Hemispheric Blood Flow in the Rat After Unilateral Common Carotid Occlusion: Evolution With Time

GASPARD DE LEY, V.M.D., JEAN-BERCHMANS NSHIMYUMUREMYI, M.D., AND ISIDOOR LEUSEN, M.D.

SUMMARY  
Acute occlusion of one common carotid artery in the anesthetized normocapnic rat results in a moderate cerebral blood flow (CBF) decrease in both cerebral hemispheres. No asymmetrical perfusion is observed when the overall flow in each hemisphere is considered. The increase in blood flow which normally occurs in hypercapnia is strongly impaired in the cerebral hemisphere on the occluded side resulting in an important asymmetrical hemispheric perfusion. The days (1, 5, 15, 30) following unilateral carotid occlusion normal control CBF values are found in both hemispheres in normocapnic conditions. Hemispheric perfusion asymmetry in hypercapnia also becomes progressively less pronounced with time but a slight asymmetry still persists one month after unilateral carotid occlusion.

RAPID ADJUSTMENT of the collateral circulation after acute occlusion of one common carotid artery is able to keep cerebral blood flow (CBF) above the critical level for appropriate metabolic supply in many animal species although blood flow may be reduced in cerebral regions dependent on the occluded vessel.4,5

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In the anesthetized rat acute unilateral carotid occlusion reduces the hemispheric blood flow on the side of the occlusion.3 Circulatory reserve is also depressed in these conditions as indicated by the inadequate adaptation of CBF to hypoxia, to hypercapnia and to hypotension.5-7 Restoration of such a circulatory reserve in the days following the occlusion is an indication that collateral circulation and CBF adaptation progressively develop in the post-occlusion period. In order to obtain more information on this eventuality, blood flow in both brain hemispheres was studied in rats at different time intervals after unilateral carotid occlusion.
Material and Methods

Two types of experiments were carried out on male Wistar rats (300–400 g). In a first type (acute experiments) the effect of two PaCO₂ levels on total cerebral blood flow and hemispheric blood flow was examined immediately after occlusion of the right common carotid artery; in a second experimental type (chronic experiments) the response of total and hemispheric brain blood flow to hypercapnia was examined at different times (1 to 30 days) after unilateral common carotid ligation.

a. Acute Experiments

These experiments were carried out under general anesthesia (Halothane 1% in N₂O 70%/O₂ 30% mixture). After cannulation of the trachea, a polyethylene catheter (PE 50) was placed in a femoral artery and vein for blood pressure monitoring, arterial blood sampling and administration of drugs.

Another catheter was placed in the caudal artery and the right common carotid artery was ligated. Thereafter, the animals were paralyzed (galamine 20 mg/kg body weight IV), artificially ventilated, and a left side thoracotomy was made at the level of the heart. A small catheter was inserted through the left ventricular wall (with its tip extending in the ventricular cavity) and kept in place with a 5-0 silk suture. Through this catheter labelled microspheres were injected for CBF and cardiac output (CO) measurement. Control animals were prepared in the same way with the exception that both common carotid arteries were left intact. At the end of the preparation halothane administration was stopped and anesthesia was continued with N₂O/O₂ (70/30%). After at least 30 minutes a first CBF and CO measurement was made under normocapnic conditions. Microspheres labelled with Ce141 were injected by giving citrated blood from a donor rat. At the end of the experiment the animal was killed with an intravenous injection of saturated KCl. Both brain hemispheres, the cerebellum, the central brain axis and the reference sample were transferred to a well scintillation counter for measurement of radioactivity. Cardiac output and CBF were calculated as described earlier.8,9

b. Chronic Experiments

These experimental groups the right common carotid artery was aseptically ligated under general anesthesia (Halothane 1% in a mixture of 70% N₂O and 30% O₂) and the animals were allowed to recover. In four groups of animals CBF and CO measurements were made respectively 1, 5, 15 and 30 days after occlusion of the right common carotid artery using the same procedure as described for the acute experiments.

Statistical evaluation of the results was made using Student’s t-test for paired observations for results obtained within the same group and the unpaired t-test for comparison of results from different groups. Each group consisted of 7 animals.

Results

The results of the experiments are summarized in table 1. Mean PaCO₂ in the different groups varied between 29.5 and 33.6 mm Hg under normocapnic conditions and between 64.2 and 75.1 mm Hg under hypercapnic conditions. Oxygenation of the animals was normal with PaO₂ values of at least 90 mm Hg.

<table>
<thead>
<tr>
<th>Experimental type</th>
<th>PaCO₂ mm Hg</th>
<th>Cardiac output ml·min⁻¹</th>
<th>Total CBF ml·g⁻¹·min⁻¹</th>
<th>Right hemi</th>
<th>Left hemi</th>
<th>R/L</th>
<th>PaCO₂ mm Hg</th>
<th>Cardiac output ml·min⁻¹</th>
<th>Total CBF ml·g⁻¹·min⁻¹</th>
<th>Right hemi</th>
<th>Left hemi</th>
<th>R/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>29.9 ± 1.3</td>
<td>70.1 ± 5.0</td>
<td>1.28 ± 0.12</td>
<td>1.41 ± 0.17</td>
<td>1.46 ± 0.14</td>
<td>0.96 ± 0.02</td>
<td>66.5 ± 2.2</td>
<td>68.7 ± 5.4</td>
<td>4.49 ± 0.05</td>
<td>5.45 ± 0.08</td>
<td>5.47 ± 1.00</td>
</tr>
<tr>
<td>Acute occlusion</td>
<td>7</td>
<td>31.9 ± 1.6</td>
<td>75.1 ± 10.6</td>
<td>0.94 ± 0.07</td>
<td>1.09 ± 0.08</td>
<td>1.07 ± 0.09</td>
<td>0.94 ± 0.05</td>
<td>67.8 ± 2.5</td>
<td>71.1 ± 10.3</td>
<td>3.06 ± 0.05</td>
<td>2.22 ± 0.04</td>
<td>4.32 ± 0.49</td>
</tr>
<tr>
<td>24 h</td>
<td>7</td>
<td>29.5 ± 0.8</td>
<td>75.1 ± 4.3</td>
<td>1.15 ± 0.07</td>
<td>1.15 ± 0.08</td>
<td>1.34 ± 0.09</td>
<td>0.86 ± 0.04</td>
<td>65.1 ± 3.4</td>
<td>55.7 ± 4.8</td>
<td>2.85 ± 0.04</td>
<td>1.88 ± 0.04</td>
<td>4.08 ± 0.46</td>
</tr>
<tr>
<td>5 d</td>
<td>7</td>
<td>31.1 ± 1.6</td>
<td>88.3 ± 6.8</td>
<td>1.43 ± 0.21</td>
<td>1.42 ± 0.12</td>
<td>1.46 ± 0.18</td>
<td>1.01 ± 0.07</td>
<td>70.7 ± 1.2</td>
<td>66.5 ± 8.6</td>
<td>4.16 ± 0.04</td>
<td>3.43 ± 0.04</td>
<td>5.39 ± 0.63</td>
</tr>
<tr>
<td>15 d</td>
<td>7</td>
<td>33.6 ± 1.3</td>
<td>78.2 ± 6.6</td>
<td>1.25 ± 0.08</td>
<td>1.36 ± 0.12</td>
<td>1.45 ± 0.18</td>
<td>0.97 ± 0.04</td>
<td>75.1 ± 1.9</td>
<td>82.5 ± 8.5</td>
<td>3.95 ± 0.04</td>
<td>4.08 ± 0.04</td>
<td>4.76 ± 0.86</td>
</tr>
<tr>
<td>30 d</td>
<td>7</td>
<td>31.1 ± 1.7</td>
<td>77.0 ± 9.4</td>
<td>1.29 ± 0.12</td>
<td>1.47 ± 0.17</td>
<td>1.56 ± 0.19</td>
<td>0.96 ± 0.07</td>
<td>64.2 ± 6.0</td>
<td>62.4 ± 4.7</td>
<td>4.07 ± 0.04</td>
<td>4.35 ± 0.04</td>
<td>5.23 ± 0.84</td>
</tr>
</tbody>
</table>

Mean values ± SEM, n = 7.
Total Brain Blood Flow (table 1)

In the control groups total brain blood flow was 1.28 ± 0.12 and 4.49 ± 0.45 ml·g⁻¹·min⁻¹ (mean ± sem) under normocapnic and hypercapnic conditions respectively.

Shortly after ligation of the right carotid artery mean total CBF of the animals was significantly lower than in the control group under normocapnic (p < 0.01) and hypercapnic (p < 0.05) conditions respectively.

Twenty-four hours after ligation, total CBF in normocapnia was not significantly different from the values found in the control group whereas in hypercapnia a significantly (p < 0.05) lower CBF value than in the control group was found.

Under normocapnia substantially normal CBF values were further found in the rats studied 5, 15 and 30 days after unilateral carotid ligation.

The fifth day after ligation total brain blood flow in hypercapnia was slightly (but statistically not significantly) lower than the value found in the control group; comparable values were also found on the 15th and the 30th day after ligature.

Hemispheric Blood Flow (table 1, fig. 1)

a. Normocapnia

In the control rats hemispheric blood flow was 1.41 ± 0.17 and 1.46 ± 0.14 ml·g⁻¹·min⁻¹ at the right and left side respectively; this results in a hemispheric right to left flow ratio of 0.96 ± 0.02.

Shortly after ligation of the right common carotid artery hemispheric CBF at the right as well as at the left side was significantly lower than in the control group (p < 0.05). The ratio (R/L) between the right hemispheric CBF (occluded side) and the left hemispheric CBF (non-occluded side) is not significantly different from control. Twenty-four hours after ligation of the right carotid artery the hemispheric blood flow ratio was 0.86 ± 0.04 (p < 0.02 compared to the control group). Five days after ligation hemispheric blood flow of both sides returned to nearly normal values in normocapnic conditions resulting in hemispheric blood flow ratio’s of 1.01 ± 0.07; 0.97 ± 0.09 and 0.96 ± 0.07 at 5, 15 and 30 days respectively.

b. Hypercapnia

In the control group hemispheric blood flow under hypercapnia was 5.45 ± 0.58 and 5.47 ± 0.58 ml·g⁻¹·min⁻¹ on the right and left side respectively, resulting in a flow ratio of 1.00 ± 0.02. Immediately after right carotid ligation right hemispheric blood flow increase in hypercapnia was more than 50% less than in the control group under the same conditions (p < 0.001), while the left hemispheric blood flow was not significantly different from the control group.

Mean hemispheric flow ratio (R/L) under hypercapnia fell to 0.49 ± 0.07 (p < 0.001 compared to control).

Twenty-four hours after ligation the reaction of the flow ratio to hypercapnia was practically the same as after acute occlusion. Five, 15 and 30 days after ligation, right hemispheric blood flow showed a progressively increased response to hypercapnia but even after 30 days hemispheric blood flow did not attained the value found in the left hemisphere and in control hypercapnic animals. As a result, the right to left hemispheric blood flow ratio under hypercapnia, which was 0.46 ± 0.05 twenty four hours after ligation, increased to 0.63 ± 0.07 after 5 days (significantly lower than the flow ratio found in the same animals under normocapnia and in the control group under hypercapnia) and attained 0.86 ± 0.05 and 0.84 ± 0.06 respectively on day 15 and 30. The latter values are not significantly different from the flow ratio in the same animals under normocapnia, but significantly lower than the hemispheric blood flow ratio of the control group under hypercapnic conditions (p < 0.05).

Discussion

The results show that in normocapnia occlusion of one common carotid artery in the anesthetized rat immediately lowers total cerebral blood flow to approximately 75% of its normal value. Hemispheric blood flow is significantly decreased to a comparable degree on the occluded and the non-occluded side; as a consequence hemispheric blood flow remains symmetrical (blood flow ratio close to unity). The persistence of a symmetrical hemispheric blood flow after unilateral carotid ligation is in accordance with the results obtained by several authors in different animal species but seems to disagree with the results obtained in rats by Salford and Siesjo who measured rCBF with the "C-ethanol method, found significantly lower CBF values in a relatively small area confined to the MCA-region of the ligated side, while other hemispheric samples showed flow values which were not significantly different from the contralateral side. The "hemispheric" blood flow we deal with in our study concerns the total cerebral hemisphere including the caudato-putamen.
In the study of Pannier et al.11 labelled microspheres were injected through a polyethylene catheter introduced in the left heart ventricle via the right common carotid artery. This procedure impeded blood flow to the right subclavian artery from which the right vertebral artery is originating. In this way, compensatory blood flow via the vertebral system must be strongly disturbed.

Under hypercapnic conditions cerebral vasodilatation takes place but total brain blood flow remains significantly lower in the animals with an acutely ligated carotid artery. Moreover, hemispheric blood flow becomes strongly asymmetrical since blood flow at the side of the occlusion is only 50% of the blood flow at the non-ligated side. The logic explanation is that following unilateral carotid occlusion, autoregulatory vasodilatation in the ipsilateral hemisphere in response to reduced perfusion pressure* and redistribution of the blood flow through the collateral vasculature act as compensatory mechanisms to keep blood supply at the occluded side above the critical level for metabolic needs. In these conditions, the residual vasodilating capacity at the occluded side must be strongly diminished. This is illustrated by the results obtained under hypercapnia, since the administration of 10% CO₂ in the inspired gas mixture results in a CBF increase that is much lower on the occluded side.

The chronic experiments indicate that after unilateral carotid occlusion total CBF tends to normalize. Twenty four hours after carotid ligation and under normocapnic conditions it is no longer significantly different from the values found in control animals and a completely normal level is found on the fifth day.

Twenty four hours after ligation, hemispheric blood flow under normocapnia is slightly asymmetrical (blood flow ratio R/L = 0.86, p < 0.02) because blood flow at the non-occluded side normalizes faster than at the occluded side. The fifth day blood flow on the occluded side has also normalized and as a consequence hemispheric blood flow is again symmetrical (R/L = 1.01) and remains so on day 15 and 30.

Normalization of total brain CBF seems to be somewhat delayed under “high-flow” conditions (hypercapnia). Twenty four hours after ligation, the CBF increase in hypercapnia is comparable to what is observed in the acutely ligated animals, which is significantly less than the response seen in the control group. However, five days after ligation the CBF adaptation to hypercapnia has largely recovered and this is maintained after fifteen and thirty days. Under “high flow” conditions some degree of asymmetrical hemispheric perfusion persists for a prolonged period, although with time hemispheric blood flow on the occluded side gradually attains values only slightly lower than in the control group.

The results indicate that in the rat adaptation of the cerebral blood flow after unilateral carotid occlusion is progressive and that restoration of a circulatory reserve takes several days. It is conceivable that such adjustment may be dependent on many parameters and that the development of compensation can be influenced by several factors. Structural and functional integrity of the blood vessel wall undoubtedly contributes largely to the possibilities of adaptation and it is evident that adjustment will be impaired in cerebral vascular disease.4

The anatomy and importance of the vascular anastomotic systems able to compensate for occlusion of a common carotid artery show important species differences6-1213 which greatly influence the impact on brain function and brain flow reserve of acute carotid artery occlusion. In man considerable individual anatomical and functional variations exist which are partly responsible for the varying clinical picture obtained after acute and chronic carotid occlusion.4, 16, 17 After acute unilateral carotid artery ligation collateral circulation is able to keep hemispheric blood flow close to normal in the monkey, cat and dog6, 16 whereas in the Mongolian gerbil unilateral hemispheric infarction is produced due to absence of the posterior communicating arteries between the basilar and carotid systems.18, 19 In the rat anastomotic connections between the vertebral and carotid arteries are present although it has been found that ponto-medullary connections between the vertebral and carotid arteries may represent a valuable model for the study of factors influencing the adjustment of collateral circulation in the rat brain.

References
8. Sasaki Y, Wagner HN Jr: Measurement of the distribution of cardi-

*In anesthetized rats under normocapnic conditions "back-pressure," measured in the cervical stump of the acutely ligated common carotid artery, was 50 ± 4 mm Hg being only 30% of the systemic blood pressure. Five days after ligation "carotid back pressure" had increased to 79 ± 7 mm Hg (De Ley, unpublished results).

Sympathetic Nerve Activity: A Link To Stroke?
SHIRLEY M. MUELLER, M.D., AND WILLIAM L. BLACK JR., B.A.

SUMMARY Spontaneously hypertensive rats (SHR) have been shown to have an increased capacity for superior cervical sympathetic nerve activity which may protect against stroke (Mueller et al: Stroke 13: 115, 1982). Sympathetic nerve activity has never been examined in the stroke-prone substrain of SHR (SP). In this study we measured superior cervical sympathetic nerve activity during rest and during a maximal sympathetic response in SHR, SP and their normotensive controls, Wistar-Kyoto (WKY). The resting superior cervical sympathetic nerve activity of SP was significantly less than SHR (p < 0.02) but not different from WKY. During central ischemia, used to induce maximal sympathetic response, the increase in SP sympathetic nerve activity was significantly less than SHR (p < 0.001) but was not different from WKY. This diminished capacity for elevated superior cervical sympathetic nerve activity in stroke-prone SHR may relate to their increased predisposition to stroke because sympathetic hyperactivity cannot protect cerebral vessels during acute hypertension.

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HYPERTENSION is among the important risk factors for stroke. However, it is seldom clear why one hypertensive individual has a stroke and another does not. Study of animal models analogous to human essential hypertension, the spontaneously hypertensive rat (SHR), and the substrain of the SHR that is susceptible to stroke as well as hypertension, stroke-prone SHR (SP), could contribute to our understanding in this regard.

Some authors1,2 have demonstrated elevated sympathetic nerve activity in the lumbar and renal nerves of the spontaneously hypertensive rat which they believed contributed to the development and maintenance of hypertension. Ikeda, et al,3 carried this concept further and postulated that if elevated superior cervical sympathetic nerve activity was present in the stroke-prone strain of SHR, decreased cerebral blood flow might result leading to cerebral ischemia and an increased incidence of stroke. However, Ikeda, et al,3 did not provide direct evidence to support this concept.

The purpose of this study was to directly measure superior cervical sympathetic nerve activity in SP, SHR and their normotensive controls, Wistar-Kyoto (WKY), during resting conditions and during a maximal sympathetic stimulus. The change in sympathetic nerve activity between these two conditions could contribute to our understanding of the animal's ability to respond to sudden changes in cerebral perfusion pressures and protect against these changes. Such information would further enhance our understanding of stroke.

Methods
Twenty-three male animals 16–26 weeks of age were used for this study. They were allowed free access to standard Purina rat chow and water. Nine of the animals were SP (original stock obtained from Carl Hansen at the National Institute of Health), eight were SHR and six were WKY (Charles Rivers, Boston, MA). All rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.). Each rat was artificially ventilated with a respirator and paralyzed with gallamine triethiodide (6 mg/kg). The left femoral artery was catheterized with thin walled PE-50 tubing filled with...
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