RESTORATION OF CEREBRAL FUNCTION AFTER PROLONGED CARDIAC ARREST*

JAMES C. FOX, JR., M.D.

Department of Neurology-Neurosurgery, Hartford Hospital, Hartford, Connecticut

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Sudden stoppage of the heart during an operation has always been a terrifying experience for the surgeon and anaesthetist. A busy surgical clinic can anticipate an average of one or two cases of cardiac arrest a year. Adequate preparation and prompt determination to meet such emergencies when they arise may prevent otherwise certain fatalities. In recent years effective methods of treating ventricular fibrillation have been developed.\textsuperscript{2,3,4,5} The procedure most recently recommended by Beck et al.\textsuperscript{4} includes exposure of the heart, injection of procaine, cardiac massage and electrical stimulation.

If such individuals are to be saved in greater numbers in the future, what about the risk of cerebral damage from prolonged anoxia? The nerve cells of the brain are more sensitive to oxygen lack than are any other cells of the body. A generally accepted dictum has been that the human brain will not stand more than five minutes of oxygen deprivation without suffering irreparable damage. The following case, already reported,\textsuperscript{5} is an example of reversible changes due to cerebral hypoxia during artificial maintenance of the circulation and respiration over a period of 27 minutes of ventricular fibrillation.

CASE REPORT

J.R., a 7-year-old boy, was admitted to the Hartford Hospital July 17, 1947 with a deep laceration of the sole of the right foot. There had been only moderate loss of blood. The child showed no sign of shock. Preoperative medication consisted of morphine sulphate gr.1/12, atropine sulphate gr.1/200 and seconal gr.3/4. The operation was performed under anaesthesia produced by open drop ether induced with cyclopropane. Cleansing and irrigation of the wound and repair of the tendons, muscles and nerves required about 75 minutes. At the close of the operation, 5 minutes after terminating the anaesthesia, the pulse suddenly stopped. The child's color became ashen, no heart sounds could be heard and respirations ceased. Approximately 2½ minutes from the time the heart stopped, the surgeon, Dr. R. S. Lampson, made an incision into the left 5th interspace, requiring 10 seconds to open the chest. The heart felt soft and lifeless but fine ripples of fibrillation were seen passing over the left ventricle beneath the pericardium.

Cardiac massage was immediately started and continued by intermittent compression of the heart against the sternum with the middle and index fingers of the left hand at a rate of 60 times per minute. A pulse could be felt at the wrist with each compression of the heart. The anaesthetist maintained artificial respiration

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with the anaesthetic machine and supplied pure oxygen to the lungs. Spontaneous respirations began 15 minutes after the onset of cardiac arrest, while the heart was still being massaged but had shown no sign of contraction. These were amplified by compression of the breathing bag. Two intravenous injections of 1 per cent procaine hydrochloride were given, the first of 3cc. 18 minutes after cardiac arrest, the second of 2cc. 26.5 minutes after cardiac arrest. Thirty seconds after this the heart stiffened beneath the massaging fingers and began to contract spontaneously. After 2 minutes of irregular contractions there developed a rapid, strong, regular pulse.

An electrocardiographic record had been started 30 minutes after cardiac arrest. This indicated ventricular fibrillation with 365 complexes per minute interrupted by a period showing no cardiac activity. Following a series of ten bizarre, aberrant, arrhythmic ventricular contractions, some of which seemed to be preceded by P waves, a gradual return of the normal mechanism took place. Observation of the heart was continued for ½ hour with the thorax open and 100,000 units of penicillin dissolved in 10cc. of procaine were flushed onto the pericardium. The chest wound was then closed and a plaster boot applied to the foot.

The chronological sequence of events during the operative period has been tabulated as follows:

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:50 P.M.</td>
<td>Anaesthesia started</td>
</tr>
<tr>
<td>7:22</td>
<td>Anaesthesia stopped</td>
</tr>
<tr>
<td>7:27</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>7:29½</td>
<td>Chest opened</td>
</tr>
<tr>
<td>7:30</td>
<td>Cardiac massage begun</td>
</tr>
<tr>
<td>7:42</td>
<td>Spontaneous respirations returned</td>
</tr>
<tr>
<td>7:45</td>
<td>3cc. of 1% procaine I.V.</td>
</tr>
<tr>
<td>7:47</td>
<td>Electrocardiogram started</td>
</tr>
<tr>
<td>7:53½</td>
<td>2 cc. of 1% procaine I.V.</td>
</tr>
<tr>
<td>7:54½</td>
<td>Spontaneous heart action resumed</td>
</tr>
<tr>
<td>7:56</td>
<td>Cardiac rhythm normal</td>
</tr>
<tr>
<td>8:07</td>
<td>Penicillin and procaine onto pericardium</td>
</tr>
<tr>
<td>8:35</td>
<td>Chest closed</td>
</tr>
</tbody>
</table>

When the patient left the operating room 2 hours after the heart had stopped, he was comatose, restless, vomiting, coughing and breathing spontaneously. He was placed in an oxygen tent under the care of a special nurse. The child could be aroused from coma for the first time 10 hours after resuscitation. Two hours later his first words were spoken. Neurological survey the following morning revealed all limbs flaccid and moving purposelessly, deep reflexes diminished, extensor left plantar response (right foot in cast), pupils equal with active light reflex. He remained semi-conscious during the balance of the day with alternating fixed stare and roving movements of the eyes. He became increasingly restless, moaned, responded to spoon feeding and lapsed into periods of sleep with repetitive chewing movements of the jaws and lips, and was incontinent.

During the second 24-hour period he became progressively wakeful and talkative. By the evening of July 18 he could give his name; the next morning he told his home address and ordered breakfast. During the course of the day he conversed with imaginary playmates, thought he was chewing bubble gum, and often replied irrelevantly when questioned. He remained very restless, mentally confused and irritable. Neurological survey showed full visual fields to confrontation tests, faulty
ocular fixation with apparent loss of visual acuity, clumsiness of the hands associated with bilateral astereognosis, return of flexor plantar response on the left.

During the third 24-hour period, he continued to talk irrationally at times and was subject to visual hallucinations—mother, dog, cat. While asleep, there occurred one brief generalized convulsion.

Neurological examination was performed in two stages on July 21, 85–90 hours postoperative, when the child was alert and in good rapport. His span of attention was shortened and he tired rapidly. He was oriented in all spheres, gave age, birthday, name of school, grade and could add and subtract single numbers. His speech was clearly enunciated with occasional dropping of syllables but no other evidence of expressive disorder. He was unable to write his name but formed a few letters. This was interpreted as due both to dysgraphia and clumsiness. He refused to read and protested vehemently when urged to do so. The special senses of smell and hearing were intact. Visual acuity was grossly impaired but could not be tested quantitatively. Color vision was intact. The eyes moved conjugately and smoothly without evidence of ocular weakness or nystagmus. However, he closed his right eye to avoid diplopia, especially on lateral gaze. The pupils were in mid position, equal, and reacted actively both directly and consensually to light and on accommodation. The other cranial nerves were normal. Ophthalmoscopic examination was negative. There was no muscular weakness or tremor but a generalized diminution of muscle tone. His hands were clumsy in the attempted performance of skilled acts. This was believed due to astereognosis. He was unable to distinguish coins of different size or identify common objects, particularly in the non-dominant left hand. Crude sensation for touch and pin prick was not impaired. The deep reflexes were uniformly diminished; abdominal and cremasteric reflexes were active; left plantar response was flexor.

During the following 10 days the child gradually regained the use of his hands with full return of discriminatory sensation. Incontinence of urine disappeared. He became overactive, talkative, irritable, fretful, sarcastic, and at times impertinent. When asked to write his name he formed a few letters and then abandoned the effort. Drawing of pictures was more successful. He was frequently remarking, "I'm a dope," and "I wish I were dead." He enjoyed the comics but when asked to read complained, "I can't see" or, "I forgot how."

By July 31 he was able to feed and dress himself but was still somewhat clumsy. He was interested in trying simple forms of occupational therapy but his hand had to be guided in lacing due both to clumsiness and impaired vision. Visual acuity on this date was R 20–70, L 20–70, both 20–50 (~1). He read Yaegger No. 4 type. The visual fields, ocular muscles and pupils were normal.

Progressive recovery took place during the last 10 days in the hospital. He began to read and write but continued to hold the page close to his eyes. On August 6 he wrote a note, "Doc, how many needles. They stink." His disposition became more cheerful and he was interested in all that went on about him. On August 7 visual acuity had increased to 20–40, R and L. He went home on August 11, the 26th postoperative day, an alert and lively but rather spoiled child.

He was re-examined on Oct. 17, 1947, 3 months after operation on return to school (3rd Grade). The mother reported that his overactivity had gradually diminished during the past 2 months. However he was still impulsive, restless, irritable, resentful of correction, and at times negativistic and difficult to manage. She interpreted this behavior as an exaggeration of former traits noted by his teachers as
well as his parents. Neurological examination was essentially negative. He could read Yaegger No. 1 type but still preferred to hold the page near his eyes. The optic nerve heads were normal. There was no remnant of dysphasia, dyslexia or dysgraphia. His talk was a bit rambling; his span of attention was shortened; and he was restless and fidgety. He responded promptly and intelligently to questions and performed simple arithmetical calculations rapidly and accurately. No memory defect could be detected. On October 6, vision was 20/15, R and L. An intelligence test performed at school on October 14 had reported an I.Q. of 108 according to Form A of the "Otis Quick Scoring Mental Ability Test."

On Dec. 20, 1947, 5 months after operation, his mother considered him the "same boy we took to the hospital" and the problems of behavior similar to those present before the injury, due chiefly to his intense enthusiasms and excessive energy. He attended school regularly and was promoted to the 4th Grade in good standing. A Stanford Achievement Test performed in May, 1948 gave a final score of 3.8 as compared with 2.6 for May, 1947, prior to the operation. When examined at his home on July 17, 1948, on the anniversary of operation, he was found to be normal in every respect. EEG July 22, 1948 revealed an essentially normal pattern although the amount of slow activity, 6–7 per second frequency, was somewhat more than might be expected for a child of this age.

SUMMARY OF NEUROLOGICAL CHANGES

The 10-hour period of unconsciousness followed by short-lived regression of behavior to an infantile level are evidence of substantial brain injury. On the other hand, the capacity for complete recovery including final preservation of a high degree of intelligence, gradual disappearance of behavioral abnormalities, full restoration of personality traits and normal EEG findings clearly indicate the reversibility of the brain changes. That the visual and sensory cortex were particularly vulnerable to the injurious anoxic effects is shown by the severe and relatively prolonged loss of visual acuity and the marked agnosia. The prominence of visual agnosia and particularly alexia are also significant in this connection. The lesser degree of susceptibility of the motor cortex is indicated by the absence of muscular weakness and the transitory development of pyramidal reflex signs. There were no persistent signs of dysfunction of the cerebellum, basal ganglia, brain stem, spinal cord, cranial or peripheral nerves.

PATHOLOGICAL CONSIDERATIONS

Susceptibility to ischemia obviously differs in the various regions of the brain. The so-called "higher" centers are more vulnerable than the lower. Lennox, Gibbs and Gibbs reported that their subjects became unconscious when oxygen saturation of blood in the jugular vein fell below 24 per cent whereas the lower centers continued to function. There is other evidence to support a decrease in the metabolic rate and also a gradient in vascularity as the neuraxis is descended from cerebral cortex to spinal cord.

Histological studies carried out by Weinberger et al. upon the brains of cats subjected to circulatory arrest of 7.5 minutes showed that the motor and visual areas of the cortex sustained the earliest and most profound...
damage. The olfactory, orbital and temporal regions of the cortex were the least susceptible. Laminae III and IV were more severely affected than I and II. Of the basal nuclei the order of vulnerability is as follows:—lateral geniculate, hypothalamus, thalamus, globus pallidus, caudate nucleus. In ischaemic experiments the basal ganglia are less affected than either the cortex or Purkinje cells of the cerebellum.

In recent years much more attention has been directed to reversible circulatory changes in the brain. Three vascular syndromes have been described by Scheinker—"vasoporosis," "vasoparalysis" and "vasothrombosis." In reality they may be considered as phases of the same morbid process depending on its duration and severity. Either because of constricted or dilated vessels there is diminished movement of blood. Stagnation results in hypoxia both of the vessel wall and the parenchyma supplied by the vessel. Hypoxia alone may cause increased permeability of the capillary wall to both fluid and cells.

Sugar and Gerard have shown that the effects of an abrupt interruption of cerebral blood flow are primarily due to anoxia, but hypoglycemia, hypercapnia and also increased extracellular potassium, induced by the anoxia, all contribute to the impairment of function. Other constituents of metabolism also play a role. The stasis in the circulation leads to local accumulations of CO₂ and other metabolites. Carbon dioxide is an active dilator. Further vascular dilatation results in increased permeability of the vessel wall, especially at the point of transition between capillary and venule. At this point oxygen tension is at its lowest and the endothelium most vulnerable to injury. Accumulation of fluid and blood cells in the dilated perivascular spaces retards the circulation even further, setting up a vicious cycle and increasing the hypoxia of the nerve tissue.

ANIMAL EXPERIMENTS

The effect of circulatory arrest on the various nervous centers has intrigued investigators for many years. The earliest recorded experiments on animals, those of Stenonis on fish and of Swammerdam on mammals in 1667, described the effects of occlusion of the abdominal aorta. Ligation of the innominate and left subclavian, or the carotids and vertebrais widely employed over the past century in the study of ischemia of the brain. These older methods gave inaccurate data because of the abundance of collateral circulation.

Two ingenious methods of studying the resistance of cerebral cells and neurones to lack of blood supply have recently been reported. Weinberger et al., by clamping the pulmonary artery of cats, arrested the entire somatic circulation. Kabat et al. were able to obtain complete temporary arrest of the cerebral circulation without the use of anaesthetics. Two weeks after ligation of both vertebral arteries, the dog is given atropine to prevent vagal inhibition, the trachea is intubated orally, and a blood-pressure cuff about the neck is inflated to a pressure of 350 mg. Hg.
According to Weinberger et al. cardiac arrest lasting 3 minutes, 25 seconds causes permanent alteration in behavior and psychic function, whereas after 6 minutes vision and sensation suffer some degree of permanent injury. On the contrary, Kabat et al. found apparent complete recovery of function after 6 minutes or less of cardiac arrest. Both groups of workers agree that 8 minutes or longer causes permanent severe damage to the brain.

After restoration of vital centers there ensues a period of hyperactivity. Coma may last for 24 hours after 4 minutes' arrest. Following coma a transition period lasts several days with gradual return of cerebral functions including righting mechanisms. Ataxia of cerebellar type is the most persisting neural dysfunction prior to recovery. Young animals are more resistant than adult but resistance is diminished to adult level at age of 4 months. Ability of the newborn to recover functionally is 400 per cent greater than the adult. The least trickle of blood can maintain activity of nerve tissue for a surprisingly long period.

THE TIME FACTOR

The total elapsed time of cardiac arrest (27 minutes) extended far beyond the accepted safety zone. It is obvious that the combination of measures to artificially maintain both the circulation and respiration and at the same time provide oxygen, saved the brain (and the heart) from irreparable damage. We have what amounts to a human experiment of circulatory arrest with brain ischemia for 2.5 minutes followed by a period of hypoxia lasting 24.5 minutes. Somewhat similar conditions prevailed in the cases of cardiac resuscitation reported by Adams and Hand\(^1\) and Beck et al.\(^4\) In both instances the duration of cardiac arrest, 20 and 35 minutes respectively, exceeded the limit of safety, established by animal experiments, but the patients survived their hypoxic experience without apparent brain damage.

It would appear, therefore, that clinical evidence is accumulating that the healthy human brain will stand the degree of hypoxia likely to be associated with the resuscitation of a heart undergoing ventricular fibrillation. In other words if cardiac arrest is promptly and effectively handled and the heart survives, it is unlikely that the brain of that individual will suffer irreparable damage. This is in striking contrast to cerebral anoxia of carbon monoxide poisoning and overdoses of anaesthetic and narcotic drugs. Here the pathological changes tend much more to be irreversible, characterized by widespread foci of necrosis and degeneration involving the corpus striatum.

SUMMARY AND CONCLUSIONS

1. A case is reported of cardiac arrest of 27 minutes due to proven ventricular fibrillation, effectively treated by cardiac massage, intravenous procaine, and adequate administration of oxygen.

2. The clinical course of recovery of cerebral functions is described in detail.
3. The prolonged loss of visual acuity and the marked astereognosis indicate that the visual and sensory cortex were particularly vulnerable to the injurious anoxic effects.

4. Final complete recovery is evidence of reversibility of the brain changes resulting from the prolonged hypoxia.

5. Both clinical and experimental data support the concept of a gradient of susceptibility as the neuraxis is descended from cerebral cortex to spinal cord.

6. The probable pathophysiology associated with interruption of cerebral blood flow is briefly discussed with reference to recent animal experiments.

7. It would appear that, if the cardiac arrest due to ventricular fibrillation is promptly and effectively handled, and the heart survives, it is unlikely that the brain of that individual will suffer irreparable damage from the degree of hypoxia occurring during the period of resuscitation.

REFERENCES


