Induced seizures as therapy of experimental strokes in dogs

RONALD R. REED, B.S., CONRAD CIESEL, B.S., AND
GUY OWENS, M.D., F.A.C.S.
Department of Surgery, University of Connecticut Medical School, Hartford, and Newington Veterans Administration Hospital, Newington, Connecticut

✓ Intracerebral pO₂, as measured in normal dog brains by a modified mass spectrometer, was found to increase following seizure activity and remain elevated at least 2 hours. These results were found with both drug- and electrically-induced seizures. The pO₂ increased to a greater degree in brain tissue rendered ischemic by middle cerebral artery occlusion. A transient reflex hypertension was observed with seizure activity, but hypertension alone failed to produce significant pO₂ changes. Since oxidative metabolism has been shown by other investigators to proceed at an elevated rate during seizure activity, the increased pO₂ must reflect improved collateral circulation following seizure activity.

Key Words . stroke . seizure therapy . carotid occlusion . dogs

How do we treat the stroke patient? Are all stroke patients to be managed identically? How soon after the cerebrovascular accident is therapy still effective? What is the prognosis? There are no answers to these questions. None of the therapies proposed for stroke to date has been able to demonstrate any results significantly better than the 35% recovery rate of the untreated stroke patient. These proposals have included: 1) anticoagulants,¹,⁵,⁶-¹⁰,¹² 2) fibrinolytic enzymes,⁷,¹¹,¹² 3) vascular surgery,² and 4) vasodilators.³,⁴

Moreover, all these assessments have been based on clinical data, and adequately controlled experimental studies have not been done. This is because until very recently there was no good parameter to measure therapeutic effectiveness quantitatively. Since cerebral anoxia precedes the neurological manifestations of a stroke, it would seem that the best way to quantitate therapeutic effects would be to monitor changes in intracerebral gas levels. Owens, et al.,¹² demonstrated that intracerebral pO₂ and pCO₂ could be measured instantaneously, simultaneously, and continuously with a modified mass spectrometer. This permits, for the first time, the focal study of tissue gases.

Seizures are known to increase both cerebral metabolism and cerebral blood flow, yet it is not known whether the increase in brain perfusion is sufficient to meet or possibly exceed the brain's increased metabolic demands during seizure activity. Our present study was undertaken to assess quantitatively the ability of seizure activity to elevate pO₂ in the ischemic brain tissue produced by experimental "strokes."

Methods

Mongrel dogs, anesthetized with pentathol and immobilized with succinyl choline, were intubated with cuffed endotracheal tubes,

178

J. Neurosurg. / Volume 34 / February, 1971
Seizures as therapy for experimental stroke

connected to a Bird respirator, and maintained on a 95% oxygen/5% carbon dioxide mixture throughout the experiment. The femoral artery and vein were cannulated to monitor aortic blood pressure and administer drugs. The membrane cannula, connected to a medical mass spectrometer (Scientific Research Instruments Corp. Mod. MMS-8), was inserted into the right temporal lobe. Gas pressures were measured by the mass spectrometer in mm Hg, after calibration in a saline bath at 37°C, which was saturated with a mixture of 95% oxygen/5% carbon dioxide gas. Continuous monitoring of intracerebral pO₂ and pCO₂, as well as systemic arterial pressures, electroencephalogram (EEG), and electrocardiogram (EKG) was carried out. Pentylenetetrazol, in quantities sufficient to produce EEG-recorded seizures, was administered intravenously to four dogs. To determine if the results observed from the pentylenetetrazol were due to seizure activity or to some inherent property of the drug itself, in a second series of animals the seizures were electrically induced by a Grass stimulator and a stimulating electrode.

Another 12 animals were prepared identically but, in addition, the right orbital contents were surgically removed and the middle cerebral artery occluded, producing an experimental “stroke.” In six dogs, pentylenetetrazol was then administered intravenously to produce corticoelectrical seizures, while the remaining six received intravenous metaraminol.

Results

Pentylenetetrazol-Induced Convulsions

Intracerebral gas levels following convulsions induced by pentylenetetrazol showed striking changes. In all four animals with unaltered cerebral circulation, intracerebral pO₂ increased while pCO₂ decreased. The average pO₂ increase was in the order of 11 mm Hg or 27% expressed in percent of change (see Table 1). The pO₂ increased linearly following the appearance of EEG-recorded seizure activity. The duration of the seizures was 3 to 5 min, yet 20 min was required post-ictally for the maximum pO₂ responses to be reached. This delay was probably due to vasomotor responses since the equilibration time for the silastic membrane was minimal. The maximum pO₂ responses persisted in all animals for at least 2 hours.

Electrically-Induced Convulsions

To demonstrate that the observed changes in pO₂ and pCO₂ were due to seizure activity and not to some inherent pharmacological property of the drug itself, seizures were electrically induced in a second series of four animals. As can be seen in Table 1, the effects of drug-induced and electrically-in-

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>pO₂ mm Hg</th>
<th>pCO₂ mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metrazol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrical Stimulation</th>
<th>pO₂ mm Hg</th>
<th>pCO₂ mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>

TABLE 1

Intracerebral pO₂ and pCO₂ responses in normal dogs during chemically and electrically-induced seizures
Fig. 1. Dog 1C. Baseline record before experimental intervention. Note pCO₂ of 48 mm Hg and pO₂ of 56 mm Hg. Bottom line indicates total evolved time during experiment.

Fig. 2. Dog 1C. Record 5 min after occlusion of right middle cerebral artery. Note pCO₂ of 55 mm Hg and pO₂ of 16 mm Hg as monitored from the right temporal lobe.

Fig. 3. Dog 1C. Record during first 2 min of chemically-induced seizures. Note pCO₂ of 80 mm Hg and pO₂ of 20 mm Hg, and blood pressure response.
Seizures as therapy for experimental stroke

Fig. 4. Dog 1C. Record 12 min after seizure response. A linear rise in pO₂ to approximately 50 mm Hg has occurred simultaneously with a fall in pCO₂ to 42 mm Hg. Note focal length change.

Fig. 5. Dog 1C. Record 32 min after seizure production and 52 min after arterial occlusion. The record has now plateaued with a pO₂ of 52 mm Hg and a pCO₂ of 42 mm Hg. This response persisted until termination of experiment 2 hours later.

duced seizure activity were identical. Moreover, both sub-ictal dosages of pentylenetetrazol and sub-ictal electrical voltage failed to produce any changes in cerebral tissue gases.

Carotid Occlusion and Pentylenetetrazol-Induced Convulsions

Six animals served as subjects for a series of further studies. Figures 1 through 5 are recorded from Dog 1C and detail the responses to artificially induced vascular insufficiency and the subsequent induction of seizure activity by pentylenetetrazol. Similar findings were recorded in the other five dogs. A baseline pO₂ of 56 mm Hg was recorded in the right temporal lobe (Fig. 1). The ipsilateral middle cerebral artery was then completely occluded at its origin from the internal carotid. The pO₂ decreased to 16 mm Hg within 3 min after occlusion. After this time there was no further change in pO₂, and the stable post-occlusion reading of 16 mm Hg was maintained (Fig. 2). Seizure activity was then induced (Fig. 3), and the pO₂ increased post-ictally from 16 mm Hg to 52 mm Hg (Figs. 4 and 5). This represented an increase of 36 mm Hg or a 225% change. Twenty minutes were required post-ictally for the maximum pO₂ value of 52 mm Hg to be reached. This reading persisted and re-
TABLE 2
Intracerebral pO₂ and pCO₂ responses to chemically-induced seizures in animals with middle cerebral artery occlusions*

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>pO₂</th>
<th>pCO₂</th>
<th>O₂ Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post Seiz.</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>16</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>26</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

* Recordings taken from the area of cerebrovascular insufficiency.

Remained stable for 2 hours at which time the experiment was concluded.

Three of the six animals “treated” with pentylenetetrazol had post-stroke increases in pO₂ greater than 100%, while the remaining three had increases of approximately 45%. Three animals showed a return to pre-stroke values (Table 2).

In two of the animals, 1 hour was allowed to elapse between the time a stable post-occlusion pO₂ was obtained and the induction of seizure activity. During this time, there was no change in pO₂. Therefore, all of the vasodilatation of the collateral supply that occurred due to the increase in pCO₂ appeared to occur within the first 3 min after occlusion. No further dilatation of the collateral vessels occurred unless seizure activity was induced.

Following the intravenous administration of pentylenetetrazol, a slight fall in blood pressure followed by a substantial rise was observed. The blood pressure rose with the beginning of seizure activity, remained elevated during its course, and declined post-ictally. Blood pressure rose an average of 40 mm Hg, and 15 min were required post-ictally for it to return to pre-seizure levels.

To assess the relative importance of opening up the collateral blood supply to the cortex area affected by seizure activity, versus the reflex hypertension that occurs with seizures, further studies were done on six animals. Following the occlusion of the middle cerebral artery, metaraminol was infused in sufficient quantities to raise systolic arterial blood pressures to 250 mm Hg. The maximum increase in pO₂ during these periods of hypertension was 6 mm Hg or a 12% change (Table 3).

In brains removed from two animals with middle cerebral artery occlusions and “treated” with pentylenetetrazol, the cannula tracts were identified on coronal sections. No gross hematomas were found.

TABLE 3
Intracerebral pO₂ and pCO₂ responses to systemic hypertension in “stroke” animals with middle cerebral artery occlusions treated with vasopressors

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>pO₂</th>
<th>pCO₂</th>
<th>O₂ Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post Vaso-press</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>57</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

J. Neurosurg. / Volume 34 / February, 1971
Seizures as therapy for experimental stroke

Discussion

Intracerebral \( pO_2 \) is definitively increased by seizure activity in animals with unaltered cerebral circulation, and more important, in the area of cerebrovascular insufficiency in animals with middle cerebral artery occlusions. The \( pO_2 \) increase results from an increase in brain perfusion that far exceeds the increased metabolic demands of seizure activity. The only alternative way to account for the increased \( pO_2 \) would be to argue that oxygen is not being utilized by the cerebral tissues. But this is contradicted by the observation of Plum, et al.,\(^{18}\) that \( pCO_2 \) in the cerebral venous blood is increased during seizure activity, a finding that indicated that oxidative metabolism proceeds at an elevated rate during seizures.

The time course of the elevated \( pO_2 \) was important in that it was not a transient phenomenon but lasted at least 2 hours after seizure activity. The \( pO_2 \) increase, which may be related to improved collateral circulation following the seizure activity, was readily observed, but the reason for this is not entirely clear. With our present state of knowledge, we can only eliminate certain factors from consideration. The reflex hypertension that accompanies seizure activity was shown to be definitely not the cause since hypertension alone produced minimal \( pO_2 \) changes. The increase in \( pCO_2 \) or decrease in pH that results from the increased metabolism of seizures is also probably not the cause, since \( pCO_2 \) and pH have probably exerted their maximal dilatory effect in the area of cerebrovascular insufficiency shortly after middle cerebral artery occlusion. Electrical stimulation can probably also be discounted since electrical stimulation studies of isolated venous preparations have never demonstrated any increase in lumen diameter.\(^{14}\) But the mechanism of apparent improvement in circulation still remains unexplained.

Conclusions

With the use of the medical mass spectrometer, we have been able for the first time to monitor the effects of experimental stroke therapy both instantaneously and continuously. It is our working hypothesis that the best therapy for stroke probably lies in making optimum use of potential collateral circu-

References


Received for publication April 20, 1970.

Supported in part by Veterans Administration Institutional Research Grant CP321.

Address reprint requests to: Guy Owens, M.D., Department of Surgery, The University of Connecticut Health Center, McCook Hospital, 2 Holcomb Street, Hartford, Connecticut 06112.