Rat Striatal Cation Shifts Reflecting Hypoxic-Ischemic Damage Can Be Predicted by On-Line Impedance Measurements

Jaep de Boer, MD, Hans C. Klein, Folkert Postema, K. Gwan Go, MD, PhD, and Jakob Korf, PhD

We investigated the earliest time at which irreversible damage takes place after hypoxia-ischemia in the Levine preparation of rats. In 60 rats anesthetized with chloral hydrate and maintained at one of three body temperatures, we unilaterally ligated the left common carotid artery and placed electrodes in the striatum to measure impedance (reflecting the extracellular space) during hypoxia, recovery, and/or cardiac arrest. We measured blood gases and pH at regular intervals during hypoxia in 47 rats and assessed blood–brain barrier function with Evans blue and tissue damage using Na⁺:K⁺ ratios. Shortly after hypoxia, impedance normalized in 24 rats without brain damage (normal Na⁺:K⁺ ratios, 4 hours of recovery). Sustained elevation of striatal impedance during recovery in six rats was related to an elevated Na⁺:K⁺ ratio and a disrupted blood–brain barrier. Damage was not obviously related to blood gases, pH, or the net reduction of the extracellular space during hypoxia. Hypothermia in 17 rats prevented impedance changes, and no striatal damage was found. Thus, irreversible brain damage very likely occurs during or very shortly after hypoxia. Persistent reduction of the extracellular space indicates tissue damage and can be used to monitor potential in vivo therapeutic measures. (Stroke 1989;20:1377–1382)

Using ion-selective microelectrodes (which measure extracellular Na⁺, K⁺, Cl⁻, and Ca²⁺ concentrations), whole-tissue impedance (which reflects extracellular space), and steady-state cortical potential deflection, it is possible to distinguish the phases that eventually lead to irreversible ischemic brain damage. These phases include a delay of 1.5 minutes (Phase I), followed by the ongoing (Phase II) and complete (Phase III) depolarization of neurons and/or glia cells and are mainly the result of ion shifts between the extracellular and intracellular compartments. These changes are often reversible in hypoxia and ischemia. Because the cells take up water, the extracellular space shrinks during Phases II and III; the shrinkage is reflected by increased impedance. Until now, however, no technique has been used to determine the time of onset of irreversible brain damage.

Brain damage caused by ischemia or hypoxia can easily be quantified by whole-tissue cation measurements, provided there is an adequately maintained or restored cerebral blood flow (CBF). We used a modified Levine model (partial ischemia due to unilateral carotid artery ligation with hypoxic ventilation in anesthetized rats) with a recovery period of 4 hours. Impedance measured during hypoxia, recovery, and cardiac arrest was compared with brain damage assessed by cation measurements and with blood–brain barrier (BBB) function. Our major aim is to predict from impedance recordings the outcome of a hypoxic-ischemic challenge and the relative effectiveness of interventions. Hypothermia, a classic intervention, was used to provide brain protection.

Materials and Methods

The electrodes consisted of two silver-plated copper wires, each Teflon-coated within 0.5 mm of the tip and glued together with epoxy (Wilsons, Biddinghuisen, The Netherlands), the tips approximately 0.5 mm apart. Using a constant biphasic block-pulse current of 30 µA delivered at 10,000 Hz, impedance was continuously recorded bilaterally as described elsewhere. Striatal impedance of 2–5 kΩ was seen after surgery.
In 60 male Wistar rats (locally bred, weighing 200–300 g, Centraal Proefdierenlab, Groningen, The Netherlands) anesthetized with 400 mg/kg chloral hydrate, bilateral electrodes were stereotactically placed in the striatum and fixed with dental cement. The left common carotid artery was ligated and proximally cannulated for blood sampling. The cannula was rinsed with 50 E/ml heparin. Each rat was then intubated, and body temperature was maintained at 38° (normothermia), 32°, or 28° C with a heating pad during the 90-minute operation.

While still anesthetized, 25 minutes of hypoxia was induced in 52 rats by connecting them to a constant-volume ventilator (mk 2, Loosco, Amsterdam, The Netherlands) that delivered a gas mixture of 12–14% O2 in N2O). After 24 minutes of hypoxia, arterial blood was sampled for blood gas analysis at body temperature (acid–base laboratory ABL 330, Radiometer, Copenhagen, Denmark). Eight control rats were subjected to unilateral carotid artery occlusion but not hypoxia. During the first 5 minutes of recovery, each rat was ventilated with 100% O2 while 0.6 ml of 2% Evans blue was injected intra-arterially.

After 4 hours of recovery, anesthesia was induced again in all rats and impedance was recorded during cardiac arrest induced by the injection of 0.5 ml of a MgCl2 solution (with 300 mg MgCl2 • 6H2O). Thirty minutes later, the brain of each rat was dissected and examined for Evans blue staining and samples were taken from the cerebellar cortex, ipsilateral and contralateral striatum, and prefrontal cerebral cortex. These samples were rapidly frozen on dry ice and stored at −80° C until Na + and K + concentrations could be measured by flame emission spectroscopy as described previously.

The study groups consisted of 30, eight, and nine rats made hypoxic at body temperatures of 37°, 32°, and 28° C, respectively. In the control rats, cardiac arrest was induced at body temperatures of 37° and 28° C (four rats at each temperature). In five rats, the Na +:K + ratio and BBB function immediately after 25 minutes of normothermic hypoxia (no recovery) were determined.

We used tissue Na + and K + concentrations to calculate mean±SEM Na +:K + ratios and changes of impedance to calculate the mean±SEM relative change in the extracellular space (expressed as a percent of that before hypoxia). Mean±SEM blood gases and pH were evaluated at body temperature; mean±SEM pH, Paco2, and Pao2 were measured and expressed as KPa; and mean±SEM O2 saturation was measured and expressed as percent. We analyzed the differences in Na +:K + ratios, extracellular space, and blood gas values nonparametrically using the two-tailed Mann-Whitney U test or the Wilcoxon test when possible. As an index of the time of onset of rapid increases in impedance, we calculated the mean±SEM time defined by the intersection of the line of basal impedance and the tangent to the curve at the time of maximal increase in impedance after the onset of hypoxia (TTH) and after the onset of cardiac arrest (TTC). We also calculated the mean±SEM time of maximal increase in impedance after the onset of hypoxia (TMH) and after the onset of cardiac arrest and the mean±SEM time at which half-maximal impedance increase during hypoxia (T50H) was reached. Differences in these time parameters were analyzed using Student’s t test. BBB function was expressed as the percentage of Evans blue-stained samples in the total number of observations in each brain region; differences were analyzed using Fisher’s exact test. Differences were considered to be significant when p<0.05.

Results

Figure 1 shows the typical impedance recordings. During hypoxia, impedance recordings in the striata ipsilateral to the carotid ligation followed a consistent pattern. During the first 3 minutes, there was a slow rise followed by a rapid increase until a plateau approximately twice the prehypoxic impedance was reached. Two patterns of ipsilateral impedance change could be distinguished during recovery and subsequent cardiac arrest. In the first pattern, return of the impedance to its prehypoxic value was fol-
**TABLE 1. Various Parameters of Rats in Levine Model Exposed to 25 Minutes of Normothermic or Hypothermic Hypoxia and 4 Hours of Normoxic Recovery Before Cardiac Arrest**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normothermic</th>
<th></th>
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<th>Hypothermic</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Infarct (n=6)</td>
<td>No infarct (n=24)</td>
<td></td>
<td>Body temperature 31.7±0.3°C (n=8)</td>
<td>Body temperature 27.9±0.2°C (n=9)</td>
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<tr>
<td></td>
<td>(body temperature 36.7±0.7°C)</td>
<td>(body temperature 36.9±0.2°C)</td>
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<tr>
<td>Na(^+)/K(^+) ratio</td>
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<td></td>
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<td></td>
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<tr>
<td>Striatum</td>
<td>0.98±0.06*</td>
<td>0.39±0.06†</td>
<td>0.44±0.02</td>
<td>0.41±0.02</td>
<td>0.41±0.01</td>
<td>0.43±0.04</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.79±0.14‡</td>
<td>0.45±0.05†</td>
<td>0.43±0.03</td>
<td>0.43±0.02</td>
<td>0.45±0.03</td>
<td>0.46±0.03</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.49±0.05</td>
<td>0.47±0.01</td>
<td>0.52±0.03</td>
<td>0.50±0.02</td>
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<tr>
<td>Evans blue staining (blue/total)§</td>
<td></td>
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<tr>
<td>Striatum</td>
<td>6/6</td>
<td></td>
<td></td>
<td>2/6§</td>
<td>4/22</td>
<td>4/22</td>
</tr>
<tr>
<td>Cortex</td>
<td>5/6#</td>
<td>2/6§</td>
<td>5/22</td>
<td>3/22</td>
<td>2/7</td>
<td>2/7</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1/6</td>
<td></td>
<td></td>
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<tr>
<td>Extracellular space (% of before hypoxia)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>During hypoxia</td>
<td>40.0±3.8</td>
<td>69.5±8.3**</td>
<td>48.5±3.0</td>
<td>67.1±4.0</td>
<td>73.5±7.3</td>
<td>85.7±4.1</td>
</tr>
<tr>
<td>After hypoxia</td>
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<tr>
<td>5 min</td>
<td>45.8±3.3††</td>
<td>81.7±11.5**</td>
<td>66.2±5.1</td>
<td>88.6±4.1</td>
<td>—</td>
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<tr>
<td>10 min</td>
<td>46.6±4.1‡†</td>
<td>85.9±12.3‡‡</td>
<td>75.5±5.6</td>
<td>94.7±3.7</td>
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<tr>
<td>15 min</td>
<td>43.8±4.4‡‡</td>
<td>86.6±12.6††</td>
<td>78.2±5.1</td>
<td>98.1±4.7</td>
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</tr>
<tr>
<td>During cardiac arrest</td>
<td>38.8±4.5*</td>
<td>84.6±6.1</td>
<td>100.0±8.3</td>
<td>93.7±3.7</td>
<td>92.6±7.2</td>
<td>95.1±9.0</td>
</tr>
<tr>
<td>After cardiac arrest (15 min)</td>
<td>33.7±4.3*</td>
<td>49.8±7.0</td>
<td>62.4±7.3</td>
<td>48.2±1.9</td>
<td>46.6±3.0</td>
<td>47.2±5.6</td>
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<tr>
<td>Time parameters (sec)</td>
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<tr>
<td>TTH</td>
<td>197±45</td>
<td>429±210</td>
<td>188±33</td>
<td>254±84</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TMH</td>
<td>394±110</td>
<td>653±215</td>
<td>250±50</td>
<td>333±84</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>T50H</td>
<td>562±138</td>
<td>688±218</td>
<td>439±63</td>
<td>583±61</td>
<td>520±101</td>
<td>705±117</td>
</tr>
<tr>
<td>Blood gas parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>pH</td>
<td>7.040±0.047</td>
<td>7.105±0.021</td>
<td>7.163±0.04</td>
<td>7.186±0.03</td>
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<tr>
<td>Paco2 (kPa)</td>
<td>6.47±1.59</td>
<td>5.60±0.38</td>
<td>7.44±0.5</td>
<td>7.46±0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paco2 (kPa)</td>
<td>5.63±0.24</td>
<td>6.61±0.26</td>
<td>5.36±0.3</td>
<td>4.37±0.4</td>
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</tr>
<tr>
<td>O2 saturation (%)</td>
<td>70.7±10.9</td>
<td>75.7±2.8</td>
<td>75.8±3.0</td>
<td>75.9±5.0</td>
<td></td>
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</tr>
</tbody>
</table>

Data are mean±SEM. TTH, time of onset of rapid impedance increase after onset of hypoxia defined by intersection of the line of basal impedance and the tangent to the curve at the time of maximal increase in impedance; TMH, time of maximal impedance increase after onset of hypoxia; T50H, time of half-maximal impedance increase after onset of hypoxia.

*†††p<0.001, 0.01, 0.05, respectively, different from no infarct by Mann-Whitney two-tailed U test.
†‡‡‡p<0.05, 0.01, 0.05, respectively, different from ipsilateral by Wilcoxon test.
§In a few cases, rats were not given Evans blue.
||#p<0.001, 0.05, respectively, different from no infarct by Fischer’s exact test.
1Ip<0.05 different from ipsilateral by Fischer’s exact test.

Lowed by a cardiac arrest curve identical to that of controls (data not shown) (see also Reference 21). In the second pattern, impedance remained high during recovery (sometimes after a transient drop, Figure 1, middle panel), but there was a reduced impedance increase during cardiac arrest. Contralateral impedance recordings showed a variety of patterns, with no or delayed rapid impedance increases, maximum increases of impedance that never exceeded that in the ipsilateral striatum, return to prehypoxic values during recovery, and impedance recordings during cardiac arrest similar to those of controls.

Using the striatal Na\(^+\)/K\(^+\) ratios of the 30 rats exposed to hypoxia at 37°C, we defined two subgroups of rats, those with (n=6) and those without (n=24) a unilateral striatal infarct, presuming that a Na\(^+\)/K\(^+\) ratio of >0.70 (normal+2SD) indicates infarction (Table 1). Only ipsilaterally was the relative change in extracellular space related to Na\(^+\)/K\(^+\) ratio elevation and BBB breakdown. Changes in extracellular space during hypoxia were not different (Figure 2), but after 5 minutes of recovery, extracellular space was reduced significantly more (p=0.0331) in the striata of the rats with infarct. This relation became stronger with ongoing recovery (Figure 2). The time parameters TTH, TMH, and T50H and the blood gas parameters did not differ between subgroups (Table 1), nor did the combinations Paco2-Paco2, Paco2×PH, or pH×O2 saturation, although there was a trend toward lower pH, higher Paco2, lower PaO2, and lower O2 saturation in the subgroup with infarct. Na\(^+\)/K\(^+\) ratios in the ipsilateral prefrontal cortex of the rats with...
The increase in impedance was bilaterally smaller than in normothermic rats and returned quickly to premalignant values during recovery. Impedance recordings during cardiac arrest were not different from those of normothermic rats without infarct. The rapid increase in impedance was often absent during hypothermia, and no elevation of the Na⁺:K⁺ ratio was observed. The relative changes in extracellular space during hypoxia were significantly lower in both ipsi and contralateral striatum of hypothermic rats than in the normothermic rats (Table 1). T50H did not differ from that in the infarcted or the noninfarcted normothermic rats for either hypothermic group, but pH was significantly higher in the 28°C group than in either the infarcted or the noninfarcted normothermic subgroups. In both hypothermic groups, Pao₂ was lower than that in the noninfarcted normothermic subgroup. Distribution of Evans blue staining in all examined brain regions did not differ from that in the noninfarcted normothermic subgroup in either hypothermic group.

Cardiac arrest was induced after unilateral carotid artery ligation without preexposure to hypoxia in eight control rats (Table 2). At 37°C, TTC was significantly sooner in the ipsilateral than in the contralateral striatum, while at 28°C TTC was delayed approximately 300% and bilateral differences disappeared. No other differences were seen in any parameter.

Na⁺:K⁺ ratios measured in five brains obtained immediately after 25 minutes of hypoxia did not increase, while relative changes in the extracellular space were similar to those of the normothermic hypoxia group (Table 3). No brain region was stained.

**Discussion**

Permanent striatal damage, expressed as tissue Na⁺:K⁺ ratio, can be predicted as soon as 5–10 minutes after hypoxia-ischemia by monitoring the extracellular space. During hypoxia, extracellular

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Graph of relative changes in mean±SEM ipsilateral striatal extracellular space (ECS) in rats with ligated left common carotid artery during hypoxia at 37°C, during recovery, and during cardiac arrest. Separate data for rats with normal (●, n=24) and rats with elevated (○, n=6) ipsilateral striatal Na⁺:K⁺ ratio. Intersection of tangent to line indicating steep ECS decrease and 100% ECS indicates mean±SEM time of onset of rapid impedance increase (TTH). Mean±SEM time of half-maximal impedance increase (T50H) is also indicated for both subgroups. *, **p<0.05, 0.005, respectively, different from ● by Mann-Whitney two-tailed U test.

### Table 2. Various Parameters of Normothermic and Hypothermic Control Rats With Cardiac Arrest 4 Hours After Left Common Carotid Artery Ligation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Body temperature</th>
<th>Normothermic (37.7±0.2°C, n=4)</th>
<th>Hypothermic (27.8±0.1°C, n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Na⁺:K⁺ ratio</td>
<td>Striatum</td>
<td>0.35±0.02</td>
<td>0.32±0.02</td>
</tr>
<tr>
<td></td>
<td>Cortex</td>
<td>0.35±0.02</td>
<td>0.32±0.01</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>0.44±0.03</td>
<td></td>
</tr>
<tr>
<td>Extracellular space</td>
<td>(% of before hypoxia)</td>
<td>53.4±3.6</td>
<td>50.7±5.8</td>
</tr>
<tr>
<td>Time parameters (sec)</td>
<td>TTC</td>
<td>73.5±12.1*</td>
<td>91.5±12.3</td>
</tr>
<tr>
<td></td>
<td>TMC</td>
<td>105±15.7</td>
<td>124±11.3</td>
</tr>
</tbody>
</table>

Data are mean±SEM. TTC, time of onset of rapid impedance increase after onset of cardiac arrest defined by intersection of the line of basal impedance and the tangent to the curve at the time of maximal increase in impedance; TMC, time of maximal impedance increase after onset of cardiac arrest.

* †p<0.05 different from contralateral by Student’s t test.

† †p<0.01 different from corresponding normothermic side by Student’s t test.
water and ions are transported across the cellular membrane. Permanently altered Na\(^+\)-K\(^+\) ratio was always accompanied by extracellular space changes which cannot discriminate permanent damage. Thus, depolarization is a prerequisite but is not the only factor that leads to permanent damage. Hypothermia effectively prevents damage. An elevated Na\(^+\):K\(^+\) ratio was always associated with BBB disruption, but BBB breakdown was also observed in some rats with normal Na\(^+\):K\(^+\) ratios, though rather infrequently. Because the Na\(^+\):K\(^+\) ratio and the BBB are still normal during hypoxia, cell depolarization itself is due to ion shifts between the intracellular and extracellular space rather than to an exchange of cations with the circulation. Cerebral cation shifts have also been observed by others in ischemic,1,13,14,22 hypoxic,16 and neurotoxic17,21 brain damage and have been used to evaluate interventions to prevent brain damage.15 This indicates the usefulness of tissue cation concentrations to assess the extent and location of tissue damage.

The size of the extracellular space of relatively large brain areas (as estimated by whole-tissue impedance) is similar to that obtained by methods such as freeze-substitution and tracer distribution.10,11,21,23 Whether these methods give similar values for the brain tissue extracellular space under pathologic conditions has not yet been established. Changes in ion and water distribution as observed with ion-selective microelectrodes or monitoring of the extracellular space during hypoxia and ischemia are often reversible.1,6 Restoration of the extracellular space, and thus of cell volume, means that water and ions are transported across the cellular membrane.1 Permanent shrinkage of the extracellular space (related to Na\(^+\):K\(^+\) ratio elevations) reflects the loss of cell membrane function. Since this can be observed only during recovery, the process leading to irreversible changes must take place during or shortly after hypoxia. However, the nature of this damaging process remains unclear in our experiment. Several hypotheses24 such as Ca\(^2+\) accumulation, lactoacidosis, free radical formation, toxic neurotransmission, or leukotriene formation have been suggested.

Using impedance recording, we can add two more phases, which reflect intact (Phase IV) or irreversibly reduced (Phase V) cell membrane function during recovery. During and after 1 hour of complete ischemia in cats, failure to normalize cortical impedance preceded the absence of neuronal recovery.9 This was attributed to a reduced CBF, the so-called no-reflow phenomenon.25 Absence of CBF is unlikely in the Levine preparation, first because in both hemispheres there is an overall increase of CBF during hypoxia with unilateral carotid artery occlusion,26 and second because the elevation of whole-tissue Na\(^+\):K\(^+\) ratio by ion transport across the BBB requires an intact circulation. Therefore, we may exclude the no-reflow phenomenon as the single cause for continued shrinkage of the extracellular space. However, we cannot exclude the possibility that CBF was insufficient to prevent damage (possibly as the result of cerebral edema and/or a steal effect) but sufficient to give the observed ion shifts across the BBB. We also observed asymmetric movement patterns in normothermic rats with ipsilateral damage, whereas hypothermic rats showed normal movement patterns, emphasizing that persistent extracellular space shrinkage, and thus Na\(^+\):K\(^+\) ratio elevation, reflects neuronal dysfunction.27,28

Because of the lack of correlations, we cannot attribute infarction to factors associated with the severity of the hypoxic challenge, such as Pa\(_{O_2}\), Paco\(_2\), arterial pH, or O\(_2\) saturation. Neither do the maximum reduction of the extracellular space during hypoxia nor TTH increase indicate the duration of depolarization.3,29 Individual differences in branching and in the collaterals of the carotid arteries, resulting in local CBF variations during hypoxia and/or recovery, might be one explanation.

The relation between ischemic brain damage and BBB disruption is still controversial. In general, there are indications that in permanent focal ischemia the BBB opens after the appearance of ischemic edema,15,30 whereas in temporary focal ischemia damage to the BBB accelerates the formation of ischemic edema.31 Our experiments support the latter observation. However, Na\(^+\):K\(^+\) ratios were also elevated in the Levine preparation16 without BBB damage. Collagenase-induced BBB opening32 caused a Na\(^+\):K\(^+\) ratio of 0.84 at 24 hours in the gray matter of rat cortex without apparent cell damage. Thus, an impaired BBB may contribute to, but is certainly not the only cause of, irreversible damage.

Hypothermia protects the brain from anoxic damage19,33 and is therefore applied in both heart surgery24 and neurosurgery.35 This protection is based on reduced metabolism36 and oxygen consumption37 of the brain.37 As in our study, hypothermia applied in experimental hypoxic brain damage12,38,39 proved to be extremely protective. The delayed or absent depolarizations during hypothermic cardiac arrest may indicate that lowered cerebral energy consum-
tion prolongs Phase I during cardiac arrest. Hypothermic hypoxia also results in a slower and reduced depolarization (Phase II). From the bilateral differences in TTC during normothermic cardiac arrest, we conclude that unilateral carotid artery ligation in rats slightly diminished ipsilateral brain energy reserves. During hypothermic cardiac arrest, however, TTCs were equal bilaterally, possibly due to hypothermic reduction of metabolism.

In conclusion, impedance measurements to monitor the extracellular space allow prediction of the irreversibility of brain damage soon after experimental hypoxia-ischemia. With such an approach, potentially therapeutic measures such as hypothermia can be evaluated quickly.

Acknowledgments
The manuscript was typed by Mrs. W. Van der Meer. Mr. W. Stadman provided the figures.

References

Key Words • anoxia • hypothermia • rats
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Stroke. 1989;20:1377-1382
doi: 10.1161/01.STR.20.10.1377

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