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THE RELATIVE ROLES OF OXYGEN CONCENTRATION AND DELIVERY IN MAIN--ETC(U)
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6 The Relative Roles of Oxygen Concentration and Delivery
in Maintaining Cell Function and Viability.

by

10 H.J. Proctor M.D.,
J.J. Wood Ph.D.

University of North Carolina
Department of Surgery
Chapel Hill, N.C. 27514

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This communication constitutes the final report of ONR Contract NO. N00014-76-595. This report is a comprehensive summary of 3 years work directed at the investigation of the relative roles of oxygen and substrate in maintenance of normal cell function. The brain was selected as the initial organ of study due primarily to the fact that CNS dysfunction is a leading cause of death secondary to severe trauma and hemorrhage.

A clinically relevant model combining hypotension and hypoxia had been developed in the rat by the investigators and has been used throughout this study. In the final series of experiments, attention was directed to the effects of glucagon on hepatic cellular energetics during low flow states.

The framework within which these studies were carried out was based on a broad hypothesis of cellular alterations in shock and trauma. This hypothesis states that with shock and diminished tissue perfusion, there seems to be an initial alteration in the cell membrane with changes in its capability to properly perform. Na^+ probably enters the cell, Na^+ ^{plus} K^+ ATP-ase is activated, ATP is used and the mitochondria are stimulated. Cyclic AMP decreases which may result in alterations in insulin, glucagon, catecholamines, and corticosteroids. Further Na^+ enters the cell; the cell swells, with mitochondrial swelling as well. Metabolic capability decreases as these alterations in cation content and hydration of the cell and intra-cellular organelles occur. Less ATP may be produced both from glycolysis and from oxidative metabolism. Toxic factors released by lysosomal action may then contribute to the persisting shock state or to altering the membranes of other cells. Ultimately, a breakdown in energy and oxidative metabolism within the mitochondrion will lead to the irreversible cessation of cellular functional activity.

Studies in our laboratory as part of this ONR contract have been conducted with the aim of correlating combined hypoxia and hypotension with changes in brain energy substrates and micro-oxygen delivery. We attempted to determine the relative effects of the lack of oxygen versus substrate availability to the brain during a 30 minute period of hypoxia ($\text{FIO}_2 = 7.5\%$) and hypotension ($\text{MABP} = 30 \text{ mm Hg}$) on the subsequent deterioration of the organism, i.e., the breakdown of whole body homeostasis secondary to irreversible damage to the CNS. In our studies, male albino rats were anesthetized with sodium pentothal and artificially ventilated. Both femoral arteries were cannulated for recording

arterial blood pressure and for withdrawal and reinfusion of blood. Control values for blood pressure and arterial pO_2 , pCO_2 and pH were established. The 30 minute hypoxic-hypotensive episode was achieved by administration of 7.5% oxygen - balance nitrogen, and lowering the mean arterial blood pressure (MABP) to 30 mm Hg. Following this period, resuscitation was initiated by administration of 30% oxygen and reinfusion of all shed blood. For the metabolic studies, brains were frozen in separate groups of animals following the 30 minute stress period, as well as 20 minutes, 1 hour and 2 hours after resuscitation. In another series of experiments, micro-oxygen electrodes were inserted into the exposed parietal cortex for determination of adequacy of oxygen delivery in the micro-circulation.

The results of these studies showed that brain tissue ATP concentrations were severely depressed at the end of the 30 minute stress period while brain glucose and glucose-6-phosphate (G-6-P) were near control levels. This would indicate that while ischemia of the brain was severe, it was incomplete. Since the brain does not store glucose, a 30 minute period of total deprivation of delivery would be expected to significantly reduce brain glucose as a result of on-going anaerobic metabolism. G-6-P during this period was also normal indicating adequate phosphorylation of glucose despite the reduced concentration of ATP. Lactate was significantly elevated at this time as would be expected, due to anaerobiosis secondary to oxygen deprivation.

The micro-oxygen electrode studies were carried out by advancing the electrode into the cortex at 10 micron steps up to a depth of 1,000 microns. Oxygen profiles were constructed relating pO_2 with frequency of occurrence. Compared to control oxygen histograms where peak frequency pO_2 values were at 40 mm Hg with a range up to 95 mm Hg, stress oxygen histograms showed a peak frequency at essentially zero with a range only as high as about 40 mm Hg.

During the three recovery periods investigated, brain glucose and G-6-P remained unchanged while the high concentration of lactate observed immediately post-stress slowly declined toward control levels at 2 hours post-resuscitation, indicating adequate lactate washout from the tissue. ATP concentration returned to control levels at the 20 minute recovery period, but fell about 40% from control at the 2 hour post-resuscitation period. Restoration of arterial blood pressure and brain high energy compounds during the recovery periods appeared to be unrelated. Thus, arterial blood pressure was still considerably depressed after

20 minutes of recovery, at which time brain ATP had returned to control values. Conversely, arterial blood pressure had returned to normal after 2 hours of recovery, at which time there was a secondary decrease in brain ATP. In the oxygen electrode studies, the oxygen profile at 20 minutes post-resuscitation showed a definite overshoot with a greater frequency in the higher pO_2 range as compared to control.

At 2 hours recovery, the histogram showed a leftward shift toward control profiles, but contained two high frequency peaks at 32 and 68 mm Hg. This bi-modal distribution of brain oxygen tension indicates a return of portions of the brain to normal perfusion, while other areas appear to remain hyperemic at 2 hours post-resuscitation. At no time did there appear to be deficient perfusion or oxygenation after resuscitation.

The prompt re-oxygenation of the brain tissue, normal brain glucose and G-6-P concentrations during the post-resuscitation period, and the diminishing lactate concentration as the post-resuscitation period progressed all indicated good cerebral perfusion after resuscitation. These observations do not support the contention that permanent perfusion deficits exist post-resuscitation, or that they are even the primary event in post-hypoxic hypotensive cerebral dysfunction. As measurements were conducted only during a 2 hour post-resuscitation period, it is possible that a late perfusion deficit such as that associated with cerebral edema might have developed. In view of the normal G-6-P concentrations, we could not incriminate substrate unavailability, or the inability to phosphorylate glucose as an etiologic factor.

Despite normal perfusion, normal oxygen tensions, and normal substrate concentrations, this model was associated with a progressively diminishing high energy phosphate concentration and was shown to be 90% fatal. We have hypothesized that the deficient production of ATP stems from an as yet undefined metabolic lesion incurred during the hypoxic/hypotensive period. In view of what appears to be preservation of adequate substrate, and the extreme deprivation of oxygen, we postulate that the lack of oxygen is the critical factor in this model.

In our most recent series of experiments, we undertook to determine hemodynamic and metabolic effects of glucagon on hepatic function in the dog following a sustained episode of hemorrhagic hypotension (see attached manuscript). It was

found that significantly lower hepatic ATP levels resulted in animals treated with glucagon following resuscitation from hemorrhagic shock. Glucagon created an adverse effect on regeneration of ATP to control levels. No difference between control and glucagon treated animals was found in values of G-6-P or lactate following resuscitation. The final observation in these studies was that even in the face of a demonstrated augmented portal vein blood flow and increased oxygen delivery, hepatic function is not improved by intravenous infusion of glucagon, and may even be adversely affected. It is felt that the routine use of glucagon in hemorrhagic shock should be discontinued for the present and that specific criteria for its use be established.

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