

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, espe-

cially 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 It is offered as a public service in several Japanese towns, according to plans originally made in the city of Roseville, a suburb of St. Paul, Minnesota.

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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 1 E and Alpha 2 E, 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. © 2005 Elsevier SAS. All rights reserved.

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, $P = 0.01151$).

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

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	184	-2.760	0.956	2.886	0.00390	0.58	0.40 0.84 (0.20)
Alpha 2E	184	-2.079	0.958	2.170	0.02999	0.66	0.45 0.96 (0.2)
Gender adjusted							
Alpha 2E	184	-2.452	0.970	2.527	0.01151	0.61	0.42 0.90 (0.2)
Gender-, age-adjusted							

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

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.

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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.

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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 brachial-ankle 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 ($DP = SBP \times HR/100$) (“dip” is defined as the Awake–Sleep difference divided by Awake ($\times 100$), 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 \pm 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 chronoeccological 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).

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

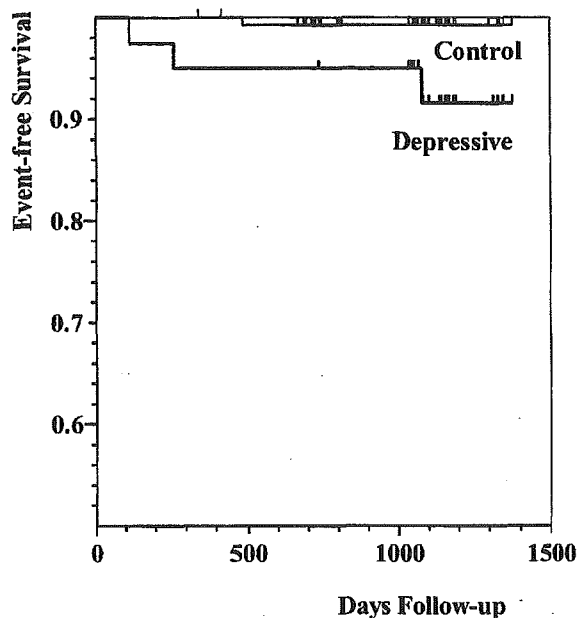


Fig. 1 Kaplan–Meier event probability curves for the incidence of vascular disease.

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).

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

Table 1 (continued)

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)

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 men and 136 women).

"dip" is defined as Awake–Sleep difference divided by Awake ($\times 100$), 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 cholesterol	mg/dl	131	204.4	30.3	37	215.5	28.0	-2.009	0.046
HDL cholesterol	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 ($\times 100$), where Awake and Sleep are average values during awake- and sleep-span, respectively.

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Modification of the functional reach test: Analysis of lateral and anterior functional reach in community-dwelling older people

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Abstract

The purpose of this study was to evaluate the validity and reproducibility of the modified lateral functional reach (FR), and to examine the associations between a variety of functional variables and the FR in community-dwelling older people (>65 years of age). A total of 383 aged Japanese participated in this study at the rural district Kahoku, Kochi, Japan, in 2002. The average age of the subjects was 78.6 years. The activity of daily living (ADL) and mental status were measured as outcomes. FR (anterior and lateral) and timed up and go (TUG) were measured as predictors. The test–retest reliability of lateral FR between the first and second measurement was very consistent. Subjects with greater lateral FR had higher basic and instrumental ADL (IADL) scores than did those with shorter lateral FR. However, there was no significant relationship between anterior FR and ADLs. The lateral FR of participants with depression was shorter than in those without depression, while the anterior FR did not correlate with the participants' scores on the geriatric depression scale (GDS). Lateral FR should be considered as a new, alternative means of assessing geriatric social activity and mental status in the elderly.

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Keywords: Lateral functional reach; Timed up and go (TUG); Activity of daily living (ADL); Depression

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1. Introduction

Elderly people that show problems in gait and balance experience difficulty in the activities of daily living (ADL). The functional reach (FR) test is a simple way to measure standing balance, that has been assessed for both validity and reliability (Duncan et al., 1990; Weiner et al., 1992). The classic FR test is inexpensive, and provides a reasonable clinical approximation of the anterior margin of stability (Duncan et al., 1990). However, the reliability of physical performance measured by the FR test has been considered to be lower than several standard self-reported measures of function (Tager et al., 1998). The anterior FR test only assesses anterior stability (Jonsson et al., 2002), and is a weak measure of the anterior stability limits. Movement of the trunk seems to influence the results of this test more than does displacement of the center of the pressure (Jonsson et al., 2002).

Elderly people frequently experience lateral falls and suffer fractures of the femoral neck. Therefore, it is important to examine the balance of the lateral side, to identify elderly people who may be at risk of falling. We improved a new procedure to measure lateral FR that involves evaluating the reach to both the right and left sides and assessing the association between the fall, many kinds of ADL, geriatric depression, and anterior FR. The purpose of this study was to assess the validity and reproducibility of the modified lateral FR test, and to document the significance of the FR in aged people.

2. Subjects and methods

2.1. Subjects

The investigated population consisted of 383 community-dwelling subjects aged 60 years and older (average age, 78.6 years) and the study was conducted in the district of Kahoku, in Kochi, Japan, in 2002. There were 234 females and 149 males ranging in age from 60 to 95 years. The subjects' average baseline characteristics are shown in Table 1.

Table 1
The baseline characteristics of the population

	Female	Male	Total
Number	234	149	383
Age (in 2002)	78.1 ± 6.2	79.3 ± 5.4	78.6 ± 5.9
Height (cm)	145.6 ± 6.7	158.5 ± 6.3	150.6 ± 9.1
Weight (kg)	57.5 ± 9.8	50.2 ± 8.9	53.0 ± 9.9
TUG (s)	12.6 ± 3.3	12.4 ± 3.1	12.5 ± 3.2
Anterior FR (cm)	24.5 ± 9.0	25.5 ± 9.8	24.9 ± 9.3
Lateral FR (cm)	17.3 ± 11.1	21.5 ± 13.6	18.9 ± 12.3
QUS (%: comparison with 20 years)	59.2 ± 14.0	68.5 ± 17.1	62.8 ± 15.9

QUS: quantitative ultrasound.

2.2. Methods

The interviews and examinations were conducted at the community plaza of Kahoku. They included a questionnaire covering physical health and functional status and a medical examination of the knee and lumbar region. Examination of functional performance such as FR and timed up and go (TUG) was also performed. The presence or absence of disease was based on the subjects' self-report of a doctor's diagnosis. Informed consent for this study was obtained from all participants.

The subjects were asked questions regarding basic ADL (BADL), such as walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming, and taking medicines. The subjects were also questioned about instrumental ADL (IADL), such as using public transportation, shopping for groceries, preparing meals, paying bills, banking, writing, reading newspapers, magazines or books, taking an interest in news about health, visiting friends, giving advice to family or friends, and talking to young people (Matsubayashi et al., 1997). We assessed the BADL and IADL scores using a 4-point scale, based on the level of assistance required for each activity: 3, completely independent; 2, some help needed; 1, much help needed; and 0, completely dependent (Matsubayashi et al., 1999).

A fall was defined as any event that led to an unplanned, unexpected contact with a supporting surface. We asked subjects to self-report the history of any falls that they had suffered in the past 6 months. The geriatric depression scale (GDS) (Gerety, 1982; Norris et al., 1987), a measure of depressive symptomatology, was assessed on a scale of 0–30 points. We assessed the items of the short form of the GDS (15 items), and a score of ≥ 6 points was considered to indicate depression.

2.2.1. The FR

FR represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position (Duncan et al., 1990; Weiner et al., 1992; Jonsson et al., 2002). In the classic FR test, the subject is asked to reach as far as forward as possible. In the modified lateral reach test, the subject is asked to reach as far as possible to the right and left sides. The measurement of lateral FR was expressed adding the measurements of reach to the right and left side (cm). We defined the threshold of anterior FR as 30 cm (Okumiya et al., 1999). In this study, lateral FR was divided into two groups of less than 20 cm, and 21 cm and more.

2.2.2. TUG test

In the TUG test (Mathias et al., 1986; Podsiadlo and Richardson, 1991), the subjects were given oral instructions to stand up from the chair, walk 3 m as quickly and as safely as possible, cross a line marked on the floor, turn around, walk back to the chair, and sit down. We defined the threshold of TUG as 16 s.

2.2.3. Statistical analysis

The ADL and GDS data were expressed as mean \pm S.D. and S.E.M. The differences between groups were evaluated using the Mann–Whitney *U*-test. The frequency of fall data

Table 2
The relation of each FR with ADLs

	Anterior FR (cm)		Lateral FR (cm)	
	Less than 30 (<i>N</i> = 265)	30 and more (<i>N</i> = 101)	Less than 20 (<i>N</i> = 214)	20 and more (<i>N</i> = 146)
BADL (points)	23.58 ± 0.99 se; 0.061	23.56 ± 1.16 se; 0.12	23.48 ± 1.11 se; 0.076	23.74 ± 0.90 se; 0.074
	<i>p</i> = 0.76		<i>p</i> = 0.039	
IADL (points)	11.58 ± 2.0 se; 0.13	11.70 ± 2.13 se; 0.21	11.34 ± 2.3 se; 0.16	12.08 ± 1.46 se; 0.12
	<i>p</i> = 0.36		<i>p</i> = 0.0016	

Mean ± S.D.; se: S.E.M.

was analyzed using the Kruskal–Wallis test. Differences were considered to be statistically significant at $p < 0.05$.

3. Results

Anterior FR and TUG were not significantly different between male and female subjects; however, lateral FR was greater in males than in females ($p = 0.0009$). The test–retest reliability of lateral FR between the first and second measurement was highly reliable (ICC = 0.90; CI: 0.89–0.96); however, the lateral FR was only weakly associated with the anterior FR (ICC = 0.32; CI: 0.22–0.41).

There was no significant association between the anterior FR and the number of falls ($p = 0.79$) or between the lateral FR and the number of falls ($p = 0.62$). There was a tendency for TUG to be associated with the number of falls, although this association failed to achieve statistical significance ($p = 0.10$).

Subjects with greater lateral FR (≥ 20 cm) had higher BADL ($p = 0.039$) and IADL ($p = 0.0016$) scores than those with shorter lateral FR (< 20 cm) (Table 2). However, subjects with greater anterior FR (≥ 30 cm) did not differ significantly from those with lesser anterior FR (< 30 cm) with regard to BADL ($p = 0.76$) or IADL ($p = 0.36$). Shorter TUG values were associated with greater BADL and IADL scores than were longer TUG ($p < 0.0001$).

Table 3
The association of anterior and lateral FR with the GDS

	GDS (points)		<i>p</i> value
	Less than 6	6 and more	
Anterior FR (cm)	25.4 ± 8.9 se; 0.65	24.8 ± 9.8 se; 0.82	0.54
Lateral FR (cm)	21.0 ± 12.4 se; 0.91	17.7 ± 9.3 se; 0.79	0.033

se: S.E.M.

The lateral FR of participants with depression ($GDS \geq 6$) was shorter than that of patients without depression ($GDS \leq 5$) ($p = 0.033$), whereas the anterior FR was not associated with GDS scores ($p = 0.54$) (Table 3).

4. Discussion

The maintenance of postural control is very important for performing the daily activities of living, especially in the elderly population. Maintaining postural control is a complex process, and there is no single measure available that can assess all the aspects of this process (King et al., 1994; Wallmann, 2001). Presently, the three tools that are commonly used to measure balance impairment are the Berg balance scale (BBS), the FR test, and the TUG test. The BBS was developed to assess balance in elderly people with neurological disorders (Daubney and Culham, 1999). In this study, we measured FR and TUG in an elderly population dwelling within the Kahoku community in Kochi, Japan.

As we have indicated, FR represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. In the original method the subjects reached forward as far as possible, to measure anterior FR. The anterior FR test is strongly influenced by factors, such as the movement of the trunk. Limits of stability are one aspect of balance (Shumway-Cook and Woollacott, 2000). Any reduction in spinal flexibility also decreases the distance of anterior FR. Newton (2001) developed a multi-directional reach test, i.e.: forward, to the right, left and backwards, that was reliable. However, the measurements in four directions require time, and leaning backwards has the risk of falling.

We have improved a modified lateral FR test, in which the subject reaches as far as possible to the right and left sides. The test–retest reliability of lateral FR is highly consistent; however, lateral FR is not strongly associated with anterior FR.

There are many reports describing the risk factors associated with accidental falls. Davis et al. (1999) reported that having a long FR was associated with a lower risk of falling. In contrast, Eagle et al. (1999) reported that the FR test is time consuming and inconvenient and is a poor predictor of falls (Thepa et al., 1996). In an attempt to clarify these discrepancies, we examined whether anterior and lateral FR tests were associated with the frequency of falling. Our findings show that there was no relationship between these FR tests and the number of falls reported by elderly subjects. Lateral FR was correlated with BADL and IADL; but the classic anterior FR was not. Therefore, it seems that lateral FR is a useful marker for the ability to perform ADL.

Although various factors are associated with falls; impaired balance and mobility have been consistently identified as risk factors. Thus, TUG is a sensitive and specific measure for identifying community-dwelling adults who are at risk of falling (Shumway-Cook et al., 2000). The present study also indicates that TUG tends to be associated with the number of falls reported. Gait speed has also been found to be a useful indicator of ability to perform ADL (Potter et al., 1995). There was an association reported between gait time and TUG in an elderly orthopaedic rehabilitation population (Freter and Fruchter, 2000). In the present study, TUG was also related to the ADL, and our findings are consistent with the studies mentioned above.

There have been only a few reports regarding the relationship between functional performance and depression. Our study demonstrates that depressed elderly subjects have shorter lateral FR, as well as reduced balance and mobility, as compared to normal elderly subjects. In contrast, there was no relationship between anterior FR and depression. Further studies are needed to determine why lateral FR was more closely correlated with geriatric depression than anterior FR. Further studies are also needed to clarify the relationship between lateral FR and TUG, and to find out the reason why ADL is associated with lateral but not anterior FR.

In conclusion, a longer lateral FR appears to be associated with a greater ability to perform ADL and a reduced chance of suffering geriatric depression, whereas anterior FR is not associated with ADLs nor depression scores. Therefore, evaluation of lateral FR should be considered a new, alternative means of assessing geriatric social activities and mental status.

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