

We also used sex-specific quintile points (lowest 20%) as the cut-off values for SMI, and these values were similar to previously reported cut-off points of >2 standard deviations less than the mean value for young Japanese adults (7.0 kg/m<sup>2</sup> in men and 5.8 kg/m<sup>2</sup> in women).<sup>20</sup> These results suggest that the lowest 20% of SMI in Japanese older adults could be a useful substitute for the value two standard deviations below the sex-specific mean SMI of young adults.

Using the EWGSOP-algorithm, 7.5% of all participants were classified as having sarcopenia. The prevalence of sarcopenia in older adults has been widely investigated in European and American countries, and most of these values ranged from 10% to 30%.<sup>3,5,21,22</sup> Reports published on the prevalence of sarcopenia in older adults in Asian countries have tended to show a lower prevalence of sarcopenia in Japan (11.3% and 10.7% in men and women, respectively),<sup>20</sup> Korea (12.1% and 11.9% in men and women, respectively),<sup>23</sup> Hong Kong (12.3% and 7.6% in Chinese men and women, respectively)<sup>24</sup> and Taiwan (23.6% and 18.6% in men and women, respectively).<sup>25</sup> The present study found a similarly low prevalence of sarcopenia. Differences in the prevalence rate of sarcopenia between races and regions. However, because of differences in the operative definitions and screening methods used to detect sarcopenia, we could not directly compare our results with other studies. In addition, the cut-off values for grip strength that we used were slightly lower than those of previous studies. This might lead to an underestimation of the prevalence rate of sarcopenia in our sample. Additional studies are required not only to confirm the validity of cut-off points, but also to determine the standardized definition of sarcopenia.

We tested two screening methods for determining sarcopenia in the present study: (i) the EWGSOP-suggested algorithm using gait speed as the first step; and (ii) the muscle mass and strength algorithm. The resulting prevalence rates of sarcopenia corresponded closely. Although the EWGSOP-algorithm uses a measurement of gait speed as the first step with a cut-off point of 0.8 m/s, there were few people whose gait speed was below 0.8 m/s in our sample of community-dwelling older adults. In addition, most participants categorized as slow (gait speed <0.8 m/s) also had muscle weakness. In fact, Buchner *et al.* reported that the relationship between muscle strength and gait speed was non-linear, and small changes in muscle strength could have substantial effects on gait speed in frail adults, whereas large changes in muscle strength have little or no effect in healthy adults.<sup>26</sup> The EWGSOP report does not specifically recommend a method for measuring gait speed, and variations in methodology exist (e.g. walking courses may or may not include acceleration and deceleration phases). Differences in the methodology used to

measure gait speed could be one reason why a cut-off point of 0.8 m/s was too low for the present study. In any case, we consider that a cut-off value of 0.8 m/s will be too slow if the acceleration and deceleration phases are excluded from the measurement of gait speed. It is debatable whether gait speed is necessary for screening sarcopenic participants in community-dwelling older adults. Future research should examine the necessity of including gait speed in algorithms and the validity of cut-off values.

The present study had several limitations that should be recognized. First, the response rate to postal invitation was 35.7%, and as a result, it is possible that our study suffered from selection bias. Second, we estimated the appendicular skeletal muscle mass by BIA methods. Although BIA is reported to be a highly reliable and accurate method of assessing muscle mass, the accuracy of BIA measurement can be affected by factors such as hydration status, food intake and exercise.<sup>27</sup> Older adults in particular can often have disturbances in water balance and/or extracellular water retention (e.g. edema). Yamada *et al.* suggested that extracellular water might mask actual muscle atrophy.<sup>28</sup> More precise methods (dual-energy X-ray absorptiometry or magnetic resonance image) should be used in future to assess muscle mass. Third, we used pragmatic cut-off points for determining sarcopenia. It is currently unclear whether the sex-specific lowest 20% was the best value for screening sarcopenic participants. Additional longitudinal studies will be required to confirm the predictive validity of the cut-off values in the future.

The present study showed that the prevalence of sarcopenia in a representative sample of older Japanese adults was 8.2% for men and 6.8% for women based on the EWGSOP-algorithm. When compared with the muscle mass and strength algorithm, the EWGSOP-algorithm classified seven additional people (0.15%) into sarcopenia. Future research should examine the necessity of including gait speed in algorithms and the validity of cut-off values.

## Acknowledgments

This study was supported in part by a Health Labor Sciences Research Grant (Comprehensive Research on Aging and Health: H23-Choju-Ippan-001) and the Research Finding for Longevity Sciences (22-16) from National Center for Geriatric and Gerontology, Japan. We thank the Obu City Office for help with participant recruitment.

## Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE: EPIDEMIOLOGY,  
CLINICAL PRACTICE AND HEALTH**Association of decreased sympathetic nervous activity with mortality of older adults in long-term care**Koji Shibasaki,<sup>1</sup> Sumito Ogawa,<sup>1</sup> Shizuru Yamada,<sup>2</sup> Katsuya Iijima,<sup>1</sup> Masato Eto,<sup>1</sup> Koichi Kozaki,<sup>2</sup> Kenji Toba,<sup>3</sup> Masahiro Akishita<sup>1</sup> and Yasuyoshi Ouchi<sup>1</sup><sup>1</sup>Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, <sup>2</sup>Department of Geriatric Medicine, Kyorin University School of Medicine, Tokyo, and <sup>3</sup>National Center for Geriatrics and Gerontology, Obu, Japan**Aim:** To investigate the relationship between physical function, mortality and autonomic nervous activity measured by heart rate variability of elderly in long-term care.**Methods:** Cross-sectional and longitudinal studies were carried out at hospitals and health service facilities for the elderly in Nagano prefecture, Japan, from July 2007 to March 2011. A total of 105 long-term care older adults and 17 control older adults with independent physical function were included. The Functional Independence Measure (FIM) and Barthel Index were determined as indices of physical function. Twenty-four-hour Holter monitoring was carried out. From RR intervals in electrocardiograms, heart rate and standard deviations of all NN intervals in all 5-min segments of the entire recording, power spectral density, low frequency, high frequency and low frequency/high frequency (LF/HF) were calculated.**Results:** FIM score and Barthel Index were  $46 \pm 26$  and  $30 \pm 31$ , respectively, in long-term care elderly. FIM and Barthel index were significantly correlated with heart rate and the standard deviations of all NN intervals after adjustment for age, sex, cardiovascular risk factors and FIM. Furthermore, LF/HF was significantly decreased in long-term care elderly compared with control elderly after adjustment for covariates. In addition, decrease in LF/HF was an independent risk factor for mortality.**Conclusion:** Low LF/HF activity was observed in long-term care elderly and was related to an increase of overall mortality. *Geriatr Gerontol Int* 2014; 14: 159–166.**Keywords:** heart rate variability, long-term care, mortality, motor activity, sympathetic nervous system.**Introduction**

The number of older adults who require long-term care (LTC) has been increasing in Japan, and it was reported that there were 4.67 million older adults in LTC in 2008.<sup>1</sup> One of the characteristics of older adults in long-term care is physical and cognitive dysfunction. Physical dysfunction, including slow gait, low handgrip strength, low physical activity, weight loss and exhaustion, are reported to be associated with increased overall mortality.<sup>2</sup> In Japan, LTC elderly is defined as those who require assistance with walking, moving, and washing their face, body and mouth, representing functional dis-

ability and high mortality.<sup>3</sup> Thus, it is important to maintain or increase physical function in LTC elderly.

The underlying causes of physical dysfunction in Japanese LTC elderly include cerebrovascular disease, dementia, fractures, falls, weakness as a result of aging, and arthritis.<sup>3</sup> Recent studies have shown that these diseases with physical dysfunction are associated with low sympathetic nervous system activity.<sup>4–7</sup>

Skin sympathetic reactivity (SSR) reflects sympathetic nervous system activity. Muslumanoğlu *et al.* showed that low SSR was associated with greater severity of paralysis, and depression of sympathetic reflex activity was associated with moderate or severely limited motor function in the chronic phase of ischemic cerebrovascular disease in elderly patients.<sup>5</sup> In addition, low plasma norepinephrine and low iodine-131-meta-iodobenzylguanidine (<sup>123</sup>I-MIBG) uptake were observed in patients with Lewy body dementia compared with normal healthy subjects.<sup>6,7</sup> RR intervals in the electrocardiogram are utilized to evaluate heart rate variability

Accepted for publication 10 March 2013.

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(HRV), which reflects autonomic nervous system activity.<sup>8</sup> In practice, low frequency/high frequency (LF/HF), a marker of sympathovagal balance or sympathetic modulation, showed a positive correlation with respiratory and skeletal muscle strength in chronic obstructive pulmonary disease.<sup>4</sup> Furthermore, decreased LF/HF was related to overall mortality in frail older adults.<sup>9</sup>

In addition to measurement of SSR, norepinephrine spillover and <sup>123</sup>I-MIBG scintigraphy uptake, HRV has recently been used as a marker of autonomic nervous function.<sup>8</sup> HF was reported to reflect parasympathetic nervous system activity and LF/HF to represent sympathovagal balance or sympathetic modulation. In addition, decreased HRV was associated with cardiovascular disease (CVD),<sup>10</sup> cardiac death<sup>11</sup> and all-cause mortality.<sup>9</sup> Whereas HRV is known to decrease with the aging process,<sup>12,13</sup> little is known about the relationship between sympathetic nervous activity and mortality in LTC elderly.

In the Framingham heart study, a cohort study in American community-dwelling people, mortality and HRV were investigated in older adults, and it was not shown that low LF/HF correlated with mortality,<sup>14</sup> whereas in a cohort study of frail older adults, low LF/HF was significantly correlated with both frailty and mortality in the Women's Health and Aging Study-I (WHAS-I).<sup>9</sup>

Aging attenuates sympathetic nervous modulation,<sup>12,13</sup> and previous studies suggested that low sympathetic nervous activity might be associated with physical and cognitive dysfunction. However, only some of the subjects were frail or LTC elderly,<sup>9,14</sup> and there is little evidence describing the relationship between physical function, mortality and sympathetic nervous activity in LTC elderly. In particular, few studies have focused on the specific characteristics of sympathetic nervous activity in LTC elderly. Therefore, we investigated the relationship between sympathetic nervous activity, measured by HRV, and physical function and mortality in older adults in LTC.

## Methods

### *Study design and participants*

The present observational study analyzed 105 consecutive older adults in LTC aged 75 years or older who were admitted to a rehabilitation unit or a health service facility for older adults that provided rehabilitation. All hospitals and health service facilities were located in Nagano prefecture, Japan. Inclusion criteria were older adults in LTC aged 75 years or older receiving rehabilitation. Exclusion criteria were treatment of acute phase diseases within the past 2 weeks, arrhythmia, administration of anti-arrhythmia drugs or  $\beta$ -blockers,

malignancy and neurodegenerative diseases other than dementia. As a control for the present study, we recruited 17 elderly outpatients with intact activities of daily living (ADL) who were matched for age, sex and CVD risk factors. The same inclusion and exclusion criteria were used for these control subjects. Medical records were reviewed to obtain information about the medical history of CVD, such as hypertension, diabetes mellitus, hyperlipidemia, chronic heart failure and ischemic heart disease, which was confirmed by the patients or their family. The present study protocol was approved by the institutional review board of the facility. Written informed consent was obtained from all participants or their families.

### *Heart rate variability*

Ambulatory Holter recording was carried out for 24 h using QR2100 (Fukuda ME Kogyo, Tokyo, Japan) and processed with HS1000VL (Fukuda ME Kogyo). For time domain analysis, the standard deviations of all NN intervals in all 5-min segments of the entire recording (SDANN) were calculated, and frequent domain analysis was carried out with fast Fourier transform. From the power spectral density, low frequency (LF; 0.04~0.15 Hz), high frequency (HF; 0.15~0.40 Hz) and low frequency/high frequency (LF/HF) were determined.

### *Anthropometric, physical function and hematological measures*

Height, weight and body mass index (BMI) were measured before Holter monitoring. The Functional Independence Measure (FIM)<sup>15</sup> and Barthel Index<sup>16</sup> were determined in order to assess physical function. Venous blood samples were obtained from participants in the morning after an overnight fast. Blood cell counts and serum levels of chemical parameters were determined by a commercial laboratory (Health Science Research Institute, Yokohama, Japan).

### *Statistical analysis*

Data were analyzed using SPSS software version 11.0.1J (SPSS Japan, Tokyo, Japan). Mann-Whitney *U*-test for continuous variables and  $\chi^2$ -test for categorical variables were used to compare controls and LTC elderly. Pearson's correlation coefficient was calculated, and standardized multiple regression analysis of HRV indices was carried out with age, sex, FIM, Barthel Index and blood nutritional data as covariates. Multiple regression analysis was used to calculate Cox hazard ratio, with adjustment for age, sex, clinical risk factors and FIM. Kaplan-Meier survival rate was computed for HRV indices.

**Table 1** Characteristics of long-term care elderly and healthy elderly controls

	LTC elderly	Controls	<i>P</i>
No. participants	105	17	
Age (years)	86.5 ± 6.0 (75–100)	86.3 ± 9.1 (75–103)	0.311
Sex, male (%)	29 (27.6)	6 (35.3)	0.999
Body mass index	19.5 ± 3.3	22.0 ± 3.5	0.009
Cardiovascular risk factors, <i>n</i> (%)			
Hypertension	57 (54.3)	11 (64.7)	0.590
Diabetes mellitus	13 (12.4)	2 (11.8)	0.999
Hyperlipidemia	14 (13.3)	3 (17.6)	0.921
Chronic heart failure	12 (11.4)	1 (5.9)	0.792
Ischemic heart disease	15 (14.3)	1 (5.9)	0.572
Physical function			
FIM	46 ± 26	116 ± 24	<0.001
Barthel Index	30 ± 31	92 ± 16	<0.001
Blood nutritional data			
Albumin (g/dL)	3.5 ± 0.5	3.9 ± 0.3	<0.001
Hemoglobin (g/dL)	12.0 ± 1.8	12.4 ± 2.2	0.188
Total cholesterol (mg/dL)	177 ± 40	175 ± 34	0.892
Heart rate variability indices			
SDANN	85.0 ± 34.3	112.1 ± 27.2	0.001
Heart rate (b.p.m.)	73.1 ± 12.1	71.5 ± 7.4	0.878
LF (ms <sup>2</sup> )	36.1 ± 25.3	42.4 ± 37.5	0.274
HF (ms <sup>2</sup> )	65.9 ± 56.3	60.7 ± 52.3	0.813
LF/HF	0.69 ± 0.27 <sup>†</sup>	0.87 ± 0.31	0.023

Values are mean ± standard deviation. <sup>†</sup>After adjusted for age, sex, cardiovascular risk factors and Function Independent Measure (FIM), low frequency/high frequency (LF/HF) were significantly lower in long-term care elderly than healthy controls (*P* = 0.049). HF, high frequency; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

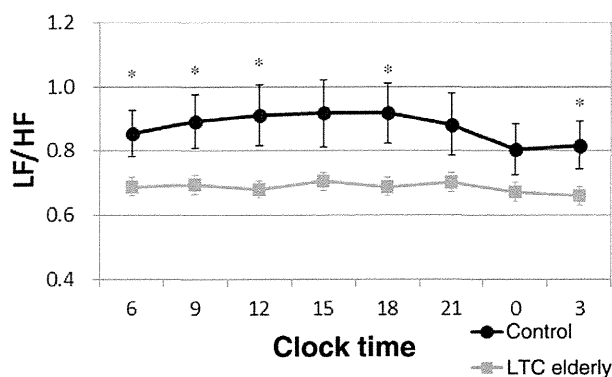
## Results

We registered 105 elderly in LTC, and assessed HRV from 24-h Holter monitoring. The underlying diseases of older adults in LTC for rehabilitation were cerebrovascular disease (*n* = 59, 56.2%), disuse syndrome (*n* = 26, 24.8%), fracture (*n* = 19, 18.1%) and dementia (*n* = 1, 1.0%). The proportions of underlying diseases were similar to those reported in Japanese older adults in LTC.<sup>3</sup>

The background data of the present study are shown in Table 1. In LTC elderly, mean age was 86.5 ± 6.0 years, blood nutritional data including albumin, hemoglobin and total cholesterol were at the lower limit of the normal range, and physical function represented by FIM and Barthel Index was significantly lower (46 ± 26 and 30 ± 31, respectively) than that in elderly controls (116 ± 24 and 92 ± 16, respectively). Scores for each FIM item were as follow: eating 3.7 ± 2.2, grooming 2.6 ± 1.8, bathing 1.5 ± 1.1, upper body dressing 2.5 ± 1.7, lower body dressing 2.2 ± 1.6, toileting 2.7 ± 2.0, bladder management 2.6 ± 2.1, bowel management 2.4 ± 2.0, bed to chair transfer 3.0 ± 1.9, toilet transfer 2.4 ± 1.7, shower transfer 1.5 ± 1.4,

locomotion (ambulatory or wheelchair level) 2.0 ± 1.8, stairs 1.2 ± 0.8, cognitive comprehension 3.6 ± 2.2, expression 3.6 ± 2.2, social interaction 3.2 ± 2.2, problem solving 2.8 ± 1.9 and memory 2.8 ± 1.9. These score showed that the overall participants required moderate care supporting physical and cognitive function. In addition, BMI, albumin, SDANN and LF/HF were significantly decreased in LTC elderly compared with elderly controls. After adjustment for covariance, of all HRV indices, only LF/HF was significantly lower in LTC elderly (Table 1). Data of HRV indices were obtained every 5 min, and averaged every 3 h to examine the circadian rhythm in both LTC elderly and healthy controls. A significant decrease of LF/HF was observed in the night-time in healthy controls, whereas there was a loss of circadian rhythm in LTC elderly (Fig. 1).

Multiple regression analysis showed that the associations between heart rate, SDANN and physical function (Barthel Index and FIM) were independent of age, sex, and CVD. Furthermore, albumin and hemoglobin were also correlated with heart rate and SDANN. In contrast, LF, HF and LF/HF were not significantly correlated with physical function and blood nutritional data (Table 2).



**Figure 1** The activity of low frequency/high frequency (LF/HF) in long-term care (LTC) elderly and controls. The RR interval data were measured every 5 min, and averaged every 3 h. \* $P < 0.05$ , mean  $\pm$  SEM,

Next, we followed the survival of LTC elderly, and 23 people died among 105 LTC elderly during a mean follow-up period of 8.9 months. The major cause of death was pneumonia ( $n = 12$ ). There was no sign of stroke among the study participants, and one participant with acute myocardial infarction was observed during the follow-up period. Mortality according to HRV indices divided by the average is shown in Table 3. After adjustment for covariates, of all HRV indices, only LF/HF was associated with mortality. Kaplan–Meier survival curves also showed an association between decreased LF/HF and high mortality (Fig. 2). In addition to adjusted covariates, BMI, Barthel Index, and blood nutritional data were not different between the high LF/HF group and low LF/HF group (data not shown).

## Discussion

In the present study, we investigated the relationship between physical function, mortality and sympathetic nervous activity measured by HRV in Japanese LTC elderly, and it was shown that LF/HF was significantly decreased in LTC elderly after adjustment for age, sex, CVD risk factors and FIM compared with elderly controls. In addition, the circadian rhythm of LF/HF was lost in LTC elderly, and low LF/HF was associated with overall mortality.

In a previous study, low LF/HF was associated with both frailty and mortality in community-dwelling people of whom one-third were frail elderly,<sup>9</sup> and these associations were consistent with the present data. Additionally, low LF/HF was also shown in LTC elderly, and was independent of physical function.

Elevated heart rate or low SDANN leads to cardiovascular disease and low physical function,<sup>17,18</sup> and the same relationship was also observed in LTC elderly. Furthermore, low albumin and low hemoglobin were

observed in the high heart rate group, and limited physical function was observed in LTC elderly. These results are supported by a previous report.<sup>19</sup> So it might be possible to improve the physical function of LTC elderly by maintaining their nutritional state. The high LF/HF group has been reported to show high physical function and muscle mass,<sup>4,20</sup> whereas the present data did not show this association. One of the reasons for this discrepancy is thought to be the effect of aging. Aging generally attenuates LF/HF, and the patients in the present study were older than those in other studies.<sup>9,14</sup> Another reason might be autonomic nervous system disturbance. In particular, the circadian rhythm of LF/HF was impaired in LTC elderly.

Circadian imbalance of LF/HF has been shown in some disorders, such as Parkinson's disease, type 2 diabetes mellitus (T2DM) and ischemic stroke;<sup>21–23</sup> and furthermore, physical activity also influences HRV indices.<sup>24,25</sup> In the present study, LTC elderly with Parkinson's disease were excluded, and CVD risk factors including T2DM were matched between LTC elderly and healthy controls, as stroke and physical activity might affect LF/HF. However, the influence of both conditions on LF/HF is controversial. High physical activity and good posture led to high LF/HF activity,<sup>26</sup> whereas it was also suggested that LF/HF was not affected by physical activity.<sup>13</sup> The effect of LF/HF on stroke is also controversial.<sup>23,27,28</sup> In ischemic stroke patients, LF/HF was higher than healthy controls in some studies,<sup>27,28</sup> whereas another study suggested that LF/HF was lower in patients.<sup>23</sup> So the mechanism of LF/HF circadian rhythm disturbance is not clear, though its recovery might be important to increase physical function in LTC elderly. Other reasons why LF/HF and physical function did not show a correlation in LTC elderly might to be the effects of stroke, insufficient exposure to daylight and posture at daytime. All participants were aged over 75 years in the present study, and there is a possibility that asymptomatic lacunar infarction might be observed. It has also been suggested that lacunar infarction disturbs the autonomic nervous system, leading to a decrease in LF/HF and the related value of the autonomic nervous system, resulting in a disappearance of the correlation between physical activity and LF/HF. In addition, exposure to daylight was known to be one of the most powerful rhythmic regulators in the environment.<sup>29</sup> All participants in the present study spent their time indoors for rehabilitation and care. Furthermore, it is known that the supine position increases HF and decreases LF/HF,<sup>30</sup> and LTC elderly participants who were at rehabilitation units or health service facilities might spend more time in bed compared with outpatient controls, leading to low LF/HF and disappearance of the correlation between LF/HF and physical activity in the present study.

**Table 2** Multiple regression analysis of heart rate variability indices with physical function and blood nutritional data after adjusted for age, sex and cardiovascular risk factors

	HR	SDANN	LF	HF	LF/HF
FIM	-0.25*	0.28*	0.19	0.15	-0.08
Barthel Index	-0.27*	0.29*	0.08	0.04	0.00
Body mass index	-0.05	0.05	0.00	-0.08	0.19
Albumin	-0.21*	0.25*	0.05	-0.02	0.11
Hemoglobin	-0.20*	0.27*	0.12	0.12	0.05
Total cholesterol	-0.01	-0.05	-0.13	-0.17	0.03

\* $P < 0.05$ , analyzed in 105 long-term care elderly. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

**Table 3** Proportional hazards regression analysis of the impact of heart rate variability measure on overall mortality

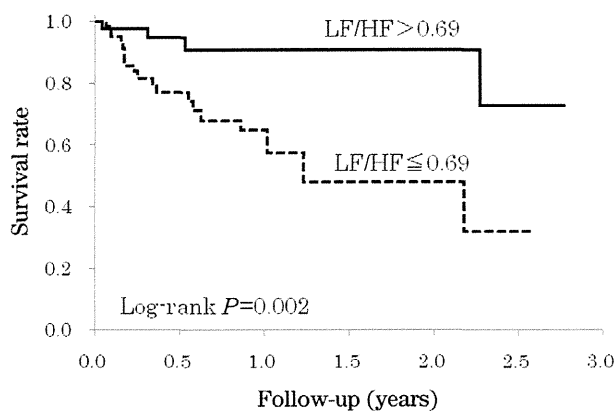
	Hazard ratio <sup>†</sup>	95% Confidence interval	<i>P</i>
Unadjusted			
SDANN (ms)	1.84	0.77–4.38	0.171
LF (ms <sup>2</sup> )	1.61	0.59–4.38	0.353
HF (ms <sup>2</sup> )	2.14	0.72–6.34	0.169
LF/HF	4.73	1.59–14.06	0.005
Age, sex and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.53	0.60–3.86	0.372
LF (ms <sup>2</sup> )	1.65	0.57–4.78	0.357
HF (ms <sup>2</sup> )	2.60	0.82–8.22	0.105
LF/HF	3.37	1.02–11.07	0.046
Age, sex, FIM and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.19	0.44–3.17	0.736
LF (ms <sup>2</sup> )	1.49	0.50–4.41	0.475
HF (ms <sup>2</sup> )	2.85	0.83–9.83	0.097
LF/HF	3.61	1.08–12.10	0.038

Based on 23 deaths among 105 participants. Mean values of heart rate variability measure are in Table 1. <sup>†</sup>Hazard ratio of death rates of participants whose heart rate variability were less than average. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Recent studies showed that decreased HRV indices including LF, HF and LF/HF were associated with CVD risk factors, and decreased LF was an independent predictor of death in elderly people.<sup>31,32</sup> However, the present findings showed that, of all HRV indices, only LF/HF was associated with mortality. This result is supported by a previous study in which, of HRV indices, LF/HF was associated with both frailty and mortality.<sup>9</sup> The major difference between the present study and other studies is whether or not the participants included frail LTC elderly. All participants were LTC elderly in the present study and WHAS-I, which was reported by

Varadhan *et al.* and consisted of one-third frail elderly, whereas in other studies the participants were community-dwelling older adults with intact ADL, and they did not consider physical function.<sup>14,32,33</sup> These results suggest that the significance of LF/HF might differ between LTC elderly and elderly with intact ADL and physical function.

There is a discrepancy in the results derived from studies of LTC elderly and studies of elderly with intact physical function regarding sympathetic nervous activity. Exercise activates the sympathetic nervous system, leading to an increase in blood pressure, muscle blood



**Figure 2** Kaplan–Meyer survival curves for death according to low frequency/high frequency (LF/HF). Mortality was significantly higher for patients with low LF/HF than for patients with high LF/HF. The mean follow-up period was 8.9 months.

flow and muscle strength by inducing muscle protein synthesis,<sup>34–37</sup> suggesting that low sympathetic nervous activity is related to not only physical dysfunction, but also the inability to maintain muscle strength, leading to a worse outcome in LTC elderly. Appropriate activation of the sympathetic nervous system might prevent muscle wasting and improve overall mortality in LTC elderly.

Activation of the sympathetic nervous system has been applied to aging or sarcopenic model rats. The  $\beta$ 2-adrenergic agonists, clenbuterol and formoterol, improved muscle mass and muscle strength, and prevented muscle aging in aging, disuse and sarcopenia<sup>38–44</sup> model rats. In contrast, inhibition of sympathetic nervous activity with  $\beta$ -blockers was associated with a worse outcome in older adults.<sup>45</sup> These findings also suggest the importance of preventing a sympathetic nervous activity decline in LTC elderly.

There were several study limitations. First, this was an observational study, and could not provide direct evidence of causality. So it will be necessary to carry out randomized controlled trials to show whether high sympathetic nervous activity leads to a good outcome or not. Second, excessive sympathetic nervous activity is associated with cardiovascular risk factors, such as hypertension, left ventricular myocardial hypertrophy and old cerebrovascular disease.<sup>46,47</sup> In addition, the number of control subjects was relatively small in the present study. Based on these results, it might be hard to apply the findings in the present study to the oldest old population in general. However, some studies, particularly in the elderly, showed that decreased sympathetic nervous activity was associated with a worse outcome.<sup>9</sup> In addition to low physical activity, poor handgrip strength and frailty are known to be important risk factors predicting death older adults,<sup>2,48–50</sup> and few reports have focused on LTC elderly. Therefore, the

present study has the possibility of providing evidence to improve physical function and mortality in LTC elderly by means of maintaining or increasing LF/HF.

In summary, the present study showed that LF/HF is a factor that distinguishes LTC elderly from elderly controls independent of physical function. In addition, the circadian rhythm of LF/HF was lost in LTC elderly. Furthermore, low LF/HF was associated with high mortality. For LTC elderly aged 75 years or over, LF/HF might be a predictive biomarker of physical function and mortality.

## Disclosure statement

There is no financial support or relationship that might pose conflicts of interest.

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Chronic lung disease was found to have a strong association with being underweight. It was one of the chronic wasting diseases with systemic inflammation and protein degradation, and the prevalence was higher in the underweight population with greater disease-specific mortality.<sup>9</sup> Sarcopenia was considered the possible pathophysiological mechanism behind the obesity paradox.

The RAP trigger for nutrition was not a good indicator of underweight or obesity. Most MDS items for nutrition were not found to be good indicators of protein or calorie malnutrition.<sup>10</sup> Other tools with better detection sensitivity and specificity, such as bioelectrical impedance analysis for sarcopenia, should be employed in assessment of nutritional risk for nursing home residents.

There are several limitations of this study. First, BMI was not necessarily correlated with measures of body composition, such as visceral adiposity and sarcopenia. Second, the dynamic change in BMI, RAP triggers, and disease diagnosis could not be fully presented in this cohort study. Weight loss, new RAP triggers, and new disease diagnoses were all considered important risk factors for mortality and morbidity. Third, all participants were male, so the results should not be generalized to women.

In conclusion, being underweight was associated with greater risk of mortality after adjustment for age and comorbidities. Chronic lung disease was significantly associated with being underweight. Other than the intervention program for malnutrition, a multidimensional approach for all associated factors would prevent further adverse health outcomes in the elderly population.

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## ACKNOWLEDGMENTS

We thank Hsiao-Ling Lin, Kai-Chun Chang, and Heng-Liang Yeh who made great efforts on longitudinal data collection during the study period.

**Conflict of Interest:** The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

**Author Contributions:** Chen, Peng, Liu: study concept, design, analysis, data interpretation, manuscript writing; Lin, Chen: data verification and analysis. Chen, Lan, Chang: critical suggestions and review before manuscript submission.

**Sponsor's Role:** None.

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## WEIGHT LOSS AND HOMEOSTATIC IMBALANCE OF LEPTIN AND GHRELIN LEVELS IN LEAN OLDER ADULTS

*To the Editor:* Appetite and food intake decline with age in elderly adults, and their decline results in unintended weight loss, which leads to frailty, morbidity, and mortality.<sup>1</sup> One reason why this anorexic state prevents elderly people from returning to their original weight is impaired regulation of food intake, which makes them likely to be

less hungry and to become rapidly satiated.<sup>2</sup> An imbalance between leptin and ghrelin, two peripheral hormones that signal changes in energy balance to the central nervous system (CNS) and act reciprocally to maintain body weight, may cause predisposition to impaired regulation of food intake.<sup>3</sup>

Sixty-eight elderly adults aged 65 and older (mean age  $80.5 \pm 5.8$  years; female:male ratio 48:20) who were making regular visits to the geriatric outpatient clinic of Kyorin University Hospital were examined. Their diseases were well controlled. Fasting plasma leptin and acylated ghrelin levels were measured using enzyme-linked immunosorbent assay. Because of the potential effects of instrumental activities of daily living (IADLs) on daily energy needs and appetite, they were evaluated by scoring them on the Lawton IADL scale.<sup>4</sup>

The results of a simple regression analysis showed a positive correlation between subjects' plasma leptin levels and their body mass index (BMI; correlation coefficient  $(r) = 0.54$ ,  $P < .001$ ), although there was no correlation between their BMI and ghrelin level ( $r = -0.23$ ,  $P = .06$ ), age ( $r = 0.12$ ,  $P = .31$ ), or sex ( $r = 0.08$ ,  $P = .54$ ). After adjustment for age and sex, the results of multiple regression analysis showed significant correlations between BMI and leptin (partial regression coefficient [prc] = 0.29,  $P = .02$ ), ghrelin (prc = -0.41,  $P < .001$ ), leptin-ghrelin interaction (prc = 0.41,  $P < .001$ ), and IADL scores (prc = 0.26,  $P = .04$ ). When the subjects were stratified into three groups according to BMI (high,  $\geq 25.0$  kg/m<sup>2</sup>; normal, 19.0–24.9 kg/m<sup>2</sup>; and low,  $< 19.0$  kg/m<sup>2</sup>), there was a significant positive correlation between leptin and ghrelin levels in the high BMI group ( $r = 0.79$ ,  $P = .008$ ) and a significant inverse correlation in the normal BMI group ( $r = -0.33$ ,  $P = .03$ ), but no significant correlation was not observed between the two peptides in the low BMI group ( $r = 0.22$ ,  $P = .39$ ) (Figure 1).

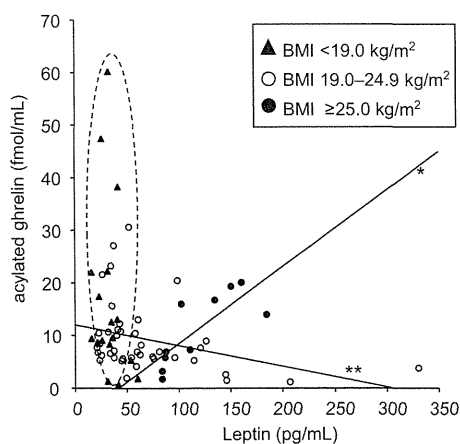
Leptin is a peptide and the product of the *OB* gene, which is expressed primarily in adipocytes, and it signals

the CNS about the quantity of stored fat, whereas ghrelin is an acylated peptide produced in the stomach that relays hunger signals to the CNS. Thus, both peptides mutually act to maintain body weight. The results of the present study confirmed the existence of a strong positive correlation between plasma leptin levels and BMI in elderly adults,<sup>5</sup> as well as a tendency for higher ghrelin levels to be associated with lower BMI,<sup>6</sup> although the results provide preliminary evidence that the feedback control of leptin and ghrelin is limited to a small body weight range.

In the high BMI group, the relationship between the two peptides shifted to a positive correlation with increasing BMI. Regardless of the potential role of leptin in ghrelin regulation, insulin may be an important peripheral peptide in regulating energy balance in obese people. A previous study found that the plasma ghrelin levels of obese subjects depended on whether they had insulin resistance, because the obese insulin-sensitive subjects in their study had higher ghrelin levels, suggesting that compensatory hyperinsulinemia mediated the relationship between obesity and ghrelin.<sup>7</sup> Attenuated postprandial ghrelin suppression in obese subjects may also contribute to impaired satiety signaling and persistent hunger feelings.<sup>8</sup>

The data obtained data in the current study showed that all three subjects with the highest ghrelin levels were in the low BMI group. This is consistent with previous observations that plasma ghrelin levels increase under conditions associated with negative energy balance, such as body weight loss or anorexia, reflecting the ghrelin compensatory response to undernutrition. However, some individuals in the low BMI group had low ghrelin levels, which may reflect aging<sup>9</sup> or atrophic changes in the gastric mucosa, and their low ghrelin levels may have caused delayed gastric emptying that in turn suppressed food intake. A sedentary lifestyle and psychological and social factors may also underlie anorexia in elderly adults because the results of the current study showed that higher IADL scores were associated with higher BMI.

Further study will be needed to determine whether treating lean elderly adults with ghrelin would increase their food intake, although a comprehensive approach to lifestyle factors is now the best conceivable approach to preventing low body weight and sarcopenia in elderly adults.<sup>10</sup>



\* $r = 0.79$ ,  $p = .008$  for BMI  $\geq 25.0$  kg/m<sup>2</sup>  
 \*\* $r = -0.33$ ,  $p = .03$  for BMI 19.0–24.9 kg/m<sup>2</sup>

**Figure 1.** Relationship between plasma leptin and acylated ghrelin levels of elderly adults attending a geriatrics clinic according to body mass index (BMI). Solid lines represent the statistically significant linear regressions of the data.

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## ACKNOWLEDGMENTS

**Conflict of Interest:** The authors have no conflicts of interest to report in regard to this letter. This work was supported by the Research Grant for Comprehensive Research

on Aging and Health from the Ministry of Health, Labor and Welfare.

**Author Contributions:** Conception and design: Kozaki, Tanaka. Analysis and interpretation of data: Tanaka, Nagai, Matsui. Drafting of the article: Tanaka, Matsui. Critical revision of the article for important intellectual content: Kozaki, Sudo. Final approval of the article: Sudo, Kozaki. Statistical expertise: Matsui, Nagai. Collection and assembly of data: Tanaka, Obara, Nagai, Koshiba.

**Sponsor's Role:** None.

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## ARE GERIATRIC SYNDROMES ASSOCIATED WITH RELUCTANCE TO INITIATE ORAL ANTICOAGULATION THERAPY IN ELDERLY ADULTS WITH NONVALVULAR ATRIAL FIBRILLATION?

*To the Editor:* Age is associated with risk of atrial fibrillation (AF) and its consequences, including stroke. In turn, stroke has been associated with mortality, disability, and health-related quality of life.<sup>1</sup> The American Association of Chest Physicians states that anticoagulation therapy (AT) must be initiated in individuals with nonvalvular AF in moderate- and high-risk categories for the development of stroke (according to congestive heart failure, hypertension, aged  $\geq 75$ , diabetes mellitus, stroke, vascular disease, aged 65-74, sex (CHA<sub>2</sub>DS<sub>2</sub>VASc) score),<sup>2,3</sup> whereas a variety of major bleeding prediction scores, such as the hypertension, abnormal (renal/liver function), stroke, bleeding tendency, labile international normalized ratio, elderly, drugs (HAS-BLED) have been developed to aid in the decision-making process in relationship to prescribing AT.<sup>4</sup> Nevertheless, recent work has shown that the net clinical benefit favors the initiation of AT over the risk of major bleeding, even in individuals at high risk of bleeding.<sup>5</sup>

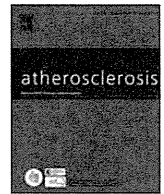
Bleeding risk in elderly adults with AF is frequently overestimated, whereas thrombotic risk is underestimated.<sup>1,6</sup> Thus, AT is underused in this context. It is likely that age-related factors such as functional status, falls, and cognitive impairment influence the decision to anticoagulate these individuals, although an association between the presence of geriatric syndromes (GSs) and the reluctance to initiate AT in elderly adults with nonvalvular

**Table 1. Multivariate Logistic Regression of the Absence of Oral Anticoagulation Therapy**

Characteristic	Univariate Analyses, n = 137	Model 1, n = 136	Model 2, n = 129	Model 3, n = 128	Model 4, n = 128
	Odds Ratio (95% Confidence Interval)				
Age	1.03 (0.97-1.08)	1.02 (0.96-1.08)	—	1.03 (0.96-1.11)	1.04 (0.96-1.12)
Female	0.70 (0.35-1.37)	0.61 (0.29-1.27)	—	0.55 (0.21-1.42)	0.58 (0.22-1.55)
Lives alone	0.67 (0.20-2.22)	0.82 (0.24-2.82)	—	1.03 (0.23-4.65)	0.94 (0.20-4.35)
Education, years	0.96 (0.90-1.02)	0.94 (0.88-1.01)	—	0.95 (0.88-1.48)	0.97 (0.89-1.06)
Hearing impairment	1.66 (0.84-3.27)	—	1.57 (0.66-3.73)	—	—
Visual impairment	2.09 (0.97-4.53)	—	2.45 (0.89-6.78)	2.84 (0.99-8.16)	—
$\geq 3$ falls/years	2.37 (1.01-5.53) <sup>a</sup>	—	1.61 (0.53-4.86)	—	—
IADLs disability	0.64 (0.26-1.56)	—	0.81 (0.26-2.56)	—	—
ADLs disability	0.49 (0.25-0.97) <sup>a</sup>	—	1.43 (0.58-3.55)	—	—
Depressive symptoms	5.12 (2.19-11.99) <sup>b</sup>	—	4.59 (1.73-12.12) <sup>a</sup>	4.94 (1.81-13.52) <sup>a</sup>	5.14 (1.84-14.34) <sup>a</sup>
Cognitive impairment	7.97 (3.62-17.53) <sup>b</sup>	—	7.32 (2.98-17.99) <sup>b</sup>	6.79 (2.73-16.87) <sup>b</sup>	6.27 (2.54-15.46) <sup>b</sup>
CHA <sub>2</sub> DS <sub>2</sub> VASc stroke risk score	1.03 (0.06-16.80)	—	—	—	1.02 (0.04-22.71)
HAS-BLED	2.58 (1.27-5.23) <sup>a</sup>	—	—	—	2.52 (1.03-6.16) <sup>a</sup>

Model 1 included age, sex, living situation, and educational level; Model 2 included hearing impairment, visual impairment, falls, instrumental activities of daily living (IADLs) and activities of daily living (ADLs) disability, depressive symptoms, and cognitive impairment; Model 3 included age, sex, living situation, educational level, visual impairment, depressive symptoms, and cognitive impairment; Model 4 included depressive symptoms and cognitive impairment and was adjusted for age; sex; living situation; educational level; congestive heart failure, hypertension, aged  $\geq 75$ , diabetes mellitus, stroke, vascular disease, aged 65-74, sex (CHA<sub>2</sub>DS<sub>2</sub>VASc) stroke risk score; and hypertension, abnormal (renal/liver function), stroke, bleeding tendency, labile international normalized ratio, elderly, drugs (HAS-BLED) major bleeding risk score. Depressive symptoms = Geriatric Depression Scale (GDS)  $> 5$ ; Cognitive impairment = Mini-Mental State Examination (MMSE)  $\leq 23$ .

$P < .05$ , <sup>a</sup>.001, <sup>b</sup>.001.



## Efficacy of combined use of three non-invasive atherosclerosis tests to predict vascular events in the elderly; carotid intima-media thickness, flow-mediated dilation of brachial artery and pulse wave velocity



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### ARTICLE INFO

#### Article history:

Received 28 December 2012

Received in revised form

25 September 2013

Accepted 30 September 2013

Available online 16 October 2013

#### Keywords:

Intima-media thickness

Flow-mediated dilation

Pulse wave velocity

Vascular event

### ABSTRACT

**Background:** Intima-media thickness (IMT) of the carotid artery, flow-mediated dilation (FMD) of the brachial artery, and pulse wave velocity of the central artery (PWV) have been widely used to evaluate progression of atherosclerosis. Our previous work has revealed that IMT, FMD and PWV are related to each other, and the combination of these measurements was useful in identifying patients with atherosclerotic disease. The aim of the present study was to investigate whether combination of these measurements would predict future cardiovascular events better than each test alone.

**Methods and results:** From November 2000 to March 2008, 274 consecutive elderly subjects (men/women; 114/160, mean age;  $71 \pm 12$  years) were enrolled in this study. We measured IMT, FMD, and PWV in all of these subjects and followed them for a mean of  $41 \pm 28$  months. During the follow-up period, vascular events occurred in 42 patients (15.3%). IMT (hazard ratio = 1.28 [95%CI, 1.09–1.50],  $p = 0.002$  per 0.1 mm increase in mean IMT) and brachial-ankle (ba) PWV (hazard ratio = 1.06 [95%CI, 1.01–1.10],  $p = 0.015$  per 1 m/s increase in baPWV) were independent predictors of future vascular events by Cox proportional hazard analysis, although FMD did not reach statistical significance (hazard ratio = 0.85 [95%CI, 0.72–1.01],  $p = 0.062$  per 1% increase in %FMD). Importantly, the number of tests showing results in the worst tertile was a more powerful predictor (hazard ratio = 2.21 [95%CI, 1.42–3.43],  $p = 0.0004$  for number of tests showing worst tertile) of future vascular events than either IMT, baPWV, or FMD alone. When both IMT and baPWV (with respective cut-off values of 0.98 mm and 19.1 m/s) were taken into consideration, the efficacy increased as compared with each test alone (odds ratio 4.9).

**Conclusion:** These results indicate that IMT and baPWV, especially when combined, are useful in predicting future vascular events in elderly subjects.

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### 1. Introduction

Recently, noninvasive tests of atherosclerosis have been clinically available, such as common carotid intima-media thickness (IMT), flow-mediated dilation (FMD) of the brachial artery, pulse wave velocity (PWV), beta stiffness index, and systemic arterial stiffness [1]. Several epidemiologic studies have shown that IMT, PWV, and FMD are important, independent determinants of cardiovascular risk in patients with cardiovascular disease [2–5], or diabetes mellitus [6,7] and healthy adults [1,8–12]. These three

tests assess different aspects of atherosclerosis; carotid IMT reflects structural changes in the artery wall [13], PWV reflects central arterial stiffness, and FMD reflects endothelial function. While the majority of previous studies utilized a single method to evaluate atherosclerosis, several recent studies showed that combination of two measurements may strengthen the predictive power for future cardiovascular events [14,15].

Consistent with these studies, our previous article showed that a combination of IMT, FMD and PWV was able to predict more reliably the prevalence of atherosclerotic disease in an elderly population than did each test alone [16]. However, it is not clear whether the combination of these three tests is more reliable in predicting future vascular events than is each single test. Thus, the purpose of the present study was to prove the hypothesis that the combination

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of the three different methods to evaluate atherosclerosis would strengthen the predictive power over each test alone. For this purpose, we followed vascular events in patients in whom IMT, FMD and PWV were measured in advance.

## 2. Methods

### 2.1. Subject background

From November 2000 to March 2008, 274 consecutive subjects from outpatients of the Department of Geriatric Medicine, Kyorin University Hospital (Tokyo, Japan) were enrolled in this study (Table 1). Three non-invasive atherosclerosis tests (IMT, FMD and PWV) were performed in these subjects for the study purpose. All participants gave written informed consent to the study, which was approved by our institutional ethics committee. The study was performed in compliance with the Helsinki declaration. We

included all subjects who agreed to participate in the study, and in whom IMT, FMD and PWV were available.

Diabetes mellitus was defined as fasting glucose of 126 mg/dL or higher, or the use of hypoglycemic medication. Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Total and high-density lipoprotein (HDL) cholesterol were measured in blood samples obtained after a 12-h fast. Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation. Framingham risk score was determined from age, sex, smoking, blood pressures, diabetes, total cholesterol and HDL cholesterol based on the report by Wilson et al. [11].

### 2.2. Participant follow-up and CV events

The occurrence of vascular events was investigated by inquiry to the attending doctor ( $n = 234$ ), examining the patient's clinical record ( $n = 9$ ), or inquiry to the patient and/or the family by either telephone ( $n = 13$ ) or mail ( $n = 18$ ). The majority of cardiovascular events ( $n = 243/274$ ) was confirmed as follows: angina and myocardial infarction were confirmed by clinical symptoms and/or coronary arteriography; cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction and transient ischemic attack were confirmed by clinical symptoms followed by computed tomography, MRI and/or angiography; heart failure, renal failure and arteriosclerosis obliterans were diagnosed according to the clinical guidelines; and aortic dissection was confirmed by contrast computed tomography.

### 2.3. Measurements of atherosclerosis

Measurements of atherosclerosis were performed as previously described [16]. All examinations were performed by the same skilled technician throughout the study. The subject reclined on the examination table for at least 15 min before the examination to obtain hemodynamic stability.

#### 2.3.1. Measurement of carotid IMT

Common carotid IMT was measured by ultrasound (PowerVision6000, Toshiba) with a 7.5 MHz linear-array transducer. The images were recorded on S-VHS videotape. IMT at the far wall of the common carotid artery was measured by B-mode scan within 10 mm proximal to the bifurcation. Four points were measured in one scan, and mean IMT was calculated [2,16]. The typical error as a coefficient of intra-observer variation in the measurement of IMT was 3.7%, and changes in mean were 2.0%.

#### 2.3.2. Measurement of FMD of brachial artery

The diameter of the artery was measured by ultrasound (PowerVision6000, Toshiba) with a 7.5 MHz linear-array transducer. The images were recorded on S-VHS videotape. The mean diameter of the brachial artery was calculated from four cardiac cycles synchronized with the R-wave peaks on ECG. After a 10 min rest in the supine position, the right brachial artery was scanned. After recording the resting diameter, a cuff was placed around the forearm distal to the target artery and inflated to a pressure of 250 mmHg. Inflation was maintained for 5 min. Maximal vasodilation was observed 45–60 s after cuff release. The change in diameter caused by the restoration of blood flow was expressed as the percent change relative to the initial diameter [16–18]. The typical error as a coefficient of intra-observer variation in the measurement of FMD was 7.4%, and changes in mean were 0.1%.

**Table 1**  
Clinical characteristics of study subjects.

	Vascular event		
	With ( $n = 42$ )	Without ( $n = 232$ )	<i>p</i>
Sex (male/female)	24/18	90/142	0.026
Age, y/o	74 ± 12	71 ± 12	0.087
Body mass index (kg/m <sup>2</sup> )	23 ± 4	23 ± 3	0.208
Number of risk factors	1.8 ± 1.1	1.6 ± 1.0	0.281
Hypertension, <i>n</i> (%)	31 (74)	126 (54)	0.019
Hyperlipidemia, <i>n</i> (%)	14 (33)	115 (50)	0.052
Diabetes mellitus, <i>n</i> (%)	12 (29)	57 (25)	0.582
Chronic pulmonary disease, <i>n</i> (%)	0 (0)	2 (0.9)	0.546
Kidney disease, <i>n</i> (%)	1 (2.4)	8 (3.4)	0.721
Chronic systemic inflammatory disease, <i>n</i> (%)	0 (0)	2 (0.9)	0.546
Smokers, <i>n</i> (%)			
Never	22 (52)	139 (60)	0.364
Past	17 (41)	69 (30)	–
Current	3 (7)	24 (10)	–
History of stroke, <i>n</i> (%)			
Cerebral infarction	7 (17)	14 (6)	0.295
Brain hemorrhage	0 (0)	3 (1)	–
Cerebral thrombosis	1 (2)	1 (0)	–
Cerebral infarction & hemorrhage	0 (0)	2 (9)	–
Multiple cerebral infarction	0 (0)	7 (3)	–
Transient ischemic attack	1 (2)	0 (0)	–
Unknown	2 (5)	6 (3)	–
History of IHD, <i>n</i> (%)			
Angina pectoris	3 (7)	7 (3)	0.560
Myocardial infarction	0 (0)	4 (2)	–
Unknown	0 (0)	3 (1)	–
Atherosclerosis measurements			
Mean IMT, mm	1.06 ± 0.21	0.94 ± 0.19	0.000
FMD, %	2.01 ± 1.71	2.83 ± 2.42	0.045
baPWV, m/s	22.5 ± 6.6	19.7 ± 6.5	0.018
Medication			
ACEI/ARB, <i>n</i> (%)	13 (33)	54 (24)	0.210
Ca blocker, <i>n</i> (%)	14 (35)	58 (16)	0.185
β-Blocker, <i>n</i> (%)	3 (8)	10 (4)	0.383
Statin, <i>n</i> (%)	5 (12)	38 (17)	0.426
Anti-platelet agent, <i>n</i> (%)	15 (38)	42 (19)	0.009

Data are expressed as mean ± SD. FMD, flow-mediated dilation of right brachial artery; IMT, intima-media thickness of common carotid artery; baPWV, brachial-ankle pulse wave velocity; IHD, ischemic heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Smoker Never, no smoking history; Smoker Past, previously smoked and quit; Smoker Current, currently regularly smoking.

Student's *t* test for continuous variables and  $\chi^2$  test for categorical variables.

### 2.3.3. Measurement of PWV

Brachial-ankle (ba) PWV was measured using an automated device (Form PWV/ABI, OMRON-COLIN, Japan). The average measurement of left and right baPWV was used for analysis. The typical error as a coefficient of intra-observer variation in the measurement of PWV was 2.0%, and changes in mean were 0.2%.

### 2.4. Statistical analysis

All data are expressed as mean  $\pm$  SD. Patients were classified according to the tertiles of IMT, %FMD and baPWV. Event rate was calculated using the Kaplan–Meier method, and the statistical significance of differences was investigated by log-rank test. A Cox proportional hazard model was used to determine the variables independently associated with vascular events. Odds ratio was calculated by logistic regression analysis to evaluate the association of event occurrence and each atherosclerosis measurement, with adjusted for age and sex as well as FRS. Receiver operating characteristic curve analysis was performed to estimate the best cut-off point in each test for predicting future vascular events. A  $p$  value  $<0.05$  was considered statistically significant.

## 3. Results

### 3.1. Subjects

In the 274 patients, the mean duration of follow-up was  $41 \pm 28$  months. During this time, 42 (15.3%) patients experienced vascular events: 14 (33.3%) had angina, 13 (31.0%) stroke, 10 (23.8%) heart failure, 6 (14.3%) renal failure, 3 (7.1%) myocardial infarction, 3 (7.1%) transient ischemic attack, 2 (4.8%) arteriosclerosis obliterans, 2 (4.8%) cerebral hemorrhage, 1 (2.4%) aortic dissection, and 1 (2.4%) subarachnoid hemorrhage.

As shown in Table 1, male sex and hypertension were more frequent in patients with vascular events than in those without events. In addition, patients with vascular events showed thicker

mean IMT, smaller %FMD, and greater baPWV than those without events.

### 3.2. Tertiles and prognostic value of each test

With regard to IMT and baPWV, Kaplan–Meier analysis showed that patients in the worst tertile experienced a higher rate of vascular events than those in the other two tertiles (Fig. 1a, b). A similar trend was also found for %FMD, although not reaching statistical significance ( $p = 0.052$  by log-rank test, Fig. 1c). Of note, patients in the three worst tertiles had a markedly higher rate of vascular events than those in the other groups (0, 1, and 2 in Fig. 1d).

In the Cox proportional hazard model, IMT, baPWV, and the number of results in the worst tertiles were significantly associated with vascular events. They remained significant after adjusting for age and sex (Table 2), and FRS (Table 3). FRS alone was not a significant predictive factor ( $p = 0.203$ , RR 0.987, 95%CI 0.966–1.007).

### 3.3. Test combination model and vascular events

Receiver operating characteristic curve analysis demonstrated that IMT of 0.98 mm (area under curve = 0.72, sensitivity = 83%, specificity = 57%) and baPWV of 19.1 m/s (area under curve = 0.67, sensitivity = 61%, specificity = 63%) were the best cut-off points for predicting future vascular events.

When the subjects were subdivided into four groups according to the cut-off values of IMT and baPWV, Kaplan–Meier curves showed a stepwise increase in the risk of vascular events (Fig. 2a). Patients with both IMT and baPWV above the cut-off values (group IV) showed the highest rate of vascular events. In addition, the odds ratio of vascular events in group IV was significantly higher than that in group I (Fig. 2b).

## 4. Discussion

Consistent with the hypothesis, the combination of the three atherosclerosis measurements (IMT, %FMD, and baPWV) was

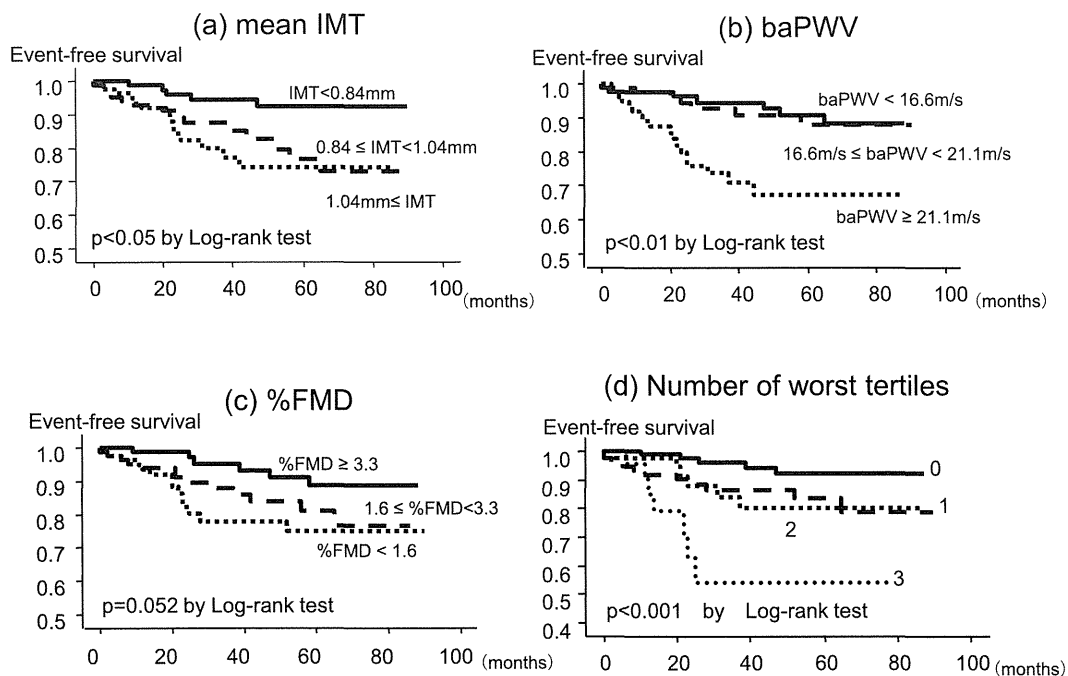


Fig. 1. Kaplan–Meier curves according to tertiles of (a) IMT, (b) baPWV, (c) %FMD, and (d) number of worst tertiles in atherosclerosis tests.



**Table 2**  
Predictive value for future vascular events by Cox proportional hazard analysis adjusted by age and sex.

Variable	Unadjusted (n = 274)		Adjusted for age and sex (n = 274)	
	HR (95%CI)	p	HR (95%CI)	p
IMT, tertile (increase of 1)	1.836 (1.187–2.840)	0.0064	1.606 (1.002–2.753)	0.0489
IMT, 0.1 mm	1.279 (1.093–1.497)	0.0022	1.226 (1.034–1.454)	0.0191
baPWV, tertile (increase of 1)	2.191 (1.365–3.516)	0.0012	1.969 (1.115–3.476)	0.0195
baPWV, 1.0 m/s	1.055 (1.010–1.101)	0.0152	1.027 (0.970–1.088)	0.3552
FMD, tertile (increase of 1)	1.691 (1.090–2.624)	0.0190	1.631 (0.925–2.342)	0.1029
FMD, 1%	0.849 (0.716–1.008)	0.0615	0.903 (0.756–1.079)	0.2608
Number of worst tertiles	1.930 (1.353–2.754)	0.0003	1.891 (1.229–2.912)	0.0038

HR, hazard ratio; CI, confidence interval; other abbreviations are as in Table 1.

shown to be more powerful in predicting future vascular events as compared with each single test. This finding is consistent with our previous study showing that the combination of these three tests more reliably reflected the prevalence of atherosclerotic disease in the elderly population than did each test alone [16]. Here, IMT, baPWV, and %FMD (although less sensitively) were shown to predict future vascular events in the elderly population. This is in agreement with previous longitudinal studies showing that IMT was a predictor of future vascular disease [2,19], including a study of an elderly population [8], as well as central PWV in a study of subjects over 70 years old [4,11].

With regard to FMD, the present study did not show a significant association with the occurrence of vascular events. Considering the low value and small difference in FMD in the two groups with and without vascular events, one possible explanation for the non-significance is the floor effect. In support of this result, a significant relationship was found between baseline FMD and future cardiovascular events in middle-aged adults [9,10], whereas the prognostic power declined linearly with advancing age from the mid-40s, reaching nearly zero around 70 years of age [20]. Considering the subjects' age in the present study, the non-significance of FMD could be attributable to the advanced age of the patients.

An important point of the present study is that while IMT, baPWV, and %FMD were useful to predict future vascular events, combination of these tests increased the predictive power (Fig. 1d). This finding was consistent with those of our previous cross-sectional study showing that the result of a combination of the three tests was more strongly related to the prevalence of vascular

**Table 3**  
Predictive value for future vascular events by Cox proportional hazard analysis adjusted by Framingham Risk Score (FRS).

Variable	Unadjusted (n = 215)		Adjusted for FRS (n = 215)	
	HR (95%CI)	p	HR (95%CI)	p
IMT, tertile (increase of 1)	1.704 (1.044–2.782)	0.0329	1.669 (1.018–2.735)	0.0422
IMT, 0.1 mm	1.277 (1.069–1.526)	0.0071	1.281 (1.064–1.544)	0.0090
baPWV, tertile (increase of 1)	2.675 (1.522–4.700)	0.0006	2.582 (1.445–4.614)	0.0014
baPWV, 1.0 m/s	1.065 (1.018–1.115)	0.0060	1.060 (1.011–1.111)	0.0166
FMD, tertile (increase of 1)	1.785 (1.072–2.973)	0.0260	1.669 (0.989–2.815)	0.0548
FMD, 1%	0.864 (0.716–1.043)	0.1281	0.888 (0.730–1.080)	0.2339
Number of worst tertiles	2.031 (1.350–3.055)	0.0007	1.991 (1.309–3.027)	0.0013

HR, hazard ratio; CI, confidence interval; other abbreviations are as in Table 1.

disease in the elderly population than was that of each single test [16]. Several longitudinal studies have shown efficacy of the combination of two different atherosclerosis tests, such as FMD and ankle-brachial pressure index [14], plaque score of the common carotid artery and FMD [15], or carotid IMT and FMD [21], in predicting vascular events. The present study showed strong predictive power of combining three atherosclerosis tests for future vascular events. From our results, it is recommended that three tests should be combined in clinical work to evaluate vascular risk. However, when cost-effectiveness is taken into account, the combination of two tests (IMT and baPWV) would be sufficiently practical for event prediction in the elderly population because FMD requires much more skill and time than does IMT or baPWV. The same idea has been introduced in the recent guidelines from the ACCF/AHA for the assessment of cardiovascular risk in asymptomatic adults [22].

Increased carotid IMT has been considered as a marker of sub-clinical atherosclerosis. Although the biological meaning of IMT remains to be debated, it seems more likely to represent target organ damage related to cardiovascular risk [13]. PWV is the mostly widely used index for evaluating central arterial stiffness. FMD is a tool that is proposed for the assessment of endothelial function and is related to cardiovascular risk, but is not yet a commonly applied method to assess CV risk. Our major finding that the combination of three tests was more predictive than each test alone may be attributable to the fact that each test reflects a different aspect of the progression of atherosclerosis.

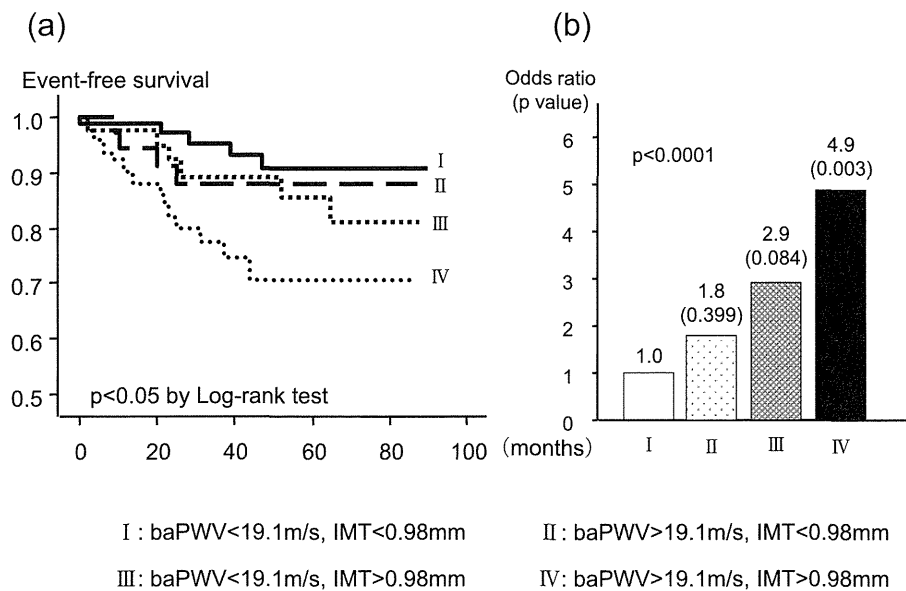
The best cutoff value of IMT calculated from event prediction was 0.98 mm in the present study. This value was comparable to previously reported values; approximately ~1.00 mm in healthy adults in spite of populations of different ages; middle age [23–25], over 55 years old [26], and 60–74 years old [27]. Although the detailed methodologies were slightly different between studies, ~1.00 mm appears to be relevant to the occurrence of vascular events.

The cutoff value of baPWV calculated from the receiver operating characteristic curve was 19.1 m/s in the present study. This value is slightly higher as compared with values reported previously; that for major cardiovascular events in patients with acute coronary syndrome was 18.0 m/s [28], and that for re-hospitalization and cardiac death in patients with heart failure was 17.5 m/s [29]. On the other hand, the cut-off value for cardiovascular death in community-dwelling elderly people (LILAC study [30]) was higher (25 m/s) than that in the present study. This difference could be explained by the susceptibility to arteriosclerosis in different subjects depending on whether they have preexisting cardiovascular disease and how old they are.

Because of the efficacy of the cut-off values of baPWV and IMT, we investigated the significance of the combination of these two measurements. A stepwise increase in the risk of vascular events was evident by Kaplan–Meier analysis and calculated odds ratio. This is important because much higher predictability can be obtained by simple non-invasive tests. Although FMD did not reach statistical significance, the combination of even three tests would strengthen the predictive power. Indeed, our previous results showed higher prevalence of atherosclerotic disease by combining three tests. Considering the efficacy and simplicity of performance of the three tests, combination of baPWV and IMT (with cut-off values of 19.1 m/s and 0.98 mm, respectively) should be of value for prediction of future occurrence of vascular events in elderly patients.

## 5. Limitations

One of the limitations of this study was that our approach of three tests for atherosclerosis did not follow the most updated



**Fig. 2.** (a) Kaplan–Meier curves and (b) adjusted relative risks of future vascular events according to cut-off values of baPWV and IMT. Odds ratio and  $p$  value, in parentheses, are indicated over the bar.

methodologies, because they were not fully established when we started this study. The most recent approaches may provide better predictive values for PWV and IMT, and statistical significance for FMD. Particularly, we manually held the echo probe for FMD measurement, which may have led to low intra-observer reproducibility and no statistical significance.

Second, despite the number of controls, the number of patients was very small.

Third, we included renal failure and heart failure as vascular events since these diseases are thought to be associated with progression of atherosclerosis in the elderly. However, it is possible that heart failure and renal failure may be caused by other etiologies such as collagen disease, infection, valvular disease, etc. Therefore, we also analyzed predictive values excluding heart failure and renal failure as vascular events, and obtained similar results. Thus, the effect of bias in selecting vascular events is considered to be small.

## 6. Conclusion

IMT, baPWV and, less significantly, FMD, especially when combined, are useful to predict future vascular events in elderly subjects. Because elderly people are at high risk for vascular disease, performing these simple and reliable non-invasive tests will add important clinical information.

## Acknowledgments

This study was supported by a Health and Labour Sciences Research Grant (H24-Ninchisho-002) from the Ministry of Health, Labour and Welfare of Japan, and by the Hakujikai Institute of Gerontology. We appreciate Mr. Shinya Ishii for his statistical advice.

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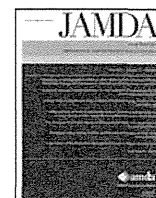
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## Original Study

## Priorities of Health Care Outcomes for the Elderly

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## A B S T R A C T

**Keyword:**  
Geriatrics  
quality of care  
health care policy

**Objectives:** Physicians are uncertain about what medical services should be provided to older and/or disabled patients. Better understanding of health outcome prioritization among health care providers and recipients may help the process of decision- and policy-making. For this purpose, surveys were conducted on priorities of health care outcomes for the elderly.

**Design:** Survey research.

**Setting:** Four groups of health care providers and four groups of health care recipients.

**Participants:** A total of 2512 health care providers and 4277 recipients.

**Measurements:** Questionnaires were sent to more than 8000 health care providers and more than 9000 health care recipients: geriatricians, physicians who commonly see older patients or work in long term care facilities, staff members and participants in adult day care, patients in outpatient geriatric clinics, family members of patients with dementia, and community-dwelling older adults. The questionnaire asked the subjects to rank 12 measures of health care outcomes.

**Results:** The mean response rate was 49%. All health care provider groups considered “improvement of quality of life” the most important. In contrast, in health care recipient groups, “effective treatment of illness,” “improvement of physical function,” and “reduction of carer burden” were given high priority, whereas “improvement of quality of life” was perceived as less important. All the groups, including health care providers and recipients, ranked “reduction of mortality” the least important, followed by “avoiding institutional care.” Stratification analysis showed that the results did not differ by sex, nursing care level, or the existence of relatives who required nursing care, whereas age slightly influenced the order of high-ranked measures.

This study was supported by a Health and Labor Sciences Research Grant (H22-Choju-Shitei-009) from the Ministry of Health, Labor, and Welfare of Japan.

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