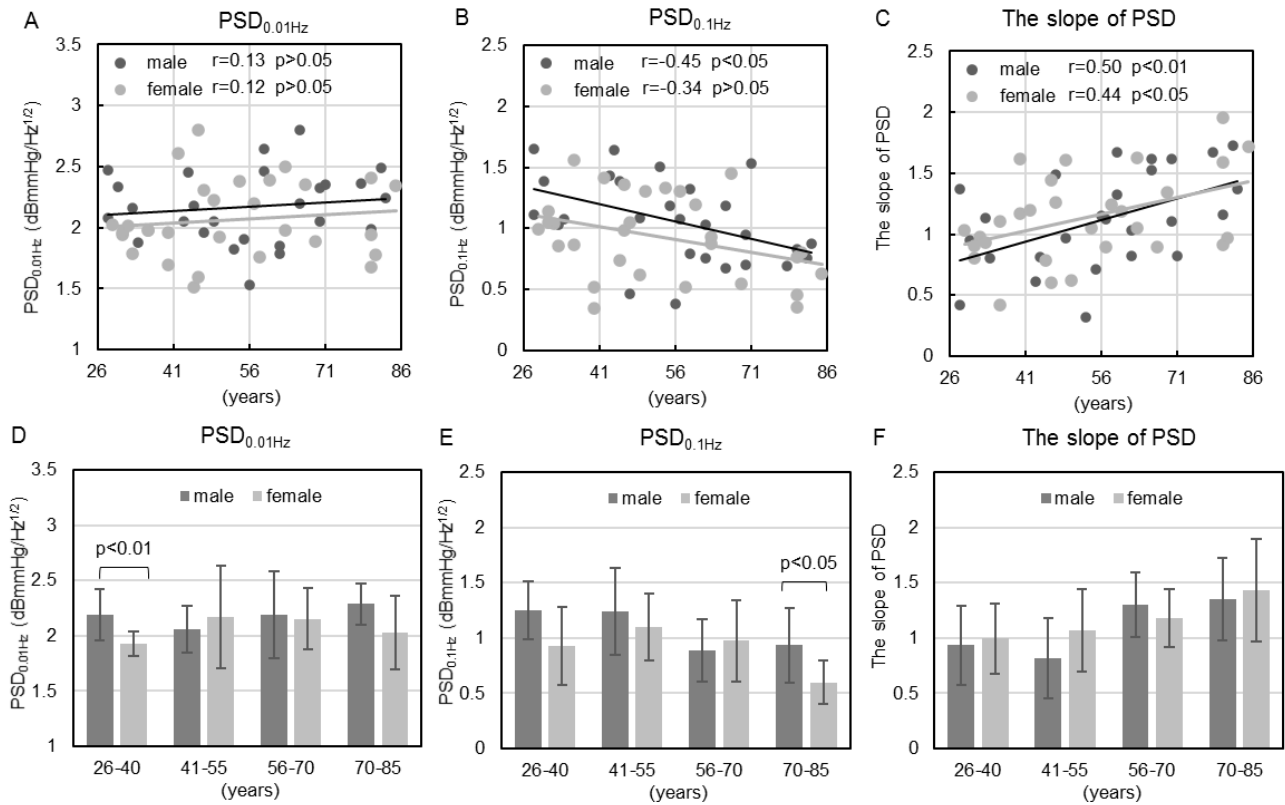
Fig 2 - 10. Impact of gender on characteristics of PSD of BP.

(A-C): Scatter plots of individual data for the relationship between age and PSD characteristics for males and females. Straight lines indicate linear regression lines. Pearson correlation coefficient (r) was used to assess the goodness-of-fit of the linear regression. (D-F): Age group comparison of PSD characteristics for males and females. Student's t-test was used to compare males and females in each age group. Data are shown as mean ± SD. $PSD_{0.01Hz}$ in males of 26-40 age group and $PSD_{0.1Hz}$ in males of 71-85 age group were significantly higher than those in females of the corresponding age groups (D and E). The trend in the slope of PSD did not differ between males and females (F).

PSD, power spectrum density; SD, standard deviations.

2.4 Conclusion

The PSD analysis of 30-min continuous BP recording characterized the very short-term BPV in healthy human subjects. Aging steepened the slope of PSD of BP without changing the magnitude of BPV. Aging-related baroreflex impairment may contribute to the increase in the slope of PSD of BP.

3. Comparison the slope of PSD with the related existing indices in healthy human subjects.

3.1 Introduction

As mentioned above, the slope of PSD by frequency analysis from very short-term continuous BP recording may evaluate aging-related baroreflex impairment.

BRS has been extensively used for assessing baroreflex function in clinical settings [25, 26]. BRS is a HR response to BP change in the closed-loop condition.

The usefulness of frequency analysis of biological data for the stratification of cardiovascular patients is also well known. The LF (0.04-0.15 Hz) of SBP is known as an index of sympathetic modulation directed to the vessels [13]. The HF (0.15 - 0.4 Hz) of HRV is reported to reflect the vagal nerve modulated HR change by respiratory fluctuation [12]. In addition, the LF/HF ratio of HRV reflects sympatho-vagal balance or the activation of sympathetic nervous system [12].

3.2 Materials and Methods

Continuous BP Analysis

Chapter 2 study data was used in this study. Beat-by-beat SBP from continuous tonometric BP and RR intervals from ECG were derived as in chapter 2.

BRS was assessed using the sequence method [27]. BRS was calculated from the slope of linear regression plots of SBP versus RR interval on spontaneous sequences, in which SBP and RR interval concurrently increase (up sequences) or decrease (down sequences) for three or more consecutive beats.

PSD of SBP was estimated from 30-min beat-by-beat SBP by frequency analysis as in chapter 2. LF of SBP was calculated as integral absolute PSD of SBP from 0.04 to 0.15 Hz.

As HRV, PSD of RR interval also were assessed from 30-min beat-by-beat RR intervals. LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz) of HRV were calculated as integral absolute PSD of RR interval. LF/HF of HRV was assessed as ratio between LF and HF.

Statistical Analysis

I performed statistical analyses using commercially available software (BellCurve for Excel version 3.21, Social Survey Research Information Co., Ltd., Tokyo, Japan). I used Pearson correlation coefficients to assess the relationship of each measurement variable with age and the slope of PSD. I divided the subjects into four age groups: 26-40, 41-55, 56-70 and 71-85 years. I compared all age groups by one-way factorial ANOVA followed by the Tukey-Kramer test. We considered differences to be statistically significant at $p < 0.05$.

3.3 Results

Relationship between age, BRS, and the slope of PSD

Figure 3-1 demonstrates the relationship between age and BRS, and the relationship between the slope of PSD and BRS. Figure 3-1A shows the scatter plot of individual data between age and BRS. Figure 3-1B compares BRS among the four age groups. BRS correlated significantly with age and tended to decrease as age increases (Fig 3-1A). BRS was significantly smaller in the 71-85 age group than in the 26-40 and 41-55 age groups (Fig 3-1B). On the other hand, BRS did not correlate significantly with the slope of PSD (Fig 3-1C).

Relationship between age, LF of SBP, and the slope of PSD

Figure 3-2 demonstrates the relationship between age and LF of SBP, and the relationship between the slope of PSD and LF of SBP. Figure 3-2A shows the scatter plot of individual data between age and LF of

SBP. Figure 3-2B compares LF of SBP among the four age groups. In our cohort, the LF of SBP did not significantly change with age (Fig 3-2A). Figure 3-2C shows the scatter plot of individual data between the slope of PSD and LF of SBP. LF of SBP did not correlate significantly with the slope of PSD (Fig 3-2C).

Relationship between age, HRV in frequency domain, and the slope of PSD

As HRV, PSD of RR interval were assessed from ECG for 30 min. Figure 3-3 demonstrates the relationship between age and HRV (LF, HF, LF/HF), and the relationship between the slope of PSD and HRV. Figure 3-3A shows the scatter plot of individual data between age and HRV. Figure 3-3B compares HRV among the four age groups. In this study, LF and HF of HRV was slightly smaller in the 71-85 age group than in the younger age groups (Fig 3-3B). Figure 3-3C shows the scatter plot of individual data between the slope of PSD and the HRV. HRV did not correlate significantly with the slope of PSD (Fig 3-3C).
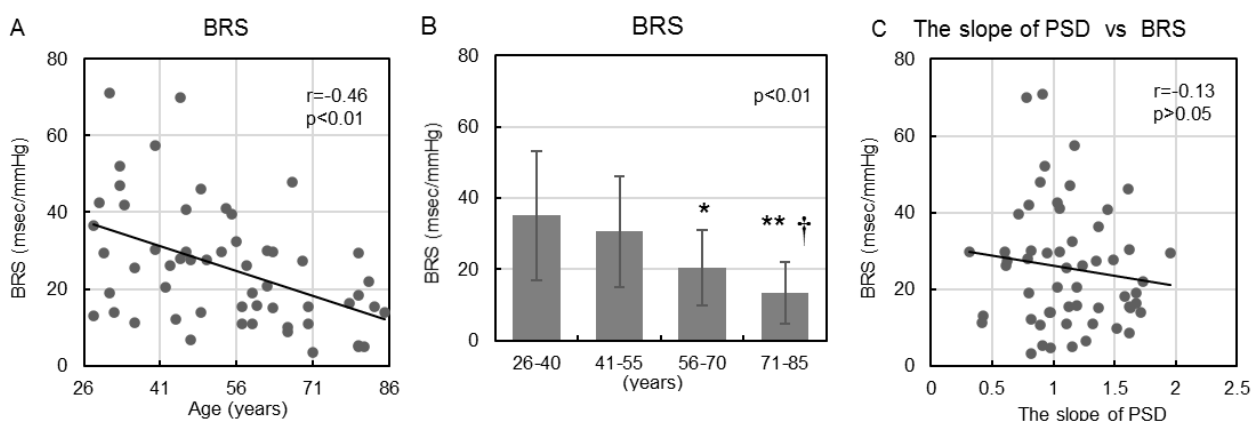

Fig 3 - 1. Relationship between age, BRS, and the slope of PSD.

(A): Scatter plot of individual data for the relationship between age and BRS. Straight line indicates linear regression line. Pearson correlation coefficient (r) was used to assess the goodness-of-fit of the linear regression. (B): Age group comparison of BRS. One-way factorial ANOVA followed by Tukey-Kramer test was used to compare the relationship among four age groups. Data are shown as mean ± SD. (C): Scatter plot of individual data for the relationship between the slope of PSD and BRS. BRS did not correlate significantly with the slope of PSD. *p < 0.05 versus 26-40 age group. **p < 0.01 versus 26-40 age group. †p < 0.05 versus 41-55 age group. BRS, baroreflex sensitivity; PSD, power spectrum density; ANOVA, analysis of variance; SD, standard deviations.
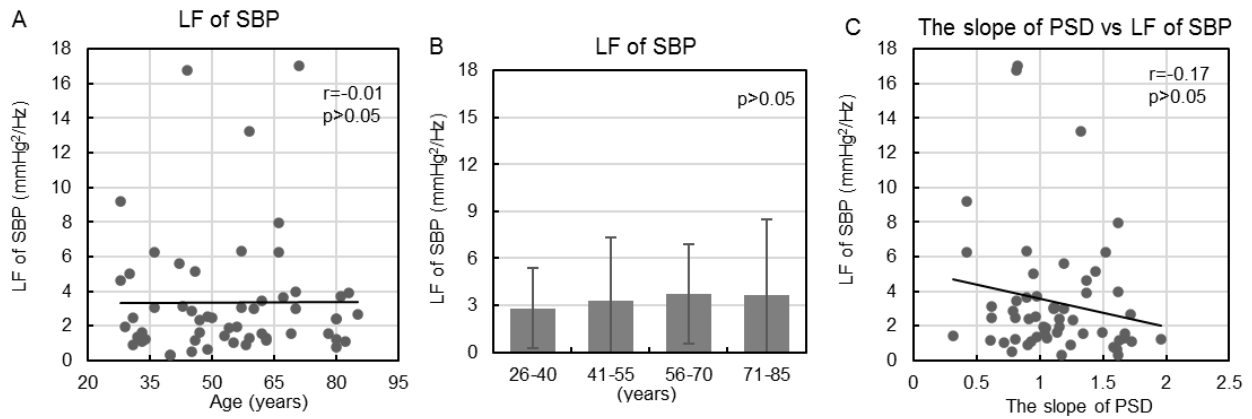
Fig 3 - 2. Relationship between age, LF of SBP, and the slope of PSD.

(A): Scatter plot of individual data for the relationship between age and LF of SBP. Straight line indicates linear regression line. Pearson correlation coefficient (r) was used to assess the goodness-of-fit of the linear regression. (B): Age group comparison of LF of SBP. One-way factorial ANOVA followed by Tukey-Kramer test was used to compare the relationship among four age groups. Data are shown as mean ± SD. (C): Scatter plot of individual data for the relationship between the slope of PSD and LF of SBP. LF of SBP did not correlate significantly with the slope of PSD. *p < 0.05 versus 26-40 age group. **p < 0.01 versus 26-40 age group. †p < 0.05 versus 41-55 age group.

LF, low frequency; SBP, systolic blood pressure; PSD, power spectrum density; ANOVA, analysis of variance; SD, standard deviations.
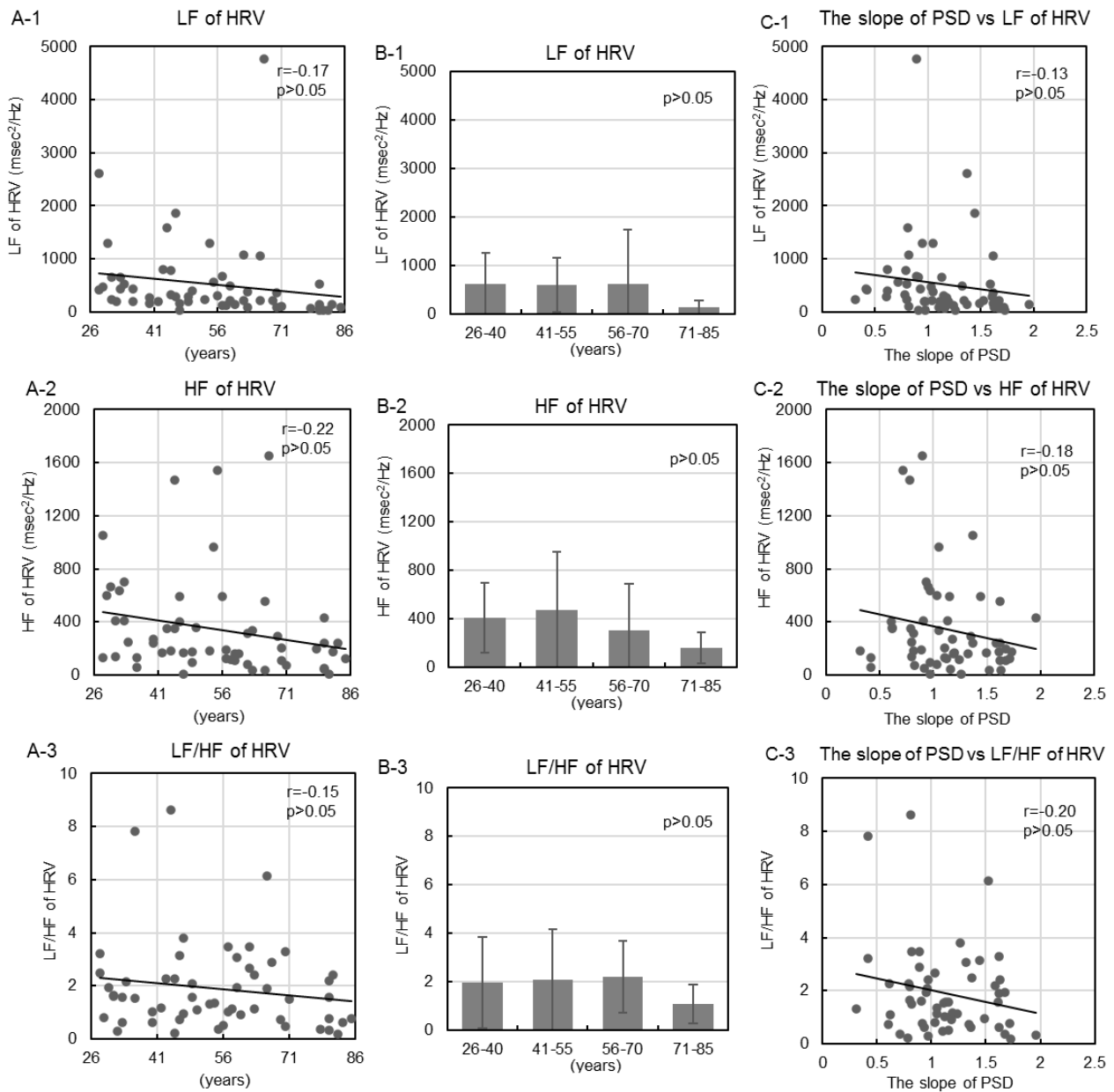
Fig 3 - 3. Relationship between age, HRV in frequency domain, and the slope of PSD.

As HRV, PSD of RR interval were assessed from ECG for 30 min.

(A-1, A-2, A-3): Scatter plot of individual data for the relationship between age and HRV (A-1: LF, A-2: HF, A-3: LF/HF). Straight line indicates linear regression line. Pearson correlation coefficient (r) was used to assess the goodness-of-fit of the linear regression.

(B-1, B-2, B-3): Age group comparison of HRV (B-1: LF, B-2: HF, B-3: LF/HF). One-way factorial ANOVA followed by Tukey-Kramer test was used to compare the relationship among four age groups. Data are shown as mean ± SD. LF and HF of HRV was slightly smaller in the 71-85 age group than in the younger age groups.

(C-1, C-2, C-3): Scatter plot of individual data for the relationship between the slope of PSD and HRV (C-1: LF, C-2: HF, C-3: LF/HF). HRV did not correlate significantly with the slope of PSD.

*p < 0.05 versus 26-40 age group. **p < 0.01 versus 26-40 age group. †p < 0.05 versus 41-55 age group.

LF, low frequency; HF, high frequency; HRV, heart rate variability; PSD, power spectrum density; ANOVA, analysis of variance; SD, standard deviations.

3.4 Conclusion

The slope of PSD did not correlate with BRS, LF of SBP and HRV, which are well-known noninvasive induces estimated from continuous biological data for the stratification of cardiovascular patients. The slope of PSD could assess damaged circulatory system that is different from those assessed by these existing indicators.

4. Discussion

This study aimed to investigate in healthy human subjects the very short-term BPV focusing on the baroreflex operating frequency range between 0.01 and 0.1 Hz. Major findings of this study include: (1) we can stably estimate PSD of BP from 30-min continuous BP recording in the baroreflex operating frequency range; (2) PSD of BP showed low-pass filter characteristics; (3) aging significantly steepened the slope of PSD of BP; (4) aging did not alter SD of BP time series, which indicate BPV in the time domain; (5) the slope of PSD of BP did not significantly correlate with BRS and HRV.

Characteristics of PSD estimated from 30-min continuous BP recording in humans

The PSD of BP in healthy human subjects was nearly flat around 0.01 Hz and decreased gradually with the increase in frequency. Previous study reported that the PSD in rats decreased with the increase in frequency with an inflection point at around 0.1 Hz [21]. In both humans and rats, PSD of BP decreased in the frequency range between 0.01 to 0.1 Hz. However, the precise shape of the PSD differs between the two species, especially the flatness around 0.01 Hz in humans and the inflection point at around 0.1 Hz in rats. Since the baroreflex dynamic function, which is the major regulator of BPV in the frequency range of 0.01 to 0.1 Hz, is similar in various animal species [19, 20, 28], I speculate that factors such as the effect of respiration on BP and neural disturbance may contribute to the differences in the shape of the PSD of BP. Further investigation is needed to characterize the PSD of BP in humans.

The PSD analysis of continuous BP recording provides insight into how BPV relates to autonomic regulation. Castiglioni et al. [29] reported that PSD between 0.0001 and 0.1 Hz exhibited low-pass filter characteristics in human subjects. My observation is consistent with the previous report that showed the frequency-dependent attenuation of PSD in humans. To characterize baroreflex-regulated BPV, I focused on the PSD in the frequency range above 0.01 Hz.

Impact of impaired baroreflex on characteristics of PSD of BP

I chose 0.01 to 0.1 Hz as baroreflex operating frequency range because previous studies in various animal species indicate that baroreflex has low-pass characteristics with the cutoff frequency at around 0.05 Hz [19, 20]. I focused on the sympathetic baroreflex, which regulate BPV via sympathetic nerve. In human studies about frequency analysis of HR and SBP data, LF component (0.04-0.15 Hz) was reported to include sympathetic activity [12, 13]. Therefore, even in humans, the baroreflex operating frequency range might be almost same for as other animal species. The baroreflex could not operate above 0.1 Hz and fully operates at 0.01 Hz, thereby the baroreflex strongly attenuates BPV at around 0.01 Hz. Therefore, the PSD analysis of BP in the baroreflex frequency range would reflect the baroreflex modulated BPV.

Mannoji et al. [21] reported that a decrease in baroreflex total loop gain increases the slope of PSD of BP in the frequency range between 0.01 and 0.1 Hz in rats. Rienzo et al. [55] also reported that impaired baroreflex increases the slope of PSD of BP in cats. The slope of PSD in healthy rats and cats was about 1, which was almost the same as that in younger human subjects (55 years or younger) in this study. The slope of PSD in rats and cats with baroreflex dysfunction was about 2, which was steeper than that in older human subjects (71-85 age group) in this study.

In human, Conci et al. [30] reported that brain death steepened the slope of PSD of BP, indicating compromised autonomic regulation of BPV. Omboni et al. [31] reported that the slope of PSD of BP was higher in patients with autonomic dysfunction than in healthy subjects. These findings indicate that the slope of PSD of BP in the frequency range of 0.01 to 0.1 Hz closely reflects the underlying baroreflex function. The slope of PSD in brain death was about 1.6. The slope of PSD in patients with autonomic dysfunction was about 1.4, which was almost the same as that in elderly people (71-85 age group) in this study.

Impact of aging on characteristics of PSD of BP

To evaluate the clinical utility of PSD analysis of 30-min continuous BP recording, I examined the relationship of PSD with aging. It is well known that aging impairs baroreflex function, one of the most powerful mechanisms in regulating BPV. Omboni al. [31] also reported that PSD of BP in older subjects showed lower power at around 0.1 Hz and higher power between 0.02 and 0.07 Hz, compared to younger subjects. Orthostatic hypotension and postprandial hypotension are common pathophysiology in older people [32, 33, 34], and aging-related autonomic dysfunction could play a significant role in worsening hypotension. Aging-related atherosclerosis and reduced arterial distensibility may blunt the baroreflex afferent loop function and result in baroreflex dysfunction [35]. Interestingly, only the frequency domain analysis of BP recording can detect the alteration of BPV with aging.

In this study, I found no significant correlation between age and SD of BP, indicating that aging does not significantly alter BPV in healthy subjects. $PSD_{0.01Hz}$ did not change significantly with age, while $PSD_{0.1Hz}$ was significantly reduced in older subjects. Since PSD is the Fourier transform of the variance of BP time series, integrated PSD is proportional to BP variance in this frequency range. Berry et al. [36] reported that ABPM-assessed BPV decreased in heart failure patients. Mannoji et al. reported that left ventricular dysfunction induced by myocardial infarction decreased integrated PSD above 0.01 Hz [21]. Thus, I need to interpret the amount of BPV carefully considering cardiac function, especially when evaluating patients with depressed cardiac function.

The renin-angiotensin-aldosterone system (RAAS) may also regulate BPV strongly. In older people, the secretion of aldosterone increases, while the renin activity decreases. This results in a blunted ability to secrete aldosterone against changes in renal blood flow, such as in sodium restriction [39]. Hence, RAAS dysregulation in older people worsens hormonal BP regulation and increases BPV. In addition, inadequate RAAS activation also increases BP and deteriorates baroreflex function through activation of sympathetic nerve activity [40]. Therefore, age-related RAAS dysregulation may steepen the slope of PSD in older subjects. Further investigations may be needed to deepen the understanding of age-related alteration of very short-term BPV in terms of RAAS regulation.

Difference of the slope of PSD with the related existing indices

BRS is a useful method for the estimation of baroreflex function. Tank et al. [37] and Boettger et al. [38] reported that BRS was significantly lower in older than in younger subjects. As shown in Fig. 3-1, BRS clearly decreased in an age-dependent manner, while there was no correlation between BRS and the slope of PSD.

Baroreflex includes sympathetic baroreflex via the sympathetic nerve and the vagal baroreflex via vagal nerve. Sakamoto et al. [56] reported that sympathetic nerve activity regulated BP in vascular properties (resistance and stressed blood volume) and ventricular properties (end-systolic elastance and HR), however ventricular properties strongly contribute to BP regulation. In this study, I focused on the sympathetic baroreflex. On the other hand, vagal nerve activity mainly contributes to ventricular properties. BRS is a HR response to BP change and partially reflects the vagal baroreflex. The slope of PSD is not equal to BRS. Further investigations may be needed to clarify the difference in the major determinant of age-related changes in BRS and the slope of PSD.

HRV (LF, HF, LF/HF) and LF of SBP are well known as index by frequency analysis of biological data. Lepsitz et al. [57] reported that marked reductions occurred in LF and HF of HRV in old compared with young subjects. As shown in Fig. 3-3 B1 and B2, LF and HF of HRV was slightly smaller in the 71-85 age group than in the 26-40 age groups. On the other hand, there was no correlation of HRV and LF of SBP with the slope of PSD.

The LF of SBP and The LF of HRV are known as an index of sympathetic modulation [12, 13]. The HF of HRV is also known as index of the vagal nerve modulation [12]. As mentioned above, the slope of PSD may reflect baroreflex function via the sympathetic nerve. In addition to the sympathetic nerve activity, the baroreflex function is affected by the baroreceptor and the cardiovascular function. The slope of PSD is associated with, but not equal to, HRV and LF of SBP.

Recording time and device for clinical application of very short-term BPV analysis

In this study, I recorded continuous BP for 30 min and estimated the PSD in the baroreflex operating frequency range. The PSD analysis enables us not only to estimate BPV from the very short-term data but also characterize the BPV regulatory system, the baroreflex system. As mentioned above, BPV is conventionally evaluated by oscillometric devices. Since 24-h ABPM and visit-to-visit BP study assess the variability of intermittent BP measurements, these methods cannot address the frequency characteristics of BPV in the baroreflex operating frequency range. In addition, these methods require long-term device attachment (at least during the night) or a prolonged period of observation (at least three visits), which pose a burden on patients. My proposed method has the potential as a novel measurement of BPV because it is noninvasive, and the recording time is only 30 min. The PSD analysis makes it possible to stratify BPV considering the BPV regulatory system.

The clinical application of the PSD method requires further investigation. Although the PSD evaluation of BPV requires much shorter time of BP recordings, the 30-min BP recording remains too long as a clinical tool in routine patient care. Thus, I need to develop a novel algorithm to estimate PSD of BP from shorter (such as 5-min) BP recordings without losing the accuracy of PSD estimation.

Although the very short-term BPV analysis has the potential for stratifying the cardiovascular risk as shown by several animal studies, the predictive power is not as high as daily BPV assessed by 24-h ABPM. The major reason for the lower predictive power of very short-term BPV may be the lack of clinical evidence [41, 42]. Since the very short-term BPV analysis requires continuous BP measurement devices, the development of those devices will change this situation. In this study, I recorded continuous BP noninvasively using an in-house developed wearable wrist-type BP monitor based on arterial tonometry [10, 23]. My algorithm of BPV analysis can be applied to any continuous BP recording system. Recently, the field of continuous BP monitor is developing rapidly due to the increasing demand for high-performance healthcare devices and optimal patient management [43]. The volume clamp method (FMS-Finapres Medical System, Arnhem, the Netherlands; CNSystems Medizintechnik AG, Graz, Austria), which can capture instantaneous BP waveform at the finger, has been used for recording continuous BP in clinical settings [44]. As for cuffless continuous noninvasive BP monitors, the Visi Mobile System (Sotera Wireless, CA, USA) based on the pulse transit time method has been shown to provide acceptable BP recording during the long-term attachment [45]. Similar wearable devices such as Caretaker (Caretaker Medical LLC, VA, USA) and BB-613 (Biobeat Technologies LTD, Israel) have been approved as medical devices in the US. With such diverse device development, translation of our method to clinical application would be rather soon.

5. Limitations

There are several limitations to this study. First, the number of subjects included in this study was relatively small, thus limiting statistical power. In addition, individual variation of PSD of BP was observed in each age group. This variation makes detailed analysis of PSD difficult. Thus, I need to investigate a larger number of healthy subjects to further understand the PSD of BP.

Second, I conjectured that the slope of PSD of BP reflects aging-induced baroreflex failure. Thus, I need to compare the baroreflex function by direct measurement to the data obtained by my proposed method. In addition, autonomic challenges such as cold pressure test, handgrip stress and vasoactive drug administration may deepen the understanding of autonomic function including baroreflex. However, I focused on very short-term BPV with a clinically applicable protocol without using such intervention. Further investigations are also needed to address this issue.

Lastly, the ultimate goal of this study is to derive indices from the PSD of BP for clinical risk stratification. As the first step to achieve this goal, I excluded patients with cardiovascular diseases in this study. In the next step, I need to clarify the significance of PSD-derived indices in patients with cardiovascular diseases, especially hypertension.

6. Future works

In this study, I proposed a new method to stratify BPV considering the BPV regulatory system by frequency analysis from short-term continuous BP recording. Next, my method requires proposal of clinical application and further investigation.

There are clinical applications for both rise and drop in BP associated with impaired baroreflex, which regulate BPV over 24 hrs. Rapid BP rise with baroreflex dysfunction in hypertension patients would trigger a cardiovascular disease event. With the developed method, it is possible to extract hypertension patients with higher risk. The problem with the clinical application of my method is that there is no treatment for impaired baroreflex. However, in current management of hypertension, mild hypertension patients take lifestyle modification without antihypertensive drug therapy. Mild hypertension patients with impaired baroreflex might ought to be taken drug therapy early.

In regard to clinical applications for drop in BP associated with impaired baroreflex, proposed method could extract hypotension patients at risk of falling/fracture. The patients are ought to pay attention to the drop in BP due to changes in posture and temperature. Furthermore, they should avoid reinforced antihypertensive drug therapy.

Research on treatment methods for impaired baroreflex is underway. Once the treatment methods are established, my proposed method can be used as a diagnostic criterion for adaptors.

7. Conclusive remarks

In healthy subjects, I recorded continuous BP for 30 min by noninvasive wearable device and estimated the PSD in the baroreflex operating frequency range. The PSD of BP showed low-pass filter characteristics as with previous rat studies. As the first step to develop new indices for assessing BP regulatory system, I evaluated the impact of aging on PSD characteristics. Aging steepened the slope of PSD of BP between 0.01 and 0.1 Hz, while aging did not significantly alter BPV in the time domain. This phenomenon may partly be related to the deterioration of the baroreflex in older subjects.

The slope of PSD did not significantly correlate with the existing index related to baroreflex function and index by frequency analysis of biological data. My proposed method to evaluate very short-term BPV may contribute to the new stratification of cardiovascular disease.

Research achievement

- The contents of chapter 2 were presented as: Mano J, Kinoshita H, Saku K, Mannoji H, Sunagawa K, Kanaya S. Aging Increases Blood Pressure Variability in the Operating Frequency Range of Baroreflex in Healthy Subjects. 84th Annual Scientific Meeting of the Japanese Circulation Society in 2020.
- The contents of chapter 2 and part of chapter 3 were published as: 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;16(3): 2021.

Acknowledgement

Competing interests

The wearable wrist-type tonometric BP monitor was a prototype device developed by Omron Healthcare Inc. ,which was institutionally approved for this clinical trial.

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