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Abstract—To investigate the association between cardiovascular mortality and short-term variabilities in blood pressure and heart rate, we performed a long-term prospective study of ambulatory blood pressure monitoring in Ohasama, Japan, starting in 1987. We obtained ambulatory blood pressure and heart rate in 1542 subjects ≥40 years of age. Blood pressure and heart rate variabilities were estimated as a standard deviation measured every 30 minutes by ambulatory monitoring. There were 67 cardiovascular deaths during the follow-up period (mean=8.5 years). The Cox proportional hazards model, adjusted for possible confounding factors, demonstrated a significant increase in cardiovascular mortality, with an increase in daytime systolic ambulatory blood pressure variability. A similar trend was observed in daytime diastolic and nighttime ambulatory blood pressures. Cardiovascular mortality rate increased linearly, with a decrease in daytime heart rate variability. Subjects in whom the daytime systolic ambulatory blood pressure variability was larger than third quintile and the daytime heart rate variability was lower than the mean−SD were at extremely high risk of cardiovascular mortality. The blood pressure and heart rate variabilities obtained every 30 minutes by ambulatory blood pressure monitoring were independent predictors for cardiovascular mortality in the general population. **(*Hypertension*. 2000;36:901-906.)**

Key Words: cohort study ■ ambulatory monitoring ■ cardiovascular diseases ■ mortality

Blood pressure (BP) variability estimated as a standard deviation of beat-to-beat BP obtained by intra-arterial BP monitoring has been suggested to be a risk factor for hypertension-related target organ damage.[1,2] BP variability estimated as a standard deviation of noninvasive ambulatory BP monitoring obtained by every 15 to 20 minutes measurement is also associated with cardiovascular morbidity and mortality.[3,4] However, the prognostic significance of BP variability for cardiovascular mortality has not been investigated in the general population. We started a long-term prospective cohort study with ambulatory BP monitoring in the general population of a rural Japanese community and monitored the survival of this population from 1987.[5–9] In this study, we investigated the association between the baseline BP and heart rate (HR) variabilities and subsequent cardiovascular mortality in the general population.

Most previous studies assessing HR variability examined beat-to-beat HR variability obtained by Holter monitoring. A clinical significance of BP and HR variability obtained by indirect and intermittent measurement may be different from that of previous studies in which beat-to-beat intra-arterial BP monitoring and Holter monitoring of HR were applied.[10] However, monitoring of ambulatory BP and HR every 30 minutes is widely used in clinical practice. Therefore, we examined the predictive power of BP and HR variability obtained every 30 minutes for cardiovascular mortality.

Methods

Study Population

The subjects took part in a longitudinal, observational study of ambulatory BP monitoring in the general population of Ohasama, a rural community of Japan, starting in 1987. The details of the Ohasama study have been reported elsewhere.[5–9] Of the 2716 individuals ≥40 years of age in 3 of the 4 districts of Ohasama, we excluded individuals who worked outside the town (n=575), were hospitalized (n=121), or were demented or bedridden (n=31). We obtained ambulatory BP data on 1542 subjects (mean age 61.7 years; ratio of men to women, 40: 60). We had confirmed previously that the subjects were representative of the general Japanese population.[7,8] Informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of Tohoku University School of Medicine.

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Ambulatory BP Monitoring

The ambulatory BP and HR were monitored every 30 minutes with a fully automatic device (ABPM630, Nippon Colin) that met the criteria of the Association for the Advancement of Medical Instrumentation.[11,12] We used the cuff-oscillometric method for analysis. Participants were told to carry on with their normal daily activities during measurement. According to the diary, "daytime" and "nighttime" were determined as the waking and sleeping periods of the patient, respectively. The mean duration of monitoring was 22.6±2.4 hours, and the mean number of measurements was 45.2±4.9 (n=1542). Artifacts of BP measurements during monitoring were defined according to previously described criteria[13] and were omitted from the analysis. We only analyzed the ambulatory BP data that were obtained for >8 hours and 4 hours during the daytime and nighttime, respectively.

Data Analysis

We investigated the association between the baseline BP and HR variabilities and subsequent cardiovascular mortality in this general population.

Residence in Ohasama as of March 31, 2000, was confirmed by examining the residents' registration cards. The mean duration of follow-up was 8.5 years (SD 2.4, maximum 11.8 years). We obtained death certificates from the Ohasama Health Department. We also reviewed hospital record forms and confirmed the cause of death. According to the recommendations of the 10th revision of the World Health Organization's International Classification of Diseases, cardiovascular death was defined as mortality related to disease of the circulatory system (ICD-10 code "I"). The characteristics of the causes of death in the Ohasama study have been described previously.[9] Of the 1542 residents who were eligible for the study, 17 (1.5%) moved away or were lost to follow-up. There were 195 deaths (12.6%) during the follow-up period, of which 67 were caused by a cardiovascular event.

In this study, we focused on BP variability every 30 minutes, that is, short-term variability rather than circadian BP variation. We previously reported that the magnitude of the nocturnal decline in BP, which is an index of circadian BP variation, was the strongest predictor of the SD of 24-hour BP, suggesting that the SD of 24-hour BP is not an appropriate index of short-term BP variability.[14] Therefore, short-term BP variability (every 30 minutes) was calculated as the SD of daytime and nighttime ambulatory BP, respectively. Similarly, we calculated the SD of daytime and nighttime HR obtained every 30 minutes by an ambulatory BP monitoring device and defined it as HR variability.

The prognostic significance of BP and HR variabilities was determined by means of the Cox proportional hazards regression model[15] with the SAS PHREG procedure.[16] The dependent variable was the number of days from the measurement of ambulatory BP to cardiovascular death or "censoring" (noncardiovascular death or withdrawal from this study for survivors on March 31, 2000). The independent variables were baseline BP and HR variabilities, BP level, gender, age, smoking status, obesity, use of antihypertensive medication, and history of hyperlipidemia, diabetes mellitus, and cardiovascular disease.

Initially, quintile analysis was applied to the baseline BP variability, in which subjects were subdivided equally into 5 groups according to the distribution of the variability. We treated the quintile associated with the lowest mortality risk as a reference category. In analyzing the association between HR variability and prognosis, participants were subdivided into 3 groups: HR variability < mean−SD, mean−SD < HR variability < mean+SD, HR variability > mean+SD, according to the previous report indicating the prognostic significance of HR variability.[17] In this analysis, we treated the tertile of HR variability associated with the lowest mortality risk as a reference category. One of the objectives of this study was to investigate whether the relation between BP variability and cardiovascular mortality risk is linear or not. To determine the linearity between BP variability and cardiovascular mortality risk, we applied quintile analysis, whereas the relation between HR variability and cardiovascular mortality risk was assessed by tertiles analysis, because the latter relation has already been reported in the previous work.[17] Differences of BP variabilities among the quintiles and of HR variabilities among 3 groups were tested for the presence of linear trends by Cox proportional hazards model. We then performed Cox proportional hazards analysis to determine the association between cardiovascular mortality and BP variability, in which HR variability was included in the regression model as a continuous variable. Similarly, in the analysis of the association between cardiovascular mortality and HR variability, BP variability was adjusted. After this, we performed Cox proportional hazards analysis again to determine the association between cardiovascular mortality and the combination of BP and HR variabilities

Information on smoking status, history of cardiovascular disease, and use of antihypertensive medication was obtained from questionnaires sent to each subject at the time of ambulatory BP monitoring and was confirmed from the medical records at Ohasama Hospital. A history of cardiovascular disease included a history of stroke incidence, transient ischemic attacks, myocardial infarction, angina pectoris, atrial fibrillation, and cardiac or renal failure.

The estimated relative hazard (RH) and 95% confidence interval (CI) of the variables were derived from the coefficient and its standard error as determined by the Cox proportional hazards model. Data are shown as mean+SD. A value of $P<0.05$ was accepted as indicating statistical significance.

Results

The baseline characteristics of participants among the quintiles of BP variability estimated as the SD of daytime systolic ambulatory BP and among the 3 groups of HR variability (HR variability < mean−SD, mean−SD < HR variability < mean+SD, HR variability > mean+SD) are shown in Tables 1 and 2, respectively. Age, BP level, the prevalence of antihypertensive medication, obesity, and hyperlipidemia increased significantly, as did daytime systolic BP variability (Table 1). The prevalence of previous cardiovascular disease tended to increase, whereas the prevalence of male gender and current or ex-smokers significantly decreased with an increase in systolic BP variability, respectively. The baseline characteristics of participants among the quintiles of daytime diastolic BP and nighttime systolic and diastolic BP variability showed similar results.

The levels of 24-hour and daytime HR significantly increased, as did daytime HR variability (Table 2). The prevalence of hyperlipidemia tended to increase with a decrease in daytime HR variability. The other variables showed no consistent association.

Figure 1 shows the RH and 95% CI for cardiovascular mortality among the quintiles of daytime and nighttime ambulatory BP variability and among the 3 groups of HR variability (HR variability < mean−SD, mean−SD < HR variability < mean+SD, HR variability > mean+SD). There was a significant linear relation between daytime systolic ambulatory BP variability and RH for cardiovascular mortality (P for linear trend=0.03). Cardiovascular mortality rate increased linearly, with a decrease in daytime HR variability (P for linear trend=0.008). Of 392 treated subjects, 105 (26.8%) were treated with β-blockers. When we adjusted the use of β-blockers, the results of RH of daytime HR variability (P for linear trend=0.009) were similar to those in which the use of antihypertensive medication was adjusted. The RH of daytime HR variability in the mid (7.2 to 14.0 bpm) and the lowest tertiles (<7.2 bpm) was 2.14 (95% CI 0.76 to 6.15, $P=0.15$) and

TABLE 1. Clinical Characteristics Among Quintiles of Daytime Ambulatory Blood Pressure Variability

	Daytime Systolic BP Variability, mm Hg					
Variables	<11.5	11.5–13	13–15.8	15.8–18.8	18.8<	*P*
No. of subjects	312	314	301	307	308	
Age, y	55	60	61	64	68	0.0001*
Ambulatory BP, mm Hg						
24-h systolic	116	122	124	126	129	0.0001*
24-h diastolic	69	72	73	73	74	0.0001*
Daytime systolic	121	126	130	132	136	0.0001*
Daytime diastolic	73	75	77	77	78	0.0001*
Nighttime systolic	105	111	113	115	118	0.0001*
Nighttime diastolic	61	64	65	65	66	0.0001*
Men, %	45	41	35	35	28	0.001†
Antihypertensive medication, %	10	25	35	34	50	0.001†
Smoking, %	29	23	20	20	16	0.005†
Obesity, %	24	25	32	31	37	0.002†
Hyperlipidemia, %	11	12	15	19	24	0.001†
Diabetes, %	14	17	18	19	18	NS
Previous cardiovascular disease, %	2	7	4	3	7	0.003†

*ANOVA, †χ^2 test.

3.64 (95% CI 1.22 to 10.8, $P=0.02$), respectively. Such an association was not observed for nighttime HR variability. The highest quintiles of daytime and nighttime systolic BP variability were associated with a significant increase in the risk of cardiovascular mortality.

To exclude the effect of a reciprocal relation between HR and BP variabilities on cardiovascular mortality, we further adjusted these variables as confounding factors against each other in the Cox regression model (Table 3). This adjustment did not change the results indicated in Figure 1, suggesting that BP and HR variabilities are associated with cardiovascular mortality independent of each other. Analysis with nighttime BP and HR variability gave a similar result to that shown in Figure 1.

Figure 2 indicates the prognostic significance of the combinations of daytime ambulatory BP and HR variabilities. These were divided at the third quintiles of daytime ambulatory BP variability (15.8 mm Hg) and the mean−SD of HR variability (7.2 bpm). Subjects in whom the daytime systolic ambulatory BP variability was larger than the third quintile and the daytime HR variability was simultaneously less than mean−SD showed an extremely high risk of cardiovascular mortality (RH=3.56, $P<0.01$).

Discussion

The prognostic value of BP variability was first confirmed in this long-term prospective study of the general population,

TABLE 2. Clinical Characteristics Among 3 Groups of HR Variability (HR Variability<Mean−SD, Mean−SD<HR Variability<Mean+SD, HR Variability>Mean+SD)

	Daytime HR Variability, bpm			
Variables	<7.2	7.2–14.0	14.0<	*P*
No. of subjects	231	1087	224	0.0001*
Age, y	64	61	62	0.0001*
24 h HR, bpm	65	69	70	0.0001*
Daytime HR, bpm	68	74	77	0.0001*
Nighttime HR, bpm	59	60	57	0.0001*
Men, %	41	35	41	NS
Antihypertensive medication, %	39	28	34	0.003†
Smoking, %	23	21	22	NS
Obesity, %	34	29	31	NS
Hyperlipidemia, %	19	16	12	NS
Diabetes, %	17	17	17	NS
Previous cardiovascular disease, %	5	4	6	NS

*ANOVA, †χ^2 test.

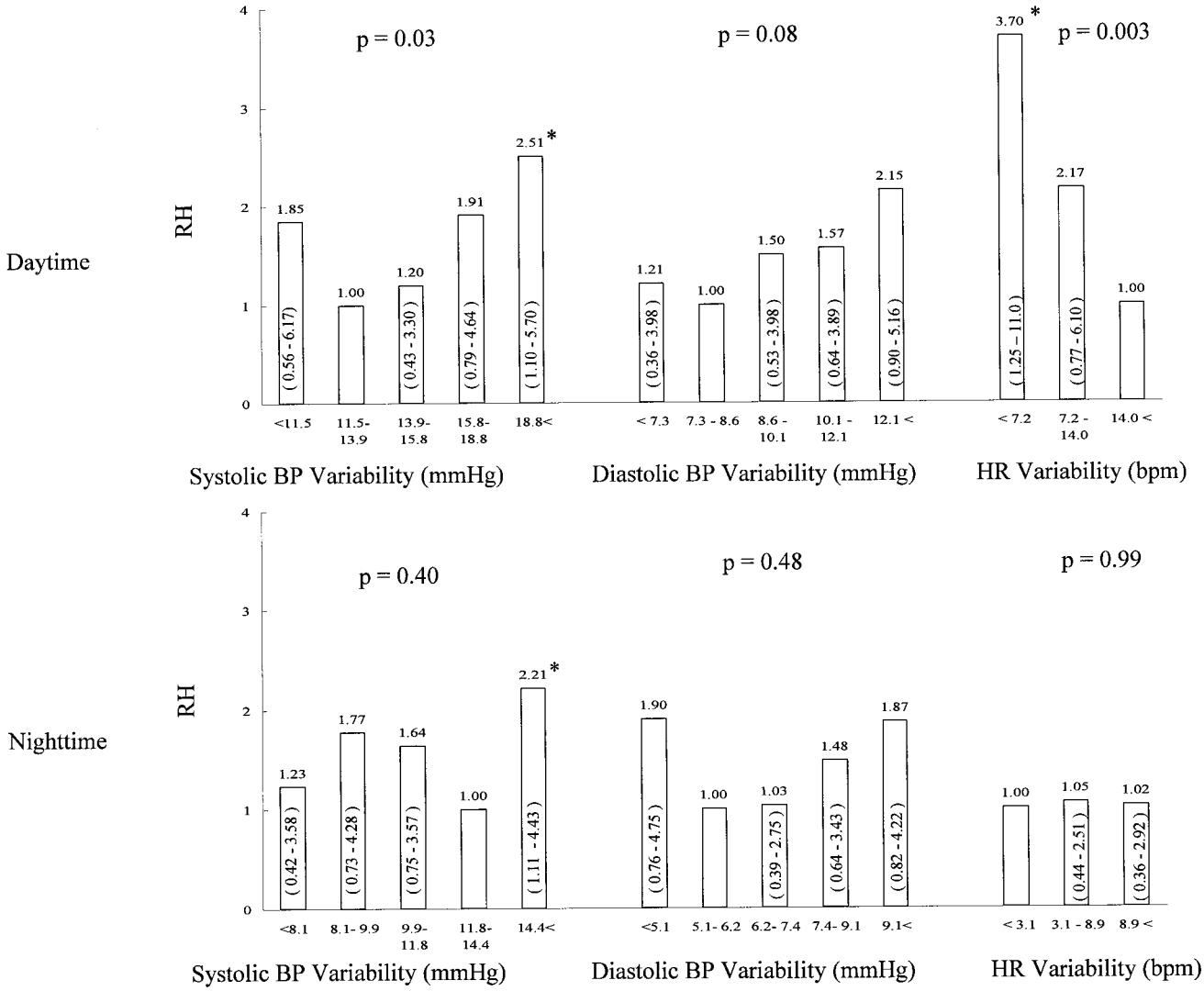

Figure 1. RH and 95% CI for cardiovascular mortality among quintiles of ambulatory BP variability and among 3 groups of HR variability (HR variability < mean−SD, mean−SD < HR variability < mean+SD, HR variability > mean+SD). RH and 95% CI were determined by Cox proportional hazards model, adjusted for gender, age, smoking status, obesity, use of antihypertensive medication, history of hyperlipidemia, diabetes mellitus, cardiovascular disease, and 24-hour systolic and diastolic BP levels. For HR variability, risk was further adjusted for 24-hour HR level. Number inside bar shows 95% CI. *P* for linear trend is indicated. **P*<0.05 vs RH=1.0.

that is, the greater the SD of ambulatory systolic BP, the greater the risk of cardiovascular mortality. BP variability monitored intra-arterially has been suggested to be a risk factor for hypertension-related target organ damage.[1,2] Every 15 to 20 minutes, BP variability estimated as a standard deviation (SD) of noninvasive ambulatory BP monitoring is also associated with cardiovascular morbidity and mortality.[3,4] For example, in the Cornell study, 729 individuals with mild hypertension were followed up for an average of 5 years, and the Cox model was adjusted for possible confounding factors to demonstrate that the SD of ambulatory diastolic BP was an independent predictor of cardiovascular morbidity.

As also described in previous reports,[4,14,18–20] this study demonstrated that BP variability increased as did BP and age. High BP variability was also associated with a prevalence of obesity and hyperlipidemia. To investigate the prognostic significance of BP variability independent from these risk factors, we adjusted the possible confounding factors for Cox analysis and confirmed a significant linear relation between daytime systolic BP variability and RH for cardiovascular mortality. Such a relation was not confirmed by Verdecchia et al,[4] who followed up 1372 hypertensive subjects for 2.9 years with noninvasive ambulatory BP monitoring every 15 minutes. The differences in the duration of the follow-up period and in the study population (general population versus hypertensive subjects) may have influenced the variation in results between the two studies. The difference in the age of the participants (61.7 years in our study versus 52 years in the study by Verdecchia et al) may also have been a significant factor.

The increase in BP variability in hypertensive and elderly subjects may be partly explained by the diminished baroreflex function associated with increased stiffness and decreased compliance of the large elastic arteries caused by aging and hypertension.[14,21,22] A disturbed baroreflex function is related to an exaggerated pressor response to mental

TABLE 3. RH and 95% CI of Daytime Ambulatory BP Variability and HR Variability for Cardiovascular Mortality, Adjusted for Gender, Age, Use of Antihypertensive Medication, Smoking Status, Obesity, History of Hyperlipidemia, Diabetes, Cardiovascular Disease, 24-Hour Systolic BP, Diastolic BP, and HR Levels

Variables	RH	95% CI	Trend *P*
Daytime systolic BP variability, mm Hg			
<11.5	1.76	0.53–5.85	
11.5–13.9	1.00		
13.9–15.8	1.22	0.44–3.38	0.02
15.8–18.8	2.08	0.85–5.07	
18.8<	2.69*	1.18–6.13	
Daytime diastolic BP variability, mm Hg			
<7.3	1.16	0.35–3.82	
7.3–8.6	1.00		
8.6–10.1	1.53	0.58–4.04	0.04
10.1–12.1	1.74	0.70–4.32	
12.1<	2.39	0.99–5.72	
Daytime HR variability, bpm			
<7.2	4.45†	1.47–13.4	
7.2–14.0	2.52	0.89–7.13	0.003
14.0<	1		

RH of daytime BP variability and daytime HR variability were further adjusted for daytime HR variability and daytime BP variability, respectively.
*P<0.05, †P<0.01.

and physical stimuli and mediates orthostatic hypotension, postprandial hypotension, and other conditions, resulting in increased BP variability. HR variability positively correlates baroreflex sensitivity.[20] An inverse relation between BP and HR variabilities also reflects baroreflex function[22]; HR variability is mediated reflexly by BP variability and buffers BP variability. High BP variability is assumed to be mediated at least in part by disturbed cardiac baroreflex function. However, after adjusting HR variability in this study, BP variability was still an independent risk factor for cardiovascular mortality. Therefore, it is unlikely that impaired baroreflex function is the sole mechanism explaining the relation between high BP variability and poor prognosis. However, it is still uncertain whether a clinical significance of BP and HR variabilities every 30 minutes are equivalent to that of beat-to-beat BP and HR variabilities and thus whether BP and HR variabilities every 30 minutes reflect baroreflex function. The mechanisms controlling short-term (beat-to-beat) and long-term (every 30 minutes) BP and HR variabilities may be different and thus relations between BP and HR variabilities obtained by measurement every 30 minutes and outcome and those obtained by beat-to-beat measurement and outcome may be mediated by different mechanisms. Another possible mechanism is that high BP variability injures the blood vessel and consequently causes cardiovascular complications. The effect of phasic BP load on cardiovascular structures is considered to be as important as that of tonic BP load.[23]

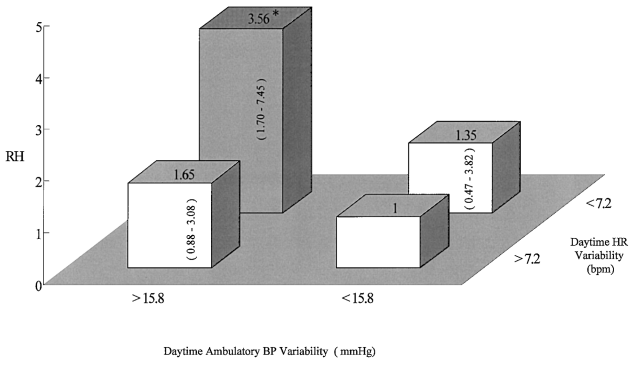

Figure 2. RH and 95% CI for cardiovascular mortality among combinations of daytime ambulatory BP variability and HR variability. BP and HR variabilities were divided at third quintile of daytime ambulatory BP variability and mean−SD of HR variability, respectively. RH and 95% CI were determined by Cox proportional hazards model, adjusted for gender, age, use of antihypertensive medication, smoking status, obesity, history of hyperlipidemia, diabetes, cardiovascular disease, and 24-hour systolic and diastolic BP and HR levels. *P<0.01 vs RH=1.0.

Poor prognosis in subjects with reduced HR variability has been reported in several types of cardiovascular disease such as congestive heart failure, post–myocardial infarction, and diabetes mellitus.[24–26] However, the clinical significance of HR variability has not been well studied in the general population. In the Framingham Heart Study, Tsuji et al[17] reported that less than the mean−SD of the SD of the total R-R intervals in individuals obtained by Holter ECG was associated with a hazard ratio of 1.47 for cardiac events. In our study, the prognostic significance of the HR variability obtained by ambulatory BP monitoring was similar to that reported by Tsuji et al, in which HR variability was obtained by Holter monitoring of ECG. HR variability obtained by ambulatory BP monitoring may be different, both qualitatively and quantitatively, from that obtained by Holter monitoring. However, our study demonstrated that the HR variability obtained even every 30 minutes has prognostic significance for cardiovascular mortality.

Only ambulatory BP monitoring can provide information on BP and BP variability as well as HR and HR variability. After adjusting BP variability in this study, HR variability was still an independent risk factor for cardiovascular mortality and vice versa, suggesting that HR and BP variabilities are associated with cardiovascular mortality independent of BP variability and HR variability, respectively. The combination of 2 independent variables such as BP and HR variabilities provided a powerful predictor of future cardiovascular mortality (Figure 2). Therefore, it is possible that indirect and intermittent ambulatory BP monitoring is more effective than the Holter ECG in predicting future cardiovascular morbidity or mortality.

Although we adjusted the use of antihypertensive medication in this analysis, it is possible that antihypertensive drugs may have affected the BP and HR variabilities. This in turn may have altered the prognostic power of BP and HR variability. To resolve this problem, a further long-term prospective study in a younger general population who are not taking antihypertensive drugs is needed.

In conclusion, the BP and HR variabilities obtained every 30 minutes by ambulatory BP monitoring were independent

predictors for cardiovascular mortality in the general population.

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