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*To Dream the Impossible Dream**

DEVELOPMENT OF A MEANS of protecting the central nervous system from the ravages of hypoxia has long been the dream of many investigators. A major approach has been the use of deliberate hypothermia to modify chemical events accompanying cerebral oxygen deprivation. In recent years, a number of authors have demonstrated that temperatures of 32,[1,2] 30,[3,4] and 27° C[1,5] diminish the rate of adenosine triphosphate (ATP) utilization as well as the extent of anaerobic metabolism. Since hypothermia is not without risk, it is only natural that workers in this field might attempt to ascertain the least amount of temperature decrease required to effect these beneficial changes in metabolism. In this issue of ANESTHESIOLOGY Berntman, Welsh, and Harp[6] present data suggesting that lowering temperature by as little as one degree might be clinically useful. In normothermic rats with a unilateral carotid ligation, an arterial oxygen tension of 22 torr for 20 min resulted in a 50 per cent decrement in brain ATP concentration in the ipsilateral side. Phosphocreatine (PCr) decreased to 36 per cent of normal and lactate concentration was increased over 7-fold. Lowering body temperature one degree totally prevented the fall in ATP concentration; PCr was reduced to only 58 per cent of control while the increase in lactate was almost halved. Further chemical protection was observed at a temperature of 34° C. These data suggest that significant benefit might be conferred by a change in temperature which should have no adverse physiological consequences.

If oxygen consumption (and presumably ATP utilization) is decreased by only 5 per cent for each degree of hypothermia,[7] how might this extremely small change in temperature produce an almost complete reversal of the effects of hypoxia on brain metabolites? In order to answer this question, it is necessary to consider the rate of change in these energy stores as well as their absolute concentration. During the early minutes of steady-state hypoxia, the increase in lactate and the decreases in ATP and PCr concentrations are linear.[4,8,9] We can therefore use the values in the normoxic animals to calculate the rate of change of the relevant metabolites. Normothermic animals were hypoxic for 20 min during which time ATP concentration decreased by 1.2 μmol/g (0.06 μmol $\cdot$ $g^{-1} \cdot min^{-1}$). Similarly, the rate of change of PCr was 0.11 $\mu mol \cdot g^{-1} \cdot min^{-1}$. This implies that the total change in the high energy phosphate pool was 0.17 $\mu mol \cdot g^{-1} \cdot min^{-1}$. However, this figure does not take into account the significant amount of ATP produced by anaerobic metabolism. The rate of lactate increase was 1.11 $\mu mol \cdot g^{-1} \cdot min^{-1}$. Since anaerobic metabolism of glucose produces an equal amount of ATP and lactate,[10] a change of one mole of lactate would theoretically accompany the production of one mole of ATP. Thus, had anaerobic metabolism been blocked, the decrease in the energy pool produced by hypoxia would have been 1.28 $\mu mol \cdot g^{-1} \cdot min^{-1}$. Put another way, the rate of cerebral oxidative production of ATP + PCr was 1.28 $\mu mol \cdot g^{-1} \cdot min^{-1}$ less than the rate of their utilization. For the purpose of this editorial, I will use the term "flux" to designate the difference between aerobic production and overall utilization of these two high energy phosphate compounds. This concept allows evaluation of interventions aimed at ameliorating the effects of hypoxia. The value for energy flux at a temperature of 36° C may be calculated as above and is 0.70 $\mu mol \cdot g^{-1} \cdot min^{-1}$ (55 per cent of that observed during normothermia). The value at 34° C is 0.40 $\mu mol \cdot g^{-1} \cdot min^{-1}$ or 31 per cent of control. Thus, although a minute decrease in temperature appears totally to abolish the effect of hypoxia on ATP concentration, the effect on energy flux is considerably less. Nonetheless, the definitive effect of small changes in temperature must be explained.

Let us first consider data obtained at 34° C since these animals are closest to control in arterial pressure and acid base status. The expected hypothermia-induced de-

* Darion J, Leigh M, Wasserman D: The Man of La Mancha.
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crease in oxygen consumption of 15 per cent[7] must be contrasted with the greater decrease in flux which was observed. However, since the latter is a measure of the interaction of energy consumption and production, this disparity may not be unreasonable. In addition to decreasing metabolic needs, hypothermia has also been postulated to have an effect on oxygen transport.[1,5] This is produced by a leftward shift in the hemoglobin dissociation curve resulting in increased oxygen content of the hypoxic blood. A further augmentation of oxygen content results from increased plasma oxygen solubility in the hypothermic animals. Consistent with this hypothesis is the finding by Berntman *et al.*[6] of a 22 per cent increase in oxygen content at 34°C compared with hypoxic animals at 37° C. However, the importance of this is minimized both by these authors and Keykhah *et al.*[2] The latter group showed that while the shift in hemoglobin dissociation curve produced by bicarbonate administration increased oxygen content, it did not have as marked an effect on energy stores as did an equal increase in arterial content produced by hypothermia alone. Their argument is not entirely satisfactory for several reasons. Metabolic[11] and respiratory[12,13] alkalosis are known to increase the rate of oxygen utilization. Thus, hypoxia and alkalosis might have interacted to produce a greater effect on the production/utilization ratio than hypoxia alone. Again, calculation of flux may provide an insight that the raw data alone cannot. In normothermic hypoxic animals, doubling of arterial oxygen content by alkalosis resulted in a flux two-thirds that of the normothermic hypoxic controls.[2] While lowered energy utilization accompanying hypothermia produced a significant additional decrease in flux, the importance of augmented oxygen supply cannot be overlooked completely.

Values for cerebral metabolities during hypothermic hypoxia are similar to those found in other studies.[1,2] There are, however, interesting differences when the data are closely compared. In normothermic animals, brain content of ATP + PCr was 4.93 μmol/g after 25 min of hypoxia (Pa_{O_2} 25.7 torr).[1] When temperature was lowered to 31.3° C during hypoxia, their concentration was increased 1.6-fold to 7.83 μmol/g. In contrast, Berntman, *et al.*[6] demonstrated a greater than twofold augmentation in these metabolites during somewhat greater hypoxia at a higher temperature (34° C). It is not clear why less hypothermia confers more "protection." It is of additional interest that the values of ATP observed by Berntman *et al.*[6] during normoxia are identical to those determined in hypoxic normothermic animals by another group.[1] Although these discrepancies are tantalizing, the present data were all obtained in the same laboratory, and at the same time, and therefore this should not pose a major problem.

What, now, may be said concerning the effects of a one degree change in temperature? While the concept of protection by such a small alteration is exciting, far more investigation must be done. The data are complicated by important physiologic changes observed during hypoxia at 36° C and 37° C but not 34° C. Normothermic hypoxic animals had a significant decrease in blood pressure as did those at a temperature of 36° C. Perhaps most important is the greater degree of acidosis in the normothermic hypoxic animals. Equilibrium considerations[10] require that as tissue acidosis increases, there is a concomitant increase in the lactate/pyruvate ratio. This would suggest that not all of the increased lactate accumulation is necessarily associated with ATP production. Although tissue *p*H was not measured, it is likely that tissue acidosis was greatest in the normothermic hypoxic animals. As a result, the flux in this group may have been overestimated compared with the less acidotic 36° C animals. This might then serve at least as a partial explanation of the remarkable effect on flux of this small temperature change. In any case, it is apparent that additional studies with firm control of all variables are necessary if the hypothesis that minute changes in temperature can have major metabolic effects is to be substantiated.

Finally, what is the relationship of the demonstrated metabolic changes to neurological function in humans? Conservation of the brain's energy pool does not necessarily result in functional recovery of an intact animal. Drewes and Gilboe[14] have documented the return of the adenylate energy charge after 10 min of complete normothermic ischemia. This was not observed with a 30-min ischemic duration. Mršulja *et al.*[15] observed restoration of ATP and PCr after as long as 60 min of normothermic ischemia. Although concentrations of these important metabolites were normalized, this degree of hypoxic insult would be irreparable in humans. The return to normal of evoked potential and EEG has been observed in cats and monkeys following one hour of ischemia.[16,17] A close relationship of the time course of electrical and chemical events could not be determined; however, EEG activity was not observed when ATP concentration was less than 0.8 μmol/g.[17] In none of the animals, was normal clinical neurological function demonstrated. Although examination of energy stores is of great importance, it is not the only parameter which should be scrutinized. The effect of ischemia on the microcirculation is well known.[18] Although the total brain concentration of ATP + PCr may remain normal following ischemia, extremely important functional areas may be lost. Finally, not all oxygen consumption is mandated for the synthesis of ATP. It has been estimated that as much as 20 per cent of basal oxygen consumption is non-mitochondrial, perhaps involving synthesis of es-

sential neurotransmitters.[19] For that reason, severe impairment of neurological function might occur in the presence of a normal energy pool.

The quest for protection from hypoxia of the central nervous system will continue. the authors have raised a number of significant questions and are to be complimented for the meticulous development and presentation of some fascinating data.

PETER J. COHEN, M.D.
Professor and Chairman
Department of Anesthesiology
University of Michigan Medical School
Ann Arbor, Michigan 48109

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Analgesia, Anesthesia and Chest Wall Motion

CHANGES in chest wall (diaphragm, thoracic plus abdominal wall) shape and motion under the influence of analgetics, anesthetics, or positive airway pressure during muscular paralysis are of interest both to the practicing anesthesiologist, who can use them in staging the depth of anesthesia[1] and to the pysiologist,[2] who can use them as a tool. In this issue of ANESTHESIOLOGY appears a stimulating report[3] documenting a reduction in tidal volume and respiratory frequency during CO_2 rebreathing after morphine administration in humans, and also demonstrating reduction in the tidal volume contribution from rib cage motion at equivalent end-tidal CO_2 concentrations, comparing the sedated to the unsedated state. When the tidal volume contributions from rib cage or diaphragm were plotted as a function of the tidal volume rather than of carbon dioxide tension, no effect of morphine could be detected comparing the sedated and unsedated states. Since the effects of halothane[4] on the rib cage appear similar, the authors suggested that both morphine and halothane act by exerting a direct action on respiratory neurones in the medulla. This conclusion implies a model of the respiratory control mechanisms in which a central pattern generator in the brainstem drives the diaphragm and intercostal/accessory muscles in set patterns which vary as tidal volume changes, in response to change in chemical stimulus. Analgetic and anesthetic agents then act by decreasing the gain of the central pattern generator in response to a given change in the chemical stimulus without altering the set pattern for a given tidal volume. This attractively simple unifying hypothesis requires careful examination. Examination of the receptor sites for endogenous or exogenous opiates in the central nervous system[5,6] and observations of the actions of opiate antagonists on the H-reflex at spinal

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