Cerebral Lactate Accumulation and Glucose Exhaustion During Circulatory Arrest[1] (34553)

DAVID YASHON, FRANKLIN C. WAGNER, JR., YOUSSEF K. DEMIAN, AND ROBERT J. WHITE

Division of Neurosurgery, Metropolitan General Hospital, Case-Western Reserve University School of Medicine, Cleveland, Ohio 44109

Transient circulatory arrest, with survival, is a frequent occurrence in medical practice. This is a true emergency, since restoration of circulation either by artificial or natural means is imperative primarily because of cerebral (and somatic organ) intolerance to hypoxia. One standard experimental model (1, 2) of circulatory standstill which is closely related to its clinical counterpart has been studied electrophysiologically (3). Effects of circulatory arrest on intracranial pressure and time limits of tolerance to prolonged arrest have been delineated (2, 3). In the present study, this experimental model has been utilized for a timed survey of cerebral lactate accumulation and glucose disappearance. Results may be compared with similar, but not identical examples described elsewhere, and correlation with those studies alluded to above employing the same model are possible since there has been adherence to strict time sequences. Also, the lactic acidosis of cerebral ischemia is possibly a critical factor in determining brain survival (4), and, although a 4- to 5-min anoxic limit for human cerebral functional restitution has been tentatively accepted in circulatory arrest, the exact time of standstill is often difficult to document. Thus, other means, including these chemical determinations, may be valuable for prediction of useful cerebral survival.

Method. Five large mongrel dogs were anesthetized with pentobarbital (30 mg/kg) and 1–2 cc of gallamine was given intravenously. After barbitalization and during the entire surgical procedure the animals were intubated and ventilated with 40% oxygen and 60% air. Arterial pH and oxygen saturation were determined immediately prior to circulatory arrest and were essentially physiologic. Thoracotomy was performed through the fourth right intercostal space, and umbilical tapes were loosely applied around the roots of the ascending aorta, inferior vena cava, and superior vena cava cephalad to the azygos vein according to techniques previously described (2, 3). Cessation of left ventricular cardiac output except for coronary flow was accomplished by near simultaneous occlusion of both vena cavae followed by occlusion of the ascending aorta. Venous blood returned through the azygos vein and coronary sinus. Isolated cardiopulmonary circulation was thus retained.

Prior to vascular occlusion a craniectomy had been performed employing hemostatic surgical technique exposing frontal, parietal, temporal, and occipital lobes bilaterally. The dura was reflected widely but venous sinuses were not disturbed. A brain sample of about 1 cc of the left frontal lobe was rapidly removed (for control analysis) utilizing sharp dissection. Vascular occlusion was then immediately instituted and at 2, 5, and 10 min identical specimens were removed from left occipital lobe, right frontal lobe, and right occipital lobe in succession. From beginning of tissue removal to complete immersion in liquid nitrogen was usually 7 but always less than 10 sec.

Femoral artery pressure, pulse, and electrocardiograph (EKG) were transmitted to a Grass polygraph. Deep body temperature was between 36.5 and 37.5° continuously monitored rectally. Coincident with vascular oc-

[1] Supported by the Heart Association of Northeastern Ohio, Inc., NINDB Grant 6-42-5721, and NIH Grant NB 5408.

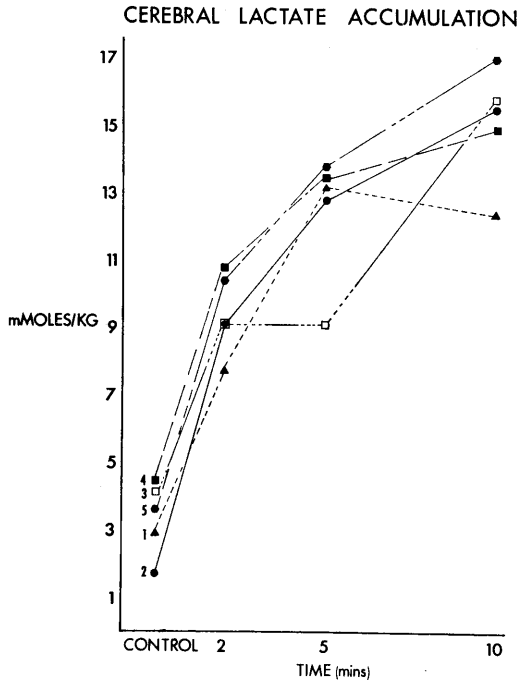

FIG. 1. Lactate accumulation.

clusion, EKG showed changes in QRS complexes, and later there were rhythm changes. Asystole occurred in one dog after 8 min of occlusion, but a good heartbeat persisted in other animals throughout as judged by EKG and cardiac palpation.

Preparation of tissue for chemical determination was after Lowry *et al.* (5). Tissue lactate studies were performed on deproteinized, neutralized, aqueous extracts utilizing a lactic dehydrogenose method (6). Glucose was determined on aqueous tissue extracts by the glucose oxidase method (6, 7).

Results. See Fig. 1 and 2.

Discussion. Conversion to anaerobic metabolism with lactate accumulation is well known to occur during cerebral hypoxia. For determination of cerebral viability (or death), multiple parameters, not the least of which is clinical neurological examination, have been utilized, and none has been found ideal. The electroencephalographic record, although valuable when isoelectric for a prolonged period, is not useful if electrical activity exists. Thus, a reliable laboratory determination could be of assistance to determine cerebral functional restitution since months of needless rehabilitation might be averted. Brockman and Jude (2) have shown that 10–12 min is the limit of canine survival applying clinical criteria in the model utilized in the present experiments. A study employing electrocortical recordings in dogs has shown that survival can be predicted by quality and timing of recurrence of activity (3). From those studies it appears that lactate accumulation recorded in the present experiment at 10 min may represent a level in dogs with which restoration of useful cerebral function becomes unlikely. Nevertheless, glucose depletion, intracellular pH aberrations, and lysosomal destruction, as well as other changes, may be more likely causes of cerebral damage.

Cerebral tissue lactate increase as well as glucose utilization was closely correlated with time of vascular occlusion, and the increase in lactate concentration was sufficient to account for about one-fourth the decrease in glucose concentration by way of anerobic glycolysis. Anaerobic glycolysis of glucose in ischemic brain produces 2/38ths as many high-energy phosphate bonds as aerobic oxidation and results in lactate accumulation (8). A 4-fold increase in mouse brain lactate was recorded 1 min after decapitation, and after 2 min and 10 min it had risen 8- and 9-fold,

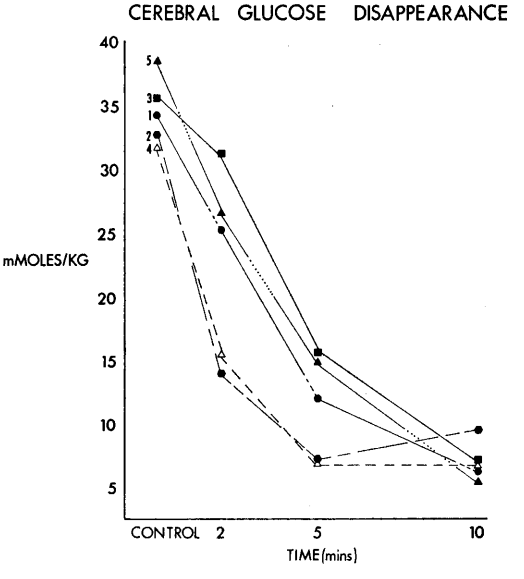

FIG. 2. Glucose disappearance.

respectively (5). Brain glucose was 25% of normal at 30 sec and 0 at 1 min after decapitation. Thorn *et al.* (9) observed a gradual rise in lactate in ischemic hypothermic (26°) and normothermic rabbit brain. This differed from the rapid rise observed by Hurwitz and Wolfson (10). The latter concluded that there appeared to be no correlation between brain lactate and cerebral viability because a 3- to 4-fold increase in brain lactate was observed in rats and dogs 6 min after circulatory arrest without significant change in the next 84 min. McGinty and Gesell (11) were able to obtain similar lactate-accumulation curves as in the present experiments by subtracting absolute lactate values of those hemispheres frozen within 10 sec of decapitation from the remaining hemisphere incubated for longer periods. Stone *et al.* (12) and Gurdjian *et al.* (13) have demonstrated that an increase in brain lactate is observed when oxygen saturation of arterial blood decreases to 55–65%. Changes were even greater if systemic hypotension was present during oxygen unsaturation. Siesjo *et al.* (14) have shown that conditions which interfere with cerebral circulation lead to increases in cerebrospinal fluid lactate/pyruvate ratio.

As to the amount of brain lactate present under normal circumstances in an isolated monkey brain preparation (15) with extracorporeal perfusion, a small amount was present but increasing increments of lactate were measured only after 1 hr with the implication that cerebral metabolism was then shifting to an anaerobic system. Gaevskaya (16) stated that true content of cerebral lactic acid can be ascertained only by *in situ* freezing of the brain with preservation of normal circulation and total absence of hypoxia until the moment of circulatory arrest. In brain examined under these conditions, a small amount of lactic acid was found. Avery *et al.* (17) summarized "normal values" obtained for lactic acid in cat and dog brain frozen *in situ*. Lactic acid content was found to be within the range 11.4–36.5 mg/100 g averaging 15.3 mg for the cat and 22.3 mg for the dog. These values are similar to control levels in the present experiments and fell within the range obtained by various investigators for lactic acid in resting muscle and blood.

Summary. Glucose and lactate content in dog brain were measured before and during arrest of circulation in a standard preparation. Comparison with other studies of the same model allowed the guarded conclusion that the cerebral lactate level in dogs after 10 min of severe hypoxia may be indicative of an irreversible state. Lactate concentration rose and glucose levels fell during a 10-min period of ischemia. The increase in lactate concentration was sufficient to account for about one-fourth of the decrease in glucose content by way of anerobic glycolysis.

1. Marshall, S. B., Owens, J. C., and Swan, H., Arch. Surg. **72**, 98 (1956).

2. Brockman, S. K. and Jude, J. R., Bull. Johns Hopkins Hosp. **106**, 74 (1960).

3. Yashon, D., White, R. J., Taslitz, N., Wolin, L. R., and Massopust, L. C., Jr., J. Neurosurg. **32**, (1970).

4. Negovskii, V. A., "Resuscitation and Artificial Hypothermia," (Consultants Bureau), New York (1962).

5. Lowry, O. H., Passonneau, J. V., Hasselberger, F. X., and Schultz, D. W., J. Biol. Chem. **239**, 18 (1964).

6. Bergmeyer, H., "Methods of Enzymatic Analysis," Academic Press, New York (1965).

7. Worthington Biochemical Corporation, Freehold, New Jersey 07728.

8. White, A., Handler, P., and Smith, E. L., "Principles of Biochemistry," McGraw-Hill, New York (1968).

9. Thorn, W., Scholl, H., Pfleiderer, G., and Mueldener, B., J. Neurochem. **2**, 150 (1958).

10. Hurwitz, B. S. and Wolfson, S. K., Jr., Exp. Neurol. **23**, 426 (1969).

11. McGinty D. A. and Gesell, R., Amer. J. Physiol. **75**, 70 (1925).

12. Stone, W. E., Marshall, C., and Nims, L. F., Amer. J. Physiol. **132**, 770 (1941).

13. Gurdjian, E. S., Stone, W. E., and Webster, J. E., Arch. Neurol. Psychiat., **51**, 472 (1944).

14. Siesjo, B. K. and Kjallquist, A., Life Sci. **7**, 45 (1968).

15. White, R. J., Albin, M. S., Davidson, E., and Yashon, D., Surgery, **64**, 60 (1968).

16. Gaevskaya, M. S., "Biochemistry of the Brain During the Process of Dying and Resuscitation," (Consultants Bureau), New York (1964).

17. Avery, B. F., Kerr, S. E., and Ghantus, M., J. Biol. Chem. **110**, 37 (1935).

Received Sept. 8, 1969. P.S.E.B.M., 1970, Vol. 133.