Serial Magnetic Resonance Imaging of Rat Brain After Induction of Renal Hypertension

Marc R. Del Bigio, MD, PhD, FRCPC; Hui Jin Yan, MD; Piotr Kozlowski, PhD; Garnette R. Sutherland, MD, FRCPC; James Peeling, PhD

Background and Purpose—Hypertension is a major risk factor for ischemic and hemorrhagic stroke and may also cause more chronic and subtle brain injury. Progressive brain changes in a rat model of renal hypertension have been assessed to better understand the pathogenesis of hypertensive brain damage.

Methods—Young adult rats were made hypertensive by partial occlusion of both renal arteries. MR images of brain were obtained weekly, and histopathological outcome was assessed. A separate group of rats was used to measure brain specific gravity and Evans blue dye content as an indicator of extravasation.

Results—Rats developed maximal mean systolic blood pressures of 173 to >300 mm Hg, reaching a plateau in 6 to 8 weeks. Rats whose mean systolic pressure never exceeded 210 mm Hg never had brain lesions, while rats whose mean systolic pressure exceeded 276 mm Hg consistently developed brain lesions. Brain T2 values increased with increasing blood pressure. Lesions seen on MRI corresponded to those seen histologically. MRI also demonstrated transient brain expansion, probably due to diffusely increased water content, and rarely demonstrated focal cortical edema, which had no histological correlate. These transient phenomena, as well as hemorrhagic and ischemic infarcts, occurred mainly during the phase of climbing blood pressure and early stages of stable hypertension.

Conclusions—Serial MRI reveals aspects of hypertensive brain disease that cannot be studied by histological examination alone. The observed phenomena are likely related to loss of autoregulation and/or blood-brain barrier integrity. Breach of blood vessel integrity is less likely once the vessels become accustomed to high pressures. (Stroke. 1999;30:2440-2447.)

Key Words: autoregulation n brain edema n hypertension n stroke, experimental n rats

Hypertension is a major cause of brain damage in humans. In some cases the outcome may be acute ischemic stroke or intracerebral hemorrhage, while in other patients brain damage may be more chronic and subtle, restricted to microvascular changes or foci of damage in deep cerebral white matter. MRI is an important tool for detecting these lesions. On T2-weighted MR images, foci of high signal intensity are present in the majority of persons older than 65 years. Their existence correlates with the presence of hypertension, and the corresponding pathological changes are usually foci of ischemic damage. White matter damage may contribute to cognitive and motor dysfunction, the most serious manifestation being Binswanger-type dementia.

While prevention of hypertension is the ideal management, it remains important to understand how hypertension affects the brain before the onset of permanent damage. Several animal models of hypertension that progress to stroke are available. The 2-kidney, 2 clip model of renal hypertension yields a very high proportion of severely hypertensive animals. The hypertension is stable and not renin dependent, apparently involving brain angiotensin and per-

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was opened in the midline, the renal arteries were exposed and isolated bilaterally, silver clips with a gap of 0.2 mm were placed on the arteries, and the wound was closed (n=75). Sham-operated control rats (n=19) were treated identically, but the arterial clips were not applied. Rats were monitored closely during recovery and treated for pain with buprenorphine (0.025 mg/kg SC). They were allowed free access to food and water for the duration of the study. Systolic blood pressure was monitored daily in awake rats by a tail cuff with a pressure transducer whose upper limit was 300 mm Hg. Venous blood was drawn from the tail vein to allow measurement of serum sodium, potassium, urea, and creatinine at the time of renal artery constriction and 7 to 13 weeks later when animals were hypertensive (systolic pressure >200 mm Hg). Rats were weighed and observed for approximately 10 minutes daily to assess their general behavior, including grooming and exploratory activities, level of alertness, and physical well-being. Rats showing severe deficits (acute paresis, severe lethargy, loss of consciousness) considered to represent strokes were given soft food and water via a medicine dropper and kept comfortable to aid recovery. Those that did not improve neurologically were killed by perfusion fixation.

**Brain Water and Vascular Permeability Studies**

Five weeks after renal artery constriction, 10 sham-operated rats and 12 rats with renal artery constriction, 6 of which exhibited severe deficits taken to represent strokes, received an injection of 5% Evans blue dye in normal saline (0.4 mL/100 g IP). They were killed 24 hours later by decapitation without clearing of the vascular contents because perfusion could potentially alter brain water content. The brain was rapidly removed, and the dorsal cerebrum, including cortex and subjacent white matter, was dissected. To measure brain water content, tissue samples (5 to 10 mg) were dissected from each side, and specific gravity was evaluated in a gradient column of kerosene and bromobenzene. To measure Evans blue dye content, the remaining cerebrum was homogenized and extracted with dimethylformamide. Evans blue dye content in the solvant was measured spectrophotometrically at 632 nm, and the concentration was determined with the use of a standard curve. Evans blue dye content in control brains was assumed to be intravascular.

**Magnetic Resonance Imaging**

Of the remaining 63 rats with renal artery constriction, 24 underwent weekly brain MRI. Those rats showing symptoms of stroke had an additional MR examination performed as soon as possible after onset of symptoms. All MR studies used a Magnex 9.4-T, 20-cm horizontal-bore magnet interfaced to a Bruker MSL-X console (Bruker Instruments). Rats were anesthetized with isoflurane administered via a nose cone. The head was positioned in a 35-mm-diameter saddle coil and held in place with an incisor bar. Sixteen contiguous 1.2-mm-thick coronal slices, centered 1.5 mm posterior to bregma, were imaged in 2 interleaved sets to minimize interslice excitation. The acquisition matrix size was 256×128, with a field of view of 4×4 cm². Spin-echo data were acquired with 2 averages as 8 echoes separated by an echo time of 21.6 ms, with a repetition time of 2000 ms. Data sets were zero filled to 256×256 before Fourier transformation. Quantitative T2 data were obtained by fitting the data pixel by pixel to a single exponential decay whose time constant was taken to be T2. The average value of T2 in a defined region of interest was then read directly from these images. All T2-weighted MR images were examined qualitatively to document the time course of focal changes and for comparison with the final histological findings. T2 values were measured directly from 4×4 pixel squares located in parasagittal cortex at the midbrain coronal level bilaterally, right lateral cortex at the coronal level of the fornix, left striatum at the same level, and from 3×3 pixel squares in anterior corpus callosum and posterior white matter bilaterally.

**Histological Analysis**

All surviving rats that were not used for measurement of brain water were killed by overdose of pentobarbital followed by perfusion through the left ventricle with 4% paraformaldehyde in 0.1 mol/L phosphate buffer at a column pressure of 130 mm Hg. Sham-operated control rats were killed 26 to 33 weeks after surgery. Hypertensive rats that did not display stroke symptoms were killed 10 to 33 weeks after renal artery constriction. Rats that showed stroke symptoms were killed 1 to 7 days after the first appearance of symptoms (2 to 24 weeks after surgery). After perfusion, hearts and kidneys were removed and weighed, and the rats were decapitated. The brain was fixed in situ for 24 to 48 hours, then removed, weighed, sectioned into 6 to 7 coronal slices 1.5 mm thick, and embedded in paraffin. Microtome sections 6 μm thick were stained with hematoxylin and eosin. Other selected sections were labeled with anti-glial fibrillary acidic protein or biotin-conjugated donkey anti-rat IgG, followed by detection with streptavidin/horseradish peroxidase and diaminobenzidine. Histological lesions and edema spread (determined by IgG labeling) were mapped on diagrams of coronal brain sections corresponding to MR images. The maximum dimension of the lesions was measured. Sequential MR images were inspected to help judge the age of the lesions.

In addition, white matter was inspected for rarefaction or cyst formation, and ventricle size was judged as normal or enlarged. An overall semiquantitative grade of damage was assigned, as follows: 0, no abnormalities; 1, mild changes, including small infarcts or hemorrhages or mild ventricular enlargement; 2, moderate changes, including cavitation of white matter, multiple small (<0.5 mm) infarcts, or hemorrhages; and 3, severe lesions, including large hemorrhages or multiple lesions damaging large areas of the brain.

**Statistical Analysis**

Data are reported as mean±SEM. Student’s t test was used to compare T2 values between time points. Regional T2 values were correlated with blood pressure with the use of linear least squares regression. The relationship between maximum blood pressure and the total number of lesions or damage grade was assessed by regression analysis. Kruskal-Wallis test was used for nonparametric data.

**Results**

Sham-operated control rats progressively gained weight and remained alert and well groomed throughout the experimental period. Nine rats with renal artery constriction died in the immediate postoperative period as a result of anesthetic complications, peritonitis, or renal failure. No data from these rats are reported. The 66 surviving rats with renal artery constriction exhibited decreased weight gain for 1 to 2 days after surgery and then exhibited progressive weight gain, although not as much as in the control rats (Table 1). Before renal artery constriction, the mean systolic blood pressure ranged from 100 to 136 mm Hg (mean, 116±3 mm Hg). This did not change in the sham-operated control rats (Figure 1). After renal artery constriction, all surviving rats developed stable hypertension. Maximum mean systolic blood pressure was reached within 6 to 8 weeks after surgery and ranged from 173 to >300 mm Hg (Figure 1), although blood pressure in 1 exceptional rat reached >300 mm Hg in only 2 weeks; this was followed by a severe hemorrhagic stroke.

Hypertensive rats suffered episodic listlessness and poor grooming associated with periods of weight loss (20 to 30 g). In most cases these episodes lasted 2 to 4 days, after which rats resumed normal behavior and weight gain. More severe deficits (including acute paresis, severe lethargy, and loss of consciousness), considered to represent strokes, developed in 44 of 66 rats. Changes in brain MR images could be identified during these episodes (see below). Among 54 hypertensive rats not used for brain.
water measurements, 38 showed signs of stroke 2 to 22 weeks after renal artery constriction (Figure 1).

After induction of hypertension, serum Na$^+$ and K$^+$ did not change in comparison to prehypertension values. There was an increase in serum urea (from 5.29$\pm$0.48 to 8.17$\pm$1.25 mmol/L) and creatinine (from 45.4$\pm$2.5 to 56.8$\pm$3.81 mmol/L) after development of hypertension, but these remained within the normal range for rats. Kidneys and hearts were examined in 8 sham-operated rats and 28 hypertensive rats. Hypertension was accompanied by a significant increase in heart weight due to left ventricle hypertrophy. However, no hypertensive rats showed signs of respiratory distress that would be suggestive of congestive heart failure. There was a decrease in kidney weight (Table 1). Seven rats had 1 kidney substantially smaller ($<$50%) than the other, and 4 of those had 1 kidney that had completely atrophied because of ischemic damage. Correlation coefficients were weak between maximum blood pressure and heart weight ($r=0.28$), kidney weight ($r=0.14$), or difference between kidney weights ($r=0.10$).

Brains of hypertensive rats were heavier than those of controls (Table 1). In comparison to control samples, cerebral cortex specific gravity was significantly lower in hypertensive rats without stroke and lower still in hypertensive rats with clinical evidence of stroke (Table 2). This indicates an increase in water content. Similarly, the content of Evans blue dye was significantly increased in cerebrum of these 2 groups (Table 3), suggesting that vascular permeability was increased.

The 9 sham-operated rats exhibited no histological abnormalities in brain. Among 54 rats that developed hypertension and were examined histologically, 32 (60%) had a neuro-pathological abnormality. From 1 to 17 discrete lesions of various types were identified in an individual brain. Acute infarcts were characterized by edema and neuronal eosinophilia; old infarcts were characterized by cavitation, gliosis, and residual macrophages. Acute lesions were surrounded by halos of extravasated IgG representing vasogenic edema. Twenty-two rats had diffuse edema in the white matter; in 18 it was related to acute hemorrhages in white matter, and in 4 it was related to infarcts in nearby gray matter. Eighteen rats exhibited chronic damage in occipital white matter characterized by expanded extracellular space, axonal loss, glial karyorrhexis, reactive astrogliosis, and rarely small hemosiderin deposits. Old cortical infarcts and chronic white matter damage exhibited negligible extravasated IgG. Among 27 rats with ischemic or hemorrhagic cortical lesions, 20 had associated surface arteries with thick hyalinized or degenerating walls and obliterated lumens, as has been previously documented. Four of these also had subarachnoid hemorrhage. Subjective thickening of small-artery walls and arterioles in cortex and basal ganglia was seen in 22 hypertensive rats. Rats with this vascular change had higher maximal systolic pressures than those without (268$\pm$6 versus 252$\pm$4 mm Hg; $P<0.02$, Student’s t test). Vessel wall size was not quantified because survival times and fixation quality varied. Six rats (11%) with no histological abnormalities suffered transient clinical deterioration that had been interpreted as stroke.

<table>
<thead>
<tr>
<th>TABLE 1. Weights of Body and Organs in Hypertensive Rats</th>
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<tr>
<td></td>
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<tr>
<td>Sham</td>
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<tr>
<td>Hypertensive</td>
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</table>

*Mean±SEM (grams) live body weight immediately before perfusion.
†Mean±SEM (grams) after perfusion fixation.
‡Mean±SEM (grams) side-to-side difference in kidney weight after perfusion fixation.
§$P<0.02$ vs sham values.

Figure 1. Combination graph showing the progressive increase in mean maximal systolic blood pressure ($\pm$SEM) (point graph, left vertical axis; $\circ$, rats with renal artery occlusion; $\bullet$, sham-operated control rats; $P<0.001$, difference from 2 weeks onward) and the times at which rats developed strokes (bar graph, right vertical axis). Note that most of the strokes occurred during the phase of climbing blood pressure and during the early period of stable hypertension but not in the late period of stable hypertension.
Rats whose mean systolic pressure never exceeded 210 mm Hg had no brain lesions, while rats whose mean systolic pressure exceeded 276 mm Hg all had brain lesions. Rats were stratified according to overall severity of histological brain damage. Mean maximum systolic blood pressure for those lacking brain lesions (grade 0, n=21) was 250±5 mm Hg compared with 260±8 for grade 1 damage (n=13), 259±7 for grade 2 damage (n=14), and 281±10 for grade 3 damage (n=6). These differences were not statistically significant (P=0.1068; Kruskal-Wallis test).

Among 24 rats with renal artery constriction that underwent weekly MRI, 16 exhibited stroke symptoms and focal brain abnormalities that were apparent on subsequent T2-weighted MR images. MR images from 4 of these rats also had abnormalities for 1 to 2 weeks before obvious stroke symptoms. Eight other rats exhibited small single infarcts that preceded a more severe stroke and death by 2 to 15 weeks. There was generally very good correspondence between lesions detected on the final MR image and larger lesions observed histologically. Of 106 large (>0.5 mm) histological lesions, 102 were detected on MR images and were of similar shape and size. However, small acute lesions (<0.5 mm), for example, white matter hemorrhages, were not resolved by MRI. Often they were included in, and hence obscured by, an edema-related large hypertensive region on the MR image. Four small hypertensive abnormalities located in the parasagittal cortex on final MR images had no apparent histological correlate. Of 13 rats with acute extensive white matter edema characterized by diffuse hyperintensity on MR, all had immunohistochemical evidence of IgG extravasation, although the geographic distribution of edema was larger on MR images. On T2-weighted images, the first appearance of an infarct was as a focus of hyperintensity due to edema, which resolved over a period of approximately 1 week (Figure 2). The location of infarcts was predominantly parasagittal in posterior aspects of the cerebrum. There were from 1 to 12 abnormal cortical foci in a given brain, and the size of these lesions ranged from 0.5 to 2.5 mm. Approximately half (15/27) of the infarcts had a hemorrhagic component. On MR images, acute hematomas were very hypointense and adjacent white matter was hyperintense because of edema spread. After 1 week, hematomas exhibited a more hyperintense signal as a result of cavity formation. Two clear examples of hemorrhage developing at a site of previous infarct were observed. In one of these, the rat developed a subdural fluid collection, possibly related to hemorrhage near the pial surface (Figure 2). Two examples were observed of a transient (1- to 2-week) focal increase in cortical signal intensity that did not correspond to any histological abnormality. These resembled parasagittal abnormalities that were subsequently found to be infarcts. Eight rats exhibited transient obliteration of the lateral ventricles, lasting 1 to 2 weeks, in the absence of other obvious MR image abnormalities. Three rats had 2 such episodes. In all cases there was correspondence between small ventricles on MR images and periods of lethargy and weight loss. Multiple lesions and severe diffuse white matter edema (Figure 3) were associated with severe neurological deficit. The final MR images demonstrated mild ventriculomegaly in 16 rats, 2 of whom had no focal lesions.

The measured T2 relaxation times for 5 different brain sites are given in Table 4. There were no significant differences between presurgery values (not shown) and postoperative week 1 values obtained before development of hypertension. Initial T2 values for white matter were significantly lower (P<0.001) than those of gray matter. As systolic blood pressure increased over the first 8 weeks after surgery, there was a corresponding progressive increase in T2 values of parasagittal cortex (r²=0.80, P=0.0028), a region found to be at high risk for hemorrhage or infarction. A similar correlation was observed between blood pressure and T2 values in lateral cortex (r²=0.76, P=0.0050) and striatum (r²=0.85, P=0.0012), although far fewer infarcts were seen in these locations. Once blood pressure stabilized, T2 values tended to return toward normal (Figure 4). The highest T2 values in gray matter were observed when the lateral ventricle size was smallest on MR images. Values tended to normalize as ventricles reexpanded (Table 4). These high T2 values were unrelated to development of focal lesions. White matter T2 values also correlated with increasing blood pressure over the first 8 weeks after surgery (r²=0.62, P=0.020) but did not change significantly when ventricles were obliterated. The highest white matter T2 values were associated with diffuse edema after an acute infarct. Separation of rats that went on to develop strokes from those that did not develop strokes revealed no differences in T2 values. T2 values for all sites in the week preceding a major stroke were no different than final values for animals that did not have a stroke.

**TABLE 2. Specific Gravity of Cerebral Tissue From Rats With Renal Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Control Mice (n=10)</th>
<th>Hypertensive Mice Without Stroke (n=6)</th>
<th>Hypertensive Mice With Stroke (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>1.0529±0.0003*</td>
<td>1.0492±0.0001*</td>
<td>1.0455±0.0002†</td>
</tr>
<tr>
<td>Left side</td>
<td>1.0529±0.0004*</td>
<td>1.0489±0.0001*</td>
<td>1.0454±0.0003†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.01 vs control.
†P<0.001 vs control and hypertensive rats without stroke.

**TABLE 3. Evans Blue Dye Content of Cerebral Tissue From Rats With Renal Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Control Mice (n=5)</th>
<th>Hypertensive Mice Without Stroke (n=6)</th>
<th>Hypertensive Mice With Stroke (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right side</td>
<td>1.00±0.19</td>
<td>1.97±0.37*</td>
<td>6.75±0.68†</td>
</tr>
<tr>
<td>Left side</td>
<td>0.91±0.19</td>
<td>1.58±0.21*</td>
<td>8.02±0.51†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Evans blue dye content in tissue is expressed in micrograms per 100 mg.
*P<0.05 vs control.
†P<0.01 vs control and hypertensive rats without stroke.

Discussion

In this experimental study using hypertensive rats, with MRI we observed transient increases in gray matter T2 relaxation times, which correlated with transient brain expansion and lateral ventricle compression and with periods of lethargy.
poor grooming, and weight loss. Increased T2 values in brain correlated with increased water content in experimental cerebral ischemia and brain injury and in hypertensive encephalopathy. Generalized brain swelling has been previously observed during acute arterial hypertension. Our specific gravity data confirm that brain water content was increased in hypertensive rats, including those that had not suffered focal brain damage. There is evidence that the capillary bed volume is expanded, independent of metabolic demand, in brains of rats with renal hypertension. There is also good evidence for focal edema generation in hypertension, presumably a consequence of disturbed autoregulation and increased permeability of blood vessels. Our data and those of others suggest that there is hydrostatic leakage of fluid from the vasculature into brain substance. Diffusion-weighted MR studies of patients with early hypertensive encephalopathy also support this notion. Episodic expansion of brain is therefore likely due to fluctuations in water content caused by mild diffuse transient changes in vascular permeability. In addition, rare foci of cortical edema appeared on MR images, with no histological damage subsequently identified. One possibility is that these foci represent a halo of edema surrounding very small infarcts that were missed in the histological assessment. An alternate possibility is that they represent foci of transient severe blood-brain barrier breakdown that do not result in permanent tissue damage.

T2 relaxation times increased during the weeks when blood pressure was climbing and then drifted toward normal values once blood pressure stabilized at a high level. This suggests that brain vasculature is more susceptible to breakdown during the phase of climbing blood pressure. Once blood pressure stabilizes, the vessels may undergo morphological and/or functional changes corresponding to a new set point of cerebral blood flow autoregulation. This allows them to function normally in the phase of chronic stable hypertension. The fact that strokes were less common during stable hypertension suggests that the modified vasculature provides at least partial protection from catastrophic infarcts and hemorrhages.

Histological lesions observed in this study were similar to those previously reported in this model and in the stroke-prone spontaneously hypertensive rat, although in earlier experiments the reported frequency of white matter damage was lower. High incidence of diffuse white matter damage might be explained by severity of hypertension in the 2-kidney, 2-clip model. The mechanism of brain damage due to hypertension has been the subject of numerous experiments. Vascular permeability increases before blood vessel injury is histologically apparent, perhaps as a result of increased pinocytotic vesicle activity. In rats with renal artery occlusion and nephrectomy, hypertension is associated with mural...
thickening and deposition of collagen, laminin, and fibronectin around the wall of pial and cerebral arterioles.25,26 Necrosis of blood vessel wall with associated infarction or hemorrhage is the end-stage result.27 Pathological changes observed in rat brain are similar to those found in brains of humans with malignant hypertension, eg, hypertrophied vessels, necrosis of vessel walls, hemorrhages, and infarcts.28,29

MRI has been useful for studying hypertensive patients. Brain edema and focal ischemic or hemorrhagic lesions characterized by changes on T2-weighted imaging in the clinical setting are similar to those described here.30 Of interest is a reversible occipital-parietal leukoencephalopathy documented by MRI in young adults with acute severe hypertension.31 The postulated pathogenesis is loss of autoregulation followed by extravasation of plasma across damaged blood-brain barrier.32 The reason for regional propensity is not known. Surprisingly, the parieto-occipital white matter is also more often damaged in rats with hypertension.33 Histologically, white matter damage in rats consisted of diffuse rarefaction apparently followed by loss of glia and axons and eventual cavity formation. This region corresponds to the boundary between middle and posterior cerebral artery distributions.34 Direct ischemic injury to white matter is a possible explanation, although the frequent proximity of small cortical infarcts suggests that secondary edema spread into white matter might also contribute.35 Because clinical examinations generally obtain T2-weighted images at relatively low magnetic field strength rather than quantitative T2 relaxation times, subtle global or diffuse edema such as that shown in this study might not be readily apparent.

MRI is a sensitive and accurate method for monitoring brain injury in rats with experimental renal artery constriction–induced hypertension.36 Use of MRI to study hypertensive animals repeatedly in a chronic situation gives some insight into dynamic brain changes and efficacy of antihypertensive treatment because one can follow the evolution of cerebrovascular lesions through their natural course. MRI also reveals transient subtle phenomena that are not detect-

### Table 4. Measured T2 Values in Brain of Hypertensive Rats

<table>
<thead>
<tr>
<th>Status</th>
<th>Parasagittal Cortex</th>
<th>Lateral Cortex</th>
<th>Striatum</th>
<th>Corpus Callosum</th>
<th>Posterior White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (n=18)</td>
<td>66.0±0.4</td>
<td>65.4±0.4</td>
<td>65.5±0.5</td>
<td>63.3±1.5</td>
<td>63.9±3.2</td>
</tr>
<tr>
<td>Week before ventricular obliteration (n=9)</td>
<td>73.1±1.0†</td>
<td>71.2±1.1†</td>
<td>73.4±1.7*</td>
<td>64.3±1.4</td>
<td>61.0±0.9</td>
</tr>
<tr>
<td>During ventricular obliteration (n=11)</td>
<td>73.5±1.2†</td>
<td>70.7±0.9†</td>
<td>75.3±1.4†</td>
<td>67.8±2.9</td>
<td>65.4±3.4</td>
</tr>
<tr>
<td>2 Weeks later with reexpanded ventricles (n=7)</td>
<td>71.2±2.6</td>
<td>69.5±2.3</td>
<td>70.2±2.9</td>
<td>68.6±4.5</td>
<td>70.1±6.5</td>
</tr>
<tr>
<td>Week before major stroke (n=13)</td>
<td>71.4±1.4*</td>
<td>67.6±1.2</td>
<td>72.0±1.8*</td>
<td>67.5±3.6</td>
<td>69.3±4.2</td>
</tr>
<tr>
<td>Final week, animals with stroke (n=15)</td>
<td>71.6±1.5*</td>
<td>68.8±2.0</td>
<td>72.5±1.9*</td>
<td>91.2±5.0†</td>
<td>98.4±3.4†</td>
</tr>
<tr>
<td>Final week, animals with no stroke (n=9)</td>
<td>70.1±2.3</td>
<td>70.5±1.5*</td>
<td>73.3±2.4*</td>
<td>68.2±3.0</td>
<td>69.8±5.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*P<0.02 vs initial (control) value.
†P<0.001 vs initial (control) value.

Figure 3. Set of T2-weighted MR images obtained 1 day before death of a rat that suffered a severe stroke. Histological and immunohistochemical examinations were used to identify the nature of the changes. Evident on all images is extensive white matter edema (hyperintense; panel a, white arrow). On panel b, there is a small focus of acute hemorrhage with surrounding edema (white arrow), an acute infarct with ischemic and hemorrhagic features (black arrow), and hypointensity in the internal capsules (*), which seems to correspond to mildly gliotic white matter. On panel c, there is an old ischemic infarct with neuronal loss, gliosis, and focal atrophy (white arrow) and a recent hemorrhagic infarct with hemosiderin-containing macrophages, mitotic cells, and vascular proliferation (black arrow). Panel d shows cavity formation in the posterior white matter (*) and an old atrophied infarct (black arrow) associated with hemosiderin and a large thrombosed blood vessel.

TABLE 4. Measured T2 Values in Brain of Hypertensive Rats
able by histological analysis.37 Furthermore, MRI yields volumetric data more easily than histological studies that require reconstruction. On the other hand, MRI was not able to resolve very small acute hemorrhagic lesions, which were often obscured by surrounding edema. Furthermore, despite the well-documented changes in brain water and T2 relaxation characteristics, these alterations were not predictive of impending stroke in an individual rat. This suggests that the immediate precursor to stroke is a catastrophic change in blood vessel integrity or patency. Nevertheless, the more subtle changes in blood-brain barrier integrity are associated with behavioral abnormalities, and it is not clear that these episodes are entirely benign. Careful analysis of transient brain water changes using MRI and quantitative T2 relaxation time analysis along with histopathological studies should allow characterization of more subtle chronic brain changes that are a consequence of hypertension and will be useful in the study of drug therapies.38

Acknowledgments
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References
Hypertension is a serious cause of cerebral blood vessel damage. Although detection and treatment of elevated blood pressure has greatly reduced the long-term damage to the blood vessels of the kidney and brain, hypertension in many patients remains undetected or poorly controlled. These patients have an increased risk of stroke and vascular dementia. \(^1\) Rapid elevation of blood pressure leads to brain edema, which is seen on MRI primarily in the posterior brain regions. \(^2\) Chronic hypertension, on the other hand, causes a progressive thickening of the blood vessel walls from a buildup of extracellular matrix macromolecules. As the population ages, long-term consequences of hypertension in subjects without stroke: a population-based study. \(^3\) Stroke, 1994;25:929–934.


Serial Magnetic Resonance Imaging of Rat Brain After Induction of Renal Hypertension
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