Impaired Cerebrovascular Reactivity as a Risk Marker for First-Ever Lacunar Infarction
A Case-Control Study
Carlos Molina, MD; José Alvarez Sabín, MD; Joan Montaner, MD; Alex Rovira, MD; Sonia Abilleira, MD; Agustín Codina, MD, PhD

Background and Purpose—Functional assessment of small arteries and arterioles could provide valuable information regarding the extent of diffuse arteriolosclerosis in patients with small-vessel disease. Therefore we attempted to clarify the role of cerebrovascular reactivity (CVR) as a risk marker for first-ever symptomatic lacunar infarction.

Methods—Forty-six patients with lacunar infarction and 46 sex- and age-matched control subjects were prospectively evaluated. Cerebral hemodynamics were studied with transcranial Doppler ultrasonography. CVR was examined by calculating the percent increase in mean flow velocity occurring after 15 mg/kg acetazolamide administration (Diamox test).

Results—CVR was significantly ($P<0.0001$, Student’s $t$ test) lower in cases (50.0 $\pm$ 12.7%) as compared with control subjects (65.2 $\pm$ 12.4%). A multiple logistic regression analysis identified male sex (odds ratio [OR] 2.3, $P=0.02$), age (OR 3.6, $P<0.005$), and the presence of lacunar infarction on magnetic resonance imaging (OR 5.3, $P<0.001$) as significant and independent factors associated with a reduction of CVR. Moreover, a cut-point of 55.6% (sensitivity 67%, specificity 82%) was established as the threshold value for distinguishing between pathological and normal CVR. CVR was significantly ($P=0.02$) lower in patients with multiple (46.38 $\pm$ 12.6%) than with single (54.83 $\pm$ 11.58%) lacunar infarction. In addition, a trend of negative correlation was found between CVR and the number of lacunar infarctions ($r=-0.26$, $P=0.08$). In the multiple logistic model, history of hypertension (OR 7.24; 95% confidence interval 2.95 to 17.79) and CVR (OR 0.8; 95% confidence interval 0.81 to 0.93) emerge as significant and independent predictors of first-ever lacunar infarction.

Conclusions—These data suggest that impaired CVR is a risk marker for first-ever lacunar infarction. (Stroke. 1999;30:2296-2301.)

Key Words: cerebrovascular reactivity $\Rightarrow$ lacunar infarction $\Rightarrow$ ultrasonography, Doppler, transcranial

Lipohialnosis and microatheromatosis are the main underlying arterial lesions in patients with lacunar infarction (LI).$^{1,2}$ These microangiopathic changes are believed to be responsible for the LI and white matter hyperintensities (WMHs) seen on magnetic resonance imaging (MRI). Therefore MRI has been proposed as a gold standard technique for the in vivo evaluation of the severity of microangiopathy.$^{3-6}$ However, functional assessment of small arteries and arterioles could provide valuable information regarding the extent of diffuse arteriolosclerosis in patients with small-vessel disease.

Cerebrovascular reactivity (CVR) reflects the compensatory dilatory capacity of cerebral arterioles to a dilatory stimulus such as carbon dioxide or acetazolamide.$^7$ In the absence of major arterial stenosis, an impaired CVR may reflect increased rigidity of the arteriolar walls$^{8}$ and has been associated with a higher risk of stroke.$^{9,10}$ Decreased CVR has been observed in patients with hypertension and in patients with insulin-dependent diabetes mellitus.$^{11-13}$ Moreover, impaired CVR in young hypertensive subjects appears to improve after the initiation of antihypertensive treatment, suggesting that hypertensive microangiopathic changes could be, at least initially, reversible.$^{13}$ In addition, long-standing and effective treatment of hypertension is associated with a strong reduction in the risk of cerebrovascular events.$^{14,15}$ Therefore CVR could be used to monitor the effect of antihypertensive therapy on the cerebral microcirculation.

Several studies focusing on the hemodynamic evaluation of patients with cerebral microangiopathy have shown contradictory results.$^{8,16-20}$ Differences may be related to selection and methodological bias such as inclusion of patients with carotid artery stenosis,$^{18-20}$ patient selection on the basis of radiological findings only, different methods used for CVR analysis, and patient characteristics.$^{8,16,18}$ In the present study, we prospectively compared patients with first-ever symptomatic lacunar infarction and matched control subjects. Cerebral hemodynamics were assessed with transcranial Doppler ultrasonography. The main finding of our study was a significantly lower cerebrovascular reactivity (CVR) in patients with first-ever symptomatic lacunar infarction compared with age- and sex-matched control subjects. Significant associations were found between CVR and major risk factors for lacunar infarction, including male sex, age, and the presence of lacunar lesions on MRI. These results suggest that impaired CVR is a risk marker for first-ever symptomatic lacunar infarction.
measurement, and the absence of a control group without MRI evidence of cerebral microangiopathy.\textsuperscript{19,20} Moreover, to our knowledge, the condition of CVR as a potential risk factor for LI has never been tested.

The purpose of the present study was to evaluate whether CVR is reduced in patients with LI compared with sex- and age-matched control subjects without MRI evidence of microangiopathy and to determine the role of decreased CVR as a risk factor for first-ever symptomatic LI.

### Subjects and Methods

From January 1997 to June 1998, we prospectively evaluated 67 consecutive patients with a first-ever symptomatic LI confirmed by standard MRI. Of these 67 patients we excluded those with carotid stenosis $\geq$50\% (n=5), patients with intracranial stenosis on transcranial Doppler (TCD; n=7), and patients with an inadequate temporal bone window (n=9). Finally, 46 patients were included in the study.

LI was defined as an acute classic lacunar syndrome with an MRI showing an ischemic lesion of $<15$ mm located in the arterial territory of the lenticulostriate, thalamoperforant, or pontineperforant arteries according to previously published criteria.\textsuperscript{21}

All patients underwent a careful neurological and cardiological examination, ECG, transthoracic echocardiography, blood chemistry, and a clinical history with particular attention to previous cerebrovascular events.

Control subjects were selected from consecutive subjects who underwent MRI studies in the evaluation of hypertension or dizziness. Subjects with vertigo possibly caused by brain stem or cerebellar dysfunction, history of migraine, transient ischemic attack, or stroke and those with LI on MRI were excluded. From a total of 59 subjects evaluated, 46 age- ($\pm$2 years) and sex-matched control subjects were selected. Informed consent was obtained for all patients and control subjects before the study. The study was approved by the local ethics committee.

On the basis of standard definitions, the presence of vascular risk factors was recorded including age, sex, hypertension (systolic blood pressure values $\geq$160 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg on 2 different determinations before stroke or after the first week of stroke or use of antihypertensive medication), condition of treatment for hypertension (regularly treated, irregularly treated, or untreated hypertension), diabetes mellitus (treated or fasting glucose levels $\geq$110 mg/dL), cigarette smoking, and hypercholesterolemia (treated or cholesterol levels $\geq$240 mg/dL).

### Hemodynamic Protocol

To avoid changes in vasomotor tone related to the acute phase of cerebral ischemia, hemodynamic evaluation was delayed in all patients until 1 month after the acute stroke. In control subjects, hemodynamic assessment was carried out within 2 weeks after MRI examination.

Carotid artery sonography was performed in all patients and control subjects by means of a high-resolution, real-time scanner equipped with a 7.5-MHz imaging transducer and a 4-MHz pulse-wave Doppler transducer. Carotid artery stenosis was defined according to the standardized criteria.\textsuperscript{22} The vertebrobasilar system was assessed as described by Bartels.\textsuperscript{23} Those patients with carotid stenosis $\geq$50\% were excluded.

To exclude the presence of intracranial stenosis that may interfere in the measuring of CVR, TCD examinations were performed in all patients and control subjects with the use of a 2-MHz pulse-wave probe. Intracranial stenosis was defined according to Lye-Pozo and Ringelstein.\textsuperscript{24}

CVR studies were performed by the same neurologist between 3 and 5 PM. Medications such as cerebral vasodilators were discontinued 48 hours before hemodynamic evaluation. Mean flow velocity (MFV) on the middle cerebral artery was continuously monitored by means of a Multi-Dop X/TCD transcranial Doppler instrument (DWL Elektronische Systeme GmbH). One dual 2-MHz transducer fitted on a headband and placed on the temporal bone window was used to obtain continuous measurements. The highest signal was sought at a depth ranging from 45 to 55 mm. This unit allows for continuous-wave Doppler recording of the intracranial artery with on-line calculation of MFV in centimeters per second. By activating the record function, it is possible to save the Doppler spectra during the entire period of each study. Reactivity was examined by calculating the percent increase in MFV occurring after 15 mg/kg acetazolamide (ACZ) administration (Diamox test). The study was carried out in a quiet room with the patient lying in a comfortable supine position without any visual or auditory stimulation. The MFV at rest was obtained by continuous recording during a 5-minute period followed by ACZ infusion during 3 minutes. Fifteen minutes after ACZ administration, the maximal increase in MFV over 2 minutes was recorded. CVR was calculated from the formula $\text{MFV}_{\text{ACZ}} - \text{MFV}_{\text{basal}} \times \text{MFV}_{\text{basal}} \times 100$. Systolic and diastolic blood pressure and heart rate were recorded before and after the Diamox test.

### MRI Examinations

All patients included in the study underwent a brain MRI scan within the first 15 days after stroke, with the use of the following scanning units: 1/1.5-T Magnetom SP63, (Siemens) and 2/1.0-T Magnetom Impact (Siemens). The studies were performed with a quadrature transmitter/receiver head coil, obtaining a dual-echo (proton density and T2-weighted) spin-echo axial scan with repetition time (TR) of 2200 to 2500 ms, an echo time (TE) of 12 to 80 ms, and 1 acquisition and a T1-weighted spin-echo axial scan using a TR of 550 ms, a TE of 12 ms, and 2 acquisitions. Both sequences were obtained with 5 mm of slice thickness, 1.5 mm of interlace gap, 192 to 256 $\times$ 256 matrix, and 230-mm field of view.

All MRIs were reviewed by the same neuroradiologist blinded to the clinical data. WMHIs on T2-weighted and proton density–weighted images in contact with the ventricular wall were defined as periventricular white matter hyperintensities (PWMHIs), whereas those separated from the ventricular wall by a strip of normal-appearing white matter situated in the deep white matter were defined as deep white matter hyperintensities (DWMHIs). Hyperintensities on T2-weighted images equivalent to cerebrospinal fluid on proton-density and T1-weighted images were regarded as old infarcts; hyperintensities on T2-weighted and proton density–weighted images that were isointense on T1-weighted images and located in a known subcortical or deep gray matter arterial distribution (lacunar) were regarded as acute infaracts. LIs were evaluated separately from the WMHIs. Perivascular (Virchow-Robin) spaces were considered a normal finding and not included in the evaluation of WMHIs or infarcts.

Periventricular hyperintensities were classified on the basis of size and shape in 4 groups: (1) small, rounded hyperintensities limited to the frontal or occipital periventricular white matter, (2) extending hyperintensities around the long axis of the lateral ventricular wall with regular margins and $<5$ mm in width, (3) extending hyperintensities with regular margins and 5 to 10 mm in width, and (4) extending hyperintensities with irregular margins and $>10$ mm in width. Only groups 3 and 4 were considered abnormal.

DWMHIs were classified on the basis of size (greatest diameter) and shape into 3 groups: (1) small, focal, punctuate hyperintensities with a diameter $<5$ mm, (2) large, focal, mostly rounded hyperintensities with a diameter between 5 and 10 mm, and (3) large, mostly irregular and diffusely confluent or with a diameter $>10$ mm.

### Statistical Analysis

For statistical purposes, CVR for the right and left sides were averaged, resulting in a single CVR value for each individual. Statistical significance for intergroup differences were assessed by the 2-tailed Fisher’s exact test and $\chi^2$ test for categorical variables and the Mann-Whitney $U$ test and Student’s $t$ test for continuous variables. Multiple linear regression analysis was performed to identify the variables that independently contributed to a reduction in CVR. To determine a threshold of CVR, a logistic regression model was applied to calculate the sensitivity and specificity for each
value of CVR configuring a receiver operator characteristic (ROC) curve. Logistic regression analysis was conducted to determine the factors that could be considered as independent predictors of first-ever symptomatic LI. Pearson’s ρ coefficient was applied to verify correlation between examined variables. The analyses were performed with the use of SPSS 6.0 software (SPSS Inc). A level of P<0.05 was accepted as statistically significant.

**Results**

Forty-six patients (men/women, 32:14) with a first-ever LI and 46 age- and sex-matched control subjects were included in the study. Demographic data and risk factor profiles of the series are presented in Table 1. The mean age of patients was 56.6±13.4 years (range 25 to 77 years), similar to 58.3±12.0 years (range 27 to 77 years) of the control group. Patients with LI were significantly more often hypertensives and cigarette smokers than their matched control subjects.

Pure motor hemiparesis was the more frequent lacunar syndrome, being observed in 17 (36%) patients, followed by sensorimotor syndrome in 14 (34%), ataxic hemiparesis in 5 (10.6%), pure sensory syndrome in 5 (10.6%), dysarthria–clumsy hand syndrome in 2 (4.2%), and isolated dysarthria–facial palsy in 3 (6.3%) patients. Acute LI was located on the right side in 20 (43%) and on the left side in 26 (57%) cases. Lesions involved the capsulothalamic region in 10 (22%) patients, limited to the corona radiata in 11 (23%), the pons in 10 (21%), the internal capsule in 6 (12.2%), the thalamus in 6 (12.2%), and the lenticular nucleus in 3 (6.3%) patients.

Systolic and diastolic blood pressures determined at the time of hemodynamic evaluation were significantly higher in patients compared with control subjects (mean systolic blood pressure 143.4±22 mm Hg and 131.3±15 mm Hg, P<0.05; mean diastolic blood pressure 83±11 mm Hg and 70.5±11 mm Hg, P<0.02, respectively). There was no significant difference in middle cerebral artery resting MFV between cases and control subjects (MFV 51.3±12 cm/s and 49.3±13 cm/s, respectively). However, CVR was significantly (P<0.0001, Student’s t test) lower in cases (50.0±12.7%) as compared with control subjects (65.2±12.4%) (Table 2). To evaluate the possible effect of symptomatic LI on side-to-side differences in CVR measurement, we compared CVR between symptomatic and asymptomatic sides among 36 hemispheric LIs. The CVR on the symptomatic side (49.3±13.6 cm/s) was not significantly (P=0.3) different from that on the asymptomatic side (51.14±14 cm/s).

In univariate analysis, age <65 years (P=0.01), male sex (P<0.002), smoking habit (P=0.024), the presence of LI on MRI (P<0.001), and untreated hypertension (P=0.039) significantly contributed to a reduction of CVR. A multiple linear regression analysis identified male sex (odds ratio [OR] 2.3, P=0.02), age (OR 3.6, P<0.005), and the presence of LI on MRI (OR 5.3, P<0.001) as significant and independent factors associated with a reduction of CVR. On the basis of ACZ-CVR values obtained in control subjects, we tried to determine a cut-point for the ACZ-CVR value under which a subject should be considered as having a pathological CVR. For this purpose, an ROC curve was applied to obtain a threshold that better distinguishes LI patients from control subjects. This approach provided a cut-point of 55.6% (sensitivity 67%, specificity 82%) as the threshold value for ACZ-CVR (Figure). Thirty-seven (80%) control subjects and 15 (33%) LI patients had ACZ-CVR values above, whereas 9

**TABLE 1. Demographics and Risk Factor Profile in Cases and Matched Control Subjects**

<table>
<thead>
<tr>
<th>Demographics and Risk Factors</th>
<th>Cases (n=46)</th>
<th>Control Subjects (n=46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>32 (69%)</td>
<td>32 (69%)</td>
<td>Matched</td>
</tr>
<tr>
<td>Age (mean), y</td>
<td>56.6±13.4</td>
<td>58.3±12.0</td>
<td>Matched</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>29 (63.1%)</td>
<td>5 (10.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated, n (%)</td>
<td>17 (37%)</td>
<td>4 (8.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Untreated, n (%)</td>
<td>12 (26.1%)</td>
<td>1 (2.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (15.2%)</td>
<td>3 (6.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>8 (17.4%)</td>
<td>3 (6.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>20 (43.5%)</td>
<td>10 (21.7%)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

**TABLE 2. Hemodynamic Parameters in Cases and Control Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mean±SD</td>
<td>143.4±22.0</td>
<td>131.3±15.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean±SD</td>
<td>83.2±11.8</td>
<td>70±11.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Resting middle cerebral artery MFV</td>
<td>51.3±12.7</td>
<td>49.3±12.9</td>
<td>0.38</td>
</tr>
<tr>
<td>ACZ middle cerebral artery MFV</td>
<td>74.0±20.2</td>
<td>80.2±17.9</td>
<td>0.32</td>
</tr>
<tr>
<td>CVR, %</td>
<td>50.0±12.7</td>
<td>65.2±12.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
TABLE 3. Differences in Risk Factor Profile Between SLI and MLI

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLI</th>
<th>MLI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.0</td>
<td>56.0</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>16</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>7</td>
<td>13</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5</td>
<td>3</td>
<td>0.79</td>
</tr>
<tr>
<td>CVR</td>
<td>54.83</td>
<td>46.38</td>
<td>0.026</td>
</tr>
</tbody>
</table>

The MRI examinations revealed the presence of a single lacunar infarction (SLI) in 20 (43%) patients and multiple lacunar infarctions (MLI) in 26 (57%) patients. The risk factor profile of patients with SLI and MLI is presented in Table 3. CVR was significantly (P=0.02) lower in patients with MLI (46.38±12.6%) as compared with SLI (54.83±11.58%). In addition, a trend of negative correlation was found between CVR and the number of LI (r=-0.26; Pearson’s r coefficient). PWMHIs and DWMHIs were present in 33 (72%) patients. PWMHIs were scored as grade 1 to 2 in 26 (78%) and 3 to 4 in 7 (22%) patients, whereas DWMHIs were scored as grade 1 to 2 in 26 (78%) and 3 to 4 in 7 (22%) patients, whereas DWMHIs were scored as grade 1 to 2 in 26 (84%) and 3 in 5 (15%). However, there was no difference in CVR between scores greater and lower than 2 in both PWMHIs and DWMHIs. In addition, CVR was unrelated neither with the extent of PWMHI (r=-0.3; P=0.1; Pearson’s r coefficient) nor with the extent of DWMHI (r=-0.001; P=0.9).

The relative contribution of different variables for first-ever LI on univariate analysis is shown in Table 4. By the replacement of the CVR as continuous variable with CVR as dichotomous factor (pathological <55%; normal >55%), history of hypertension (OR 18.2; 95% confidence interval [CI] 5.8 to 56.9), CVR <55% (OR 9.5, 95% CI 3.4 to 26.5), and smoking habit (OR 3.42; 95% CI 1.3 to 8.6) were associated with a significantly increased risk for first-ever LI. Age, sex, diabetes mellitus, hypercholesterolemia, and blood pressure at the time of investigation were not associated with an increased risk for first-ever LI.

In a multiple logistic regression model, only history of hypertension (OR 7.24; 95% CI 2.95 to 17.79) and untreated hypertension patients had a higher risk (OR 4.42; 95% CI 1.58 to 33.66) than those regularly treated, and the regularly treated had a higher risk (OR 2.24; 95% CI 1.55 to 9.17) than the normotensives. The remaining variables that were found significant with univariate analysis did not enter into the model.

Discussion

Prior studies have shown a decreased vasodilatory capacity in subjects with risk factors for arteriolosclerosis,12,13,25 CVR appears to be reduced in patients with long-term insulin-dependent diabetes11 and in those with proliferative diabetic retinopathy.26 Furthermore, vasomotor tone appears to be increased in severe, noncontrolled hypertensives as compared with controlled hypertensives and normotensive subjects, and an inverse association was found between ACZ-CVR and the degree of echocardiographic left atrial enlargement.12 CVR has also been noted to be markedly decreased in cerebrovascular diseases, especially in patients with large-vessel occlusive disease.8,27,28 However, reports on hemodynamic reserve capacity in patients with symptomatic LI are scarce,8,19,20 and its role as a risk factor for first-ever LI has not been previously evaluated.

Our results demonstrate a significantly impaired CVR in patients with first-ever symptomatic LI as compared with sex- and age-matched control subjects. These findings strongly support the assumption that microangiopathic changes (arteriolosclerosis) may be an independent contributor to impaired reactivity unrelated to the presence of carotid stenosis.8,29 Unlike prior studies,8,19,20 we compared CVR in patients with LI with subjects without MRI evidence of microangiopathy, establishing an ACZ-CVR value of 55.6% as a threshold for differentiating patients from control subjects. However, an overlap was observed between patients and control subjects regarding ACZ-CVR values, resulting in 33% of patients with LI above the threshold and 20% of control subjects below the threshold. Normal values of ACZ-CVR reported range from 35% to 60%.11,30 The relatively higher ACZ-CVR in our control group (65%) may be due to exclusion of subjects with large-vessel stenosis and those with asymptomatic LI on MRI. Furthermore, to our knowledge this is the first time that CVR has been tested in subjects without MRI evidence of cerebral microangiopathy. The unexpected direct association observed between age and CVR could be related to bias, such as the relatively younger population studied (mean age 55 years) and small number of patients older than 70 years.

TABLE 4. Predictors for First-Ever Lacunar Infarction on Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;=65 y</td>
<td>1.16</td>
<td>0.44–3.07</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>2.43</td>
<td>0.8–6.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18.2</td>
<td>5.8–56.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.9</td>
<td>0.7–12.2</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>3.42</td>
<td>1.3–8.6</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3.5</td>
<td>1.0–12.2</td>
</tr>
<tr>
<td>CVR&lt;55%</td>
<td>9.5</td>
<td>3.4–26.5</td>
</tr>
</tbody>
</table>

TABLE 5. Predictors for First-Ever Lacunar Infarction on Multiple Logistic Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>7.24</td>
<td>2.95–17.79</td>
</tr>
<tr>
<td>Treated</td>
<td>2.24</td>
<td>1.55–9.17</td>
</tr>
<tr>
<td>Untreated</td>
<td>4.42</td>
<td>1.58–33.66</td>
</tr>
<tr>
<td>CVR</td>
<td>0.87</td>
<td>0.81–0.93</td>
</tr>
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</table>
In the present case-control study, CVR was significantly lower in patients with MLI than in SLI, and a trend of negative correlation was found between CVR and the number of symptomatic and asymptomatic LI seen on MRI. These results support the hypothesis that single symptomatic LI may be related to microatheromatosis, and multiple, usually silent LI may represent a widespread arteriolarlsclerotic disease. Therefore CVR could be a useful test to evaluate the degree of diffuse arteriolarlsclerosis. Our results contradict a previously reported study in which no correlation was found between vasoconstriction and the presence of silent LI on MRI but are in agreement with a recent study in which cerebral blood flow and ACZ-CVR were significantly more reduced in patients with MLI than in those with SLI. Unlike previous studies, we found that in patients with first-ever LI, vasodilatory capacity was not related to the extent of both PWMHI and DWMHI. Although these results may be related to a type II error in view of the small number of patients with higher grades of abnormalities, both clinical and pathological studies have shown a great variation in the extent of PWMHI among patients with LI. Our findings are in line with recent observations in which blood flow and acetazolamide reactivity in the cerebral cortex were significantly lower in patients with leukoariosis with LI than in those with leukoariosis without LI, suggesting that a reduction of reactivity in patients with leukoariosis mainly depends on the presence of LI. Kobayashi et al. reported a decreased cerebral blood flow in patients with lacunes, but no difference in PWMHI was found between patients with and those without lacunes, indicating that lacunes may be more related to severe cerebral arteriosclerosis than to PWMHI. Systemic hemodynamic factors such as an excessive fall in nocturnal blood pressure, systolic hypertension, heart disease whereas diabetes mellitus may contribute to the progression and extent of white matter lesions on MRI.

Arterial hypertension is the strongest risk factor for first-ever and recurrent LI. Uncontrolled hypertension has been shown to produce arteriosclerosis in cerebral small vessels of experimental hypertensive animals. We observed a strong and independent markers of increased risk for first-ever symptomatic LI. Prospective studies are needed to elucidate the role of a decreased CVR as a risk factor for first-ever and recurrent LI.

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References

21. Jennings JR, Muldoon MF, Ryan CM, Mintun MA, Meltzer CC, Townsend DW, Sutton-Tyrrel K, Shapiro AP, Manuck SB. Cerebral blood flow in hypertensive patients: an initial report of reduced and


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