—**Original**—

Prognostic Value of Heart Rate Variability in Comparison with Annual Health Examinations in Very Elderly Subjects

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Abstract

The prognostic value of heart rate variability (HRV) in patients with cardiac conditions has been investigated for many years. However, the HRV is superior to annual health examinations for predicting the longevity of very elderly residents of long-term care facilities is unknown. Annual health examinations and subsequently ambulatory Holter ECG recording were performed in 2008 for 71 very elderly subjects, who were then followed up for 3 to 48 months. The patients were divided into 2 groups on the basis of whether they were alive (86 ± 14 years, n=37) or deceased (90 ± 16 years, n=34) at end of follow-up. To assess cardiac autonomic function, HRV was obtained with the MemCalc/Chiram software program after Holter ECG. Age, sex, body-mass index, plasma levels of C-reactive protein and albumin, and the low-frequency/high-frequency ratio did not differ between the 2 groups. However, the standard deviation of all NN intervals (SDNN) and the coefficient of variation of RR intervals (CVRR) were higher in living subjects than in deceased subjects (SDNN: 73.2 ± 13.5 milliseconds vs. 53.2 ± 9.8 milliseconds, CVRR: 9.3% ± 1.7% vs. 7.6% ± 1.3%, $p<0.05$). The relative risks with an SDNN <65 milliseconds was 1.85 ($p<0.05$) and that with a CVRR <8% was 1.84 ($p<0.05$). Kaplan Meier analysis showed that SDNN and CVRR were useful markers for the longevity of very elderly subjects. The present data suggest that annual health examination data does not predict longevity, but that HRV does. The modulation of parasympathetic tone in daily activities plays an important role in the longevity of very elderly residents of long-term care facilities.
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Key words: heart rate variability, annual health examination, very elderly subjects

In 2006, 20.8% of the Japanese population was 65 years or older, the highest rate in the world[1]. This aging of the population is expected to continue for the next few decades, and the country's aging population has become a serious concern. The percentage of the population aged 65 to 85 years,

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which was 6% in 1985, is expected to increase to 15% in 2025[2,3]. Furthermore, because the prevalence of chronic vascular disease increases with age, resources for treating chronic vascular disease in the elderly are expected to come under severe strain. Because Japan has a National Health Insurance program that provides universal coverage, all Japanese persons are eligible for annual health examinations[4].

Although these annual health examinations have been performed in long-term geriatric care facilities, whether these examinations increases longevity is unclear. Elderly persons are affected by emotional stress, which causes physical and mental illness[5,6]. Heart rate variability (HRV) is reportedly a useful noninvasive tool for assessing autonomic nervous function[7,8] and the risk stratification for arrhythmic events after myocardial infarction, the severity of heart failure severity and serum norepinephrine levels[9–12]. Therefore, the aim of the present study was to determine the prognostic significance of HRV determined during annual health examinations.

Materials and Methods

Subjects and Study Designs

Among the subjects being cared for in our long-term geriatric care facility because of due to chronic vascular diseases, such as ischemic heart diseases, ventricular hypertrophy and various arrhythmias, or for cerebro-vascular infarction, chronic pulmonary diseases, or other physical or mental conditions, 71 subjects were enrolled in this study after informed consent had been obtained from them or their legal representatives in accordance with the principles of the Declaration of Helsinki[13]. All subjects had undergone annual health examinations including, determination of body-mass index (BMI), blood chemical studies, electrocardiography (ECG), and chest radiography, because these examinations have been recognized as standard items of annual physical examination by the Japanese government. Ambulatory ECGs were then obtained within 1 week. The HRV was obtained with a digital Holter ECG recorder (FM-160, Fukuda Denshi Co., Ltd., Tokyo) weighing 45 g. Spectral power results were obtained from 5-minute segments, with a total spectrum of 320 points. Over a bandwidth of 0.01 to 1.0 Hz, the low-frequency (LF) band (0.04 to 0.15 Hz), the high-frequency (HF) band (0.15 to 0.40 Hz), and all power values were calculated with the Mem/Calc/Chiram software program (Suwa Trust Co., Ltd., Tokyo)[14]. The LF and HF components were measured in milliseconds squared and are expressed as power. The HF reflects mainly parasympathetic activity, whereas the LF/HF ratio reflects mainly sympathetic activity and sympatho-vagal balance[15]. Time-domain methods using standard deviation of all NN intervals (SDNN) in all 5-minute segments of the entire recording and the coefficient of variation of RR intervals (CVRR) were selected as items to be analyzed from among the 11 variables[15]. The SDNN and the CVRR were calculated with the same software used for the frequency-domain analysis and reflect parasympathetic activities. The HRV was measured from 14:30 to 16:30, because the mental and physical conditions of the subjects have been demonstrated to be largely stable during this time.

Blood samples were collected in the morning with subjects in the fasting state within 1 week before or after Holter ECGs were obtained, and plasma was stored at −70℃ in a single bath until analysis. Among the plasma levels, those of C-reactive protein (CRP) and albumin were selected for analysis, because both variables in our experience reflect prognostic survival[16]. The intra-assay coefficient of variance was <5% for all assays.

After these procedures were performed concomitantly in annual health examinations in 2008, the subjects were followed up for 3 to 48 months with our standard daily care regimen, and the data were analyzed retrospectively.

The relative risks (RRs) and odd ratios (ORs) for cardiac death were then calculated for values of variables less than selected cut-off levels. Age greater than 85 years was based on the average age of our subjects being cared for in nursing homes. The cut-off value of SDNN <65 milliseconds was based on report by Huiklu et al[17], that of CVRR <8% was based on our previous data[18], and that of LF/HF ratio >2.0 was based on recommendations of the American Heart Association, the American College

Table 1 Comparison of baseline health examination and HRV data in subjects who were living or deceased at the end of follow-up

	Living (n=37)	Deceased (n=34)	P value
Age (years)	86 ± 14	90 ± 16	NS
Sex (M/F)	7/30	8/26	NS
BMI (kg/m²)	21 ± 3.6	19.6 ± 3.5	NS
CRP (mg/dL)	0.2 ± 0.06	0.3 ± 0.08	NS
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 0.6	NS
SDNN (ms)	73.2 ± 13.5	53 ± 9.8	p<0.05
CVRR (%)	9.3 ± 1.7	7.6 ± 1.3	p<0.05
LF/HF ratio	1.8 ± 0.4	1.9 ± 0.3	NS
Follow-up (months)	39.4 ± 6.6	20.4 ± 4.2	p<0.001

(mean ± SEM)
BMI: body-mass index; CRP: C-reactive protein; SDNN: standard deviation of all NN intervals in all 5-minute segments of the entire recording; CVRR: coefficient of variation R-R interval; LF/HF: low frequency/high frequency

of Cardiology, and the European Society of Cardiology[15].

Statistics

All variables were analyzed with repeated measures analysis of variance and are presented as means ± SEM. The groups were compared with unpaired *t*-tests and 2-way analysis of variance with repeated measurements. Univariate and multivariate regression analyses were used to identify predictors of cardiac death. The RR, OR, risk ratio, sensitivity and specificity were calculated. Kaplan-Meier curves[19] were constructed and compared by means of log-rank tests. A p value of <0.05 was considered to indicate statistical significance. The statistical analyses were performed with the software program StatMate IV for Windows (ATMS Co., Ltd., Tokyo).

Results

No significant differences were found in annual health examination data, such as age, sex, BMI, and plasma CRP and albumin levels, between living subjects and deceased subjects (**Table 1**). However, both the SDNN and CVRR were significantly higher in living subjects than in deceased subjects (SDNN: 73.2 ± 13.5 milliseconds vs. 53 ± 9.8 milliseconds, p< 0.05, CVRR: 9.3% ± 1.7% vs. 7.6% ± 1.3%, p<0.05), but the LF/HF ratio did not differ significantly between the groups (living subjects: 1.8 ± 0.4 vs. 1.9 ± 0.3, NS). The RRs for SDNN <65 milliseconds and CVRR <8% were both significantly higher, but the RRs for age, plasma albumin, plasma CRP, dementia, cerebral vascular infarction, and hypertension were not significantly higher. In contrast, the ORs of these variables were not significantly higher but SDNN and CVRR in RR (**Table 2**). Kaplan-Meier survival curves showed that subjects with SDNN ≥65 milliseconds lived longer, starting at around 35 months, than did subjects with SDNN <65 milliseconds (**Fig. 1**). The sensitivity of SDNN at this cut-off value for predicting greater survival had a sensitivity of 61.1% and a specificity of 61.7%. The Kaplan-Meier survival curves show that subjects with CVRR ≥8% lived longer, starting at about 35 months. than did subjects with CVRR <8% (**Fig. 2**). This cut-off value had a sensitivity of 52.4% and a specificity of 85.3%.

Discussion

The main finding of this study was that the short-term HRV is more useful as a predictor of life longevity than is annual health examination data as Kleiger RE et al[20]. Furthermore, the present findings show the significance of parasympathetic tone activation.

With recent advances in medical care such as surgical techniques, medications and acute medical care systems (including emergency hospital care and

Table 2 Relative risks and odd ratios

	RR	P	OR	P
Age ≥85 years	0.6 (0.37–1.03)	NS	0.5 (0.47–1.03)	NS
SDNN <65 ms	1.85 (1.06–3.23)	p<0.05	2.5 (0.96–0.64)	NS
CVRR <8%	1.84 (1.06–3.22)	p<0.05	1.90 (0.58–6.15)	NS
LF/HF ratio >2.0	0.97 (9.56–1.76)	NS	2.53 (0.96–6.64)	NS
Albumin <3.5 g/dL	1.35 (0.72–2.6)	NS	1.92 (0.6–6.22)	NS
CRP >0.3 mg/dL	0.72 (0.38–1.38)	NS	0.57 (0.19–1.94)	NS
Dementia	0.45 (0.29–0.70)	NS	0.91 (0.30–2.73)	NS
Cerebral Vascular Infarction	0.95 (0.52–1.72)	NS	0.91 (0.3–2.72)	NS
Hypertension	0.90 (0.51–1.61)	NS	0.91 (0.30–2.74)	NS

RR: relative risk; OR: odds ratio; SDNN: standard deviation of all NN intervals in all 5-minute segments of the entire recording; CVRR: coefficient of variation of RR interval; LF/HF: low frequency/high frequency; CRP: C-reactive protein

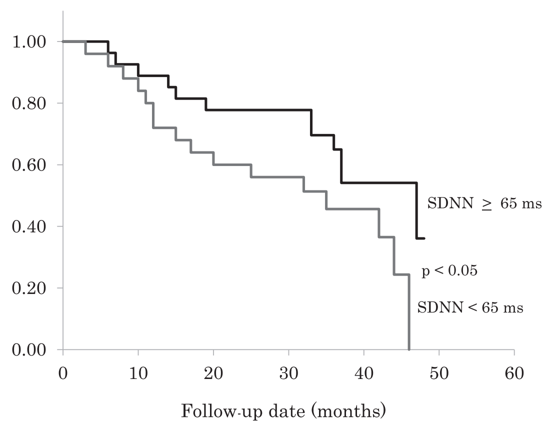

Fig. 1 Longevity of subjects with SDNN ≥65 milliseconds and SDNN <65 milliseconds by Kaplan-Meier prognostic analysis

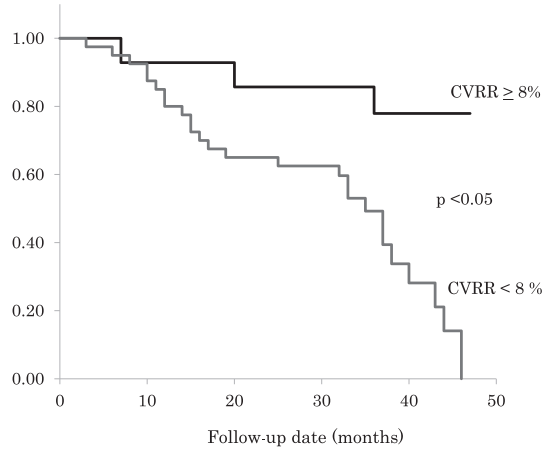

Fig. 2 Longevity of subjects with CVRR ≥8% and <8% by Kaplan-Meier prognostic analysis

transportation systems), increasing numbers of patients are able to survive acute illnesses but often have secondary disabilities. These patients usually require hospitalization or stays in long-term care facilities for months or even years until death because their families are not able to provide adequate daily care at home. Changes in the prevalence of place of deaths have shown that Japanese elderly to die in hospital or long-term care facilities have been increased[21]. Therefore, the increasing use of hospitals and long-term care facilities for elderly persons has become an important social problem. In 2012, about 420,000 elderly persons receive their daily care at 6,200 long-term geriatric care facilities[22]. However, about 90,000 persons were waiting for these services[22]. Because the Japanese government has provided universal health insurance coverage, all Japanese persons are eligible to undergo annual physical examinations. These annual physical examinations are also performed for persons older than 75 years.

When the longevity of subjects in our geriatric long-life care facilities was analyzed for 3 to 48 months starting in 2008, no significant differences were found in age, sex, BMI, or plasma levels of CRP, or albumin between those who died by the end of follow-up and those who were alive, but the baseline HRV variables of SDNN and CVRR were significantly greater in living subjects than in deceased subjects **(Table 1)**. The RRs of both SDNN and CVRR, at our selected cut-off levels, were significantly greater, but those of other variables, including the LF/HF ratio and plasma levels of CRP and albumins, were not **(Table 2)**. Furthermore, the longevity of subjects with SDNN ≥65 milliseconds was significantly greater than that of subjects with SDNN <65 milliseconds subjects from about 35 months **(Fig. 1)**. The SDNN at this cut-off value had a sensitivity of 61.1% and a specificity of 61.7%. In addition, the longevity of subjects with a CVRR ≥8% was greater than that of subjects with CVRR <8% from about 35 months **(Fig. 2)**. The CVRR at this cut-off had a sensitivity of 52.4% and a specificity of 85.3%. These data suggest that the autonomic nervous system affecting SDNN or CVRR or both plays an important role in life expectancy.

Assessment of HRV based on ambulatory ECG monitoring is an inexpensive and noninvasive technique that has become widely used in cardiology. Assessment of HRV is considered the most appropriate method for assessing quantitative markers of cardiac autonomic nervous activity, as reported by a Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology[15]. According to reports[15], recordings of 2 to 5 minutes can be used to evaluate autonomic nervous tone either through spectrum calculations of the frequency domain or through time-domain analysis.

In the present study, the maximum entropy calculation method with the Mem Calc/Chiram software program[14] was used to evaluate autonomic nervous function, because this system can analyze both spectral and time domains of HRV every 5 minutes for 2 hours using the exponential method of power spectral density analysis. The SDNN and CVRR were selected as variables for time-domain analyses in recordings averaging 2 hours, because both are commonly used and accurately reflect parasympathetic tone. Because both SDNN and CVRR but not the LF/HF ratio, were significantly higher at baseline in subjects alive at the end of follow-up than in subjects who had died, we can speculate about the prognostic significance of parasympathetic activity in our very elderly subjects. Decreased HRV in time-domain analysis is associated with heart failure and ischemic heart diseases[10]. Although low HRV indicates a poor prognosis, the mechanism of this effect has not been clarified; however, scopolamine administered intravenously to dogs after myocardial infarction increases the risk of ventricular fibrillation[9]. Furthermore, in patients with heart failure of New York Heart Association class III or IV, the SDNN is decreased and HRV could be an important predictor of mortality[23]. Thus, a better understanding of the pathophysiological relationship between low HRV and mortality would be useful for developing strategies to increase HRV and prolong the lives of the very elderly.

The present study had several limitations. First, the cohort was small and the follow-up period was short. However, few previous studies have obtained data similar to ours, from 71 very elderly subjects after 3 to 48 months of follow-up. Furthermore, fewer than 150 physicians are working in nursing homes in Japan[3]. Thus we believe the present data are valuable. A second limitation was that HRV was not assessed at the same time as physical examination, although it was assessed within 1 week later. Therefore, the association between autonomic tone and physical health variables might be weak. However, the very elderly subjects were generally calm and not as active in their daily lives as are middle-aged people. A third limitation of the present study was that the exact cause of death were not determined, because our facility is a long-term nursing home and not a hospital. Thus, the present data might not be entirely unreliable.

Although larger, longer, randomized studies should be performed with simultaneous HRV assessment and annual physical examinations, we believe the present data are of value for healthcare providers at long-term geriatric care facilities. In our experience, both music[24,25] and spiritual activation by chaplains[26] are able to enhance parasympathetic tone and have beneficial effects on plasma catecholamine and cytokine levels. In conclusion, the modulation of parasympathetic tone in daily activities has an important role in the longevity of very elderly subjects in long-term care facilities.

Conflict of Interest: The authors declare no conflict of interest.

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