Background and Purpose—It has been demonstrated that left ventricular hypertrophy (LVH) confers an increased risk for major cerebrovascular events. However, it is still uncertain whether there is an association between LVH and asymptomatic cerebrovascular damage in hypertensive patients. In this study, we investigated the relation between LVH, evaluated by both echocardiography (Echo-LVH) and electrocardiography (ECG-LVH), and preclinical cerebral damage, as identified by magnetic resonance imaging.

Methods—One hundred ninety-five consecutive patients were enrolled in the study. We evaluated other risk factors such as age, sex, presence of diabetes, cholesterol levels, smoking status, heart rate, and systolic and diastolic blood pressure. Asymptomatic cerebrovascular damage was considered silent cerebral lesions: punctate lesions, lacunes, and territorial lesions. Patients were divided into 2 groups according to the presence of asymptomatic brain lesions.

Results—The 2 groups of patients differed only in terms of age and systolic pressure. More importantly, the prevalence of Echo-LVH (83% versus 47.7%, \( P<0.001 \)) and ECG-LVH (56% versus 22%, \( P<0.001 \)) was significantly higher in patients with asymptomatic brain lesions. A multivariate analysis allowed us to recognize LVH as the only independent predictor for the presence of ischemic lacunes (\( P<0.001 \)). Moreover, we evaluated the impact of left ventricular geometry on asymptomatic cerebrovascular damage, and we found that hypertensives with concentric hypertrophy displayed more pronounced asymptomatic cerebrovascular damage compared with patients with eccentric hypertrophy.

Conclusions—Our study demonstrates that LVH is associated with cerebral damage even in the absence of clinical symptoms. Thus, the presence of cardiac damage provides important prognostic clues about the presence of asymptomatic cerebral damage. (Stroke. 2003;34:1766-1770.)

Key Words: cerebral infarction ■ electrocardiography ■ hypertension ■ magnetic resonance imaging ■ risk factors

Although arterial hypertension is a main risk factor for cardiovascular and cerebrovascular accidents, in the initial stages of hypertensive disease, most patients do not suffer any symptoms. In fact, high blood pressure (BP) only rarely causes headache, buzzing, palpitations, or vertigo. Therefore, most patients do not know that they are hypertensive, and when this is later diagnosed, it is difficult to establish an accurate duration of the hypertensive condition. This is a major health problem, because untreated hypertension can lead to serious consequences in several organs, such as the heart, brain, kidney, and eye. In clinical practice, it is important to identify early lesions in these organs, which give sound information about the duration of high BP, may precisely predict the long-term prognosis, and thus, lead to timely preventive measures. Actually, preclinical hypertensive lesions for most target organs are clearly identified: left ventricular hypertrophy (LVH) for the heart, microalbuminuria for the kidney, and fundus abnormalities for the eye. In contrast, preclinical hypertensive lesions in the brain have not been well characterized. Indeed, the degree of risk for hypertension-induced cerebrovascular disease increases progressively with the rise in BP levels. In particular, high BP accelerates atherosclerosis in large arteries and causes hypertrophy and thickening of the media of intracerebral vessels, leading to hypoperfusion and ischemic rarefaction of white matter. This is not an “all-or-none” phenomenon, as was once thought. In fact, a reduction in cerebral blood flow can produce any degree of brain injury, from an asymptomatic condition, such as “silent” cerebral infarction, to a reversible or persistent loss of function, such as transient ischemic attack and stroke. The different impact of cerebral blood flow abnormalities on brain damage depends on the duration and intensity of ischemia and efficiency of the collateral circulation and cardiac output.

Previous studies on hypertension-induced brain injury have mostly focused on major cerebrovascular events, such as

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transient ischemic attack and stroke, rather than on preclinical hypertensive brain lesions.\textsuperscript{14,15} In these studies, it has been demonstrated that the increased incidence of stroke or transient ischemic attack is associated not only with the hypertensive condition but also with hypertension-induced cardiac injury. In particular, in hypertensive patients, the presence of LVH confers an increased risk for subsequent major cerebrovascular events. This evidence suggests that major cerebrovascular injury can be preceded by asymptomatic cerebrovascular damage, which parallels the onset of cardiac hypertrophy. On this issue, it is still unclear whether hypertension-induced LVH and asymptomatic cerebrovascular damage can occur concomitantly.

Today, magnetic resonance imaging (MRI) allows the assessment of asymptomatic cerebral damage by ascertaining the presence of low-intensity signals in the brain, so-called lacunes. Lacuna is the most common consequence of hypertensive cerebral lesions, consisting of focal damage to small, intracerebral arteries that is known as lipohyalinosis, causing them to occlude and giving rise to a small, ischemic lesion.\textsuperscript{16} Therefore, in this study, we focused our attention on the presence of asymptomatic brain injury, as revealed by MRI, in hypertensive patients with and without cardiac organ damage.

**Methods**

**Study Population**

One hundred ninety-five hypertensive patients were enrolled in the study. They were consecutive patients who visited the Department of Angio-Cardio-Neurologia, IRCCS Neuromed, from January 2000 to March 2002 for evaluation of hypertension. All participants agreed to have a brain MRI examination performed. Patients were classified as hypertensive if they were taking antihypertensive medications or if the average of 3 measurements was $\geq 140$ mm Hg for systolic or $\geq 90$ mm Hg for diastolic BP on 2 or more separate clinic visits. Office BP was measured by a physician using a mercury sphygmomanometer after the subjects had rested for 5 to 10 minutes, according to standard procedures. A structured questionnaire was administered to each patient to investigate his or her personal or family history of cardiovascular and cerebrovascular disease, and an accurate medical history was compiled by a physician. All patients underwent the clinic visit, urinalysis, blood studies, electrocardiography (ECG), echocardiography, and cerebral MRI. In this group of patients, we also evaluated risk factors such as age, sex, presence of diabetes, serum cholesterol levels, smoking habits, heart rate, and systolic and diastolic BP. Subjects with a history of diabetes or those who were receiving any anti-diabetic medication were considered diabetic. A large proportion of hypertensive individuals ($\sim 90\%$) were being treated with 1 or more medications in different combinations, including angiotensin-converting enzyme inhibitors, calcium channel blockers, $\beta$-blockers, diuretics, and others. Therefore, antihypertensive medication classes were considered as covariates in our analyses. Patients with secondary hypertension, congestive heart failure, documented permanent or paroxysmal atrial fibrillation, previous myocardial infarction, a history of symptomatic cerebrovascular accident, or evident cognitive dysfunction or those for whom a good-quality echocardiographic recording could not be obtained were excluded from the study.

**Echocardiographic Measurement of LVH (Echo-LVH)**

All echocardiographic studies were performed with a General Electric Vingmed System Five performance ultrasound machine. Echocardiograms (parasternal and apical views) were obtained at rest with the patients supine in the left lateral position. The overall 1-dimensional LV measurements and the 2-dimensional views were obtained according to the recommendations of the American Society of Echocardiography.\textsuperscript{17,18} LV mass was estimated from the formula of Devereux et al.\textsuperscript{19} $LVM (g) = 0.832 \times [VSTD + LVIDd + PWTd]^3 - (LVIDd)^3] + 0.6$, where $LVM$ is LV mass. $VSTD$ is the ventricular septal thickness at end-diastole, $LVIDd$ is LV internal dimension at end-diastole, and $PWTd$ is LV posterior wall thickness at end-diastole. $LVM$ is normalized for body height\textsuperscript{2} ($LVM^\text{b}$) and expressed in units of grams per meter\textsuperscript{2}. The presence of LVH was defined as an $LVM > 50$ g/m\textsuperscript{2} in either sex.\textsuperscript{20} Relative wall thickness (RWT) was measured at end-diastole as the ratio $2PWT/LVID$. A partition value of 0.44 for RWT, representing approximately the 99th percentile value in normotensive control subjects, was used for both male and female subjects.\textsuperscript{21,22} Four different patterns of LV anatomic adaptation to sustained hypertension were identified by categorizing patients according to the values of $LVM$ and RWT.\textsuperscript{23,24} Patients with increased $LVM$ and increased RWT were considered to have LV concentric hypertrophy, and those with increased $LVM$ and normal RWT were considered to have LV eccentric hypertrophy. Those with normal $LVM$ and either increased or normal RWT were considered to have concentric remodeling or normal LV, respectively.

**ECG Measurement of LVH (ECG-LVH)**

A standard 12-lead ECG was recorded at 25 mm/s, 1 mV/cm calibration. The Perugia score was used for diagnosis of LVH, because it has been demonstrated that this score is the most sensitive in detecting LVH.\textsuperscript{24,25} In brief, the score requires positivity of 1 or more of the following conditions: $SV + R + AVL > 2.4$ mV (men) or $> 2.0$ mV (women), typical LV strain, or a Romhilt-Estes score $\geq 5$.

**Magnetic Resonance Imaging**

Brain MRI was performed with a 0.5-T magnet (Philips Gyroscan II), consisting of axial proton density (PD)/T2 spin-echo (repetition time [TR] 2720 msec, echo time [TE] 2090 msec, field of view [FOV] 210 mm, slice thickness [THK] 5 mm, and gap 0.5 mm), sagittal T1 spin-echo (TR 500 msec, TE 24 msec, FOV 250 mm, THK 5 mm, and gap 0.5 mm), and coronal T2 fluid-attenuated inversion recovery turbo spin-echo (TR 6000 msec, TE 150 msec, inversion recovery time 2200 msec, FOV 210 mm, THK 6 mm, and gap 0.6 mm) images, and with a 1.5-T superconducting magnet (Signa, General Electric) for axial PD/T2 fast spin-echo (TR 4000 msec, TE 81/117 msec, FOV 24\times24 mm, THK 5 mm, and sp [space] 1.5 mm), coronal T2 fluid-attenuated inversion recovery fast spin-echo (TR 8000 msec, TE 110 msec, inversion recovery time 2000 msec, FOV 24\times24 mm, THK 5 mm, and sp 1.5 mm), and sagittal T1 spin-echo (TR 440 msec, TE 14 msec, FOV 24\times24 mm, THK 5 mm, and sp 1.5 mm). The imaging findings were analyzed by 2 neuroradiologists who were blinded to all clinical, echocardiographic, and ECG information, and their agreement was 92%.

Three different types of asymptomatic brain lesion were identified by MRE: disseminated punctate lesions, lacunes, and territorial lesions involving the anterior, the middle, and the posterior cerebral arteries. Punctate lesions were defined as small, hyperintense areas ($\leq 5$ mm), visible only on T2-weighted sequences; lacunes (within 1 cm) were instead detectable as hyperintense areas on T2-weighted images and as hypointense areas on T1-weighted images; and territorial lesions (up to 2 cm) were observed as hyperintense areas on T2-weighted images and as isointense areas on T1-weighted images. Asymptomatic brain lesions were also stratified with regard to their extent: no lesions, 1 to 5 lesions, 6 to 10 lesions, 11 to 20 lesions, and $> 20$ lesions.

**Statistical Analysis**

Differences between hypertensive patients with and without asymptomatic cerebrovascular damage were analyzed by the 2-tailed, unpaired, Student’s $t$ test for numeric variables. $\chi^2$ was applied as appropriate for categorical variables. Multivariate analysis was performed with all of the considered variables included in the regression to obtain independent risks associated with each variable analyzed. Values are expressed as mean $\pm$ SE.

**Results**

Essential-hypertensive patients were classified into 2 groups according to the presence or absence of asymptomatic cere-
brovascular damage as punctate lesions, lacunes, and/or territorial lesions. Preclinical cerebrovascular damage was present in 107 of the 195 patients. Table 1 shows the baseline characteristics of the 2 groups. Subjects with asymptomatic cerebrovascular damage were older (67±1 versus 54±1 years, P<0.001) but did not differ from subjects without the damage with respect to sex and smoking habit. Diabetes was more common in subjects with asymptomatic cerebrovascular damage, although this difference did not reach statistical significance (P=0.072).

Serum cholesterol level, heart rate, and diastolic BP did not differ between the 2 groups. Moreover, both the anamnestically derived duration of hypertension and the number and distribution of antihypertensive agents used for treatment, which could reflect severity of hypertension, were not different between the 2 groups. Essential-hypertensive patients with asymptomatic cerebrovascular damage showed significantly higher values of systolic BP (147±2 versus 140±2 mm Hg, P=0.017) compared with hypertensive patients without such brain damage. More important, the presence of echocardiographically determined LVH was much more frequent in patients with asymptomatic cerebrovascular damage (83% versus 47.7%, P<0.001). In addition, when LVH was determined by a less sensitive method such as ECG, only 60% of echocardiographically determined hypertrophic patients were classified as hypertrophic; also in this case, LVH was significantly correlated with asymptomatic cerebrovascular damage (56% versus 22%, P<0.001).

In addition to analyzing the risk of having asymptomatic cerebrovascular damage associated with each variable, multivariate analysis demonstrated that only LVH was associated with the presence of asymptomatic brain damage (P<0.05). Next, to evaluate the impact of LV geometry on the presence of asymptomatic cerebrovascular damage, we classified our study population according to the presence of concentric or eccentric remodeling. Asymptomatic cerebrovascular damage was significantly augmented in hypertensive patients with both eccentric and concentric LVH compared with those with normal ventricular geometry. Interestingly, hypertensive patients with concentric hypertrophy displayed more pronounced asymptomatic cerebrovascular damage than did patients with LV eccentric hypertrophy (Figure 1).

Regarding the type of lesions, we observed that more serious lesions, such as lacunes and cerebral artery territorial lesions, were distributed significantly more in LVH patients, irrespective of LV geometry (Figure 1). Finally, as shown in Table 2, the extent of the lesion was also significantly correlated with LVH (P<0.001 in univariate and P=0.003 in multivariate analysis).

**Discussion**

Our findings demonstrate a strong relation between echocardiographically or ECG-determined LVH and asymptomatic cerebrovascular damage in hypertensive patients. Moreover, the results of the present study also indicate that concentric LVH is associated with the risk of having preclinical brain damage more strongly than is eccentric LVH.

The association between cardiac and cerebral injury in hypertension confirms the increasing evidence that LVH can

**Table 1. Clinical Characteristics of Hypertensive Patients According to the Presence of Asymptomatic Brain Lesions**

<table>
<thead>
<tr>
<th></th>
<th>Absence of Lesions (n=88)</th>
<th>Asymptomatic Brain Lesions (n=107)</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±1</td>
<td>67±1*</td>
<td>&lt;0.001*</td>
<td>0.249</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>40</td>
<td>46</td>
<td>0.730</td>
<td>0.936</td>
</tr>
<tr>
<td>F</td>
<td>48</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, %</td>
<td>46.6</td>
<td>44</td>
<td>0.614</td>
<td>0.153</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>15</td>
<td>25</td>
<td>0.072</td>
<td>0.315</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>228±4</td>
<td>226±4</td>
<td>0.928</td>
<td>0.346</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±1</td>
<td>71±1</td>
<td>0.929</td>
<td>0.645</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140±2</td>
<td>147±2*</td>
<td>0.017*</td>
<td>0.386</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>86±1</td>
<td>85±1</td>
<td>0.249</td>
<td>0.167</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>9±2</td>
<td>10±1</td>
<td>0.901</td>
<td>0.602</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>Echo 47.7</td>
<td>83</td>
<td>&lt;0.001*</td>
<td>0.001†</td>
</tr>
<tr>
<td></td>
<td>ECG 22</td>
<td>56</td>
<td>&lt;0.001*</td>
<td>0.009†</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>48%</td>
<td>46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>30%</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>44%</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>24%</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>15%</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01 in univariate.
†P<0.01 in multivariate.
be considered a potent sign of generalized preclinical disease in hypertensive patients and that concentric hypertrophic LV remodeling is related to an advanced degree of target-organ disease in hypertension. On this issue, Shigematsu et al have shown that extracardiac target-organ damage, such as preclinical hypertensive retinopathy and renal damage, is already present in hypertensive patients with concentric hypertrophy. However, early studies on the presence of brain injury in hypertension have mainly focused on major cerebrovascular events. In fact, the Framingham Heart Study and, subsequently, Verdecchia et al demonstrated the association between LVH and symptomatic cerebrovascular disease, such as stroke and transient ischemic attack. Our study is the first that clearly demonstrates in hypertensive patients the close association between LVH, particularly concentric hypertrophy, and preclinical cerebrovascular damage in a large, white population with detailed characterization of asymptomatic brain disease.

LVH is strictly related not only to the presence but also to the kind and extent of asymptomatic lesions. In particular, smaller lesions, such as punctate lesions, are also present in patients without LVH, probably because of the age of our study population, whereas larger lesions, such as lacunes and cerebral artery territorial lesions, are closely associated with the occurrence of LVH. Moreover, our statistical analysis has revealed that in hypertensive patients, only LVM remained significantly associated with asymptomatic cerebrovascular disease after additional adjustment for the other common risk factors. In this way, we have demonstrated that the presence of LVH predicts the presence of preclinical brain damage independently of other risk conditions that predispose to cerebrovascular disease. Although only a few studies have investigated asymptomatic cerebrovascular damage in hypertensive patients, all previous observations support our results. The Cardiovascular Health Study, limited to elderly patients with a history of coronary heart disease or congestive heart failure, first discussed the association between white matter lesions and LVH. In a further study limited to a Japanese population, Kohara et al showed the relation of LVH and concentric geometry to asymptomatic cerebrovascular damage in essential hypertension. Finally, Sierra et al have recently reported in a small number of hypertensive patients the increased incidence of asymptomatic brain damage.

The mechanisms connecting LVH to cerebrovascular injury are still unclear. It has been hypothesized that the association of cardiac and cerebral injury could be due to a generalized impact of arterial hypertension that underlies both phenomena. On this issue, it is well documented that both the brain and heart are targets of hypertension-induced organ damage. Moreover, LVH, in particular concentric hypertrophy, induces diastolic dysfunction that has been demonstrated to be an independent indicator of nonvalvular atrial fibrillation. Thus, LVH that predisposes to atrial fibrillation could also facilitate cerebral lesions through a cardiac thromboembolic mechanism.

The occurrence of LVH in our patients was detected by 2 independent methods. In fact, although echocardiography should be the noninvasive procedure of choice in evaluating the cardiac effects of systemic hypertension because it is more sensitive and specific than ECG, in clinical practice almost every patient with hypertension receive a standard ECG, whereas echocardiography is performed only in selected cases. The lower sensitivity of ECG in detecting LVH was confirmed by our study, in which only 60% of echocardiographically diagnosed hypertrophic patients were also found to be hypertrophic by ECG. However, what is important is detecting cardiac damage, because the correlation between LVH and asymptomatic cerebrovascular damage was found, irrespective of the method of detection.

The main conclusion of our study is that LVH can also provide information that facilitates identification of individuals

---

**TABLE 2. Extent of Asymptomatic Brain Lesions in Hypertensive Patients According to Echocardiographically Determined Left Ventricular Hypertrophy**

<table>
<thead>
<tr>
<th>No. of Lesions</th>
<th>No LVH (%)</th>
<th>LVH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>46 (73)</td>
<td>42 (32)</td>
</tr>
<tr>
<td>0–5</td>
<td>11 (17)</td>
<td>40 (31)</td>
</tr>
<tr>
<td>6–10</td>
<td>2 (3)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>11–20</td>
<td>1 (2)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>4 (6)</td>
<td>20 (15)</td>
</tr>
</tbody>
</table>

---

*Percentage of asymptomatic cerebral damage according to ventricular geometry. Open bars represent punctate lesions, striped bars represent lacunes, and filled bars represent territorial lesions. \(^{*}P<0.05\) versus normal ventricle, \(^{#}P<0.05\) versus eccentric hypertrophy.*
at high risk for future stroke but who present with only silent brain damage at the moment. This has important prognostic value, because there are several lines of evidence showing that asymptomatic brain injury is a main independent risk factor for future stroke. In particular, Lechner et al.33 and Kobayashi et al.34 have demonstrated that subjects with silent cerebrovascular infarction showed a higher incidence of future stroke.

In light of our results, we suggest that the possibility of cardiac hypertrophy be explored in hypertension, whatever the means of detection, not only to discover cardiac damage but also to distinguish patients at high risk of developing brain injury. Moreover, cerebral neuroimaging analysis in hypertensive patients with LVH will allow more precise estimation of the asymptomatic cerebrovascular disease and the need to begin specific, antihypertensive and antiplatelet treatments. In particular, in these patients at high risk for symptomatic cerebral events, proper antihypertensive treatment should be targeted not only to normalize BP values but also to limit cardiac damage, which could help lessen some of the pathophysiological mechanisms involved in the further progression of brain injury.

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Left Ventricular Hypertrophy Is Associated With Asymptomatic Cerebral Damage in Hypertensive Patients

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