表2　随時血圧・家庭血圧の長所・短所

	長所	短所
随時血圧	・簡便な血圧測定，評価 ・広く認められた基準値の存在	・測定回数少ない ・医療環境における昇圧反応(白衣効果)などのバイアスが存在 ・再現性不良
家庭血圧	・血圧の長期変動性を測定可能 ・白衣効果なし ・再現性最良 ・自己管理により血圧コントロール状況，QOLを改善 ・安静時脈拍測定が可能 ・随時血圧と比べ臓器障害，予後と密接に関連	・患者あるいは一般住民に血圧計を購入させる必要性 ・正しい使用法の教育と較正の必要性 ・まれに家庭血圧に対する忍容性のない対象が存在

て，心血管死亡リスクの予測において家庭血圧が随時血圧に優ることを示した[2]．また，家庭血圧の収縮期血圧が拡張期に比べ高い予後予測能力を有することを明らかにした[3]．さらに，家庭血圧と同時に測定される家庭「心拍数」も，家庭血圧と独立した心血管死亡リスクの予測因子であることが近年明らかになっている．ほか家庭血圧では，血圧日内変動，週間変動，季節変動などの「血圧変動」を観測することができる．大迫研究における検討から，過大な血圧日内変動を持つ群は心血管死亡が高い傾向があることがわかっている．

3. 家庭血圧の基準値とコントロール状況

日本高血圧学会の指針[7]では，大迫研究のデータを主な根拠として，家庭血圧135/80mmHg以上をもって高血圧と診断し，135/85mmHg以上なら確実な高血圧として降圧治療の対象とするとしている(表1，指針8)．

われわれは，一般住民集団を対象とした大迫研究に対応する形で，外来降圧薬治療を受けている本態性高血圧患者における臨床疫学研究としてJ-HOME(Japan Home vs. Office blood pressure Measurement Evaluation)研究を開始した．中間報告の結果[10]では，降圧薬服用中の本態性高血圧患者1,533例のうち63%において，早朝家庭収縮期血圧は135mmHg以上であった．これより，一般的に降圧治療を受けている高血圧患者の少なくとも半数は，各ガイドラインの基準値によれば，家庭血圧コントロールが十分ではないことが推測され，家庭血圧コントロール状況の改善が必要と考えられた．

おわりに

家庭血圧には，随時血圧にないさまざまな利点がある．したがって高血圧診療の強力な手段である．現在，家庭血圧計は年間300万台が販売されているといわれ，一般家庭に広汎に普及している家庭血圧計を用いた家庭血圧測定は，今後の高血圧診療の主役になり得よう．

●文献

1) Imai Y, Satoh H, Nagai K, *et al*：*J Hypertens* 1993；11：1441-1449.
2) Ohkubo T, Imai Y, Tsuji I, *et al*：*J Hypertens* 1998；16：971-975.
3) Hozawa A, Ohkubo T, Nagai K, *et al*：*Arch Intern Med* 2000；160：3301-3306.
4) The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997；157：2413-2446.
5) 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999；17：151-183.
6) 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003；21：1011-1053.
7) 日本高血圧学会：家庭血圧測定条件設定の指針．ライフサイエンス出版，東京，2003.
8) Kikuya M, Chonan K, Imai Y, *et al*：*J Hypertens* 2002；20(4)：629-638.
9) Johnson KA, Partsch DJ, Rippole LL, *et al*：*Arch Intern Med* 1999；159：2689-2693.
10) 大久保孝義，他：*Ther Res* 2003；24：1849-1855.

協賛　日本ベーリンガーインゲルハイム株式会社

— Review —

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]

[a]Department of Clinical Pharmacology and Therapeutics, [b]Department of Planning for Drug Development and Clinical Evaluation, and [c]Department of Environmental Health Sciences, Tohoku University Graduate School of Pharmaceutical Science and Medicine, 1–1 Seiryomachi, Sendai 980–8574, Japan

(Received November 25, 2003)

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. Referece Values of Home BP Value by JNC-VI and 1999 WHO/ISH

	HBP value (Ohasama) (mmHg)	Reference value (mmHg)
Hypertension	≥ 138/≥ 83	≥ 135/≥ 85 (JNC-VI)
Cox model (non-parametric)		
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 study[4] 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 Committee[9] and 1999 World Health Organization/International Society of Hypertension guidelines[10] (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] ≥ 160 mmHg and/or diastolic blood pressure [DBP] ≥ 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 hypertension. 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]

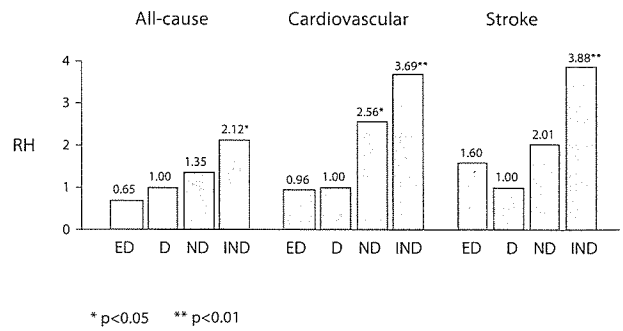

Fig. 1. Circadian Blood Pressure Variation and All Cause Mortality, Cardiovascular Mortality and Stroke Mortality in Ohasama Population[17]

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

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

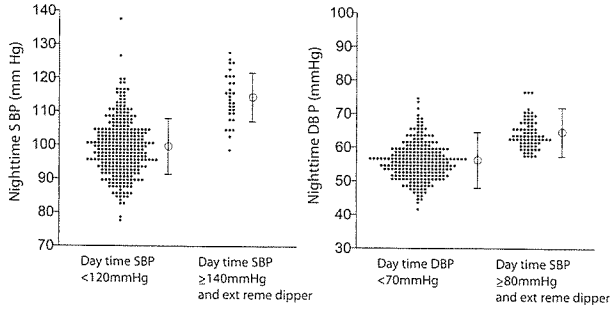

Fig. 2. The Nocturnal Blood Pressure Level in Daytime Normotensive Subjects and in Extreme Dippers with Daytime Hypertension[18]

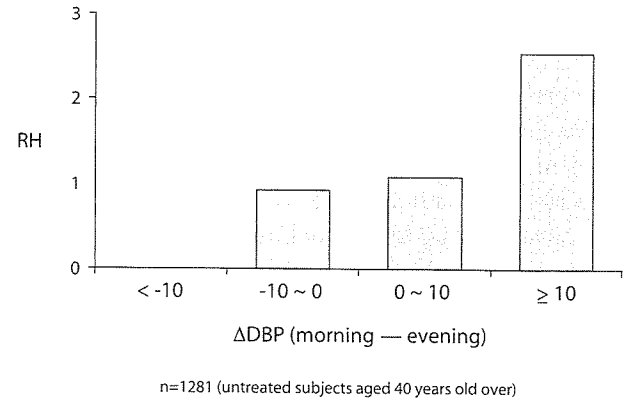

Fig. 3. Relative Hazard (RH) for Cardiovascular Mortality in Relation to Morning High Blood Pressure Determined by the Difference Between Home BP in the Morning and That in the Evening (n = 1281 Untreated Subjects aged 40 years and Above)[19]

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 normotensivie 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 population, 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

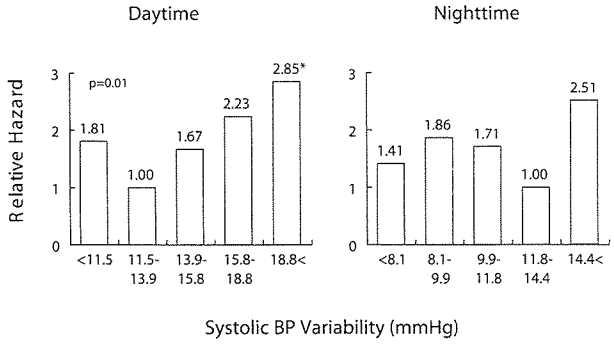

Fig. 4. Relative Hazard for Cardiovascular Mortality in Relation to Blood Pressure Variability Determined by Ambulatory BP Monitoring[19]
$p < 0.05$ *vs* relative hazard 1.

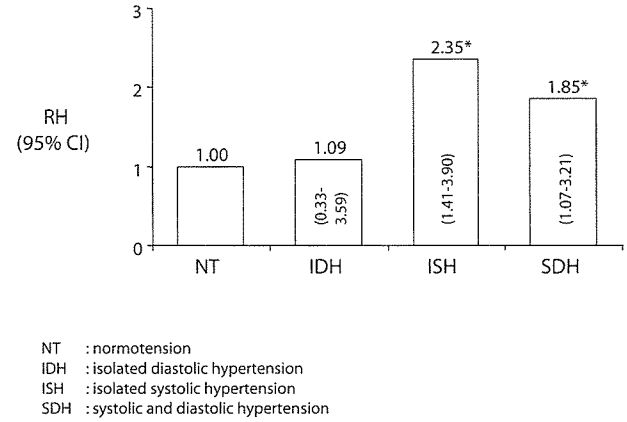

Fig. 5. Relative Hazard for Cardiovascular Mortality in Isolated Systolic Hypertension (ISH) in Comparison to Normotension (NT)[20]
$p < 0.00$ *vs* NT.

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 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.

REFERENCES

1) Thijs, L., Staessen, J. A., Celis, H., de Gaudemaris, R., Imai, Y., Julius, S. and Fagard, R. (1998) Reference values for self-recorded blood pressure A meta-analysis of summary data. *Arch. Intern. Med.*, **158**, 481–488.
2) Imai, Y., Satoh, H., Nagai, K., Sakuma, M., Sakuma, H., Minami, N., Munakata, M., Hashimoto, J., Yamagishi, T., Watanabe, N., Yabe, T., Nishiyama, A., Nakatsuka, H., Koyama, H. and Abe, K. (1993) Characteristics of a community based distribution of home blood pressure in Ohasama, a northern part of Japan. *J. Hypertens.*, **11**, 1441–1449.
3) Mancia, G., Sega, R., Bravi, C., De Vito, G., Valagussa, F., Cesana, G. and Zanchetti, A. (1995) Ambulatory blood pressure normality: results from the PAMELA study. *J. Hypertens.*, **13**, 1377–1390.
4) Staessen, J. A., Bieniaszewski, L., O'Brien, E. T., Imai, Y. and Fagard, R. (1996) An epidemiological approach to ambulatory blood pressure monitoring: the Belgian population study. *Blood Press Monit.*, **1**, 13–26.
5) Imai, Y., Ohkubo, T., Tsuji, I., Nagai, K., Satoh, H., Hisamichi, S. and Abe, K. (1996) Prognostic value of in ambulatory and home blood pressure measurements in comparison to screening blood pressure measurements: A pilot study in Ohasama. *Blood Press Monit.*, **1** (Suppl 2), S51–S58.
6) Imai, Y., Ohkubo, T., Sakuma, M., Tsuji, I., Satoh, H., Nagai, K., Hisamichi, S. and Abe, K. (1996) Predictive power of screening BP, ambulatory BP and BP measured at home for overall cardiovascular mortality: A prospective observation in a cohort of northern Japan, Ohasama. *Blood Press Monit.*, **1**, 251–254.
7) Tsuji, I., Imai, Y., Nagai, K., Ohkubo, T., Watanabe, N., Minami, N., Itoh, O., Bando, T., Sakuma, M., Fukao, A., Satoh, H., Hisamichi, S. and Abe, K. (1997) Proposal of reference values for home blood pressure measurement: Prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am. J. Hypertens.*, **10**, 409–418.
8) Ohkubo, T., Imai, Y., Tsuji, I., Nagai, K., Ito, S., Satoh, H. and Hisamichi, S. (1998) Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion: The Ohasama Study. *Hypertension*, **32**, 255–259.
9) National Institute of Health, National Heart, Lung, and Blood Institute (1997) The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch. Intern. Med.*, **157**, 2413–2446.
10) Guideline Subcommittee: 1999 World Health Organization - International Society of Hypertension (1999) Guidelines for the Management of Hypertension. *J. Hypertens.*, **17**, 151–183.
11) Ohkubo, T., Imai, Y., Tsuji, I., Nagai, K., Watanabe, N., Minami, N., Ito, O., Sakuma, M., Fukao, A., Satoh, H., Hisamichi, S. and Abe, K. (1996) Prognostic significance for mortality among "white coat" and "reversed white coat" hypertension. *Ann Noninvasive Ambulatory Monit.*, **1** (Pt2), 212.
12) Imai, Y., Poncelet, P., DeBuyzere, M., Padfield, P. L. and Van Montfrans, G. A. (2000) Prognostic significance of self-measurements of blood pressure. *Blood Press Monit.*, **5**, 137–143.
13) Kario, K., Matsuo, T., Kobayashi, H., Imiya, M., Matsuo, M., Shimada, K. and Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly patients (1996) Advanced silent cerebrovascular damage in extreme dippers. *Hypertension*, **27**, 130–135.
14) Imai, Y., Nishiyama, A., Ohkubo, T., Tsuji, I., Nagai, K., Kikuchi, N., Satoh, H. and Hisamichi, S. (1997) Factors affecting the nocturnal decrease in blood pressure: a community based study in Ohasama. *J. Hypertens.*, **15**, 827–838.
15) Ohkubo, T., Imai, Y., Tsuji, I., Nagai, K., Watanabe, N., Minami, N., Kato, J., Kikuchi, N., Nishiyama, A., Aihara, A., Sekino, M., Satoh, H. and Hisamichi, S. (1997) Relation between nocturnal decline in blood pressure and mortality: The Ohasama Study. *Am. J. Hypertens.*, **10**, 1201–1207.
16) Nishiyama, A., Imai, Y., Ohkubo, T., Tsuji, I., Nagai, K., Kikuchi, N., Kato, J., Sekino, M., Aihara, A., Kikuya, M., Satoh, H. and Hisamichi, S. (1997) Determinants of circadian blood pressure variation: a community-based study in Ohasama. *Tohoku J. Exp. Med.*, **183**, 1–20.
17) Imai, Ym., Hozawa, A., Ohkubo, T., Tsuji, I., Yamaguchi, J., Matsubara, M., Michimata, M., Hashimoto, J., Fujiwara, T., Nagai, K., Kitaoka, H., Satoh, H. and Hisamichi, S. (2001) Predictive values of automated blood pressure measurement: what can we learn from the Japanese population - the Ohasama Study. *Blood Press Monit.*, **6**, 335–339.
18) Kamoi, K., Kaneko, S., Miyakoshi, M., Nakagawa,

O. and Soda, S. (2002) Usefulness of home blood pressure measurement in the morning in type 2 daibetic patients. *Diabetes Care*, **25**, 2218–2223.
19) Kikuya, M., Hozawa, A., Ohokubo, T., Tsuji, I., Michimata, M., Matsubara, M., Ota, M., Nagai, K., Araki, T., Satoh, H., Ito, S., Hisamichi, S. and Imai, Y. (2000) Prognostic significance of blood pressure and heart rate variabilities. *Hypertension*, **36**, 901–906.
20) Hozawa, A., Ohkubo, T., Nagai, K., Kikuya, M., Matsubara, M., Tsuji, I., Ito, S., Satoh, H., Hisamichi, S. and Imai, Y. (2000) Prognosis of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of blood pressure at home. The Ohasama Study. *Arch. Intern. Med.*, **160**, 3301–3306.
21) Hozawa, A., Ohkubo, T., Nagai, K., Kikuya, M., Kitaoka, H., Matsubara, M., Tsuji, I., Ito, S., Hisamichi, S. and Imai, Y. (2001) Prognostic significance of pulse rate assessed by the device for self-measured blood pressure at home: The Ohasama Study. *Hypertens. Res.*, **24**, A11.

Practical Aspect of Monitoring Hypertension Based on Self-measured Blood Pressure at Home

Yutaka IMAI, Takayoshi OHKUBO*, Masahiro KIKUYA* and Junichiro HASHIMOTO*

Abstract

Devices for home blood pressure (BP) measurement are produced worldwide at a rate of more than 10 million a year and 30 million such devices have already been distributed in Japan. The clinical significance of home BP measurement is obvious; patients can recognize the effects of antihypertensive treatment. Home BP measurements encourage medication compliance, follow-up clinic visits, and active participation in the medical treatment, thus resulting in improved management of hypertension. Home BP measurements more accurately reflect damage to target organs and the prognosis of cardiovascular diseases. The purpose of home BP measurements is to obtain information on the patient's inherent BP pattern using long-term, repetitive measurement under controlled conditions. Since home BP is measured under controlled condition, values are reproducible, and thus, useful in the diagnosis and treatment of hypertension. Blood pressures measured under standardized condition are indispensable when comparing data among individuals, among groups and among institutes. Working Group of Japanese Society of Hypertension (JSH) established JSH Guidelines for Self-Monitoring of Blood Pressure at Home in 2003. Standardization of the measurement procedure may elevate the position of home BP measurements for the purpose of diagnosing and treating hypertension. As a result, home BP measurements may improve the accuracy of screening for hypertension and assessment of BP control during treatment and encourage drug compliance. Home BP measurements, under such controlled conditions, should have a beneficial effect on the economics of diagnosing and treating hypertension.
(Internal Medicine 43: 771–778, 2004)

Key words: blood pressure, home measurements, drug effect, compliance, guidelines

Introduction

Devices for home blood pressure (BP) measurement are produced worldwide at a rate of more than 10 million a year and 30 million such devices have already been distributed in Japan. The clinical significance of home BP measurement is obvious; patients can monitor the effects of antihypertensive treatment and obtain objective information on medication response. Patients can also recognize elevations of BP when they discontinue or fail to take routine doses of medication. The immediate feedback of home BP measurements encourages medication compliance, follow-up clinic visits, and active participation in medical treatment, thus resulting in improved management of hypertension.

Recent guidelines for the treatment of hypertension such as the Sixth and Seventh Reports of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI and 7) (1, 2), the 1999 World Health Organization-International Society of Hypertension (WHO-ISH) Guidelines for the Management of Hypertension (3), the 2003 European Society of Hypertension—European Society of Cardiology (ESH-ESC) Guidelines for the Management of Arterial Hypertension (4), and the Japanese Society of Hypertension (JSH) Guidelines for the Management of Hypertension (5) have all emphasized the importance of home BP measurements in clinical applications of practice, research, and epidemiology. Home BP measurements more accurately and reliably reflect target organ damage and the prognosis of cardiovascular disease. These guidelines include the reference values of hypertension and normotension for home BP measurements. However, none of the guidelines have defined measurement procedure for home BP.

The purpose of home BP measurements is to obtain information on the patient's inherent BP pattern using long-term, repetitive measurement under controlled conditions. Since home BP is measured under controlled conditions, values are

From the Department of Clinical Pharmacology and Therapeutics and *the Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai
Received for publication April 22, 2004; Accepted for publication May 14, 2004
Reprint requests should be addressed to Dr. Yutaka Imai, Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Science and Medicine, Tohoku University Hospital, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574

reproducible, and thus, useful in the diagnosis and treatment of hypertension. Blood pressures measured under standardized conditions are indispensable for comparing data among individuals, among groups and among institutes. However, such standards for the measurement of home BP have not been fully established. The Working Group of JSH established the JSH Guidelines for Self-Monitoring of Blood Pressure at Home in 2003 (6). This review referred to the practice aspect of monitoring hypertension based on self-measured BP at home and also to the JSH Guideline for home BP measurements.

History of Home Blood Pressure Measurements

In 1896, Riva-Rocci developed the indirect arm-cuff method for the measurement of BP (7), and in 1905 Korotkoff introduced the use of auscultation in conjunction with the indirect method (8). Since then, the indirect method for BP measurement has remained essentially unchanged for 100 years. Over the past 100 years, BP has been measured in the clinic or other medically oriented settings and has been called casual-clinic BP (CBP). Since the development of indirect BP measurement, hypertension research and treatment methodologies have substantially advanced. The gold standard of BP measurement for practice and research has been CBP. However, an alternative to the CBP was proposed soon after the introduction of indirect BP measurements. The rationale for BP measurement outside the clinical setting is based on the acknowledged and marked variability of BP. Time-dependent and incidental BP variations are well known phenomenon since the 18th century when Stephen Hale observed such variabilities. Clinically, Bevan et al initially demonstrated marked and time-dependent variability of BP in an unrestricted human male subject using direct, continuous BP monitoring for 24 hours (9). In 1940, Ayman and Goldshine reported the concept of "self-BP measurement" and demonstrated an apparent difference between the CBP and the self-measured BP (10). Initially, self-measurement was done using the auscultation method. In the 1970s, an electric device based on the microphone method was marketed, but not widely distributed because of high price, mechanical difficulties, and the issue of auscultation gap. Explosive distribution of home measurement devices since the 1980s is mediated by the development of devices based on the cuff-oscillometric principle.

The Problems of Home Blood Pressure Measurements

Although the mercury column sphygmomanometer with auscultation is becoming obsolete, we should remember that the gold standard for clinical practice is the Korotkoff sound method using a mercury column sphygmomanometer. The differential properties of the Korotkoff sounds and cuff-oscillation lead to an unavoidable difference in BP values between the two methods. The basic algorithm of cuff-oscillometric principle has been improved by including procedures to correctly approximate the characteristic changes in cuff-oscillation during phase I and phase V Korotkoff sounds. Furthermore, the accuracy of the automatic device is determined by comparison with the auscultation method, and no other standard method is currently available for this purpose. The issue here is the subjectivity and the possible inaccuracy of auscultation when the auscultation method is used as a standard.

Since BP measurements in clinical settings are now primarily obtained by cuff-oscillometric devices, it is inevitable that cuff-oscillometric devices be used in home BP measuring systems. The accumulation of clinical and epidemiological data obtained by authorized cuff-oscillometric devices may finally validate the efficacy of these tools for clinical decision making.

At present, three types of electrical devices for home BP measurements are commercially available: the arm-cuff device, the wrist-cuff device, and the finger-cuff device. Ten million such electrical devices are produced each year in the Far East (including Japan, Korea, Taiwan and China), which represents 85% of the world production (11). Of those, 35% are wrist-cuff devices (11). Previously, finger-cuff devices commanded a considerable portion of the market share due to their convenience and ease-of-use. However, it is now apparent that finger BP is physiologically different from brachial BP, and issues of vasospasm in the winter season as well as hydrostatic difference are inevitable. Therefore, manufacturers have now decreased production of finger-cuff devices and extensively increased production of wrist-cuff devices. In Japan, wrist-cuff devices possess 30% of the market share (12). Wrist-cuff devices are much easier to handle and more portable, but include serious shortcomings. The most important issue is the necessity for correction of the hydrostatic pressure. The reference level for BP measurement is the right atrium. When the measurement site is 10 cm below (above) the right atrium, systolic BP (SBP) and diastolic BP (DBP) are measured 7 mmHg higher (lower) than those at the level of the right atrium. Even after appropriate correction of the hydrostatic pressure, another issue remains concerning the anatomy of the wrist (11). At the wrist, the radial and ulnar arteries are surrounded by the radial bone, the ulnar bone and several long tendons, including the palmaris longus tendon. Therefore, even a sufficient amount of cuff pressure over the arterial area does not necessarily occlude these arteries completely. As a result, wrist-cuff devices sometime provide erroneous readings, especially for SBP (11). Therefore, arm-cuff devices based on the cuff-oscillometric method are recommended for home BP measurement (1–6).

Practical Aspect of Monitoring Hypertension based on Home Blood Pressure Measurements

Home BP measurements and ambulatory BP monitoring are characterized by increased measurement frequency, and

Table 1. Characteristics of Casual, Ambulatory, and Home Blood Pressure Measurements

	Casual BP (office, clinic, screening)	Ambulatory BP	Home BP
Characteristic	including reactive pressor response	measurements under several psychological and physical conditions	measurements under relatively stable condition
Measurement bias	+	−	−~±
Measurement frequency	few	many	many
Estimation of circadian BP variation	impossible	possible	partially possible
Estimation of night-time BP	impossible	possible	possible
Estimation of short-term BP variation	impossible	adequate	inadequate
Estimation of long-term BP variation	inadequate	inadequate	adequate
Reproducibility	poor	poor fair	good
Estimation of drug effect	insufficient due to placebo effect	occasionally insufficient due to regression to the mean	adequate
Estimation of duration of drug action	impossible	possible	adequate
Estimation of drug resistance	inadequate	adequate	adequate
Estimation and diagnosis of white-coat effect (hypertension)	impossible	adequate	adequate
Estimation of paroxysmal hypertension or episodic hypotension	impossible	adequate	occasionally possible

thus, increased information on BP. In addition, these methods provide BP information in relation to time. Such characteristics of home BP measurements provide advantages and superiority when compared to CBP (Table 1).

Home blood pressure measurement and diagnosis of hypertension

References value of home blood pressure

Although home BP measurement devices are distributed widely throughout the world, the practice of monitoring hypertension using these devices has not been established because of the deficiency of reference values for hypertension and normotension using this home equipment. Another issue is that standardization of home BP measurements has not been established.

Since 1986, we have been conducting an epidemiological survey of hypertension using home BP in Ohasama, in the northern part of Japan. Ohasama initially had a population of 9,400, but this has now dropped to 6,800. Over the past 18 years, we have obtained home BP data from 5,000 subjects aged over 7 years, as well as long-term clinical outcomes and information on risk factors and predictors. One of the initial purposes of the study was to define reference values for home BP measurements with respect to prognosis in a long-term prospective study.

Several methods are available for obtaining these reference values. The first involves the distribution criteria, for example mean +SD, mean +2SD or 95th percentile value of the reference population. These values provided us with the distribution of home BP level in the population, but clinical significance of these values is still uncertain.

Another method uses correspondence criteria, which derives home BP levels corresponding to CBP of 140/90 mmHg. However, the relationship between CBP and home BP has not been defined well enough to obtain accurate corresponding values; the correlation coefficient of the relationship between CBP and home BP has been calculated to be approximately 0.5 (13). However, the linear regression analysis deduced that 140/90 mmHg for CBP corresponds to 125/80 mmHg for home BP, suggesting that the normative value of home BP is less than 125/80 mmHg.

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 worldwide. The Ohasama study was initiated 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 10.6 years. Home BP and CBP values were classified equally into quintiles on the basis of BP level. The relationship between BP level and stroke incidence being analyzed by a Cox regression model was adjusted for age, sex, and drug treatment. No specific tendency was observed in CBP. In subjects in the highest quintile of home BP (≧135/85 mmHg), a significant increase in relative hazard was observed, suggesting the higher predictability of home BP when compared with CBP (14) (Fig. 1).

These results obtained from Ohasama studies were cited in the JNC-VI (1) and 1999 WHO-ISH guidelines (3) and were the basis of reference values (Table 2) for home BP measurements given in these guidelines.

Definition of white-coat hypertension and white-coat effect

White-coat hypertension - reproducible hypertension in

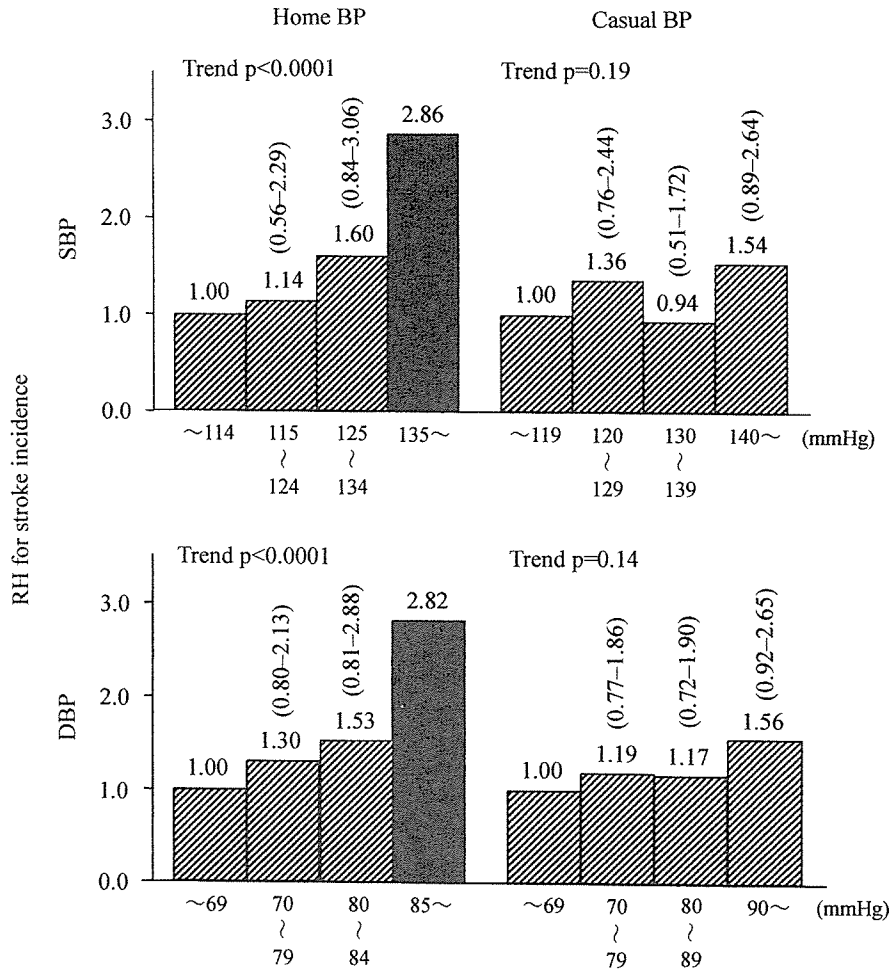

Figure 1. Association between home and casual-screening blood pressure (BP) values and stroke risk. Relative hazards (RH) and 95% confidence intervals (CI) of home and casual-screening systolic BP (SBP) and diastolic BP (DBP) level adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolemia, and diabetes for first symptomatic stroke. The group with the lowest risk was treated as the reference category (RH=1) (14).

Table 2. Reference Values of Home BP Value by JNC VI and WHO/ISH

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

medical settings and normotension in non-medical settings is accurately defined using the normative value of home BP, i.e., CBP equal to or higher than 140/90 mmHg and home BP less than 125/80 mmHg. The Ohasama study examined the prognostic significance of white-coat hypertension (15). According to the Cox regression 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 (hypertension in the non-medical setting and normotension in the medical setting) carried a significantly higher relative hazard for cardiovascular mortality (Fig. 2) (15). However, 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 a 10-year observation period, suggesting that white-coat hypertension is a

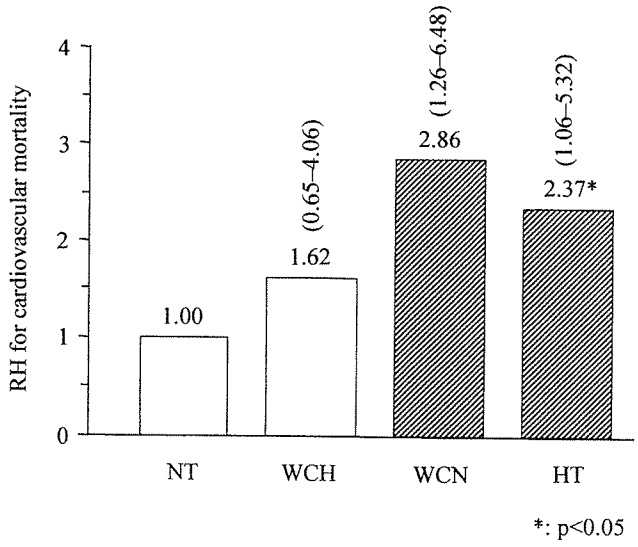

Figure 2. Risk of white-coat hypertension, white-coat normotension and sustained hypertension for cardiovascular mortality. Relative hazard (RH) for cardiovascular mortality and 95% confidential intervals (CI). NT: normotension, WCT: white-coat hypertension, WCN: white-coat normotension (masked hypertension), HT: sustained hypertension. Normotension was treated as the reference category (RH=1) (15).

benign condition during short-term observation periods but it becomes a cardiovascular risk during long-term observation periods.

Definition of the white-coat effect leads to the diagnosis of resistant hypertension or intractable hypertension. For example, in cases of essential hypertension, patients whose CBP was continuously higher than 160/100 mmHg and home BP was higher than 135/90 mmHg were treated with a calcium antagonist. The antihypertensive effect of the drug was never observed in CBP, while the drug sufficiently decreased home BP (Fig. 3). The clinical significance of home BP is apparent from this case; the white-coat effect is resistant to an antihypertensive regimen.

Circadian blood pressure variation and home blood pressure measurements

Recently, circadian BP variation has received attention as a risk factor in cardiovascular diseases. In the Ohasama study, non-dipper and inverted dipper circadian BP variations were apparent cardiovascular risk factors. However, the so-called extreme-dipper circadian BP variation was a benign condition (16). Such BP information was obtained only by ambulatory BP monitoring. Recently, we developed new equipment for self-BP measurements which allows monitoring of BP during sleep (17). Thus, the nocturnal BP level is

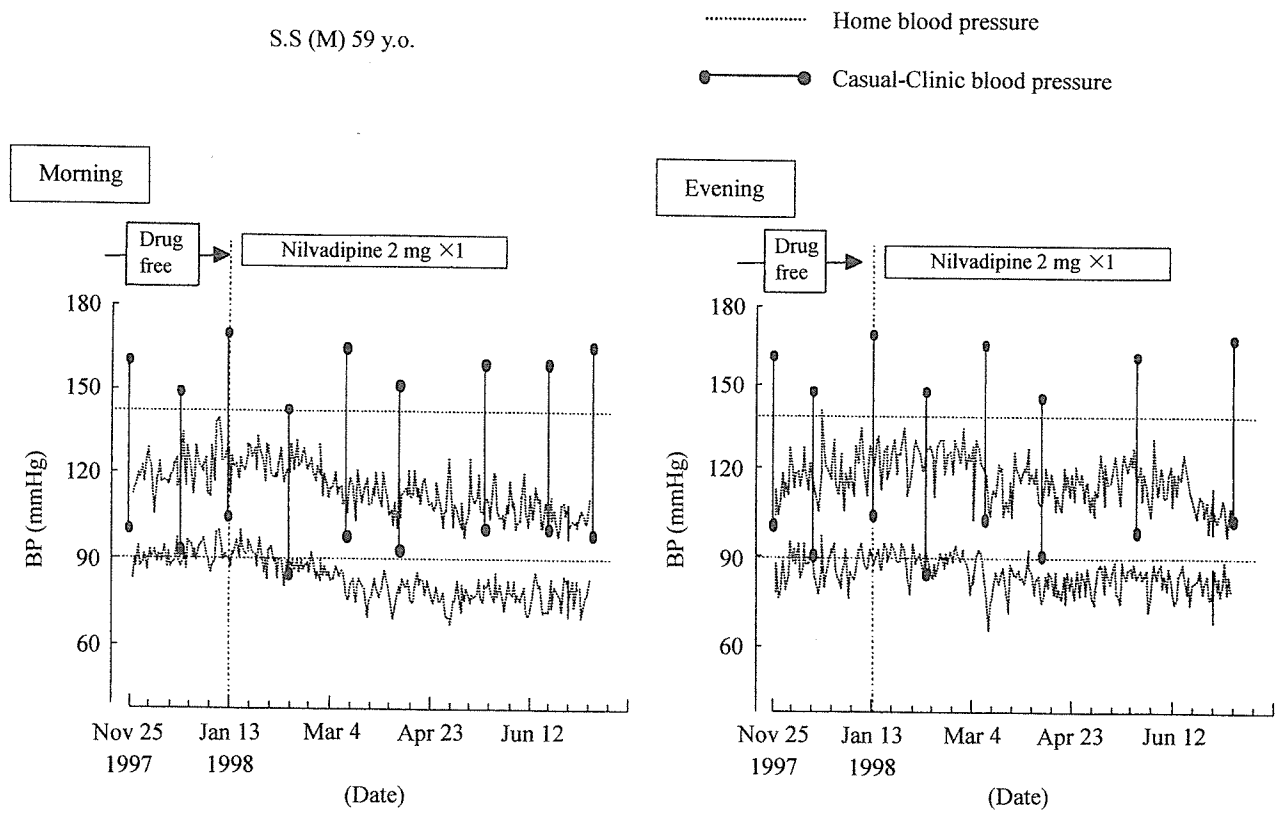

Figure 3. Effects of nilvadipine, a calcium antagonist, on white-coat effect in a hypertensive patient. Nilvadipine did not decrease casual-clinic blood pressure (CBP), but decreased home BP both in the morning and evening. SBP: systolic BP, DBP: diastolic BP, HBP: home BP, HR: heart rate.

now available from home BP measurements. However, the most common routine for home BP measurements is in the morning and in the evening.

Recently, the concept of hypertension in the morning is an issue in the management of hypertension. Morning hypertension is mediated by a morning surge and non-dipper or inverted dipper circadian BP variation. The morning surge of BP represents a mirror image of nocturnal dipping, and thus, is essentially observed in extreme dippers. In the Ohasama study, morning hypertension is primarily mediated by non-dipper or inverted dipper circadian BP variation and only 10% of patients with morning hypertension have an extreme dipper pattern, and thus, a morning surge. Recently, Kamoi et al reported that in normotensive (per CBP) patients with diabetes mellitus only those with high BP in the morning obtained during home BP measurements had severe target organ damage (18). It is well known that patients with diabetic target organ damage usually have non-dipper or inverted dipper circadian BP variation, suggesting that the morning hypertension reported by Kamoi et al reflects the overall BP load throughout 24 hours. Morning hypertension reported by Kamoi et al is also defined as reverse white-coat hypertension or white-coat normotension, which was related to poor prognosis in the Ohasama study (15). This concept was later reported as masked hypertension by Pickering et al (19). We found that masked hypertension is mediated by non-dipper circadian BP variation, inverted dipper circadian BP variation and insufficient duration of action of the antihypertensive medication (20). Home BP measurement is the only a practical method to determine the occurrence of morning hypertension.

Day-by-day variability of blood pressure

Short-term BP variability is a risk factor for cardiovascular diseases (21). Such short-term information is available from ambulatory BP monitoring, while the information on day-by-day variability is obtained only with home BP measurements. The Ohasama study demonstrated that day-by-day variability reflects the risk of cardiovascular diseases. Thus, home BP measurements can now replace ambulatory BP monitoring.

Treatment of hypertension based on home blood pressure measurements

Evaluation of antihypertensive effect

Since home BP is measured under controlled conditions using a standardized method, the reproducibility of home BP is assured and no placebo effect is observed in the measurements (22). Therefore, the accuracy and validity of home BP measurements reflects the physiological response to the clinical pharmacology of antihypertensive drugs; e.g., a decrease in systolic BP by 6 mmHg is determined by 15 subjects when based on the home BP measurements. Home BP measurement improves the quality in clinical pharmacological studies.

Evaluation of duration of action of antihypertensive effect

Home BP measurements can be used to evaluate medication effects and the duration of action. Figure 4 demonstrates that when trichlomethiazide was administered, once in the morning, home BP was decreased when measured before taking the next dose; this suggested that the duration of action for this drug is more than 24 hours. Such characteristics of home BP measurements provide an index of duration of action of drugs, i.e., the morning effect vs. evening effect ratio (M/E ratio), which is comparable to trough/peak (T/P) ratio obtained by ambulatory BP monitoring. The M/E ratio is more reliable than the T/P ratio, since the former is obtained by the average of multiple measurements of the difference between the period before treatment and the treated period.

JSH Guidelines for self-monitoring of blood pressure at home

Home BP measurements are indispensable for the improvement of management of hypertension in medical practice as well as for the recognition of hypertension in the population. Therefore, practice of self-measurement of BP is the first priority and for this purpose it is not necessarily expected that strict measurement conditions will be set. However, the presence of a standard for home BP measurements may be convenient and useful for practitioners as well as for patients. Such standards should be intended to instruct patients and subjects in the general population on how to measure BP at home and may provide a shared basis of information for clinical decision making. The Working Group for Establishment of Guidelines for Measurement Procedure of Self-Monitoring of Blood Pressure at Home of the JSH has established standard for all techniques and procedures of home BP measurements (6).

The recommendations are as follows:

1) For home BP use, arm-cuff devices are recommended. They should be based on the cuff-oscillometric method, validated officially, and confirmed for accuracy in each individual.
2) BP should be measured in the upper arm. Finger-cuff devices and wrist-cuff devices should not be used for home BP measurements.
3) Devices for home BP measurement should be adapted from the American Association Medical Instrumentation (AAMI) standard and the British Hypertension Society (BHS) guidelines. In addition, the difference between the BP measured by the auscultatory method and that measured using the device should be 5 mmHg or less in each individual. Accuracy and function of the home measurement device should be validated before use and at regular intervals.
4) Home BP should be monitored under the following conditions.

   The morning measurements:

   · within 1 hour after waking

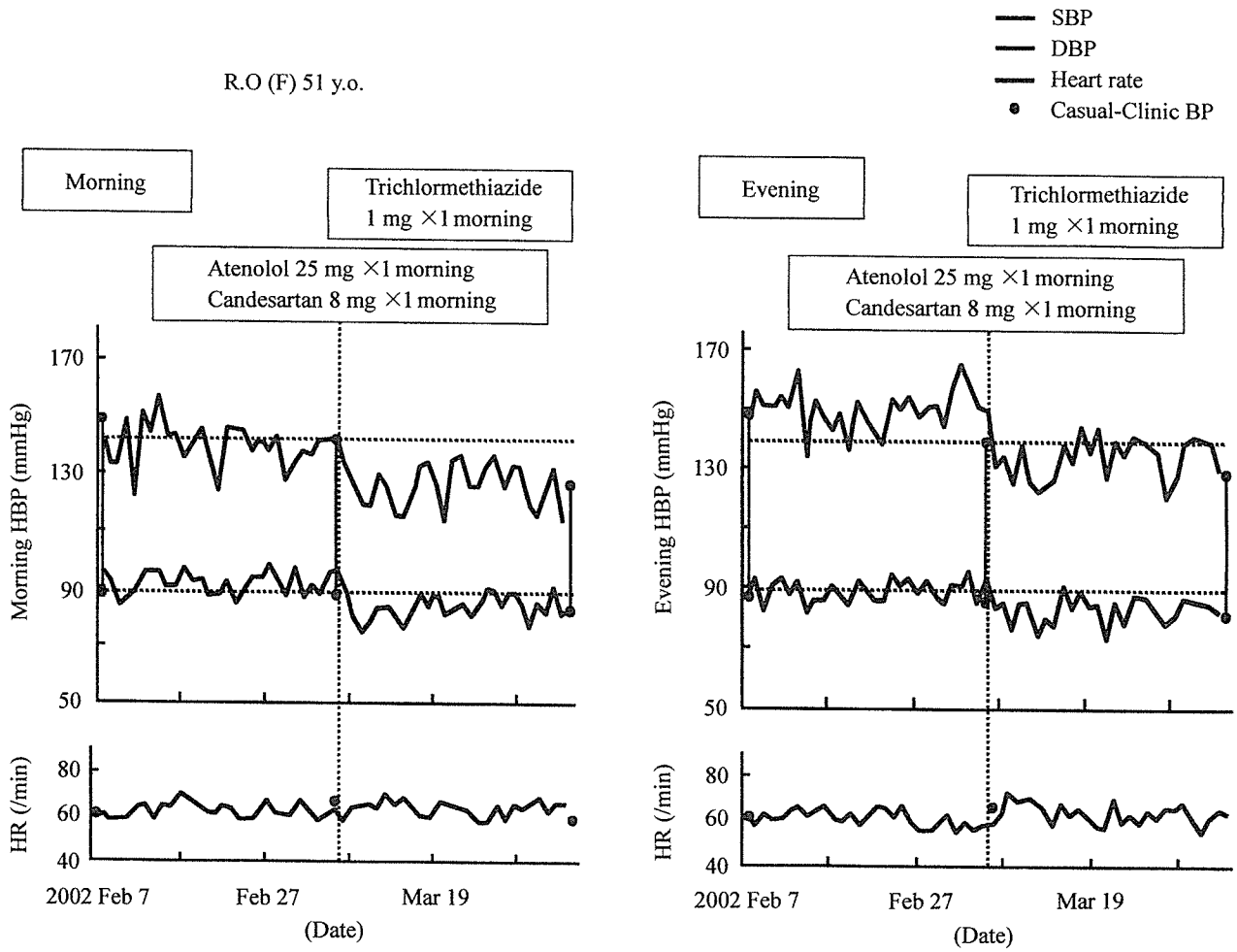

Figure 4. Effect of trichlormethiazide, administered once in the morning, on home blood pressure (HBP) in the morning and evening in a patient with essential hypertension. The HBP in the morning was measured before morning dose, thus, reflecting that the duration of action of thiazide is over 24 hours.

- after micturition
- after 1 to 2 minutes of sitting at rest
- before drug ingestion
- before breakfast

The evening measurements:

- just before going to bed
- after 1 to 2 minutes of sitting at rest

5) Home BP should be measured at least once in the morning and once in the evening.
6) All home BP measurements should be documented without selection or omission and include the date, time, and pulse rate. Use of a device with a printer or an integrated circuit memory is useful to avoid selection bias.
7) The home BP in the morning and that in the evening should be averaged separately for a certain period. The first measurement on each occasion should be used for totaling.
8) Home BP values that average 135/80 mmHg and over, for a certain period, indicate hypertension. Average values of 135/85 mmHg and over indicate definite hypertension. Normotension is defined as less than 125/80 mmHg and definite normotension as less than 125/75 mmHg.

The guidelines aimed to establish practical advice which would not restrict casual daily life of the subjects. For example, one to two minutes of rest before measurements would be acceptable by the majority of people who measure BP at home every day. In the guidelines, prohibition of smoking and taking coffee before measurement was not addressed. Since BP values obtained after smoking and taking coffee would reflect daily behavior and lifestyle, regulation may actually interfere with the validity of the BP readings. Room temperature was also not addressed by the guidelines, since casual temperature *per se* is an important factor for daily BP level. In the present guidelines, it has been emphasized that home BP should be routinely measured at least once per occasion. "At least once" means that more than one measure-

ment during that occasion is also permissible. Actually subjects measure their BP repeatedly, until a reasonable value is obtained when their home BP is high. We must evaluate all values recorded. However, to compare data among individuals, groups and institutes a standardized measurement is necessary. The first measurement would be considered a common denominator in all cases. Therefore, the average of the first measurement for a certain period is an important commonality for clinical decision making.

Conclusion

At present, international reference values have been established. However, the treatment goal for home BP level has not yet been established. The normotensive value of home BP is set at the level of 125/80 mmHg. This value is approximately equivalent to a CBP level of 140/90 mmHg. Therefore, it seems that a value of less than 125/80 mmHg would be the goal for home BP. However, setting the goal for home BP must be based on the results of large-scale intervention studies. Among such studies the Hypertension Objective Treatment on Measurements by Electrical Device of BP (HOMED-BP) study is ongoing in Japan (23)

Standardization of the measurement procedure may elevate the position of home BP measurements in the practice of diagnosing and treating hypertension, and as a result, home BP measurements may bring greater accuracy in the screening for hypertension and assessment of BP control during treatment and improved drug compliance. Home BP measurements under such controlled conditions are expected to have a beneficial effect on the economics of the diagnosis and treatment of hypertension.

References

1) National High Blood Pressure Education Program. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med **157**: 2413–2446, 1997.
2) Chobanian AV, Bakris GL, Black HR, et al. The National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA **289**: 2560–2572, 2003.
3) Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens **17**: 151–183, 1999.
4) Guideline Committee. 2003 European Society of Hypertension—European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens **21**: 1011–1053, 2003.
5) Guidelines Subcommittee for the Japanese Society of Hypertension. Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2000). Japanese Society of Hypertension 2000.
6) Imai Y, Otsuka K, Kawano Y, et al. Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home. Hypertens Res **26**: 771–782, 2003.
7) Riva-Rocci S. Un nuovo sfigmomanometro. Gazz Med Torino **47**: 981–1001, 1896.
8) Korotkoff N. To the question of methods of determining the blood pressure. Rep Imp Mil Acad **11**: 365–367, 1905.
9) Bevan AT, Honour AJ, Stott FH. Direct arterial pressure recording in unrestricted man. Clin Sci **36**: 329–344, 1969.
10) Ayman D, Goldshine A. Blood pressure determinations by patients with essential hypertension. Am J Med Sci **200**: 465–474, 1940.
11) Kikuya M, Chonan K, Imai Y, et al. Accuracy and reliability of wrist-cuff devices for self measurement of blood pressure. J Hypertens **20**: 629–638, 2002.
12) Shirasaki O, Terada H, Niwano K, et al. The Japan Home-Health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. Blood Press Monit **6**: 303–307, 2001.
13) Imai Y, Satoh H, Nagai K, et al. Characteristics of community based distribution of home blood pressure in Ohasama, in northern Japan. J Hypertens **11**: 1441–1449, 1993.
14) Ohkubo T, Asayama K, Kikuya M, et al. How many times should blood pressure be measured at home for better prediction of stroke risk? 10-year follow-up results from the Ohasama study. J Hypertens **22**: 1099–1104, 2004.
15) Ohkubo T, Imai Y, Tsuji I, et al. Prognostic significance for mortality among "white coat" and "reversed white coat" hypertension. Ann Noninvasive Ambulatory Monit **1** (pt2): 212, 1996.
16) Ohkubo T, Imai Y, Tsuji I, et al. Relation between nocturnal decline in blood pressure and mortality: The Ohasama Study. Am J Hypertens **10**: 1201–1207, 1997.
17) Chonan K, Kikuya M, Araki T, et al. Device for the self-measurement of blood pressure that can monitor blood pressure during sleep. Blood Press Monit **6**: 203–205, 2001.
18) Kamoi K, Miyakoshi M, Soda S, et al. Usefulness of home blood pressure measurements in the morning in type 2 diabetic patients. Diabetes Care **25**: 2218–2223, 2003.
19) Pickering TG, Davidson K, Gerin W, Shwartz JE. Masked hypertension. Hypertension **40**: 795–796, 2002.
20) Chonan K, Hashimoto J, Ohkubo T, et al. Insufficient duration of action of antihypertensive drugs mediates high blood pressure in the morning in hypertensive population: The Ohasama Study. Clin Exp Hypertens **24**: 261–275, 2002.
21) Kikuya M, Hozawa A, Ohokubo T, et al. Prognostic significance of blood pressure and heart rate variabilities. Hypertension **36**: 901–906, 2000.
22) Imai Y, Ohkubo T, Hozawa A, et al. Usefulness of home blood pressure measurements in assessing the effect of treatment in a single-blind placebo-controlled open trial. J Hypertens **19**: 179–785, 2001.
23) Fujiwara T, Nishimura T, Ohkuko T, et al. Rationale and design of HOMED-BP Study: hypertension objective treatment based on measurement by electrical devices of blood pressure study. Blood Press Monit **7**: 77–82, 2002.

Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 43, No. 7, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.10.049

Adiponectin I164T Mutation Is Associated With the Metabolic Syndrome and Coronary Artery Disease

Koji Ohashi, MD,* Noriyuki Ouchi, MD, PHD,* Shinji Kihara, MD, PHD,* Tohru Funahashi, MD, PHD,* Tadashi Nakamura, MD, PHD,* Satoru Sumitsuji, MD,‡ Toshiharu Kawamoto, MD, PHD,§ Satoru Matsumoto, MD,‖ Hiroyuki Nagaretani, MD,* Masahiro Kumada, MD,* Yoshihisa Okamoto, MD,* Hitoshi Nishizawa, MD, PHD,* Ken Kishida, MD, PHD,* Norikazu Maeda, MD,* Hisatoyo Hiraoka, MD, PHD,* Yoshio Iwashima, MD,† Kazuhiko Ishikawa, MD, PHD,† Mitsuru Ohishi, MD, PHD,† Tomohiro Katsuya, MD, PHD,† Hiromi Rakugi, MD, PHD,† Toshio Ogihara, MD, PHD,† Yuji Matsuzawa, MD, PHD*

Suita, Izumisano, Kure, and Toyonaka, Japan

OBJECTIVES This study examined the association of mutations in adiponectin gene with the prevalence of coronary artery disease (CAD).

BACKGROUND Coronary artery disease is a major cause of mortality in the industrial countries. Adiponectin gene locus, chromosome 3q27, is the candidate site for CAD. We have reported that adiponectin has antiatherogenic and antidiabetic properties, and that the plasma levels negatively correlated with body mass index (BMI) are significantly low in patients with CAD or type 2 diabetes.

METHODS The study subjects were 383 consecutive patients with angiographically confirmed CAD and 368 non-CAD subjects adjusted for age and BMI in the Japanese population. Single nucleotide polymorphisms (SNPs) in the adiponectin gene were determined by Taqman polymerase chain reaction (PCR) method or a PCR-based assay for the analysis of restriction fragment length polymorphism. The plasma adiponectin concentration was measured by enzyme-linked immunosorbent assay.

RESULTS Among SNPs, the frequency of I164T mutation was significantly higher in CAD subjects (2.9%) than in the control (0.8%, $p < 0.05$). The plasma adiponectin levels in subjects carrying the I164T mutation were significantly lower than in those without the mutation, and were independent of BMI. In contrast, SNP94 and SNP276, which are reported to be associated with an increased risk of type 2 diabetes, were associated neither with CAD prevalence nor with plasma adiponectin level. Subjects with I164T mutation exhibited a clinical phenotype of the metabolic syndrome.

CONCLUSIONS The I164T mutation in the adiponectin gene was a common genetic background associated with the metabolic syndrome and CAD in the Japanese population. (J Am Coll Cardiol 2004;43:1195–200) © 2004 by the American College of Cardiology Foundation

Cardiovascular disease is a major cause of morbidity and mortality in industrial countries. Both environmental and genetic factors contribute to the development of cardiovascular disease (1). Among various adipocyte-derived bioactive substances, adipocytokines, dysregulated production of leptin, tumor necrosis factor (TNF)-α, and plasminogen activator inhibitor type 1 is closely associated with increased cardiovascular mortality and morbidity (2–6). Adiponectin is an adipocyte-specific adipocytokine, which we identified in the human adipose tissue complementary DNA library (7). The mouse homologue of adiponectin was identified as ACRP30 and AdipoQ (8,9). Hypoadiponectinemia (low plasma adiponectin level) has been identified in patients with coronary artery disease (CAD) (10) and type 2 diabetes, and is a predictor of cardiovascular outcome in patients with end-stage renal failure (11). Plasma adiponectin rapidly accumulates in the subendothelial space of an injured human artery (12). We have reported that human recombinant adiponectin suppresses endothelial adhesion molecule expression, vascular smooth muscle cell proliferation, and macrophage-to-foam cell transformation as well as TNF-α production by macrophages in vitro (13,14). Recently, we reported that the adiponectin-knockout mice exhibited enhanced neointimal thickening after vascular injury (15). In addition, we and others demonstrated that adiponectin treatment improved insulin resistance and glucose metabolism in diabetic mice model (16–18). These findings suggest that adiponectin has both antiatherogenic and antidiabetic properties and acts as an endogenous mediator of vascular and metabolic diseases.

We have previously identified several mutations of the adiponectin gene, including missense mutations (R112C, I164T, R221S, and H241P) in the globular domain and the G/T single nucleotide polymorphism at nucleotide 94

From the *Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Suita, Japan; †Department of Geriatric Medicine, Graduate School of Medicine, Osaka University, Izumisano, Japan; ‡Department of Cardiology, Rinku General Medical Center, Rinku, Japan; §Department of Cardiology, National Hospital Kure Medical Center, Kure, Japan; and ‖Department of Cardiology, Toyonaka Municipal Hospital, Toyonaka, Japan. Supported by grants from the Japanese Ministry of Education, the Japan Society for Promotion of Science-Research for the Future Program, the Takeda Medical Research Foundation, and the Fuji Foundation for Protein Research. Drs. Ohashi and Ouchi contributed equally to this work.

Manuscript received April 21, 2003; revised manuscript received September 12, 2003, accepted October 20, 2003.

JACC Vol. 43, No. 7, 2004
April 7, 2004:1195–200

Abbreviations and Acronyms

BMI	= body mass index
CAD	= coronary artery disease
HbA1C	= hemoglobin A1C
HDL-chol	= high-density lipoprotein cholesterol
HOMA	= homeostasis model assessment
PCR	= polymerase chain reaction
SNP	= single nucleotide polymorphism
T-chol	= total cholesterol
TG	= triglyceride
TNF	= tumor necrosis factor

(SNP94) in the Japanese population (19,20). Among these mutations, the I164T mutation correlated with type 2 diabetes (19); SNP94 was reported to be associated with type 2 diabetes and obesity (21,22). A weak association was observed between SNP94 and plasma adiponectin levels in French Caucasians, although no significant association was found in the Japanese population (23). Recently, SNP at position 276 (SNP276) was reported to be associated with type 2 diabetes (21); SNP276 was associated with plasma adiponectin levels in French Caucasians and only in obese Japanese subjects (21,23). In addition, the haplotype identified by SNP94 and SNP276 was related with obesity and other features of the insulin resistance syndrome in Caucasians (24). A susceptibility locus for type 2 diabetes was mapped on chromosome 3q27, which harbors the adiponectin gene (25). A genome-wide scan for CAD replicated linkage with the metabolic syndrome on the region 3q27, suggesting that adiponectin might be one of the candidate genes susceptible for the metabolic syndrome-linked CAD (26). Although the metabolic syndrome includes insulin resistance, it is very important to elucidate the genetic contribution of adiponectin in the development of CAD.

In the present study, we investigated the frequency and the clinical significance of I164T, SNP94, and SNP276 of adiponectin gene in consecutive CAD patients and age- and body mass index (BMI)-matched non-CAD subjects.

METHODS

Study subjects. Consecutive 383 CAD patients were recruited from the inpatients who were admitted to Osaka University Hospital. The criteria for CAD were a 75% ≤ organic stenosis of at least one segment of a major coronary artery confirmed by coronary angiogram. The control subjects were selected from people who received medical check in Osaka University Hospital or our affiliated hospitals. In these latter subjects, it was unethical to perform coronary angiography to rule out the presence of asymptomatic CAD. Therefore, the following inclusion criteria were used: no history of angina or other atherosclerotic vascular diseases, and normal exercise electrocardiogram stress testing. They were matched with CAD patients for age and BMI. All patients and subjects enrolled in this study were Japanese and gave written informed consent. This study was approved by the Ethics Committee of Osaka University.

Laboratory methods. Venous blood was drawn from all patients and control subjects after an overnight fast. Plasma samples were kept at −80° centigrade for subsequent assay. Plasma concentration of adiponectin was evaluated by a sandwich ELISA system (Adiponectin ELISA Kit, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan) as previously reported (27). Serum total cholesterol (T-chol) and triglyceride (TG) concentrations were determined by an enzymatic method. High-density lipoprotein cholesterol (HDL-chol) was also measured by an enzymatic method after heparin and calcium precipitation. Plasma glucose was measured by a glucose oxidase method. The value of hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography. Insulin resistance was assessed by homeostasis model assessment (HOMA) (insulin resistance index = [fasting glucose (mmol/l) × fasting insulin (U/ml)]/22.5 (28). Body mass index was calculated as weight/height^2.

Definitions of risk factors. Diabetes mellitus was defined according to World Health Organization criteria, and/or having received treatment for diabetes mellitus (29). Dyslipidemia was defined as a T-chol concentration >5.69 mmol/l, a TG concentration >1.69 mmol/l, an HDL-chol concentration <1.03 mmol/l, and/or having received treatment for dyslipidemia. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or having received treatment for hypertension. We did not exclude the subjects under medical treatment for diabetes mellitus, dyslipidemia, and hypertension.

DNA extraction and genotyping. Genomic DNA was prepared from frozen whole blood with the use of a QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, California). We determined the missense mutation I164T and the SNP276 of adiponectin gene by the TaqMan (Roche Molecular Systems Inc., Pleasanton, California) polymerase chain reaction (PCR) chemistry method as previously described (30). The TaqMan probe is a fluorogenic probe that consists of an oligonucleotide labeled with both a fluorescent reporter dye and a quenched dye. The fluorescent reporter dye, such as VIC and FAM (Applied Biosystems Inc., Foster City, California), is covalently linked to the 5′ end of the nucleotide. Each of the reporters is quenched by minor groove binder, typically located at the 3′ end. The following primers were used for the missense mutation I164T: a forward primer, 5′-AACATTCCTGGGCTGTACTACTTTG-3′; a reverse primer, 5′- GGCTGACCTTCACATCCTTCATA-3′; a T-allele-specific probe, 5′-VIC-ACCACATCA-CAGTCTA-MGB-3′; a C-allele-specific probe, 5′-FAM-CCACACCACAGTCT-MGB-3′. The following primers were used for the G/T SNP at position 276: a forward primer, 5′-AGAATGTTTCTGGCCTCTTTCATC-3′; a reverse primer, 5′- TTCTCCCTGTGTCTAGGCCTTAGT-3′; a G-allele-specific probe, 5′-FAM-CTATATGAAGGCAT-TCATTA-MGB-3′; T-allele-specific probe, 5′-VIC-

Table 1. Clinical Characteristics of Control Subjects and CAD Patients

	Control Subjects (n = 368)	CAD Patients (n = 383)	p Value
Age, yrs	62.3 ± 0.6	63.0 ± 0.4	NS
Gender, M/F	240/128	270/113	NS
Adiponectin, μg/ml	7.7 ± 0.2	6.1 ± 0.2	< 0.001
BMI, kg/m^2	23.8 ± 0.2	24.1 ± 0.2	NS
Family history of diabetes mellitus, n (%)	(15.8)	(18.5)	NS
Diabetes mellitus, n (%)	58 (10.3)	71 (48.0)	< 0.001
FPG, mmol/l	38 ± 0.04	184 ± 0.14	< 0.001
	5.40	6.67	
HbA1c, %	5.11 ± 0.04	6.09 ± 0.08	< 0.001
Dyslipidemia, n (%)	179 (48.6)	259 (67.6)	< 0.001
T-chol, mmol/l	5.23 ± 0.05	5.29 ± 0.05	NS
TG, mmol/l	1.57 ± 0.05	1.77 ± 0.06	<0.05
HDL-chol, mmol/l	1.52 ± 0.03	1.19 ± 0.02	< 0.001
Hypertension, n (%)	272 (73.9)	264 (68.9)	NS
SBP, mm Hg	134.6 ± 1.0	132.9 ± 0.9	NS
DBP, mm Hg	80.1 ± 0.7	75.4 ± 0.8	< 0.001

Data represent means ± SE.
BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HbA1c = hemoglobin A1C; HDL-chol = high-density lipoprotein cholesterol; SBP = systolic blood pressure; T-chol = total cholesterol.

AAACTATATGAAGTCATTCATTA-MGB-3′. The fluorescence level of PCR products was measured with the ABI PRISM 7200 Sequence Detector (Applied Biosystems, Inc.). We determined the SNP94 in exon 2 of adiponectin gene by a PCR-based assay for the analysis of restriction fragment length polymorphism as previously described (20).

Statistical methods. For continuous variables, results are presented as mean ± SE. Differences in continuous parameter, such as BMI, between two groups were calculated by the Student *t* test, and differences in continuous parameter, such as plasma adiponectin level, among more than three groups were evaluated by analysis of variance. Because plasma adiponectin level, HOMA, and TG were skewed, these three parameters were log-transformed before analysis, and the parameters presented were back-transformed. Categorical variables were presented using frequency counts, and intergroup comparisons were analyzed by chi-square test. A level of $p < 0.05$ was accepted as statistically significant. All calculations were performed using a standard statistical package (JMP for Macintosh, version 4.0, SAS Institute Inc., Cary, North Carolina).

RESULTS

The clinical characteristics of CAD patients and non-CAD control subjects are shown in Table 1. The mean plasma adiponectin level in CAD patients was significantly lower than the control ($p < 0.001$), as we described previously (10). Patients with CAD had significantly higher levels of fasting plasma glucose, HbA1c, TG, numbers of diabetes mellitus, dyslipidemia, and lower levels of HDL-chol and diastolic blood pressure than the control group. There were no significant differences in age, gender, BMI, number of family history for diabetes, T-chol, systolic blood pressure, and number of hypertension between the two groups.

The frequency of I164T mutation in CAD patients (11 [2.9%] of 383) was significantly higher than that in non-CAD subjects (3 [0.8%] of 368, $p < 0.05$) (Table 2). All subjects with the mutation were heterozygotes. In contrast to this mutation, no significant differences in the distribution of SNP94 and SNP276 genotypes were observed between the two groups. The plasma adiponectin levels in subjects carrying the I164T mutation (3.2 ± 0.5 μg/ml) were significantly lower than in subjects without the mutation (6.9 ± 0.2 μg/ml, $p < 0.0001$) (Fig. 1A), although no

Table 2. Frequency of Mutation and Polymorphism in Adiponectin Gene

		Control Subjects	CAD Patients	
n		368	383	p Value
I164T, n (%)		3 (0.8)	11 (2.9)	<0.05
	G/G	29 (7.9)	33 (8.6)	
SNP94, n (%)	G/T	148 (40.2)	140 (36.6)	NS
	T/T	191 (51.9)	210 (54.8)	
	G/G	190 (51.6)	185 (48.3)	
SNP276, n (%)	G/T	149 (40.5)	164 (42.8)	NS
	T/T	29 (7.9)	34 (8.9)	

CAD = coronary artery disease; SNP = single nucleotide polymorphism.

JACC Vol. 43, No. 7, 2004
April 7, 2004:1195–200

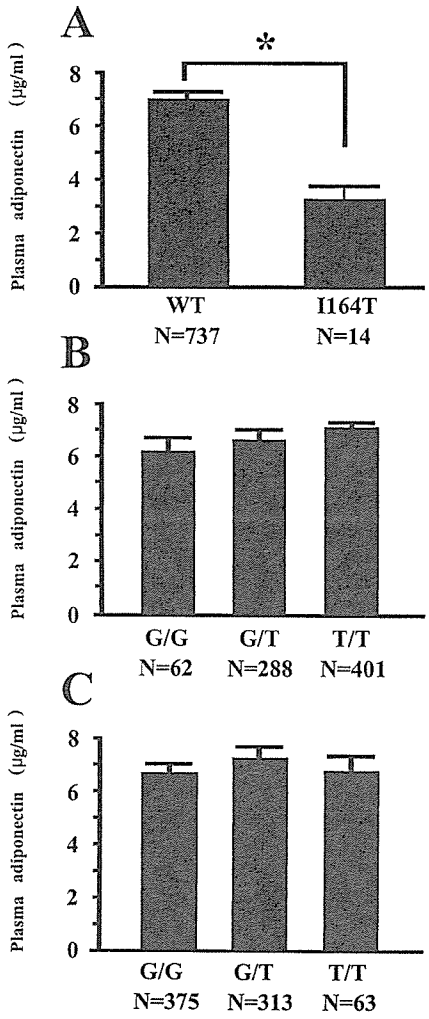

Figure 1. Association of I164T mutation, SNP94, and SNP276 with plasma adiponectin concentrations. **(A)** Plasma adiponectin levels in the subjects with wild type (WT) or I164T mutation in adiponectin gene. **(B)** Relationship between SNP94 genotypes and plasma adiponectin levels. **(C)** Relationship between SNP276 genotypes and plasma adiponectin levels. Columns and vertical bars denote mean and SE of the indicated sample numbers. *$p < 0.05$ vs. WT.

significant difference was observed in BMI between the subjects with and without I164T mutation (24.4 ± 1.2 vs. 24.0 ± 0.1 kg/m^2). The plasma adiponectin levels in subjects with the mutation were markedly low in both CAD and control groups (2.9 ± 0.6 vs. 4.3 ± 1.2 μg/ml, respectively), and did not correlate with BMI. The negative correlation between plasma adiponectin levels and BMI was observed in subjects without the mutation (data not shown). These data indicated that hypoadiponectinemia in subjects with the mutation was independent of BMI. The plasma adiponectin levels of the subjects with G/G, G/T, and T/T allele at SNP94 were 6.2 ± 0.6, 6.6 ± 0.2, and 7.1 ± 0.2 μg/ml, respectively (Fig. 1B). The plasma adiponectin level in the subjects having G allele at SNP94 tended to be lower, but it was not statistically significant. On the other hand, no differences were observed in plasma adiponectin levels of the subjects with G/G, G/T, and T/T allele at SNP276 (6.6 ± 0.2, 7.2 ± 0.2, and 6.7 ± 0.5 μg/ml, respectively) (Fig. 1C).

As shown in Table 3, all subjects carrying I164T had at least one risk factor including diabetes mellitus, hypertension, and dyslipidemia. Six (case 4 to 8, and 11) of the 11 CAD patients with the I164T mutation and 75 of 372 wild type CAD patients had all three metabolic abnormalities, which is a key feature of the metabolic syndrome. The percentage of the subjects with all three metabolic abnormalities was significantly higher in I164T mutation (54.5%) than that in wild type (20.2%) ($p < 0.01$). Nine (case 4 to 8 and 11 to 14) of 14 subjects with I164T mutation had diabetes mellitus, and cases 13 and 14 had received insulin treatment. However, except three cases (3, 4, and 8), six diabetic I164T patients had no apparent insulin resistance assessed by HOMA-insulin resistance (IR) compared with CAD patients (n = 383, HOMA-IR; 2.4 ± 0.2). In addition, there were no differences in HOMA-IR levels between nondiabetic I164T subjects (case 1 to 3, 9, and 10) and control subjects (n = 368, HOMA-IR; 1.8 ± 0.1).

DISCUSSION

In the present study, we found that the I164T mutation of adiponectin gene was associated with CAD prevalence and hypoadiponectinemia in the Japanese population. In contrast, the genotypes of SNP94 and SNP276, which were reported to be present in type 2 diabetes, influenced neither the prevalence of CAD nor the plasma adiponectin level.

Table 3. Clinical Profile of the Subjects With I164T Mutation

Case Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age, yrs	53	65	78	52	59	59	61	69	71	72	65	67	70	73
Gender	M	M	F	M	M	M	M	M	M	M	F	F	F	F
Plasma adiponectin, μg/ml	2.7	6.7	3.7	0.4	2.7	2.8	2.6	3.7	3.5	0.9	4.4	2.0	1.6	7.2
BMI, kg/m^2	23.6	ND	24.0	27.0	25.4	29.2	25.6	21.7	19.2	23.8	34.1	25.0	19.0	19.2
FPG, mmol/l	3.5	4.7	5.3	7.6	16.6	5.8	8.2	8.6	5.2	5.4	6.3	6.1	4.8	7.5
FIRI, μU/ml	8.0	4.0	5.0	13.0	5.7	6.0	3.0	10.9	6.2	4.8	6.4	10.2	3.5	2.3
HOMA-IR	1.8	0.8	1.2	3.3	4.2	1.5	2.3	4.2	1.4	1.2	1.4	2.8	0.7	0.8
Number of risk factors*	1	2	2	3	3	3	3	3	1	1	3	2	2	2
Coronary artery disease	-	-	-	AP	AP	AP	AP	MI	AP	MI	AP	AP	AP	AP

*Risk factors: diabetes mellitus, hypertension, and dyslipidemia.
AP = angina pectoris; BMI = body mass index; FIRI = fasting immunoreactive insulin; FPG = fasting plasma glucose; HOMA-IR = homeostatis model assessment of insulin resistance; MI = myocardial infarction.