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Diastolic blood pressure influences cerebrovascular reactivity measured by means of ^{123}I-iodoamphetamine brain single photon emission computed tomography in medically treated patients with occlusive carotid or middle cerebral artery disease

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Objective: Impaired cerebrovascular reactivity (CVR) to vasodilating agents is a predictor of the onset and prognosis of ischemic stroke. It is realized that the CVR improves or worsens when measured periodically during the clinical course in medically treated patients with occlusive cerebrovascular disease. In these patients, we investigated the possible relationship between the interval change in CVR and that in systemic blood pressure (BP). ***Methods:*** Forty-two patients (14 females and 28 males, mean age ± SD: 65.3 ± 8.8 years) with severe stenosis or occlusion of the common carotid, internal carotid, or middle cerebral arteries repeatedly underwent single photon emission computed tomography (SPECT) studies using ^{123}I-iodoamphetamine to measure cerebral blood flow (CBF) distribution and CVR at a more-than-6-month interval (mean ± SD: 18.5 ± 8.8 months). The CVR was separately estimated in cerebral hemispheres ipsilateral and contralateral to the most severe vascular lesion as the % increase in CBF after acetazolamide loading to CBF at rest. Systemic BP was measured four times at enrollment and the follow-up SPECT studies during resting and acetazolamide loading. Average BP at each SPECT study was an average of BP measurements during resting and acetazolamide loading. Interval changes in CVR were correlated with those in average systolic BP, average diastolic BP, and average mean arterial BP. ***Results:*** The interval changes in CVR were significantly correlated with those in average diastolic BP in the ipsilateral hemisphere ($y = 0.71x + 1.43$, $r^2 = 0.11$, $p < 0.05$) and in the contralateral hemisphere ($y = 0.88x - 0.46$, $r^2 = 0.16$, $p < 0.05$) but not with those in average systolic BP or average mean arterial BP. ***Conclusions:*** In medically treated patients with steno-occlusive carotid artery or middle cerebral artery lesions, the interval change in CVR to acetazolamide by means of ^{123}I-IMP SPECT was influenced by the diastolic BP at the SPECT studies. Monitoring diastolic BP is important to evaluate interval change in CVR.

Key words: blood pressure; cerebral blood flow; autoregulation; carotid artery disease; tomography, emission computed, single-photon

INTRODUCTION

CEREBROVASCULAR REACTIVITY (CVR) is a major factor for predicting ischemic stroke onset and prognosis in patients with carotid or cerebral arterial diseases. Many studies using various techniques such as transcranial Doppler (TCD),[1–3] cold-Xenon-CT,[4] or single photon emission computed tomography (SPECT)[5,6] have revealed that impaired CVR to apnea, CO_2 inhalation, or acetazolamide

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injection is an indicator of high risk of ischemic stroke onset.

The CVR is not stable in medically treated patients with carotid occlusion during follow-up periods. Impaired CVR spontaneously improved in patients with unilateral carotid artery occlusion.[7] In patients with unilateral occlusive disease of the carotid or middle cerebral artery, 40% of patients with an initially abnormal CVR showed a normalization of their CVR within 1–2 years, while 17.6% of patients with an initially normal CVR developed an abnormal CVR.[8] In a similar patient group, Ogasawara et al. found that the CVR returned to normal within a 2-year follow-up period in 4 of 9 stroke recurrence-free survivors with internal carotid artery occlusion.[6] However, the factors influencing long-term CVR change have not been precisely studied.

In an experimental study, Harper AM and Glass HI observed that CVR was reduced or absent in hypotensive dogs using Krypton-85 clearance method.[9] In healthy volunteers[10] or patients with carotid artery disease,[11] CVR assessed by measurement of cerebral blood flow velocity change with TCD in response to CO_2 elevation was significantly influenced by variability of blood pressure (BP). Based on these previous observations, we investigated the possible relationship between CVR for acetazolamide injection and systemic blood pressure in medically treated patients with carotid or middle cerebral artery steno-occlusive lesions by repeatedly quantifying CVR using ^{123}I-iodoamphetamine (IMP) SPECT.

MATERIALS AND METHODS

Patients

We retrospectively investigated 42 consecutive patients with stenoses or occlusions in cervical segments of the internal carotid artery (ICA) or the common carotid artery (CCA), as evaluated by ultrasonography, or occlusions of the intracranial ICA or M1 segment of the middle cerebral artery (MCA), as evaluated by magnetic resonance (MR) angiography. These patients repeatedly underwent ^{123}I-IMP SPECT with an acetazolamide (ACZ) challenge test during a 3-year follow-up period. Patients with aortitis, moyamoya disease, or a history of head and neck surgery were excluded. All patients gave their informed consent to participate in the study. The study was approved by the Ethics Committee of Osaka University Graduate School of Medicine.

Of the 42 patients, 14 were asymptomatic at enrollment, 13 had a history of transient ischemic attacks or amaurosis fugax, and the remaining 15 had a history of non-disabling cerebral infarction (modified Rankin scale of 0 or 1). Twenty-three of the patients had vascular occlusions in the MCA or ICA. Five of the 42 patients had tandem lesions in the ipsilateral anterior circulation, and 21 had other steno-occlusive lesions in the contralateral anterior circulation or posterior circulation. Three of the 42 patients were normotensive (systolic/diastolic BP < 140/90 mmHg), 18 were normotensive under receiving antihypertensive drugs, 5 were hypertensive (> 140/90 mmHg) but were not receiving antihypertensive drugs, and 16 were being treated for hypertension. Table 1 summarizes the patients' profiles at enrollment, including the presence of arterial diseases, concomitant diseases, and medication for normal, impaired, and improved CVR groups. The definition of each group is described below.

SPECT imaging

We used a high-performance, 4-head rotating gamma camera equipped with a low-energy, general-purpose, parallel-hole collimator with a spatial resolution of 13.0-mm full-width-at-half-maximum (Gamma View SPECT 2000H; Hitachi Medical Co., Tokyo, Japan). Data were acquired in a continuous rotating mode in reciprocal directions at 20 seconds per revolution for 66 minutes from 96 directions in a 64 × 64 matrix. The transaxial images were reconstructed with a Butterworth filter.

The CBF distribution and CVR were measured according to the split-dose method described previously.[12] Briefly, 111 MBq of ^{123}I-IMP (Nihon Medi-Physics Co., Ltd., Hyogo, Japan) was intravenously injected at the start of dynamic SPECT imaging, and 1 g of acetazolamide (ACZ) (Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan) was slowly injected intravenously over a 1-minute period 9 minutes after the initial ^{123}I-IMP injection. An additional 111 MBq of ^{123}I-IMP was injected 27 minutes after the start of imaging. Two perfusion images, resting and vasodilated, were obtained using a subtraction technique. The SPECT study at enrollment was performed at least one month after the most recent symptomatic stroke in patients with a history of TIA, amaurosis fugax, or cerebral infarction. Three patients suffered from cerebral infarctions during the follow-up period. The follow-up SPECT studies were performed one month or later after symptom onset in these patients.

Magnetic resonance imaging

The MR study was performed using a 1.5-T Signa Horizon (GE Yokogawa Medical Systems, Ltd., Tokyo, Japan) or a 1.5-T Magnetom Vision (Siemens-Asahi Medical Technologies Ltd., Tokyo, Japan). The whole brain was scanned, and 20 axial images were produced; the slice thickness was 5 mm, and the interslice gap was 2 mm. The imaging protocol consisted of a T2-weighted spin-echo (repetition time/echo time [TR/TE] 5000/130 ms), a T1-weighted spin-echo (TR/TE 500/9 ms), and fluid-attenuated inversion-recovery (TR/TE 8000/155 ms, inversion time 2000 ms) imaging. MR angiography was performed using the 3D time-of-flight method (TR = 39 ms, TE = 6.5 ms, flip angle 20º, 20-cm field of view, 1-mm slice thickness, number of excitations = 1, 60-mm slab thickness, partition 60, matrix size 128 × 128).

Infarction was defined as a focal area with prolonged

Table 1 Patient profiles

	Normal CVR group	Impaired CVR group	Improved CVR group
No. (male/female)	18 (12/6)	15 (10/5)	9 (6/3)
Age (y)	66 ± 9	65 ± 10	64 ± 7
Body weight (kg)	63 ± 10	62 ± 14	62 ± 13
Height (cm)	163 ± 7	162 ± 11	161 ± 11
Examination interval (d)	619 ± 275	514 ± 232	503 ± 294
History of CVD			
Asymptomatic	5	5	4
Symptomatic			
TIA/amaurosis fugax	4	6	3
Non-disabling infarction	9	4	2
Medications			
ACEI	7	9	6
ARB	3	5	1
Calcium antagonist	11	11	6
Beta-blocker	4	5	2
Diuretic	1	3	1
HMG-CoA inhibitor	11	10	7
Antiplatelet agent	16	13	9
Anticoagulate agent	4	2	1
Concomitant diseases			
Hypertension	16	13	6
Hyperlipidemia	14	11	7
Diabetes mellitus	7	7	5
Arterial diseases			
Occlusion	8	11	4
Stenosis	10	4	5
Multiple occlusive lesions			
Ipsilateral	2	3	0
Contralateral/Posterior	8	7	6
Cerebral ischemic events during follow-up			
Transient ischemic attack	0	2	0
Cerebral infarction	1	0	0

CVR: Cerebrovascular reactivity, No.: number, CVD: Cerebrovascular disease, TIA: Transient ischemic attack, ACEI: Angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, HMG-CoA: Hydroxymethylglutaryl-coenzyme

T1 and T2 relaxation times. Occlusion of the M1 segment of the MCA and intracranial ICA was evaluated using MR angiography according to a previously described method.[13] Occlusion was defined as a disruption in the signal intensity of the intracranial ICA or MCA.

Ultrasonography

Duplex carotid ultrasonography (US) was performed to evaluate the severity of CCA or ICA atherosclerosis. All US examinations were performed using a SONOS 5500 (Phillips Medical Systems Japan, Tokyo, Japan) equipped with a 7.5-MHz linear-array transducer. Carotid stenosis ≥ 50% or occlusion was evaluated according to the criteria of Bluth et al.[14]

Systemic blood pressure measurements

At each SPECT examination, systemic BP was measured using an automated sphygmomanometer (Omron Healthcare Co., Ltd., Kyoto, Japan). Systemic BP was measured twice, once with the patient lying supine and at rest on the scanner bed during the SPECT examination and once at acetazolamide loading. The mean arterial BP was calculated as follows: Mean arterial BP = Diastolic BP + (Systolic BP – Diastolic BP)/3. Average BPs at the each SPECT study were averages of BP measurements during resting and acetazolamide loading. We also investigated whether the systemic BP at the SPECT study correlated with that measured within one month before or after the SPECT study at our outpatient-clinic in 32 of 42 patients.

Data analysis

Four sets of SPECT images were obtained: at rest and at ACZ loading in the initial and follow-up studies. All data were analyzed using Dr. View LINUX (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan). The initial image obtained at ACZ loading and the follow-up images obtained at rest and at ACZ loading were registered on the initial

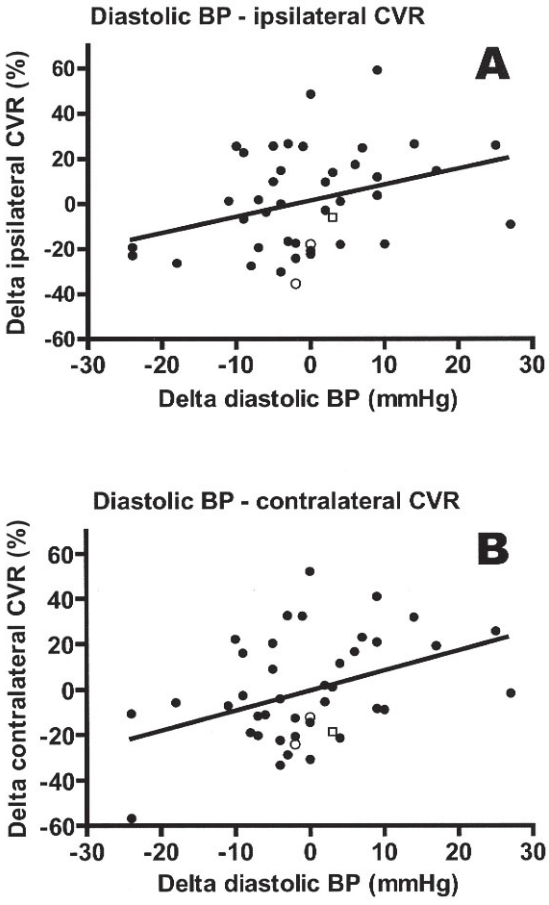

Fig. 1 Interval change in CVR (delta CVR) versus interval change in systemic BP (delta BP). Linear regression plots for delta diastolic BP and delta CVR in the ipsilateral hemisphere (slope = 0.71; intercept = 1.43%; Pearson $r^2 = 0.11$; $p < 0.05$; A) and in the contralateral hemisphere (slope = 0.88; intercept = −0.46%, Pearson $r^2 = 0.16$, $p < 0.05$; B). Delta CVR was significantly correlated with delta diastolic BP in both hemispheres. Each plot shows patients without ischemic strokes (*closed circles*), ipsilateral TIA (*open circles*), or ischemic infarction in the cerebellum (*open rectangles*) during the follow-up period.

image obtained at rest in each patient. Four slices in each patient, two sequencing slices at the levels of the basal ganglia (lower MCA territory) and the parietal lobe (upper MCA territory), were selected for the analysis. Three circular regions of interest (ROIs), 20 mm in diameter, were placed over the cortex of both hemispheres in each slice. Cerebral hemisphere ipsilateral and contralateral to the most severe vascular lesion was separately analyzed. Mean count in each hemisphere was defined as the average count of 12 ROIs.

CVR was defined as follows: CVR (%) = (mean count at ACZ loading SPECT – mean count at resting SPECT)/ mean count at resting SPECT × 100. CVR was then classified as follows: normal (CVR ≥ 34.1%), mild impairment (25.3% < CVR < 34.1%), or severe impairment (CVR ≤ 25.3%). The above CVR thresholds of 34.1% and 25.3% corresponded to the mean CVR – 1SD and the mean CVR – 2SD of the control group, respectively, previously described elsewhere.[15] We categorized the patients into three groups according to their longitudinal changes in CVR classification as follows. The impaired CVR group consisted of patients with worsened CVR in the ipsilateral hemisphere (normal to mild or severe impairment, mild to severe impairment) or those with continuously impaired CVR in the ipsilateral hemisphere. The improved CVR group consisted of patients with improved CVR in the ipsilateral hemisphere (mild or severe impairment to normal, or severe to mild impairment). The normal CVR group consisted of patients with normal CVR in the ipsilateral hemisphere initially and at follow-up.

Statistical analysis

The age, body weight, height, and examination interval were analyzed by analysis of variance among the three groups. The incidence of cerebrovascular diseases, concomitant diseases, arterial occlusion/stenosis, and multiple occlusive lesions was analyzed by chi-square test. The difference in the distribution of medications was analyzed by chi-square test. The correlation between the BP at the SPECT study and the BP at outpatient-clinic was analyzed by linear regression analysis.

Simple regression analyses were performed for all the patients using the difference between their CVR at enrollment and at follow-up as a dependent variable. The differences in systemic systolic BP, diastolic BP, and calculated mean arterial BP at enrollment and follow-up were used as independent variables. Using a Student paired t-test, the differences between the diastolic BP, systolic BP, and mean arterial BP of the patients in each group at enrollment and at follow-up were assessed. All analyses were performed using PRISM 4 for Windows (GraphPad Software, Inc., San Diego, CA).

RESULTS

There were no significant differences in the parameters listed in Table 1 among the normal, impaired, and improved CVR groups. The systolic, diastolic, and mean arterial BPs at the SPECT study were significantly correlated with those at the outpatient-clinic ($p < 0.05$).

Figure 1 shows the correlation between the interval changes in CVR and systemic blood pressure for the ipsilateral (Fig. 1A) and contralateral hemisphere (Fig. 1B). Two patients who had ipsilateral TIA during the follow-up period (*open circles*) and one patient who had a cerebellar infarction (*open rectangle*) are also shown. Overall, the interval changes in CVR were significantly correlated with those in diastolic BP in the ipsilateral hemisphere ($y = 0.71x + 1.43$, $r^2 = 0.11$, $p < 0.05$) and in the contralateral hemisphere ($y = 0.88x - 0.46$, $r^2 = 0.16$,

Table 2 Initial and follow-up systemic BPs of each group

	Normal CVR group	Impaired CVR group	Improved CVR group
Diastolic BP (mmHg)			
At enrollment	76.6 ± 10.4	78.6 ± 10.2	71.6 ± 7.60
At follow-up	77.9 ± 10.9	71.9 ± 11.6*	78.1 ± 9.87
Systolic BP			
At enrollment	134 ± 20.1	142 ± 15.1	134 ± 13.6
At follow-up	137 ± 24.1	133 ± 20.6	135 ± 14.6
Mean arterial BP			
At enrollment	95.7 ± 11.6	99.6 ± 10.5	92.4 ± 8.24
At follow-up	97.9 ± 12.8	92.5 ± 12.7*	97.0 ± 10.1

* $p < 0.05$ vs. at enrollment

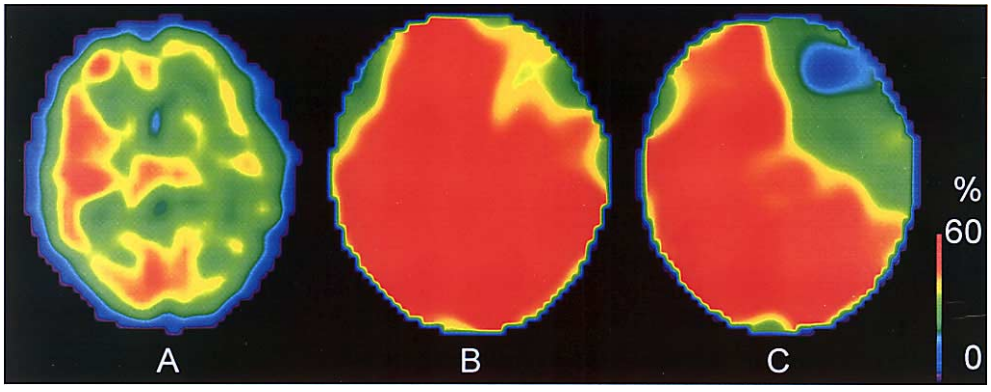

Fig. 2 Single photon emission computed tomography images of a typical patient belonging to the impaired cerebrovascular reactivity (CVR) group. A, resting cerebral blood flow image of the basal ganglial level at enrollment. B, CVR image of the same level at enrollment. C, CVR image of the same level at follow-up. There was a significant decrease of CVR from enrollment (B, 47%) to follow-up (C, 21%) in the left anterior and middle cerebral artery territories. Diastolic blood pressure of this patient was 70 mmHg at enrollment and 52 mmHg at follow-up.

$p < 0.05$). The interval changes in CVR were not significantly correlated with those in systolic BP or mean arterial BP.

Table 2 summarizes the mean initial and follow-up systemic BPs for the impaired, improved, and normal CVR groups. The impaired CVR group showed a significant decrease in diastolic BP ($p < 0.05$) during the follow-up period. Figure 2 shows the resting CBF image at enrollment and the CVR images at enrollment and follow-up study for a typical patient of this group. The improved CVR group showed an increase in diastolic BP during the follow-up period, although the change was not significant. The normal CVR group showed no significant change in diastolic BP. No significant interval changes in the systolic or mean arterial BPs were seen. Two patients who had ipsilateral TIA and one patient with a cerebellar infarction belonged to the impaired CVR group and the normal CVR group, respectively.

DISCUSSION

The present study demonstrated that the reduction in CVR to acetazolamide in the brain SPECT is associated with lowering of diastolic BP at the SPECT measurement in medically treated patients with carotid or middle cerebral artery steno-occlusive disease. This was further validated by the fact that the impaired CVR group showed a significant reduction in diastolic BP.

Acetazolamide loading produces cerebral vasodilatation and increases CBF. When cerebral perfusion pressure decreases in the territory of the occluded cerebral artery and compensatory vasodilatation occurs, acetazolamide loading results in less CBF response due to less residual vasodilatory capacity.[16] Therefore, the CVR to acetazolamide has been used as an alternative estimate of cerebral autoregulatory perfusion reserve in patients with occlusive cerebrovascular diseases.[5,6] The present study indicated that the diastolic BP reduction predominantly affected the CVR worsening. Previous studies indicated that the lower limit of systemic BP to maintain cerebral autoregulation shifted to a higher level in hypertensive patients than in normotensives.[17] The present study and the previous observations suggested the importance of systemic BP control, especially diastolic BP, to maintain

cerebral hemodynamic status in patients with occlusive cerebrovascular diseases. In the present study, the contralateral hemisphere showed a similar relationship between the interval change in CVR and that in diastolic BP. This is partly due to the inclusion of patients with multiple occlusive lesions as shown in Table 1.

Does the systemic BP measured at the SPECT study reflect the systemic BP at the outpatient-clinic or patient's daily-life? In the present analysis, systemic BP (systolic, diastolic, and mean arterial BP) at the SPECT measurement was significantly correlated with that at the outpatient clinic. The mechanism of their blood pressure lowering between the SPECT studies remains unknown. We analyzed the distribution of antihypertensive drugs administered to the patients, but could not find any significant difference in the distribution of antihypertensive drugs among the three subgroups.

The relationship between BP and stroke incidence has been debated. The PROGRESS[18] and HOPE[19] trials reported that the lower the BP, the lower the stroke recurrence rate for a wide range of BP levels. On the other hand, several studies have suggested that a threshold BP exists below which the stroke risk may increase. Irie et al. studied the stroke recurrence rate in relation to post-stroke BP. They found that patients with a post-stroke diastolic BP below 80 mmHg had higher recurrence rates of brain infarction and lacunar infarction than those with a diastolic BP ranging from 80 to 84 mmHg.[20] Somes et al. found that a decrease in diastolic BP below 70 mmHg increased the risk of stroke in patients with isolated systolic hypertension.[21] Voko et al. found that a decrease in diastolic BP below 65 mmHg significantly increased the risk of first-time stroke in elderly patients receiving antihypertensive drugs.[22] Although the patient populations of these studies were different from that of the present study, the increased stroke risk associated with a reduction in diastolic BP may be due in part to the CVR impairment.

To reduce the probability of stroke onset, an impaired CVR when found in medically treated patients with cerebral occlusive arterial disease may indicate the need for additional treatments to restore cerebral perfusion. Large randomized trials have proved that carotid endarterectomy (CEA) prevents stroke in patients with symptomatic carotid stenosis.[23,24] In patients with asymptomatic carotid stenosis, a significant reduction in the risk of ipsilateral stroke was found in the CEA group.[25] Medication with angiotensin-converting enzyme inhibitor has also been reported to improve the CVR in patients with minor stroke.[26] An angiotensin receptor blocker lowered the BP without changing the CVR in hypertensive patients.[27] Before considering invasive surgical or interventional treatments, diastolic BP control should be considered.

The present study had several limitations. First, this was not a prospective randomized case-controlled study. Some of the enrolled patients had hypertension or controlled hypertension treated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, beta-blockers, diuretics, or a combination of these drugs. We preliminarily analyzed the interval changes in relation to the anti-hypertensive agents that were administered. In this small population, the choice of anti-hypertensive agent was not significantly correlated with an improvement or worsening of the CVR.

Second, the study consisted of patients with heterogeneous baseline characteristics at enrollment. Both symptomatic and asymptomatic patients were enrolled. Patients with arterial occlusion and those with stenosis were also both included. The interval change in carotid artery stenosis was evaluated in 13 of 19 patients with ICA stenosis with carotid echosonography. In one patient, 50% stenosis advanced to complete occlusion. The CVR reduced from 25% to 7%, while diastolic BP was not changed (90 mmHg initially and at the follow-up). In this patient, the worsening of the arterial lesion rather than BP change may have affected the interval change in CVR. In the other 12 patients, 4 of them showed 10 to 18% worsening of stenosis and 8 of them showed less than 10% worsening. There was no significant difference in the interval change in CVR between the former (2.05 ± 15.75%) and the latter (1.98 ± 12.79%) groups. In these patients, the worsening of carotid stenosis would not be a predominant factor determining the interval change in CVR.

Third, the BP was measured at resting and after acetazolamide loading during the SPECT study. Acetazolamide loading is known to have no effect on systemic BP.[28] The mean BP after acetazolamide loading was not significantly different from that at rest.

Fourth, the acetazolamide loading occasionally induces hyperventilation and subsequent $PaCO_2$ reduction. Okazawa et al. reported no significant change in $PaCO_2$ after acetazolamide loading in healthy volunteers.[28] Although we did not measure $PaCO_2$ in the present study, no patients showed hyperventilation in both the initial and follow-up SPECT studies. We therefore consider there to have been little effect of $PaCO_2$ change on the CBF and the CVR in our patients.

In conclusion, despite the methodological limitations and design of this study, the present findings suggest that the long term CVR change is affected by the diastolic BP in medically treated patients with steno-occlusive CCA, ICA, or MCA lesions. Monitoring diastolic BP is important for predicting a worsening in CVR and preventing ischemic strokes in this patient population.

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