Regional Cerebral Blood Flow in Chronic Hypertension
A Correlative Study

Flavio Nobili, MD; Guido Rodriguez, MD; Stefano Marenco, MD; Fabrizio De Carli, PhD; Monica Gambaro, PhD; Cristoforo Castello, MD; Roberto Pontremoli, MD; Guido Rosadini, MD

Background and Purpose: Cerebral hypoperfusion has occasionally been reported during essential hypertension. We explored regional cerebral blood flow in a large series of neurologically asymptomatic hypertensive patients to determine relations among cerebral blood flow, concomitant main vascular risk factors, and the most common signs of end-organ damage.

Methods: Regional cerebral blood flow was measured by the $^{133}$Xe inhalation method in 101 hypertensive patients without clinically apparent central nervous system involvement, including 39 mild to moderate untreated and 62 mild to severe treated patients.

Results: Compared with age- and sex-matched normal control subjects, cerebral blood flow was significantly reduced in untreated hypertensive patients ($P<.01$) and to a lesser extent in treated patients ($P=.047$). Both regional and global cerebral blood flow reductions were observed in approximately one third of patients in both groups. Analysis of variance failed to show significant correlations between cerebral blood flow and total cholesterol concentration, mean arterial blood pressure, duration of disease, or the presence of retinopathy or left ventricular hypertrophy. In the treated group, the quality of control of hypertension significantly influenced both global cerebral blood flow ($P=.007$) and cerebrovascular resistance ($P<.0001$).

Conclusions: Focal or diffuse cerebral hypoperfusion is present even in neurologically asymptomatic hypertensive patients, especially when untreated; good control of blood pressure may preserve cerebral perfusion and reduce cerebrovascular resistance. Regional cerebral blood flow examination represents a relatively simple and low-cost technique to explore the perfusional condition of the brain, one of the main target organs of hypertensive disease. (Stroke 1993;24:1148-1153)

Key Words • cerebral blood flow • hypertension • hypoperfusion

Main end-organs of hypertensive disease, such as the retina and the heart, are routinely investigated by morphofunctional techniques. In contrast, available means to study the brain as an end-organ are more limited; they are usually expensive or involve radiation exposure for the patient (eg, computed tomography), and the specificity of the electroencephalogram is generally considered too low for this purpose.

In recent years the growing availability of atraumatic and sensitive methods to assess cerebral metabolism and cerebral blood flow (CBF) (including positron emission tomography, $^{133}$Xe clearance, and single-photon emission computed tomography) offered a unique opportunity to better understand cerebral function during either cerebral or systemic disorders. These methods seem adequate to assess cerebrovascular involvement due to hypertension.

Indeed, considerable effort has been expended to define modifications of CBF autoregulation during hypertension by acute manipulation of blood pressure (BP), but it is not feasible to apply such a complex and risk-prone procedure as a screening test on a broad patient population. On the other hand, only a few reports concerning cerebral perfusion in patients with chronic hypertension without acute modifications of BP have appeared. Although the early work by Kety et al did not show global CBF (gCBF) abnormalities in a small, poorly selected group, more recent studies have shown that cerebral hypoperfusion may be found both in hypertensive patients with neurological complaints, such as transient ischemic attacks, and in those without clinically evident cerebral involvement, especially if untreated; it was also shown that hypertension enhances the CBF decrease that naturally occurs with age.

To substantiate on a wider series than previously reported the finding of regional CBF (rCBF) reduction in chronic hypertension and to determine relations...
Prevalence of Vascular Risk Factors and Signs of End-Organ Damage in Untreated (n=39) and Treated (n=62) Groups of Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
<th>Total</th>
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<tbody>
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<td></td>
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<td>%</td>
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<tr>
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<td>34</td>
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<tr>
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<td>2.6</td>
<td>6</td>
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<tr>
<td>Extracerebral vascular disease</td>
<td>1</td>
<td>2.6</td>
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*All patients had a grade I or II retinopathy, according to Wegener-Keith classification.

among CBF, signs of involvement of main target organs, and concomitant vascular risk factors, rCBF was measured by the $^{133}$Xe inhalation method in untreated and treated hypertensive patients who were apparently free of neurological disease.

**Subjects and Methods**

All hypertensive patients studied for a period of 6 years (1985 to 1990) were referred to us by two city centers for the diagnosis and treatment of hypertension. The diagnosis of hypertension was made by the two referring centers following common criteria for the diagnosis of essential hypertension, after excluding subjects with secondary hypertrophy. All patients matching the inclusion criteria for the study were selected, without randomization. Patients with previous history or with signs or symptoms referable to central nervous system disease of any kind were excluded. Patients with overt renal or hepatic failure, uncontrolled diabetes, or hematologic disorders, including anemia, were also excluded.

Thirty-nine patients (28 men, 11 women; age range, 19 to 64 years [mean, 42.69±14.07 years]) were affected by mild or moderate essential hypertension and were never treated with antihypertensive drugs (untreated group; mean known duration of disease, 28.28 months).

Sixty-two patients (30 men, 32 women; age range, 35 to 78 years [mean, 56.46±11.05 years]) were affected with mild to severe essential hypertension at the time of diagnosis; all were being treated with one or more antihypertensive drugs at the time of the study (treated group; mean known duration of disease, 84.14 months).

In the treated group, the quality of control of BP was established by the referring centers. BP was recorded every other week for 2 months by the referring centers or by the general practitioner. Control was evaluated according to the following system: 0, good control (BP lower than 140/90 mm Hg in at least three of four recordings); 2, poor control (BP values higher than 140/90 mm Hg in at least three of four recordings); and 1, intermediate control (BP higher than 140/90 mm Hg on two occasions). According to these criteria the treated group was divided into 22 patients with good control, 27 patients with intermediate control, and 13 patients with poor control.

The study was approved by the ethics committee of our institution; all patients gave their informed consent, and women were examined within the first 5 days of their menstrual cycle, according to Italian radiological conventions. We considered it unethical to expose all patients to the radiation involved in brain computed tomographic examination; however, we suggested that it might be useful in patients with significant hypoperfusion. Six patients accepted this procedure; for one patient we were able to obtain a magnetic resonance imaging examination, which was not readily available at the time of the study.

In 63 (62.4%) of the 101 patients continuous-wave Doppler sonography of neck vessels (Angioscan III, Unigon Company) was also performed, disclosing mild to moderate stenosis (less than 70% of lumen reduction) of an internal carotid artery in 4 patients (3 of these in the treated group) and a 50% stenosis of the right subclavian artery in 1 patient (treated group). In 9 more patients slight vessel wall irregularities were found.

In all patients, creatinine clearance, urinalysis, electrocardiogram, funduscopic optic examination, and serum total cholesterol concentration were determined within 1 week from the day of rCBF examination. Serum total cholesterol was measured after overnight fasting by an enzymatic method (Monotest Cholesterol High Performance method; Boehringer Mannheim GmbH, Germany). Hypertensive retinopathy was graded by the two ophthalmologists working in the two referring centers. The results of echocardiography were not taken into account in this study because they were not available in all patients.

To obtain indexes of end-organ damage, a 0/1 score was used to indicate the absence or presence, respectively, of renal (by creatinine clearance, urinalysis), cardiac (by electrocardiogram), and retinal (by funduscopic optic examination) involvement. The same score was also used to indicate diabetes mellitus, substantial smoking (more than 15 cigarettes per day), and the presence of signs or symptoms of extracerebral vascular disease (such as coronary heart disease and peripheral vascular disease).

The prevalence of end-organ damage and vascular risk factors concomitant to hypertension is shown in the Table. Left ventricular hypertrophy was observed somewhat more frequently in the treated group, probably as a consequence of more advanced age and duration of hypertension.

Variables with a prevalence of 10% or less in the whole patient group (ie, diabetes mellitus, presence of reduced glomerular filtration rate, extracerebral vascular disease, and smoking) were not taken into consider-
ation because they were not considered of statistical interest.

crCBF data from 189 healthy control subjects (the data base of the laboratory) were used for statistical comparison as well as to obtain two groups of 39 and 62 subjects matched according to age and sex with the untreated and treated groups.

crCBF was measured at rest by the $^{133}$Xe inhalation method (Novo Cerebrograph 32-c, Hadsund, Denmark)\(^\text{10}\) with 32-probe equipment (16 for each hemisphere), according to the procedure described in detail elsewhere.\(^\text{6}\) Briefly, the subject lies in a supine position in a quiet and dark room and breathes through a face mask a mixture of air and $^{133}$Xe (5 to 6 mCi/L) for 1 minute, then room air for 10 minutes. A two-compartment analysis\(^\text{10}\) was performed on the washout curves of the tracer from the head, and both compartmental and noncompartmental flow parameters were computed. Because of its greater reliability in low-flow conditions,\(^\text{11}\) the initial slope index (ISI) was used in the present study.

Expired Pco$_2$ (Peco$_2$) was monitored during the examination by a capnograph; all subjects were normocapnic (mean Peco$_2$: untreated group, 39.6±2.1 mm Hg; control subjects of untreated group, 39.1±1.8 mm Hg; treated group, 39.3±2.0 mm Hg; control subjects of treated group, 37.8±1.4 mm Hg), and individual ISI values were not adjusted for Peco$_2$, as suggested by others.\(^\text{12}\)

BP was measured at the beginning of the rCBF examination, and mean arterial BP (MABP) was computed as Diastolic BP+[Systolic BP–Diastolic BP] ÷ 3. MABP ranged between 98 and 160 mm Hg in the untreated group (mean±SD, 120.97±12.64 mm Hg) and between 97 and 157 mm Hg in the treated group (mean, 116.84±12.73 mm Hg). Cerebrovascular resistance (CVR) was computed as the ratio between MABP and global CBF: CVR=MABP/CBF. Mean CVR was 2.44±0.44 in the untreated group and 2.46±0.45 in the treated group.

rCBF data were displayed by a bidimensional color mapping system developed in our laboratory, allowing for statistical comparisons.\(^\text{6}\)

**Statistical Analysis**

Absolute values. A gCBF value was obtained for each patient and control subject by averaging the 32 probe values. Mean values for each of the 32 probes as well as a mean gCBF value were computed for both patient groups and control subjects. Mean values for each patient group were then compared with matched control subjects by the unpaired t test.

**Standardized normal deviate (z).** To identify individual patients who deviated from the normal reference sex-matched group of the same age decade, both gCBF and rCBF values were transformed to z values by the formula\(^\text{13}\):

$$Z_{ij} = \frac{X_{ij} - \overline{X}_i}{S}$$

where $X_{ij}$ is the absolute CBF value, $i$ indicates the probe, $j$ the subject, $\overline{X}_i$ is the corresponding mean value for the reference group, and $S$ its standard deviation. To reduce type I error resulting from multiple simultaneous tests, a hypoperfused region was detected when at least two adjacent probes gave a z value lower than $-1.96.\(^\text{14}\)

**Correlations.** Because of the well-known influence of age on CBF, absolute gCBF values were normalized for age by calculating the standardized normal deviate $z^{13}$ as:

$$\frac{X_j - X_e}{S}$$

where $j$ indicates the patient, $X_j$ the patient’s gCBF value, $X_e$ the value estimated by regression of gCBF vs age on a normal reference group, and $S$ the estimated pooled standard deviation.

Values of $z$ were then used in the analysis of variance (ANOVA), which was performed by the Statistical Analysis System (SAS, Cary, NC) on the overall patient group to explore the relations between CBF and known duration of disease, MABP, total cholesterol concentration, presence of retinopathy, and left ventricular hypertrophy. In the treated group, relations between the quality of BP control and MABP, CBF, and CVR were also explored by ANOVA.

**Results**

**Group Comparisons (Absolute Values)**

Even without signs or symptoms of cerebral damage at the time of the study as well as in the medical history, mean gCBF was significantly ($P<.01$) lower in the untreated group (50.2±6.1 ISI) compared with control subjects (54.5±5.9 ISI); statistical comparison showed significant CBF reduction in all explored regions and particularly ($P<.001$) in the left occipital and the right frontoparietal parasagittal regions (Fig 1); less pronounced hypoperfusion ($P<.02$) was found in the left frontotemporal and the right temporo-occipital regions, while the remaining areas exhibited hypoperfusion of intermediate severity ($P<.01$).

Mean gCBF differed slightly ($P=.047$) between the treated group (48.6±6.2 ISI) and control subjects (50.7±5.4 ISI). In the treated group the hypoperfused ($P<.05; P<.02$) areas were found in the left frontal and parietal regions and right frontorolandic regions (Fig 2).

**Deviations of Individual Patients**

In the untreated group, 9 (23.1%) patients showed one or more significantly hypoperfused regions (6 patients in one or both frontorolandic areas, 1 in the left parietal region, 2 with a multifocal hypoperfusion pattern) and 6 (15.4%) a reduced gCBF, with an overall frequency of rCBF abnormality of 38.5%. In the treated group, 11 (17.7%) patients had focal hypoperfusion (5 in one or both frontorolandic regions, 3 in one parietal area, 3 with a multifocal hypoperfusion pattern); 11 patients (17.7%) showed a significant decrease of gCBF, with an overall frequency of rCBF abnormality of 35.5%.

Two of the four patients with internal carotid artery stenosis showed global hypoperfusion, one a focal hypoperfusion in the hemisphere contralateral to stenosis, and one a normal rCBF; the patient with subclavian stenosis had normal rCBF values.
Correlations

The ANOVA failed to show significant correlations between CBF and duration of hypertension, MABP, total cholesterol level, and the presence of retinopathy or left ventricular hypertrophy in the whole group of patients.

Relation to Quality of Blood Pressure Control

Among treated patients, mean MABP was 107.05±7.61 mm Hg in patients with good BP control, 117.37±7.78 mm Hg in patients with intermediate control, and 132.31±12.13 mm Hg in those with poor control; mean CVR was 2.18±0.3 in patients with good BP control, 2.44±0.28 in patients with intermediate control, and 2.94±0.52 in those with poor control.

Quality of BP control was inversely correlated (ANOVA) to MABP (P<.0001) and to CVR (P<.0001) and directly correlated to CBF (P=.007; Fig 3).

Discussion

Approximately one third of neurologically asymptomatic hypertensive patients, both untreated and treated, showed cerebral hypoperfusion, either focal or diffuse. Untreated patients had significantly lower mean rCBF.

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Discussion

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values than normal control subjects; treated patients showed a milder reduction. These results agree with previous data on smaller series from our laboratory as well as from other laboratories. Although these differences were small in absolute terms, it should be stressed that the power of our statistics was greatly enhanced by the random selection of control subjects matched for age and sex. This consideration may also explain differences from an early study of gCBF in hypertension, which differed from the present investigation also in the number of patients and in their physiological condition (general anesthesia).

However, our group may not be considered as representative of the general population of hypertensive patients (patients were not randomized by the two referring centers), and it cannot be ruled out that some patients with silent cerebral infarction were included (because of the lack of morphological examination of the brain in the majority of cases).

It has been suggested that CBF reduction may be due to vascular hypertrophy of either medium- or small-sized vessels and capillaries. This hypothesis is supported by data in stroke-prone spontaneously hypertensive rats (SHR-SP), which showed that rCBF together with glucose utilization was reduced during the development of hypertension and that effective control of hypertension in early stages restored CBF to normal, whereas CBF reduction in old SHR-SP was irreversible because of long-standing arterial wall thickening.

Another reason for rCBF reduction could be the presence of white matter lesions or of lacunae in hypertensive subjects, which could lead to cortical deafferentation and a decrease in metabolism. The prevalence of white matter lesions reported by Schmidt et al was similar to the prevalence of hypoperfusion in our patients, and in two studies asymptomatic lacunae were associated with gray and white matter CBF reduction. All seven morphological brain examinations available in hypoperfused patients showed neither lacunae (often below the resolution of computed tomographic scanners) nor periventricular white matter lesions.

The most common site of lacunae is the watershed zone between the middle and anterior cerebral arteries (frontal and parietal white matter), and we found the highest incidence of hypoperfusion in individual cases in areas directly overlying these territories. A previous positron emission tomography study showed prefrontal hypoperfusion, and in a more limited series we observed mainly left frontotemporal hypoperfusion, but the number of cases with regional hypoperfusion in each of these studies is too small to provide a definite picture of the topography of rCBF reduction in hypertension.

In treated patients, CBF was dependent on the quality of BP control, suggesting the possibility that effective treatment can preserve CBF at least in some patients, possibly an indication of regression of simple vascular hypertrophy. CVR was progressively higher in patients with intermediate and poor BP control compared with patients with good control, differentiating the three groups even more significantly than CBF; CVR is therefore a sensitive index of cerebrovascular status in hypertensive patients.

The relative preservation of CBF in treated patients might also be due to the effect of drugs such as propranolol or clonidine, which were reported to increase CBF in hypertensive patients. Those results lack replication, and other studies showed no CBF increase for other commonly used antihypertensive medications. We were unable to perform an appropriate analysis because too many different drug regimens had been used in this cohort.

Total cholesterol concentration did not correlate with CBF. This would be consistent with data that show that intracranial circulation is relatively unaffected by total cholesterol concentrations, even though there is one study suggesting that lower rCBF can be found in hyperlipemic patients.

Finally, cerebral hypoperfusion does not parallel the most common signs of damage of both the retina and the heart. Morphofunctional changes associated with hypertension appear to proceed heterogeneously in different target organs; indeed, a lack of correlation between CBF and markers of end-organ damage has also recently been reported in diabetic patients.

In conclusion, evidence for cerebral hypoperfusion in a large group of both treated and untreated neurologically asymptomatic hypertensive patients is given. In treated patients the quality of BP control is significantly related to both CBF and CVR. Follow-up studies, which are now ongoing at our institution, may add relevant information, especially regarding the question of recovery of rCBF during effective treatment.
References


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