Original Article

Association between Carotid Hemodynamics and Asymptomatic White and Gray Matter Lesions in Patients with Essential Hypertension

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The aim of this study was to clarify the magnitude of common carotid artery (CCA) structural and hemodynamic parameters on brain white and gray matter lesions in patients with essential hypertension (EHT). The study subjects were 49 EHT patients without a history of previous myocardial infarction, atrial fibrillation, diabetes mellitus, impaired glucose tolerance, chronic renal failure, symptomatic cerebrovascular events, or asymptomatic carotid artery stenosis. All patients underwent brain MRI and ultrasound imaging of the CCA. MRI findings were evaluated by periventricular hyperintensity (PVH), deep and subcortical white matter hyperintensity (DSWMH), and état criblé according to the Japanese Brain dock Guidelines of 2003. Intima media thickness (IMT), and mean diastolic (V_d) and systolic (V_s) velocities were evaluated by carotid ultrasound. The V_d/V_s ratio was further calculated as a relative diastolic flow velocity. The mean IMT and max IMT were positively associated with PVH, DSWMH, and état criblé (mean IMT: ρ=0.473, 0.465, 0.494, p=0.0007, 0.0014, 0.0008, respectively; max IMT: ρ=0.558, 0.443, 0.514, p=0.0001, 0.0024, 0.0004, respectively). V_d/V_s was negatively associated with état criblé (ρ=−0.418, p=0.0038). Carotid structure and hemodynamics are potentially related to asymptomatic lesions in the cerebrum, and might be predictors of future cerebral vascular events in patients with EHT. (*Hypertens Res* 2005; 28: 797–803)

***Key Words*: essential hypertension, asymptomatic lesions, white matter lesions, deep gray matter lesions, Doppler ultrasound**

Introduction

Recently, MRI studies have rendered it possible to assess asymptomatic cerebral white matter lesions and basal ganglial change. White matter lesions are generally considered to be associated with a high risk of stroke (*1–3*). Numerous studies have demonstrated that age and hypertension are highly and independently correlated with white matter lesions, periventricular hyperintensity (PVH) and subcortical white matter hyperintensity (DSWMH) (*4–7*). The incidence of a type of ganglial gray matter lesion, état criblé, has also been reported to be increased with aging and has been associated with hypertension (*8*).

Prospective population-based studies in Europe and the United States have reported that carotid intima-media thickness (IMT) and plaques diagnosed by ultrasound (US) imaging are positively associated with a subsequent occurrence of stroke (*9–12*). The aim of the current study was to clarify the relationship between the hemodynamics and the structure of the common carotid artery (CCA) and white and gray matter lesions in the brain of patients with essential hypertension (EHT).

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Table 1. Clinical Characteristics of Participants

N (male/female)	49 (27/22)
Age (years)	58.7±15.6
BMI (kg/m^2)	25.2±4.6
SBP (mmHg)	153±23
DBP (mmHg)	87±15
Pulse pressure (mmHg)	65±19
Pulse (beats/min)	74±12
Mean 24-h SBP (mmHg)	140±16
Mean 24-h DBP (mmHg)	85±16
TC (mg/dl)	203±36
HDL-C (mg/dl)	52.9±15.8
FBG (mg/dl)	93.1±13.5
Smoking (yes/no)	24/25

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose. Values are mean±SD.

Table 2. Vascular Wall and Hemodynamic Characteristics of Common Carotid Artery in Participants

Mean IMT (mm)	0.78±0.17
Max IMT (mm)	0.90±0.23
Plaque number	0.41±0.78
D_s (mm)	7.06±0.93
D_d (mm)	6.57±0.92
Arterial strain (%)	6.97±3.16
β	10.2±7.6
V_s (cm/s)	41.6±12.8
V_d (cm/s)	19.7±7.1
V_d/V_s	0.47±0.07
PI	1.92±0.50
RI	0.76±0.07

IMT, intima-media thickness; D_s, end-systolic diameter; D_d, end-diastolic diameter; β, carotid arterial stiffness index; V_s, mean systolic velocity; V_d, mean diastolic verocity; V_d/V_s, relative diastolic flow velocity; PI, pulsatility index; RI, resistive index. Values are mean±SD.

Methods

Study Population

Forty-nine hospitalized patients with EHT participated in this study. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, averaged by a three-fold determination and measured using a brachial sphygmomanometer while the patient was sitting down. The participants were recruited from consecutive cases that were admitted to Ehime University Hospital for the evaluation of hypertension. Patients with congestive heart failure, previous myocardial infarction, atrial fibrillation, diabetes mellitus (fasting blood glucose [FBG] level >126 mg/dl), impaired glucose tolerance (FBG level <126 mg/dl, and oral glucose tolerance test [OGTT] 2-h data >200 mg/dl), chronic renal failure (serum creatinine ≥3.0 mg/dl), or history of stroke were excluded from the study. All subjects received a diet containing 7 g of NaCl per day, and all medications were discontinued on admission. All procedures were performed after a stabilization period of at least 2 weeks. Informed consent was obtained from each subject for blood sampling and ultrasound evaluation. All patients agreed to undergo an MRI study of the brain.

Blood Sampling

Measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and FBG were carried out using an automatic analyzer (model TBA-60S; Toshiba Inc., Tokyo, Japan).

Intermittent 24-h Ambulatory Blood Pressure Monitoring (ABPM)

Twenty-four-hour SBP and DBP were measured by a cuff-oscillometric method using an FB-250 oscillometer (Fukuda Denshi Co., Tokyo, Japan). Blood pressure was measured every 30 min from 6:00 AM to 10:00 PM and every 60 min from 10:00 PM to 6:00 AM of the following day.

Ultrasound Evaluation

Ultrasound evaluation of the CCA was performed with an SSD-2000 (Aloka Co., Tokyo, Japan) using a 7.5-MHz probe equipped with a Doppler system, as described previously (*13*). After the subjects had rested in the supine position for at least 10 min with the neck in slightly hyperextended position, we performed optimal bilateral visualization of the carotid artery. Based on multiple visualizations, plaque formation was identified as the presence of a wall thickening that was at least 50% greater than the thickness of the surrounding wall (*13*, *14*). The IMT of the far wall was measured in the CCA at both 1 and 2 cm proximal to the bulb from the anterior, lateral, and posterior approaches, and then was averaged to obtain the mean IMT values (*13*, *14*). No measurements were carried out at the level of discrete plaques.

Two-dimensional guided M-mode tracing of the right CCA at a point 2 cm proximal to the bulb was recorded simultaneously by both electrocardiogram and phonocardiogram. M-mode images were obtained in real time using a frame grabber. The axial resolution of the M-mode system was 0.1 mm. The internal diameter of the CCA at end-diastole (D_d) and peak-systole (D_s) was determined by continuous tracing of the intimal-luminal interface of the near and far walls of the

Table 3. Rank Correlation Coefficients (Risk Factors)

	PVH	DSWMH	État criblé
Age	0.643‡	0.558†	0.591‡
BMI	−0.188	−0.182	−0.053
SBP	0.194	0.071	0.112
DBP	−0.238	−0.273	−0.302
PP	0.446†	0.321	0.348
Mean 24-h SBP	0.115	0.074	0.092
Mean 24-h DBP	−0.190	−0.144	−0.292
TC	−0.016	−0.073	−0.127
HDL-C	0.157	0.158	0.169
FBG	0.080	0.138	0.141
Smoking	0.328	−0.142	−0.171

PVH, periventricular hyperintensity; DSWMH, deep subcortical white matter hyperintensity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose. †$p<0.01$, ‡$p<0.001$.

Table 4. Rank Correlation Coefficients (Ultrasound Parameters)

	PVH	DSWMH	État criblé
Mean IMT	0.473†	0.465†	0.494†
Max IMT	0.558‡	0.443*	0.514†
Plaque number	0.356	0.300	0.247
D_s	0.210	0.091	0.324
D_d	0.203	0.102	0.344
Arterial strain	−0.104	−0.135	−0.328
β	0.291	0.290	0.345
V_s	−0.071	−0.049	−0.192
V_d	−0.193	−0.131	−0.353
V_d/V_s	−0.309	−0.220	−0.418†
PI	−0.166	−0.170	−0.010
RI	0.113	0.055	0.254

IMT, intima-media thickness; D_s, end-systolic diameter; D_d, end-diastolic diameter; β, carotid arterial stiffness index; V_s, mean systolic velocity; V_d, mean diastolic verocity; V_d/V_s, relative diastolic flow velocity; PI, pulsatility index; RI, resistive index. *$p<0.05$, †$p<0.01$, ‡$p<0.001$.

CCA in three cycles, and the results were averaged (*13*). The cross-sectional distensibility coefficient (CSDC) and the carotid arterial stiffness index (β) were calculated using the following formulae (*12*, *15*).

$$\mathrm{CSDC} = (D_s^2 - D_d^2)/[D_d^2 \times (\mathrm{SBP} - \mathrm{DBP})]$$

$$\beta = \ln (\mathrm{SBP}/\mathrm{DBP}) \times [D_d/(D_s - D_d)]$$

Doppler evaluation was performed by scanning the right CCA in the anterior projection. Under guidance using color flow mapping, the sample volume was located at the center of the vessel. Flow velocity-time integrals of the systolic and diastolic phases were computed automatically by electronic integration of the instantaneous flow velocity curves, and further systolic (V_s) to diastolic flow velocity (V_d) values were calculated to assess the hemodynamics in the CCA (*12*).

MRI

MRI was performed in all patients with a superconducting magnet with a main field strength of 1.5 T in order to evaluate the asymptomatic cerebrovascular damage. The MRI findings were classified according to the following parameters: PVH, DSWMH, and état criblé, according to the Japanese Brain-dock Guidelines 2003 (*15*).

PVH and DSWMH were defined as exhibiting high intensity lesions by T_2-weighted and proton density images or by fluid-attenuated inversion recovery (FLAIR) (*16*, *17*), and low intensity determined by T_1-weighted images. État criblé was assessed at the basal ganglial level, as high-intensity signals evaluated by T_2-weighted images (*18*).

PVH exhibits white matter hyperintensities (WMHIs) in contact with the ventricular wall. PVH were further classified as follows. 0: absent or only a "rim"; 1: limited lesion-like "caps"; 2: irregular "halo"; 3: irregular margins and extension into the deep white matter; 4: extension into the deep white matter and the subcortical portion.

DSWMH indicates WMHIs that are separated from the ventricular wall by a strip of normal-appearing white matter; these WMHIs were situated in the deep white matter and were sparsely present in the subcortical U-fiber region. DSWMH were further classified as follows. 0: absent; 1: ≤3 mm, small foci and regular margins; 2: ≥3 mm, large foci; 3: diffusely confluent; 4: extensive changes in the white matter.

État criblé was found to be <3 mm, with small focal points and regular margins in the basal ganglia. État criblé was further classified as follows. 0: absent; 1: 1–5 dots; 2: 6–10 dots; 3: ≥11 dots.

A lacuna was defined as an area of low signal intensity ≥3 mm and ≤15 mm by T_1-weighted proton density images, or an area of high intensity by T_2-weighted proton density images or FLAIR.

One of the present authors (M.K.) interpreted all of the MRI in a manner blinded with respect to the clinical status of the subjects.

Statistical Analysis

All values are expressed as the means±SD. Spearman's rank correlation coefficient was used to test the association. The Kruskal-Wallis test was used to compare differences among groups. Stepwise regression analysis was used to evaluate the independent parameters for PVH, DSWMH, and état criblé. Values of $p<0.05$ were considered to be statistically significant.

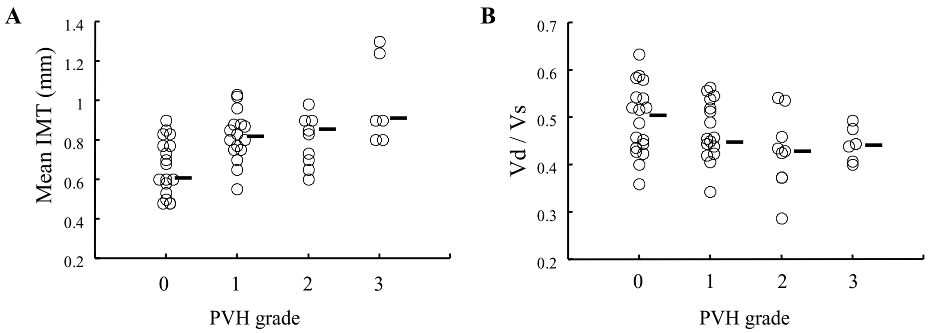

Fig. 1. *The relationship between PVH grades and IMT (A) and relative diastolic velocity (V_d/V_s) (B). PVH grades were positively correlated with mean IMT. IMT, intima-media thickness; PVH, periventricular hyperintensity; ▬, mean values of mean IMT and* V_d/V_s*.*

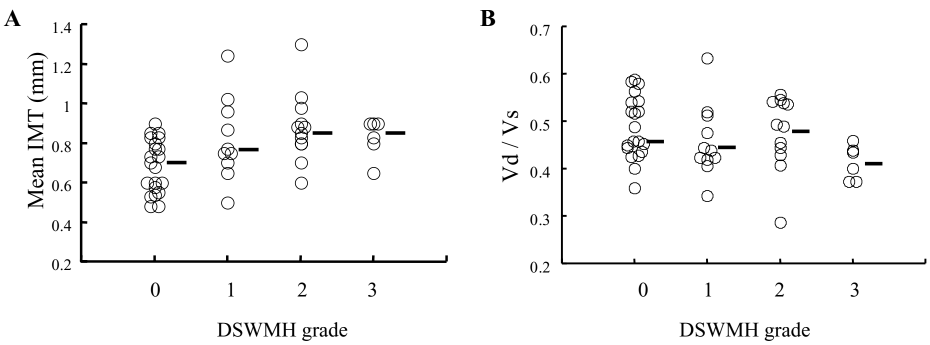

Fig. 2. *The relationship between DSWMH grades and IMT (A) and relative diastolic velocity (B). DSWMH was positively correlated with mean IMT. DSWMH, deep and subcortical white matter hyperintensity, ▬, mean values of mean IMT and* V_d/V_s*.*

Results

Patient Characteristics

Table 1 summarizes the characteristics of all hypertensive subjects included in the present study, and the hemodynamics and structure of CCA are summarized in Table 2.

Rank Correlation Coefficients between Risk Factors and MRI Findings

The numbers of patients with PVH grades 0, 1, 2, 3, and 4 were 18, 16, 9, 6, and 0, respectively. DSWMH grades 0, 1, 2, 3, 4 were observed in 21, 10, 12, 6, and 0 patients, respectively. The état criblé grades 0, 1, 2, and 3 were observed in 16, 20, 8, and 5 patients, respectively. The relationships between each of age, SBP, DBP, pulse pressure (PP) and TC and each of PVH, DSWMH, and état criblé are summarized in Table 3. Age was positively associated with PVH, DSWMH, and état criblé (ρ=0.643, 0.558, and 0.591, at p<0.0001, <0.0001, and <0.0001, respectively). PP was positively associated with PVH (ρ=0.446, p=0.002).

Rank Correlation Coefficients between US Parameters and MRI Grades

The relationships between carotid US parameters and PVH, DSWMH, and état criblé are summarized in Table 4. The mean IMT and max IMT were positively associated with PVH, DSWMH, and état criblé (mean IMT: ρ=0.473, 0.465, and 0.494, p=0.0007, 0.0014, and 0.0008, respectively; max IMT: ρ=0.558, 0.443, and 0.514, p=0.0001, 0.0024, and 0.0004, respectively). With increasing PVH grades, relative diastolic flow velocity, V_d/V_s, tends to decrease. In particular, état criblé showed a significant negative association with V_d/V_s (ρ=−0.418, p=0.0038; Figs. 1–3).

Determinant factors for PVH, DSWMH, and état criblé were analyzed by a stepwise regression analysis with age, PP, TC, mean IMT and V_d/V_s as independent variables. Age was independently associated with PVH, DSWMH and état criblé (the partial correlation coefficients were 0.606, 0.554 and 0.593; p< 0.0001, 0.0001 and 0.0001, respectively).

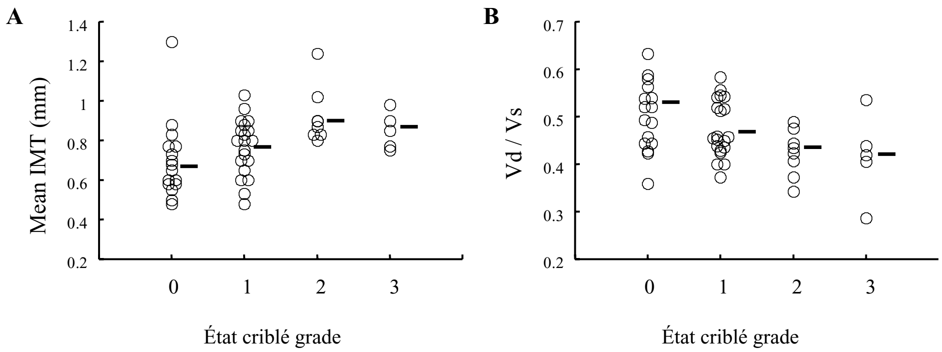

Fig. 3. *The relationship between état criblé grades and IMT (A) and relative diastolic velocity (B). The état criblé grades were positively correlated with IMT and negatively correlated with* V_d/V_s*. ▬, mean values of mean IMT and* V_d/V_s*.*

Discussion

The advent of brain imaging methods, particularly MRI, has revealed a multitude of focal, patchy, and diffuse signal changes in the cerebrum (*19–21*). There are variable visual rating scales for these lesions, but these scales are not consistent (*21*). In this study, we employed the Japanese Braindock Guidelines based on Fazekas's scale (*16*) in order to classify the incidence of PVH, DSWMH, and état criblé. The pathogenesis of cerebral white matter abnormalities, PVH, and DSWMH are sometimes described as "leukoaraiosis," and it has been reported that these features are the result of ischemic injury to the brain (*22*). Silent, small hyperintense foci of the basal ganglia and thalamus are also frequently noted on MRI. These foci are lacuna infarctions and perivascular spaces (état criblé). Lacuna and état criblé are distinguished by their size and margin type (irregular or smooth) (*23*). We determined that état criblé have the following features on MRI: high-intensity T_2-weighted images, smooth margins, and lesions of <3 mm in diameter. It has been reported that état criblé increases with the age and is associated with hypertension. Progressive arteriolosclerosis of the perforating arteries is assumed with a histopathology of état criblé, which renders cerebral tissue compressed and atrophied (*8*).

In this study, we evaluated white and deep gray matter lesions using MRI in hypertensive patients without diabetes, impaired glucose tolerance, arrhythmia, or a previous cardiovascular event. We first investigated the relationships between the MRI findings and the following atherosclerotic risk factors: age, PP, body mass index (BMI), TC and smoking. There was a strong correlation between MRI findings and age (Table 3). Previous studies (*4–7*, *24–28*) have demonstrated that age and hypertension were strongly and independently correlated with white matter lesions and état criblé. Similar to previous studies, the present study also demonstrated that age was positively related to the severity of hyperintensity changes in both the white matter and deep gray matter.

In addition, we found a positive correlation between PVH and PP. As the mechanism of PP increase, decreases in Windkessel function and increases in arterial stiffness appeared to be involved (*29*, *30*). Arterial stiffness increases SBP and reduces DBP. Increases in PP lead to decreases in diastolic blood flow to the brain (*31*, *32*). The Rotterdam Scan Study (*33*) and the Framingham Heart Study (*34*) also demonstrated that low DBP was a risk for subsequent brain infarction. Drops in DBP and increases in PP are consequences of arterial stiffening, as part of the progression of arteriolosclerosis possibly associated with PVH. In this study, PVH grade was significantly associated with PP, but DSWMH grade was not. The periventricular white matter is an arterial border zone, already marginally perfused under physiologic circumstances, which makes it especially vulnerable under a decrease of cerebral blood flow. In contrast, the subcortical white matter is better vascularized and is not an arterial watershed area (*35*, *36*). Because of this pathophysiological characteristic, PVH may be more susceptible to PP than DSWMH.

Furthermore, we evaluated the relationship between the MRI findings and the carotid US parameters. The Cardiovascular Health Study previously demonstrated strong relationships between white matter lesions and carotid IMT and stenosis (*37*). Kitamura *et al*. reported that increased IMT is a risk factor for stroke in Japanese elderly men (*38*). In the present study, PVH, DSWMH, and état criblé were positively associated with the IMT. This indicated that severity of PVH, DSWMH, and/or état criblé reflect hypertensive organ damages and might be high risk for further stroke.

We previously evaluated changes in the hemodynamics of the CCA using Doppler US (*39*, *40*). The relative diastolic flow (V_d/V_s) of the CCA in hypertensive patients with insulin resistance (IR) or left ventricular hypertrophy (LVH) is lower than that of normotensive subjects (*12*, *41*). The V_d/V_s represent the resistance of the peripheral arteries. In the current study, V_d/V_s was more strongly associated with état criblé than PVH. The white matter adjacent to the lateral ventricle walls, which is called a "watershed zone," receives from ventriculofugal vessels arising from the subependymal arteries. Poor vascularity in these parts easily causes hypoxic/ischemic injury due to the low perfusion. Pathogenesis of PVH is due to these anatomical characteristics. On the other hand, état criblé is characterized by vascular ectasia and dilated perivascular spaces, and reflects shrinkage or atrophy of the brain parenchyma around blood vessels (*35*). The état criblé may reflect the peripheral vascular resistance more strongly than PVH depending on the difference in the pathophysiological characteristics between them.

There were some limitations in this study. First, the study population was relatively small, because we excluded the patients with congestive heart failure, previous myocardial infarction, atrial fibrillation, diabetes mellitus, impaired glucose tolerance, chronic renal failure, and history of stroke. Second, we did not evaluate the maximum IMT of the internal carotid artery (ICA). In their cohort study, Kitamura *et al*. reported that the combination of CCA and ICA wall thickness was a better predictor of the risk of stroke than was CCA wall thickness alone (*38*). Further study is needed to clarify the relationship between the max IMT of ICA and asymptomatic MRI findings.

In conclusion, in patients with EHT, asymptomatic white matter hyperintensity and deep gray matter lesions were related to the severity of carotid atherosclerosis, *i.e.*, the IMT. The blood flow velocity, as estimated by the relative diastolic blood flow in the CCA, was decreased in patients with severe état criblé. Carotid structure and hemodynamics are potentially related to asymptomatic lesions in the cerebrum and may be predictors of future cerebral vascular event in patients with EHT.

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