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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 brachia-lankle 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).

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.

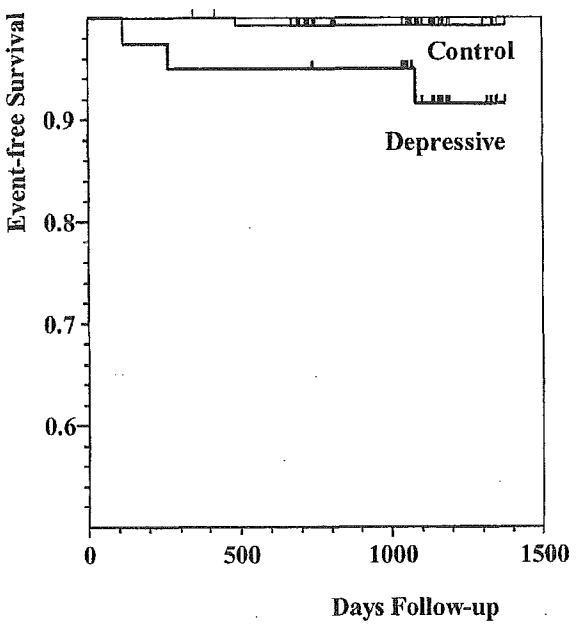

Fig. 1 Kaplan–Meier event probability curves for the incidence of vascular disease.

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).

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)*

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.

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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 $\geq$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 ($N = 265$)	30 and more ($N = 101$)	Less than 20 ($N = 214$)	20 and more ($N = 146$)
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
	$p = 0.76$		$p = 0.039$	
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
	$p = 0.36$		$p = 0.0016$	

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)		
	Less than 6	6 and more	p value
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 ≥ 6) was shorter than that of patients without depression (GDS ≤ 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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ORIGINAL ARTICLE

Association between arterial stiffness and platelet activation

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Increased arterial stiffness is strongly associated with atherosclerosis, while platelet activation is an important trigger of thrombotic events in patients with atherosclerosis. However, little is known about the effect of arterial stiffness on platelet activation. We therefore investigated the association between arterial stiffness and platelet activation in 38 normal volunteers (20 men and 18 women) aged 23–77 years (mean = 49 ± 15 years). Arterial stiffness was assessed by measuring brachial–ankle pulse wave velocity (ba-PWV) and heart–brachial PWV (hb-PWV). Flow cytometric analyses were performed to evaluate platelet activation by measuring surface expression of P-selectin and platelet–neutrophil complexes (PNC) before and after activation by ADP. We also calculated the difference between basal and stimulated states of P-selectin and PNC to assess platelet activation reserve. PWVs were significantly correlated with age and BP (r = 0.60–0.81). For platelet activation and activation reserve, correlations with age were less strong but remained significant (r = 0.36–0.61), with the exception of P-selectin (not significant, NS), and correlations with SBP were similar (r = 0.35–0.53). A significant correlation was found between PWVs and platelet activation (r = 0.43–0.74). Multiple regression analysis demonstrated significant correlations between platelet activation and reserve and PWVs (coefficient = 2.17–6.59), when both age and BP were adjusted for simultaneously. In conclusion, platelet activation was associated with arterial stiffness, suggesting that arterial stiffness may play an important role in thrombotic events.
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Introduction

Platelet activation and aggregation are important triggers of thrombotic events in patients with atherosclerosis. In such patients, platelets are activated at the site of atheroma[1] due to increased shear stress in the narrowed vessels.[2,3] Increased platelet activation is observed in patients with coronary risk factors and cardiovascular events.[4–12]

Increased arterial stiffness, measured with pulse wave velocity (PWV), has been shown to be associated with atherosclerosis and risk factors of atherosclerotic cardiovascular disease,[13–21] and is an independent predictor of cardiovascular events,[22,23] Therefore, although platelets are likely to be activated in patients with atherosclerotic disease who exhibit increased arterial stiffness, little is known about the relation of arterial stiffness itself to platelet activation.

Recently, platelet activation has been widely evaluated by measuring soluble P-selectin; a platelet surface molecule also termed CD62P.[4,6–8,11] Although the measurement of soluble P-selectin is simple and useful, it is an indirect method of evaluating platelet activation. On the other hand, platelet activation can be detected directly by measuring surface antigen CD62P using flow cytometry.[2,3,5,9,10,12] Furthermore, detection of platelet–neutrophil complexes (PNC), which are formed as a result of interaction with CD62P provides an additional means to detect platelet activation.[24]

The purpose of this study was to investigate the association between arterial stiffness and platelet activation by measuring PWV, P-selectin, and PNC in subjects without atherosclerotic disease.

Materials and methods

Subjects

We studied 38 healthy nonsmoking volunteers (20 men and 18 women), aged 23–77 years

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(mean = 49 ± 15 years) with no evidence of heart disease on physical examination, standard 12-lead electrocardiography, chest radiography, echocardiography, or blood chemistry analysis. Subjects had no self-reported past history or current evidence of cardiovascular disease, hypertension, hypercholesterolaemia, diabetes mellitus or renal disease. Basic characteristics of subjects are shown in Table 1. None of the subjects had frequent ectopic beats or atrial fibrillation and none had taken any medication for at least 10 days. Informed consent was obtained before performing the study and the study protocol was approved by the Local Ethics Committee of Kochi Medical School.

Evaluation of arterial stiffness

Arterial stiffness was evaluated by PWV, measured using volume-plethysmographic apparatus (Colin, Komaki, Japan).[18–21] Data were acquired with subjects lying supine in a quiet and temperature-controlled room at 11 AM, at least 3 h after breakfast. Surface electrodes were attached to both wrists for ECG measurement, a microphone was positioned at the left sternal edge to detect heart sounds, and cuffs incorporating plethysmographic and oscillometric sensors were fastened around both the brachial regions and ankles to measure pulse wave forms and blood pressure. Brachial–ankle PWV (ba-PWV) and heart–brachial PWV (hb-PWV) were measured as follows. The time interval between the wave foot of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachial region and ankle, while the time interval between the heart and the right brachial artery was defined as the time interval between the second heart sound and the right brachial waveform. The distance between these sampling points was calculated automatically according to the height of the subject. PWVs were calculated by dividing each distance by the respective time interval. Right brachial blood pressure (systolic and diastolic) and pulse rate were concurrently measured.

Table 1 Clinical characteristics of subjects

Parameters	*All subjects (n = 38)*
Age (years)	49 ± 15
Gender, male/female	20/18
Systolic blood pressure (mmHg)	125 ± 16
Diastolic blood pressure (mmHg)	77 ± 10
Pulse rate (bpm)	66 ± 10
Blood sugar (mg/dl)	98.5 ± 18.5
Total cholesterol (mg/dl)	192.6 ± 20.7
Blood urea nitrogen (mg/dl)	14.0 ± 18.5
Creatinine (mg/dl)	0.69 ± 0.15
PNC (%)	9.5 ± 4.9
PNC(ADP) (%)	20.2 ± 9.9
Δ-PNC	10.7 ± 6.9
P-selectin (%)	13.1 ± 1.7
P-selectin(ADP) (%)	36.6 ± 9.2
Δ-P-selectin	23.6 ± 9.1
hb-PWV (m/s)	5.3 ± 0.9
ba-PWV (m/s)	13.8 ± 3.0

Values are expressed as mean ± s.d.
PNC = platelet neutrophil complexes; ADP = adenosine diphosphate; Δ-PNC = PNC (ADP)−PNC; Δ-P-selectin = P-selectin (ADP)−P-selectin; hb-PWV = heart–brachial pulse wave velocity; ba-PWV = brachial–ankle pulse wave velocity.

Measurement of platelet activation

Sample preparation and measurement of platelet P-selectin (CD62P) and PNC levels were performed according to the method described by Peters *et al*.[24] To minimize platelet activation during blood collection, blood was drawn via a 21 G butterfly needle without the use of a tourniquet. After discarding the first 2 ml of blood, a further 2 ml was collected and immediately added to 200 μl of sodium citrate (3.13%). All antibodies were sourced as follows: Fluorescein isothiocyanate (FITC) labelled IgG1 anti-CD62P from Dainippon Pharmaceutical, Osaka, Japan, phycoerythin (PE) labelled IgG2a anti-CD42b and FITC labelled IgG1 anti-CD11b from Beckman Coulter, Fullerton, CA, USA. As negative controls, FITC-labelled IgG1 (Beckman Coulter, Fullerton, CA, USA) and double-stained (FITC/PE) IgG1 and IgG2a (Dako, High Wycombe, Bucks, UK) irrelevant antibodies were included.

Sample preparation for the measurement of platelet CD62P level: In all, 5 μl of blood was added to a round-bottomed polystyrene tube containing 50 μl of platelet buffer (10 mmol/l HEPES, 145 mmol/l NaCl, 5 mmol/l KCl, 1 mmol/l $MgSO_4$; pH 7.4), and 5 μl of anti-CD62P or control IgG1 antibody. Following gentle suspension, samples were incubated in the dark at room temperature for 20 min without stirring. Then 250 μl of fixative was added and the tubes were incubated for an additional 10 min. The samples were then diluted with 500 μl of buffer and analysed. Flow cytometric analysis was performed within 1 h of fixation.

Sample preparation for the measurement of PNC level: In all, 50 μl of blood was added to a round-bottomed polystyrene tube containing 5 μl of anti-CD42b, and 5 μl of anti-CD11b or isotype control antibodies. Following gentle mixing, samples were incubated in the dark at room temperature for 10 min without stirring. Then 500 μl of fixative was added and the tubes were incubated for additional 10 min. Flow cytometric analysis was performed within 1 h of preparation.

Flow cytometric analysis

Blood samples were analysed in a COULTER EPICS XL Profile Flow Cytometer, Miami, FL, USA, using either single or double fluorochromes. The peak emission intensity of FITC fluorescence was

detected at 515 nm and that of phycoerythin fluorescence at 580 nm.

Measurement of platelet CD62P level: After forward and side scatter measurements were made with gain setting in logarithmic mode, platelet-sized events were counted. CD62P-positive platelets were defined as those with a fluorescence intensity exceeding that of 98% of the platelets staining with control antibody.

Measurement of PNC level: After forward and side scatter measurements were made with gain setting in linear mode, neutrophil-sized events were selected. Results were defined as positive when the fluorescence intensity exceeded that of 98% of the isotype-matched (IgG1 and IgG2a) control antibodies staining. Events positive for both CD11b and CD42b were considered to represent PNCs and were expressed as percentages of events with positive CD11b staining.

Evaluation of platelet activation reserve: We evaluated platelet activation reserve, that is, the ability of the platelets to be activated, in a separate experiment. Platelets were activated with 5 μl of adenosine diphosphate (ADP). We also calculated the difference between basal and stimulated states of P-selectin expression (Δ-P-selectin) and PNC level (Δ-PNC) to determine activation reserve.

Statistical analysis

Data are presented as mean ± s.d. Univariate linear correlation analysis and multiple regression analysis were used for statistical evaluation. The variables significantly associated with platelet activation on univariate analysis were included in a multiple regression analysis in order to adjust PWV for each variable. Gender differences were evaluated with ANOVA. *P*-values <0.05 were considered to represent statistical significance.

Results

Both ba-PWV and hb-PWV exhibited significant positive correlations with age, systolic, and diastolic blood pressure ($r=0.60$–0.81, $P<0.05$ or <0.01), and pulse rate ($r=0.44$, $P<0.05$, $r=0.65$, <0.01, respectively) (Table 2). For platelet activation and activation reserve, correlations with age were less strong but remained significant ($r=0.36$–0.61, $P<0.05$ or <0.01) with the exception of Δ-P-selectin (not significant, NS), and correlations with systolic and diastolic blood pressure were similar ($r=0.35$–0.53, $P<0.05$ or <0.01) with the exception of P-selectin (NS) (Table 3). However, platelet activation and activation reserve exhibited no significant correlation with pulse rate, blood glucose, total cholesterol, blood urea nitrogen or creatinine. No significant gender-related differences were observed in any of these correlations (Tables 2 and 3).

Table 2 Correlation between PWV and clinical indices

	hb-PWV	*ba-PWV*
Age	0.74**	0.80**
Systolic blood pressure	0.61**	0.81**
Diastolic blood pressure	0.60**	0.74**
Pulse rate	0.44*	0.65**
Blood sugar	−0.05	−0.17
Total cholesterol	−0.03	−0.30
Blood urea nitrogen	−0.32	0.32
Creatinine	0.04	−0.14
Gender		
Male	5.5±1.0	14.1±3.0
Female	5.2±0.8	13.6±3.1

PNC = platelet neutrophil complexes; ADP = adenosine diphosphate; Δ-PNC = PNC (ADP)−PNC; Δ-P-selectin = P-selectin (ADP)−P-selectin; hb-PWV = heart–brachial pulse wave velocity; ba-PWV = brachial–ankle pulse wave velocity.
For parameters from age to creatinine, values are correlation coefficients.
*$P<0.05$.
**$P<0.01$.
For gender, values are mean ± s.d., with differences evaluated with ANOVA.

PWVs exhibited significant positive correlations ($r=0.43$–0.74, $P<0.05$ or <0.01) to all indices of platelet activation and reserve (Table 4, Figure 1). When age or blood pressures were adjusted for on multivariate analysis, some indices of platelet activation and reserve were significantly related to PWVs ($r=0.34$–7.67, $P<0.05$ or <0.01). When both age and blood pressures were simultaneously adjusted for, significant correlations remained between platelet activation and reserve and PWVs ($r=2.17$–6.59, $P<0.05$ or <0.01) (Table 4). In other words, although the relationship between PWVs and the indices of platelet activation was strongly affected by age and blood pressure, a significant association remained when these factors were adjusted for.

Discussion

The main finding of this study was that platelet activation and activation reserve were associated with arterial stiffness when analyses were adjusted for age and blood pressure. This suggests that increased arterial stiffness might play an important role in thrombotic events.

Patients with hypertension, cerebrovascular disease, coronary heart disease, diabetes mellitus, and renal failure are recognized to have less arterial compliance than normal subjects.[13–15,17–19] Increased PWV has also been reported to be an independent predictor of cardiovascular events in patients with hypertension or renal failure, and in elderly subjects.[22,23] The association between increased arterial stiffness and high incidence of cardiovascular events may be explained by the existence of atherosclerosis. Hirai *et al*[25] have demonstrated strong associations between abdominal aortic and