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Hypertension Research (2010) 33, 1192–1198

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ORIGINAL ARTICLE

Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study

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Masked hypertension (MHT) is considered to be associated with organ damage, whereas the association of white-coat hypertension (WCHT) with organ damage remains controversial. Using home blood pressure measurements, we have previously reported that MHT is associated with a risk of chronic kidney disease (CKD) compared with sustained normal blood pressure (SNBP), although WCHT was not significantly related to CKD in a general Japanese population. The objective of this study was to examine CKD risk associated with WCHT and MHT as determined by ambulatory blood pressure (ABP) monitoring. Among 1023 residents in the general Japanese population of Ohasama, ABP and casual blood pressure (CBP) levels were recorded and blood and urine samples were collected. CKD was defined as a positive proteinuria and/or estimated glomerular filtration rate $<60\,ml\,min^{-1}$ per $1.73\,m^2$. Participants were categorized into four groups using daytime ABP of 140/85 mm Hg and CBP of 140/90 mm Hg as cutoff points: SNBP, 60.0%; WCHT, 15.4%; MHT, 15.0%; and sustained hypertension (SHT), 9.6%. Odds ratios (ORs) for prevalence of CKD were calculated using a multiple logistic regression model. Compared with SNBP, risk of CKD was significantly higher in SHT (OR, 2.81; 95% confidence interval (CI), 1.66–4.75; P=0.0001), MHT (OR, 2.29; 95% CI, 1.45–3.63; P=0.0004) and WCHT (OR, 1.67; 95% CI, 1.03–2.71; P=0.0368). CKD was significantly associated with MHT and WCHT on the basis of ABP monitoring compared with SNBP in the general Japanese population.
Hypertension Research (2010) **33**, 1192–1198; doi:10.1038/hr.2010.139; published online 12 August 2010

Keywords: ambulatory blood pressure; chronic kidney disease; masked hypertension; white-coat hypertension

INTRODUCTION

Ambulatory blood pressure (ABP) has recently been the focus of large amounts of research, and the utility and usefulness of this technique have been recognized and established in the diagnosis and management of hypertension.[1–3] ABP is also considered as a useful tool for detecting overall blood pressure (BP) load, nighttime BP level and circadian and short-term variations in BP. These parameters contribute to the diagnosis and treatment of hypertension.[4–6] The measurement of ABP has enabled us to identify a subgroup of individuals with white-coat hypertension (WCHT), showing persistent hypertensive casual BP (CBP) but normal ABP, and a subgroup of individuals with masked hypertension (MHT), showing normal CBP but hypertensive ABP. MHT is reported to be associated strongly with high risk of morbidity and mortality from cardiovascular disease (CVD).[7] Conversely, controversy remains about whether WCHT is a benign condition[8] or linked to an increased risk of target-organ damage and CVD.[9,10]

Chronic kidney disease (CKD) is now considered as a major public health issue. The prevalence of end-stage renal disease is increasing in Japan, and is currently more than 2000 per million population. In 2007, the number of patients with end-stage renal disease on chronic hemodialysis exceeded 275 119.[11] Moreover, a recent study showed that CKD, defined as an estimated glomerular filtration rate (eGFR) of $<60\,ml\,min^{-1}$ per $1.73\,m^2$, has been increasing in Japan. Prevalence of stage 3–5 CKD was estimated as 19.1 million among the general Japanese adult population of 103.2 million.[12] On the other hand,

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Received 8 December 2009; revised 3 June 2010; accepted 20 June 2010; published online 12 August 2010

prevalence of stage 4–5 CKD was estimated as 200 000 after excluding patients on dialysis. Early detection and appropriate intervention for CKD are thus necessary to prevent further increases in the number of patients with end-stage renal disease. Hypertension is a key risk factor for progression of CKD. To prevent progression of CKD, strict BP control is considered essential. In a recent study, we demonstrated that CKD risk of WCHT based on home BP (HBP) was no different from that of sustained normal blood pressure (SNBP).[13]

Although several clinical studies have reported associations between ABP and CKD,[14,15] only limited information is available from the general population. The objective of this study was to examine CKD risk associated with WCHT and MHT, as determined by ABP monitoring.

METHODS

Design

This cross-sectional study is a part of the Ohasama study, a BP measurement project conducted in the rural community of Ohasama in Iwate Prefecture, Japan. Ohasama had a total population of 7496 in 1992. The socioeconomic and demographic characteristics of this region and details of this project have been described previously.[16] This project was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Study population

Among the 7496 residents of Ohasama, 3076 were eligible for annual health checkups in 1992.[13] Of the 2013 residents who participated in checkups from 1992 to 1997, data on serum creatinine levels, dipstick test for spot urine and confounding factors were unavailable for 214 subjects. Of the remaining 1799 individuals, ABP measurements were recorded in 1073 participants. A total of 27 participants were excluded because of missing data from ABP monitoring, that is, fewer than 14 measurements during the day or fewer than seven measurements during the night based on the guidelines of the European Society of Hypertension.[17] This study population thus consisted of 1023 individuals, representing 33% of the total eligible population. All participants provided written, informed consent to participate in the study, which was approved by the Institutional Review Board of Tohoku University School of Medicine.

ABP monitoring

ABP was monitored using an ABPM 630 (Nippon Colin, Komaki, Japan), a fully automatic device that uses the cuff-oscillometric method to measure BP. The device was preset to measure BP every 30 min. All devices were validated[18] and satisfied the criteria outlined by the Association for the Advancement of Medical Instrumentation.[19] Each ABP monitoring device was attached by well-trained public health nurses who visited the participants on a weekday morning and detached the device the next morning.[16] Participants were asked to report their daily activities, including the times at which they went to bed and awoke. Normal daily activities were allowed and participants were instructed to keep the nondominant arm still and relaxed to the side during measurements. A nondipper was defined as a patient showing a ratio of nighttime to daytime ambulatory systolic BP >0.9.

CBP measurement

CBP was measured twice by nurses or technicians at local medical centers using a semiautomatic BP measuring device (USM-700F; UEDA Electronic Works, Tokyo, Japan) based on the microphone method with subjects in a seated position after resting for 2 min, and the average of the two readings was used in this analysis. The device has been validated previously[20] and meets the criteria of the Association for the Advancement of Medical Instrumentation.[19]

Data collection

Information on smoking status, habitual drinking, use of antihypertensive medications at baseline, as well as history of cardiovascular disease (CVD), diabetes mellitus or hypercholesterolemia, was verified on the basis of the medical charts of the Ohasama Hospital and a questionnaire administered during annual health checkups. History of CVD was defined as disease of the circulatory system, stroke or transient ischemia attack. Subjects treated with lipid-lowering drugs or with levels of serum total cholesterol $\geqslant$220 mg per 100 ml were considered to have hypercholesterolemia. Subjects receiving treatment with antihyperglycemic agents or with fasting serum glucose level $\geqslant$126 mg per 100 ml or casual glucose level $\geqslant$200 mg per 100 ml were defined as having diabetes mellitus.

Measurement of eGFR and proteinuria

Serum creatinine (Scr) was measured using the Jaffé method. Kidney function was estimated by the calculated glomerular filtration rate using a modified three-variable equation based on insulin clearance for Japanese as follows: eGFR (ml min^{-1} per 1.73 m^2)=194$\times$(Scr in enzymatic method)$^{-1.094}\times$ age$^{-0.287}$ ($\times$0.739, if female).[21] We used the following equation to convert the level of Scr from the Jaffé method to that for the enzymatic method (Scr in enzymatic method=Scr in Jaffé method−0.2). After adjustment, mean Scr ($\pm$s.d.) was 0.67$\pm$0.16 mg per 100 ml. Proteinuria was diagnosed with a dipstick test for spot urine (Urohemabonbix 5G08C; Bayer Medical, Tokyo, Japan). Proteinuria was considered to be present for a dipstick result of 1+ or more, which corresponds to a urinary protein level $>$30 mg per 100 ml. CKD was defined as a composite result of eGFR $<$60 ml min^{-1} per 1.73 m^2 and/or positive proteinuria.

Diagnostic criteria for hypertension at each measurement

The criterion for hypertension in CBP was defined as 140/90 mm Hg on the basis of the cutoff values from several guidelines.[17,22] With ABP, the results of the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) study were applied as diagnostic criteria for hypertension as follows: 24-h hypertension, 130/80 mm Hg; daytime hypertension, 140/85 mm Hg; and nighttime hypertension, 120/70 mm Hg.[23]

In addition, participants were categorized into four groups on the basis of daytime ABP and CBP: sustained hypertension (SHT), with daytime ABP $\geqslant$140/85 mm Hg and CBP $\geqslant$140/90 mm Hg; MHT, with daytime ABP $\geqslant$140/85 mm Hg and CBP $<$140/90 mm Hg; WCHT, with daytime ABP $<$140/85 mm Hg and CBP $\geqslant$140/90 mm Hg; or SNBP, with daytime ABP $<$140/85 mm Hg and CBP $<$140/90 mm Hg.

Statistical analysis

Continuous variables are expressed as means $\pm$ s.d. Discrete variables are presented as numbers and percentages. Statistical differences in means among groups were analyzed using one-way analysis of variance (ANOVA) or χ^2-test as appropriate. A multivariate logistic regression model was used to examine associations between CKD and clinical parameters, and we incorporated the following clinical variables into the model as independent variables: age, gender, current smoking status, current habitual drinking status, body mass index, diabetes mellitus, hypercholesterolemia, history of CVD and use of any antihypertensive medications. To compare the association of different BP indices in CBP and ABP with CKD, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for a 1-s.d. elevation in each BP index. The likelihood ratio of the χ^2-value was used as a measure of improvement in the goodness of fit between models containing each single CBP or ABP index and models containing two BP indices. Data were analyzed using SAS version 9.1 software (SAS Institute, Cary, NC, USA).

RESULTS

Comparison of characteristics among four groups

The characteristics of subjects as classified by daytime ABP and CBP into four groups are presented in Table 1. Of the 1023 study subjects, 216 (21.1%) were receiving antihypertensive medication. Among them, 63.4% were prescribed with calcium channel blockers, 26.4% with diuretics, 11.5% with angiotensin-converting enzyme inhibitors, 2.3% with α-blockers and 5.9% with other drugs. Compared with

Table 1 Clinical characteristics in four blood pressure groups

Variable	*SNBP (N=614)*	*WCHT (N=158)*	*MHT (N=153)*	*SHT (N=98)*	P *(adjusted)*
Age (year)	65.6 ± 8.5	69.0 ± 8.0†	68.4 ± 7.2†	68.4 ± 7.8†	<0.0001
Gender (%female)	76.7	63.9†	71.8	59.1†	0.0003
BMI ($kg\,m^{-2}$)	23.0 ± 2.9	23.5 ± 3.2	23.5 ± 3.2	24.1 ± 2.7†	0.0038
Serum creatinine (mg per 100 ml)	0.85 ± 0.14	0.89 ± 0.18†	0.87 ± 0.16	0.92 ± 0.22†	<0.0001
Proteinuria (%)	3.1	7.6	8.5†	14.2†	<0.0001
Estimated GFR ($ml\,min^{-1}$ per $1.73\,m^2$)	77.9 ± 16.9	75.3 ± 17.1	74.6 ± 16.3	73.3 ± 17.5	0.0142
Estimated GFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ (%)	8.6	15.1	20.2†	22.4†	<0.0001
CKD (%)	10.9	19.6	24.8	28.5	<0.0001
Current smoker (%)	8.6	12.6	12.4	13.2	NS
Current drinker (%)	16.9	22.1	16.3	29.5†	0.0139
Diabetes mellitus (%)	12.3	12.0	13.0	15.3	NS
Hypercholesterolemia (%)	29.4	36.7	35.2	38.7	NS
History of cardiovascular disease (%)	3.1	7.0	7.2	6.1	0.0450
Antihypertensive therapy (%)	12.5	27.2†	30.7†	28.5†	<0.0001
Casual SBP (mm Hg)	120.9 ± 11.9	149.6 ± 10.8†	125.6 ± 9.4†,§	150.5 ± 10.7†	<0.0001
Casual DBP (mm Hg)	68.1 ± 8.7	81.8 ± 9.8†	69.8 ± 8.0†,§	80.1 ± 10.6†	<0.0001
24 h SBP (mm Hg)	118.5 ± 9.0	124.4 ± 7.8†	140.0 ± 8.6†,§	140.9 ± 8.3†,§	<0.0001
24 h DBP (mm Hg)	69.1 ± 5.5	71.0 ± 5.1†	80.5 ± 5.5†,§	79.6 ± 6.0†,§	<0.0001
Daytime SBP (mm Hg)	123.6 ± 9.5	128.9 ± 7.5†	147.8 ± 7.8†,§	148.9 ± 7.9†,§	<0.0001
Daytime DBP (mm Hg)	72.8 ± 6.0	74.6 ± 5.3†	86.0 ± 5.3†,§	85.1 ± 6.4†,§	<0.0001
Nighttime SBP (mm Hg)	108.8 ± 11.5	116.0 ± 12.3†	125.6 ± 13.8†,§	127.0 ± 12.5†,§	<0.0001
Nighttime DBP (mm Hg)	62.0 ± 6.4	64.4 ± 6.9†	70.4 ± 8.0†,§	70.0 ± 7.2†,§	<0.0001
Nighttime/daytime SBP	0.88 ± 0.07	0.90 ± 0.08†	0.84 ± 0.08†,§	0.85 ± 0.07†,§	<0.0001
Nighttime/daytime DBP	0.85 ± 0.07	0.86 ± 0.08	0.81 ± 0.07†,§	0.82 ± 0.06†,§	<0.0001
Non-dipper (%)	39.0	46.2	28.1§	22.4†,§	<0.0001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; NS, no significance; PP, pulse pressure; SBP, systemic blood pressure; SNBP, sustained normal blood pressure, WCHT, white-coat hypertension.
Values are expressed as percentages or means ± s.d. adjusted by age, sex and BMI.
†$P<0.05$ *vs.* SNBP group, §$P<0.05$ *vs.* WCHT group.

SNBP, prevalence of proteinuria was significantly higher in MHT and SHT. ABP levels in MHT were similar to those in SHT. Subjects with MHT and SHT were more likely to be prescribed with antihypertensive drugs and to show cardiovascular complications. Scr was significantly higher in SHT and WCHT than in SNBP. In addition, we performed a stratified analysis between the genders; however, there was no significant difference with regard to the prevalence of positive proteinuria, eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD between them.

Adjusted ORs for CKD among four BP groups

Adjusted ORs for the presence of proteinuria were significantly higher in SHT, MHT and WCHT groups than in the SNBP group (Figure 1a). Adjusted ORs for the presence of eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ in SHT and MHT groups were significantly higher than that in the SNBP group (Figure 1b). In addition, adjusted ORs for the presence of CKD were significantly higher in SHT, MHT and WCHT groups than in the SNBP group (Figure 1c).

Furthermore, there is also a possibility that, using a 140 mm Hg threshold for daytime ABP, prevalence of ambulatory hypertension is underestimated. Therefore, we performed a reanalysis with the use of the 135/85 mm Hg threshold for daytime ABP. As a result, prevalence of WCHT was decreased from 15.4 to 12.0%, whereas that of MHT was increased from 15.0 to 22.4%, respectively. Using 135/85 mm Hg threshold for daytime ABP, adjusted ORs for the presence of proteinuria in the WCHT group (OR, 3.27; 95% CI, 1.44–7.40; $P<0.01$) and the MHT group (OR, 2.57; 95% CI, 1.23–5.38; $P=0.01$) were significantly higher than that in the SNBP group, which were similar to the results in the case of 140/85 mm Hg threshold. Regarding the OR for eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ or CKD, results similar to those of 140/85 mm Hg threshold were observed.

When the WCHT group was subdivided into two groups (WCHT-1 (those with lower systolic daytime ABP) and WCHT-2 (those with higher systolic daytime ABP)) around the median systolic daytime ABP (130.6 mm Hg), CBP was significantly higher in the WCHT-1 and WCHT-2 groups than in the SNBP group (Table 2). Daytime, nighttime and 24-h ABP measurements were significantly higher in the WCHT-2 group than in the SNBP group, although there were no significant differences in ABP values between the WCHT-1 and SNBP groups (Table 2). The systolic ABP in the WCHT-2 group was also significantly higher than that in the WCHT-1 group (Table 2).

The adjusted OR for proteinuria was significantly higher in the WCHT-2 group compared with the SNBP group (OR, 2.73; $P=0.04$).

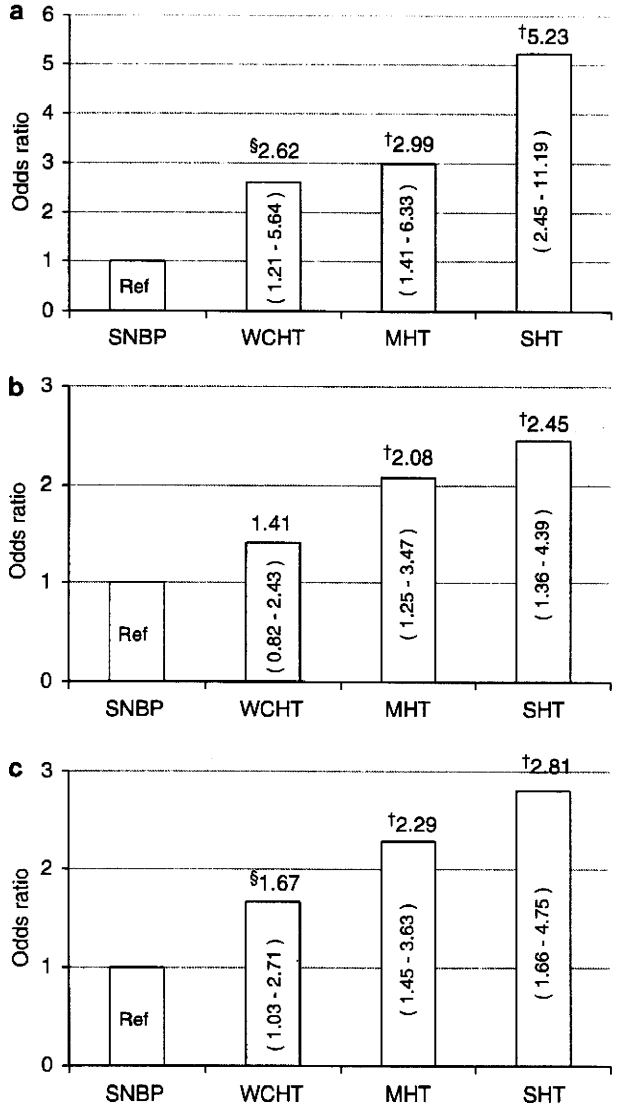

Figure 1 Odds ratios and 95% confidence intervals for the presence of (**a**) proteinuria, (**b**) estimated glomerular filtration rate $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and (**c**) chronic kidney disease (CKD) associated with combinations of groups with and without hypertension in daytime ambulatory blood pressure (ABP) and casual blood pressure (CBP), adjusted for age, gender, body mass index, smoking status, alcohol intake, antihypertensive medication, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. §$P<0.03$ *vs.* reference; †$P<0.01$ *vs.* reference. MHT, masked hypertension; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.

Corresponding OR in the WCHT-1 group was almost significantly higher than that in the SNBP group (OR, 2.51; $P=0.06$) (Figure 2a). Adjusted OR for CKD also tended to be higher in the WCHT-1 (OR, 1.54; $P=0.19$) and WCHT-2 groups (OR, 1.81; $P=0.06$) than in the SNBP group (Figure 2b). On the other hand, when we conducted logistic regression analysis treating the WCHT-1 group as the reference category, adjusted ORs in the WCHT-2 group for the presence of proteinuria (OR, 1.09; 95% CI, 0.33–3.60; $P=0.89$) and CKD (OR, 1.18; 95% CI, 0.53–2.64; $P=0.69$) were almost similar to those in the WCHT-1 group without any significant differences. No significant differences in adjusted ORs of eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD were seen between WCHT and SNBP.

Table 2 Comparison of CBP and ABP in the SNBP and subdivided WCHT groups

	SNBP (N=614)	*WCHT-1 (N=79)*	*WCHT-2 (N=79)*
Systolic CBP (mm Hg)	121 ± 12	149 ± 10†	151 ± 12†
Diastolic CBP (mm Hg)	68 ± 9	83 ± 9†	81 ± 11†
Systolic daytime ABP (mm Hg)	124 ± 10	123 ± 6	135 ± 3†,‡
Diastolic daytime ABP (mm Hg)	73 ± 6	72 ± 5	77 ± 4†
Systolic nighttime ABP (mm Hg)	109 ± 12	112 ± 13	120 ± 10†,‡
Diastolic nighttime ABP (mm Hg)	62 ± 6	63 ± 8	66 ± 6†
Systolic 24 h ABP (mm Hg)	118 ± 10	119 ± 7	130 ± 4†,‡
Diastolic 24 h ABP (mm Hg)	69 ± 6	69 ± 5	73 ± 4†,‡

Abbreviations: ABP, ambulatory blood pressure; CBP, casual blood pressure; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.
†$P<0.05$ *vs.* SNBP group, ‡$P<0.05$ *vs.* WCHT-1 group. Values are expressed as means ± s.d.

The adjusted OR for CKD was significantly higher in the MHT and SHT groups than in the SNBP group, in spite of antihypertensive treatment (Figure 3). When subjects with and without medication were analyzed separately, similar results were obtained (data not shown).

When nighttime ABP was further added into logistic regression models, the adjusted OR for the presence of proteinuria in the WCHT group remained significantly higher than that in the SNBP group ($P=0.03$), whereas the adjusted OR in the MHT group was not significantly different ($P=0.09$). Similarly, after adjustment of nighttime ABP, the significance for proteinuria of WCHT on the basis of higher daytime systolic ABP disappeared ($P=0.08$).

Association of ABP and CBP as continuous variables with risk of proteinuria, estimated GFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD

For systolic BP, daytime, nighttime and 24-h ABPs were significantly associated with prevalence of proteinuria, eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD, whereas no such associations were observed for systolic CBP in Table 3. For diastolic BP, ABP and CBP were similarly associated with prevalence of proteinuria, eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD in Table 3.

DISCUSSION

In this study, we demonstrated that MHT, WCHT and SHT were significantly associated with higher risks of proteinuria and CKD compared with SNBP on the basis of ABP monitoring in the general population.

We have already reported that risk of cardiovascular mortality and stroke morbidity is significantly higher in subjects with MHT than in those with SNBP.[7] We have also previously reported that MHT on the basis of HBP is significantly associated with creatinine clearance $<60\,ml\,min^{-1}$ with proteinuria when compared with SNBP in the general population.[13] Consistent with those findings, this study demonstrated that individuals with MHT on the basis of ABP showed a higher prevalence of proteinuria, eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD.

In this study, we compared the 140/85 mm Hg threshold with the 135/85 mm Hg threshold of daytime ABP, which is proposed by the Japanese, American and European hypertension guidelines. As a result, adjusted ORs for proteinuria, eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$ and CKD showed almost similar results; therefore, it is considered that the difference in threshold of daytime ABP did not have a significant impact on CKD risk.

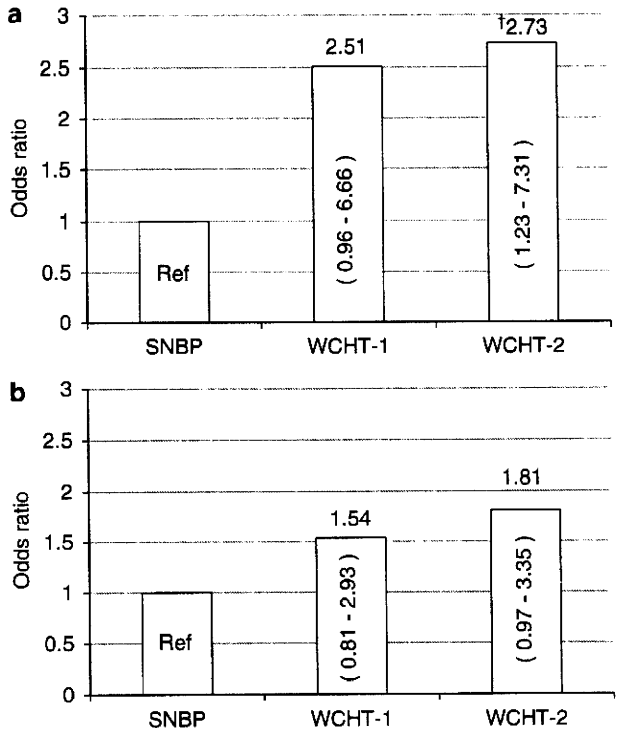

Figure 2 Odds ratios and 95% confidence intervals for the presence of (**a**) proteinuria and (**b**) chronic kidney disease (CKD) associated with the comparison of the sustained normal blood pressure (SNBP) group, adjusted for age, gender, body mass index, smoking status, alcohol intake, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. †$P<0.05$ *vs.* reference. WCHT, white-coat hypertension.

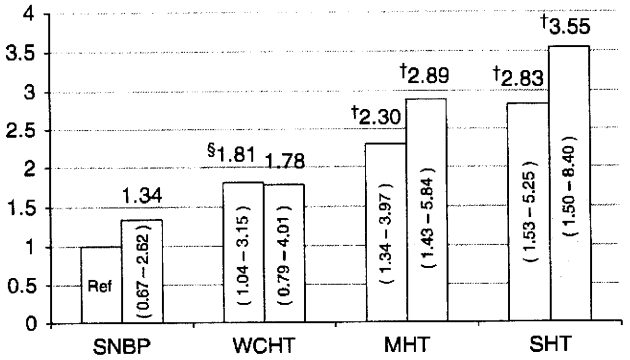

Figure 3 Odds ratios and 95% confidence intervals for the presence of chronic kidney disease (CKD) in the presence or absence of antihypertensive treatment, adjusted for age, gender, body mass index, smoking status, alcohol intake, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. Antihypertensive medication (−), ■ antihypertensive medication (+). §$P<0.05$ *vs.* reference; †$P<0.01$ *vs.* reference. MHT, masked hypertension; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.

In the previous study, we reported that treated individuals with optimal BP had a higher stroke risk than untreated ones with optimal BP.[24] Therefore, in this study, we thought that it is necessary to verify whether there is a residual CKD risk in treated hypertensive patients; hence we added Figure 3. As a result, among SHT, MHT groups, ORs for CKD in the treated hypertensive population were shown to be higher than in untreated hypertensive patients.

When we included nighttime ABP into the multivariate logistic regression model, MHT was no longer associated with CKD. MHT is considered to be mediated mainly by nondipper and riser status, and thus by nocturnal elevation of BP.[25] Nocturnal BP may represent a common mechanism related to risk of CKD in subjects with MHT defined by daytime ABP.[25]

WCHT has recently been reported to be associated with a higher risk of coronary artery disease when compared with subjects without WCHT.[26] In our 8-year follow-up study, WCHT was a significant predictor for the development of HBP hypertension.[10] In addition, one-third of patients with nondialytic CKD of stage 3–5 reportedly show WCHT.[27] In this study, WCHT with a relatively higher daytime ABP showed increased risk of proteinuria. This result is different from that of the previous study on the basis of HBP. This might be partly because ABP includes a comprehensive BP information, that is, an average daily BP load, a component of short-term variability of BP, BP in the morning and circadian variation of BP more than HBP. These results indicate that WCHT is not innocent, but is a condition warranting a follow-up. Individuals with WCHT should receive careful long-term follow-up.

In our study, when we subdivided the WCHT group into two groups, the daytime ABP was almost similar between the WCHT group with lower systolic daytime ABP and the SNBP group, whereas adjusted OR for the presence of proteinuria and CKD tended to be higher in the WCHT group with lower systolic daytime ABP than in the SNBP group. On the other hand, even though systolic ABP in the WCHT group with higher systolic daytime ABP was significantly higher than that in the WCHT group with lower systolic daytime ABP, there was no difference in the adjusted ORs for the presence of proteinuria and CKD between the subdivided WCHT groups. However, CBP was almost similar between these two groups. These results suggest a possibility that the risk in the WCHT group might be largely attributable to the higher CBP rather than to the higher ABP levels.

It has been documented that sympathetic hyperactivity occurs in WCHT.[28] It is also reported that sympathetic activity is increased in patients with CKD.[29] In addition, sympathetic nerve activity is shown to be related to kidney injury, especially proteinuria.[30] However, there is no conclusion about whether sympathetic activity itself leads to kidney injury or whether an increased sympathetic nerve system is derived as a result of development of kidney injury. In the previous study, it was examined that sympathetic blocking agents inhibited albuminuria and glomerulosclerosis without lowering blood pressure[31]. In clinical research, it was shown that sympathetic blocking agents decrease urine albumin excretion in normotensive diabetes patients.[32] These reports indicate that it is possible that inhibition on sympathetic nerve activity would alleviate kidney injury. These pathophysiological conditions of WCHT and CKD might suggest a relationship between WCHT and kidney injury.

WCHT was significantly related to the prevalence of proteinuria, but this association was less marked for the prevalence of eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$. It is possible that the underlying mechanisms might thus differ between proteinuria and decreased eGFR. WCHT may reflect a phasic component of BP, whereas SHT and MHT may be associated with tonic load of BP, suggesting that proteinuria may be associated with phasic BP changes, and that decreased eGFR may be related to the tonic load under high BP. Estimated GFR of females is smaller than that of males. The

Table 3 Comparison of adjusted odds ratio for each condition of renal disorder (per elevation of 1-s.d. of the BP indices)

Models	*Proteinuria*			*eGFR< 60 ml min^{-1} per 1.73 m^2*			*CKD*		
BP variables	*Odds ratio (95% CI)*	*P-value*	*LR*	*Odds ratio (95% CI)*	*P-value*	*LR*	*Odds ratio (95% CI)*	*P-value*	*LR*
Systolic BP									
Casual+24 h									
Casual	1.27 (0.97–1.69)	NS	2.9	1.09 (0.89–1.34)	NS	0.7	0.98 (0.74–2.29)	NS	2.3
24 h	1.66 (1.25–2.20)	0.0004	12.4	1.28 (1.04–1.58)	0.0193	5.5	1.36 (1.13–1.64)	0.0011	10.7
Casual+daytime									
Casual	1.30 (0.98–1.72)	NS	3.2	1.09 (0.89–1.34)	NS	0.7	1.16 (0.97–1.39)	NS	2.5
Daytime	1.54 (1.16–2.04)	0.0030	8.8	1.29 (1.05–1.59)	0.0164	5.8	1.34 (1.11–1.61)	0.0021	9.5
Casual+nighttime									
Casual	1.30 (0.98–1.71)	NS	3.4	1.12 (0.91–1.37)	NS	1.1	1.17 (0.98–1.41)	NS	3.0
Nighttime	1.65 (1.25–2.18)	0.0005	12.3	1.19 (0.97–1.46)	NS	2.8	1.30 (1.09–1.57)	0.0042	8.2
Diastolic BP									
Casual+24 h									
Casual	1.22 (0.93–1.66)	NS	2.0	1.25 (1.03–1.52)	0.0269	4.9	1.30 (1.09–1.56)	0.0035	8.5
24 h	1.39 (1.06–1.82)	0.0181	5.6	1.27 (1.04–1.56)	0.0223	5.2	1.37 (1.06–1.52)	0.0105	6.6
Casual+daytime									
Casual	1.25 (0.95–1.64)	NS	2.4	1.25 (1.03–1.53)	0.0265	4.9	1.31 (1.10–1.56)	0.0030	8.8
Daytime	1.31 (0.99–1.73)	NS	3.6	1.28 (1.04–1.58)	0.0182	5.6	1.26 (1.05–1.51)	0.0149	5.9
Casual+nighttime									
Casual	1.22 (0.93–1.61)	NS	2.0	1.26 (1.04–1.53)	0.0205	5.4	1.31 (1.10–1.57)	0.0027	9.0
Nighttime	1.41 (1.08–1.84)	0.0116	6.4	1.19 (0.97–1.45)	NS	2.8	1.24 (1.03–1.48)	0.0205	5.4

Abbreviations: BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; LR, likelihood ratio; NS, not significant.

percentage of females in the WCHT group of this study was significantly lower than that of the SNBP group (Table 1). Therefore, we imagine that if the proportion of females in the WCHT group had been similar to that in the SNBP group, the percentage of 'subjects with eGFR <60' in the WCHT group might have been significantly higher than that in the SNBP group.

This study should be interpreted within the context of its potential limitations. First, the level of CBP and the prevalence of hypertension in CBP are overestimated because of the use of single-visit clinic BP measurements. Second, proteinuria was diagnosed in this study using a semiquantitative dipstick test for spot urine, with results of ⩾30 mg per 100 ml representing a positive finding. This approach does not allow subjects with microalbuminuria and overt proteinuria to be distinguished. Third, serum creatinine was measured using the Jaffé method, and this value was corrected to obtain an equivalent value for the enzymatic method using a modified equation. Finally, this study was cross-sectional in design and thus cannot provide any insights into causal relationships between BP parameters and CKD.

This study demonstrated that WCHT, as well as MHT, is an independent risk factor for prevalence of proteinuria and CKD. In the earlier stage of CKD, evaluation of albuminuria and renal function, as well as therapeutic intervention, may be important to prevent future development and progression of CVD, in addition to the development and progression of CKD.[33–35] These results thus revealed that CKD is significantly related to MHT and WCHT on the basis of ABP monitoring in the general population. Further prospective studies are needed to clarify the role of ABP measurements in predicting future occurrence of CKD and associated disorders in the general population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported in part by Grants for Scientific Research (15790293, 16590433, 17790381, 18390192, 18590587, 19590929, 19790423, 20590629, 21390201 and 21591016) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; by Grant-in-Aid (H17-Kenkou-007, H18-Junkankitou(Seishuu)-Ippan-012, and H20-Junkankitou(Seishuu)-Ippan-009, 013) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; by Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16. 54041, 18.54042, 19.7152, 20.7198, 20.7477 and 20.54043); by Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; by the Japan Atherosclerosis Prevention Fund; the Uehara Memorial Foundation; the Takeda Medical Research Foundation; by National Cardiovascular Research Grants; and by Biomedical Innovation Grants.

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20 YEARS
Cerebrovascular Diseases

Original Paper

Cerebrovasc Dis 2010;30:43–50
DOI: 10.1159/000313612

Received: September 7, 2009
Accepted: February 26, 2010
Published online: April 29, 2010

Association of Kidney Dysfunction with Silent Lacunar Infarcts and White Matter Hyperintensity in the General Population: The Ohasama Study

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Key Words
Chronic kidney disease · Ambulatory blood pressure · White-matter hyperintensity · Lacunar infarcts · General population

Abstract
Background: No previous study has investigated the association of kidney dysfunction with silent lacunar infarcts and white-matter hyperintensity (WMH) independent of ambulatory blood pressure (BP). ***Methods:*** A cross-sectional study involving 1,008 participants (mean age 66 years) from a general population of Ohasama, Japan, was conducted. Calculated creatinine clearance (CCr) was estimated using the Cockcroft-Gault equation. In continuous and categorical analyses, the association between CCr and the prevalence of silent lacunar infarcts and WMH was investigated. Silent lacunar infarcts and WMH were detected on MRI. Multiple logistic regression analysis adjusted for 24-hour ambulatory BP, sex, age, body mass index, smoking and drinking status, antihypertensive medication, and histories of hypercholesterolemia, diabetes mellitus and heart disease was performed. ***Results:*** On univariate analysis, decreased CCr (continuous variable) and CCr <60 ml/min/1.73 m^2 (categorical variable) were significantly associated with lacunar infarcts and WMH. After adjustment, each 1-standard-deviation decrease in CCr (odds ratio = 1.22; p = 0.036) and CCr <60 ml/min/1.73 m^2 (odds ratio = 1.68; p = 0.007) was significantly associated with a high prevalence of lacunar infarcts. Even when 24-hour ambulatory BP was within the normal range (<130/80 mm Hg), CCr <60 ml/min/1.73 m^2 was associated with a high prevalence of lacunar infarcts (odds ratio = 1.62; p = 0.047). CCr <60 ml/min/1.73 m^2 and 24-hour ambulatory BP had additive effects on lacunar infarcts. After the same adjustment, the association between CCr and WMH was not significant. ***Conclusions:*** CCr is closely associated with lacunar infarcts, suggesting that kidney dysfunction in the elderly is an independent risk factor or predictor for silent lacunar infarcts.

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Introduction

It has recently been recognized that chronic kidney disease (CKD) is an independent risk factor for all-cause mortality, including cardiovascular disease events and stroke, in the general population [1–3]. Silent lacunar infarcts and white-matter lesions (i.e. hyperintensities, WMHs), which are frequently observed on magnetic resonance imaging (MRI) scans of elderly individuals, are an independent predictor of the risk of stroke [4], and they are associated with an increased risk of cognitive impairment or dementia [5]. From the viewpoint of preventing stroke and dementia, it is important to investigate the association of CKD with silent lacunar infarcts and WMHs. However, few studies have examined this association [6, 7].

Hypertension is a major risk factor for CKD [8], stroke [9] and silent lacunar infarcts [10, 11]. However, it is still uncertain whether hypertension affects the association between CKD and stroke [3, 9]. The Suita study [9], a prospective study of the general population, demonstrated that the impact of CKD on the risk of stroke was more evident in hypertensive patients than in subjects with optimal blood pressure (BP). Meanwhile, in another population-based prospective study, there was no evidence of heterogeneity in the association among BP level categories [3]. All the above-mentioned studies [3, 9] were based solely on casual BP. Few studies have reported associations between ambulatory BP and CKD [12] and associations of ambulatory BP with silent lacunar infarcts and WMHs [13]. No previous study has investigated the association of CKD with silent lacunar infarcts and WMHs independent of ambulatory BP, which is known to provide more reproducible information and is more closely correlated with target organ damage and prognosis than casual BP [14–17]. Therefore, we conducted a cross-sectional study to determine the association of kidney dysfunction with silent lacunar infarcts and WMHs in a general population with adjustment for ambulatory BP.

Methods

Design

This investigation was a part of the Ohasama study. The socioeconomic and demographic characteristics of this region and the full details of the project have been described elsewhere [18]. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government.

Study Population

In 1998, the population of Ohasama, a rural Japanese community, was 7,202, of whom 3,077 were 55 years or older. Individuals (n = 492) who were not at home during the normal working hours of the study nurses, and those hospitalized, mentally ill or bedridden (n = 185) were not eligible for inclusion. Of the remaining 2,400 eligible individuals, 1,174 subjects (49%) gave their written informed consent and participated in the MRI examination [13]. We excluded 110 subjects whose BP and serum creatinine levels were not adequately measured, as well as 55 subjects with a history of previous stroke or TIA. We obtained information on history of stroke and TIA from the participants themselves and by checking their medical records. Therefore, of the 2,400 eligible individuals, 1,008 (42%) were included in the present analysis.

Magnetic Resonance Imaging

Brain MRI was performed using a 0.5-tesla superconducting magnet [13]. The brain was imaged in the axial plane in 10-mm-thick slices, and T_1- and T_2-weighted images were collected. A silent lacunar infarct was defined as an area of low signal intensity measuring $\leq$15 mm and $\geq$3 mm on T_1-weighted images that was visible as a hyperintense lesion on T_2-weighted images, without a history of a stroke or TIA. Hyperintense punctate lesions evident only on the T_2-weighted images were not counted as lacunar infarcts. WMHs were defined as hyperintensities only on T_2-weighted images, and they were graded according to Fazekas et al. [19] as follows: absent (grade 0), punctate (grade 1), early confluent (grade 2) and confluent (grade 3). Small caps (<5 × 10 mm) on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal. Larger caps ($\geq$5 × 10 mm) were considered grade 2. Because of the limited number of study subjects, grades 2 (n = 100) and 3 (n = 17) were combined. A neurosurgeon and 4 trained observers directed by the neurosurgeon evaluated the MRI findings independently. In the case of disagreement, a consensus reading was held. Both intrareader and interreader studies (n = 111) showed good agreement; kappa statistics were between 0.68 and 0.86 for lacunar infarct and between 0.72 and 0.86 for WMH.

Data Collection

At the time of the carotid ultrasound examination, blood samples were collected to measure serum creatinine, total cholesterol, glucose and glycosylated hemoglobin (HbA_{1c}). Serum creatinine (mg/dl) was measured using the Jaffe assay (n = 801) or using an enzymatic assay (n = 207). Serum creatinine levels using the Jaffe assay were known to be higher than those obtained by enzymatic assay when the creatinine levels on the Jaffe assay were under 2.0 mg/dl [20]. Therefore, serum creatinine levels obtained using the enzyme assay in the present study were calibrated to the levels of the Jaffe assay by adding 0.2 mg/dl.

Trained public health nurses interviewed the participants and administered a standardized questionnaire inquiring into smoking and drinking status, use of antihypertensive medication, and history of hypercholesterolemia, diabetes mellitus, and cardiovascular disease. These data were confirmed by the medical records. Hypercholesterolemia was defined as total cholesterol $\geq$220 mg/dl, use of medication for hypercholesterolemia and/or a history of hypercholesterolemia [21]. Diabetes mellitus was defined as a random blood glucose $\geq$11.11 mmol/l (200 mg/dl), an HbA_{1c} $\geq$6.5%, use of medication for diabetes and/or a history of diabetes mellitus.

Table 1. Population characteristics by number of lacunar infarcts

	None	1 and 2 infarcts	≥3 infarcts	p value
Number of subjects	722	204	82	
Men, %	28.5	36.3	40.2	<0.0001
Age, years	65.4 ± 5.5	68.6 ± 5.8	69.7 ± 4.9	<0.0001
BMI	23.7 ± 0.3	23.3 ± 3.3	23.3 ± 3.1	0.2
24-hour systolic BP, mm Hg	123.6 ± 12.3	127.7 ± 12.3	133.5 ± 13.1	<0.0001
24-hour diastolic BP, mm Hg	71.9 ± 7.2	74.0 ± 6.9	76.4 ± 7.5	<0.0001
Casual systolic BP, mm Hg	140.1 ± 20.2	140.7 ± 20	146.2 ± 20.8	0.03
Casual diastolic BP, mm Hg	77.6 ± 11.0	78.3 ± 10.6	77.8 ± 9.4	0.7
Ever smoker, %	17.0	19.6	39.0	<0.0001
Ever drinker, %	25.8	27.0	42.7	0.005
Antihypertensive medication, %	31.7	54.9	67.1	<0.0001
Hypercholesterolemia, %	37.7	35.8	24.4	0.06
Diabetes, %	14.4	18.6	20.7	0.2
History of heart disease, %	9.8	16.7	24.4	<0.0001
Serum creatinine, mg/dl	0.82 ± 0.17	0.87 ± 0.2	0.91 ± 0.28	<0.0001
CCr, ml/min/1.73 m^2	74.5 ± 25.9	67.2 ± 15.7	68.7 ± 25.9	0.0002
CCr <60 ml/min/1.73 m^2, %	15.8	35.8	32.9	<0.0001

BMI = Body mass index. Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl, use of medication for hypercholesterolemia, and/or a history of hypercholesterolemia [21]. Diabetes mellitus was defined as a random blood glucose level of ≥11.11 mmol/l (200 mg/dl), an HbA_{1c} level of ≥6.5%, use of medication for diabetes and/or a history of diabetes mellitus.

BP Measurements

Ambulatory BP was monitored using a fully automatic ABPM630 device (Nippon Colin, Komaki, Japan) [22] preset to measure BP every 30 min. Mean 24-hour, daytime and nighttime ambulatory BP values were calculated for each participant. Daytime and nighttime values were estimated from the subjects' diaries. High BP was defined as a 24-hour ambulatory BP of 130 mm Hg systolic or 80 mm Hg diastolic [23, 24]. Casual BP was measured twice consecutively in the sitting position, after a minimum 2-min interval of rest, by a physician using a mercury sphygmomanometer or an automatic device (HEM907; Omron Healthcare Co. Ltd., Kyoto, Japan) [25] at the time of MRI examination. The average of the two readings was defined as the casual BP. The devices used to measure ambulatory BP and casual BP were validated [22, 25] and met the criteria of the Association for the Advancement of Medical Instrumentation [26].

Data Analysis

Kidney function was estimated by the calculated creatinine clearance (CCr) using the Cockcroft-Gault equation [27] with adjustment for body surface area of 1.73 m^2: CCr = [(140 – age in years) × weight in kg] × 1.73/[serum creatinine × 72] × [0.85 if women] × body surface area in m^2. Body surface area was calculated for each participant according to the formula of Du Bois and Du Bois [28]. Continuous and categorical (CCr <60 vs. ≥60 ml/min/1.73 m^2) analyses were used to investigate whether CCr was associated with the prevalence of silent lacunar infarcts and WMHs. To analyze the univariate associations of lacunar infarcts and WMHs with subjects' characteristics, the χ^2 test was used for categorical data, and analysis of variance was used for continuous data. Then, multiple logistic regression analysis, adjusted for cardiovascular risk factors, including 24-hour ambulatory systolic BP, sex, age, body mass index (≥25 vs. <25), ever smoking, ever drinking, use of antihypertensive medication, and a history of hypercholesterolemia, diabetes mellitus and heart disease, was conducted [13]. All statistical analyses were conducted using SAS software, version 9.1 (SAS Institute Inc., Cary, N.C., USA). The values are expressed as means ± standard deviation (SD). $p < 0.05$ was considered statistically significant.

Results

Population Characteristics

Among the 1,008 subjects, the mean age ± SD was 66.4 ± 5.7 years; 67.3% were women. The mean BMI was 23.6 ± 3.1, the 24-hour ambulatory systolic/diastolic BP was 125.3 ± 12.7/72.7 ± 7.3 mm Hg, and the casual BP was 140.7 ± 20.2/77.8 ± 10.8 mm Hg. Overall, 19.4% of subjects were ever smokers, 27.4% were ever drinkers, 39.3% were treated with antihypertensive medication, and 6.2, 15.8 and 12.4% of subjects were classified as having a history of hypercholesterolemia, diabetes mellitus and cardiovascular disease, respectively. The mean serum creatinine was 0.84 ± 0.19 mg/dl, the mean esti-

Table 2. Multivariate ORs and 95% CIs for lacunar infarcts [present (n = 286) vs. absent (n = 722)] with cardiovascular risk factors

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
CCr (per 1-SD decrease)	1.22	1.01–1.47*	–	–
CCr <60 ml/min/1.73 m^2	–	–	1.68	1.15–2.44*
24-hour systolic BP (per 10 mm Hg)	1.23	1.08–1.39*	1.24	1.09–1.40*
Sex (men = 1)	1.72	1.09–2.67*	1.69	1.07–2.66*
Age (per 10 years)	2.41	1.79–3.24*	2.24	1.65–3.05*
BMI ≥25	0.91	0.65–1.27	0.91	0.65–1.27
Ever smoker	1.01	0.63–1.61	0.98	0.61–1.56
Ever drinker	1.13	0.74–1.73	1.14	0.74–1.75
Antihypertensive medication	2.14	1.56–2.94*	2.08	1.51–2.86*
Hypercholesterolemia	0.97	0.70–1.36	1.01	0.72–1.41
Diabetes	1.09	0.73–1.62	1.11	0.74–1.65
History of heart disease	1.51	1.00–2.29	1.47	0.97–2.24

OR = Odds ratio; CI = confidence interval; BMI = body mass index. These variables were simultaneously included in a multiple logistic regression model. Model 1 included decreased CCr (continuous variable), and model 2 included CCr <60 ml/min/1.73 m^2 (categorical variable). * $p < 0.05$.

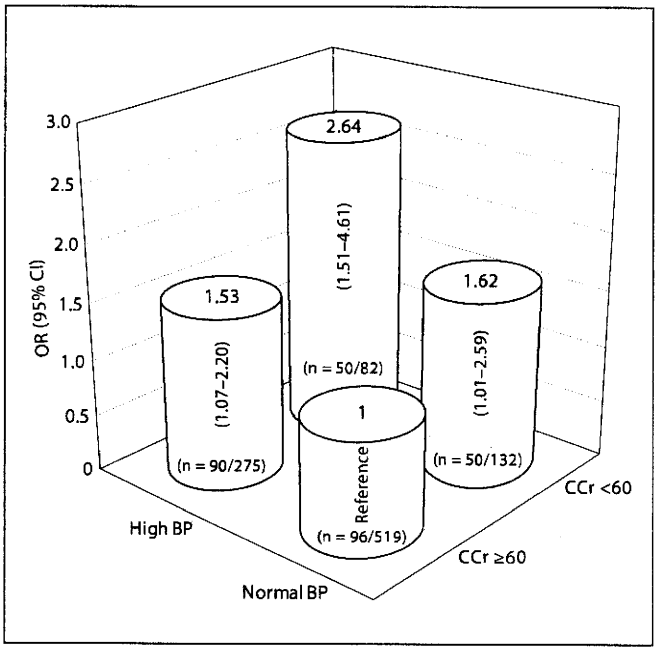

Fig. 1. Adjusted ORs and 95% confidence intervals (inside the bars) for lacunar infarcts associated with the combination of CCr <60 ml/min/1.73 m^2 and 24-hour ambulatory BP levels. Adjustments were made for sex, age, body mass index, smoking status, drinking status, use of antihypertensive medication, and history of hypercholesterolemia, diabetes mellitus and heart disease; n = number having lacunar infarcts/number of participants in group. High BP was defined as 24-hour ambulatory BP levels ≥130/80 mm Hg [23]. Kidney dysfunction was defined as CCr <60 ml/min/1.73 m^2. Interaction p = 0.25.

mated CCr was 72.6 ± 24.3 ml/min/1.73 m^2, and 21.2% of subjects had a CCr <60 ml/min/1.73 m^2.

Kidney Dysfunction and Lacunar Infarcts

Lacunar infarcts were associated with sex, age, BP values except for casual diastolic BP, smoking status, drinking status, antihypertensive medication, history of heart disease, serum creatinine, CCr levels and the proportion of CCr <60 ml/min/1.73 m^2 (table 1). The 722 individuals without lacunar infarcts had better kidney function than the 286 individuals with lacunar infarcts ($p < 0.0001$ for CCr levels, $p < 0.0001$ for the proportion of CCr <60 ml/min/1.73 m^2).

A multiple regression model was constructed including lacunar infarcts (present vs. absent) as the dependent variable, and 24-hour ambulatory systolic BP levels and other cardiovascular risk factors as independent variables (table 2). Each 1-SD (24.3 ml/min/1.73 m^2) decrease in CCr, 24-hour ambulatory systolic BP, male sex, older age and use of antihypertensive medication were significantly associated with lacunar infarcts (model 1). With the same adjustment applied, CCr <60 ml/min/1.73 m^2 was also independently associated with lacunar infarcts (model 2). When daytime or nighttime ambulatory systolic BP was used in this model instead of 24-hour ambulatory systolic BP, the odds ratios (ORs) of each 1-SD decrease in CCr (OR >1.22; $p < 0.04$) and those of CCr <60 ml/min/1.73 m^2 (OR >1.67; $p < 0.008$) remained significant. Furthermore, when the 24-hour ambulatory systolic BP and the casual systolic BP were used in the same model, only 24-hour ambulatory systolic BP was associated with lacunar infarcts (OR = 1.28; p = 0.0003 for 24-hour ambulatory systolic BP, OR = 0.94; p = 0.15 for casual systolic BP). Stratified analyses by sex (male/female), age group (<65/≥65 years) and antihypertensive medication (treated/untreated) were also performed. All stratified analyses were confirmatory. None of the interaction terms of sex, age and use of antihypertensive medication with lacunar infarcts reached significance (all $p > 0.4$). The association between kidney function and lacunar infarcts was also examined using the Modi-

Table 3. Population characteristics classified by the grade of WMH

	Grade 0	Grade 1	Grade ≥2	p value
Number of subjects	566	325	117	
Men, %	31.4	37.5	24.8	0.03
Age, years	65.0 ± 5.6	67.7 ± 5.3	69.6 ± 5.5	<0.0001
BMI	23.7 ± 3.1	23.5 ± 3.1	23.4 ± 3.2	0.4
24-hour systolic BP, mm Hg	122.8 ± 12.3	127.5 ± 12.4	130.7 ± 13.0	<0.0001
24-hour diastolic BP, mm Hg	71.7 ± 7.0	73.6 ± 7.4	75.1 ± 7.5	<0.0001
Casual systolic BP, mm Hg	139.5 ± 20.4	142.2 ± 19.6	142.3 ± 20.7	0.1
Casual diastolic BP, mm Hg	77.5 ± 11.0	78.0 ± 10.7	78.6 ± 9.8	0.5
Ever smoker, %	17.8	22.8	17.1	0.2
Ever drinker, %	28.3	28.6	19.7	0.1
Antihypertensive medication, %	29.0	49.2	61.5	<0.0001
Hypercholesterolemia, %	36.2	35.7	37.6	0.9
Diabetes, %	14.0	19.7	13.7	0.06
History of heart disease, %	10.3	13.5	19.7	0.01
Serum creatinine, mg/dl	0.83 ± 0.17	0.86 ± 0.2	0.83 ± 0.24	0.04
CCr, ml/min/1.73 m^2	74.6 ± 24.4	70.6 ± 25.9	68.1 ± 18.0	0.0007
CCr <60 ml/min/1.73 m^2, %	15.0	28.6	30.8	<0.0001

BMI = Body mass index. Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl, use of medication for hypercholesterolemia and/or a history of hypercholesterolemia [21]. Diabetes mellitus was defined as a random blood glucose level of ≥11.11 mmol/l (200 mg/dl), an HbA_{1c} level of ≥6.5%, use of medication for diabetes and/or a history of diabetes mellitus.

fication of Diet in Renal Disease study equation [29], and similar results were observed: each 1-SD decrease in estimated glomerular filtration rate tended to be associated with a high prevalence of lacunar infarcts after adjustment for cardiovascular risk factors (OR = 1.18; p = 0.063).

Association of 24-Hour Ambulatory BP and Kidney Dysfunction with the Prevalence of Lacunar Infarcts

Kidney dysfunction (CCr <60 ml/min/1.73 m^2) and higher 24-hour ambulatory BP (≥130/80 mm Hg) were independently associated with a high prevalence of lacunar infarcts (fig. 1). The combination of kidney dysfunction and high BP was related to a remarkably high prevalence of lacunar infarcts (OR = 2.64; 95% confidence interval, CI = 1.51–4.61; p < 0.0006). Even when 24-hour ambulatory BP values were within the normal range (<130/80 mm Hg), kidney dysfunction was associated with a high prevalence of lacunar infarcts (OR = 1.62; 95% CI = 1.01–2.59; p < 0.05). Kidney dysfunction and 24-hour ambulatory BP category (high BP = 1, normal BP = 0) had an additive effect on lacunar infarcts (interaction p = 0.25). There were no significant interactions between 24-hour ambulatory BP level and CCr <60 ml/min/1.73 m^2 for the prevalence of lacunar infarcts either (interaction p = 0.69).

Kidney Dysfunction and WMH

On univariate analysis of the association between kidney dysfunction and WMH (table 3), a higher WMH grade was associated with male sex, advanced age, 24-hour ambulatory BP, antihypertensive medication, history of heart disease, serum creatinine, CCr levels and CCr <60 ml/min/1.73 m^2 (table 3). However, on multiple logistic regression analysis, WMH lost its significance for both a 1-SD decrease in CCr and CCr <60 ml/min/1.73 m^2 (p > 0.11).

Discussion

In the present cross-sectional study, kidney dysfunction was significantly associated with the prevalence of silent lacunar infarcts and WMHs in a comparatively large general population. On univariate analysis, CCr levels and CCr <60 ml/min/1.73 m^2 were associated with lacunar infarcts. The association between CCr <60 ml/min/1.73 m^2 and lacunar infarcts remained statistically

significant even after adjustment for cardiovascular risk factors, including 24-hour ambulatory BP. Conversely, only on univariate analysis were WMHs associated with CCr levels and CCr <60 ml/min/1.73 m^2.

The relationship between renal function and lacunar infarcts was previously reported in clinical studies that examined a small number of patients [7, 30]. Kobayashi et al. [7] investigated the prevalence of lacunae in 51 primary CKD patients (43.1% women; mean age 52.7 years) and 80 patients with essential hypertension with normal renal function (41.2% women; mean age 57.2 years), and they found that decreased renal function was statistically associated with silent lacunar infarcts. Nakatani et al. [30] reported that renal failure increased the prevalence of asymptomatic cerebral infarction in 123 hemodialysis patients (35.0% women; mean age 55.6 years). In the present study, a larger number of participants (n = 1,008; 67.3% women; 66.4 ± 5.7 years) from a general population was examined, and the results are in line with these previous studies of CKD patients [7, 30] even after adjustment for various cardiovascular risk factors, including 24-hour ambulatory BP. To the best of our knowledge, this is the first study to demonstrate the association between kidney dysfunction and the prevalence of lacunar infarcts in the general population.

The present study indicated that ambulatory BP values are more closely associated with silent lacunar infarcts and WMHs than with casual BP at one visit. This result is consistent with previous studies [14–17] that reported that 24-hour ambulatory BP was more strongly correlated with target organ damage than casual BP. The 24-hour ambulatory BP and kidney dysfunction were independently associated with the prevalence of lacunar infarcts. The combination of kidney dysfunction and hypertension was related to a remarkably high prevalence of lacunar infarcts, and even in normotensive patients, the risk was significantly increased when there was kidney dysfunction (fig. 1). In line with a previous study [3], our study showed the additional effect of the combined association of 24-hour ambulatory BP and CCr <60 ml/min/1.73 m^2 for the risk of lacunar infarcts (fig. 1). On the other hand, in the Suita study [9], the effect was not additional but synergistic. Differences among study populations might have played a role in the inconsistent interaction of BP. The present study population (67.3%) and that of the previous study [3] (62.0%) consisted mainly of women. Moreover, among the Suita population [9], the synergistic interaction of BP was observed only in men (p = 0.03) but not in women (p = 0.90).

Lammie et al. [31] suggested that renal insufficiency may contribute to the pathogenesis of cerebral small-vessel disease, such as lacunar infarcts, enhancing the permeability of small vessels. However, the exact mechanism by which kidney dysfunction might contribute to lacunar infarcts remains unknown. Glomerulosclerosis and renal arteriosclerosis depress the glomerular filtration rate [32], and they are also closely associated with generalized arteriosclerosis [33]. Then, decreased renal function, indicated by depression of the glomerular filtration rate, is a marker of generalized vascular disease. Because atherosclerosis may be one of the underlying mechanisms of lacunar infarcts [34], it is possible that decreased renal function is associated with lacunar infarcts as a marker of generalized vascular disease.

The relationship between kidney dysfunction and lacunar infarcts remained significant after adjustment for various traditional cardiovascular risk factors, including 24-hour ambulatory BP. This suggests that there might be other confounding factors among them. Several studies [7, 13, 35–41] indicated some nontraditional cardiovascular risk factors that could be associated with renal dysfunction and with lacunar infarcts. In CKD patients, homocysteine, lipoprotein(a), and fibrinogen levels were increased [35]. Renal dysfunction was associated with low-grade inflammation, endothelial dysfunction [36] and oxidative stress. [37]. Meanwhile, it has been reported that the prevalence of silent lacunar infarcts and WMHs is associated with homocysteine [38, 39], low-density lipoprotein 3 [40], plasma fibrinogen levels [13] and endothelial dysfunction [41]. Moreover, hyperhomocysteinemia and increased lipoprotein(a) levels were associated with the development of lacunar infarcts in CKD patients [7]. Therefore, these nontraditional cardiovascular risk factors [7, 13, 35–40] could mediate the relationship between CKD and lacunar infarcts.

Previous studies [6, 42] reported the relationship between renal function and WMHs. Predialysis CKD patients have significantly more WMHs than subjects with normal renal function [6]. In a general urban population in the USA, CKD is associated with a greater WMH burden [42]. In the present study, however, there was no association between kidney dysfunction and WMHs after adjustment for various cardiovascular risk factors. The different results might be attributable to differences in residence (urban or rural), ethnicity and BP measurement. The previous studies [6, 42] adopted casual BP for the diagnosis of hypertension [42] or for adjustment [6]. Conversely, in the present study, 24-hour ambulatory BP, which is known to provide more reproducible informa-

tion and to be more closely correlated with target organ damage [14–17] than casual BP, was used for adjustment. Therefore, it is possible that adjustments for the effect of BP on WMH were inadequate in previous studies.

There are some methodological issues to address. First, marked differences exist in the epidemiological studies of cerebrovascular disease between Asian and Western countries. Further research in other ethnic and cultural populations is needed to confirm the generalizability of our findings. Additionally, elderly subjects made up the majority of the Ohasama participants. To some extent, this imbalance in the age distribution might limit the generalizability of the current findings. Second, serum creatinine levels were measured using two different methods (i.e. the Jaffe assay and the enzymatic assay). However, measurement methods did not significantly interact with the association between kidney dysfunction and lacunar infarcts (p for interaction = 0.3). Furthermore, the measurement method was used as a covariate in the multivariate model (Jaffe assay = 1, enzymatic assay = 0), and the results were consistent (data not shown). Third, we did not have data about initial antihypertensive medication and the duration of hypertension. In addition, measurements of 24-hour ambulatory BP and casual BP are only coarse approaches for identifying the effect of cumulated vascular risk factors and their treatment over many years. Therefore, all these data can be considered at the arterial level as being approximations and cannot be considered as explaining all of the variance in target organ damage. Moreover, statistical adjustment does not necessarily exclude all of the confounding effects. Finally, we could not perform CCr tests because we did not collect 24-hour urine samples.

In conclusion, the present study demonstrated that kidney dysfunction as assessed by CCr is closely associated with lacunar infarcts, suggesting that kidney dysfunction in the elderly is an independent risk factor or predictor of silent lacunar infarcts.

Acknowledgements

This study was supported in part by: Grants for Scientific Research (15790293, 16590433, 17790381, 18390192, 18590587, 19590929 and 19790423) from the Ministry of Education, Culture, Sports, Science and Technology, Japan; Grants-in-Aid [H17-Kenkou-007, H18-Junkankitou (Seishuu)-Ippan-012 and H20-Junkankitou (Seishuu)-Ippan-009, 013] from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Grants-in-Aid for Japan Society for the Promotion of Science fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477 and 20.54043); Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; Uehara Memorial Foundation; Takeda Medical Research Foundation; National Cardiovascular Research Grants, and Biomedical Innovation Grants.

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Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2011;31:329–337
DOI: 10.1159/000322599

Received: May 7, 2010
Accepted: Novemer 2, 2010
Published online: January 7, 2011

Association of Arterial Stiffness with Silent Cerebrovascular Lesions: The Ohasama Study

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Key Words

Arterial stiffness · Silent cerebrovascular lesions · Lacunar infarct · White matter hyperintensity · Ambulatory blood pressure

Abstract

Background: Arterial stiffness is a risk factor for symptomatic stroke, and is associated with symptomatic cerebral infarction and cognitive impairment. Hence, we hypothesized that arterial stiffness would be a significant determinant of silent cerebrovascular lesions. ***Methods:*** The subjects were 363 individuals without symptomatic cerebrovascular lesions who had their arterial stiffness assessed by brachial-ankle pulse wave velocity (baPWV) measurement. The subjects were classified into two groups by the presence or absence of lacunar infarcts, as well as into three groups by grade of white matter hyperintensity (WMH). baPWV was compared among these groups. ***Results:*** Eighty-six subjects had lacunar infarcts. Of 138 subjects with WMHs, 102 were classified as having grade 1 and 36 as having grade 2 or 3 WMHs. baPWV was significantly higher in subjects with lacunar infarcts than in those without (17.3 ± 0.3 vs. 16.4 ± 0.2 m/s). baPWV tended to increase with higher WMH grade (16.2 ± 0.2, 16.9 ± 0.3, and 17.8 ± 0.5 m/s in grade 0, 1, and 2 or 3, respectively) after adjustments for confounding factors. The adjusted odds ratio (OR) for lacunar infarcts in subjects with middle-tertile baPWV was significantly higher (OR, 2.37; 95% confidence interval, CI, 1.10–5.11) and the OR in subjects with the highest-tertile baPWV tended to be higher (OR 2.26; 95% CI 0.99–5.45) compared with the lowest-tertile baPWV. The adjusted OR for WMH tended to increase with increased baPWV. ***Conclusions:*** Arterial stiffness appeared to be associated with the presence of a lacunar infarct and WMH, independently of the risks for other cerebrovascular diseases.

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Introduction

Silent cerebrovascular lesions (SCLs) such as lacunar infarcts and white matter hyperintensities (WMHs) are frequently observed on magnetic resonance imaging (MRI) scans in elderly individuals. SCLs are evidence of microvascular damage and constitute an independent predictor of the risk for symptomatic stroke [1, 2]; such lesions are associated with cognitive impairment or dementia [3].

Arterial stiffness can be assessed noninvasively by the measurement of pulse wave velocity (PWV), a simple and reproducible method [4, 5]. In addition to conventional carotid-femoral PWV measurements, brachial-ankle PWV (baPWV) measurements can provide useful information on arterial stiffness [6, 7], particularly in large populations [8] because the method is convenient. In many previous longitudinal studies, arterial stiffness was an independent predictor of all-cause and cardiovascular mortality [9–12]. Some studies also showed that arterial stiffness was an independent predictor of the risk for symptomatic stroke [13] and was associated with symptomatic cerebral infarction [14] and cognitive impairment [15, 16].

For these reasons, we hypothesized that arterial stiffness would be a significant determinant of SCLs, which lead to symptomatic stroke, cognitive impairment or dementia. Thus, the aim of the present study was to explore the association between arterial stiffness based on PWV and SCLs in the general population.

Materials and Methods

Study Population

The present study was part of a longitudinal observational study of subjects who have been participating in a blood pressure (BP) measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. The socioeconomic and demographic characteristics of this region and the full details on the project have been described previously [17]. No specific inclusion or exclusion criteria were applied except for the exclusion of subjects whose ambulatory BP could not be measured, that is subjects who worked in cities away from home, were in hospital, were aged and bedridden or worked outside Ohasama throughout the week. The present analysis was based on a health survey of general adult residents of Ohasama, Japan, aged ≥50 years [18]. Of 1,648 individuals who underwent the health examination, 572 underwent both baPWV measurements and MRI. Subjects with a history of previous stroke or transient ischemic attack (n = 31) were excluded from the present analysis. Another 178 individuals with missing anthropometric measurements, biomedical tests, 24-hour ambulatory BP monitoring, and medical questionnaires were excluded as well. Eventually, 363 individuals (mean age 65.9 ± 6.3 years; 101 men, 262 women) were included in the present study.

The study protocol was approved by the institutional review board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government. Informed consent was obtained from each subject.

Magnetic Resonance Imaging

As previously reported [19–21], MRI scans were obtained using a 0.5-tesla superconducting magnet. The brain was imaged in the axial plane in 10-mm-thick slices, and T_1- and T_2-weighted images were collected. A lacunar infarct was defined as an area of low signal intensity measuring ≤15 and ≥3 mm on T_1-weighted images and an area of high signal intensity on T_2-weighted images. These criteria were chosen to reduce the risk of misclassification due to dilated perivascular spaces. High signal intensity areas only on the T_2-weighted images were not counted as lacunar infarcts. WMHs were defined as hyperintensities only on T_2-weighted images, and were graded according to Fazekas et al. [22] as follows: absent (grade 0), punctate (grade 1), early confluent (grade 2) and confluent (grade 3). Small caps (<5 × 10 mm) on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal. Larger caps (≥5 × 10 mm) were considered grade 2. SCLs were defined as the presence of a lacunar infarct, WMHs of grade 1 or more, or any combination of these findings [19, 21]. A neurosurgeon and four technical experts directed by the neurosurgeon independently evaluated the MRI findings in a blinded manner. In case of disagreement, a consensus reading was done. Both intrareader and interreader evaluations (n = 111) showed good agreement. κ-Statistics ranged between 0.68 and 0.86 for lacunar infarcts and between 0.72 and 0.86 for WMHs.

Measurement of Arterial Stiffness

baPWV, a measure of aortic stiffness, was assessed using an automatic device (Form PWV/ABI; Colin Co., Ltd., Komaki, Japan); the measurements were done on subjects in the supine position after at least 5 min of rest. The methodology for measuring baPWV using this device has been described previously [6, 8, 23]. Briefly, pressure waveforms of the brachial and tibial arteries were simultaneously recorded by placing occlusion cuffs connected to a plethysmographic sensor around both the arms and ankles. The time delay (T) of the two waveforms was measured between the feet. The path lengths from the suprasternal notch to the arm (Lb) and from the suprasternal notch to the ankle (La) were automatically calculated by individual height. baPWV was calculated using the following equation: baPWV = (La – Lb)/T (m/s). baPWV was measured for an average of 10 s, and the right-arm to right-ankle baPWV was used. The validity and reproducibility of this method have been reported in the literature [8]; the intraobserver repeatability coefficient is 0.87, and the interobserver repeatability coefficient is 0.98. The rationale for using baPWV rather than the carotid-femoral PWV was based on the finding that baPWV closely correlates with aortic PWV determined by invasive and noninvasive methods [7, 8, 23].

Ambulatory BP Monitoring

Ambulatory BP monitoring was performed with the ABPM-630 (Nippon Colin, Komaki, Japan), a fully automatic cuff-oscillometric device, which was preset to measure BP every 30 min.

Table 1. Clinical characteristics of the subjects classified by the presence or absence of lacunar infarcts

	Lacunar infarct		p
	yes (n = 86)	no (n = 277)	
Age, years	68.6 ± 6.4	65.0 ± 6.1	<0.001
Sex, men/women	32/54	69/208	0.03
BMI, kg/m^2	23.2 ± 3.2	24.2 ± 2.9	0.008
24-hour SBP, mm Hg	125.0 ± 11.6	121.3 ± 11.3	0.009
24-hour DBP, mm Hg	72.3 ± 6.7	71.2 ± 6.7	0.15
24-hour PP, mm Hg	52.6 ± 7.1	50.1 ± 6.9	0.004
24-hour MAP, mm Hg	89.9 ± 8.0	87.9 ± 7.9	0.04
24-hour HR, beats/min	67.6 ± 8.1	67.9 ± 6.4	0.73
baPWV, m/s	18.0 ± 3.5	16.1 ± 2.9	<0.001
Total cholesterol, mg/dl	208.1 ± 32.6	207.1 ± 30.8	0.80
HDL cholesterol, mg/dl	58.0 ± 13.7	58.2 ± 14.8	0.90
Triglycerides, mg/dl	140.0 ± 123.4	132.3 ± 82.3	0.53
HbA_{1c}, %	5.37 ± 0.7	5.30 ± 0.5	0.08
Antihypertensive medication, %	50.0	31.4	0.002
Medication for diabetes mellitus, %	7.0	1.8	0.02
Medication for hyperlipidemia, %	9.3	7.9	0.69
Past history of heart disease, %	10.5	7.6	0.40
Smoking, %	15.1	7.9	0.049
Alcohol consumption, %	36.0	28.9	0.21

BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; HR = heart rate; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; HbA_{1c} = hemoglobin A_{1c}.

The device has been validated [24] and meets the criteria of the Association for the Advancement of Medical Instrumentation [25]. An ambulatory BP monitoring device was fitted by well-trained public health nurses, who visited each participant on a weekday morning and detached the monitor the next morning. Mean 24-hour values for ambulatory BP measurements were calculated for each individual. Pulse pressure (PP) and mean arterial pressure (MAP) were calculated according to the following formulae: PP = systolic BP (SBP) – diastolic BP (DBP) and MAP = DBP + PP/3.

Baseline Examination

Blood samples were collected to determine plasma total cholesterol, high-density lipoprotein cholesterol, hemoglobin A_{1c} (HbA_{1c}), serum creatinine and glucose levels on the day of the baPWV measurements. Information on current smoking status, alcohol intake, past history of heart disease and medication for hypertension, hypercholesterolemia and diabetes was taken from questionnaires sent to the subjects before the examinations and confirmed by trained staff on the day of the baPWV measurements.

Data Analysis

Subjects were classified into two groups by the presence or absence of lacunar infarcts, three groups by WMH grade (grade 0, grade 1, and grade 2 or 3), and two groups by the presence or absence of SCLs. The characteristics of the subjects were compared by univariate analysis using the χ^2 test for categorical data and Student's t test or analysis of variance for continuous data. Then, analysis of covariance was performed to obtain a multivariate comparison of baPWV between two groups by the presence or absence of lacunar infarcts, among three groups by WMH grade and between two groups by the presence or absence of SCLs using covariates such as age, sex, body mass index, past history of heart disease, total cholesterol, HbA_{1c}, antihypertensive medication, medication for hyperlipidemia, medication for diabetes mellitus, smoking, alcohol consumption, and 24-hour SBP. In the analysis of WMH, the grade 0 group was treated as the reference group and analysis of covariance was repeated. Finally, three models using different sets of explanatory variables were created and multivariate logistic regression analysis was performed to evaluate the likelihood of a lacunar infarct, WMHs and SCLs in relation to 24-hour SBP and baPWV. Intermediate models were adjusted for age and sex. Fully adjusted models were adjusted for age, sex, body mass index, past history of heart disease, total cholesterol, HbA_{1c}, antihypertensive medication, medication for hyperlipidemia, medication for diabetes mellitus, smoking and alcohol consumption. In addition to these variables, model 1 and model 2 included 24-hour SBP and baPWV, independently. Model 3 included both 24-hour SBP and baPWV, simultaneously. All statistical analyses were performed using SPSS software, version 11.0 (SPSS Inc., Chicago, Ill., USA). Values are expressed as means ± SD. A two-tailed $p < 0.05$ was considered significant.

Results

The clinical characteristics of the subjects classified by the presence or absence of lacunar infarcts, WMH grade and the presence or absence of SCLs are displayed in tables 1–3, respectively. Of the 363 subjects, 86 (24%) had 1 or more lacunar infarcts on the MRI scan. Subjects with lacunar infarcts were significantly older and were more likely to be taking antihypertensive medications, have diabetes mellitus, smoke, and have lower body mass indexes, higher 24-hour ambulatory BPs (SBP, MAP and PP), and higher baPWVs (table 1). The prevalence of WMHs was 62, 28, and 10% in the grade 0, 1, and 2 or 3 groups, respectively. Age, frequency of antihypertensive medication, past history of heart disease, 24-hour ambulatory BP (SBP and PP) and baPWV increased with increased WMH grade (table 2). Subjects with SCLs (45.2%) were significantly older and were more likely to be taking antihypertensive medications and to have lower body mass indexes, higher 24-hour ambulatory SBPs and PPs and higher baPWVs (table 3).

As shown in figure 1, even after adjustment, baPWVs were significantly higher in subjects with lacunar infarcts than in those without (17.3 ± 0.3 vs. 16.4 ± 0.2 m/s) (fig. 1a). baPWVs tended to increase with higher WMH grade (16.2 ± 0.2, 16.9 ± 0.3, and 17.8 ± 0.5 m/s in the grade 0, 1, and 2 or 3 groups, respectively) (fig. 1b). These

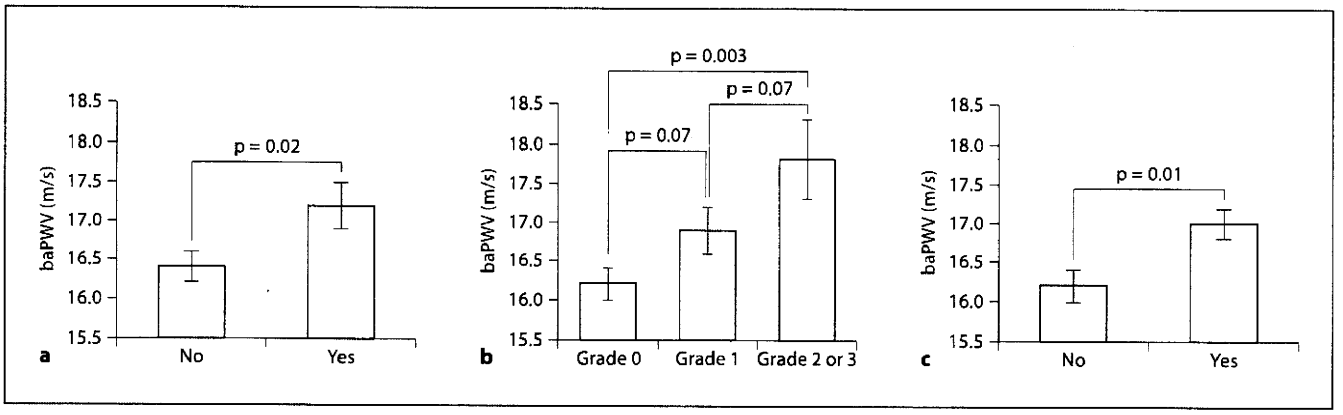

Fig. 1. Multivariate comparison of baPWV between the two groups classified by the presence or absence of lacunar infarcts (**a**), among the three groups classified by grade of WMH (**b**), and between the two groups classified by the presence or absence of SCLs (**c**). baPWV was adjusted for age, sex, body mass index, past history of heart disease, total cholesterol, hemoglobin A_{1c}, antihypertensive medication, medication for hyperlipidemia, medication for diabetes mellitus, smoking, alcohol consumption, and 24-hour ambulatory SBP using analysis of covariance.

Table 2. Clinical characteristics of the subjects classified by WMH grade

	WMH grade			p
	0	1	2 or 3	
n	225	102	36	
Age, years	63.8 ± 5.7	68.6 ± 6.0	70.6 ± 5.9	<0.001
Sex, men/women	65/160	28/74	8/28	0.71
BMI, kg/m^2	24.2 ± 2.9	23.5 ± 3.1	23.8 ± 2.8	0.17
24-hour SBP, mm Hg	121.1 ± 11.7	123.3 ± 10.5	125.6 ± 11.9	0.049
24-hour DBP, mm Hg	71.2 ± 6.7	72.0 ± 6.4	71.7 ± 7.5	0.58
24-hour PP, mm Hg	50.0 ± 7.0	51.3 ± 6.6	53.9 ± 6.9	0.005
24-hour MAP, mm Hg	87.8 ± 8.0	89.1 ± 7.4	89.7 ± 8.6	0.24
24-hour HR, beats/min	67.9 ± 6.7	67.3 ± 6.9	68.8 ± 7.6	0.52
baPWV, m/s	15.8 ± 2.7	17.4 ± 3.2	19.0 ± 3.9	<0.001
Total cholesterol, mg/dl	206.7 ± 31.1	207.4 ± 32.8	210.6 ± 27.8	0.79
HDL cholesterol, mg/dl	57.3 ± 14.7	60.3 ± 14.8	57.0 ± 11.4	0.21
Triglycerides, mg/dl	140.7 ± 105.1	122.3 ± 74.3	125.7 ± 55.8	0.22
HbA_{1c}, %	5.3 ± 0.5	5.4 ± 0.6	5.4 ± 0.5	0.58
Antihypertensive medication, %	28.4	43.1	61.1	<0.001
Medication for diabetes mellitus, %	2.2	3.9	5.6	0.46
Medication for hyperlipidemia, %	7.6	8.8	11.1	0.75
Past history of heart disease, %	6.2	8.8	19.4	0.03
Smoking, %	9.8	8.8	11.1	0.92
Alcohol consumption, %	30.7	30.4	30.6	0.999

BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; HR = heart rate; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; HbA_{1c} = hemoglobin A_{1c}.