Post-ischemic Hypermetabolism in Cat Brain

EDWIN M. NEMOTO, PH.D., KONSTANTIN-ALEXANDER HOSSMANN, M.D.,
AND HELEN K. COOPER, PH.D.

SUMMARY Delayed postischemic brain hypoperfusion and hypermetabolism are likely detrimental factors to neurologic recovery after transient global brain ischemia and may be mediated by catecholamines acting via adrenergic receptors. We evaluated the effects of alpha and beta receptor blockade on cerebral blood flow (CBF) and metabolism after 16 min transient global brain ischemia.

Ischemia was induced by arterial hypotension and a high pressure neck tourniquet in 13 anesthetized cats. Six cats were untreated, 4 received propranolol 1 mg/kg, IV and 3 a combination of propranolol and phentolamine, one mg/kg injected one min before recirculation. Total CBF was measured by continuous monitoring of cerebral venous 

133Xe clearance after bolus intra-arterial injection. Arterial and cerebral venous oxygen, glucose and lactate were measured. Cerebral cortex glucose and lactate were measured 3 hours post-ischemia after in situ freezing with liquid N2. The cerebral cortex of 3 cats anesthetized, but not subjected to ischemia, was similarly frozen and analyzed for glucose and lactate.

Total CBF was relatively constant for up to 3 h post-ischemia in all groups, but significant changes in fast and slow-flow rates and compartment sizes were observed. In untreated cats, the normal 60/40 percent relative weight of the fast and slow-flow compartments was reversed to 30/70 percent by 1 hr post-ischemia. Propranolol attenuated the size of the fast-flow compartment in the first 30 min post-ischemia which was partially restored by phentolamine. Brain oxygen consumption increased 2 to 3-fold by 1 h post-ischemia in all groups. Propranolol compromised CBF and impaired glucose and lactate oxidation which was partly reversed by phentolamine.

We concluded that within the first 30 min post-ischemia, beta, and to a lesser extent, alpha receptors predominate in the modulation of cerebrovascular tone. By 1 h post-ischemia, however, adrenergic modulation of cerebrovascular tone is lost. Delayed post-ischemic hypermetabolism unlike stress-induced, but like hypoxia-induced hypermetabolism is only partially affected by beta blockade. Propranolol apparently compromises brain oxygen consumption secondary to a reduction in brain O2 supply while phentolamine improves perfusion and oxygen consumption.

Stroke, Vol 12, No 5, 1981

POST-ISCHEMIC ENCEPHALOPATHY after transient global brain ischemia may be due to brain hypoxia secondary to the no-reflow phenomenon, delayed hyperperfusion and hypermetabolism, suggesting that these phenomena may be mediated by adrenergic receptors. Central and peripheral release of catecholamines (CA) during ischemic anoxia could explain many of the pathophysiological and biochemical changes observed after ischemia, but definitive proof on the mechanisms of which have not been defined. Beta adrenergic stimulation increases cerebral blood flow (CBF) while beta blockade prevents stress-induced brain hypermetabolism, suggesting that these phenomena may be mediated by adrenergic receptors. Central and peripheral release of catecholamines (CA) during ischemic anoxia could explain many of the pathophysiological and biochemical changes observed after ischemia, but definitive proof on the specific processes directly attributable to CA has yet to be provided. The effects of endogenous and exogenous CA on CBF and cerebral metabolic rate (CMR), are apparently mediated by both cerebrovascular and parenchymal adrenergic receptors. The aim of this study was to evaluate the effects of alpha and beta receptor blockade on cerebrovascular dynamics, and brain metabolism after 16 min transient global brain ischemia.

Methods and Materials

Sixteen cats of either sex, 3 to 4 kg body weight, were anesthetized with halothane, 4 percent in oxygen, and glass cannulae were tied into the tracheas. The cats were immobilized with pancuronium bromide (0.4 mg) and mechanically ventilated on halothane 1 percent, oxygen 33 percent, and nitrogen 66 percent. Respiratory rates and tidal volumes were adjusted to maintain continuously monitored end-tidal CO2 between 4 and 5 percent. Rectal temperature and electrocardiogram were continuously monitored.

Polyethylene catheters inserted in femoral veins and arteries were used for drug infusion, intravenous fluid replacement (5 percent dextrose/0.45 percent NaCl, 3 to 5 ml/kg hour), arterial pressure monitoring, blood sampling and reinfusion of cerebral venous blood from the extracorporeal circulation system. Catheters inserted into the right brachial artery, with their tips in the innominate artery, were used for bolus injection of 123I-saline for CBF measurements. Optimal position of the catheter tips was verified by test injections of 1 mCi 123I- and monitoring of activity over the common carotid artery and the thoracic aorta. Low or no activity in the aorta and high activity in the common carotid indicated optimal catheter placement. Catheters inserted into the superior sagittal sinus with the tip in the torcular were used for continuous sampling of cerebral venous blood at a rate of about 2–3 ml/min.

From the Anesthesia and Critical Care Research Laboratories, Department of Anesthesiology and Critical Care Medicine Program, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, and Max-Planck-Institut für Hirnforschung (Dr. Hossmann and Cooper), Forschungsstelle für Hirnkreislauforschung, Cologne, West Germany.

Supported by the Deutsche Forschungsgemeinschaft and USPHS Grant No. NS 12150.

Reprints: Dr. Nemoto, Anesthesia Research Laboratories, University of Pittsburgh School of Medicine, 1081 Scaife Hall, Pittsburgh, PA 15261
The cats were then placed in the prone position with the head fixed in a stereotaxic device. The cerebral venous catheters were connected to a lead-shielded glass coil placed on the face of a shielded one-half inch scintillation probe (Meditronik, Lyngby, Denmark) and returned to the femoral artery via a peristaltic pump. After reflection of the skin and muscle overlying the calvarium, a second flat-field collimated scintillation probe was placed over the parietal-occipital cortex at an angle 45° from the vertical for continuous monitoring of brain 133Xe activity. Thirty min were allowed for hemostasis prior to heparinization (150 U/kg body weight) for extracorporeal circulation. During this time, a pediatric tourniquet was loosely wrapped around the neck.

CBF was measured by the venous outflow technique previously described by Shinohara et al. in monkeys and Meyer and Shinohara in man.

Mean cerebral blood flow (f) was calculated from the mean transit time (t) after intraarterial bolus injection of Xe-133 as described by Meier and Zieler,

\[ t = \frac{\int_{0}^{\infty} c(t) \, dt}{\int_{0}^{\infty} c(t) \, dt} \]

where \( c(t) \) is the concentration of the tracer in the venous blood at time \( t \). Also,

\[ t = \frac{\lambda}{f} \]

where \( \lambda \) is the mean blood/brain partition coefficient of 133Xe at the respective hemoglobin values.

Compartmental flows of the rapidly perfused regions were calculated by exponential curve analysis. The assumptions made for this approach for extracranial residue detection of tissue concentrations of the indicator are also valid for venous outflow curves because the latter is a first derivative of the former:

\[ c(t) = a \cdot e^{-at} + b \cdot e^{-bt} \]

\[ c'(t) = -a \cdot \alpha \cdot e^{-at} - b \cdot \beta \cdot e^{-bt} \]

where \( c(t) \) is the tracer concentration of brain tissue and \( c'(t) \), the tracer concentration in the venous outflow at time \( t \). Since the exponents of tissue and venous clearance curves are the same, conventional curve fitting techniques can also be applied to venous outflow curves.

For calculation of the weight ratios from the venous outflow curves, according to Hoedt-Rasmussen et al., for residue detection:

\[ W_i = \frac{a}{a_f} / (a_f/a + b / b_f) \]

where \( W_i \), \( a \), and \( f_i \) are the weight ratio, the intercept and the flow of the fast compartment, respectively, and \( b \) and \( f_0 \), the intercept and flow of the slow compartment. The intercepts \( a \) and \( b \) can be calculated from the venous clearance curves since:

\[ a' = a \cdot \alpha \] and \( b' = b \cdot \beta \]

where \( a \) and \( b \) are the intercepts of tissue clearance and \( a' \) and \( b' \), the intercepts of venous clearance. Since

\[ f_1 = a \cdot \lambda_i \] and \( f_2 = b \cdot \lambda_i \]

\[ W_1 = a'/\alpha \cdot \lambda_1/a'/\alpha^2 + b'/\beta \cdot \lambda^2 \]

All analyses of the cerebral venous clearance curves were performed on a PDP-8 computer. Hemoglobin was determined during each CBF measurement and the appropriate blood tissue partition coefficient used. During each CBF measurement, cerebral uptake of oxygen and glucose were determined from the products of CBF and cerebral arterial-venous difference of oxygen and glucose, respectively.

Control measurements of CBF and CMR of oxygen \((O_2)\), glucose \((G)\) and lactate \((L)\), arterial and cerebral venous blood gases and pH were made 15 min before ischemia. Arterial and cerebral venous sampling was precisely timed to ensure matched samples beginning 60 sec after intraarterial bolus injection of 133Xe for CBF measurement.

Global brain ischemia was induced in 13 of the 16 cats by a previously described method. Briefly, mean arterial pressure (MAP) was rapidly reduced to about 50 torr by intravenous bolus injection of trimethaphan camsylate (Arfonad, Roch Laboratories, Nutley, NJ). 133Xe was injected into the innominate artery, the high pressure neck tourniquet immediately inflated to 1500 torr, and inspired gas changed to 100 percent O2. Throughout ischemia, MAP was controlled at 50 torr by trimethaphan infusion, manipulation of positive-end expiratory pressure (PEEP) and increasing inspired halothane up to 4 percent. Halothane was usually discontinued within 5 min after the onset of ischemia. Complete arrest of brain circulation was verified by constant brain 133Xe activity during ischemia. Thirty sec before the end of ischemia, MAP was gradually restored to 100 torr by IV infusion of norepinephrine. At the end of 16 min ischemia, the neck tourniquet was rapidly deflated.

Four of the 16 cats received 1 mg/kg propranolol (Inderal, Ayerst Laboratories) IV; and 3 cats received a combination of propranolol, 1 mg/kg and phenolamine, 1 mg/kg (Regitine, CIBA Pharmaceuticals) IV 1 min before the end of ischemia to insure adequate systemic distribution before reperfusion of the brain. Six cats (controls) did not receive any drugs except for norepinephrine infusion. Three cats not subjected to global ischemia were used to obtain normal values of cortical glucose and lactate.

CBF measurements were made at 0, 15, 30, 45, 60 and every 30 min thereafter for up to 3 h post-ischemia with sampling of cerebral venous and arterial blood for PO2, PCO2 and pH measurements. Arterial and cerebral venous blood samples for CMR measurements were obtained at 0, 15, 30, 60, 120 and 180 min post-ischemia. Blood samples for glucose and lactate assays were injected into ice-cold 6 percent perchloric acid immediately after sampling. Oxygen content was determined using a Lexicon oxygen content analyzer and glucose and lactate were assayed enzymatically using kit assays (Boehringer-
Mannheim). At 3 hours post-ischemia, the cortex was exposed and frozen with liquid nitrogen in situ for brain glucose and lactate analysis. Two-tailed Student's t-tests for unpaired comparisons were used for statistical analyses. P values equal to or less than 0.05 were considered statistically significant.

Results

Mean PaCO<sub>2</sub> was similar between and within groups except for significantly lower values than pre-ischemia in the propranolol treated cats (table 1-3). Mean PaCO<sub>2</sub> ranged between 162 and 211 torr pre-ischemia and 240 and 462 torr post-ischemia. Hematocrit increased by 11 to 16 percent within one h post-ischemia. Arterial hyperglycemia and lactic acidosis was marked in control and propranolol plus phentolamine treated cats. The 2-fold increase in arterial glucose in the propranolol groups was not significant. Variability in arterial glucose and lactate values in propranolol cats was greater than in the other 2 groups.

The effects of beta and alpha plus beta blockade on total CBF were unremarkable (fig. 1). Total CBF was unaltered post-ischemia compared to either pre-ischemic values or between treatment groups. Mean arterial pressure (MAP) was generally lower in the ischemic values or between treatment groups. Mean PaCO<sub>2</sub>, was similar between and within groups.

<table>
<thead>
<tr>
<th>Time</th>
<th>PaO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>PaCO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>pHa</th>
<th>Hct</th>
<th>T&lt;sub&gt;tr&lt;/sub&gt;</th>
<th>CaO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Ga</th>
<th>La</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ischemia</td>
<td>X</td>
<td>162</td>
<td>30</td>
<td>7.38</td>
<td>36</td>
<td>36.5</td>
<td>6.63</td>
<td>7.95</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>12</td>
<td>30</td>
<td>7.38</td>
<td>36</td>
<td>36.5</td>
<td>6.63</td>
<td>7.95</td>
</tr>
<tr>
<td>Post-ischemia</td>
<td>0'</td>
<td>X</td>
<td>383*</td>
<td>31</td>
<td>7.38</td>
<td>44*</td>
<td>37.1</td>
<td>9.18*</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>32</td>
<td>2</td>
<td>7.38</td>
<td>37</td>
<td>3.0</td>
<td>0.52</td>
<td>0.29</td>
</tr>
<tr>
<td>15'</td>
<td>X</td>
<td>339*</td>
<td>32</td>
<td>7.32</td>
<td>46*</td>
<td>37.1</td>
<td>9.09*</td>
<td>17.03*</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>43</td>
<td>1</td>
<td>7.32</td>
<td>46</td>
<td>0.4</td>
<td>0.64</td>
<td>1.35</td>
</tr>
<tr>
<td>30'</td>
<td>X</td>
<td>304</td>
<td>32</td>
<td>7.35</td>
<td>43</td>
<td>37.3</td>
<td>8.46*</td>
<td>17.17*</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>60</td>
<td>2</td>
<td>7.35</td>
<td>43</td>
<td>0.4</td>
<td>0.73</td>
<td>1.60</td>
</tr>
<tr>
<td>60'</td>
<td>X</td>
<td>324*</td>
<td>30</td>
<td>7.34</td>
<td>41</td>
<td>37.0</td>
<td>8.35*</td>
<td>16.50*</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>30</td>
<td>2</td>
<td>7.34</td>
<td>41</td>
<td>0.2</td>
<td>0.67</td>
<td>1.66</td>
</tr>
<tr>
<td>120'</td>
<td>X</td>
<td>383*</td>
<td>30</td>
<td>7.34</td>
<td>41</td>
<td>37.1</td>
<td>7.91</td>
<td>13.30</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>49</td>
<td>1</td>
<td>7.34</td>
<td>41</td>
<td>0.1</td>
<td>0.76</td>
<td>1.65</td>
</tr>
<tr>
<td>180'</td>
<td>X</td>
<td>373*</td>
<td>30</td>
<td>7.36</td>
<td>43</td>
<td>37.2</td>
<td>8.01</td>
<td>12.67</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>35</td>
<td>2</td>
<td>7.36</td>
<td>43</td>
<td>0.1</td>
<td>0.76</td>
<td>1.35</td>
</tr>
</tbody>
</table>

*Global brain ischemia induced by trimethaphan hypotension to a mean arterial pressure of about 50 torr and high pressure (1500) neck tourniquet.
CaO<sub>2</sub> = arterial O<sub>2</sub> content; Ga = arterial glucose; La = arterial lactate.
*p < 0.05 compared to pre-ischemic value.
TABLE 2  Physiological Variables After 16 Min Global Brain Ischemia in 4 Propranolol (1 mg/kg) Treated Cats

<table>
<thead>
<tr>
<th>Time</th>
<th>PaO&lt;sub&gt;2&lt;/sub&gt; (torr)</th>
<th>PaCO&lt;sub&gt;2&lt;/sub&gt; (torr)</th>
<th>pH</th>
<th>Hct</th>
<th>Tr</th>
<th>CaO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Ga</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ischemia</td>
<td>X</td>
<td>175</td>
<td>32</td>
<td>7.31</td>
<td>27</td>
<td>36.9</td>
<td>5.13</td>
<td>7.96</td>
</tr>
<tr>
<td>SEM</td>
<td>12</td>
<td>2</td>
<td>0.02</td>
<td>3</td>
<td>0.1</td>
<td>0.88</td>
<td>2.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Post-ischemia</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0'</td>
<td>388</td>
<td>27</td>
<td>7.24</td>
<td>44</td>
<td>37.5</td>
<td>5.26</td>
<td>7.08</td>
<td>4.91</td>
</tr>
<tr>
<td>15'</td>
<td>3</td>
<td>1</td>
<td>0.03</td>
<td>4</td>
<td>0.2</td>
<td>1.16</td>
<td>4.80</td>
<td>1.43</td>
</tr>
<tr>
<td>60'</td>
<td>2</td>
<td>0.09</td>
<td>3</td>
<td>0.2</td>
<td>1.80</td>
<td>3.91</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>120'</td>
<td>1</td>
<td>0.02</td>
<td>3</td>
<td>0.3</td>
<td>2.10</td>
<td>5.80</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>180'</td>
<td>1</td>
<td>0.02</td>
<td>3</td>
<td>0.3</td>
<td>2.10</td>
<td>5.80</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

Propranolol injected intravenously during ischemia about one min before recirculation. See table 1 for other details.

Partly prevented these propranolol-induced changes. In the first 30 min after recirculation W<sub>f</sub> and W<sub>r</sub> were about equal, but W<sub>f</sub> gradually rose to 75 percent and W<sub>r</sub> progressively fell to a mean of 30 percent with values at 3 h similar to those observed in the other 2 groups, namely, the relative weights of W<sub>f</sub> and W<sub>r</sub> were about 75 and 25 percent, respectively.

CMRO<sub>2</sub> changes were similar in all groups for the first 60 min post-ischemia (fig. 4). In the first 20 min post-ischemia, it was unchanged or lower than pre-ischemia, but then increased 2 to 3-fold at 60 min. Thereafter, it fell slightly in control and propranolol cats more than in the other group, in which it was significantly elevated until 3 hours post-ischemia.

TABLE 3  Physiological Variables After 16 Min Global Brain Ischemia in 3 Propranolol (1 mg/kg) and Phentolamine (1 mg/kg) Treated Cats

<table>
<thead>
<tr>
<th>Time</th>
<th>PaO&lt;sub&gt;2&lt;/sub&gt; (torr)</th>
<th>PaCO&lt;sub&gt;2&lt;/sub&gt; (torr)</th>
<th>pH</th>
<th>Hct</th>
<th>Tr</th>
<th>CaO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Ga</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ischemia</td>
<td>X</td>
<td>211</td>
<td>28</td>
<td>7.33</td>
<td>33</td>
<td>36.6</td>
<td>6.9</td>
<td>6.04</td>
</tr>
<tr>
<td>SEM</td>
<td>12</td>
<td>1</td>
<td>0.01</td>
<td>3</td>
<td>0.1</td>
<td>0.47</td>
<td>0.31</td>
<td>0.11</td>
</tr>
<tr>
<td>Post-ischemia</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0'</td>
<td>375*</td>
<td>23 *</td>
<td>7.29</td>
<td>42</td>
<td>36.8</td>
<td>9.56*</td>
<td>12.08*</td>
<td>3.66*</td>
</tr>
<tr>
<td>SEM</td>
<td>25</td>
<td>3</td>
<td>0.03</td>
<td>4</td>
<td>0.1</td>
<td>0.78</td>
<td>1.27</td>
<td>0.77</td>
</tr>
<tr>
<td>15'</td>
<td>443*</td>
<td>29</td>
<td>7.26</td>
<td>49*</td>
<td>36.9</td>
<td>10.20*</td>
<td>11.88*</td>
<td>3.71*</td>
</tr>
<tr>
<td>SEM</td>
<td>20</td>
<td>2</td>
<td>0.03</td>
<td>2</td>
<td>0.1</td>
<td>0.49</td>
<td>1.16</td>
<td>0.65</td>
</tr>
<tr>
<td>60'</td>
<td>455*</td>
<td>30</td>
<td>7.33</td>
<td>47*</td>
<td>37.1</td>
<td>9.62*</td>
<td>10.54*</td>
<td>3.43*</td>
</tr>
<tr>
<td>SEM</td>
<td>20</td>
<td>2</td>
<td>0.06</td>
<td>2</td>
<td>0.1</td>
<td>0.53</td>
<td>1.07</td>
<td>0.73</td>
</tr>
<tr>
<td>120'</td>
<td>450*</td>
<td>32</td>
<td>7.34</td>
<td>44*</td>
<td>36.9</td>
<td>9.77*</td>
<td>9.21*</td>
<td>3.30*</td>
</tr>
<tr>
<td>SEM</td>
<td>31</td>
<td>1</td>
<td>0.04</td>
<td>3</td>
<td>0.2</td>
<td>0.54</td>
<td>0.93</td>
<td>0.69</td>
</tr>
<tr>
<td>180'</td>
<td>462*</td>
<td>27</td>
<td>7.39</td>
<td>43*</td>
<td>37.2</td>
<td>10.03*</td>
<td>8.10*</td>
<td>3.24*</td>
</tr>
<tr>
<td>SEM</td>
<td>15</td>
<td>1</td>
<td>0.03</td>
<td>2</td>
<td>0.3</td>
<td>0.30</td>
<td>0.83</td>
<td>0.71</td>
</tr>
<tr>
<td>180'</td>
<td>455*</td>
<td>27</td>
<td>7.37</td>
<td>42*</td>
<td>38.1</td>
<td>9.47*</td>
<td>7.51</td>
<td>3.45*</td>
</tr>
<tr>
<td>SEM</td>
<td>35</td>
<td>2</td>
<td>0.03</td>
<td>3</td>
<td>0.5</td>
<td>0.41</td>
<td>0.44</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Propranolol (1 mg/kg) and phentolamine (1 mg/kg) injected intravenously during ischemia about one min before recirculation. See table 1 for other details.

*p < 0.05 compared to pre-ischemic value.
Oxygen utilization coefficient (O\textsubscript{2}UC), a ratio of O\textsubscript{2} consumed to that delivered to the brain, was reduced at 15 min post-ischemia in control and propranolol plus phentolamine treated cats, but not in propranolol cats. The higher O\textsubscript{2}UC at 15 min post-ischemia in propranolol cats was correlated with lower cerebral venous oxygen content. O\textsubscript{2}UC rose above pre-ischemic values at 60 min post-ischemia and continued to rise at a slower rate between 60 and 180 min post-ischemia. A parallel fall in cerebral venous oxygen content (CVO\textsubscript{2}) occurred.

AVDO\textsubscript{2}/AVDG, an indication of oxidative glucose utilization, was about 5.5 in all groups pre-ischemia (fig. 5). Post-ischemia, the ratio fell to about 2.0 in all groups and remained at that level for the first 15 min. For the first 30 min it increased, suggesting improved oxidative glucose metabolism. After 30 min, it remained at about 2.5 in control and propranolol cats while in propranolol plus phentolamine treated cats it returned toward pre-ischemic values. Between 120 and 180 min, AVDO\textsubscript{2}/AVDG in propranolol cats fell to 1.0, significantly (p < 0.05) lower than in the other 2 groups. CMR-L increased 2 to 3-fold in all groups at 15 min post-ischemia. It returned to control levels by 120 and 180 min in propranolol and propranolol plus phentolamine treated cats, but remained elevated in untreated cats.

At 3 hours post-ischemia, brain tissue lactate was higher and glucose lower in propranolol and propranolol plus phentolamine treated cats compared to ischemic controls (i.e., untreated animals) (fig. 6). Brain glucose was significantly higher in ischemic controls compared to non-ischemic control cats.

Discussion

In contrast to the post-ischemic early hyperemia and delayed hypoperfusion reported in earlier studies, total CBF in this study was relatively constant in all groups. The discrepancy may be attributable to the CBF methods used. CBF measured by external scintillation monitoring of \textsuperscript{133}Xe clearance is biased for cortical flow, whereas the cerebral venous clearance method with sampling from the torcular measures total CBF. Kofke et al measured CBFs simultaneously by both methods after 16 min global ischemia in monkeys and found similar differences in total versus regional CBF. These observations corroborate previous reports of differences in post-ischemic changes of gray and white matter blood flow after global brain ischemia.

The heterogeneity of reperfusion after transient global brain ischemia and the delayed low-flow state has been well documented, but the time course of regional changes in CBF is difficult to
FIGURE 2. Cerebral blood flow in the fast-flow compartment (CBF_{ff}) and slow-flow compartment (CBF_{sf}) before and after 16 min global brain ischemia in cats. CBF measured by continuous monitoring of cerebral venous \textsuperscript{133}Xe clearance after intra-arterial injections with exponential analysis of the clearance curve. Propranolol plus phentolamine one mg/kg injection IV one min before the end of ischemia. * = p < 0.001 compared to control at the corresponding time. + = p < 0.05 to 0.001 compared to pre-ischemic value in the same group.

Our findings of the development of a small, fast-flow compartment and a large slow-flow compartment after 15 to 30 min of recirculation is comparable to the marked heterogeneity in local CBF reported by Ginsberg et al.\textsuperscript{18} in cats. The mechanism of this phenomenon is unknown. It may be attributable to higher flow rates through microcirculatory anatomic shunts found in normal brain\textsuperscript{16} and, as reported by Jackson et al.\textsuperscript{24} in ischemic brain. However, Hossmann et al.\textsuperscript{11} found no evidence of shunting with microspheres after 60 min of ischemia.

The marked reduction in W_{sf} between zero and 15 min post-ischemia in propranolol treated cats suggests that the maintenance of W_{sf} in the first 15 min post-ischemia in untreated animals is attributable to beta receptor stimulation rather than a metabolic coupling effect since CMRO\textsubscript{g} was unchanged and oxygen extraction increased. Accordingly, alpha plus beta receptor blockade maintained W_{sf} at normal levels longer post-ischemia than in untreated cats. Eventually, however, a reversal of the relative weights of the fast and slow-flow compartments occurred in all groups by 90 min post-ischemia with or without adrenergic receptor blockade. These results indicate that adrenergic regulation of cerebrovascular tone persists for the first 30 min post-ischemia.
Some caution is warranted in the interpretation of these data since the sampling sites within the torcular and individual anatomical variations in the cerebral venous system could influence the pattern of compartmental flow rates and weights. However, it is unlikely that this occurred since variation in these factors should be random and the patterns observed in the different groups, especially in terms of the compartment sizes, were quite constant within the treatment groups. In addition, the slow sampling rate of 2-3 ml/min should influence neither the origin of the venous blood sampled nor CBF even in low flow states. Finally, significant extracerebral contamination of cerebral venous blood would have been reflected by a third slow-flow compartment which was not the case.

The disappearance of differences between groups in terms of flow rates and relative weights of the fast and slow-flow compartments by 3 h post-ischemia may be interpreted in 3 ways. First, by 90 min post-ischemia, brain concentrations of propranolol and phentolamine, both of which are competitive blockers, may have fallen to concentrations ineffective for receptor blockade relative to the endogenous concentrations of receptor agonists. Both propranolol and phentolamine penetrate the blood brain barrier in sufficient quantities to block brain alpha and beta receptors at the doses used. However, the duration of their effects are less certain and subject to species differences. For example, at an IV dose of 0.1 ml/kg in the dog and monkey, plasma T½ clearance times were 45 min and 6 h, respectively. In children receiving propranolol at a dose of 0.1 mg/min, plasma T½ for rapid clearance was 10 min and for slow clearance, 2.3 h. In the absence of information on brain and plasma propranolol clearance times relative to its beta receptor blocking effects, studies in other species suggest that both propranolol and phentolamine should have provided effective receptor blockade for at least 2 h post-ischemia. A complicating factor arises from the fact that both propranolol and phentolamine are competitive receptor blockers and the large doses of norepinephrine used to maintain MAP at normal levels throughout post-ischemia may have been sufficient to overcome receptor blockade.

Second, exposure of the receptors to high endog-
enous or exogenous concentrations of norepinephrine may have altered receptor sensitivity such that by 60 min post-ischemia the response of the receptors to endogenous agonists was accentuated.

Third, and probably the most likely explanation, is that adrenergic receptor control of cerebrovascular tone progressively diminishes with time post-ischemia as it is overridden by other factors such as edema, intravascular aggregation of blood elements, or capillary compression by swollen astrocytes. If this is the case, these observations suggest that therapies aimed at preventing the development of post-ischemic encephalopathy should be applied within 30 min post-ischemia to prevent the development of the low-flow state as indicated in studies on barbiturate therapy.

The improvement of CBF\(_{et}\) and \(W_{et}\) early post-ischemia by alpha and beta adrenergic blockade compared to beta blockade alone, is supported by the improved cerebral venous oxygenation. The sustained increase in CMRO\(_2\) at 2 and 3 h post-ischemia in phentolamine plus propranolol treated cats also indicates that the increase in \(W_{et}\) limits brain oxygen consumption and strengthens the hypothesis that delayed secondary brain hypoxia occurs after global brain ischemia.

CMR

In contrast to earlier reports of a decrease in CMRO\(_2\) in the first 20 min post-ischemia, our results showed that CMRO\(_2\) was unchanged from pre-ischemic values in the first 30 min after recirculation. This discrepancy may be related to the anesthetic procedures used. In studies reporting a reduction in CMRO\(_2\), either barbiturate or \(N_2O\) anesthesia was used and was continued post-ischemia whereas in this study, halothane was discontinued during ischemia and the animals were unanesthetized post-ischemia. Thus, our pre-ischemic CMRO\(_2\) values were about 30 percent lower than in the unanesthetized state. If we were to correct for the differences in anesthesia post-ischemia, the CMRO\(_2\) values we observed in the first 30 min post-ischemia would probably be lower than pre-ischemic values.

Hypermetabolism occurred between 30 and 60 min post-ischemia in all groups and was sustained for 2 and 3 h in control and propranolol plus phentolamine
Figure 5. Indices of brain glucose metabolism before and after 16 min global brain ischemia in cats. AVDO₄ = cerebral arterial-venous oxygen difference. AVDG = cerebral arterial-venous differences for glucose. CMRL = cerebral metabolic rate for lactate = CBF times AV minus lactate. * = p < 0.05 compared to pre-ischemic values.

The mechanism of post-ischemic hypermetabolism is unknown. However, unlike immobilization stress, and like the increase in CMRO₂ during hypoxia, CMRO₂ after global brain ischemia was not totally suppressed by propranolol or a combination of propranolol plus phentolamine, suggesting that the mechanisms causing the increase in CMRO₂ during hypoxia and post-ischemia differ from those involved in immobilization stress. Levy and Duffy suggested that post-ischemic hypermetabolism may be due to increased protein synthesis. Our data do not support this suggestion since protein synthesis was not increased.

The secondary fall in CMRO₂ in propranolol treated cats and the sustained increase in CMRO₂ with beta blockade suggest that the secondary decline in CMRO₂ was flow-limited. Accordingly, cerebral venous oxygen was lower and oxygen utilization coefficient higher in this group between one and 3 h post-ischemia. Alpha combined with beta blockade appeared to improve brain oxygen consumption and cerebral venous oxygenation. This interpretation is supported by the significant (p < 0.05) reduction in AVDO₄/AVDG at 3 hours post-ischemia in the propranolol group compared to the other 2 groups. Compared to controls, CMRL was lower in beta and alpha plus beta blocked groups at 3 h post-ischemia which may be partly attributable to suppression of glucose utilization by propranolol. In patients with focal...
ischemia, propranolol suppressed brain lactic acid release and CMRO₂. Cerebral cortex, glucose and lactate measurements also support the suspicion that propranolol reduces the ability of the brain to utilize lactate and mobilize glucose stores. In summary, our studies show that the early reactive hyperemia and delayed hypoperfusion post-ischemia are events primarily associated with the alterations in the fast-flow compartment whereas total CBF remains relatively unchanged. They also show that significant differences in fast and slow-flow compartment sizes occur post-ischemia resulting in a relative distribution of about 70 percent slow-flow and 30 percent fast-flow, exactly opposite to the normal distribution. This decrease in the fast and increase in the slow-flow compartments suggests that therapeutic procedures for amelioration of ischemic brain damage should be begun within 30 min post-ischemia for optimal therapeutic effects and to prevent the development of the slow-flow state. The nature of the response in CBF with adrenergic receptor blockade suggests that in the early post-ischemic period cerebral vascular tone is modulated by alpha and beta receptors, but are affected by other factors such as intravascular obstruction, regional edema and capillary compression with time post-ischemia or that sensitivity of the receptors are markedly reduced after one hour post-ischemia.

References
adrenergic receptor blockade on circulatory and metabolic effects of disordered neurotransmitter function in stroke patients. Stroke 7: 158-167, 1976


Post-ischemic hypermetabolism in cat brain.
E M Nemoto, K A Hossmann and H K Cooper

Stroke. 1981;12:666-676
doi: 10.1161/01.STR.12.5.666

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/12/5/666

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/