Comparisons of Oxygen Metabolism and Tissue \( \text{Po}_2 \) in Cortex and Hippocampus of Gerbil Brain

Pankajam K. Nair, Donald G. Buerk, and James H. Halsey Jr.

Recessed oxygen microelectrodes (tip diameter <2 \( \mu \)m) were positioned stereotactically into either the cerebral cortex or the hippocampus of sodium pentobarbital anesthetized gerbils \((n = 21)\). The mean tissue \( \text{Po}_2 \) levels \( (\pm \text{SEM}) \) were not significantly different between cortex \((35.4 \pm 1.7 \text{ torr})\) and hippocampus \((33.6 \pm 1.4 \text{ torr})\) although differences in the tissue \( \text{Po}_2 \) distributions were seen. The disappearance rate for oxygen \((\frac{-d\text{Po}_2}{dt})\) was measured after brief \((< 15 \text{ seconds})\) bilateral carotid artery (total brain blood flow) occlusion. The mean \( (\pm \text{SEM}) \) disappearance rate was significantly higher \((p<0.05)\) in the cortex \((23.8 \pm 1.5 \text{ torr/sec}, 160 \text{ locations in } 21 \text{ gerbils})\) than in the hippocampus \((17.0 \pm 0.7 \text{ torr/sec}, 119 \text{ locations in } 16 \text{ gerbils})\). The maximum oxygen consumption rates \((\text{Vo}_2_{\text{max}})\) for Michaelis-Menten kinetics were calculated from the disappearance rates, correcting for gerbil oxyhemoglobin. The mean \( \text{Vo}_2_{\text{max}}\) was 8.28 \pm 0.51 and 6.13 \pm 0.25 ml \( \text{O}_2/100 \text{ g/min} \) for the cortex and hippocampus, respectively. The apparent Michaelis-Menten kinetic constants \((K_m)\) for the 2 regions were not significantly different (overall mean 3.3 \pm 0.4 \text{ torr}). Differences in the recovery of tissue \( \text{Po}_2 \) after releasing the occlusion were seen, with more hyperemic responses in the hippocampus. \( \text{Stroke} 1987;18:616-622 \)

We have previously used our recessed oxygen microelectrode\(^\text{12}\) to measure tissue \( \text{Po}_2 \) distributions in vivo in cat cortex\(^2\) and have determined metabolic parameters in vitro from slices of cat cortex,\(^*\) rat cortex,\(^5,6\) and guinea pig olfactory cortex\(^7\) by fitting curves of measured \( \text{Po}_2 \) gradients to mathematical models for oxygen consumption, including Michaelis-Menten kinetics. We have also determined local metabolic rates in vivo by measuring oxygen disappearance following total blood flow occlusion in extensive studies of the cat carotid body.\(^8-11\) Martin et al\(^12\) and Reneau and Halsey\(^13\) have previously used needle-type oxygen microelectrodes for similar oxygen disappearance measurements in the gerbil cortex. An earlier study by Leniger-Follert\(^14\) used a multiwire electrode with relatively large cathodes for surface \( \text{Po}_2 \) measurements after occlusion. Microelectrode studies permit measurements at deeper locations with more spatial detail than surface \( \text{Po}_2 \) measurements. However, there are difficulties in interpreting either type of oxygen disappearance measurement; the measurement is delayed by continued release of oxyhemoglobin. Measurements were made in 2 regions of the gerbil brain, the cortex and the hippocampus, which are of interest due to marked differences in susceptibility to ischemic damage (selective vulnerability), even within a region. The gerbil model of ischemia was chosen because blood flow to the brain can be stopped completely with bilateral carotid artery occlusion since the circle of Willis has no connections to the basilar artery for a source of collateral blood flow.

Avoid these complications, Martin et al\(^12\) used hyperoxic conditions, and Leniger-Follert\(^14\) used hyperoxic breathing so the initial oxygen disappearance measurement occurred under conditions of completely saturated oxyhemoglobin. Reneau et al\(^13,15\) have developed a simplified mathematical model to characterize the oxygen disappearance curve based on 2 compartments, blood and tissue. However, the useful range of application was limited since the Hill equation used for blood is not accurate at low \( \text{Po}_2 \). More recently, Buerk et al\(^16\) have improved the compartmental model using a new, more accurate algorithm for the oxyhemoglobin equilibrium curve developed by Buerk\(^17\) and Buerk and Bridges.\(^18\)

The present study was undertaken to quantify oxygen metabolism at highly localized sites by the oxygen disappearance technique, correcting for the influence of oxyhemoglobin. Measurements were made in 2 regions of the gerbil brain, the cortex and the hippocampus, which are of interest due to marked differences in susceptibility to ischemic damage (selective vulnerability), even within a region. The gerbil model of ischemia was chosen because blood flow to the brain can be stopped completely with bilateral carotid artery occlusion since the circle of Willis has no connections to the basilar artery for a source of collateral blood flow.

Materials and Methods

Mongolian gerbils, aged 3-4 months, weighing 50-90 g, were maintained on standard laboratory food and water ad libitum. They were anesthetized with 30-40 mg/kg i.p. sodium pentobarbital, tracheotomized, and allowed to breathe spontaneously. Both common carotid arteries were exposed through ventral midline cervical incisions and isolated from the accompanying nerves and vein. Surgical sutures were placed around the arteries for causing occlusions. In

\( \text{Stroke} 1987;18:616-622 \)
some gerbils, a small 0.024 in. o.d. polyethylene catheter was inserted into the tail artery for blood pressure measurements. Each gerbil was maintained at normal body temperature (38–39°C) with a heating pad, and the head was mounted in a modified head holder. The skin and muscles were removed from the skull, and a small hole was made in the skull using a dental drill. A rubber O-ring was glued to the skull to provide a well for continuous superfusion of a physiologic saline solution, with pH adjusted to 7.3–7.4, equilibrated with 21% O₂, and maintained at the animal’s body temperature. The dura was left intact.

Tissue Po₂ was measured polarographically using our recessed oxygen microelectrode 1,2 calibrated in the superfusion solution prior to penetrating the brain. Zero values were obtained during total blood flow occlusion. The microelectrode was positioned using a hydraulic microdrive (David Kopf Instruments) at a rate of about 1 μm/sec, and the depth of penetration from the cortical surface was recorded after stopping at each location. The thickness of the cortex is reported to be 1.055 ± 0.059 mm and the ventral side of the hippocampus about 1.9 mm from the cortical surface.19 Penetrations were observed through a low-power microscope to locate the surface of the brain and to identify whether tissue was distorted (dimpled). The microelectrode reading was allowed to stabilize at each location for several minutes, and then a disappearance curve was obtained by briefly occluding both carotid arteries for 10–15 seconds. No measurements were obtained at depths < 350 μm from the brain surface due to the possible influence of the superfusion solution. The recovery of tissue Po₂ was followed for several minutes after releasing the occlusion. The microelectrode was then driven to a new, deeper location, and the occlusion and measurements were repeated. In a few cases, measurements were repeated at the same location. The microelectrodes were recalibrated in the superfusion solution after withdrawal from the brain.

The data were analyzed graphically to determine the initial oxygen disappearance rate (−dPo₂/dt) and the apparent Michaelis-Menten constant (Kₐ) when the rate fell to 50% of the initial value. Histograms of the initial tissue Po₂ prior to occlusion were compiled, with recovery data tabulated for any Po₂ overshoot after release of the occlusion and the final Po₂ for each region. The maximum oxygen consumption rate (Vo₂max) was calculated from the initial slope of the disappearance curve, correcting for gerbil oxyhemoglobin as described in Appendix 1.

**Results**

Data were analyzed from 160 different locations in the cortex of 21 gerbils and from 119 locations in the hippocampus of 16 gerbils. An example of an electrode penetration from the calibrating solution into the brain to a final depth of just over 2 mm is shown in Figure 1. Variations in Po₂ with depth can be seen. At several different depths during this penetration (breaks in record), oxygen disappearance curves were measured. Examples of these curves are shown in Figure 2, measured in the cortex (upper panel) and the hippocampus (lower panel). In the example for the cortex,
the initial \(P_o2\) value is 36 torr, with a disappearance rate of \(-14\) torr/sec and an estimated apparent \(K_m\) of 2.3 torr. For the hippocampus example, the initial \(P_o2\) is 65 torr, with one of the highest disappearance rates we found, \(-36\) torr/sec, and an apparent \(K_m\) of 4.3 torr. The fairly linear disappearance rate shown in both examples, down to low tissue \(P_o2\) levels, was seen in the overwhelming majority of measurements. A summary of all 279 measurements from the 2 regions is listed in Table 1, with standard errors based on equally weighted observations; ranges for the mean values from individual experiments are also included. Although there was no significant difference between initial tissue \(P_o2\) in the 2 regions, there was some difference in the distribution of tissue \(P_o2\), shown in Figure 3. The frequency distribution for tissue \(P_o2\) in the hippocampus is shifted to the left of that in the cortex.

To examine whether there was any relation between the disappearance rates and the depth of penetration, a linear regression analysis was performed using data from gerbils in which measurements were obtained in both regions. A scattergram of the disappearance rates measured at 204 different depths in 16 gerbils is shown in Figure 4. The remaining 75 measurements from the cortex of 5 gerbils are not shown. A wide range of values were found, even within individual gerbils. The resulting regression line has a downward trend (intercept 17.76 torr/sec, slope \(-0.35\) torr/sec/mm), although it was not significantly different from 0 \((r = 0.03)\) due to the wide scatter of data. However, when the mean values from each region are compared by Student's \(t\) test with equal weighting for each observation, a significantly higher oxygen disappearance rate is found in the cortex \((p<0.05)\), indicated in Table 1. The disappearance data from the cortex of 1 gerbil was markedly higher (mean 53.5 torr/sec, 21 measurements) than the cortex data from all other gerbils. If the data from this gerbil are excluded from analysis, the mean disappearance rate is reduced to 19.3 ± 1.1 torr/sec, which is still significantly higher than the mean disappearance rate from the hippocampus \((p<0.05)\).

The relation between disappearance rate and initial \(P_o2\) was also examined. The disappearance data were normalized with respect to the mean for each gerbil, and a linear regression against initial tissue \(P_o2\), was performed. After normalization, the data from the cortex of the gerbil with high disappearance rates was similar to the other data sets. The normalized disappearance rate increased with \(P_o2\) by \(1.5\%\)/torr in the cortex (\(r = 0.33\)) and by \(1.7\%\)/torr in the hippocampus \((r = 0.55)\). The correlation coefficients for each region were not highly significant since normalization did not reduce the wide scatter of data. The regression lines based on this analysis are shown in Figure 5 along with the mean values from individual gerbils. This relation was used to estimate the conversion factor needed to compute \(V_o2_{max}\) listed in Table 1, as described in Appendix 1. The values of \(V_o2_{max}\) after correcting for oxyhemoglobin are shown in Figure 6 for individual

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**Table 1. Summary of Oxygen Disappearance Measurements in Gerbil Brain**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of gerbils</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Number of measurements</td>
<td>160</td>
<td>119</td>
</tr>
<tr>
<td>Depth (mm)</td>
<td>0.64±0.03</td>
<td>1.72±0.06*</td>
</tr>
<tr>
<td>Initial (P_o2) (torr)</td>
<td>35.4±1.7</td>
<td>33.6±1.4</td>
</tr>
<tr>
<td>Range</td>
<td>28-62</td>
<td>26-44</td>
</tr>
<tr>
<td>(-dP_o2/dt) (torr/sec)</td>
<td>23.8±1.5</td>
<td>17.0±0.7*</td>
</tr>
<tr>
<td>Range</td>
<td>10-53.5</td>
<td>9.8-37.6</td>
</tr>
<tr>
<td>(V_o2_{max}) (ml O2/100 g/min)</td>
<td>8.28±0.51</td>
<td>6.13±0.25*</td>
</tr>
<tr>
<td>Range</td>
<td>3.88-19.3</td>
<td>3.50-12.5</td>
</tr>
<tr>
<td>(K_m) (torr)</td>
<td>3.2±0.5</td>
<td>3.4±0.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.8-4.0</td>
<td>1.5-5.0</td>
</tr>
</tbody>
</table>

\(P_{o2}\) units, 1 torr = 1 mm Hg = 0.1333 kPa.

\(*p < 0.05\).
gerbils, including the data from the cortex of the gerbil with high disappearance rates. If the data from this gerbil are excluded, the average value for the cortex is reduced to 6.72 ± 0.39 ml O₂/100 g/min. The mean values for VO₂max in the cortex (excluding the high data set) and the hippocampus are shown as horizontal lines in Figure 6.

Gerbils were classified into 2 groups based on tissue PO₂ recovery data: those gerbils that recovered to within 5 torr of the initial value (good recovery) and those that did not (poor recovery), as summarized in Table 2. For those gerbils that demonstrated good recovery, 2 types of responses were seen. An overshoot in tissue PO₂, which would be expected from blood flow hyperemia after occlusion, was seen more often in the hippocampus. The magnitude of the overshoot in the hippocampus was also significantly higher (p < 0.05) than that in the cortex. The remaining gerbils classified as good recovery (listed as “other” in Table 2) returned to control without any overshoot. This type of response was seen more frequently in the cortex. In gerbils categorized as poor recovery, hyperemia was also seen in both regions, although more often in the hippocampus.

**Discussion**

We observed some differences in tissue PO₂ recovery from very brief blood flow occlusion, with more hyperemic responses (overshoot) seen in the hippocampus. There does not appear to be any relation between good and poor recovery and the metabolic rate at that site. In the small sample of gerbils in which disappearance curves were repeatedly measured, we saw some evidence of hypermetabolism, with a higher disappearance rate for the second occlusion. However, decreases were also seen. We limited our experimental protocol to brief occlusions so we could make more measurements in the same animal. It would be of interest to determine whether there are differences in recovery responses after longer periods of occlusion. Although we believe that we allowed sufficient time for the brain to recover, we cannot rule out the possibility that our repeated measurements (up to 30 in some gerbils) may have altered the metabolic state. However, when the duration of occlusion is < 30 seconds and the interval between occlusions is > 30 minutes, we have not seen evidence of cumulative brain damage due to accumulating cerebral edema manifested by decreasing tissue PO₂ between successive occlusions.

Our results show a wide degree of heterogeneity for VO₂max in both the cortex and the hippocampus, although the average difference between the 2 regions is not very large. It should be pointed out that higher values for VO₂max would be calculated if a smaller difference between blood and tissue PO₂ is assumed. We also made the same correction for oxyhemoglobin in both regions, which may not be accurate. Although we can make an approximate correction for the oxyhemoglobin effects, we do not have sufficient information about microelectrode tip distances from capillaries, relative tissue and blood volumes, blood PO₂, pH, PCO₂, hematocrit, and other factors at the measurement site to fully correct the disappearance measurement.

**Figure 3.** Frequency distributions of initial tissue PO₂ from oxygen disappearance measurements in gerbil cortex and hippocampus.
Additionally, both the maximum slope of the oxyhemoglobin curve and its location (P*) are shifted with blood pH, PCO₂, and temperature. Based on preliminary computer simulations, it appears that many of these effects would be relatively small compared with the correction using a standard equilibrium curve. An alternate possibility is that the blood flow at the measurement site does not fall immediately to 0, or that some collateral blood flow remains after occlusion. In the latter case, we would expect the final PO₂ after occlusion to be > 0. We did not find this to be the case, and there was consistently a PO₂ of 0 for all occlusions.

Our previous experiments have shown that unilateral carotid ligation is highly unreliable to produce predictable cerebral ischemia in individual cases. Overall, about 40% of unilateral carotid ligations result in significant ischemia producing infarctions because of the high level of competence of the connection between the two sides of the circle of Willis at the origins of the anterior and posterior cerebral arteries. By contrast, bilateral carotid occlusion causes total permanent cerebral ischemia in > 95% of cases because of the almost invariable absence of connection between the basilar artery and the circle of Willis. Even in the rare cases of residual connection between basilar artery and circle of Willis, the initial oxygen disappearance curve is not slowed. The only difference is that PO₂ may not fall to 0 or may not remain at 0 in a sustained occlusion. We feel that residual input in rare cases would not disturb the oxygen disappearance rate.

Another factor that might influence our measurement is the possible displacement of the microelectrode tip during the occlusion by edema, tissue shrinkage, or other motion artifacts. However, since the microelectrode remained at a location for only a few minutes at most and since the length of occlusion was only 10–15 seconds, we do not expect movement to be significant. With prolonged periods of ischemia, this could be a problem. Also, since the period of occlusion was brief and since several minutes were allowed for recovery, we do not expect significant alterations in intracellular potassium during the measurement because large changes are seen only after approximately 2 minutes of occlusion. Further, in separate experiments we have measured the potassium flux with ion exchange potassium electrodes and noticed that the fast phase of the potassium flux associated with the DC potential shift usually does not occur until after >1 minute of total ischemia.

The scatter in calculated VO₂max values might be reduced if more detailed histologic information about each measurement site could be obtained. Although we have developed a technique for marking the location of our microelectrode tip, we have not yet used this technique in brain. Despite variability of the influence that oxyhemoglobin could have on oxygen disappearance data, we do not attribute all of the variation to oxyhemoglobin. We believe that our results suggest a significant degree of heterogeneity of metabolism in both the cortex and the hippocampus, with as much as a fivefold range in values found within individual gerbils. We speculate that these differences are most likely related to cell type, with higher disappearance rates associated with electrically active neurons and lower rates with glial cells. Further experimental work is needed to correlate our measurements with anatomical location and to examine any correlation between metabolic rate and selective vulnerability to ischemic damage at different locations.

We were somewhat surprised that there was relatively little variation in the estimated Michaelis-Menten constants. There was no real difference between apparent Kₘ's for the 2 regions (overall mean 3.3 torr), although Kₘ was higher than we had previously found (0.8 torr) in rat cortex slices. The higher apparent Kₘ was expected to be due to the influence of oxyhemoglobin, as shown by Buerk et al. Using Kₘ = 3.3 torr in Equation 2 (see Appendix 1), the metabolic correction is roughly 10% for the range of tissue PO₂ we encountered. Hence, the oxygen consumption rate (VO₂) is >90% of maximum at normal tissue PO₂. The true metabolic Kₘ is unquestionably lower, depending on both the initial oxygen tension and the high-energy substrates. Rough calculations from our data give estimates for the true metabolic Kₘ of <1 torr, depending on the blood PO₂, pH, and PCO₂ near

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial PO₂</strong></td>
<td>33.6 ± 1.7</td>
<td>30.5 ± 6.2</td>
</tr>
<tr>
<td><strong>Final change</strong></td>
<td>-2.6 ± 0.3</td>
<td>-3.5 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.05.
the measurement sites. Therefore, it is more likely that \( V_{O_2} \) is >95% of maximum at most locations.

Some of the variation in the oxygen disappearance rate with tissue \( P_{O_2} \) might be attributed to an alternate metabolic pathway for oxygen, a possibility suggested from the recent data of Piantadosi et al\textsuperscript{26} obtained by optical methods in bloodless rat brain. The oxygen disappearance data would be more concentration-dependent for such a case. Oxygen disappearance rates that we have measured from the carotid body\textsuperscript{*} show much more curvature, with apparent \( K_m \) values well above those we found in gerbil brain. We suspect that a second, low-affinity cytochrome may play an important role in chemoreception.\textsuperscript{8} However, virtually all of our data from both regions of the gerbil brain fell to 0 in a more linear manner than we have found in the cat carotid body. We saw no evidence for a second cytochrome with high \( K_m \) (low affinity) in the regions of brain that we investigated.

Information about the metabolic properties in highly localized regions of the gerbil cortex and hippocampus can be derived from analysis of the oxygen disappearance rate measured with oxygen microelectrodes after total blood flow occlusion, correcting for the influence of oxyhemoglobin on the measurement. The maximum oxygen consumption rate, \( V_{O_2}\text{max} \), was found to be higher in the cortex than in the hippocampus, but no difference in the Michaelis-Menten kinetic constant, \( K_m \), was seen. A wide range of heterogeneity in metabolism was seen in both regions. Regional differences in the tissue \( P_{O_2} \) distributions and the tissue \( P_{O_2} \) recovery responses after release of the occlusion were also seen.

**Appendix 1.**

**Calculating Oxygen Consumption From Disappearance Rate**

**Nomenclature**

\[
\begin{align*}
A & \quad \text{Oxygen solubility in tissue} \\
B & \quad \text{Conversion constant} \\
K_m & \quad \text{Tissue } P_{O_2} \text{ where oxygen consumption is half of maximum (Michaelis-Menten constant)}
\end{align*}
\]

\[
\begin{align*}
dP_t/dt & \quad \text{Initial oxygen disappearance rate} \\
dS/dP & \quad \text{Slope of oxyhemoglobin equilibrium curve} \\
P & \quad \text{Blood } P_{O_2} \\
P^* & \quad \text{Blood } P_{O_2} \text{ where slope of oxyhemoglobin equilibrium is maximum} \\
P_{50} & \quad \text{Blood } P_{O_2} \text{ at 50% saturation} \\
P_T & \quad \text{Tissue } P_{O_2} \\
V_{O_2} & \quad \text{Oxygen consumption rate} \\
V_{O_2}\text{max} & \quad \text{Maximum oxygen consumption rate}
\end{align*}
\]

To calculate the local oxygen consumption rate, the initial oxygen disappearance rate must be multiplied by an appropriate conversion factor, which includes oxyhemoglobin effects. Based on the previous modeling for oxygen disappearance by Renaeu et al\textsuperscript{13,13} and the recent improvement by Buerk et al,\textsuperscript{16} the oxygen consumption rate is given by

\[
V_{O_2} = A (1 + B dS/dP) dP_t/dt
\]

If Michaelis-Menten kinetics are assumed, the maximum oxygen consumption rate can be calculated as

\[
V_{O_2}\text{max} = A (1 + B dS/dP) (1 + K_m/P_T) dP_t/dt
\]

The slope can be computed from the blood algorithm developed by Buerk\textsuperscript{17} and Buerk and Bridges,\textsuperscript{18} using appropriate parameters for gerbil blood. For human blood at standard conditions, the maximum slope is 0.026 torr\textsuperscript{-1} at \( P^* = 20.7 \) torr, with \( P_{50} = 26.8 \) torr.\textsuperscript{18} For dog blood, the maximum slope is 0.022 torr\textsuperscript{-1} at \( P^* = 24.5 \) torr, with \( P_{50} = 31.7 \) torr.\textsuperscript{17} We have not found detailed gerbil blood saturation data in the literature to directly fit curves, but we can estimate the properties based on a \( P_{50} \text{ value of } 40 \) torr. Extrapolating from dog and human blood \( P^* \text{ values, we estimate that the maximum slope is } 0.017 \) torr\textsuperscript{-1} at \( P^* = 30 \) torr for gerbil blood. The different slopes as functions of the blood \( P_{O_2} \) computed from the blood algorithm are shown in Figure 7 for these 3 species.

**Figure 7.** Slopes of oxyhemoglobin equilibrium curves as a function of blood \( P_{O_2} \) for humans (●), dogs (○), and gerbils (▲).
At high PO₂, the slope of the oxyhemoglobin curve is nearly 0 and Equation 1 would be identical to that used by Leniger-Follert. In this case, A = 0.186 to convert from disappearance rate units (torr/sec) to oxygen consumption units (ml O₂/100 g/min). At lower PO₂, the constant B must be determined. As defined by previous compartmental models, B depends on the relative sizes of the blood and tissue compartments, the oxygen carrying capacity of blood, and the ratio of PO₂ in blood and tissue. For further details, see Buerk et al. or Reneau et al. By assuming a 20-torr difference between P_b and P, and by comparing the slope of the regression lines for the disappearance data shown previously in Figure 5, we estimate B = 70 torr. With this value, the conversion factor in Equation 1 ranges from a maximum of 0.402 at P_b = 30 torr, falling almost linearly to 0.239 at P_b = 80 torr. These values were used to compute VO₂max shown in Figure 6.

Acknowledgments

Technical assistance from Mr. Scott Doughty and Ms. Jeanene Bunch is appreciated.

References


Key Words • cortex • hippocampus • Michaelis-Menten constant • oxygen metabolism • oxygen microelectrode
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*Stroke*. 1987;18:616-622
doi: 10.1161/01.STR.18.3.616

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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