Experimental Cerebral Circulatory Arrest: Effect on Electro cortical Potentials

DAVID YASHON, M.D., F.R.C.S.(C),* R. J. WHITE, PH.D., M.D., N. TASLITZ, PH.D.,
L. R. WOLIN, PH.D., AND L. C. MASSOPUST, JR., PH.D.
Division of Neurosurgery, Metropolitan General Hospital, Case Western Reserve University School of
Medicine, and Laboratory of Neurophysiology, Cleveland Psychiatric Institute, Cleveland, Ohio

SPONTANEOUS cerebral electrical potentials have been used clinically for prognosis following destructive cerebral lesions, and a persistently isoelectric electroencephalographic recording (EEG) has been considered one criterion of cerebral nonviability both for cessation of artificial maintenance of vital functions and for subsequent somatic organ transplantation. Prominent among causes of cerebral nonviability are those related to circulatory arrest, which include shock, arterial occlusive disease, cardiopulmonary insufficiency, and cardiac arrest. Diminution of cerebral blood flow as well as greatly increased intracranial pressure causes stagnant (ischemic) hypoxia, which in turn is reflected in profound EEG changes.

These types of ischemic or anoxic cerebral insults may be reproduced experimentally and their effects on electrocorticographic (EEG) activity recorded. In such experiments, intrathoracic vascular occlusion causing immediate circulatory arrest has been produced to determine patterns of electrocortical silence, recovery, and the sensitivity of cortical electrical function related to survival. However, the preparation is not comparable to stepwise obliteration of the four major cervical vessels since simultaneous occlusion is difficult and a certain amount of cerebral damage can occur during experimental ligation, which make exact timing of anemia difficult. Also, a potentially large amount of collateral circulation exists. In man, for example, cases have been reported in which only minimal neurological dysfunction was caused following occlusion of all major cervical vessels, although acute lengthy occlusions may not be well tolerated. In animals, ligation of the major cervical vessels frequently produces little deficit. Both patients and experimental preparations have survived with excellent cerebral electrical activity because of extensive collateral circulation.

Therefore, an experimental preparation used previously by Brockman and Jude and Marshall, et al., was employed because it results in complete, immediate, but temporary cerebral circulatory arrest.

Material and Method

We used 30 large mongrel dogs for this investigation, of which 20 were considered successful experiments. Ten dogs were not counted in the results, six because of ventricular fibrillation following lengthy occlusion periods with inability of rapid resuscitation, and four because they were used to evaluate the cerebral blood flow during occlusion.

All animals were anesthetized with pentobarbital or thiamylal, 20 to 30 mg per kilogram body weight. Gallamine supplementation was necessary occasionally. Following barbituralization and during the entire surgical procedure, the animals were intubated and ventilated with 40% oxygen and 60% room air by positive pressure. Thoracotomy was performed through the fourth right intercostal space, and umbilical tapes were loosely placed around the roots of the ascending aorta, inferior vena cava, and superior vena cava cephalad to the aygys vein according to the techniques quoted.

The aygys vein was not ligated. Umbilical tapes were threaded through a length of rubber tubing for the purpose of temporary occlusion of these vessels. Cessation of left ventricular cardiac output except for coronary flow was accomplished by near-simultaneous occlusion of both vena cavae and the ascending aorta. Venous blood returned through the aygys vein and coronary sinus.
The vena cavae were occluded first, followed immediately by the ascending aorta. After variable periods of cessation of extra-cardiopulmonary circulation, the vena cavae were released approximately 10 sec prior to the aorta, and the period of occlusion was timed from aortic occlusion to aortic release. Following vascular release, the lungs were reexpanded under direct vision and the chest closed airtight in layers.

Following chest closure, the animals were ventilated as long as necessary and until adequate spontaneous respirations returned.

Deep body temperature was between 36.5° and 37.5°C in all animals. Femoral artery pressure and pulse were obtained via Statham strain gauge and transmitted to a Grass polygraph. Respiratory rate and electrocardiograph (EKG) were registered simultaneously on a Grass polygraph. Periodic measurements of hematocrit, pH, PCO₂, PO₂, and oxygen saturations were performed for evaluation of homeostasis during the various experiments. The ECoG was monitored on a Grass Model-6 8-channel electroencephalograph utilizing silver ball recording electrodes 3.5 mm in diameter which were implanted snugly at the time of the acute surgical procedure into the epidural space using small twist drill holes and fixed with acrylic cement. Standard recordings were taken from frontal and parieto-occipital areas using bipolar techniques. The four main channels consisted of paired left and right electrodes. All experiments were conducted with identical standardization and calibration. Control records of animals anesthetized with thiamylal were slower than those anesthetized with pentobarbital but this was generally not reflected in post-occlusion records.

The ECoG rather than the EEG was employed because, particularly in the experimental preparation, much muscle and other artifact as well as damping effect were eliminated. The ECoG was discontinuously followed up to several days during the post-occlusion periods by detaching and then reconnecting the wires of the permanently placed silver ball electrodes.

Results

With vascular occlusion, femoral arterial pressure dropped to baseline levels indicating no blood pressure within 2 to 5 sec. The ECoG from bifrontal and biparietal dural electrodes became and remained isoelectric within 10 to 20 sec and for the duration of vascular occlusion (Fig. 1); this rapid change served as a control for adequacy of occlusion and non-interference by the beating heart, respirations, or other artifact. Occasionally, isoelectric recordings remained for considerable periods even after reestablishment of cerebral blood flow and were always present following death. The isoelectric recording at death during ventilation also served as a control for the demonstration of lack of electrical artifact by ventilators. Coincident with occlusion, the EKG showed changes in QRS complexes and, often, transient changes in rhythm. Following restoration of circulation, these dysrhythmias returned to normal sinus rhythm.

Ten animals succumbed between 6 and 48 hrs following 8 to 20 min of occlusion (Table 1). Ten animals survived 2 to 12

---

**Fig. 1.** Isoelectric recording obtained during occlusion. (Horizontal bar 1.0 sec, vertical bar 50 μV; F = bifrontal recording, P = biparietal recording, FPR = right frontoparietal recording, FPL = left frontoparietal recording.)
Yashon, White, Taslitz, Wolin and Massopust

TABLE 1
Summary of electrocortigraphical activity recorded from dogs that ultimately died following cerebrovascular occlusion

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Occlusion Duration (min)</th>
<th>Isoelectric Record (sec)</th>
<th>Minor Activity (min)</th>
<th>Major Activity (hrs)</th>
<th>Normal ECoG (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>12</td>
<td>76</td>
<td>3 1/2</td>
<td>No return in 24 hours</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>11</td>
<td>135</td>
<td>2 11/12</td>
<td>No return in 9 hours</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>18</td>
<td>100</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>14</td>
<td>60</td>
<td>4</td>
<td>6 1/2</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>15</td>
<td>106</td>
<td>10 1/2</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>10</td>
<td>240</td>
<td>5 1/2</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>10</td>
<td>240</td>
<td>6 1/2</td>
<td>22</td>
</tr>
<tr>
<td>8*</td>
<td>15</td>
<td>19</td>
<td>240</td>
<td>never appeared</td>
<td>never normal</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>15</td>
<td>none</td>
<td>never appeared</td>
<td>never normal</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>12</td>
<td>300</td>
<td>12 1/2</td>
<td>never normal</td>
</tr>
</tbody>
</table>

* Thiamylal

min of occlusion (Table 2). Analysis of post-occlusion ECoG waveforms showed predominant frequencies of 6 to 15 cycles/sec and low amplitudes of 10 to 50 µV (see progression of minor activity in Figs. 2–4), returning between 5 to 30 min in survivors and not until 60 to 300 min in non-survivors. The earliest return of ECoG activity

TABLE 2
Summary of electrocortigraphical activity recorded from dogs that ultimately survived following cerebrovascular occlusion

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Occlusion Duration (min)</th>
<th>Outcome</th>
<th>Interval Before Appearance of</th>
<th>Isoelectric Record (sec)</th>
<th>Minor Activity (min)</th>
<th>Major Activity (min)</th>
<th>Normal ECoG (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>2</td>
<td>alert,</td>
<td>interval before appearance</td>
<td>20</td>
<td>4</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>12*</td>
<td>3 1/2</td>
<td>alert,</td>
<td>minor activity</td>
<td>19</td>
<td>2</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>13*</td>
<td>4</td>
<td>alert,</td>
<td>major activity</td>
<td>16</td>
<td>6</td>
<td>29</td>
<td>105</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>alert,</td>
<td>normal ECoG</td>
<td>13</td>
<td>5</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>15*</td>
<td>5</td>
<td>alert,</td>
<td>11</td>
<td>16</td>
<td>35</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>alert,</td>
<td>10</td>
<td>16</td>
<td>30</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>8</td>
<td>alert,</td>
<td>18</td>
<td>20</td>
<td>139</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td>alert,</td>
<td>14</td>
<td>30</td>
<td>200</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>9</td>
<td>alert,</td>
<td>19</td>
<td>13</td>
<td>23</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>alert,</td>
<td>18</td>
<td>10</td>
<td>15</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

* Thiamylal
ECoG in Cerebral Circulatory Arrest

(minor activity*) was signalled by low-frequency low-voltage activity (Fig. 2) with isoelectric periods that occasionally took the form of spindles (Fig. 3) with rapid frequencies. In those cases where spindles were present, they gradually merged to form the minor activity indicated in Fig. 4. Two predominant and simultaneous frequencies of 6 to 12 and 12 to 24 cycles/sec with higher amplitudes of 5 to 100 μV and 25 to 50 μV (see major activity in Fig. 5) occurred within 200 min in survivors but not until 210 min or later in non-survivors. In one non-survivor, major activity returned in 175 min but minor activity returned in 135 min. In surviving animals, normal activity (Fig. 6) returned as early as 18 min (Table 2) and was associated with short occlusion periods. Even in some non-survivors, normal activity (Fig. 6) returned in 6 hrs (Table 1) or later. Normal activity was seen in survivors within 6 hrs. This type of activity was nearly identical to pre-occlusion control recordings. Survival could thus be closely correlated with the time and quality of return of ECoG activity, whereas overlap in survival and morbidity existed with timing of vascular occlusions. The two surviving animals that could not stand seemed to have suffered anemic thoracic spinal cord injury. In the non-survivors, death was preceded by a period of decerebration if the acute phase of temporary plasticity was passed. In all animals excepting Dog 9, electrical activity returned at some time; Dog 9 survived for 6 hrs with an isoelectric recording following a 15-min occlusion.

In two instances, 8 cc of 1% sodium fluorescein were injected into the left ventricle

* The designations minor and major activity are arbitrarily used for convenience of description.

Fig. 2. Minor activity. This type of activity interspersed with near-isoelectric recording signalled the earliest return of electrical activity. Standardization as in Fig. 1.

Fig. 3. Minor spindle activity. Early return of EEG activity took this form in six instances. Standardization as in Fig. 1.
Fig. 4. Minor activity with greater amplitude and frequency. This type of activity was a precursor of a major return of ECoG activity. Standardization as in Fig. 1.

Fig. 5. Major ECoG activity returned within 200 min in those destined to survive. Standardization as in Fig. 1.

Fig. 6. Normal activity comparable to pre-occlusion control activity appeared within 18 min to 6 hrs in those destined to survive. Standardization as in Fig. 1.

with the aorta and vena cavae temporarily occluded; with a Wood's lamp no fluorescein could be seen in the exposed cortex. After 2 min of occlusion the clamps were released and fluorescein was visualized almost immediately in cortical vessels by operative microscope. In two further animals, frontal lobectomy during intrathoracic vascular occlusion showed back-bleeding but no active blood flow.

Discussion

The EEG has been used to determine brain death in humans, and the primary criterion is in isoelectric record for a timed recording of 1 hr and repeated later, usually at 12 to 24 hrs. In our experiment the extreme sensitivity of surface electrical recording, both as to vascular perfusion and prognosis, has been demonstrated. Scalp electrode recording, when used clinically,
ECOg in Cerebral Circulatory Arrest

has a greater tendency to show artifacts than the dural placements we used. In all but one instance in this series, some electrical activity recurred, even in those severely damaged dogs in which death supervened soon thereafter. Prognostic predictions based on the qualitative characteristics of a single record were not justified. However, when these were combined with the time of restitution of electrical activity the ECOg evidence did become significant.

Levin and Kinnell have reported a human case of successful cardiac resuscitation despite prolonged EEG silence. In that case, cardiac resuscitation had taken approximately 45 min, and the EEG remained isoelectric although the actual time of isoelectric recording was not provided. One day following arrest, however, the EEG showed high-voltage slow activity and continued to improve thereafter. No other clinical case of recovery following prolonged electrical silence has been recorded.

Therefore, several authors advocate utilization of the EEG as a major criterion for cerebral non-viability. However, it is well known that hypothermia of about 25°C or less will produce an isoelectric EEG which will return to normal following rewarming. Bellville and Howland state that recovery without evidence of residual abnormalities is possible from almost any type or degree of electroencephalographic disorder; nevertheless, if the electroencephalographic activity continued flat for over 4 hrs, they presumed that cortical damage was not completely reversible. Gibbs, et al., demonstrated that cortical frequencies may be modified, but not made isoelectric, by changes in CO₂, blood glucose, and O₂. Lennox, et al., showed relationships of cerebral activity to cerebral blood flow and various blood constituents.

In six patients who had experienced cerebral hypoxia, Gronqvist, et al., found that the initial tracings of those who recovered showed considerable EEG activity marked by moderately low frequency and moderately high amplitude, with superimposed higher frequency components. In those cases in which the patient died, the initial EEG tracing was nearly a flat line in two cases and in two others, there were superimposed upon the flat line very low amplitudes but sharp high-frequency waves, giving the tracing the appearance of the cross section of a file (file pattern). This pattern did not occur in our experiments.

Brechner, et al., found that in humans the time lapse from restoration of circulation until onset of continuous EEG activity could be used as an indication of brain survival following an unexpected ischemic episode. They found that, in dogs, the duration of a single circulatory arrest could be correlated with the time elapsed before return of continuous EEG activity meant a poor prognosis. Our experiments corroborate and extend these conclusions although exact correlations with timing of arrest of circulation could not be made.

Spoerel showed the EEG aberrations occurring with low arterial oxygen in dogs. Hale and Moraca found the EEG to be useful in patients undergoing cardiotomy as an indicator of cerebral oxygenation. Bellville, et al., demonstrated that the EEG could be used to essay adequacy of cerebral circulation during anesthesia and surgery. Lee, et al., observed that in the monkey a single internal carotid artery can adequately perfuse the brain when the arterial pressure is maintained between 60 and 170 mm of mercury. When all four arteries were occluded, a mean arterial pressure of 160 mm of mercury or more was necessary to retain adequate EEG activity.

Simpson and Derbyshire reported that 20 sec of severe ischemia was sufficient to obliterate electrical activity of the motor cortex. Abrupt and functionally complete anemia of the brain of cats was produced by Sugar and Gerard with temporary occlusion of one carotid after ligation of the other three main cervical vascular channels. Changes in potentials of known anatomic structures were observed during and following anemia. The duration of occlusion necessary to abolish electrical activity, or so-called survival time, varied fourfold from one brain region to another, and the most highly evolved brain structures were the most susceptible. Older brain structures such as the medulla had the longest survival time. The interval between restoration of circulation and return of electrical potentials increased with the duration of anemia.

Ten Cate and Horsten found that exclu-
sion of the common carotid arteries alone led to a transient decrease in amplitude of the EEG in cats and dogs while exclusion of the vertebral arteries had little effect. Ligation of all of these vessels led to a pronounced decrease of amplitude in the EEG and on occasion to total disappearance of electrical activity. Naquet and Fernandes-Guardiola\textsuperscript{19} found that, with ischemic or asphyxic hypoxia, evoked potential activity showed no change in the optic tract and lateral geniculate body until the late stages of hypoxia; when the negative wave disappeared, the amplitude of the positive wave progressively diminished. This was to be differentiated from those evoked potentials recorded (from specific cortex) which underwent marked changes during all stages of hypoxia and were constant no matter what type of hypoxic preparation was employed.

Bokonjić and Buchta\textsuperscript{4} found that, following episodes of stagnant anoxia in six patients who did not recover clinically, the period of post-anoxic unconsciousness was accompanied by complete or almost complete absence of electrical activity. In two patients who survived, the electrical activity that first reappeared was dominated by low frequencies; later there was an increasing mixture of normal frequencies but the abnormal EEG persisted even after clinical conditions had become stabilized. Thus, they attributed a certain amount of prognostic value to the EEG.

Van Harreveld\textsuperscript{31} produced brain asphyxia by introducing saline into the cisterna magna at a pressure higher than blood pressure, thus interrupting cerebral circulation. Shorter and lengthier periods of asphyxia were accompanied by characteristic EEG patterns. Thies-Puppel and Wiener\textsuperscript{30} studied 30 patients undergoing cardiac surgery during hypothermia and found that the onset of ischemia and disappearance of all electrical activity of the brain varied from 12 to 60 sec after circulatory arrest. With restoration of blood flow, the return of EEG activity varied from 30 sec to 4 min when the ischemic period had been less than 7 min, and was delayed up to 25 min when the ischemia had lasted 8 min or more. Wise, \textit{et al.},\textsuperscript{32} in reporting EEG patterns in 13 patients after carotid artery ligation, found that the EEG was of limited value in predicting cerebral complications of carotid artery ligation.

Several authors have studied the effects of cerebral anemia on the neurological status. Among them Pollock and Davis\textsuperscript{21-23} produced anemic decerebration by ligating first the basilar artery and then the carotid arteries. A few of the animals in this series that succumbed were decerebrate prior to death, but this was unpredictable. Kabat and Dennis\textsuperscript{14} caused decerebration by temporary cerebral circulatory deprivation (ligation of both vertebral arteries); after a suitable interval a large blood pressure cuff was wrapped around the neck, the trachea intubated, and the cuff inflated to a pressure of 350 mm of mercury and maintained for 15 to 20 min. One dog lived for 9 days after 19 min of complete anemia, although he was comatose throughout. Boyd and Connolly\textsuperscript{8} created cerebral ischemia modified after the technique of Kabat and Dennis\textsuperscript{14} and found that the dog will tolerate up to 8 min of total cerebral ischemia without evidence of permanent brain damage. Total cerebral ischemia of 9 min or more produced severe permanent brain damage or immediate death. Two of our animals survived 9 min of arrest and one after 12 min. Marshall, \textit{et al.},\textsuperscript{21} created temporary circulatory occlusion in a manner comparable to ours. Normothermic dogs tolerated occlusion up to 10 min. During hypothermia the tolerance was prolonged to 22 min. Permanent microscopic brain damage was first seen at 8 min of occlusion time in normothermic animals and in 14 min in hypothermic animals.

Weinberger, \textit{et al.},\textsuperscript{32} abruptly stopped the circulation of the entire body of the cat by clamping the pulmonary artery. Arrest of the circulation for 3 min and 10 sec or less was tolerated without neurological disturbances. Permanent alterations in neurological function occurred in animals subjected to 3 min and 25 sec or more of circulatory arrest. When the circulation was interrupted for 8 min and 45 sec or longer, life could not be restored for more than a few hours.

Brockman and Jude,\textsuperscript{7} utilizing the same experimental preparations as that in our study, accomplished total arrest of the cerebral circulation in 55 dogs at normothermia. All animals subjected to periods of cerebral...
ischemia up to 9 min recovered without any apparent ill effects (35 dogs); transient cerebral damage occurred in five dogs subject to between 9 and 12 min of ischemia; death occurred within 24 hours in eight dogs after 13 min or more of vascular occlusion.

Although in our experiments the designation of major and minor activity was stated as a sharp delineation, in fact, there was a gradual progression from minor activity to major activity over a period of several minutes to several hours. The longer progressions were particularly evident in those recordings in which activity was slow in returning (non-survivors). In those cases in which electrical recovery was rapid (survivors), an exact delineation could be determined without difficulty at minute-to-minute intervals. Hence the separate designation of major and minor activity are somewhat artificial although useful for determining prognosis in this experiment.

From these results it appears that in dogs electrocortical activity recovery patterns are reliable for determining the prognosis following cerebral circulatory deprivation. Under these experimental conditions electrocortical activity is a sensitive indicator of cerebral anemia and is valuable in estimating potential recovery during the early phases following cerebral circulatory arrest.

**Summary**

Patterns of recovery of electrical activity in the cerebral cortex have been delineated in 20 dogs following arrest of the extra-cardiopulmonary circulation by intrathoracic occlusion of the ascending aorta and vena cava. Although the electrical waveform restored was similar in vascular occlusions ranging from 2 to 20 minutes, consideration of its quality combined with the rapidity of its reappearance provided reliable prognostic clues. In all but one animal post-occlusion potentials were recorded after they had been absent. Although electrical activity returned in lethal lesions, it did so later than in non-lethal lesions. The relevant clinical and experimental literature has been reviewed.

**References**

25. Yashon, White, Taslitz, Wolin and Massopust


