Journal of Atherosclerosis and Thrombosis Vol. 12, No. 4

Original Article

Isolated Home Hypertension in the Morning is Associated with Target Organ Damage in Patients with Type 2 Diabetes

Kazuhiko Sakaguchi, Takahiro Horimatsu, Minoru Kishi, Akihiko Takeda, Yutaka Ohnishi, Takashi Koike, Takashi Fujisawa, and Mitsuo Maeda

Division of Internal Medicine, the Harima Hospital of the Ishikawajima Harima Heavy Industries Health Insurance Society, Hyogo, Japan.

To investigate the relationship between the blood pressure control level and cardiovascular risk in type 2 diabetic patients, we evaluated home blood pressure, office blood pressure, biochemical data, and carotid echographic and echocardiographic findings in 148 patients with type 2 diabetes. According to the criteria for hypertension in the guidelines of the Japanese Society of Hypertension, we classified patients into a normotensive group with home systolic blood pressure in the morning (morning HSBP) < 135 mmHg and office systolic blood pressure (OSBP) < 140 mmHg, an office hypertension group with a morning HSBP < 135 mmHg and OSBP ≥ 140 mmHg, an isolated home hypertension in the morning group with morning HSBP ≥ 135 mmHg and OSBP < 140 mmHg, and a sustained hypertension group with morning HSBP ≥ 135 mmHg and OSBP ≥ 140 mmHg. In the isolated home hypertension in the morning group, the fasting insulin level, urinary albumin excretion, maximum carotid artery intima-media complex thickness, and left ventricular posterior wall thickness were significantly higher and the coefficient of variation for RR intervals was significantly lower than in the normotensive group. These results suggest that isolated home hypertension in the morning is a risk factor for target organ damage in type 2 diabetic patients. ***J Atheroscler Thromb, 2005; 12: 225–231.***

Key words: Isolated home hypertension, Type 2 diabetes, Home blood pressure, Office blood pressure

Introduction

A Japanese survey of diabetes in 2002 found that 7.4 million people were strongly suspected of having diabetes and that the total number of people with diabetes was as high as 16.2 million. The prevention of target organ damage in patients with diabetes is one of the most serious health concerns in Japan.

The United Kingdom Prospective Diabetes Study (UKPDS) involving patients with type 2 diabetes and hypertension has shown that both blood glucose control and strict blood pressure control decrease the incidence of cardiovascular disease and cerebrovascular disease (1, 2). Recently, Kamoi et al. have reported high incidences of nephropathy, retinopathy, coronary disease, and stroke in patients with type 2 diabetes who have home blood pressure (HBP) in the morning (morning HBP) ≥ 130/85 mmHg (3). Therefore, adequate blood pressure control is a crucial issue in the care of patients with type 2 diabetes.

In addition, recent studies of hypertension indicate that morning hypertension is a strong predictor of death, the incidence of cardiovascular or cerebrovascular disease, and target organ damage (4–6). The Self measurement of blood pressure at Home in the Elderly: Assessment and Follow-up (SHEAF) study showed that the incidence of cardiovascular disease was increased in those with

Address for correspondence: Kazuhiko Sakaguchi, Division of Internal Medicine, the Harima Hospital of the Ishikawajima Harima Heavy Industries Health Insurance Society, Asahi 3–5–15, Aioi, Hyogo 678–0031, Japan
E-mail: kzhkskgc@apple.kci.ne.jp
Received October 18, 2004
Accepted for publication June 2, 2005

"masked hypertension" having normal office blood pressure (OBP) and high HBP (7).

In this study, we attempted to clarify the relation between HBP and target organ damage in patients with type 2 diabetes by comparing the characteristics of groups classified by blood pressure.

Methods

Subjects and study design

This study involved 148 patients (66 men and 82 women; mean age, 69.8 years) with type 2 diabetes diagnosed according to the criteria of the Japanese Society of Diabetes (fasting plasma glucose levels ≥ 126 mg/dl, 2 hours after glucose load ≥ 200 mg/dl) (8). Of the 148 patients, 108 were taking one or more antihypertensive medications. The patients were treated at the outpatient clinic of the Harima Hospital of the Ishikawajima Harima Heavy Industries Health Insurance Society and had had no marked changes in medication during the past year. Subjects with renal failure (serum creatinine ≥ 1.5 mg/dl) or severe liver dysfunction (aspartate aminotransferase or alanine aminotransferase ≥ 50 IU/l) were excluded. Clinical information about the subjects, including the duration of diabetes and smoking habits, was obtained with a questionnaire. Subjects included in the study had HBP measurements taken by themselves or their family. The details of the study had been explained to all subjects previously, and informed consent was obtained.

According to the criteria for hypertension in the guidelines of the Japanese Society of Hypertension (JSH2000) (9), the patients were classified into four groups on the basis of their systolic HBP (HSBP) and systolic OBP (OSBP): 1) a normotensive group with morning HSBP < 135 mmHg and OSBP < 140 mmHg, 2) an office hypertension group with morning HSBP < 135 mmHg and OSBP ≥ 140 mmHg, 3) an isolated home hypertension in the morning group with morning HSBP ≥ 135 mmHg and OSBP < 140 mmHg, and 4) a sustained hypertension group with morning HSBP ≥ 135 mmHg and OSBP ≥ 140 mmHg (Fig. 1). Because the number of patients in the office hypertension group (*n* = 10, 6.7%) was too small for statistical analysis, the comparison of laboratory data was performed with just three groups.

Measurement of morning HBP

In accordance with "The Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home" (10), the subjects were requested to measure their blood pressure at home with the cuff-oscillometric method, using an upper-arm cuff blood pressure meter. Blood pressure wasmeasured in the sitting position after 1 or 2 minutes of rest, in the morning within 1 hour after waking up, after urination, and before eating breakfast or taking drugs. The frequency of measurements was not designated, however, all results were recorded for 2 to 3 weeks, and the mean of all records was used for analysis.

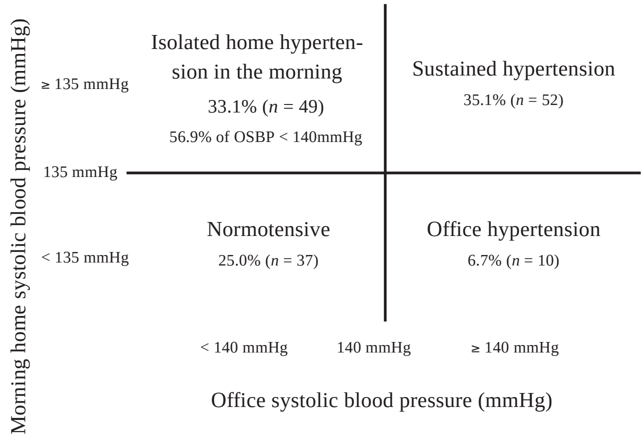

Fig. 1. Blood pressure control in 148 patients with type 2 diabetes
In 148 patients with type 2 diabetes, OSBP and morning HSBP were measured and used to classify the patients into four groups.
Normotensive group: OSBP < 140 mmHg and morning HSBP < 135 mmHg
Isolated home hypertension in the morning group: OSBP < 140 mmHg and morning HSBP ≥ 135 mmHg
Sustained hypertension group: OSBP ≥ 140 mmHg and morning HSBP ≥ 135 mmHg
Office hypertension group: OSBP ≥ 140 mmHg and morning HSBP<135 mmHg

Measurement of OBP

The OBP was measured by attending physicians using a mercury sphygmomanometer with the patient in the sitting position after 5 minutes of rest between 9 AM and 12:30 PM. The OBP was measured once a month, and the mean of 6 months of measurements was used for analysis.

Electrocardiogram

Twelve-lead electrocardiography with the patient at rest was performed by trained medical staff using an FCP5000 (Fukuda Denshi Inc., Tokyo, Japan). The QTc was measured, and the Sokolow-Lyon voltage ($SV_1 + SV_5$) and the coefficient of variation for RR intervals (CV_{R-R}) were calculated.

Carotid echography and echocardiography

Carotid echographic and echocardiographic examinations were performed with a LOGIQ 7(GE Yokokawa Medical System Inc, Tokyo, Japan) by a cardiologist and two trained sonographers blinded to the patient's clinical data.

The carotid artery was evaluated with 10 MHz linear probes at two points, the common carotid artery and the area between the carotid bulb and the internal carotid artery, according to the examination/measurement methods described by the Society for the Study of Early Arteriosclerosis (11), and the maximum carotid artery intima-media complex thickness (IMT_{max}) was calculated.

M-mode, B-mode, and pulsed Doppler echocardiography were performed with 3 MHz probes, and the left ventricular end-diastolic dimension, end-systolic dimension, interventricular septal thickness, and left ventricular posterior wall thickness (LVPWth) were measured according to the recommendations of the American Society of Echocardiography (12). The left ventricular mass index was calculated for each patient by dividing the left ventricular mass by body surface area. The ratio between the peak velocities of the early diastolic filling wave and the atrial filling wave (E/A) and the E-wave deceleration time (DT) were obtained from pulse-wave Dopper recordings as an index of the diastolic function of the left ventricle.

Table 1.

	All (n=148)
Men (%)	44.6
Age (years)	69.8 ± 8.9
Body Mass Index (kg/m^2)	24.2 ± 3.9
Office systolic blood pressure (mmHg)	140.6 ± 13.9
Office diastolic blood pressure (mmHg)	77.2 ± 7.5
Morning home systolic blood pressure (mmHg)	143.1 ± 18.2
Morning home diastolic blood pressure (mmHg)	79.7 ± 11.1
Duration of diabetes (year)	14.4 ± 12.5
History of smoking *n* (%)	15 (10.1%)
Number of cigarettes × years	171.0 ± 414.9
Number of the patients taking one or more antihypertensive drugs	109

Biochemical examination

Blood samples for biochemical measurements were obtained at the clinic after the patient had fasted for 9 hours. Levels of fasting plasma glucose (glucose oxidase method), fasting insulin (enzyme immunoassay method), uric acid (uricase/peroxidase method), total cholesterol (cholesterol/peroxidase method), triglycerides (glycerol kinase/glycerol-3-phosphate oxidase method), low-density lipoprotein cholesterol (enzymatic method), and high-density lipoprotein cholesterol (enzymatic method) were measured with the automatic analyzer JCA-Bio Majesty 8 (JEOL Ltd., Tokyo, Japan). Levels of glycosylated hemoglobin (HbA_{1c}) were measured with high-performance liquid chromatography. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated with the formula [glucose (mg/dl) × insulin (μU/ml)/405] and used as an index of insulin resistance. Uric albumin was measured with the immunonephelometric method using first morning urine samples.

Statistical analysis

The Stat View 5.0J software program (HULINKS Inc., Tokyo, Japan) was used for statistical analysis. Data are expressed as the mean ± SD. Between-group comparisons were performed using Student's *t*-test or the Mann-Whitney U test. A p value of less than 0.05 was considered to indicate statistical significance.

Results

The status of blood pressure control

The characteristics of all subjects are shown in Table 1. The mean OSBP and diastolic OBP (ODBP) were 140.6 ± 13.9 mmHg and 77.2 ± 7.5 mmHg, respectively. The OSBP was less than 140 mmHg, which is the OSBP criterion for hypertension in JSH2000, in 58.1% of patients. On the other hand, the morning HSBP was greater than 135 mmHg, which is the HSBP criterion for hypertension in JSH2000, in 68.2% of patients. The percentage of patients with uncontrolled hypertension was greater on the basis of morning HSBP than on the basis of OSBP. Of the patients with OSBP < 140 mmHg (33.1% of the patients overall), 56.9% had morning HSBP ≥ 135 mmHg (Fig. 1).

Characteristics of patients according to blood pressure control level

Characteristics of the patients in the three groups with different blood pressure levels are shown in Table 2. There were no significant differences in the male-to-female ratio, age, duration of diabetes, or history of smoking among the groups. However, the body mass index (BMI) was significantly higher in the sustained hypertension group than in the normotensive group.

Parameters of metabolic disturbance and target organ damage

Results of biochemical examination, electrocardiography, carotid echography, and echocardiography in the three groups with different blood pressure levels are shown in Table 3. In the isolated home hypertension in the morning group and the sustained hypertension group, urinary albumin excretion, a predictor of nephropathy and cardiovascular events, was significantly higher (Fig. 2-a) and the CV_{R-R}, an index of neuropathy, was significantly lower than in the normotensive group (Fig. 2-b). The

Table 2.

	Normotensive group ($n = 37$)	Isolated home hypertension in the morning group ($n = 49$)	Sustained hypertension group ($n = 52$)
Men (%)	51.8	44.8	44.8
Age (years)	69.1 ± 9.7	69.9 ± 8.2	69.0 ± 8.3
Body Mass Index (kg/m^2)	23.0 ± 3.6	23.2 ± 2.7	25.3 ± 4.1*
Office systolic blood pressure (mmHg)	128.7 ± 8.0	133.6 ± 4.2*	153.1 ± 11.7*†
Office diastolic blood pressure (mmHg)	74.7 ± 7.3	76.2 ± 8.0	79.3 ± 9.0
Morning home systolic blood pressure (mmHg)	122.5 ± 9.6	150.3 ± 12.6*	155.6 ± 14.2*
Morning home diastolic blood pressure (mmHg)	74.2 ± 8.6	80.7 ± 11.4*	83.7 ± 12.2*
Duration of diabetes (year)	15.1 ± 18.3	14.9 ± 8.90	14.2 ± 11.8
History of smoking *n* (%)	4 (10.8%)	6 (12.2%)	4 (7.6%)
number of cigarettes × years	323.3 ± 583	179.4 ± 423.0	166 ± 393.9
Number of the patients taking one or more antihypertensive drugs *n* (%)	14 (37.8%)	37 (75.5%)**	51 (98.1%)**
Number of the patients taking ACE-I *n* (%)	1 (2.7%)	9 (18.4%)**	16 (30.8%)**
Number of the patients taking ARB *n* (%)	1 (2.7%)	15 (30.6%)**	23 (44.2%)**

*: $p < 0.05$ vs Normotensive group
**: $p < 0.05$ vs Normotensive group (χ^2 test, Fisher's direct method)
†: $p < 0.05$ vs Isolated home hypertension in the morning group

Table 3.

	Normotensive group ($n = 37$)	Isolated home hypertension in the morning group ($n = 49$)	Sustained hypertension group ($n = 52$)
Metabolic parameters			
Fasting plasma glucose (mg/dl)	131.8 ± 20.0	130.6 ± 27.0	130.0 ± 24.0
Fasting Insulin (μU/ml)	6.42 ± 4.79	9.39 ± 7.00*	9.90 ± 6.48*
HbA_{1c} (%)	6.33 ± 0.95	6.12 ± 0.75	6.33 ± 0.82
HOMA-IR	2.24 ± 1.37	2.77 ± 2.25	3.09 ± 2.24
Total cholesterol (mg/dl)	199.4 ± 33.2	189.3 ± 27.5	196.3 ± 27.4
LDL cholesterol (mg/dl)	125.2 ± 27.0	111.0 ± 24.7	119.2 ± 26.3
Triglycerides (mg/dl)	126.3 ± 52.6	118.7 ± 51.5	129.0 ± 58.5
HDL cholesterol (mg/dl)	55.5 ± 11.0	58.0 ± 14.6	53.2 ± 12.7
Uric acid (mg/dl)	5.20 ± 1.61	5.70 ± 1.25	5.16 ± 1.47
Urine albumin/Creatinine (mg/g•Cr)	20.0 ± 23.2	114.7 ± 20.3*	182.1 ± 32.3*
Electrocardiogram			
QTc	0.408 ± 0.064	0.405 ± 0.003	0.380 ± 0.051
$SV_1 + SV_5$ (mm)	24.4 ± 9.1	26.3 ± 7.5	23.9 ± 5.9
CV_{RR}	3.92 ± 1.34	2.88 ± 1.61*	2.95 ± 1.30*
Carotid echography			
Caroid IMTmax (mm)	1.37 ± 0.46	1.89 ± 0.89*	1.60 ± 0.54
Caroid IMTmean (mm)	0.87 ± 0.18	0.94 ± 0.24	0.90 ± 0.15
Echocardiography			
Left ventricular end-diastolic dimension (mm)	43.5 ± 3.9	43.4 ± 5.2	44.2 ± 6.8
Left ventricular end-systolic dimension (mm)	26.8 ± 3.7	27.3 ± 4.6	26.6 ± 5.9
Interventricular septal thickness (mm)	8.1 ± 2.1	10.8 ± 2.8	10.9 ± 1.8
Left ventricular posterior wall thickness (mm)	9.0 ± 2.1	10.9 ± 1.4*	10.6 ± 1.8
Left ventricular mass index (g/m)	123.0 ± 42.1	145.7 ± 62.4	135.8 ± 74.0
E/A	0.955 ± 0.516	0.688 ± 0.147	0.738 ± 0.051
DT (msec)	314 ± 80.6	248 ± 68.3	190.5 ± 70.4

*: $p < 0.05$ vs Normotensive group

IMT_{max}, an index of great-vessel complications, was significantly greater in the isolated home hypertension in the morning group than in the normotensive group (Fig. 2-c). The LVPWth, an index of cardiac hypertrophy, was also significantly greater in the isolated home hypertension in the morning group than in the normotensive group (Fig. 2-d).

Discussion

HBP and OBP

The OSBP of 41.9% of patients and the morning HSBP of 68.2% of patients exceeded the criteria for hypertension in the JSH2000 guidelines. We evaluated the blood pressure level with the hypertension criteria because the JSH2000 guidelines don't show the goals of treatment for HBP in patients with diabetes. However, because the World Health Organization/International Society of Hypertension (WHO/ISH) guidelines in 1999 indicated that an OBP of 140/90 mmHg applied to an HBP of 125/80 mmHg (13), the status of blood pressure control would be worse than the above percentages if we evaluated with the treatment goals of OBP (less than 130/85 mmHg) and applicable HBP. Therefore, the status of blood pressure control in this study was not sufficient, and more aggressive antihypertensive treatment should be performed to prevent the development of cardiovascular disease, cerebrovascular disease, and target organ damage.

Blood pressure and target organ damage

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to reduce urinary albumin excretion (14, 15) and left ventricular hypertrophy (16, 17). Although ACE inhibitors and ARBs were used more in the isolated home hypertension in the morning group and the sustained hypertension group than in the normotensive group in this study (Table 2), urinary albumin excretion was significantly greater in the isolated home hypertension in the morning group and the sustained hypertension group and LVPWth was significantly higher in the isolated home hypertension in the morning group than in the normotensive group. These findings suggest that the protective effects upon target organs by ACE inhibitors and ARBs would be weaker if sufficient blood pressure control is not achieved.

The CV_{R-R}, an index of neuropathy, was significantly lower in the isolated home hypertension in the morning group and the sustained hypertension group than in the normotensive group. The reduction of CV_{R-R} indicates dysfunction of the parasympathetic nervous system and relative activation of the sympathetic nervous system (18). Because hypertension, especially hypertension in the morning, is closely related to activation of the sympathetic nervous system, this result may indicate that the sympathetic nervous system is activated in patients with low CV_{R-R} and causes hypertension.

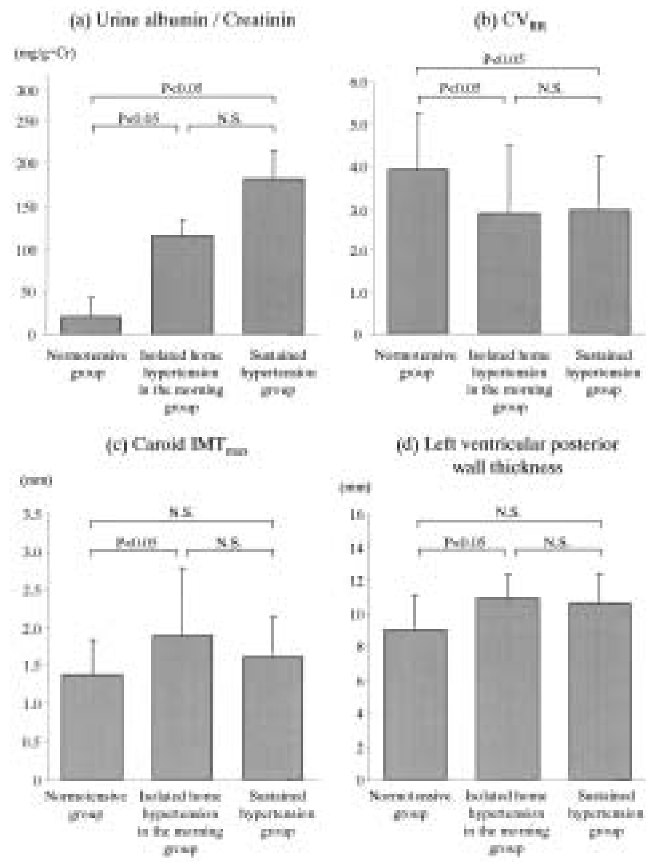

Fig. 2. Comparison of an index of organ damage with respect to blood pressure control
(a) Urinary albumin excretion, (b) CV_{R-R}, (c) IMT_{max},
(d) LVPWth
Means ± S.D

An important finding of this study was that thickening of the carotid artery, to approximately 1.9 mm, was observed in the isolated home hypertension in the morning group. The IMT_{max} of healthy persons is less than 1.1 mm, even in the elderly (11), and the incidences of myocardial infarction and stroke increase with the IMT_{max} (19). Yamasaki *et al.* have reported that predictors of increasing carotid IMT in Japanese patients with type 2 diabetes were a baseline IMT and average HbA_{1c} level (20). Mannami *et al.* have reported that IMT increases in the presence of hypertension or hyperlipidemia (21). In this study, the IMT was greatest in the isolated home hypertension in the morning group.

Chao-Yu Miao *et al.* reported that early wall thickness in the thoracic aorta and left ventricular hypertrophy were observed in chronic sinoaortic denervated rats, which had a significant increase in blood pressure variability but no change in the mean of blood pressure over a 24 hour period (22, 23). Eto *et al.* suggested that increased blood pressure variability impaired endotherial function of the aorta by inhibiting NO production in experiments using chronic sinoaortic denervated rats (24). Thus, our finding indicates that blood pressure variability, especialy in the morning, is related to increased carotid IMT.

Handa et al. have reported that the incidence of ischemic cerebrovascular damage is high in patients with carotid lesions (25). In the present study, the number of patients reporting a history of cerebrovascular damage was higher in the isolated home hypertension in the morning group (18.4%) and in the sustained hypertension group (18.9%) than in the normotensive group (5.4%) (data not shown). Kario *et al.* have reported that a morning rise in blood pressure increases the incidence of asymptomatic cerebral infarction (5). Therefore, our finding that IMT was greater in patients with isolated home hypertension in the morning may indicate the progression of such arterioscrelotic damage in the brain, suggesting an increased risk for cerebrovascular events.

Antihypertensive drugs and home blood pressure in the morning

In this study, morning HSBP exceeded the hypertension criteria for HSBP in the JSH2000 (135 mmHg) in 68.2% of patients and in 56.9% of patients with an OSBP less than 140 mmHg (33.1% of all patients). The SHEAF study suggested that self-measured HBP is a stronger predictor of cardiovascular morbidity and mortality than is OBP (7). With respect to blood pressure control in patients with diabetes, treatment should aggressively target both OBP and HBP. To treat hypertension in the morning, antihypertensive agents with effects sufficient to persist until administration the next morning must be selected. In addition, agents specifically effective in the morning should also be administered. Enhancement of sympathetic activity, especially that of α receptors, is closely involved with morning increases in blood pressure (26, 27), and administration of doxazosin, an α_1-blocker, before retiring is useful for preventing these increases (28). Specific treatment for morning hypertension with these agents should be aggressively performed in the future.

Conclusion

Patients with type 2 diabetes and isolated home hypertension in the morning who have morning HSBP ≥ 135 mmHg, despite an OSBP less than 140 mmHg, have organ damage equal to that in patients with poor blood pressure control. Morning HSBP must be checked in the treatment of hypertension so that the risk of organ damage is not increased.

References

(1) UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet, 352: 837–853, 1998

(2) UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macro-vascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ, 317: 703–713, 1998

(3) Kamoi K, Miyakoshi M, Soda S, Kaneko S, and Nakagawa O: Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. Diabetes Care, 25: 2218–2223, 2002

(4) Imai Y, Ohkubo T, Tsuji I, Nagai K, Satoh H, Hisamichi S, and Abe K: Prognostic value of ambulatory and home blood pressure measurements in comparison to screening blood pressure measurements: a pilot study in Ohasama. Blood Pressure Monitoring, 1: S51–S58, 1996

(5) Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, and Shimada K: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. Circulation, 107: 1401–1406, 2003

(6) Tsunoda S, Kawano Y, Horio T, Okuda N, and Takishita S: Relationship between home blood pressure and longitudinal changes in target organ damage in treated hypertensive patients. Hypertens Res, 25: 167–173, 2002

(7) Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, and Mallion JM: Cardiovascular prognosis of “Masked Hypertension” detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA, 291: 1342–1349, 2004

(8) Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K, Sasaki A, Seino Y, Ito C, Shima K, Nonaka K, and Kadowaki T: The Committee of Japan Diabetes Society for the Diagnostic Criteria of Diabetes Mellitus: Report of the committee of Japan diabetes society on the classification and diagnostic criteria of diabetes mellitus. J Japan Diab Soc, 42: 385–404, 1999

(9) Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the management of hypertension for general practitioners. Hypertens Res, 24: 613–634, 2001

(10) Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K; Japanese Society of Hypertension: Japanese Society of

Hypertension (JSH) guidelines for self-monitoring of blood pressure at home. Hypertens Res, 26: 771–782, 2003
(11) Kosugi K and Yamasaki Y: Evaluation of cerebrovascular risk by carotid echography. Practice, 20: 660–664, 2003
(12) Sahn DJ, DeMaria A, Kisslo J, and Weyman A: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation, 58: 1072–1083, 1978
(13) Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens, 17: 151–183, 1999
(14) Lewis EJ, Hunsicker LG, Bain RP, and Rohde RD: For the Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med, 329: 1456–1462, 1993
(15) Lacourciere Y, Belanger A, Godin C, Halle JP, Ross S, Wright N, and Marion J: Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. Kidney Int, 58: 762–769, 2000
(16) Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, and Anderson RJ: Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. Circulation, 95: 2007–2014, 1997
(17) Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Dahlof B; Losartan Intervention for Endpoint reduction in hypertension Study Investigations: Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study. Circulation, 108: 684–690, 2003
(18) Komori K: Heart rate variability as an autonomic function test, 1. Assessment of autonomic function by the time domein analysis of HRV. Brain Science and Mental Disorders, 7: 231–237, 1996
(19) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, and Wolfson SK Jr: For the Cardiovascular Health Study Collaborative Research Group: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med, 340: 14–22, 1999
(20) Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, and Hori M: Carotid intima-media thickness in japanese type 2 diabetic subjects. Diabetes Care, 23: 1310–1315, 2000
(21) Mannami T, Baba S, and Ogata J: Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: The Suita Study. Arch Intern Med, 160: 2297–2303, 2000
(22) Miao CY, Tao X, Gong K, Zhang SH, Chu ZX, and Su DF: Arterial Remodeling in Chronic Sinoaortic-Denervated Rats. J Cardiovasc Pharmacol, 37: 6–15, 2001
(23) Chao-Yu Miao and Ding-Feng Su: The importance of blood pressure variability in rat aortic and left ventricular hypertrophy produced by sinoaortic denervation. J Hypertens, 20: 1865–1872, 2002
(24) Eto M, Toba K, Akishita M, Kozaki K, Watanabe T, Kim S, Hashimoto M, Sudoh N, Yoshizumi M, and Ouchi Y: Reduced Endothelial Vasomotor Function and Enhanced Neointimal Formation after Vascular Injury in a Rat Model of Blood Pressure Lability. Hypertens Res, 26: 991–998, 2003
(25) Handa N, Matsumoto M, Maeda H, Hougaku H, and Kamada T: Ischemic stroke events and carotid atherosclerosis: Results of the Osaka Follow-up Study for Ultrasonographic Assessment of Carotid Atherosclerosis(the OSACA study). Stroke, 26: 1781–1786, 1995
(26) Panza JA, Epstein SE, and Quyyumi AA: Circadian variation in vascular tone and its relation to α-sympathetic vasoconstrictor activity. N Engl J Med, 325: 986–990, 1991
(27) Muller JE, Tofler GH, Stone PH: Circadian variation and triggers of onset of acute cardiovascular disease. Circulation, 79: 733–741, 1989
(28) Kario K, Pickering TG, Hoshide S, Eguchi K, Ishikawa J, Morinari M, Hoshide Y, and Shimada K: Morning blood pressure surge and hypertensive cerebrovascular disease: Role of the alpha adrenergic sympathetic nervous system. AJH, 17: 668–675, 2004