Background—It is uncertain whether left ventricular hypertrophy (LVH) confers an increased risk for cerebrovascular disease in apparently healthy patients with essential hypertension.

Methods and Results—A total of 2363 initially untreated hypertensive patients (mean age 51±12 years, 47% women) free of previous cardiovascular disease were followed up for up to 14 years (mean 5 years). At entry, all patients underwent diagnostic tests, including ECG, echocardiography, and 24-hour ambulatory blood pressure (BP) monitoring. At entry, the prevalence of LVH was 17.6% by ECG (Perugia score) and 23.7% by echocardiography (LVM >125 g/m²). Over the subsequent years, 105 patients experienced a first stroke or transient ischemic attack. The cerebrovascular event rate was higher among patients with LVH at entry, diagnosed by either ECG or echocardiography, than among those without hypertrophy (both P<0.01). After control for the significant influence of age, sex, diabetes, and 24-hour mean ambulatory BP, LVH by ECG conferred an increased risk for cerebrovascular events (relative risk [RR] 1.79; 95% CI 1.17 to 2.76). LVH by echocardiography also conferred a higher risk for cerebrovascular events (RR 1.64; 95% CI 1.07 to 2.68). For each increase in LV mass of 1 SD (29 g/m²), there was a significant independent increase in the risk for cerebrovascular events (RR 1.31; 95% CI 1.09 to 1.58).

Conclusions—In apparently healthy patients with essential hypertension, LVH diagnosed by ECG or echocardiography confers an excess risk for stroke and transient ischemic attack independently of BP and other individual risk factors.

Key Words: hypertension ■ stroke ■ hypertrophy ■ prognosis ■ blood pressure ■ epidemiology
BP from a direct contribution of LVH to the increased risk of developing stroke. As pointed out by Devereux, long-term prognostic studies of stroke in populations with baseline measurements of both LVM and ambulatory BP are needed to resolve this uncertainty.

In the present study, we investigated whether LV hypertrophy at baseline predicts acute cerebrovascular events at follow-up in a large cohort of initially untreated, uncomplicated hypertensive patients of a wide range of ages in whom basal measurements of LVM and ambulatory BP had been obtained.

**Methods**

The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study was established in 1986 as an observational registry of morbidity and mortality in initially untreated subjects with essential hypertension. Approximately 50 family doctors are involved in referring their patients with elevated BP for complete diagnostic checkup and therapeutic advice. At entry, all patients had office BP $\geq 140$ mm Hg systolic and/or $\geq 90$ mm Hg diastolic on $\geq 3$ visits. BP was measured by a physician with a mercury sphygmomanometer with subjects sitting and relaxed for $\geq 10$ minutes. Three measurements were averaged for analysis. Ambulatory BP was recorded with an oscillometric device (SpaceLabs) set to take a reading every 15 minutes throughout 24 hours.

A standard 12-lead ECG was recorded at 25 mm/s, 1 mV/cm calibration. None of the subjects were receiving digitalis. An ECG score previously developed and validated in our laboratory (Perugia score) was used for diagnosis of LVH. The score requires positivity of $\geq 1$ of the following: $SV_{1}+RaVL \geq 2.4$ mV (men) or $\geq 2.0$ mV (women), typical LV strain, or a Romhilt-Estes score of $\geq 5$. M-mode echocardiographic study of the LV was performed under cross-sectional control. Details about reading procedures and reproducibility in our laboratory are reported elsewhere. LV mass was calculated according to Devereux and corrected by body surface area expressed in square meters. LVH was defined by an LVM $>125$ g/m², a cutoff supported by prognostic evidence.

**Follow-Up**

Follow-up was primarily the responsibility of family doctors, in cooperation with our hospital staff. Treatment was aimed at reducing office BP to $<140/90$ mm Hg by use of lifestyle and pharmacological measures. Diuretics, $\beta$-blockers, ACE inhibitors, calcium channel blockers, and $\alpha_{1}$-blockers, alone or combined, were the antihypertensive drugs most frequently used. Periodic contacts with family doctors and phone interviews with patients were arranged to ascertain vital status and occurrence of major cardiovascular events.

**Assessment of End Points**

Hospital records and other source documents of patients who died or suffered an end-point event were reviewed in conference by the authors. Stroke was defined as a new neurological deficit lasting $>24$ hours, in the absence of underlying potentially important nonvascular causes. Patients with stroke were hospitalized during the acute phase, and brain imaging and other diagnostic tests were carried out for determination of stroke type (ischemic, hemorrhagic, or unknown) according to the classification of the Stroke Data Bank. Transient ischemic attack (TIA) was diagnosed by a neurologist or internist in the presence of a rapid onset of a focal neurological deficit lasting $>30$ seconds and $<24$ hours and presumably due to ischemia. The PIUMA protocol required the deficit to be present during the qualifying clinical examination to be accepted and coded as a terminating event.

**Statistical Analysis**

Statistical analysis was performed with SPSS (SPSS Inc) and SAS-Stat (SAS Institute). Parametric data are reported as mean±SD. For subjects who experienced multiple events, analysis was restricted to the first event. Survival curves were estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated with stepwise Cox models. We first tested a baseline model using the following covariates: age (years), sex (female, male), family history of premature cerebrovascular disease (no, yes), diabetes (no, yes), serum cholesterol (mmol/L), serum triglycerides (mmol/L), smoking habits (nonsmokers, current smokers), body mass index (kg/m²), left atrial dimension (cm), antihypertensive treatment at follow-up (lifestyle measures alone, diuretics, and $\beta$-blockers alone or combined, ACE inhibitors and calcium antagonists alone or combined, other drug combinations), and incident atrial fibrillation during follow-up (no, yes). Subsequent improvements in the model fitting were tested by entering, one at a time, office BP and average 24-hour ambulatory BP. Mean BP was calculated as diastolic BP+(pulse pressure)/3. Finally, LVH diagnosed by ECG or echocardiography (no, yes) was entered into different models. LVM (g/body surface area) was also entered as a continuous variable. Population-attributable risk, an estimate of the proportion of outcome events that can be attributed to a given risk marker taking into account its prevalence and hazard ratio, was defined as $100\times[(\text{prevalence} \times (\text{hazard ratio} - 1)) / (\text{prevalence} \times (\text{hazard ratio} - 1) + 1)]$. Prevalence was the number of patient-years of observation with a risk marker present divided by the total observation time. In 2-tailed tests, values of $P<0.05$ were considered statistically significant.

**Results**

Follow-up data were available in 2363 of 2390 subjects (98.9%), and only 1.1% were lost to follow-up. The main baseline characteristics of the study population are reported in Table 1. Systolic and mean BP, both office and ambulatory, were higher in the subgroup with future events than in subjects without events (all $P<0.01$). Diastolic BP did not differ between the subgroups.

In the overall population, the prevalence of LVH by ECG at entry was 17.6%. LVH by ECG was present in 37.5% of patients who subsequently developed a cerebrovascular event and 16.7% of those who did not ($P<0.01$).

Echocardiograms were not obtained because of administrative reasons in 103 subjects. In the remaining 2260, echocardiographic tracings were of good quality for determination of LVM in 87.3% of subjects ($n=1972$). Prevalence of LVH by echocardiography was 23.7% in the total population and significantly more frequent in patients with future events (46.7%) than in those without events (22.8%; $P<0.01$).

Over a mean follow-up period of 5 years (range 0 to 14 years), there were 105 new cases of stroke ($n=76$) or TIA ($n=29$). Brain imaging was carried out during hospitalization in all subjects with stroke. Stroke was ischemic in 58 subjects, hemorrhagic in 12, and of unknown origin in 6. The overall rate of cerebrovascular events (per 100 person-years) was 0.89 in the total population, 0.73 in the subgroup without, and 2.04 in that with LVH by ECG ($P<0.001$). Similarly, event rate was 0.57 in the subgroup without versus 1.50 in that with LVH by echocardiography ($P<0.001$). Figure 1 reports survival curves and event rates in either group. The increased risk of cerebrovascular events associated with LVH was significant both over and under the age of 60 years (Figure 2). The incidence of cerebrovascular events (per 100 person-years) was 1.12 among the subjects with suboptimal echocar-
diographic tracings versus 0.80 among those with optimal tracings (P<0.20; log-rank test).

At the time of the terminating event or censoring contact, 41.7% of the subjects were receiving lifestyle measures alone, 10.8% β-blockers alone or combined with diuretics, 20.0% ACE inhibitors or calcium antagonists alone or combined, and 27.5% other drug combinations.

Impact of Atrial Fibrillation
All patients were in sinus rhythm at entry. During follow-up, there were 50 new cases of atrial fibrillation, and 9 of these patients subsequently developed a cerebrovascular event. The rate of events (per 100 person-years) was 1.23 among patients without atrial fibrillation during follow-up and 3.23 among patients with incident atrial fibrillation (log-rank test, P=0.013). At entry, patients with future atrial fibrillation were older (58±11 years) and had higher values of 24-hour ambulatory BP (145±15/89±11 mm Hg) and LVM (129±40 g/m²) than subjects who stayed in sinus rhythm (51±12 years, 138±15/87±10 mm Hg, and 108±29 g/m², respectively; all P<0.05).

Multivariate Analysis
The relative risk (RR) for cerebrovascular events (Table 2) was 1.17 (95% CI 0.98 to 3.90; P=NS) for every 10 mm Hg increase in office mean BP and 1.31 (95% CI 1.09 to 1.57; P=0.004) for every 10 mm Hg increase in 24-hour mean BP. After control for age, sex, diabetes, and 24-hour mean BP, LVH diagnosed by ECG conferred an increased risk for cerebrovascular events (RR 1.79; 95% CI 1.17 to 2.76). When echocardiographic data entered the equation in place of ECG data, for each increase in LVM of 1 SD (29 g/m²) there was a significant independent increase in the risk for cerebrovascular events (RR 1.31; 95% CI 1.09 to 1.58). When

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population</th>
<th>No Event (n=2258)</th>
<th>Event (n=105)</th>
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<tbody>
<tr>
<td>Age, y</td>
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<td>Sex, % male</td>
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<td>Body mass index, kg/m²</td>
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<td>Office mean BP, mm Hg</td>
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<td>Office HR, bpm</td>
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<td>24-h systolic BP, mm Hg</td>
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<td>24-h HR, bpm</td>
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<td>LV hypertrophy at ECG, %</td>
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<td>Interventricular septum, cm</td>
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<td>LVM, g</td>
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<td>LVM index, g/BSA (m²)</td>
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<td>LV hypertrophy at echocardiography, %</td>
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HR indicates heart rate; BSA, body surface area. Data are mean (±SD). See text for details. *P<0.01 vs subjects without event.
LVH by echocardiography entered the model as a binary (yes-no) variable, the associated RR for cerebrovascular events was 1.64 (95% CI 1.07 to 2.68). When LVH by ECG and LVM as a continuous variable or categorized as >125 versus <125 g/m² were forced into the same model, the echocardiographic measures lost statistical significance (P=0.41 and 0.56, respectively).

When the 3 components of the Perugia score were separately forced into the same model, after control for age, sex, diabetes, and 24-hour mean BP, the association of typical strain with future cerebrovascular events was significant (RR 2.14; 95% CI 1.14 to 4.07; P=0.018), that of modified Cornell voltage bordered significance (RR 1.62; 95% CI 0.97 to 2.70; P=0.06), and that of the Romhilt-Estes score (5 points) was not significant (P=0.64).

The population-attributable risk for cerebrovascular events was 13.2% for LVH by ECG and 12.2% for LVH by echocardiography.

Figure 3 shows that the age-adjusted 5-year probability of cerebrovascular events markedly increased with LVM at any level of mean 24-hour ambulatory BP. The other tested covariates (see Statistical Analysis), including incident atrial fibrillation, did not yield significance.

Discussion

In our large sample of patients of all ages with essential hypertension, LVH diagnosed by ECG or echocardiography identified a large subgroup at increased risk of stroke and TIA over a subsequent follow-up lasting up to 14 years. To maximize assessment of the predictive value of BP, thereby providing a more precise estimate of the independent prognostic value of LVH, ambulatory BP was used. In a previous study from our group, 24-hour mean BP was the most important ambulatory BP component for prediction of stroke.21 Even after a control for 24-hour mean BP, the link between LVH and cerebrovascular events remained strong and independent.

Previous Studies

An association between LVH and risk of stroke had been reported previously in studies limited to elderly subjects (mean age 68 years in the report from Framingham10 and 82 years in the study by Aronow et al11) and without ambulatory BP data. The present study extends such observations and provides novel information. For the first time, the prognostic value of LVM for stroke risk is recognized in the specific setting of patients with essential hypertension without previous cardiovascular disease. Second, our observations were not limited to elderly subjects, because the age span covered 8 decades. Third, and perhaps most important, our data provide the first consistent evidence that LVM is independent of BP for prediction of cerebrovascular events because its prognostic value remained significant after not only office but also 24-hour ambulatory BP had been taken into account.
Role of ECG

Our findings also provide evidence that the standard ECG may have an important role for prediction of stroke in patients with uncomplicated hypertension. The prevalence of LVH by ECG is generally believed to be low, being 3% in the general population and only slightly higher in hypertensive subjects. In contrast, although the prevalence of LVH by echocardiography in our population was comparable to that in the literature, the prevalence of LVH by ECG was as high as 17.6% owing to use of a score characterized by greater sensitivity and prognostic value than traditional ECG criteria and whose performance is not affected by obesity. By this criterion, a consistent subset of patients was identified as being at increased risk of cerebrovascular events (2.04 events/100 person-years versus 0.73 events in those without hypertrophy).

Possible Mechanisms

Our study was not designed to clarify the mechanisms by which LVH confers a higher risk of cerebral vascular events in patients with hypertension. Atrial fibrillation, a potential precursor of stroke, is predicted by LVH. In our study, which enrolled only subjects in sinus rhythm at entry, cases of atrial fibrillation occurring during follow-up were not excluded, so as to avoid a potential source of selection bias of the sample. This was unlikely to affect the link between LVH and cerebral vascular events, however, because only a small fraction of events (9 of 105) occurred in patients who eventually experienced atrial fibrillation. Furthermore, when incident atrial fibrillation was analyzed as a covariate in the Cox model, it did not yield significance.

In the present study, the predictive value of LVH was independent of that of BP. This is not surprising, because it is known that interindividual variation in LVM is explained only slightly by BP. Thus, LVM might reflect long-term exposure to several factors in addition to BP (such as genetic, hormonal, or metabolic) that might be active both in the growth of LVM and progression of atherosclerosis. In our experience, only 5% of LVM variability was accounted for by 24-hour systolic BP, whereas 60% of variability was associated with postload insulin, sex, insulin-like growth factor 1, and body mass index. In other studies, LVH showed an association with carotid structural changes and asymptomatic cerebral vascular lesions, and a connection between dyslipidemia and development of LVH was recently reported.

Limitations

Because the PIUMA population includes only white subjects, caution is needed in extrapolating our results to different ethnic groups. Another limitation, inherent to observational cohort studies, is the lack of control for occasional changes in antihypertensive regimen over time. Furthermore, because TIAs had to be symptomatic at the time of clinical examination, their incidence may have been underestimated. Finally, because only 31.4% of subjects repeated baseline tests during follow-up before the terminating event, we could not assess the prognostic impact of serial changes of risk factors.

Implications

Our data provide a rationale for intervention studies to assess the value of pharmacological measures to prevent stroke in high-risk subjects with LVH. It will also be important to establish whether regression of LVH per se confers a lesser risk for stroke and whether prevention of LVH by control of hypertension and obesity may reduce the burden of stroke. In stroke-prone hypertensive rats, LVH regression induced by treatment reduced stroke incidence. Finally, our findings show for the first time that hypertensive patients at increased risk of cerebral vascular events can be identified by improved interpretation of the traditional ECG.

Conclusions

In a large cohort of patients with essential hypertension, the association between LVH diagnosed by ECG or echocardiography and subsequent cerebral vascular events was independent of multiple risk markers, including age, sex, diabetes, and, most notably, ambulatory BP. These findings indicate
that LVH represents an independent risk factor for acute cerebrovascular disease in hypertensive patients.

Acknowledgments

The study was supported by grants from the Associazione Umbra Cuore e Ipertensione, Perugia, and by grant 9906104773-006 from MURST, Rome, Italy. We thank Mariano Cecchetti and Paolo De Luca for nursing assistance.

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Left Ventricular Hypertrophy as an Independent Predictor of Acute Cerebrovascular Events in Essential Hypertension

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Circulation. 2001;104:2039-2044
doi: 10.1161/hc4201.097944

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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