will still need to be developed for the evaluation of this group in future studies.

A variety of factors, including stroke events and other CVDs, as well as the progression of bone/joint diseases and dementia, contributes to disability among the elderly (*32*). The present study demonstrated for the first time that those elderly persons with a mean home SBP≥135 mmHg were susceptible to a loss of functional independence, even if they did not experience an event of symptomatic stroke. However, the present study did not reveal any direct mechanism to generate this relationship between hypertension reflected by the home BP monitoring value and a loss of independence. The relationships between hypertension or morning BP elevation and pathological conditions such as asymptomatic small infarctions and white matter lesions have previously been reported (*33–36*). It is thus possible that these lesions are related to BP elevation and may be involved in the impairment of functional abilities required for daily life. To clarify the association between home BP values, asymptomatic brain lesions, and disability among the very elderly, further study is warranted.

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BIOMEDICINE & PHARMACOTHERAPY
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Arterial stiffness independently predicts cardiovascular events in an elderly community – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

We investigated the predictive value of arterial stiffness to assess cardiovascular risk in elderly community-dwelling people by means of a multivariate Cox model. In 298 people older than 75 years (120 men and 178 women, average age: 79.6 years), brachial-ankle pulse wave velocity (baPWV) was measured between the right arm and ankle in a supine position. The LILAC study started on July 25, 2000, consultation was repeated yearly, and the last follow-up ended on November 30, 2004. During this follow-up span of 1227 days, there were nine cardiovascular deaths, the cause of death being myocardial infarction for two men and three women or stroke for two men and two women. In Cox proportional hazard models, baPWV as well as age, Mini-Mental State Examination (MMSE), Hasegawa Dementia Scale Revised (HDSR) and the low-frequency/high-frequency (LF/HF) ratio showed a statistically significant association with the occurrence of cardiovascular death. A two-point increase in MMSE and HDSR score significantly protected against cardiovascular death, the relative risk (RR) being 0.776 (P = 0.0369) and 0.753 (P = 0.0029), respectively. The LF/HF ratio also was significant (P = 0.025), but the other indices of HRV were not. After adjustment for age and HDSR, a 200 cm/s increase in baPWV was associated with a 30.2% increase in risk (RR = 1.302, 95% CI: 1.110–1.525), and a 500 cm/s increase in baPWV with a 93.3% increase in risk (RR = 1.933, 95% CI: 1.300–2.874, P = 0.0011), whereas the LF/HF ratio was no longer associated with a statistically significant increase in cardiovascular mortality. In elderly community-dwelling people, arterial stiffness measured by means of baPWV predicted the occurrence of cardiovascular death beyond the prediction provided by age, gender, blood pressure and cognitive functions. baPWV should be added to the cardiovascular assessment in various clinical settings, including field medical surveys and preventive screening. The early detection of risk

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by chronomics allows the timely institution of prophylactic measures, thereby shifting the focus from rehabilitation to prehabilitation medicine, as a public service to several Japanese towns.

Keywords: Pulse wave velocity; Cardiovascular risk; Cognitive function; Elderly community-dwelling people

1. Introduction

As the incidence of myocardial infarction has increased in Japan and since cardiovascular disease, including stroke is the leading cause of mortality and morbidity, the prevention of these conditions is a major goal. Atherosclerosis is an important cause of morbidity and mortality in the elderly, and arterial stiffness may predict cardiovascular events [1]. Several cardiovascular indices, such as blood pressure (BP), heart rate (HR) and heart rate variability (HRV) are predictors of vascular disease risk [2]. This study aimed at assessing their role in association with arterial stiffness in predicting cardiovascular mortality. Arterial stiffness can be assessed non-invasively by measuring pulse wave velocity (PWV), which is a simple and reproducible endpoint.

Recent cohort studies suggested that PWV might be a strong predictor of atherosclerotic cardiovascular events, cardiovascular mortality, and all-cause mortality, independently of age and conventional atherosclerotic risk factors [3–5]. Most studies, however, focused on patients of occidental ancestry, often affected by specific diseases, rather than on Japanese populations. In 2000, we began a community-based study to longitudinally investigate the longevity and aging of a rural population in Hokkaido County (LILAC), and to evaluate this population's neurocardiological function. Our goal was the prevention of cardiovascular events, including strokes and myocardial ischemic events, and to prevent the associated decline in cognitive function of the elderly in this community dwelling.

As the first step of the LILAC study, we focused on the relationship between aortic stiffness measured by PWV and cardiovascular mortality. We assessed the predictive value of arterial stiffness in predicting cardiovascular risk in an elderly population using a multivariate Cox model.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 people older than 75 years (average age, 79.6 years). BP was measured in a sitting position at the beginning of the study, and brachial-ankle PWV (baPWV) was measured between the right arm and ankle in a supine position, using an ABI/Form instrument (Nippon Colin Co., Ltd., Komaki, Japan). The baPWV was measured using a volume-plethysmographic method. ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the left edge of the sternum, and cuffs were wrapped on both arms and ankles. The cuffs were connected to a plethysmographic sensor that determines the volume pulse form and oscillometric pressure waveforms were recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV was set at 1200 Hz). baPWV was measured in duplicate after at least a 5-min rest in each case. Only baPWV measures from participants showing an ankle/brachial pressure index (ABI) value above 0.90 were used for analysis.

We used the first hour of ambulatory ECG recording obtained during routine medical examinations conducted each year in July. The data were processed for HRV using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain measures (SDNN, pNN50, SDANN and Lorenz plot indices: Length (L), Width (W), and L/W ratio) and frequency-domain measures (spectral power in the "very low frequency"—VLF: 0.003–0.04 Hz, "low frequency"—LF: 0.04–0.15 Hz, and "high frequency"—HF: 0.15–0.40 Hz regions, and the LF/HF ratio) were determined. Except for SDNN and HR, calculated over the whole 1-h record, all indices were computed as averages over consecutive 5-min intervals. Spectral indices were obtained by the maximum entropy method (MEM) with the MemCalc/CHIRAM program (Suwa Trust Co., Ltd., Tokyo, Japan).

The Japanese versions of the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale Revised (HDSR) tests were used to measure the overall cognitive function, including verbal orientation, memory, and constructional ability (Kohs' block test). The Up and Go test measured, in seconds, the time it took the subject to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down again. This test is a simple measure of physical mobility and demonstrates the subject's balance, gait speed, and functional ability. A lower time score indicates better physical mobility. Functional Reach (FR), used to evaluate balance, represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. A higher score indicates better balance. Manual dexterity was assessed using a panel with combinations of 10 hooks, 10 big buttons, and five small buttons. There were three discrete measurements of time recorded for each participant (10 "hook-on"s, 10 big "button-on-and-off"s, and five small "button-on-and-off"s). The total manual dexterity time in seconds, defined as the button score (Button-S), was calculated by adding the average times for one hook-on and one big or small button-on-and-off. A lower button score indicates better manual dexterity.

2.2. Cardiovascular mortality

The LILAC study was started on July 25, 2000 and consultations were repeated every year (end of July, or beginning of August). In addition, one or two doctors of our team visited every 3 months and offered several kinds of health consultation, rehabilitation of disordered function, healthy lifestyle modification by promoting complete cessation of smoking, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake, as well as providing prescription advice to the local general medical practitioner.

In this investigation, the follow-up ended on November 30, 2004. During this follow-up span, there were nine cardiovascular deaths, the cause of death being myocardial infarction or stroke. Follow-up time was defined as the time elapsed between the first (reference) examination and the time of first cardiovascular event or death.

2.3. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). The effects of classic risk factors on baPWV were assessed by a multivariate regression analysis. We used Cox's regression analysis to calculate the unadjusted and adjusted relative risks (RRs) and 95% confidence intervals (CIs) for cardiovascular death. To identify independent predictors of cardiovascular death in relation to baPWV, we used a multivariate Cox regression analysis with stepwise selection. Variables included in the multivariate models were age, gender, BP, HR, HRV, MMSE, HDSR and Kohs' block test.

An abnormal value of baPWV (>2500 cm/sec) was independently assessed by logistic regression analysis. Kaplan–Meier event probability curves were computed with two groups, stratified by the abnormal value of baPWV, and the cumulative probability of events of two groups was compared by means of the log-rank test. Statistical significance was considered at a value of $P < 0.05$.

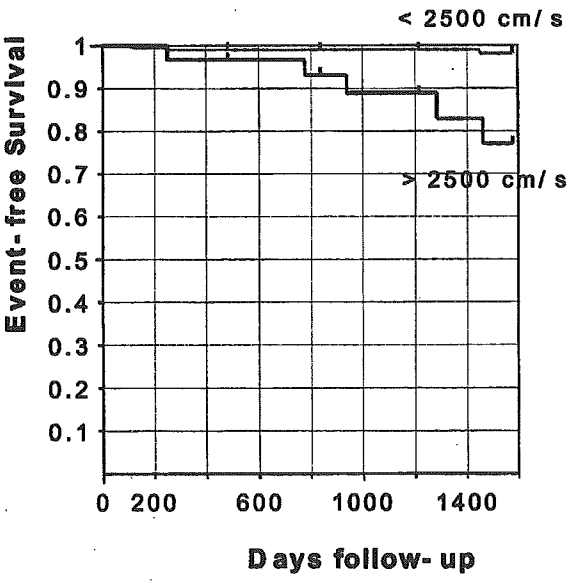

Fig. 1. Kaplan–Meier event probability curves for cardiovascular death.

3. Results

The characteristics of the 298 subjects at the start of study (reference) are given in Table 1. The sample comprises 120 men and 178 women. The mean age of participants at entry was 79.6 years. The mean follow-up time was 1227.2 days, during which 9 subjects died (myocardial infarction: 2 men and 3 women; stroke: two men and two women).

Out of the 298 participants, baPWV was measured in 245 subjects, and a baPWV above 2500 cm/s was observed in 33 subjects, five of whom died (three from a myocardial infarction and two from a stroke). Their reference characteristics are given in Table 2, which shows that an increased baPWV is associated with older age, higher systolic and diastolic BP, increased pulse pressure and shorter FR. Subjects with an increased value of baPWV included fewer event-free survivors. Kaplan–Meier curves for event-free survival revealed a significant difference between the two groups stratified by a baPWV of 2500 cm/s ($P < 0.00005$, log-rank test) (Fig. 1).

Among the variables used in Cox proportional hazard models, PWV as well as age, MMSE, HDSR and the LF/HF

Table 1
Reference characteristics of subjects

Endpoint	Mean	SD
Gender	0.403	
Age	79.0	4.75
BMI	23.4	3.74
SBP	141.2	19.56
DBP	75.5	10.57
PP	65.8	16.41
HR	70.8	11.46
PWV	2097	504.6
ABI	1.02	0.14
Up&Go	16.5	6.54
FR	25.6	7.77
Button	15.7	7.16
MMSE	24.2	4.43
HDSR	23.6	5.30
Kohs	19.1	11.17
GDS	4.8	2.96
VLF	912.3	743.3
LF	207.2	299.0
HF	102.7	250.3
LF/HF	2.84	1.70
pNN50	4.36	8.87
CVRR	5.04	1.95
RMSSD	22.6	12.5
SDNN	37.4	16.0

Gender: Man = 1, Woman = 0 (120 men and 178 women)

Table 2
Reference Characteristics of Subjects with Acceptable or Increased baPWV

Endpoint	$n = 212$ baPWV <2500		$n = 33$ baPWV >2500		t-value	p-value
	Mean	S.D.	Mean	S.D.		
Gender	0.396		0.424		0.304	N.S.
Age	78.7	4.39	80.4	4.54	2.045	0,0420
BMI	23.5	3.88	23.0	3.41	-0.722	N.S.
SBP	139.2	18.14	154.2	25.81	4.087	0,0001
DBP	74.3	9.82	79.6	14.33	2.635	0,0090
PP	64.9	15.80	74.7	18.66	3.158	0,0018
HR	70.1	11.24	72.5	12.77	1.090	N.S.
PWV	1949	292.0	3045	555.0	17.298	0,0000
ABI	1.03	0.12	0.99	0.17	-1.704	N.S.
Up&Go	16.1	6.36	17.5	6.77	1.128	N.S.
FR	26.2	7.66	22.5	7.64	-2.533	0,0120
Button	15.2	7.05	16.1	4.53	0.682	N.S.
MMSE	24.3	5.18	23.7	5.33	-0.827	N.S.
HDSR	24.0	5.18	22.6	5.13	-1.444	N.S.
Kohs	19.6	11.08	17.1	10.42	-1.177	N.S.
GDS	4.8	2.85	4.8	3.16	0.125	N.S.
VLF	938.7	788.5	738.6	440.9	-1.187	N.S.
LF	211.1	303.7	133.2	113.7	1.216	N.S.
HF	98.8	235.1	63.8	52.1	-0.711	N.S.
LF/HF	2.88	1.70	2.70	1.51	-0.482	N.S.
pNN50	4.28	8.24	2.70	3.68	-0.908	N.S.
CVRR	4.98	1.55	4.79	1.34	-0.571	N.S.
rMSSD	22.1	9.7	20.8	7.3	-0.624	N.S.
SDNN	37.7	16.2	33.3	9.8	-1.242	N.S.

Gender: Man = 1, Woman = 0.
Statistical significance of difference in PWV between the 2 groups validates classification.

Table 3
RR of CV Death in relation to PWV, HRV, Cognitive function and classic CV Risk factors

Endpoint	RR	95% CI	p-value
Gender			N.S.
Age (5)	1.859	1.008–3.427	0.0469
BMI			N.S.
SBP			N.S.
DBP			N.S.
PP			N.S.
HR			N.S.
PWV (200)	1.335	1.147–1.553	0.0002
PWV (500)	2.058	1.410–3.005	0.0002
PWV (200)*	1.302	1.110–1.525	0.0011
PWV (500)*	1.933	1.300–2.874	0.0011
ABI			N.S.
Up&Go			N.S.
FR			0.0696
Button			N.S.
MMSE (2)	0.776	0.612–0.985	0.0369
HDSR (2)	0.753	0.624–0.907	0.0029
Kohs			0.0991
GDS			N.S.
VLF			N.S.
LF			N.S.
HF			N.S.
LF/HF (0.20)	0.821	0.690–0.976	0.0255
pNN50			N.S.
CVRR			N.S.
RMSSD			N.S.
SDNN			N.S.

* After adjustment for age and HDSR

ratio were statistically significantly associated with the occurrence of cardiovascular death (Table 3). In univariate analyses, a 200 or 500 cm/s increase in baPWV was associated with a RR of cardiovascular death of 1.335 or 2.058, respectively ($P < 0.0002$). A two-point increase in MMSE and HDSR score significantly protected against cardiovascular death, being associated with RRs of 0.776 ($P = 0.0369$) and 0.753 ($P = 0.0029$), respectively. The LF/HF ratio also showed significant predictive value ($P = 0.025$), but other HRV indices did not.

In multivariate analyses, when both baPWV and age were used as continuous variables in the same model, baPWV remained statistically significantly associated with the occurrence of cardiovascular death. After adjustment for age and HDSR, a 200 cm/s increase in baPWV was associated with a 30.2% increase in risk (RR = 1.302, 95% CI: 1.110 to 1.525), and a 500 cm/s increase in baPWV with a 93.3% increase in risk (RR = 1.933, 95% CI: 1.300 to 2.874), $P = 0.0011$. In multivariate analyses, when both the LF/HF ratio and age were used as continuous variables in the same model, the LF/HF ratio was no longer statistically significantly associated with cardiovascular mortality.

4. Discussion

The main result of the present study is that in elderly community-dwelling people, arterial stiffness measured by means of baPWV predicted the occurrence of cardiovascular death beyond the prediction provided by age, gender, blood pressure and cognitive functions, assessed by a multivariate Cox model. The baPWV measure is a novel noninvasive technique, which has been developed to assess pulse wave transmission between the brachial and tibial arteries [6]. PWV is known to be an indicator of arterial stiffness and a marker of vascular damage [7]. Traditionally, carotid-femoral PWV is an established method for measuring PWV. Contrary to this traditional PWV, baPWV includes peripheral components of the arterial tree. We need to consider the role of this arterial tree because the influence of age changes in different parts of the arterial tree. Although baPWV values are larger compared to those obtained by the traditional method, their validity has been demonstrated by Yamashina et al. [6]. Findings herein suggest the usefulness of baPWV for clinical use. It has also been argued that baPWV is strongly affected by blood pressure [8] and that this effect should be considered in clinical

practice. This investigation showed that baPWV but not BP was predictive of cardiovascular mortality. Hence, baPWV should be added to the cardiovascular assessment in various clinical settings, including field medical surveys and preventive screenings. Other advantages of this method are that it is not time consuming, that it has good reproducibility, and that it does not require highly skilled technicians.

We have started a novelty medicine focusing on a comprehensive cardiovascular assessment, namely a new field of chrono-ecology in medicine, which is important for a better diagnosis and a more effective treatment. We need to get information about the disease not only from the patient, but also from the natural environment. Often the most important key originates not from the patients themselves, but from their whole environment. Most organisms on Earth, including humans, have developed "clock" genes underlying the circadian, and probably many other components in the spectral element of chronomes, beyond about-yearly (circannual) and about-weekly (circaseptan) features, as a product of adaptation to, or rather integration with, cycles in the cosmos. While life originally integrated itself into the cycles of an anthropogenically unpolluted environment, the environmental cycles are now being changed in keeping with the schedules of societal life, as in the case of global temperature, and perhaps the geomagnetic index.

Hence, a variety of cognitive, neurobehavioral and neuropsychological as well as cardiovascular functions will need to be investigated to more precisely map their chronomes in space and time, in order to understand chronoastrobiology, based on both the system times and time horizons yielded by chronomes assessed in communities worldwide. Fortunately, this mapping in the field has been sought not only in several rural Japanese towns, but also in old towns in the Karakoram and the Andes, by Matsubayashi et al. We have also started a novelty project for stroke prevention based on a comprehensive assessment, especially of elderly community-dwelling people, as shown herein. This kind of new project stands on the viewpoint of chronomics, aiming at prehabilitation medicine in preference to sole rehabilitation. It is offered as a public service in several Japanese towns, according to plans originally made in the city of Roseville, a suburb of St. Paul, Minnesota.

Acknowledgements

This study was supported by Japan Arteriosclerosis Prevention Fund.

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BIOMEDICINE & PHARMACOTHERAPY
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Fractal analysis of heart rate variability and mortality in elderly community-dwelling people – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

Aim. – Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups. Aim of this study is to examine the prognostic power of detrended fluctuation analysis (DFA) and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

Methods. – We examined 298 people older than 75 years (average age: 79.6 years) and 1-h ambulatory ECG was monitored. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. Time-domain and frequency-domain measures were determined by the maximum entropy method. Scaling exponents of short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) were determined by the DFA method. Six estimates, obtained from 10-min segments, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, estimates obtained during the first 10-min segment Alpha 1 S and Alpha 2 S, and those during the last 10-min segment Alpha 1E and Alpha 2E, respectively. The LILAC study started on July 25, 2000 and ended on November 30, 2004. We used Cox regression analysis to calculate relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. Significance was considered at a value of $P < 0.05$.

Results. – Gender, age and Alpha 2E showed a statistically significant association with all-cause mortality. In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a RR of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a RR of 1.49 ($P = 0.01809$). The RR of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a RR of 0.61 (95% CI: 0.42–0.90, $P = 0.01151$).

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Conclusion. – An intermediate-term fractal-like scaling exponent of RR intervals was a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (alpha 2) rather than the short-term fractal component (alpha 1) showed predictive value for all-cause mortality, which suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.

Keywords: Fractal; Heart rate variability; Detrended fluctuation analysis; All-cause mortality; Elderly community-dwelling people

1. Introduction

Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups [1–3]. Several new methods have been developed to quantify complex HR dynamics and to complement the conventional measures of HR variability. These methods have provided powerful prognostic information in different populations, but their prognostic power has not been studied in elderly community-dwelling people. In this study, we examine the prognostic power of fractal detrended fluctuation analysis and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 people older than 75 years (average age: 79.6 years). One hour of ambulatory ECG recording was obtained during routine medical examination conducted each year in July. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. The data were processed for HRV using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain measures (CVRR, SDANN, rMSSD and pNN50) and frequency-domain measures (spectral power in the "very low frequency" – VLF: 0.003–0.04 Hz, "low frequency" – LF: 0.04–0.15 Hz, and "high frequency" – HF: 0.15–0.40 Hz regions, and LF/HF ratio) were determined. All indices were computed as averages over consecutive 5-min intervals. Spectral indices were obtained by the maximum entropy method (MEM) with the MemCalc/CHIRAM program (Suwa Trust Co., Ltd., Tokyo, Japan).

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term RR intervals. The root-mean-squares fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log–log scale. The details of this method were shown elsewhere by Peng et al. [4]. The HR correlations were defined separately for short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) RR interval data (scaling exponent). Six estimates of both alpha 1 and alpha 2, obtained from 10-min segments based on 4000 RR intervals, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, respectively. Estimates obtained during the first 10-min segment were denoted Alpha 1 S and Alpha 2 S, respectively, and those obtained during the last 10-min segment Alpha 1E and Alpha 2E, respectively.

2.2. Follow-up

The LILAC study started on July 25, 2000. Consultations were repeated every year (end of July, or beginning of August). In addition, one or two doctors of our team visited every 3 months and offered several kinds of health consultation regarding the rehabilitation of disordered functions, healthy lifestyle modifications, such as the promotion of complete smoking cessation, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake, and advice in terms of medical prescriptions for the local general practitioner.

In this investigation, the follow-up ended on November 30, 2004. The follow-up time was defined as the time elapsed between the date of first (reference) examination and the date of all-cause mortality.

2.3. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). We used Cox regression analysis to calculate the unadjusted and adjusted relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. To identify independent predictors of all-cause mortality, we used multivariate Cox regression analyses with stepwise selection. Variables included in the multivariate models were age, gender, body mass index (BMI) and HR variability indices. Significance was considered at a value of $P < 0.05$.

3. Results

The reference characteristics of the 298 subjects are given in Table 1. The sample comprised 120 men and 178 women. The mean age of the participants at entry was 79 years. The mean follow-up time was 1152 days, during which 30 subjects died (21 men and nine women). Out of the 298 participants, HR variability was analyzed in 260 subjects, excluding subjects with cardiac arrhythmias, such as atrial fibrillation and frequent atrial and ventricular ectopies. Out of the 260 subjects, fractal analysis of HR variability was done in 184 subjects.

Table 1
Reference characteristics of the 298 subjects

Variables	Number	Mean	S.D.	Minimum	Maximum
Days Follow-up	298	1152.0	462.2	114.0	1578.0
Gender	298	0.403	0.491	0	1
Age	298	79.0	4.7	70.0	96.0
BMI	284	23.5	3.5	13.9	33.3
Average HR	273	74.4	12.4	44.0	117.0
CVRR	260	5.21	2.13	1.80	22.47
SDANN	258	37.9	13.8	12.9	109.3
rMSSD	261	23.6	17.3	5.2	169.6
pNN50	261	4.6	9.1	0	76.3
VLF	261	926.9	720.8	62.7	6124.0
LF	260	212.1	274.7	6.8	1898.7
HF	259	108.0	261.4	5.1	2717.1
L/H	260	3.02	1.97	0.32	10.99
Alpha 1	184	1.045	0.234	0.45	1.49
Alpha 2	184	1.054	0.121	0.58	1.33
Alpha 1 S	184	1.028	0.271	0.35	1.52
Alpha 2 S	184	1.060	0.185	0.56	1.51
Alpha 1 E	184	1.061	0.250	0.35	1.53
Alpha 2 E	184	1.099	0.202	0.36	1.73

Gender: $M = 1$, $F = 0$ (120 men and 178 women).

Among the variables used in Cox proportional hazard models, gender, age and Alpha 2E showed a statistically significant association with all-cause mortality (Table 2). In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a relative risk of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a relative risk of 1.49 ($P = 0.01809$). The relative risk of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a relative risk of 0.61 (95% CI: 0.42 to 0.90, $P = 0.01151$).

Table 2
Relative risk (RR) of the all-cause mortality in elderly community-dwelling people

Variables	Number	β	S.E. (β)	z-value	P-value	RR	95% CI	
Gender	298	1.277	0.398	3.204	0.00136	3.59	1.64	7.83
Age (5)	298	0.080	0.034	2.364	0.01809	1.49	1.07	2.08
BMI	284	-0.049	0.054	0.905	N.S.			
Average HR	273	0.016	0.015	1.059	N.S.			
CVRR	260	0.055	0.088	0.622	N.S.			
SDANN	258	0.003	0.015	0.181	N.S.			
rMSSD	261	0.008	0.009	0.952	N.S.			
pNN50	261	0.012	0.017	0.721	N.S.			
VLF	261	0.000	0.000	0.775	N.S.			
LF	260	0.000	0.000	0.428	N.S.			
HF	259	0.000	0.000	0.030	N.S.			
L/H	260	-0.168	0.116	1.456	N.S.			
Alpha 1	184	-1.364	0.873	1.563	N.S.			
Alpha 2	184	-2.899	1.547	1.874	0.06090			
Alpha 1 S	184	-0.890	0.765	1.163	N.S.			
Alpha 2 S	184	-1.112	1.192	0.934	N.S.			
Alpha 1 E	184	-1.198	0.816	1.468	N.S.			
Alpha 2E (0.20)	184	-2.760	0.956	2.886	0.00390	0.58	0.40	0.84
Alpha 2E (0.2) Gender adjusted	184	-2.079	0.958	2.170	0.02999	0.66	0.45	0.96
Alpha 2E (0.2) Gender-, age-adjusted	184	-2.452	0.970	2.527	0.01151	0.61	0.42	0.90

Gender: $M = 1$, $F = 0$ (120 men and 178 women).

4. Discussion

The main finding of this study is that an intermediate-term fractal-like scaling exponent of RR intervals is a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (alpha 2) rather than the short-term fractal component (alpha 1) showed predictive value for all-cause mortality. This result contrasts with most previous studies reporting that a short-term fractal component was a better predictor in different patient populations [1–3]. It should also be kept in mind that in this study, a predictive value was found for alpha 2E, corresponding to the last 10 min of ambulatory ECG monitoring, when deep breathing was repeated in a supine position.

The advantages of fractal exponent analysis over traditional indices of HR variability have been well known. The higher sensitivity of this approach stems from its ability to detect abnormalities in HR behavior in cases where abrupt temporal changes in RR intervals occur in a window of time of seconds or minutes. This observation suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.

Acknowledgements

This study was supported by Fukuda Foundation for Medical (Grant in 2004 for the study on association between arterial stiffness and cognitive impairment in community-dwelling subjects over 70 years old).

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Depressive mood is independently related to stroke and cardiovascular events in a community

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Abstract

By means of a multivariate Cox model, we investigated the predictive value of a depressive mood on vascular disease risk in middle-aged community-dwelling people. In 224 people (88 men and 136 women; mean age: 56.8 ± 11.2 years) of U town, Hokkaido (latitude: 43.45 degrees N, longitude: 141.85 degrees E), a chronoecological health watch was started in April 2001. Consultations were repeated every 3 months. Results at the November 30, 2004 follow-up are presented herein. 7-day/24-h blood pressure (BP) and heart rate (HR) monitoring started on a Thursday, with readings taken at 30-min intervals between 07:00 h and 22:00 h and at 60-min intervals between 22:00 h and 07:00 h. Data stored in the memory of the monitor (TM-2430-15, A&D company, Japan) were retrieved and analyzed on a personal computer with a commercial software for this device. Subjects were asked to answer a self-administered questionnaire inquiring about 15 items of a depression scale, at the start of study and again after 1–2 years. Subjects with a score higher by at least two points at the second versus first screening were classified as having a depressive mood. The other subjects served as the control group.

The mean follow-up time was 1064 days, during which four subjects suffered an adverse vascular outcome (myocardial infarction: one man and one woman; stroke: two men). Among the variables used in the Cox proportional hazard models, a depressive mood, assessed by the Geriatric Depression Scale (GDS), as well as the MESOR of diastolic (D) BP (DBP-MESOR) and the circadian amplitude of systolic (S) BP (SBP-Amplitude) showed a statistically significant association with the occurrence of adverse vascular outcomes. The GDS score during the second but not during the first session was statistically significantly associated with the adverse vascular outcome. In univariate analyses, the relative risk (RR) of developing outcomes was predicted by a three-point increase in the GDS scale (RR = 3.088, 95% CI: 1.375–6.935, $P = 0.0063$). Increases of 5 mmHg in DBP-MESOR and of 3 mmHg in SBP-Amplitude were associated with RRs of 2.143 (95% CI: 1.232–3.727, $P = 0.0070$) and 0.700 (95% CI: 0.495–0.989, $P = 0.0430$), respectively. In multivariate analyses, when both the second GDS score and the DBP-MESOR were used as continuous variables in the same model, GDS remained statistically significantly associated with the occurrence of cardiovascular death. After adjustment for DBP-MESOR, a three-point increase in GDS score was associated with a RR of 2.172 (95% CI: 1.123–4.200). Monday endpoints of the 7-day profile showed a statistically significant association with adverse vascular outcomes. A 5 mmHg increase in DBP on Monday was associated with a RR of 1.576 (95% CI: 1.011–2.457, $P = 0.0446$).

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The main result of the present study is that in middle-aged community-dwelling people, a depressive mood predicted the occurrence of vascular diseases beyond the prediction provided by age, gender, ABP, lifestyle and environmental conditions, as assessed by means of a multivariate Cox model. A depressive mood, especially enhanced for 1–2 years, was associated with adverse vascular outcomes. Results herein suggest the clinical importance of repetitive assessments of a depressive mood and the need to take sufficient care of depressed subjects.

Another result herein is that circadian and circaseptan characteristics of BP variability measured 7-day/24-h predicted the occurrence of vascular disease beyond the prediction provided by age, gender, depressive mood and lifestyle, as assessed by means of a multivariate Cox model. Earlier, we showed that the morning surge in BP on Mondays was statistically significantly higher compared with other weekdays. Although a direct association between the Monday surge in BP and cardiovascular events could not be demonstrated herein, it is possible that the BP surge on Monday mornings may also trigger cardiovascular events. We have shown that depressive people exhibit a more prominent circaseptan variation in SBP, DBP and the double product (DP) compared to non-depressed subjects.

In view of the strong relation between depression and adverse cardiac events, studies should be done to ascertain that depression is properly diagnosed and treated. Chronodiagnosis and chronotherapy can reduce an elevated blood pressure and improve the altered variability in BP and HR, thus reducing the incidence of adverse cardiac events. This recommendation stands at the basis of chronomics, focusing on prehabilitation in preference to rehabilitation, as a public service offered in several Japanese towns.

Keywords: Depressive mood; Seven-day ambulatory blood pressure; Cardiovascular diseases; Stroke

1. Introduction

Several lines of evidence suggest that clinical depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease, especially after an acute myocardial infarction (MI). Major depression is associated with a fourfold increase in the risk of mortality during the first 6 months after an acute MI, and its prognostic significance is comparable to that of left ventricular dysfunction and a history of MI. Depression is not unusual among individuals with coronary heart disease, with studies indicating that between 15% and 22% of patients suffer from depression after a cardiac event.

Not only circadian, but also circannual, circaseptan (about 7-day) and other variations characterize the incidence of adverse vascular events, such as acute myocardial infarctions, strokes and sudden cardiac deaths, carrying important pathophysiological implications. Most studies showed an increased incidence in the morning, peaking between 06:00 and 12:00. Ambulatory blood pressure monitoring (ABPM) has become an important tool in the diagnosis and management of hypertension. Several studies have indicated that target organ damage and cardiovascular morbidity are more strongly associated with circadian BP endpoints than with office BP values. We reported that circadian and other patterns are synchronized by socio-ecologic factors, such as human lifestyles, as well as economic and environmental conditions. We demonstrated the presence of a weekly BP variation in community-dwelling subjects, including a surge in BP on Mondays, and we showed that it was most prominent in depressed people.

In 2000, we began a community-based study to longitudinally investigate the longevity and aging of a population in Hokkaido County (LILAC) [1,2], including the evaluation of the younger population aged from 40 to 74 years (Health Watch) [3]. Our goal is the prevention of cardiovascular events, notably strokes and myocardial ischemic events in a community. Herein, we examine whether a depressive mood is associated with an increased risk of stroke and cardiovascular mortality, and we estimate the predictive value of a depressive mood on the incidence of adverse vascular events, using a multivariate Cox model.

2. Methods

2.1. Subjects and Health Watch study design

The 224 subjects monitored between April 2001 and March 2004 were between 24 and 79 years of age (88 men and 136 women; mean age: 56.8 ± 11.2 years), living in U town in Hokkaido (latitude: 43.45 degrees N, longitude: 141.85 degrees E). All subjects visited and utilized the free health screening, counseling, and educational services of the U town office. Subjects with definite neurological diseases, such as Parkinsonism and stroke, and those who were too severely ill to stand without help were excluded. Lifestyle, including nutritional and sleep quality was investigated by several types of questionnaires. BP was measured at the beginning of the study in a sitting position, and brachialankle pulse wave velocity (baPWV) was measured between the right arm and ankle in a supine position, using an ABI/Form instrument (Nippon Colin Co., Ltd., Komaki, Japan). In all studies, baPWV was measured twice after at least a 5-min rest. For the assessment of the predictive value, only baPWV measures from participants showing normal ankle/brachial pressure index (ABI) values (>0.90) were used.

2.2. Ambulatory blood pressure monitoring

The 7-day/24-h BP recordings were obtained with a commercially available ambulatory BP recorder (TM-2431, A&D Company, Japan) [4]. Subjects were fitted with the recorder in the morning, usually between 10:00 and 11:30 h of the first day of monitoring. The recorder was set to take measurements at

intervals of 30 min between 07:00 and 22:00 h, and of 60 min between 22:00 and 07:00 h. Subjects were instructed to follow their usual daily routine after they left the office. Subjects were instructed to remain motionless each time a reading was to be taken, and then to record their activity on a diary sheet. Stored data were retrieved and analyzed on a personal computer with commercially available software for the device (TM-2430-15, A&D Company, Japan). The data were further analyzed by sphygmochron for the entire 7-day span and separately for each day of monitoring (provided by corne001@umn.edu for all interested comers). In addition to the circadian rhythm characteristics, estimates were also obtained for mean values during 24-h, waking and sleeping spans, and for the day–night ratio (as a gauge of "dipping") for SBP, DBP and HR, and also for mean blood pressure (MBP = 1/3SBP +2/3DBP), pulse pressure (PP = SBP – DBP), and the double product (DP = SBP × HR/100) ("dip" is defined as the Awake–Sleep difference divided by Awake (×100), where Awake and Sleep are average values during the awake- and sleep-span, respectively).

2.3. Depression screening scale

Numerous depression rating scales are currently available, which represent a mixture of observer-rated and self-rating scales. In this investigation, subjects were asked about 15 items on a depression scale, by means of a self-administered questionnaire [5]. When the depression score was 5, subjects were considered to have a depressed mood. A depression score was obtained again 1–2 years later. Subjects with a score during the second screening higher by at least two points compared to that of the first screening were assigned to the enhanced depressive mood group (irrespective of the score at the start of study). All other subjects were assigned to the control group.

2.4. Stroke and cardiovascular mortality

The Health Watch study was started on April 12, 2001.One or two doctors of our team visited and provided repeated consultations every 3 months. They offered advice in relation to the rehabilitation of disordered functions, and healthy lifestyle modifications (promoting complete cessation of smoking, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake). They also advised in terms of medical prescriptions for the local general practitioner.

The follow-up herein ended on November 30, 2004. During this time, nine subjects died of myocardial infarction or stroke. The follow-up time was defined as the time elapsed between the date of the first (reference) examination and the date of first cardiovascular event or death.

2.5. Statistical analysis

Results are reported as mean ± S.D. Student's *t*-tests served to compare the enhanced depressed and control groups. A *P*-value below 0.05 was considered to indicate statistical significance (and below 0.10, borderline statistical significance).

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). We used Cox's regression analysis to calculate the unadjusted and adjusted relative risks (RRs) and 95% confidence intervals (CIs) for cardiovascular death. To identify independent predictors of stroke and cardiovascular disease in relation to a depressive mood, we used a multivariate Cox regression analysis with stepwise selection, including as variables age, gender, BMI, lifestyle, sleep quality, QOL, baPWV and ABP endpoints.

The independent correlation of the enhanced depressive mood was determined by means of a logistic regression analysis. Kaplan–Meier event probability curves were computed with two groups, and the cumulative probability of events of two groups was compared by means of the log-rank test. Significance was considered at a value of $P < 0.05$.

3. Results

Reference characteristics of the 224 subjects are given in Table 1. The sample comprised 88 men and 136 women. The mean age of participants at entry was 56.8 years. The mean follow-up time was 1064 days, during which four subjects suffered from adverse vascular outcomes (myocardial infarction: one man and one woman, stroke: two men).

Table 1 lists the mean, standard deviation (S.D.), minimum and maximum of the different variables considered in this chronoecological health watch. Items include indices of environmental conditions, lifestyle, quality of sleep, QOL and 7-day ABP endpoints, such as the 7-day (from Thursday to Wednesday) and daily averages of SBP, DBP, HR, the incidence of SBP- and DBP-CHAT (circadian hyper-amplitude-tension) and of SBP, DBP and HR "dipping" (SBP-dip, DBP-dip, and HR-dip), estimates of the circadian amplitude and acrophase of SBP, DBP and HR, as well as estimates of the percentage time elevation (PTE) of SBP, DBP and HR. Averages over 7 days were also computed (not shown) as SBP 1-7, DBP 1-7, pulse pressure (PP) 1-7, double product (DP) 1-7, 24-h S.D. of HR (HRSD1-7), SBP-dip 1-7, DBP-dip 1-7, HR-dip 1-7, MAPdip 1-7, PPdip 1-7, and DPdip 1-7.

Depression scores were obtained for 218 of the 224 citizens at the start of study and from 179 subjects after 1–2 years (177 subjects provided a score during both sessions). Scores obtained during the first and second sessions averaged 4.11 ± 3.11, and 4.42 ± 3.14, respectively. Of the 177 citizens who answered both questionnaires, 39 were assigned to the enhanced depressive mood group. A comparison of characteristics between the two groups is shown in Table 2. It can be seen that depressive subjects had a higher body mass index (BMI), they consumed smaller meals (less amount of rice), and their total serum cholesterol was higher as compared to the control subjects. The time to

fall asleep was also slightly longer in the depressive group (P = 0.051). Kaplan–Meier curves for event-free survival revealed a significant difference between the two groups (P = 0.0124, log-rank test) (Fig. 1). Subjects in the control group had a better event-free survival than depressed subjects.

Among the variables used in Cox proportional hazard models, a depressive mood, assessed by the Geriatric Depression Scale (GDS), as well as DBP-MESOR and SBP-Amplitude showed a statistically significant association with the occurrence of vascular outcomes (Table 3). It should be noted that GDS during the second but not during the first session was statistically significantly associated with adverse vascular outcomes. In univariate analyses, an increase by two or three points of the GDS score during the second session was associated with a RR of 2.121 (95% CI: 1.237–3.637) or 3.088 (95% CI: 1.375–6.935), respectively (P = 0.0063). A 5 mmHg increase in DBP-MESOR and a 3 mmHg increase in SBP-Amplitude were associated with RRs of 2.143 (95% CI: 1.232–3.727, P = 0.0070) and 0.700 (95% CI: 0.495–0.989, P = 0.0430), respectively. In multivariate analyses, when both the second GDS score and DBP-MESOR were used as continuous variables in the same model, GDS remained statistically significantly associated with the occurrence of cardiovascular death. After adjustment for DBP-MESOR, a three-point increase in GDS score was associated with a RR of 2.172 (95% CI: 1.123–4.200).

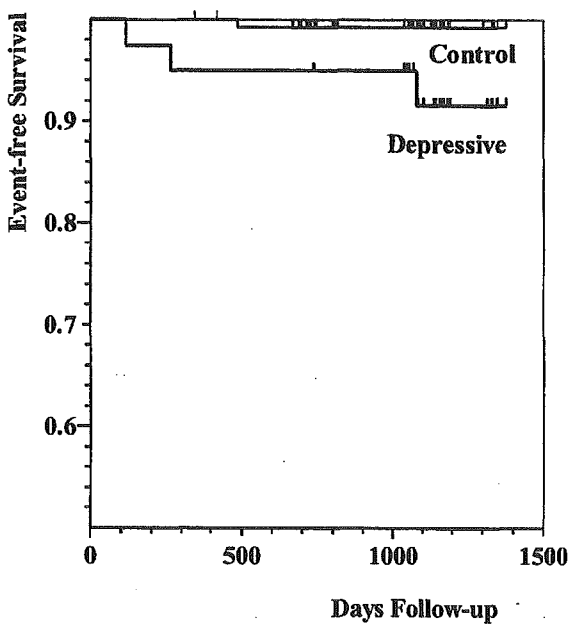

Fig. 1 Kaplan–Meier event probability curves for the incidence of vascular disease.
Calculation of Kaplan–Meier curves for event-free survival revealed a significant difference between the control and depressive groups (P = 0.0124, log-rank test). A depression score was obtained again after 1–2 years, and when the score during the second screening had increased by more than 2 points compared to the first screening, such subjects were assigned to the enhanced depressive mood group, shown as "Depressive", while the other subjects were assigned to the control group, shown as "Control". It can be seen that subjects in the control group had fewer adverse vascular events (better event-free survival).

Monday and/or Tuesday endpoints of the 7-day ABP showed a statistically significant association with adverse vascular outcomes. A 5-mmHg increase in DBP-5 or DBP-6, namely in the arithmetic mean of DBP from data collected on Mondays and Tuesdays, was associated with RRs of 1.576 (95% CI: 1.011–2.457, P = 0.0446) and 1.666 (95% CI: 1.052–2.639, P = 0.0297), respectively. A 20-unit increase in DP-5 (double product on Mondays) and a 3% increase in MAP-dip-5 were associated with RRs of 3.067 (95% CI: 1.075–8.753, P = 0.0362) and 0.824 (95% CI: 0.683–0.995, P = 0.0439), respectively. Saturday endpoints also related to adverse vascular outcomes. A 3% increase in PP-dip-3 (dipping ratio of pulse pressure on Saturday nights) and a 5-unit increase in DP-dip-3 (dipping ratio of Saturday's double product) were inversely associated with adverse vascular outcome, with RRs of 0.865 (95% CI: 0.756–0.989, P = 0.0337) and 0.752 (95% CI: 0.596–0.948, P = 0.0158), respectively.

4. Discussion

Depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease [6–8]. Anda et al. [9] followed a cohort of 2832 persons for an average of 12.4 years. During the reference stage, 11.1% of the study cohort had a depressed affect. The adjusted relative risk of fatal CHD was 1.4 for patients with depressed affect, compared with patients who were not depressed. For non-fatal CHD, the adjusted relative risk was 1.6. For both fatal and non-fatal CHD, the increased risk associated with depression was independent of established risk factors for CHD (e.g. smoking, cholesterol concentration, family history). Barefoot and Schroll [10] reported that high scores on a measure of symptoms of depressed mood were associated with an increased risk for AMI and early mortality during a 27-year follow-up, and that the impact of a depressed affect on health did not differ between men and women. We also observed in middle-aged community-dwelling people that a depressive mood, assessed by GDS, predicted the occurrence of vascular diseases beyond the prediction provided by age, gender, ABP, lifestyle and environmental conditions, as assessed by means of a multivariate Cox model. A depressive mood, especially when enhanced for 1–2 years, was associated with adverse vascular outcomes. Results herein suggest the clinical importance of repeated assessment of a depressive mood and of taking sufficient care of depressed subjects.

Another result of the present study is that in community-dwelling people, circadian and circaseptan characteristics of BP variability derived from 7-day/24-h ABP predicted the occurrence of vascular diseases beyond the prediction

Table 1
Reference characteristics of the 224 subjects

Variables	Units	n	Mean	S.D.	Min.	Max.
Age	years	224	56.8	11.2	24	79
Gender ratio		224	0.393	0.489	0	1
BMI	kg/m^2	220	24.6	2.8	17.5	34.7
Days Follow-up	days	224	1063.7	271.6	114	1378
Outside temperature	°C	192	3.7	8.7	−16	25
Room temperature	°C	206	22.3	3.9	0	34
Temperature difference	°C	199	18.4	9.2	−5	42
Time of sunrise	h:min	218	05:53	0.043	03:54	07:30
Time of sunset	h:min	218	17:17	0.046	16:00	19:21
Sunshine duration	h:min	216	11:24	0.087	08:57	15:22
Smoking I		218	252.1	463.8	0	2720
Smoking II		217	9.88	15.16	0	55
Family history of CVD	points	219	2.19	2.16	0	8
Exercise	points	220	1.79	1.21	0	4
Alcohol	points	219	1.00	3.53	0	50
GDS1	points	218	4.11	3.11	0	13
GDS2	points	179	4.42	3.14	0	15
Subjective healthiness	%	220	65.38	17.50	19.8	100
Subjective mood	%	220	69.13	18.19	14.3	100
Family relations	%	218	79.86	19.40	7.4	100
Relations with friends and relatives	%	220	77.90	18.32	8.7	100
Financial satisfaction	%	218	62.65	24.87	0	100
Life satisfaction	%	220	70.56	21.77	0	100
Sense of happiness	%	220	74.19	19.31	3.5	100
Total score of QOL		216	496.6	107.7	118.8	692.0
Getting up		216	06:08	0.035	04:00	09:00
Going to bed		216	22:33	0.042	19:59	01:59
Duration of sleep	h:min	156	07:51	0.043	05:30	11:00
Time from getting up to going to bed		156	16:08	0.043	13:00	18:30
Sleep well?		188	1.21	0.41	1	2
Time to fall asleep	min	188	4.05	2.20	2	12
Duration of snoring	years	112	4.54	2.49	0	12
Not feeling sufficiently refreshed		187	1.67	0.75	1	3
Duration of not feeling refreshed	months	167	5.13	6.70	0	15
Quality of sleep		184	19.79	2.53	14	24
Condition during sleep		184	21.33	0.90	18	22
Salt intake (Summer)	g/day	169	13.57	2.08	9.37	20.27
Salt intake (Winter)	g/day	169	13.47	2.02	9.37	20.27
Amount of meal (rice)	cups	169	2.50	0.89	0.5	6
Soybean soup	cups	169	1.52	0.77	0	3.3
Vegetables (Summer)		172	9.67	5.64	0	48
Vegetables (Winter)		172	9.02	5.75	0	48
Fruit		170	4.61	3.46	0	21
R baPWV	cm/s	202	1486.6	323.5	735	2561
L baPWV	cm/s	203	1526.3	336.5	748	2718
R ABI		204	1.11	0.09	0.60	1.33
L ABI		204	1.11	0.08	0.82	1.30
CTR	%	128	48.31	5.27	37.3	62.0
SV1 + RV5	Mm	151	27.99	9.03	11.6	60.0
SBP-MESOR	mmHg	223	126.66	14.75	95.2	172.6
DBP-MESOR	mmHg	223	77.49	8.44	57.6	103.5
HR-MESOR	mmHg	223	69.76	7.09	48.2	92.9
SBPdip	%	223	15.62	7.29	−7.08	33.18
DBPdip	%	223	17.17	7.17	−3.13	32.53
HR dip	%	223	16.81	7.78	−18.89	34.84
SBP CHAT		223	0.152	0.360	0	1
DBP CHAT		223	0.054	0.226	0	1
SBPAmp	mmHg	223	24.98	10.55	0.78	56.25
DBPAmp	mmHg	223	16.48	6.80	0.61	36.96
HR Amp	mmHg	223	15.80	6.30	1.17	35.74
SBPAcro	h:min	222	13:51	0.10	01:27	21:07
DBPAcro	h:min	222	13:51	0.08	06:11	23:40
HRAcro	h:min	222	14:10	0.09	00:25	22:38
SBP PTE	%	223	12.53	23.16	0	97.9
DBP PTE	%	223	6.97	14.90	0	91.4
HR PTE	%	223	0.56	2.31	0	18.0
SBP1	mmHg	219	129.86	16.50	90.46	186.79
SBP2	mmHg	221	128.53	15.83	93.49	182.64
SBP3	mmHg	220	127.19	14.84	89.41	172.54
SBP4	mmHg	220	126.82	15.18	93.23	167.71
SBP5	mmHg	215	127.55	15.32	95.11	176.11
SBP6	mmHg	209	127.84	15.35	96.58	175.94
SBP7	mmHg	176	127.71	15.57	90.08	173.63
DBP1	mmHg	219	79.57	9.51	53.07	104.59
DBP2	mmHg	221	78.90	9.19	56.22	106.23
DBP3	mmHg	220	78.04	8.81	50.87	97.76
DBP4	mmHg	220	77.65	8.87	50.94	103.45
DBP5	mmHg	215	78.44	9.08	56.23	111.47
DBP6	mmHg	209	78.42	9.28	54.06	108.69
DBP7	mmHg	176	78.45	9.11	57.89	105.85
Ppaver1	mmHg	222	50.51	10.49	30.36	88.94
Ppaver2	mmHg	222	49.92	9.94	31.00	81.06
Ppaver3	mmHg	222	49.50	9.79	31.46	81.95
Ppaver4	mmHg	220	49.54	9.81	30.05	79.14
Ppaver5	mmHg	216	49.41	9.78	31.42	84.93
Ppaver6	mmHg	210	49.76	9.92	33.16	83.03
Ppaver7	mmHg	176	49.65	10.20	31.03	92.04
Dpaver1	mmHg	222	91.06	15.32	56.79	157.91
Dpaver2	mmHg	222	92.48	15.69	57.03	158.19
Dpaver3	mmHg	222	91.27	14.03	63.94	145.57
Dpaver4	mmHg	220	90.80	14.94	62.57	142.29
Dpaver5	mmHg	216	92.28	15.57	59.89	145.66
Dpaver6	mmHg	210	92.11	15.27	55.48	137.98
Dpaver7	mmHg	176	92.28	14.70	59.38	134.26
HRSD1		222	11.27	4.62	2.42	33.78
HRSD2		222	11.74	4.17	3.11	27.68
HRSD3		222	12.12	4.49	3.03	27.92
HRSD4		220	11.87	4.52	4.18	34.11

Table 1 *(continued)*

Table 1 *(continued)*

HRSD5		216	11.39	4.07	3.09	27.25
HRSD6		211	11.64	4.37	3.53	33.61
HRSD7		177	11.79	4.29	4.27	26.74
SBP dip 1	%	216	17.49	9.80	−16.66	41.44
SBP dip 2	%	210	15.21	10.35	−23.19	42.36
SBP dip 3	%	218	14.64	10.58	−22.4	40.9
SBP dip 4	%	211	15.59	10.49	−15.36	46.89
SBP dip 5	%	210	15.80	10.33	−33.1	36.29
SBP dip 6	%	200	16.89	10.03	−31.18	39.96
SBP dip 7	%	174	16.47	9.18	−13	38.41
DBP dip 1	%	216	18.46	10.71	−11.43	49.73
DBP dip 2	%	210	16.65	10.55	−17.33	43.29
DBP dip 3	%	218	16.36	10.62	−12.44	43.26
DBP dip 4	%	210	16.41	11.15	−22.51	50.65
DBP dip 5	%	209	17.82	10.18	−29.05	42.56
DBP dip 6	%	199	18.51	10.84	−24.9	39.67
DBP dip 7	%	173	17.52	10.40	−18.06	41.82
HR dip 1	%	216	14.75	12.24	−42.82	41.96
HR dip 2	%	210	16.01	11.36	−28.93	42.57
HR dip 3	%	218	17.60	10.25	−23.78	42.32
HR dip 4	%	211	16.42	12.59	−54.08	45.99
HR dip 5	%	210	17.42	10.12	−19.99	43.87
HR dip 6	%	199	17.61	10.57	−27.61	40.08
HR dip 7	%	173	17.46	10.83	−24.94	43.29
MAP dip 1	%	216	18.16	9.59	−13.85	41.81
MAP dip 2	%	210	15.99	9.92	−20.11	42.47
MAP dip 3	%	218	15.55	10.17	−13.59	42.26
MAP dip 4	%	211	16.13	10.39	−16.66	49.11
MAP dip 5	%	210	17.00	9.75	−30.87	39.3
MAP dip 6	%	199	17.82	9.93	−27.87	37.47
MAP dip 7	%	173	17.14	9.27	−12.66	39.07
PP dip 1	%	216	14.48	17.72	−42.37	53.11
PP dip 2	%	210	12.22	16.55	−47.26	55.36
PP dip 3	%	218	11.54	15.90	−47.8	45.64
PP dip 4	%	211	13.24	16.05	−35.93	54.82
PP dip 5	%	210	11.46	17.36	−65.85	48.88
PP dip 6	%	199	12.84	16.26	−56.39	46.5
PP dip 7	%	173	13.86	15.06	−44.22	52.95
DP dip 1	%	216	29.82	12.93	−15.58	58.08
DP dip 2	%	210	29.12	12.38	−30.23	54.21
DP dip 3	%	218	29.87	12.65	−29.7	56.7
DP dip 4	%	211	29.69	13.58	−17.23	58.52
DP dip 5	%	210	30.61	12.14	−20.4	55.15
DP dip 6	%	199	31.63	11.72	−1.94	58.3
DP dip 7	%	173	31.15	11.88	−15.43	59.39

Gender: $M = 1$, $F = 0$ (88 mean and 136 women).
"dip" is defined as Awake–Sleep difference divided by Awake (×100), where Awake and Sleep are average values during awake- and sleep-span, respectively.

provided by age, gender, depressive mood and lifestyle, as assessed by means of a multivariate Cox model.

Ambulatory 24-h blood pressure monitoring has become quite popular in recent years, offering a number of advantages from the viewpoint of both diagnosis and treatment [11]. One advantage rests on the fact that clinic blood pressure is not representative of blood pressure values outside the clinic. Results obtained herein show that blood pressure is characterized not only by a circadian but also by a weekly variation. The 24-h averages of SBP and DBP are seen to differ from one day to another in the same citizen in the same 7-day record. In middle-aged community-dwelling people, DBP-MESOR and SBP-Amplitude predicted the occurrence of vascular diseases, assessed by means of a multivariate Cox model. We found that several endpoints from data collected on Mondays predicted adverse outcomes, suggesting that circaseptan as well as circadian characteristics are associated with the occurrence of vascular disease. We reported on weekly BP characteristics earlier [12]. Most citizens in a community showed a novelty effect (the first day effect), a holiday dip, and a Monday morning surge of SBP. A Monday peak has been reported for the incidence of acute myocardial infarction, sudden cardiac death, and stroke [13–17]. Our previous studies showed that the morning BP surge on Mondays was statistically significantly higher compared with other weekdays [18]. Although a direct association between the Monday surge in BP and cardiovascular events could not be demonstrated directly, it is possible that a morning surge of BP on Mondays may trigger cardiovascular events. This possibility is supported by the fact that we found that depressive citizens had a more prominent circaseptan component for SBP, DBP and DP, compared with non-depressive subjects [19].

Results herein indicate the clinical importance of taking care of depressed subjects. In view of the strong relation between depression and adverse cardiac events, studies should be done to ascertain whether treatment of depression, especially from the standpoint of chronodiagnosis and chronotherapy, can reduce elevated blood pressure values and improve the altered variability in BP and HR, so as to reduce the incidence of adverse cardiac events. Fewer than 7 days of monitoring means a greater chance of a false diagnosis, on which a treatment decision may depend for the long term, including perhaps a potentially unnecessary treatment for decades. Less than 7 days of monitoring can be compared with taking the pulse for less than a cardiac cycle, if the circaseptan aspect of time structures (chronomes) is viewed as one of many new spectral components, with even longer periods, including transyears characterizing series of blood pressure and heart rate covering at least 5 and up to 38 years [20]. When the ECG and EEG, as well as the blood pressure of small rodents can be monitored continuously for most of their lifetime, this study is but a small step toward universal 7-day and eventually continuous monitoring of BP and HR, or the ECG.

Table 2
Comparison of subject characteristics between the control and enhanced depressive mood groups

		Control			Enhanced depressive mood			*t*-value	*P*-value
	Units	N	Mean	S.D.	n	Mean	S.D.		
GDS 1	Points	138	4.34	3.13	39	3.26	2.70	1.980	0.049
GDS 2	Points	138	3.75	2.83	39	6.80	3.07	–5.827	0.000
Difference of GDS scores	Points	138	–0.61	1.57	39	3.54	1.85	–13.976	0.000
Age	Years	138	56.7	11.7	39	57.7	10.3	–0.462	N.S.
Gender		138			39			0.896	N.S.
BMI	kg/m^2	138	24.1	2.6	39	25.2	2.9	–2.202	0.029
Smoking	points	135	9.5	14.9	39	8.3	14.2	0.455	N.S.
Family Hx	points	138	2.27	2.22	39	2.18	2.02	0.243	N.S.
Alcohol	points	137	0.77	1.24	39	0.82	0.97	–0.238	N.S.
Vegetables	times daily	138	2.12	0.80	39	2.27	0.77	–1.019	N.S.
Subjective healthiness	%	138	65.6	17.6	39	65.0	17.5	0.182	N.S.
Subjective mood	%	138	69.8	17.9	39	65.9	19.0	1.219	N.S.
Sense of happiness	%	138	74.3	19.3	39	72.6	17.2	0.514	N.S.
Getting up Time	clock time	138	06:13	0.03	39	06:02	0.03	1.294	N.S.
Duration of Sleep	clock time	115	07:50	0.04	33	07:51	0.04	–0.051	N.S.
Time for falling asleep	min	133	18.5	12.7	39	24.1	23.1	–1.964	0.051
Sleep well?	points	135	1.2	0.4	39	1.3	0.5	1.255	N.S.
Sleep Quality Score	points	135	19.8	2.4	39	19.5	2.8	0.834	N.S.
Salt intake daily	g	123	13.6	2.2	39	13.3	1.7	0.966	N.S.
Rice	cups	123	2.60	0.95	39	2.20	0.64	2.442	0.016
rt baPWV	cm/s	127	1458.1	309.1	35	1520.6	335.4	–1.039	N.S.
lt baPWV	cm/s	127	1500.6	330.1	35	1555.7	340.2	–0.870	N.S.
rt ABI		127	1.12	0.08	35	1.09	0.08	1.761	0.080
lt ABI		127	1.11	0.08	35	1.09	0.09	1.332	N.S.
ECG (SV1+RV5)	mm	98	28.0	9.3	24	29.7	10.0	–0.794	N.S.
CTR	%	81	47.9	5.5	28	49.4	4.9	–1.310	N.S.
Total choresterol	mg/dl	131	204.4	30.3	37	215.5	28.0	–2.009	0.046
HDL choresterol	mg/dl	130	58.8	14.2	37	59.6	13.0	–0.304	N.S.
Triglyceride	mg/dl	131	123.3	85.3	37	128.9	83.9	–0.353	N.S.
Uric acid	mg/dl	128	5.0	1.3	35	5.0	1.6	–0.243	N.S.
Serum creatinine	mg/dl	125	0.88	0.33	34	0.88	0.16	0.046	N.S.
FBS	mg/dl	128	99.5	16.5	36	96.7	12.9	0.939	N.S.
Follow up days	days	138	1085.8	227.9	39	1128.1	260.5	–0.991	N.S.
Uric acid	mg/dl	128	5.0	1.3	35	5.0	1.6	–0.243	N.S.
Serum creatinine	mg/dl	125	0.88	0.33	34	0.88	0.16	0.046	N.S.
FBS	mg/dl	128	99.5	16.5	36	96.7	12.9	0.939	N.S.
Follow up days	days	138	1085.8	227.9	39	1128.1	260.5	–0.991	N.S.

Gender: $M = 1$, $F = 0$.
GDS scores and difference of GDS scores used for classification.

Table 3
Relative risk (RR) of adverse vascular outcome accounted for by variables investigated in chronoecological health watch

Variables	Number of data	β	S.E. (β)	z-value	P-value	RR	95% CI	
Age	221	0.1163	0.0654	1.7769	0.0756			
Gender	221	1.5365	1.1548	1.3306	N.S.			
BMI	217	0.1964	0.1667	1.1780	N.S.			
Smoking	215	0.0002	0.0010	0.2238	N.S.			
Family history	216	−0.1854	0.2771	0.6692	N.S.			
Exercise	217	0.1482	0.3847	0.3852	N.S.			
Alcohol	216	0.0366	0.0860	0.4248	N.S.			
GDS 1	215	0.0329	0.1557	0.2113	N.S.			
GDS 2 (2 points)	176	0.3759	0.1376	2.7323	0.0063	2.121	1.237	3.637
GDS 2 (3 points)	176	0.3759	0.1376	2.7323	0.0063	3.088	1.375	6.935
Subjective healthiness	217	−0.0293	0.0272	1.0763	N.S.			
Subjective mood	217	−0.0261	0.0269	0.9681	N.S.			
Sense of happiness	217	−0.0050	0.0248	0.2007	N.S.			
Getting up time	213	−10.3425	13.8703	0.7457	N.S.			
Duration of sleep	153	12.1102	12.0658	1.0037	N.S.			
Time for falling asleep	185	−0.0104	0.2293	0.0452	N.S.			
Sleep well?	185	0.1778	1.1547	0.1540	N.S.			
Sleep quality score	181	−0.1019	0.1946	0.5234	N.S.			
Daily salt intake	167	−0.1249	0.2612	0.4782	N.S.			
Vegetables	170	0.0540	0.0559	0.9654	N.S.			
SBP-MESOR	220	0.0540	0.0290	1.8595	0.0630			
DBP-MESOR (5 mmHg)	220	0.1524	0.0565	2.6988	0.0070	2.143	1.232	3.727
HR-MESOR	220	−0.0020	0.0699	0.0281	N.S.			
SBP-dip	220	−0.1170	0.0607	1.9275	0.0539			
DBP-dip	220	−0.1158	0.0695	1.6661	0.0957			
HR-dip	220	0.0029	0.0659	0.0434	N.S.			
SBP-CHAT	220	−30.2348	2588781	0.0000	N.S.			
SBP-Amp (3 mmHg)	220	−0.1191	0.0589	2.0240	0.0430	0.700	0.495	0.989
DBP-Amp	220	−0.1368	0.0859	1.5937	N.S.			
HR-Amp	220	−0.0030	0.0791	0.0382	N.S.			
HR-Acro	219	−3.2113	3.8626	0.8314	N.S.			
SBP-PTE	220	0.0152	0.0151	1.0058	N.S.			
HR-PTE	220	−38.8712	943727.8	0.0000	N.S.			
DBP-5 (5)	212	0.0910	0.0453	2.0085	0.0446	1.576	1.011	2.457
DBP-6 (5)	206	0.1021	0.0470	2.1740	0.0297	1.666	1.052	2.639
DP-5 (20)	213	0.0560	0.0268	2.0946	0.0362	3.067	1.075	8.753
DP-6	207	0.0457	0.0289	1.5814	N.S.			
SBP-dip-3	215	−0.0699	0.0373	1.8738	0.0610			
SBP-dip-7 (3%)	173	−0.0966	0.0485	1.9929	0.0463	0.749	0.563	0.995
MAP-dip-5 (3%)	207	−0.0644	0.0320	2.0155	0.0439	0.824	0.683	0.995
HR-dip-3	215	−0.0468	0.0372	1.2562	N.S.			
PP-dip-3 (3%)	215	−0.0485	0.0228	2.1242	0.0337	0.865	0.756	0.989
DP-dip-3 (5)	215	−0.0571	0.0237	2.4125	0.0158	0.752	0.596	0.948
DP-dip-5	207	−0.0446	0.0325	1.3745	N.S.			
Right baPWV	200	0.0015	0.0013	1.1678	N.S.			
Left baPWV	201	0.0018	0.0012	1.4543	N.S.			
Right ABI	202	−1.1412	4.8159	0.2370	N.S.			
Left ABI	202	−3.9975	5.7243	0.6984	N.S.			

"Dip" is defined as Awake–Sleep difference divided by Awake (×100), where Awake and Sleep are average values during awake- and sleep-span, respectively.

Acknowledgements

This study was supported by Fukuda Foundation for Medical (Grant in 2004 for the study on association between arterial stiffness and cognitive impairment in community-dwelling subjects over 70 years old).

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