Chronic Antihypertensive Treatment in the Rat Reverses Hypertension-Induced Changes in Cerebral Blood Flow Autoregulation

Sisse Vorstrup, David I. Barry, Jens Ole Jarden, Ulrik Gerner Svendsen, Otto Braendstrup, David I. Graham, and Svend Strandgaard

SUMMARY Cerebral blood flow (CBF) autoregulation was studied in renal hypertensive rats receiving chronic antihypertensive treatment. Young Wistar Kyoto rats (WKY) were made hypertensive by the Loomis procedure i.e. partial infarction of one kidney with contralateral nephrectomy. Systolic tail blood pressure was measured at 2-week intervals throughout the study. After two months, by which time the rats had been severely hypertensive for 5-6 weeks, antihypertensive treatment was begun; reserpine, dihydroalazine and hydrochlorothiazide were administered in the drinking water. Blood pressure fell rapidly to normotensive levels and remained so. Following two months of antihypertensive treatment, the lower blood pressure limit of CBF autoregulation was studied during controlled bleeding. In age-matched untreated renal hypertensive WKY, the lower limit of autoregulation was in the mean arterial pressure range 90-109 mm Hg, as compared to 50-69 mm Hg in age-matched normotensive WKY. In contradistinction to the untreated rats, the treated rats had a normal lower limit of autoregulation, i.e. 50-69 mm Hg. It was inferred that the reversal of the functional change in CBF autoregulation reflected reversal of hypertension-induced cerebrovascular hypertrophy/hyperplasia.

Stroke Vol 15, No 2, 1984

IN CHRONIC HYPERTENSION, resistance vessel walls thicken in order to increase vascular resistance and protect against high intraluminal pressure. One consequence of these adaptive changes is resetting of the blood pressure range over which cerebral blood flow (CBF) can be maintained constant by autoregulation. The lower blood pressure limit of CBF autoregulation is the pressure at which autoregulatory dilatation becomes inadequate and flow decreases with pressure. In hypertension, the lower limit of CBF autoregulation is shifted towards high pressure, presumably as autoregulatory vasodilatation is impaired by resistance vessel wall thickening and luminal narrowing. This hypertension-induced shift in the lower limit of CBF autoregulation has been shown in man, 1,2 in the baboon3 and in the rat.4 Hypertension-induced adaptation has also been shown for the upper limit of CBF autoregulation in the baboon.3 Hence as regards CBF, hypertensive vascular changes impair the tolerance to acute hypotension, but improve the tolerance to acute rises in blood pressure. The clinical consequence of the shift in the limits of CBF autoregulation is that if the blood pressure of a hypertensive patient is rapidly lowered to normotensive levels, CBF will fall, possibly causing ischaemic brain damage. Thus rapid and severe pharmacological reduction of blood pressure as in emergency treatment of hypertension has been criticised.5,7 With chronic treatment of hypertension and a gradual normalisation of blood pressure there is time for reversal of some of the structural and haemodynamic consequences of hypertension. This may apply to CBF autoregulation in man8 and old spontaneously hypertensive rats, the latter being better able to maintain CBF during an acute blood pressure drop than are untreated rats.9 The present study examined whether chronic antihypertensive treatment of renal hypertensive rats would reverse the autoregulatory shift known to be present after 2 months of hypertension8 and restore a normal lower limit of autoregulation to the cerebral circulation.

Material and Methods

The experiments were performed on male Wistar Kyoto rats (WKY, F24) supplied by Møllegaard Ltd., Denmark. All rats were housed in the same room, and had free access to food and water. No salt or corticosteroids were given.

Induction of Hypertension and Treatment

At the age of one month, 60 rats were made chronically hypertensive by a modification of the Loomis technique.6 During halothane anaesthesia the right kidney was removed and one branch of the left renal artery was ligated, immediately resulting in ischaemia of approximately 50-70% of the kidney surface. The kidney was then placed subcutaneously, where it would become encapsulated by fibrous tissue. An age matched unoperated group of 15 WKY served as a control group. Systolic blood pressure (SAP) was measured at 2-week intervals by the tail-cuff photoelectric pulse pick-up method. In about 60% of the rats, tail pressure rose to between 200 and 240 mm Hg within 3-4 weeks, as compared to 130 mm Hg in the unoperated control WKY. The remaining rats either died, remained normotensive or developed severe debilitating hypertension, and were thus discarded. After two months, 30 of the renal hypertensive rats (RHR) were chosen for further study. These were sturdy, growing normally and without signs of neurological

From the Departments of Neurology and Psychiatry, Rigshospitalet, Copenhagen; Medical Department C, Gentofte Hospital; Pathology Department, Glostrup Hospital; Medical Department B, Herlev Hospital, Copenhagen, Denmark; and the Neuropathology Department, Institute of Neurological Sciences, South General Hospital, Glasgow, Scotland.

Address correspondence to: David J. Barry, Psychiatry Department, Rigshospitalet, 2100-DK Copenhagen, Denmark.

Received June 9, 1983; revision 1 accepted August 31, 1983.
impairment. The development of hypertension in those rats subsequently used for the autoregulation study is shown in Fig. 1. It was known from our earlier work that 2 months after becoming hypertensive, RHR exhibit an adaptive shift in the lower limit of CBF autoregulation of 20–30 mm Hg. Thus antihypertensive treatment was started at this point.

Of the 30 RHR chosen for further study, 15 were placed on chronic antihypertensive treatment and 15 were untreated. The number of rats was in excess of the number of good autoregulation studies required (six) in order to allow for deaths, inadequate treatment and experimental failures. Treatment was administered in the drinking water in the form of reserpine 1.4 mg/l, dihydralazine 80 mg/l, and hydrochlorothiazide 100 mg/l. For the first 4 days the solution was diluted 50% in order that blood pressure should not fall too rapidly. Daily intake per rat averaged 44 ml. After 2 months of treatment, 6 of the rats were used for the CBF autoregulation study, together with 6 untreated RHR and 6 normotensive control WKY. Antihypertensive treatment was withdrawn 5–6 hr before the autoregulation study.

**CBF Measurement**

CBF was measured with the intraarterial 133Xenon technique modified for rat studies. Anaesthesia was induced with 4% halothane, and maintained with 0.8% halothane in 30% O2:70% N2O. The rats were tracheostomised, paralysed with suxamethonium (40 mg/kg, and artificially ventilated. Both femoral arteries were cannulated, one for recording blood pressure, the other for blood sampling. A femoral vein was also cannulated for blood or drug administration. All extra- cerebral branches of the right common carotid artery were ligated, and the scalp and muscle overlying the right side of the calvarium was removed in order to minimize the extracerebral distribution of injected 133Xenon. The animals were heparinised (5000 IU/kg), and a polyethylene catheter (PP25) introduced retrogradely into the external carotid stump, with the tip positioned at the carotid bifurcation. The common carotid artery was not clamped during the cannulation. Surgery lasted for approximately 45 minutes, after which the animal was left to stabilize for one hour.

For each determination of CBF a 10–15 μl saline bolus containing 133Xenon (5–10 mCi/ml, Amersham) was injected into the carotid catheter. Clearance of 133Xenon from the brain was followed by external detection with a heavily collimated NaI(Th) crystal placed over the head, ipsilateral to the injection side. CBF was calculated by the initial slope method using the formula:

\[
\text{CBF} = -\frac{\lambda}{\text{In} \times 10} \times D_e \times 100 \text{ (ml/100g·min)}
\]

where the blood-brain partition coefficient for grey matter, \(\lambda\), is 0.87 ml/g, and \(D_e\) is the initial slope (the first 10–15 s) of a semilogarithmic recording of the clearance curve. The peak value of around 2000 cps ensured that the linearity of the clearance curve was not affected by low counting statistics. A correction curve was used to correct for the activity remaining from previous measurements when that activity exceeded 2% of the peak activity. Such correction was rarely necessary however.

Arterial tension of carbon dioxide (PaCO2) and oxygen (PaO2) together with pH (pHa), were measured at intervals during surgery/stabilization, and at each CBF measurement, with conventional microelectrodes (Radiometer, Copenhagen). The blood withdrawn for these measurements were substituted with blood from donor rats of the same condition (i.e. treated RHR, untreated RHR or normotensive). The rats were maintained at normocapnia (PaCO2 39–41 mm Hg) by adjustment of ventilation volume. Body temperature was maintained close to 37°C by means of a rectal-thermistor-controlled heating table. Arterial blood pressure was recorded throughout the study, with mean arterial pressure (MAP) and heart rate (HR) being calculated from the recording.

**Autoregulation Study**

The lower limit of CBF autoregulation was determined by controlled stepwise haemorrhagic hypotension in the 3 groups of rats. Following the one hour stabilization period, 2–3 baseline measurements were performed at 10 minutes intervals. To permit CBF measurements along the autoregulatory plateau in the normotensive control group and the treated RHR, blood pressure was raised in approximately 10 mm Hg increments by a slow intravenous infusion of angiotensin II amine (Hypertensin, CIBA), 5–20 μg/min. Blood pressure was then reduced stepwise by controlled withdrawal of sufficient blood to lower MAP by 10 mm Hg. At each level, MAP was allowed to stabilize for 10 minutes before CBF was measured. In this way, an autoregulation curve based on 8–12 measurements was delineated for each rat. The study typically lasted 3 hours.

**Neuropathology**

Following the CBF study, a neuropathological examination was undertaken. The rats were maintained in a stable condition for another two hours after the lowest blood pressure had been reached, that is 30–40 mm Hg. They were then sacrificed by perfusion fixation with FAM (40% formaldehyde/glacial acetic acid:methanol, 1:1:8 by volume). The brains were left in situ for 24 hours, then removed and immersed in FAM for another 48 hours before being processed for light microscopy. Each brain was cut in a similar way into eight coronal slices (five forebrain and three hindbrain) and embedded in paraffin. Particular care was taken to identify the left and right hemispheres. Seven-to eight-micrometer sections were stained using a technique combining Luxol fast blue and cresyl violet, and taken to identify the left and right hemispheres. Seven-to eight-micrometer sections were stained using a technique combining Luxol fast blue and cresyl violet, and also with hematoxylin-eosin. All brains were coded in a random number such that the neuropathological examination was performed blind, with the code being broken only after completion of this and related studies.
Statistics

Data for each series are given as the mean ± 1 SD after grouping according to MAP, using intervals of 20 mm Hg. Comparisons within the series were made by one way analysis of variance together with the Dunnett multiple comparison test16 using the MAP range in which baseline MAP fell as control range. The lower limit of CBF autoregulation in the present study is defined as the MAP range at which CBF (% baseline) fell significantly below the autoregulatory plateau of around 100% baseline CBF. Interseries statistical comparisons were not made. Results were accepted as significant at \( p < 0.05 \).

Results

Blood Pressure

The awake SAP was between 100 and 130 mm Hg in the control normotensive rats. After the Loomis procedure, hypertension ensued with SAP reaching 200–240 mm Hg within 4–5 weeks. In the untreated RHR, SAP remained at that level during the following 2–3 months. In those RHR that were given antihypertensive treatment, SAP fell to between 80 and 120 mm Hg over 4–5 days, remaining at that level throughout the treatment period. The individual SAP curves are shown in figure 1. At the time of the autoregulation study, SAP was 121 ± 10 mm Hg in control rats, 221 ± 15 in untreated RHR and 88 ± 10 in treated RHR (\( x \) ± 1 SD, \( n = 6 \)). Under anaesthesia, the corresponding MAP was 70 ± 4, 133 ± 11 and 80 ± 7 mm Hg, respectively (table 1). Thus anaesthesia had a marked barodepressant effect in the control and untreated rats, but not in the treated RHR.

Body and Heart Weight

Body weight increased from around 80g to 380 ± 12g in the control rats, 348 ± 30g in untreated RHR and 364 ± 13g in treated RHR, indicating that all rats were growing fairly normally. Left ventricular mass at the end of the study was 0.40 ± 0.04% in treated RHR and 0.32 ± 0.03% in untreated RHR, indicating reversal of the structural changes in cardiac muscle in the treated RHR.

Autoregulation Study

Baseline measurements of CBF, MAP and other relevant physiological parameters are shown in table 1. Control and untreated RHR were similar in all respects except for the significantly higher MAP in the untreated RHR. Treated RHR were similar to control for all parameters.

In table 2, all data measured during the autoregulation study are shown grouped according to MAP. Intervals of 20 mm Hg have been used except for the range 20–29 mm Hg. CBF has been calculated as percent of baseline CBF. The autoregulation curves for the three groups of rats are shown in figure 2. For statistical comparison, all results have been compared with the pressure range of the baseline MAP i.e. 70–89 mm Hg for controls and treated RHR, and 130–149 mm Hg for untreated RHR. The lower limit of autoregulation is defined in the present study as the MAP range that which CBF% baseline fell significantly below the autoregulatory plateau of around 100%. In control normotensive rats, values of CBF around 100% were maintained down to the MAP range 70–89 mm Hg, the lower limit of autoregulation being in the range 50–69 mm Hg. The untreated RHR were only able to autoregulate effectively to a MAP range of 110–129 mm Hg, the lower limit of autoregulation being 90–109 mm Hg. This indicates a 40 mm Hg shift in the lower limit of CBF autoregulation after 4 months of hypertension, as compared to a 20–30 mm Hg shift after 2–3 months of hypertension.4 In contradistinction to the untreated RHR, the treated RHR were able to autoregulate CBF down to the blood pressure range 70–89 mm Hg, and thus had a normal lower limit of CBF autoregulation of 50–69 mm Hg.

Neuropathology

As judged by uniform blanching and hardness of the specimen, satisfactory fixation was achieved in all animals, and cytological artefacts such as ‘dark cell’ and ‘hydropic cell’15,17 were absent. The ischaemic lesions found in 4 of the rats, usually small foci involving microvacuolation of cells, incrustation and shrinkage of cytoplasm and nucleus, were of the type reported previously in FAM fixed rat brain.15,18,19 Such lesions were found in RHR after haemorrhagic or acute pharmacological blood pressure lowering.4,20,21

Lesions were found in 1 of 6 normotensive control WKY, 1 of 6 treated RHR and 2 of 6 untreated RHR. In the normotensive control WKY there were 10 small lesions in the right hemisphere. In both untreated RHR the lesions were bilateral; in one rat there were 4 small lesions, two of which were situated posteriorly in the arterial boundary zone between the distribution of the middle and anterior cerebral arteries: in the other rat there was extensive necrosis of the right hemisphere and two left-sided lesions. In the single treated RHR there were 5 small right-sided lesions. In an earlier

---

**Figure 1.** Systolic arterial pressure in the normotensive control WKY and renal hypertensive WKY used for the autoregulation study. Pressure was measured in awake animals with the tail cuff-photoelectric pulse pickup method. Measurements were made at 2-week intervals, with additional measurements during the first week of treatment. Individual curves are shown.
study, lesions were found in 4 of 8 untreated RHR after haemorrhagic hypotension. The ischaemic lesions probably result from the combined effect of the hypertensive insult and carotid cannulation. The study indicates that the treated RHR were less susceptible to ischaemia during severe haemorrhagic hypotension. The ischaemic lesions were less susceptible to hypertensive treatment.

The main finding was that chronic treatment of renal hypertensive cerebral vascular disease was seen in one of the untreated hypertensive animals in which there was fibrinoid necrosis of a single pial artery.

**Discussion**

The main finding was that chronic treatment of renal hypertension in the rat restored a normal lower limit of autoregulation to the cerebral circulation. That only minor ischaemic lesions were induced by haemorrhage in a single treated rat is a reflection of their normal autoregulation. It is generally assumed that the functional shift in CBF autoregulation induced by hypertensive rats were thickened compared with the control and treated groups of animals. Definite evidence of hypertensive cerebral vascular disease was seen in one of the untreated hypertensive animals in which there was fibrinoid necrosis of a single pial artery.

---

### TABLE 1: Baseline Values of Cerebral Blood Flow, Mean Arterial Pressure and Other Relevant Physiological Parameters in the Normotensive (WKY) and Hypertensive (RHR) Rats That Were Subsequently Subjected to Controlled Haemorrhagic Hypotension

<table>
<thead>
<tr>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 g-min)</th>
<th>HR (b/min)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pH₂</th>
<th>PaO₂ (mm Hg)</th>
<th>T (°C)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>141 ± 9</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>133 ± 20</td>
</tr>
<tr>
<td>110-129</td>
<td>76 ± 9</td>
<td>97 ± 7</td>
<td>101 ± 3</td>
<td>25 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.4 ± 0.02</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>70-89</td>
<td>73 ± 9</td>
<td>77 ± 7</td>
<td>231 ± 36</td>
<td>39.7 ± 2.4</td>
<td>7.4 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>62 ± 17*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>30-49</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.07</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>20-29</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>263 ± 21</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
<tr>
<td>Control WKY</td>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>133 ± 20</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>110-129</td>
<td>76 ± 9</td>
<td>97 ± 7</td>
<td>25 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.4 ± 0.02</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>90-109</td>
<td>73 ± 9</td>
<td>77 ± 7</td>
<td>231 ± 36</td>
<td>39.7 ± 2.4</td>
<td>7.4 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>70-89</td>
<td>62 ± 17*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.07</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>30-49</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>263 ± 21</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
<tr>
<td>Untreated RHR</td>
<td>150-169</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>133 ± 20</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>133 ± 20</td>
</tr>
<tr>
<td>110-129</td>
<td>74 ± 16</td>
<td>97 ± 7</td>
<td>25 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.4 ± 0.02</td>
<td>155 ± 20</td>
<td>37.0 ± 0.6</td>
</tr>
<tr>
<td>90-109</td>
<td>73 ± 9</td>
<td>77 ± 7</td>
<td>231 ± 36</td>
<td>39.7 ± 2.4</td>
<td>7.4 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>70-89</td>
<td>62 ± 17*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.07</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>30-49</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>263 ± 21</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
<tr>
<td>Treated RHR</td>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>133 ± 20</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>110-129</td>
<td>76 ± 9</td>
<td>97 ± 7</td>
<td>25 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.4 ± 0.02</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>90-109</td>
<td>73 ± 9</td>
<td>77 ± 7</td>
<td>231 ± 36</td>
<td>39.7 ± 2.4</td>
<td>7.4 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>70-89</td>
<td>62 ± 17*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.07</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>30-49</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>263 ± 21</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
</tbody>
</table>
| Values are mean ± 1 SD. Each range vs baseline MAP range i.e. Control WKY and Treated RHR 70-89 mm Hg; Untreated RHR 130-149 mm Hg. *p < 0.01; t p < 0.05.
Lower Limit of Autoregulation

The lower limit of CBF autoregulation is the blood pressure at which autoregulatory vasodilatation of cerebral blood vessels becomes inadequate to maintain CBF, which then falls. This should not be equated with maximum dilatation of cerebral vessels as it has been shown that pial vessels will continue to dilate as blood pressure is brought below the lower limit of autoregulation i.e. whilst CBF is falling. In animal studies the lower limit of CBF autoregulation can be influenced by experimental conditions and the means of lowering pressure. The sympathetic activation provoked by haemorrhagic lowering of blood pressure is known to exert a weak vasoconstrictory effect on cerebral vessels. The latter tends to shift the lower limit of autoregulation to a slightly higher blood pressure, although the effect is minor compared with that in other organs such as the kidney. Pharmacological ganglion blockade will prevent this effect and thus a 'true' lower limit of autoregulation may be that obtained during ganglion blockade. In the present rat studies, the animals were anaesthetised with 0.8% halothane and paralysed with suxamethonium, both of which have slight ganglion blocking properties. In a similar study, the lower limit of CBF autoregulation in SHR and WKY during haemorrhagic hypotension was not influenced by the ganglion blocker trimetaphan (166 μg/kg/min) (Barry et al, unpublished observation). Furthermore, chemical sympathectomy (intraventricular 6-hydroxy dopamine) does not influence the lower limit of autoregulation during haemorrhagic hypotension in SHR.25 Thus under the experimental conditions used the lower limit of autoregulation is not influenced by sympathetic activity and the hypertensive shift in the lower limit reflects mainly structural changes in the cerebral vessels. For this reason we consider the choice of a lower limit of autoregulation during controlled bleeding as suitable for the present study of the effect of chronic antihypertensive treatment.

The results in the treated RHR must be interpreted with due regard to possible direct effects of the drugs used. Thus whether reserpine, dihydralazine and hydrochlorothiazide could have had an influence on CBF autoregulation by means other than their combined antihypertensive action deserves comment. Acute blood pressure lowering by certain drugs (e.g. the direct vasodilator dihydralazine) may bring pressure below the lower limit of autoregulation in RHR without any fall in CBF.21 This dilatation of cerebral vessels appears to 'extend' the lower limit of autoregulation. As drug treatment was withdrawn from the RHR 5–6 hr prior to the autoregulation study, and as dihydralazine is fairly rapidly metabolized, little residual effect would be expected. Reserpine, which accumulates in the body, could prevent a sympathetic shift during haemorrhagic hypotension but as discussed above, there is probably little such influence on CBF autoregulation under the present experimental conditions. The diuretic hydrochlorothiazide might influence resistance vessel water-logging and thus augment the reversal process. These direct effects could supplement the effects on CBF autoregulation of the reversal of structural changes that probably resulted from lowering of blood pressure. However, they would not be expected to account for the normal lower limit of CBF autoregulation in the treated RHR. Furthermore, it is generally accepted that the reversal of peripheral structural and haemodynamic changes is due to blood pressure lowering rather than any direct effect of the drugs used: hence findings are similar with a number of antihypertensive regimes and, in the case of hypertension induced by renal artery clipping, clip removal.

Resistance Vessel Adaptation in Hypertension

As CBF is the same in the untreated RHR as in the treated and control rats, despite a higher arterial pres-
sure, cerebrovascular resistance must be higher in the
former. The mechanism behind the increased resistance
in hypertension is probably structural adaptive
changes in cerebral resistance vessels i.e. arterioles, as
is the case elsewhere in the body.26 Medial thickening
with encroachment of cerebral arterial and arteriole
lumen has been demonstrated morphometrically in man,27, 28 and rat.22 The morphological changes are bet-
ter described for peripheral vessels than cerebral ves-
sels. In the early phase of hypertension, these changes
consist of smooth muscle cell hypertrophy and medial
hyperplasia, largely proportional to the pressure lev-
el,29 together with an increased logging of water and
electrolytes in the vessel wall.30 In longstanding hyper-
tensive disease, additional changes include accumula-
tion of fibrous proteins, elastin and collagen, and de-
generation of the muscle cells.31 The reversibility of
the functional adaptive changes would be expected to
depend on the nature of the underlying structural
changes: the initial changes of smooth muscle cell hy-
pertrophy and water-logging probably are reversible
following normalisation of blood pressure, whereas
this is less likely with the degenerative changes and
connective tissue proliferation.

Development or complete regression of the structur-
al adaptation can occur in a matter of weeks. The
former depends mainly on the degree of hypertension
whereas the latter depends in addition on the duration
of hypertension and age of the animal. Adaptive
changes in the cerebral circulation have been demon-
strated after 2 months of hypertension in baboon3-3 and
rat.22 The morphological changes are bet-
ter described for peripheral vessels than cerebral ves-
sels. In the early phase of hypertension, these changes
consist of smooth muscle cell hypertrophy and medial
hyperplasia, largely proportional to the pressure lev-
el,29 together with an increased logging of water and
electrolytes in the vessel wall.30 In longstanding hyper-
tensive disease, additional changes include accumula-
tion of fibrous proteins, elastin and collagen, and de-
generation of the muscle cells.31 The reversibility of
the functional adaptive changes would be expected to
depend on the nature of the underlying structural
changes: the initial changes of smooth muscle cell hy-
pertrophy and water-logging probably are reversible
following normalisation of blood pressure, whereas
this is less likely with the degenerative changes and
connective tissue proliferation.

Development or complete regression of the structur-
al adaptation can occur in a matter of weeks. The
former depends mainly on the degree of hypertension
whereas the latter depends in addition on the duration
of hypertension and age of the animal. Adaptive
changes in the cerebral circulation have been demon-
strated after 2 months of hypertension in baboon3-3 and
rat.22 The morphological changes are bet-
ter described for peripheral vessels than cerebral ves-
sels. In the early phase of hypertension, these changes
consist of smooth muscle cell hypertrophy and medial
hyperplasia, largely proportional to the pressure lev-
el,29 together with an increased logging of water and
electrolytes in the vessel wall.30 In longstanding hyper-
tensive disease, additional changes include accumula-
tion of fibrous proteins, elastin and collagen, and de-
generation of the muscle cells.31 The reversibility of
the functional adaptive changes would be expected to
depend on the nature of the underlying structural
changes: the initial changes of smooth muscle cell hy-
pertrophy and water-logging probably are reversible
following normalisation of blood pressure, whereas
this is less likely with the degenerative changes and
connective tissue proliferation.

In the present study, antihypertensive treatment was
started 2 months after induction of hypertension, by
which time the rats had been severely hypertensive for
about 6 weeks. In an earlier study of RHR and SHR,4 we
have shown that the lower limit of CBF autoregulation
is shifted 20-30 mm Hg to the right on the blood
pressure axis after a similar period of hypertension.
Thus the RHR in the present study would be expected
to have undergone adaptation of the cerebral circula-
tion by the time that treatment was started. Anti-
hypertensive treatment effectively maintained blood
pressure at low-normal levels and reversed the hyper-
tensive adaptive change in the lower limit of CBF
autoregulation. In the untreated RHR, the lower limit
of autoregulation was shifted 30-40 mm Hg towards
higher pressure after 4 months as compared to 20-30
mm Hg after 2-3 months in the earlier study, indicat-
ing that the structural vascular changes were not com-
plete at the time of starting treatment, and that the
treatment prevented further development of vascular
changes. Whether more longstanding hypertensive ad-
aptation of the cerebral circulation could be reversed
by antihypertensive treatment is unknown, although
partial reversal is indicated by the study in SHR men-
tioned above.4 Similarly, peripheral vascular changes
could only be partially reversed by antihypertensive
treatment of elderly animals with long-standing hyper-
tension.35

Although no precise time factor can be derived, it
can be inferred from the above-mentioned observa-
tions and the findings of the present study that reversal
of the hypertension-induced adaptive changes will take
place during the first few weeks or months after lower-
ing of blood pressure towards normal levels. There-
after, only moderate changes with only minor in-
fluence on the haemodynamic parameters will occur.
However, longstanding antihypertensive treatment
may prevent or postpone the development of further
degenerative adaptive changes. These findings are rel-
vant to clinical antihypertensive treatment of young
and middle-aged patients, in whom a gradual but com-
plete normalization of blood pressure may lead to a
normal autoregulation of cerebral blood flow.

Acknowledgment

This study was supported by the Danish Heart Foundation and the
Danish Medical Research Council. We are extremely grateful to Anne
Mette Elle and Anne-Ise Aanonsen for excellent technical and secretar-
ial assistance.

Reference

1. Strandgaard S, Olesen J, Skinhoj F, Lassen NA: Autoregulation of
brain circulation in severe arterial hypertension. Br Med J 1: 507-
510, 1973

2. Strandgaard S: Autoregulation of cerebral blood flow in hyperten-
sive patients. Circ 53: 720–727, 1975

Lower limit of cerebral blood flow autoregulation in experimental
renovascular hypertension in the baboon. Circulat Res 39: 555-
557, 1976

4. Barry DI, Strandgaard S, Graham DJ, Braendstrup O, Svendsen
UG, Vorstrup S, Hemmingsen R, Bolwig TG: Cerebral blood flow
in rats with renal and spontaneous hypertension: resetting of the
353, 1982

of cerebral blood flow autoregulation in experimental renovascular


Chronic antihypertensive treatment in the rat reverses hypertension-induced changes in cerebral blood flow autoregulation.
S Vorstrup, D I Barry, J O Jarden, U G Svendsen, O Braendstrup, D I Graham and S Strandgaard

Stroke. 1984;15:312-318
doi: 10.1161/01.STR.15.2.312

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/15/2/312

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/