Periventricular White Matter Lucency and Cerebral Blood Flow Autoregulation in Hypertensive Patients

Kohji Matsushita, Yoshihiro Kuriyama, Kazuyuki Nagatsuoka, Masaichi Nakamura, Tohru Sawada, Teruo Omae

Abstract The goal of this study was to elucidate the association between the development of periventricular white matter lucency and autoregulation of cerebral blood flow in hypertensive patients through the arteriovenous oxygen saturation difference method. We studied 51 hypertensive patients who had previously suffered from minor strokes (lacunar infarction, 43; deep basal minor hemorrhage, 8). Patients were divided into three groups based on the findings of periventricular white matter lucency. We measured the absolute value of resting cerebral blood flow using the argon inhalation method, and stepwise reduction of blood pressure was obtained with patients on a tilting table. Intracerebral venous blood sampling was accomplished by direct cannulation into the jugular vein up to the jugular bulb. We calculated several cerebral circulatory parameters, such as cerebrovascular resistance and cerebral oxygen consumption, and also delineated individual autoregulation curves. Cerebrovascular resistance was significantly greater in patients with severe periventricular white matter lucency than in patients without it (P<0.05). Impaired autoregulation was also significantly more prevalent in patients with more severe periventricular lesions (P<0.05). Multiple regression analysis revealed that the impaired autoregulation was significant and an independent determinant of the severity of such periventricular lesions (R=0.34, P<0.05). In conclusion, our findings indicated that hypertensive patients with severe periventricular white matter lucency were more likely to have impaired autoregulation of cerebral blood flow and suggest that stricter blood pressure control is required in such patients to prevent deterioration of the cerebral microcirculation. (Hypertension. 1994;23:565-568.)

Key Words • vascular resistance • homeostasis • arteriosclerosis • hypertension, chronic

Clinical-pathological studies suggest that arteriosclerosis resulting from the effects of chronic hypertension is related to the development of periventricular white matter lucency (PVL) or leukoaraiosis.6-8 Clinical studies have indicated a connection between this radiological finding and neurological changes,Binswanger's disease in particular.6-8 Hypertension profoundly influences the autoregulation of cerebral blood flow (CBF) by shifting both lower and upper limits of autoregulatory range toward a higher blood pressure.6-9 This phenomenon has also been attributed to structural alterations in the small arteries related to hypertension.

To our knowledge, a direct association between PVL and CBF autoregulation has not been investigated. We examined the relation between these two factors in patients with chronic hypertension to determine whether brain computed tomographic (CT) evidence of severe PVL was associated with impaired CBF autoregulation.

Methods

We studied 51 inpatients (34 men, 17 women; age range, 46 to 77 years; mean, 59±9.9 years) with chronic hypertension who had previously experienced some type of stroke (lacunar infarction in 43 and hypertensive deep basal brain hemorrhage in 8). No patient had experienced a cardioembolic brain infarction. Brain CT images were obtained along the orbitomeatal line of a 1-cm-thick slice using an X-force apparatus (Toshiba Inc.). We classified PVL according to the method proposed by Hijdra et al in 1990: 0=normal periventricular low density at the lateral ventricular level; 1=localized low density in the region adjacent to the ventricles; and 2=marked low density extending to the neighboring cortex. Patients were divided into three subgroups based on the sum of scores for both hemispheres: PVL0 (score of 0), PVL1 (score of 1 to 3), and PVL2 (score of 4) (Fig 1).

Cerebral angiography was performed in 18 of 22 patients in the PVL0 group, 12 of 13 in the PVL1 group, and 11 of 16 in the PVL2 group. Unilateral occlusion of the main trunk was detected in 2 patients, both of whom were in the PVL1 group. In 1 patient, occlusion involved the extracranial internal carotid artery and in the other the horizontal portion of the middle cerebral artery. We detected significant stenosis (>75%) of the ipsilateral extracranial internal carotid artery in 1 patient in the PVL0 group and 1 patient in the PVL1 group. We estimated the size of the ventricle using the bicaudate index, frontal horn index, and occipital horn index, determined from the same CT slice.

CBF was measured with the patient in the supine position by the argon inhalation method,6-11 in which CBF was calculated from the argon desaturation curve.11 Hemoglobin and oxygen saturation of sampled blood were estimated with a hemoximeter (Radiometer). We measured PaO2, PaCO2, and pH with an ABL2 (Radiometer). We inserted a catheter directly into the brachial artery for continuous monitoring of arterial blood pressure at the level of the carotid body as well as blood sampling. We cannulated the unilateral jugular vein up to the jugular bulb for cerebral venous sampling.

Stepwise reduction of systemic blood pressure was accomplished by passive postural changes on a head-up tilting table.
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If blood pressure was not sufficiently reduced by this method, an initial dose of trimethaphan camysylate (1.0 mg/min), which was thought too insignificant to decrease blood pressure itself, was administered supplementarily. The orthostatic index was based on the decreases in mean arterial blood pressure (MAP) from the supine position to a 30° head-up position. Changes in CBF at various pressure levels were estimated using Fick's principle, by changes in cerebral arteriovenous oxygen difference (A-VDO₂), at approximately every point of a 10% decrease of MAP from the previous value. We divided resting MAP by resting CBF to determine cerebrovascular resistance (CVR). We multiplied resting A-VDO₂ by resting CBF to estimate cerebral oxygen consumption (CMRO₂).

We used these data to determine individual CBF autoregulation curves. Preserved CBF autoregulation was defined as less than a 10% change of resting CBF, accorded as a 20% decrease in MAP from its resting value. Impaired CBF autoregulation was defined as more than a 10% change of resting CBF in the same condition (Fig 2).

Measurements were obtained at least 2 weeks after the discontinuation of antihypertensive drugs and at least 4 weeks after the onset of stroke to exclude the influences of these factors on CBF autoregulation.

All participants gave informed consent to this study, which was approved by the Ethics Review Committee of the National Cardiovascular Center (Serial No. 62-1).

Results were analyzed by the χ² method and Williams' multiple comparison test. To determine the independent effects of factors on the development of PVL, independent variables, such as age, sex, bicaudate index, MAP, orthostatic index, CBF, CVR, CMRO₂, diabetes mellitus, hyperlipidemia, and CBF autoregulation, were analyzed by regression analysis using the stepwise method. A probability value of less than .05 was considered statistically significant.

Results

There were no significant differences in mean age or prevalence of cardiovascular risk factors such as diabetes mellitus or hyperlipidemia among the three PVL groups. CT evidence of ventricular dilatation was rare, even in the subgroup with severe PVL, and the average values for the indexes of ventricular size did not differ significantly among the groups (Table 1).

MAP elevation after the 2-week discontinuation of antihypertensive agents averaged +6 mm Hg and varied little among the three PVL groups. Arterial PacO₂ was measured before and during the hypotension. PacO₂ values did not change significantly throughout the examination in any group. There was a trend toward an increased MAP and a decreased CBF in association with increasing severity of PVL, but differences among groups were not significant. However, the mean CVR was significantly higher in the PVL2 group than in the PVL0 group (Williams' multiple comparison test, P<..05) (Table 2).

There was a significantly higher prevalence of impaired CBF autoregulation in the more severe PVL subgroup (Fig 3). Multiple regression analysis identified CBF autoregulation as a significant and independent determinant of the severity of PVL findings (R=.34, P<.05).
TABLE 1. Clinical Profiles of Three PVL Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>PVLO (n=22)</th>
<th>PVL1 (n=13)</th>
<th>PVL2 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.7±6.36</td>
<td>62.4±6.58</td>
<td>58.2±7.50</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/6</td>
<td>9/4</td>
<td>10/6</td>
</tr>
<tr>
<td>Hb, mg/dL</td>
<td>12.8±1.77</td>
<td>12.0±1.18</td>
<td>13.1±1.94</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>HL</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BCI</td>
<td>0.11±0.050</td>
<td>0.14±0.046</td>
<td>0.12±0.053</td>
</tr>
<tr>
<td>FHI</td>
<td>0.26±0.096</td>
<td>0.29±0.095</td>
<td>0.26±0.106</td>
</tr>
<tr>
<td>OHI</td>
<td>0.40±0.142</td>
<td>0.43±0.140</td>
<td>0.40±0.164</td>
</tr>
</tbody>
</table>

PVLO indicates periventricular white matter lucency; Hb, hemoglobin concentration; DM, diabetes mellitus; HL, hypercholesterolemia or hypertriglyceridemia; BCI, bicaudate index; FHI, frontal horn index; and OHI, occipital horn index. Values are counts or mean±SD.

Discussion

Bogousslavsky et al reported that lesions of periventricular white matter were associated with chronic hypertension and suggested that hypertensive arteriosclerosis of medullary arteries was involved in the pathogenesis of these lesions. Deep basal brain hemorrhage has been found to be caused by hypertension-related damage to small penetrating arteries, which results in microaneurysmal formations, fibrinoid degeneration, or hyalnosis. These pathogenetic features are similar to those seen in lacunar infarction.

Our patients had chronic hypertension and had experienced lacunar infarction or deep basal minor hemorrhage, suggesting the presence of hypertension-related arteriosclerosis. The present study did not include either physically disabled or demented patients, two common results of major stroke or multiple lacunar infarction. A decrease in CBF secondarily caused by chronic brain dysfunction was unlikely to be a significant factor in the present study. Therefore, the significantly higher CVR in patients with severe PVL suggests that these patients had experienced more severe morphological alterations in cerebral resistance vessels. In fact, some studies found that the resting CBF in hypertensive patients without neurological deficits was not lower than in normotensive individuals, also suggesting that CVR is higher in hypertensive patients in association with a higher MAP.

Experimental studies have suggested that chronic hypertension reduces the distensibility of arterioles. Impaired dilatation of small arteries could attenuate cerebrovascular responses to dilator stimuli, such as autoregulatory expansion of vascular beds during severe hypotension. A long-standing hypertensive state may result in adaptive processes in the vessel wall, such as connective tissue proliferation, muscular hyperplasia, and degenerative changes.

In our study PVL severity and CBF dysautoregulation were positively correlated, suggesting that impaired CBF autoregulation may have been caused by a lack of distensibility of damaged small arteries in patients with severe PVL. However, other investigators have suggested that adequate antihypertensive therapy may normalize impaired CBF autoregulation in the early stages of chronic hypertension. Strandgaard and Paulson suggested that this therapeutic effect might depend on the reversibility of the structural changes in hypertensive arterioles, including muscular hypertrophy or storage of salt and water in the vessel walls.

Our study consisted of patients who suffered from minor stroke, and in some, the unilateral major cerebral artery was affected. All cerebral arteries or arterioles are unlikely to be affected simultaneously by chronic
hypertension. It is intriguing to suppose that the extent of the impairment in the autoregulatory system is not homogeneous in the whole brain. However, it is difficult to evaluate such regional CBF autoregulation even by using applicable methods such as positron-emission tomography. Further studies are needed to investigate this point. Alternatively, an A-VDOS method is thought to be practical and preferable for evaluating the real-time changes of CBF reserves in total during stepwise-induced hypotension.

Our definition of preserved CBF autoregulation as less than a 10% change of resting CBF at a 20% decrease of resting MAP value was based on the finding of Strandgaard that the MAP associated with the lower limit of autoregulatory range was 79 ± 10% of the resting MAP in patients with uncontrolled hypertension. Therefore, our definition of impaired autoregulation could include the following two different cases: one case in which impaired autoregulation exactly meant that a plateau phase of CBF was completely lost in all levels of MAP, and the other case which was actually preserved in autoregulation; nevertheless, because the MAP level during pretreatment was close to its lower limit, CBF did decrease by relatively mild hypotension. Clinically, in both of these cases, the warning must be given that a nonnegligible decrement of CBF could be caused by the seemingly appropriate antihypertensive therapy. The main purpose of the present study, in other words, was to demonstrate the recommended safety range for decreasing untreated blood pressure levels in each hypertensive patient.

Evidence suggests that PVL is a marker of stroke or the early stage of vascular dementia. In the London Ontario Dementia Study, stroke was four times more common in demented patients with PVL than in those without PVL. A recent study found a higher rate of stroke recurrence and a poorer prognosis in lacunar infarction cases with PVL than in cases without PVL. Taking these epidemiologic studies into account, we propose that impaired CBF autoregulation may play an important role in the recurrence of stroke and increased susceptibility to lower perfusion pressures. Meyer et al reported that appropriate control of hypertension prevented multi-infarct dementia. In most hypertensive patients, antihypertensive treatment is not associated with a risk of cerebral ischemia. However, in patients with multi-infarct dementia, Meyer et al reported that the optimal range for systolic blood pressure is 135 to 150 mm Hg; their patients' cognitive function tended to deteriorate if systolic blood pressure fell below this level. Because arteriosclerotic damage in cerebral small vessels is usually advanced in patients with multi-infarct dementia, it is easy to speculate that these patients may already have impaired CBF autoregulation. Therefore, optimal cerebral perfusion in these patients may require relatively higher blood pressure, with hypotension resulting in infarction.

In conclusion, our findings suggest that when hypertensive patients exhibit a severe PVL appearance on CT, CBF autoregulation is likely to be impaired. In these patients, strict blood pressure control is needed to prevent deterioration of the cerebral microcirculation.

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