The Clinical Use of Hypothemia Following Cardiac Arrest *

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Cardiac arrest can usually be treated successfully by massage. When the time interval between arrest and restoration of circulation exceeds three or four minutes, central nervous system injury prevents survival of the patient. The clinical picture of unconsciousness, evidence of progressive brain swelling, and finally death, following apparently successful treatment of cardiac arrest, is all too familiar. Hypothermia has been found to reduce cerebral swelling in patients undergoing intracranial operation and has been reported to be beneficial in patients with brain injury. For these reasons it seemed advisable to use hypothermia in treating patients with evidence of central nervous system damage after cardiac arrest. This paper records our experiences with four such patients treated with hypothermia following arrest.

Case Reports

Case 1. *D. J. S., J.H.H. #13768.* This five-year-old colored male was well known in the Pediatric Out-patient Department, having been seen on numerous occasions with respiratory infections. He was admitted to the Pediatric Service on January 21, 1957, in an asymptomatic period for diagnostic studies to evaluate the underlying pulmonary disease. No abnormalities were found on physical examination. Bronchography under general anesthesia was performed the following day. Pre-anesthetic medication and induction were uneventful. The patient was intubated. Cyanosis was noted and absence of pulse detected 11 minutes after introduction of contrast media. Four minutes elapsed before thoracotomy was completed and the heart found to be in standstill. The heart beat was readily established with massage. Respiratory efforts began 14 minutes after arrest. After the thoracotomy wound was closed, the blood pressure and respiratory rate were adequate. The child was unconscious and unresponsive to painful stimuli. The pupils were dilated and fixed. Hypothermia with a water-cooled mattress ** was begun immediately. During the next two hours some extensor spasm became evident and extensor plantar responses were noted. The level of unconsciousness did not change, and the pupils remained dilated and fixed. Temperature was maintained at 32° to 34° C. Twenty-four hours later, extensor spasm was gone and the patient responded to painful and verbal stimuli; pupillary reflexes were present. Forty-eight hours after arrest the patient could move all extremities, recognized his relatives and attempted to speak. Plantar responses became normal. At 72 hours, hypothermia was stopped. Further recovery was rapid, and the child was discharged 14 days after arrest. An electroencephalogram one week after arrest was normal; psychometric testing revealed a low normal score. Three months after discharge the patient was asymptomatic.

Case 2. *S. P. J.H.H. #56 79 82.* This nine-year-old colored female had been an out-patient for several years because of severe bronchial asthma beginning at two years of age. After an asymptomatic period of several months, she complained suddenly on the morning of August 20, 1957, of substernal pain and cough. Respiratory difficulty became progressively severe, and the patient was brought to the hospital 30 minutes after the onset of symptoms. The child walked into the Emergency Department and collapsed. She was found to be pulseless and cyanotic. Endotracheal intuba-

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** Hypo-hyper Unit, Thermo-rite Products Corporation, Buffalo, New York.

tion was quickly done and cardiac massage begun in an estimated three minutes. The heart beat was easily restored. After the thoracotomy wound was closed, the patient was unconscious and unresponsive, with dilated, fixed pupils and deep, even respiration. Hypothermia was begun immediately, and the temperature kept at 30° to 33° C. During the first several hours, there were episodes of extensor rigidity. Voluntary movements began about 18 hours after arrest, and pupillary reflexes returned at about the same time. Hypothermia was stopped 24 hours after arrest and the patient allowed to warm slowly. Forty-eight hours after arrest the patient was conscious and responsive. Further convalescence was uneventful, and she was discharged on September 1, 1957. No abnormalities were found on examination two months later.

Case 3. *W. S. J.H.H. #58 82 31.* This 38-year-old colored male was admitted to the Emergency Department during the evening of September 28, 1957, after sustaining a knife wound of the left chest. On admission he was unconscious and pulseless but was breathing. Neck veins were distended. About two minutes after admission the shallow respiration ceased entirely. Endothracheal intubation and left thoracotomy were quickly performed. The pericardium was distended with blood; the heart was in complete arrest. When the pericardium was opened, bleeding from a laceration of the right ventricle was controlled by pressure while cardiac massage was begun. Good contractions began quickly, and the wound in the ventricle was closed with catgut sutures. The estimated time between arrest and establishment of effective massage was five minutes. The patient was deeply unconscious and unresponsive, with dilated pupils slightly responding to light. There was an increase in extensor tone with hyperactive deep tendon reflexes. Cooling was begun immediately. Temperature was maintained at 32° to 33° C. A tracheotomy was performed. Twenty hours after injury the patient would respond to spoken voice, and motor power was present in all extremities. At the end of 48 hours, the patient was responsive and except for amnesia concerning recent events, there was no neurologic deficit. Cooling was stopped at 48 hours, and the patient was discharged in good condition nine days later. No abnormalities were found on examination one month after discharge.

Case 4. *C. L. J.H.H. #17 98 75.* A 39-year-old colored female was admitted to the Emergency Department on November 16, 1957, after receiving multiple ice pick wounds of the chest. There was a history of pulmonary tuberculosis and left upper thoracoplasty. Initial chest x-ray showed a small right pneumothorax. Respiratory distress gradually appeared over a period of several hours and following an episode of vomiting, sudden collapse and cardiac arrest occurred. Thoracotomy and cardiac massage were carried out with difficulty because of adhesions, but effective heart beat was established about five minutes after arrest was detected. The right pneumothorax was treated by catheter drainage under negative pressure. After closure of the thoracotomy wound, the patient was deeply unconscious and unresponsive with dilated, fixed pupils. There was generalized extensor spasm with extensor plantar reflexes. Tracheotomy was performed and cooling begun immediately. Temperature was maintained at 32° to 33° C. Vasopressors were required to maintain blood pressure. After 24 hours very slight response to painful stimuli was noted. The pupils were smaller but remained fixed. At 48 hours the level of consciousness was unchanged but extensor spasm was less marked. Cooling was stopped after 72 hours at which time the patient responded to verbal stimuli. After 96 hours normal muscle tone was present and the patient attempted to speak. Vasopressors were not used after the fourth day. Neurologic examination five days after arrest revealed severe visual defect with only light perception remaining. This was considered cortical in origin. There was no other neurologic abnormality. The patient continued to improve and at the time of discharge four weeks after admission some visual return was noted. One month after discharge further visual improvement was noted. The patient was otherwise well.

Discussion

Injury to the central nervous system following circulatory arrest is caused by anoxia. The principal effects of anoxia on the brain are direct injury to nerve cells and the appearance of cerebral swelling. The extent, reversibility, and clinical importance of nerve cell injury are poorly understood.[6, 7, 24] Cerebral swelling is a complex, non-specific reaction to injury which is simply defined as any increase in brain volume.[3] The process apparently begins with capillary endothelial injury and the escape of fluid from the vascular space. Carbon dioxide retention causes vasodilation and the increase in intravascular fluid adds to brain swelling. When the increase

in brain volume exceeds the capacity of the subarachnoid space, shifts in brain position occur. Temporal and brain stem herniation through the tentorial opening result in blockage of spinal fluid circulation, direct neurone injury and small mid brain hemorrhages. These shifts produce the clinical signs associated with brain swelling, and by producing local anoxia lead to increasing vascular injury and further swelling.[3, 20]

Whatever the exact mechanism of injury it is clear that circulatory arrest of more than four minutes duration will result in fatal central nervous system injury in most cases.[12, 13] This time figure is modified by such factors as individual variation, age, presence of vascular disease, and presence of anoxemia before arrest. It is, therefore, impossible to predict the extent of brain injury in a particular instance even when an accurate time sequence is known. In general, early clinical evidence of severe brain injury following anoxia is associated with a grave prognosis.[2]

Generalized hypothermia has been a subject of wide interest in recent years, and its effects on the central nervous system have been extensively studied. Hypothermia will reduce normal brain volume.[5, 17] In addition it has been repeatedly demonstrated that hypothermia will *protect* the brain against anoxic injury.[10, 12, 13, 15, 16] This protection appears related to the demonstrable reduction in cerebral oxygen consumption and cerebral blood flow present in hypothermic individuals.[1, 4, 10, 18, 22, 23] The effects of hypothermia on *already established* brain injury have been much less extensively studied. Reduction of cerebral swelling has been observed at craniotomy for brain tumor.[11, 21] Furthermore, a number of cases have been reported in which patients with head injury appeared to have benefited from hypothermia.[9, 19] The mechanisms by which hypothermia may reduce cerebral swelling or by which reduced cerebral metabolism may minimize cellular injury are not understood at this time.[11, 14]

Few conclusions can be drawn from uncontrolled clinical series such as the one presented. The prognosis in patients with head injury is notoriously difficult to predict. In addition, the detection of cardiac arrest is not without error and establishment of accurate time sequence following an emergency may be difficult. On the other hand, in each of the presented cases cardiac standstill was directly observed. As each instance of arrest occurred outside the operating room, it is likely that the time required for instituting effective massage was longer than estimated. Anoxemia was certainly present before arrest in each case. All patients showed signs of severe neurological injury soon after arrest and their subsequent courses were consistent with the diagnosis of cerebral swelling (Table 1). Finally, though no controls are available, it seems significant that in The Johns Hopkins Hospital during the past ten years

TABLE 1

Case Number	1	2	3	4
Date	Jan. 1957	Aug. 1957	Sept. 1957	Nov. 1957
Age	5 yr. C. M.	9 yr. C. F.	38 C. M.	39 C. F.
Cause of arrest	Bronchogram	Asthma	Stab wound	Stab wound
Duration of arrest	5 minutes	5 minutes	5 minutes	5 minutes
Neurologic damage	Severe	Severe	Severe	Severe
Hypothermia: Range	32–34° C.	30–32° C.	32–33° C.	32–34° C.
Duration	72 hours	24 hours	48 hours	72 hours
Residual neurologic defect	None	None	None	Moderate

no more than five patients, exclusive of the ones reported, have survived cardiac arrest occurring outside the operating room area.

This problem has been investigated in the laboratory by producing circulatory arrest of ten minutes duration in dogs. The results are summarized in Table 2 and clearly indicate that hypothermia instituted after anoxic injury will increase survival rate in dogs. This work will be more completely reported in another publication.[25]

As a result of clinical and experimental experience, we have come to consider the following points important. Patients who show evidence of central nervous system damage following cardiac resuscitation should be promptly cooled to 32° to 34° C. and maintained there until there is evidence of return of neurologic function. This has not been longer than three days in our cases. The Thermorite circulating mattress has proven quite satisfactory for this purpose. Tracheotomy should be performed at the outset and respirations supported by a mechanical respirator if necessary. Shivering has not been a problem. Early attention to blood volume, electrolyte balance, and renal function is essential.

TABLE 2

Treatment	Number of Experiments	Percentage of Recovery
None	12	25%
Hypothermia 32–34° C. 18–36 hours	12	83%

Summary

Four patients with cardiac arrest occurring outside the operating room area are reported. Cardiac massage was instituted within four to six minutes. All patients exhibited signs of severe neurological injury and were treated promptly with hypothermia (30° to 34° C.) which was maintained up to 72 hours. Three patients recovered completely; the residual neurologic defect in the fourth is of moderate severity. The beneficial effect of hypothermia is thought to be in the reduction of cerebral swelling. Similar patients treated without hypothermia have rarely survived.

Bibliography

1. Adams, J. E., H. Elliot, V. C. Sutherland, E. J. Wylie and R. D. Dunbar: Cerebral Metabolic Studies of Hypothermia in the Human. Surgical Forum VII, page 535, 1956.
2. Allison, R. S., P. D. Delford and A. Meyer: Discussion on the Clinical Consequences of Cerebral Anoxia. Proceedings of the Royal Society of Medicine, **49**:609, 1956.
3. Atkinson, W. J.: Cerebral Swelling: Its Physiology, Pathology, Clinical Symptoms and Signs, Differential Diagnosis and Treatment. Annals of the Royal College of Surgeons of England, **11**:367, 1952.
4. Bering, E. A., Jr., J. A. Taren, J. D. McMurrey and W. F. Bernhard: Studies on Hypothermia in Monkeys. II. The Effect of Hypothermia on the Cerebral Physiology and Cerebral Metabolism of Monkeys in the Hypothermic State. Surg., Gynec. & Obst., **102**: 134, 1956.
5. Botterell, E. H., W. M. Lougheed, J. W. Scott and S. L. Vandewater: Hypothermia and Interruption of Carotid or Carotid and Vertebral Circulation in the Surgical Management of Intracranial Aneurysms. J. of Neurosurg., **13**:1, 1956.
6. Courville, C. B.: Case Studies in Cerebral Anoxia. Bulletin of the Los Angeles Neurological Society, **19**:135, 1954.
7. Edstrom, R. F. S. and H. E. Essex: Swelling of the Brain Induced by Anoxia. Neurology, **6**:119, 1956.
8. Isaacs, J. P.: Personal Communication.
9. Lazorthes, G. and L. Campan: Hypothermia in the Treatment of Craniocerebral Traumatism. J. Neurosurg., **15**:163, 1958.
10. Lougheed, W. M. and D. S. Kahn: Circumvention of Anoxia During Arrest of Cerebral Circulation for Intracranial Surgery. J. Neurosurg., **12**:226, 1955.
11. Lundberg, M., K. C. Neilsen and E. Nilsson: Deep Hypothermia in Intracranial Surgery. J. Neurosurg., **13**:235, 1956.
12. Marchand, P. and J. C. Allan: An Experimental Study of the Effect of Hypothermia on the Heart and Brain. South African. J. Med. Sci., **21**:127, 1956.

13. Marshall, S. B., J. C. Owens and H. Swan: Temporary Circulatory Occlusion to the Brain of the Normothermic Dog. Arch. Surg., 72:98, 1956.
14. Meyer, J. S. and J. Hunter: Effects of Hypothermia on Local Blood Flow and Metabolism During Cerebral Ischemia and Hypoxia. J. Neurosurg., 14:210, 1957.
15. McMurrey, J. D., W. F. Bernhard, J. A. Taren and E. A. Bering: Studies on Hypothermia in Monkeys. I. The Effect of Hypothermia on the Prolongation of Permissable Time of Fatal Occlusion of the Afferent Circulation of the Brain. Surg., Gynec. & Obst., 102:75, 1956.
16. Pontius, R. G., R. D. Bloodwell, D. A. Cooley and M. E. DeBakey: The Use of Hypothermia in the Prevention of Brain Damage Following Temporary Arrest of Cerebral Circulation. Experimental Observations. Surgical Forum, V:224, 1954.
17. Rosomoff, H. L. and R. Gilbert: Brain Volume and Cerebrospinal Fluid Pressure During Hypothermia. Amer. J. Physiol., 183:19, 1955.
18. Rosomoff, H. L. and D. A. Holaday: Cerebral Blood Flow and Cerebral Oxygen Cosumption During Hypothermia. Amer. J. Physiol., 179:85, 1954.
19. Rowbotham, G. F., K. Bell, J. Akinhead and A. Cairns: A Serious Head Injury in a Pregnant Woman. Lancet, 272:1016, 1957.
20. Scheinker, I. M.: Cerebral Swelling. J. Neurosurg., 4:255, 1947.
21. Sedzemer, C. B. and J. W. Dundee: Hypothermia in the Treatment of Cerebral Tumors. J. of Neurosurg., 15:199, 1958.
22. Stone, H. H., T. N. Mackrell, M. R. Truher, C. Donnelly and A. S. Frobese: The Effect of Lowered Body Temperature on the Cerebral Hemodynamics and Metabolism of Man. Surgical Forum, 6:129, 1956.
23. Stone, H. H., C. Donnelly and A. S. Frobese: The Effect of Lowered Body Temperature on the Cerebral Hemodynamics and Metabolism of Man. Surg., Gynec. & Obst., 103: 312, 1956.
24. White J. C., M. Verlot, B. Silverstone and H. K. Beecher: Changes in Brain Volume During Anesthesia: The Effects of Anoxia and Hypercapnia. Archives of Surgery, 44:1, 1947.
25. Zimmerman, J. McK. and F. C. Spencer: To be Published.

Discussion

Dr. Wilfred G. Bigelow: This is a most ingenious use for hypothermia, and judging from the essayists' report, it is an effective therapeutic agent. As Dr. Williams mentioned, it is difficult to assess a small series with so many variables, but I think he has presented a very strong case.

I have had no experience with this use of hypothermia. I would like to ask a question, which I don't want to detract from the presentation. There were four cases presented, one 4, one 9 years of age, and two in their 30's. I think there is good evidence that children can tolerate cerebral hypoxia or anoxia better than adults, and perhaps the younger the individual, the longer this can be tolerated. It would be interesting to know, in the cases which they have looked at over the past ten years that have done less well what their average age was.

As for commenting on the mechanism, there is experimental evidence which is certainly related, but with no direct bearing on this problem, by Rosamoff, which shows that the brain reduces in volume with reduced intracranial pressure at low body temperatures.

The neurosurgeons, of course, are using this technic successfully in brain injuries, and Botterell and Lougheed in Toronto have observed in three instances a compression flap which is bulging, diminish in size with long-term hypothermia over several days.

The key to the local cellular problem apparently is: does brain swelling occur following anoxia and interruption of the circulation? And although it probably does occur, it's remarkable that there is very little evidence to confirm that it does, experimentally or otherwise.

Some years ago, Dr. Heimbecker and I, using a quartz rod technic, studied circulation *in vivo* in the mesentery. We repeatedly saw diffusion of fluid from the capillary arterial network following local occlusion of the circulation, so there is certainly a physiologic basis for the application of hypothermia.

Presumably, hypothermia dissipates this reaction to anoxia, and extends the reaction over a longer period of time in the brain, and thus prevents final nerve damage.

This is a stimulating and interesting new line, and I think these investigators deserve a good deal of credit.

Dr. J. C. White: Working with Dr. Beecher and Dr. Selverstone in the early 1940's, we were