Editorial Views

Cerebral Metabolic Rate in Hypercarbia —A Controversy

IN THIS ISSUE of the Journal, Artru and Michenfelder[1] report results of experiments designed to study the influence of hypercarbia on metabolic rate and blood flow in the brain. The background of this work can be summarized as follows. Since Kety and Schmidt[2] devised the inert gas technique for measuring cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}), several groups have studied how hypercarbia affects these variables, using the original nitrous oxide technique, modifications thereof, or techniques that have been validated against it. Until quite recently, it was generally accepted that hypercarbia increases CBF but leaves CMR_{O_2} unchanged. Two conflicting studies have now been published. Berntman et al.,[3] using rats receiving N_2O, 70 per cent, and using a modification of the Kety-Schmidt procedure designed to facilitate measurements of very high flow rates, reported that hypercarbia (Pa_{CO_2} about 80 torr) *increased* CMR_{O_2} by about 25 per cent. They further found that if the animals were pretreated with propranolol or given sedative or anesthetic doses of diazepam, CMR_{O_2} *decreased* during hypercarbia. In experiments on phencyclidine-anesthetized baboons, Kliefoth et al.[4] found that hypercarbia (Pa_{CO_2} about 70 torr) decreased CMR_{O_2} by 30 per cent. These authors used the ^{15}O technique described by Ter-Pogossian et al.,[5] which does not require measurement of arteriovenous oxygen content difference [$C(a-v)_{O_2}$].

Artru and Michenfelder[1] worked on dogs maintained on N_2O, 70 per cent, and halothane, <0.1 per cent, and increased the Pa_{CO_2} to either 80 or 100 torr. Cerebral blood flow was estimated both directly, by timed collections from a catheter in the superior sagittal sinus, and indirectly, from the clearance of

^{133}Xe injected into the lingual artery. Clearance was measured by an external collimated detector and CBF was calculated both by the half-peak time ($T_{1/2}$) method described by Waltz et al.[6] and by the initial slope technique.[7] The authors found a good correspondence between CBF values obtained with the direct and indirect techniques provided "indirect CBF" was derived with the $T_{1/2}$ method. Derivation of CMR_{O_2} from CBF and $C(a-v)_{O_2}$ showed no change at Pa_{CO_2} 80 torr but a 10 per cent decrease at Pa_{CO_2} 100 torr. The authors conclude that their values agree with those showing no change in CMR_{O_2} during hypercarbia, or a decrease.[4] In support of this conclusion they quote results of Des Rosiers et al.,[8] who reported that hypercarbia decreases CMR_{O_2} and glucose utilization (CMR_{gl}) equally in rats, and Kogure et al.,[9] who found that hypercarbia in the same species decreased high-energy phosphate (~P) utilization in the brain following decapitation by about 15 per cent. Accordingly, Artru and Michenfelder[1] conclude that the only major discrepancy is with the study of Berntman et al.[3] They consider the possibility that the results obtained by Berntman et al. reflect either the difficulty of accurately deriving CMR_{O_2} at the excessively high flow rates encountered in hypercarbic rats or a peculiar response to hypercarbia in that species.

It is the purpose of this editorial to put the question under debate, *i.e.*, the effect of hypercarbia on cerebral metabolic rate, into a somewhat broader perspective, and to attempt a critical evaluation of results presented in the medical literature.

Hypercarbia and Brain Function

Hypercarbia profoundly affects integrated brain function and various neurophysiologic events.[10-13] Many of these effects mimic those elicited by depressant drugs. For example, moderate hypercarbia

increases the threshold for electrically or chemically induced seizures, and more severe hypercarbia induces anesthesia. In the rat, anesthesia is observed when inspired CO_2 concentrations exceed about 40 per cent ($Pa_{O_2} \approx 300$ torr).[10] In the dog, CO_2 has no narcotic effect until Pa_{CO_2} values of about 250 torr are reached.[14]

Probably, many of the effects discussed reflect neurophysiologic inhibition at the cerebral cortical level, with hyperpolarization of neurons. However, it must be emphasized that evidence of excitation also exists. Outside the central nervous system signs of sympathoadrenal activation are often conspicuous,[15] and hypercarbia is known to release catecholamines from the adrenals.[16] In the brain, the rates of synthesis of catecholamines and of serotonin are increased during hypercarbia.[17] One interpretation of these results is that hypercarbia enhances activity in noradrenergic and in 5-hydroxytryptamine (5-HT) neurons, and depresses dopaminergic impulse traffic.[18] Moderate hypercarbia stimulates the brainstem reticular activating system, and the overall functional effect may be cortical arousal, with a high-frequency, low-amplitude EEG pattern. Furthermore, rats exposed to CO_2, 30 per cent, are subject to spontaneous seizures.[19]

Clearly, hypercarbia induces a complex pattern of inhibition and excitation. It is conceivable, if not likely, that the balance between inhibition and excitation is influenced by experimental conditions, e.g., by the anesthetic used. In view of the results discussed, it appears difficult to predict the cerebral metabolic effects of hypercarbia, except when it is of sufficient severity to induce stupor or unconsciousness. Even then, predictions will be nothing more than guesses, since the relevant medical literature gives evidence of anesthetic drugs that induce unconsciousness without lowering cerebral metabolic rate. To my knowledge, though, this literature gives no evidence that metabolic rate can be appreciably lowered in the absence of gross signs of reduced consciousness. It is, therefore, somewhat difficult to accept without reservation the results of Kliefoth et al.[4]

Hypercarbia and Cerebral Metabolic State

Kliefoth et al.[4] discuss the 30 per cent decrease in CMR_{O_2} during hypercarbia as reflecting a "toxic" effect of CO_2 on cerebral metabolism. Such a conclusion receives no support from studies demonstrating unchanged tissue concentrations of ATP, ADP and AMP in animals exposed to CO_2 concentrations as high as 40–50 per cent.[19–22]

Although hypercarbia does not perturb the energy balance in the brain, it profoundly affects tissue concentrations of glycolytic metabolites, citric acid cycle intermediates, and some associated amino acids.[20–23] In summary, these changes involve accumulation of glucose, glucose-6-phosphate, and fructose-6-phosphate, and decreases in the concentrations of fructose-1,6-diphosphate and "downstream" glycolytic metabolites, as well as most citric acid intermediates. Changes in amino acids are dominated by an increased aspartate/glutamate ratio, but experiments with very high CO_2 concentrations reveal an increase in ammonia concentration as well, and a decrease in the size of the pool of free amino acids. In many respects, this pattern of changes resembles that observed in insulin-induced hypoglycemia.

Cerebral Glucose Utilization in Hypercarbia

In order to appreciate the meaning of the perturbation in concentrations of carbohydrate intermediates and amino acids in hypercarbia, we must consider glucose utilization (CMR_{gl}). In the nonketonic man or experimental animal overall metabolism in the brain is approximated by the equation

$$Glucose + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O \qquad (1)$$

The equation expresses the fact that the oxidation of 1 mole of glucose requires 6 moles of O_2. Normally, glucose consumption is in slight excess of oxygen utilization, mainly because there is some "spillover" of lactate from tissue to blood. In order to quantitate this fraction, Cohen et al.[24] derived the oxygen/glucose index (OGI)

$$OGI = \frac{C(a\text{-}v)O_2}{6 \cdot C(a\text{-}v)_{gl}} \cdot 100 \qquad (2)$$

Obviously, when the OGI is close to 100 per cent we can assume that all glucose extracted is oxidized to CO_2 and water, and the rate of cerebral "energy flux" can be estimated by measuring either CMR_{O_2} or CMR_{gl}.

In their studies of metabolic and circulatory effects of halothane anesthesia in man, Cohen et al.[24] found that the OGI varied directly with Pa_{CO_2}. Thus, their results obtained in studies of hypercarbia suggested that oxygen consumption was greater than could be accounted for in terms of glucose extraction. The explanation for this finding came when two groups independently deduced that hypercarbia inhibits glycolysis at the phosphofructokinase step, necessitating mobilization of substrate ("carbon skeletons") from endogenous carbohydrate and amino acid stores. The conclusion was corroborated by direct measurements of

CMR_{gl} with a kinetic ^{14}C-glucose technique.[25,26] The results showed that hypercarbia is accompanied by a decrease in CMR_{gl}, which, at least during the first few minutes, may decrease to a third of control. A corresponding decrease in CMR_{O_2} was not observed, and the mismatch between CMR_{gl} and CMR_{O_2} is illustrated by the results reported by Miller et al.,[25] who found an increase in the OGI from 0.9 to 1.9 in rats exposed to CO_2, 20 per cent, for 5 min. It is, therefore, difficult to explain the results of Des Rosiers et al.,[8] who found stoichiometrically similar decreases in CMR_{gl} and CMR_{O_2} in rats during hypercarbia.

CBF–CMR_{O_2} in Hypercarbia: Effect of Drugs

Artru and Michenfelder[1] remark that if the results of Berntman et al.[3] are to be accepted as reported, there must be major species differences between the rat and other animals. Clearly, species differences do exist, and a mere inspection of CBF values obtained in monkeys, dogs, and rats emphasizes the point. However, it is probably a mistake not to consider also the large variations obtained in the same species under different experimental conditions. In order to illustrate this variation, we can compare absolute CBF values recently measured at Pa_{CO_2} values of 70–80 torr in ventilated rats under the following conditions: 1) N_2O, 70 per cent, infusion of isoproterenol, iv, at a dose of 2 $\mu g/kg/min$; 2) N_2O, 70 per cent, "control"; 3) N_2O, 70 per cent, with prior injection of propranolol, 2.5 mg/kg, iv; 4) diazepam, 2.25 mg/kg, iv; 5) N_2O, 70 per cent, with prior injection of indomethacin, 10 mg/kg, iv.[3,27,28] In none of the groups 1, 3, 4 and 5 did CMR_{O_2} deviate from "control" (group 2) before hypercarbia was induced. During hypercarbia, the mean CBF values, measured with the modified Kety-Schmidt technique, were 8.1, 6.8, 3.9, 2.0, and 1.3 ml/g/min, respectively.

The dramatic changes induced in the circulatory response to hypercarbia by drugs that probably mainly influence either catecholamine or prostaglandin metabolism raise the question whether anesthetic drugs also modulate the metabolic response to hypercarbia. As already mentioned, the results of Berntman et al.[3] demonstrate that this is so. To take one example, if the experiments had been performed only on animals given diazepam as an "anesthetic," the inescapable conclusion would have been that hypercarbia decreases CMR_{O_2}. At present, we do not know why diazepam or propranolol transforms an increase in CMR_{O_2} during hypercarbia into a decrease, neither do we know why diazepam and propranolol decrease both CBF and CMR_{O_2}[3] while indomethacin dramati-

cally reduces CBF without affecting CMR_{O_2}.[27] Whatever the underlying mechanisms are, it seems unwarranted to omit a discussion of anesthetic conditions when results obtained in hypercarbia are debated.

Cerebral Metabolic Rate in Hypercarbia

Artru and Michenfelder[1] give a clear account of the discrepant results of studies of cerebral metabolic rates in hypercarbia, but they do not discuss all relevant data. The following is an attempt to review the major studies published.

I agree with Artru and Michenfelder[1] and with Kliefoth et al.[4] that results in man are inconclusive, mostly because the hypercarbia was so moderate that any change from the normal may have escaped detection. The results obtained by Alberti et al.,[29] who increased Pa_{CO_2} to 65 torr and measured CBF with the Kety-Schmidt technique in the dog, agree with those of Artru and Michenfelder (Pa_{CO_2} 80 torr), i.e., they show no change in CMR_{O_2}. It should be mentioned, though, that the dogs studied by Alberti et al.[29] were given pentobarbital and maintained on halothane, 1 per cent.

Artru and Michenfelder accept the 30 per cent decrease in CMR_{O_2} obtained by Kliefoth et al.[4] in phencyclidine-anesthetized monkeys, but they do not mention the results of Pickard and MacKenzie,[30] who estimated CBF in phencyclidine–N_2O-anesthetized baboons from ^{133}Xe clearance (height over area analyses) and calculated CMR_{O_2} from CBF and $C(a-v)_{O_2}$ (superior sagittal sinus). These authors remarked that hypercarbia produced an increase in CMR_{O_2} of 15 per cent, but that the change was not significant. There is clearly a large difference in results (+15 versus −29 per cent) obtained in primates.

Results obtained in rats are controversial. In our previous studies, which showed no change in CMR_{O_2} during hypercarbia, the CBF technique was probably not sensitive enough to detect a moderate change in CMR_{O_2} (see Berntman et al.[3]). Artru and Michenfelder[1] quote the results of Kogure et al.[9] and Des Rosiers et al.,[8] which suggest a decrease in cerebral energy flux during hypercarbia. They do not mention two other studies that give different results. In one (Miller et al.[22]), the authors deduced CBF from CMR_{gl} and $C(a-v)_{gl}$, and CMR_{O_2} from CBF and $C(a-v)_{O_2}$, and concluded that hypercarbia increases CMR_{O_2} (normocarbic and hypercarbic values were 3.5 and 4.7 $\mu mol/g/min$, respectively). Admittedly, this is a rather indirect way of estimating CMR_{O_2}. However, Hemmingsen et al.[31] calculated CBF from the initial slope of ^{133}Xe clearance and CMR_{O_2} from CBF and $C(a-v)_{O_2}$. The results showed that hypercarbia significantly in-

creased CMR_{O_2}, *i.e.*, they confirmed those reported by Berntman *et al.*[3] There are, thus, three studies in the rat suggesting that CMR_{O_2} increases during hypercarbia, and two showing the opposite. Of the latter, one (Des Rosiers *et al.*[8]) has been reported in abstract form only. The results of the other (Kogure *et al.*[9]) are based on a technique for assessing cerebral metabolic rate whose general validity is not known. Lowry's "closed-system" technique is based on the assumption that, following decapitation and the rapid consumption of oxygen dissolved in the tissue (or bound in blood available for O_2 transport), the preischemic metabolic flux is reflected in the expenditure of existing high-energy phosphate compounds, and of ATP formed anaerobically. One of the problems with the technique is that with ischemic periods as short as 10 sec the oxygen content of the tissue is not negligible.[32] In hypercarbia, this content is appreciably increased and a decrease in $\sim$P utilization could reflect merely a delay in the exhaustion of available oxygen stores.

Why These Discrepant Results?

Quite naturally, anyone confronted with these divergent reports must inquire into the reasons. Possibly some of the major differences in results are due to the anesthetics used, and one cannot exclude species differences. However, it seems necessary to scrutinize the CBF/CMR_{O_2} techniques used. The ideal technique for measuring CBF has not yet been devised. Since the inert-gas technique of Kety and Schmidt[2] is based on the law of conservation of matter, and since it involves few simplifying assumptions, it has remained the method of reference. However, the method gives correct values only if one can exclude the presence of very slowly perfused tissue masses, of extracerebral contamination, and of arteriovenous shunts. The first two of these potential errors are most likely to present problems at low flow rates, and a bias may be introduced when the method is used for comparisons of CMR_{O_2} values obtained at high and low flow rates.

Calculations of CBF from the clearance rates of intraarterially injected radioactive tracers conform to the law of conservation of matter only when stochastic (height over area) analyses are performed.[33,34] Derivation of CBF by the initial slope or $T_{1/2}$ procedures is practically useful, but the quantitative significance of values obtained is doubtful, and when they are used to calculate CMR_{O_2} one must introduce the further assumption that the CBF values derived reflect flow in areas delivering blood to the site of sampling of venous blood.

The direct CBF technique used by Artru and Michenfelder[1] has previously been validated against the Kety and Schmidt technique.[35] The validity of the technique rests on the assumption that venous outflow occurs from a constant mass of tissue. To test this assumption for a hypercarbic situation, the authors compared the direct CBF values with those calculated from ^{133}Xe clearance, using either the $T_{1/2}$ or the initial slope procedure. With the former, agreement was excellent in normo- and hypercarbia. With the latter, agreement was good in hypercarbia but not in normocarbia. If one accepts the $T_{1/2}$ values (and the direct CBF), the results show that hypercarbia (Pa_{CO_2} 80 torr) does not change CMR_{O_2}. However, if the initial slope values were correct, the results would have shown an increase in CMR_{O_2} during hypercarbia. Unfortunately, there is no information available to suggest whether the $T_{1/2}$ or the initial slope values truly reflect changes in flow rates in structures draining their blood into the sinus.

Concluding Remarks

Since hypercarbia is a common pathophysiologic condition, its effects on cerebral metabolism and blood flow are of obvious concern to many scientists and clinicians, anesthesiologists included. It is disconcerting that 30 years after the first quantitative report,[36] we still do not know how hypercarbia affects cerebral metabolic rate. The meticulous study of Artru and Michenfelder[1] adds valuable information. In my opinion, though, it does not resolve the existing controversy. The study of Berntman *et al.*[3] suggests that, in the rat, CMR_{O_2} is increased at Pa_{CO_2} 80 torr, normal at 160 torr, and decreased at 240 torr. Artru and Michenfelder[1] report that, in the dog, CMR_{O_2} is unchanged at Pa_{CO_2} 80 torr, and decreased at 100 torr. If we confine ourselves to "moderate" hypercarbia (Pa_{CO_2} 60–80 torr), their results are in line with those of many others, but they seem contrary to those obtained in several studies in the rat suggesting an increase in CMR_{O_2} and other studies indicating that CMR_{O_2} is decreased. Perhaps future work will shed light on the discrepancies.

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