Title: DOES INCREASED F_IO_2 ALTER NADH REDOX STATE AND PROTECT BRAIN CELLS FROM ICP CHANGES IN RABBITS?

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Introduction: Elevated intracranial pressure (ICP) is an important pathophysiologic feature of head injury, post-ischemic reperfusion, and a variety of disease states including cerebral edema, infection, and hemorrhage. Reduced blood flow to the brain and brain stem and imbalance between oxygen supply and demand are viewed as key mechanisms of injury from elevated intracranial pressure. Despite the importance of these mechanisms, there is little information on the relationship of intracranial pressure to brain tissue oxygenation. Therefore, we designed this study to examine the effect of progressive changes in ICP on cerebrocortical oxygenation and cerebral blood volume, and also to determine if increased inspired oxygen concentration protects brain cells against these intracranial pressure changes.

Methods: We continuously recorded systemic arterial pressure, central venous pressure (CVP) and ICP in 6 male rabbits, weighing 2.8-3.5 kg, who were anesthetized with urethane and paralyzed with pancuronium. Body temperature was maintained at 39°C by servocontrolled heat lamp. All animals were mechanically ventilated to maintain normocarbia. F_IO_2 was varied between 0.21 and 1.0. End-tidal gas samples were analyzed by mass spectrometer. The head was fixed in a stereostatic apparatus and two burr holes were drilled. The dura mater was left intact. ICP was measured from an epidural bolt and also from a 22 guage short lumbar puncture needle positioned in the cisterna magna. The 22 gauge needle was connected to a Y-connector to allow injection of artificial cerebrospinal fluid to increase ICP. The ICP bolt was sealed around the burr hole to avoid any pressure leak. Cerebrocortical NADH fluorescence and ultraviolet reflectance were measured by a microfluoreflectometer;[1,2] the NAD/NADH redox state and relative cerebrocortical blood volume were determined from these measurements. NADH fluoresence measurement in vivo is based on the fact that only the reduced nicotine-amide-adenoside dinucleotide fluoresces when it is illuminated at 366 nm; therefore, oxygen decreases fluorescence because it oxidizes NADH. Fluorescence during 100% O_2 and normocarbia was used to determine the baseline (NADH); then any change in fluorescence represented change in relative (NADH). Cerebrocortical oxygenation was estimated by the measured change in relative (NADH). Relative vascular volume (i.e. capillary blood volume) was estimated by the measured change in reflected light (the sum of reflected and scattered light) at 366 nm. The data was analyzed by multiple analysis of variance and a $p < 0.05$ was considered statistically significant.

Results: In all 6 animals, (NADH) increased when ICP was greater than 18 ± 2.2 cmH_2O. Above this threshold, the change in (NADH) was inversely proportional to the change in F_IO_2 over a range from 0.21 to 0.5 ($p < 0.05$). However, raising the F_IO_2 above 0.5 gave little additional benefit in cerebrocortical oxygenation (i.e. cerebrocortical oxygenation at F_IO_2 of 1.0 was not statistically better than at 0.5) (Figure 1). Capillary blood volume, which is proportionate to cerebrocortical blood volume, increased as ICP increased until the ICP exceeded 30 ± 1.8 cmH_2O, and then capillary blood volume decreased. This suggests that either the pressure applied by the tip of the fluorometry probe was great enough to mechanically decrease capillary blood flow at the highest ICP pressures, or the obstruction to blood flow produced by increased ICP was not only applied to the venous circulation, but also to the arterial supply.

Discussion: These results indicate that high ICP definitely decreases cellular oxygen supply. Moreover, another indication of this decrease in cellular oxygenation is the measured increase in cerebrocortical blood volume; this increase in blood volume is acutely determined by an increase in cerebrocortical blood flow in response to hypoxia. Others have shown that this increase in cerebrocortical blood flow produces improved cellular oxygenation and that this is a cellular defense mechanism. In summary, we have shown that with elevated ICP: (1) increased oxygenation of blood gives greater cellular protection against changes in ICP, and (2) little additional benefit to cerebrocortical oxygenation is achieved by increasing F_IO_2 above 0.5. This should be an important consideration in neurological intensive care units where it has been common practice to increase the F_IO_2 to any patient with high ICP even though pulmonary oxygen toxicity may result. Our data supports that giving an $F_IO_2 > 0.5$ will not improve cerebrocortical oxygenation and may, in fact, damage the lungs.

References:
1. Chance B, Cohen P, Jobsis FF, Shoener B. Intracellular oxidation-reduction states in vivo. Science 137:499-508, 1962
2. Jobsis FF, O'Connor MJ, Vitale A, Vreman H. Intracellular redox changes in functioning cerebral cortex. J Neurophysiol 34:735-749, 1971

FIGURE 1