

Epidemiology of Hypertension Based on Ambulatory Blood Pressure Monitoring and Self-Measurement of Blood Pressure at Home

Yutaka Imai,^{*,a} Takayoshi Okubo,^b Kei Asayama,^a Hirohito Metoki,^a Masahiro Kikuya,^a Junichiro Hashimoto,^b Takashi Ugajin,^a Kazuhito Totsune,^a and Hiroshi Satoh^c

^aDepartment of Clinical Pharmacology and Therapeutics, ^bDepartment of Planning for Drug Development and Clinical Evaluation, and ^cDepartment of Environmental Health Sciences, Tohoku University Graduate School of Pharmaceutical Science and Medicine, 1-1 Seiryomachi, Sendai 980-8574, Japan

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Measurements of ambulatory blood pressure (ABP) and of home blood pressure (HBP) as an adjunct to casual/clinic BP (CBP) measurements are currently widely used for the diagnosis and treatment of hypertension. We have monitored a rural cohort of people from the population of Ohasama, Japan, with respect to their prognosis and have previously reported that ABP and HBP are superior to CBP for the prediction of cardiovascular mortality. We examined the prognostic significance of white-coat hypertension for mortality and found that the relative hazard for the overall mortality of patients with white-coat hypertension was significantly lower than that for true hypertension during 5-year observation period but observed that the development of sustained hypertension was more frequent in patients with white-coat hypertension than those with true normotension during 10-year observation period. Our results also confirmed that day-by-day variability as well as short-term blood pressure variability (as measured every 30 min) was independently associated with cardiovascular mortality. In addition, research has recently focused on isolated systolic hypertension and pulse pressure as independent risk factors for poor cardiovascular prognosis. The Ohasama study also clearly demonstrated that isolated systolic hypertension and increased pulse pressure, as assessed by HBP, were associated with an increase in the risk of cardiovascular mortality. Concerning diurnal blood pressure variation, the relative hazard for cardiovascular mortality increased in non-dippers and inverted dippers while that in extreme dipper did not. The Ohasama study also clearly demonstrated that nocturnal BP levels in hypertensive patients with extreme dipper were significantly higher than those in normotensive subjects. The Ohasama study showed that the level and variability of hypertension as assessed by ABP and HBP are independent predictors of cardiovascular morbidity and mortality. It also demonstrated an independent association between the prognosis of hypertension and each component of ABP and HBP, indicating the prognostic significance of these blood pressure measurements.

Key words — blood pressure, home measurement, ambulatory monitoring, variability, pulse pressure, heart rate

INTRODUCTION

The most vital blood pressure information related to hypertension in clinical practice is the casual/clinic blood pressure (CBP). Blood pressure

information for epidemiological purposes is generally also obtained in medical environments similar to those used for mass screening. Several questions have, however, recently been posed regarding the true representativeness of CBP, so research has focused on the other ways of measuring blood pressure, such as ambulatory blood pressure (ABP) monitoring and self-measured blood pressure at home (HBP). Each method of blood pressure measurement has its own specific features.

Since 1985, we have been conducting an epide-

*To whom correspondence should be addressed: Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Science and Medicine, 1-1 Seiryomachi, Sendai 980-8574, Japan. Tel.: +81-22-717-7770; Fax: +81-22-717-7776; E-mail: imai@tinet-i.ne.jp

Table 1. Reference Values of Home BP Value by JNC-VI and 1999 WHO/ISH

	HBP value (Ohasama) (mmHg)	Reference value (mmHg)
Hypertension	$\geq 138/\geq 83$	$\geq 135/\geq 85$
Cox model (non-parametric)		(JNC-VI)
Normotension		
Cox model (non-parametric)	120–127/72–76	
Corresponding value of 140/90 mmHg (Clinic BP)	123/77	< 125/< 80 (WHO/ISH)
Mean home BP value + 1 S.D. (with normal Clinic BP value)	125/77	

miological survey of hypertension using ABP and HBP in Ohasama, in the northern part of Japan. Ohasama initially had a population of 9400, but this has now dropped to 6800. Over the past 18 years, we have obtained 3000 ABP monitorings from subjects aged 20 years and over, and 5000 HBP measurements from subjects aged 7 years and over, as well as outcome and information on risk factors and predictors. One of the initial purposes of the study was to define reference values for these measurements with respect to prognosis in a long-term prospective study.

REFERENCE VALUES OF AMBULATORY BLOOD PRESSURE AND SELF-MEASURED BLOOD PRESSURE

Several methods are available for obtaining these reference values. The first involves the distribution criteria, for example mean + S.D., mean + 2 S.D. or 95th percentile value of the reference population. A meta-analysis of distribution criteria using an international database has been conducted.¹⁾ These values provided us with the distribution of ABP and HBP levels in the population, but the clinical significance of these values is still uncertain.

Another method uses correspondence criteria, which derives ABP and HBP levels corresponding to a casual blood pressure of 140/90 mmHg or 160/95 mmHg. Such values were obtained in the Ohasama study,²⁾ the PAMELA study,³⁾ the Belgian population study⁴⁾ and others. The relationship between CBP and ABP or HBP has not, however, been well enough characterized to obtain sufficiently accurate corresponding values (the correlation coefficient of the relationship between CBP and ABP or

HBP having been calculated to be approximately 0.5).

The most meaningful reference values would be provided by a long-term prospective study based on the resultant cardiovascular morbidity and mortality. Several observational and interventional studies are currently ongoing world-wide, of which the Ohasama study started first and is the only study aiming to provide such reference values. Subjects from the Ohasama population aged 40 years and over were followed up for an average of 5 years.⁵⁻⁷⁾ ABP and CBP values were classified equally into quintiles on the basis of blood pressure level, the relationship between blood pressure level and cardiovascular mortality being analyzed by a Cox regression model adjusted for age, sex and drug treatment.

No specific tendency was observed in systolic CBP in the 1300 subjects ≥ 40 years followed. In subjects in the highest quintile of systolic ABP, however, a significant increase in relative hazard was observed. A tendency towards an increased relative hazard was also observed in the lowest quintile. The higher predictability of HBP when compared with CBP was also confirmed in the Ohasama study.^{5,6,8)} These results were cited in the Sixth Report of the Joint National Committee⁹⁾ and 1999 World Health Organization/International Society of Hypertension guidelines¹⁰⁾ (Table 1), and were the basis of the reference values (Table 1) for ABP monitoring and HBP measurements given in these guidelines.

WHITE-COAT HYPERTENSION

White-coat hypertension — reproducible hypertension in the medical setting and normotension in the non-medical setting — is more accurately defined using normative values of ABP and HBP. The

Ohasama study examined the prognostic significance of white-coat hypertension.¹¹⁾ According to the Cox proportional hazard model, the relative hazard in white-coat hypertensive patients was similar to that seen in true normotensive subjects, whereas true hypertension and reversed white-coat hypertensive subjects (masked hypertension: hypertension in the non-medical setting and normotension in the medical setting) carried a significantly higher relative hazard of cardiovascular mortality. Recent analysis demonstrated that the development of sustained hypertension was more frequent in patients with white-coat hypertension than in those with true normotension during 10-year observation period.

In the Ohasama population, 24.8% of the 117 subjects with hypertension measured by CBP (systolic blood pressure [SBP] \geq 160 mmHg and/or diastolic blood pressure [DBP] \geq 95 mmHg) were normotensive when measured by 24 hr ABP monitoring (SBP < 125 mmHg and DBP < 75 mmHg). The results again suggest that ABP and HBP have more predictive power and are more representative of individual blood pressure than in conventional CBP.

BLOOD PRESSURE VARIABILITY AND PROGNOSIS

Both new techniques for blood pressure measurement have several advantages over CBP, these advantages essentially being mediated by multiple measurements of blood pressure over a given period.¹²⁾ ABP monitoring, for example, provides 50–100 measurements during the course of a day, whereas HBP monitoring provides more than 60 measurements during the course of a month. Such detailed information enables a wider scope of parameters to be derived from the data set, such as 30 min blood pressure variation, circadian blood pressure variation, day-by-day variation and the weekly and yearly variation of blood pressure and provides additional information, including multiple measurements of heart rate, which are not available from CBP measurements.

Circadian Blood Pressure Variation

Circadian blood pressure variation (a higher blood pressure level during the day and a lower one at night) is usually observed both in subjects with normotension and in those with essential hyperten-

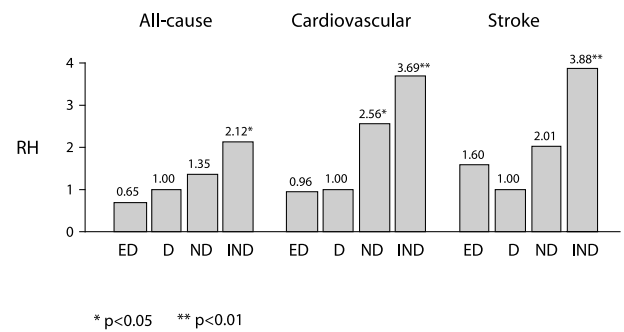


Fig. 1. Circadian Blood Pressure Variation and All Cause Mortality, Cardiovascular Mortality and Stroke Mortality in Ohasama Population¹⁷⁾

p-Values are expressed vs relative hazard 1. ED: extreme dippers, ND: non-dippers, D: dippers, IND: inverted dippers.

sion. Under several pathophysiological conditions, however, circadian blood pressure variation is diminished, even in patients with essential hypertension, sometimes being inverted to show a nocturnal elevation of blood pressure. Subjects who showed normal nocturnal dipping were called dippers, whereas those with diminished nocturnal dipping or a nocturnal elevation of blood pressure (inverted dippers) were classified as non-dippers. (Kario *et al.* have used the term 'extreme dipper' for subjects with a nocturnal dip of 20% or more of diurnal blood pressure).¹³⁾

The Ohasama study examined the relationship between diurnal blood pressure level and circadian blood pressure variation.¹⁴⁾ The amplitude of nocturnal dipping increased with the increase in diurnal blood pressure level, and it should be noted that the nocturnal blood pressure level rose according to the elevation of diurnal pressure level. These results suggest that mean daily blood pressure in hypertensive subjects should be lower over 24 hr. A significantly higher relative hazard for cardiovascular mortality, especially for stroke mortality was observed in non-dippers and inverted dippers, while the relative hazard for cardiovascular mortality in extreme dippers was similar to that in normal dippers (Fig. 1).¹⁵⁾

The nocturnal blood pressure level in hypertensive extreme dippers needs to be identified: in this group, it was significantly higher than was encountered in normotensive subjects (Fig. 2).¹⁶⁾ Thus, extreme dipper hypertensive subjects do not have an inappropriately low blood pressure level. If circadian blood pressure variation were associated with a risk of cardiovascular complications in extreme

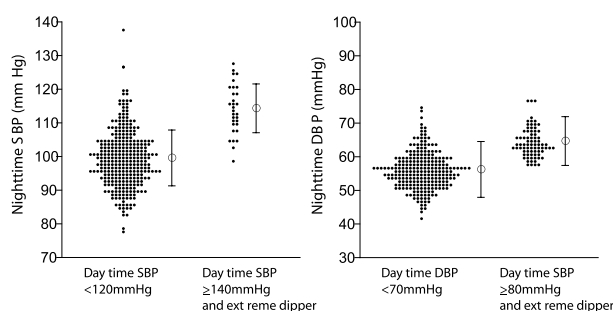


Fig. 2. The Nocturnal Blood Pressure Level in Daytime Normotensive Subjects and in Extreme Dippers with Daytime Hypertension¹⁸⁾

dippers, a greater amplitude and slope for nocturnal dipping and higher 24 or daytime ABP levels would therefore be postulated.

Morning Hypertension

The morning rise of blood pressure represents a mirror image of nocturnal dipping. As described for nocturnal dipping, the morning rise has several measurable factors - the blood pressure level itself and the amplitude and slope of the morning rise.

The clinical significance of the high morning blood pressure was suggested by the results of the Ohasama study in terms of its examination of the relative hazards ratio for cardiovascular mortality on the basis of the difference in blood pressure between morning and evening HBP. The higher the morning blood pressure was relative to the evening blood pressure, the greater the relative hazard ratio of cardiovascular mortality that was seen (Fig. 3).¹⁷⁾ Controlling the morning blood pressure seems to give a better prognosis in the hypertensive population. Recently Kamoi *et al.* reported that in normotensive patients with diabetes mellitus on the basis of clinic BP, only those with high BP in the morning obtained by HBP had severe target organ damage, suggesting that morning BP has a specific clinical relevance to hypertensive complications.¹⁸⁾

Blood Pressure Variability and Heart Rate Variability

ABP monitoring provides us with information on blood pressure every 30 min as well as on heart rate variability and average blood pressure and heart rate. The issue remains, however, of whether blood pressure variability *per se* has any prognostic significance. The clinical significance of heart rate variability has scarcely been studied in the general popu-

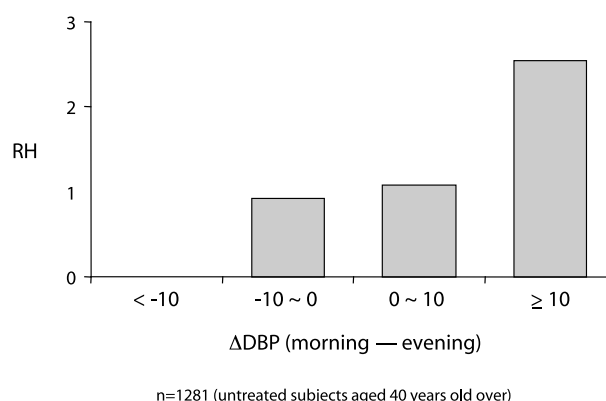


Fig. 3. Relative Hazard (RH) for Cardiovascular Mortality in Relation to Morning High Blood Pressure Determined by the Difference Between Home BP in the Morning and That in the Evening ($n = 1281$ Untreated Subjects aged 40 years and Above)¹⁹⁾

lation, and the prognostic significance of blood pressure variability for cardiovascular mortality has not been investigated at all in this group. The poor prognosis of subjects with reduced heart rate variability has, however, been widely recognized in several types of cardiovascular disease.

In the Ohasama Study, we obtained 30 min blood pressure and heart rate variability by means of indirect ABP monitoring in the general population, following subjects for up to 10 years. We can therefore examine the prognostic significance of blood pressure variability, heart rate variability and combinations of these variables.¹⁹⁾ We obtained ABP and heart rate in 1542 subjects aged 40 years and over. The variability of blood pressure and heart rate was estimated as the standard deviation of the daytime or night-time average, measured every 30 min.

Quintile analysis was initially applied to the baseline blood pressure variability, subjects being subdivided into five equal groups according to the distribution of the baseline blood pressure variability. There was a significant linear relationship between daytime systolic ABP variability and relative hazard for cardiovascular mortality (Fig. 4). The highest quintile of daytime systolic blood pressure variability revealed a significant increase in relative hazard for cardiovascular mortality. In analyzing the association between heart rate variability and prognosis, participants were subdivided into three groups: those with a heart rate variability less than the mean minus 1 S.D., greater than the mean plus 1 S.D. and values in between. Cardiovascular mortality increased linearly with the decrease in daytime and

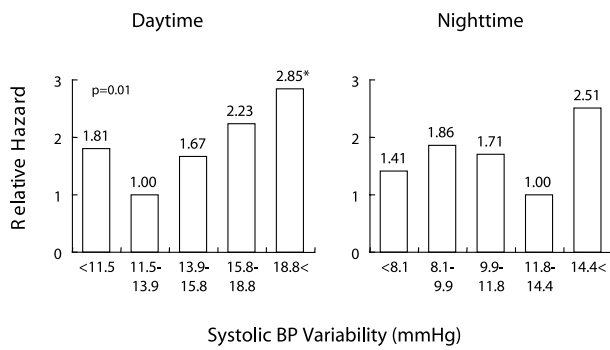


Fig. 4. Relative Hazard for Cardiovascular Mortality in Relation to Blood Pressure Variability Determined by Ambulatory BP Monitoring¹⁹⁾
p < 0.05 vs relative hazard 1.

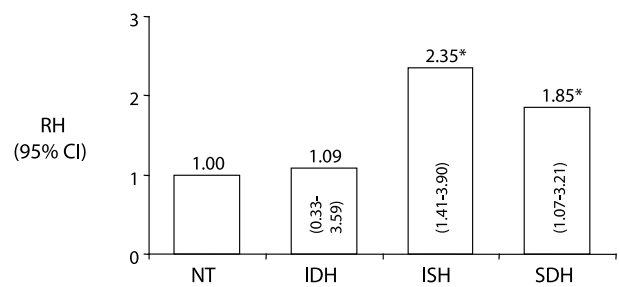
the night-time heart rate variability. These results suggest that blood pressure variability and heart rate variability are associated with cardiovascular mortality independently of each other.

We then examined the risk of cardiovascular mortality associated with a combination of daytime ABP variability and heart rate variability. Daytime systolic blood pressure variability was divided into two by the cut-off point to separate the fourth and third quintiles of daytime systolic blood pressure, that is, 15.8 mmHg. Daytime heart rate variability was also divided into two groups by the cut-off point at the mean minus 1 S.D. of heart rate variability, that is 7.2 bpm. Subjects whose daytime systolic ABP variability was more than 15.8 mmHg and whose daytime heart rate variability was less than 7.2 bpm had an extremely high relative hazard for cardiovascular mortality. The clustering of high blood pressure variability and low heart rate variability increases cardiovascular mortality risk synergistically.

Recent analysis demonstrated that day-by-day variability of BP obtained by HBP also has a prognostic significance; the high day-by-day variability of BP associates poor prognosis.

PULSE PRESSURE

It has recently been reported that pulse pressure is a powerful determinant of cardiovascular outcome, and we also found this to be true in the Ohasama population aged 40 years and over.²⁰⁾ The relative hazard for cardiovascular mortality was highest in isolated systolic hypertension defined on the basis of HBP measurements, greater even than that for



NT : normotension
 IDH : isolated diastolic hypertension
 ISH : isolated systolic hypertension
 SDH : systolic and diastolic hypertension

Fig. 5. Relative Hazard for Cardiovascular Mortality in Isolated Systolic Hypertension (ISH) in Comparison to Normotension (NT)²⁰⁾
p < 0.00 vs NT.

combined systolic and diastolic hypertension, suggesting that pulse pressure is the best determinant of cardiovascular mortality (Fig. 5).

HEART RATE

As mentioned above, heart rate is automatically available from ABP monitoring and HBP measurements. The prognostic significance of heart rate has recently been confirmed in several large-scale cohort studies. We also examined the prognostic significance of heart rate obtained from HBP monitoring.²¹⁾ Simultaneous measurements of blood pressure and heart rate at home were obtained in 1500 subjects from Ohasama over 40 years of age. Measurements were taken in the morning for 21 days, the relationship between the average of these parameters and the outcome being examined. Relative hazard for cardiovascular mortality increased linearly with increase in heart rate even after adjusting for blood pressure level, suggesting that heart rate is an independent predictor of cardiovascular mortality. It is surprising that heart rate is even better than blood pressure for prediction.

CONCLUSION

If HBP measurements become the gold standard because of their high predictive power and reliability, they could also be used for population screening. The exclusion of false-negative and false-posi-

tive cases by means of HBP measurement could result in highly cost-effectiveness for screening and treatment of hypertension. Further qualitative and quantitative improvements in measuring hypertension are expected to introduce additional information besides blood pressure level obtained by ABP monitoring and HBP measurements.

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