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Cerebral Blood Flow Autoregulation: Effect of Hypercapnia on Cerebral Tissue Gas Concentrations[1]

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In clinical medicine many conditions are encountered which adversely affect the oxygenation and perfusion of the cerebral cortex. Shock, sepsis, and posttraumatic pulmonary insufficiency or adult respiratory distress syndrome are frequently encountered complications of major surgical illness. Prolonged cerebral hypoxia may result in diffuse cerebral damage while other organ systems remain viable. Cerebral oxygen consumption remains relatively constant in conditions of arterial hypoxemia but cerebral utilization of glucose rises sharply. With hypoxia moderate changes in arterial pO_2 do not cause significant changes in cerebral blood flow; but more severe hypoxia results in increased blood flow.

Hypercapnia causes a profound increase in cerebral blood flow and markedly improves task performance of humans exposed to acute ambient hypoxia [3]. The latter phenomenon was demonstrated in eight volunteers exposed to mixtures of 6% carbon dioxide in nitrogen. In all eight subjects, breathing 6% oxygen resulted in marked confusion or loss of consciousness; however, when the mixture was changed to 6% oxygen, 5% carbon dioxide, and 89% nitrogen, all eight recovered normal intellectual function. Furthermore, subjects were able to tolerate 2% oxygen with 5% CO_2 [3].

Hypercapnia does not significantly change cerebral oxygen consumption [7]; but because cerebral blood flow is increased, the arterial–venous oxygen difference is reciprocally decreased. It seems logical, therefore, that hypercapnia increases both jugular venous and cerebral interstitial oxygen tensions and that this phenomenon may be important in the amelioration of the effects of hypoxia, perhaps by maintaining aerobic metabolism.

The purpose of this experiment was to observe cerebral oxygen and carbon dioxide tensions in hypercapnic but fully conscious rhesus monkeys during exposure to normal oxygen tensions (21%) and ambient hypoxia. Interstitial oxygen and carbon dioxide tension was monitored by a mass spectrometer using the Teflon diffusion catheter [1, 10]. A permanent cranial implant which allows use of the catheter in conscious monkeys has been described

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TABLE 1

CEREBRAL OXYGEN AND CARBON DIOXIDE TENSIONS (mm Hg) DURING SEQUENTIAL EXPOSURE TO AMBIENT GASES IN FOUR RHESUS MONKEYS

MONKEY		Air[a]	5% CO_2 in Air	Air[a]	12% O_2 Nitrogen	Air[a]	12% O_2 5% CO_2 in Nitrogen	Air[a]
1	pO_2	13	19	15	4	17	15	19
	pCO_2	52	54	50	44	48	50	49
2	pO_2	20	27	22	3	19	18	19
	pCO_2	43	49	42	43	42	47	44
3	pO_2	16	23	20	8	20	16	21
	pCO_2	54	58	51	43	50	55	53
4	pO_2	17	25	20	5	20	16	20
	pCO_2	48	51	47	43	47	49	47
MEAN	pO_2	16.5 ± 2.9	23.5 ± 3.4	19.2 ± 3.0	5.0 ± 2.2	19.0 ± 1.4	15.7 ± 0.5	19.7 ± 1.0
(± SD)	pCO_2	49.2 ± 4.9	53.0 ± 3.9	47.5 ± 4.0	43.2 ± 5.0	46.7 ± 3.4	50.2 ± 3.4	48.2 ± 3.8

[a] Air refers to rest period in compressed air.

[5] and has been used previously in this laboratory to study the response to ambient hypoxia [6].

MATERIALS AND METHODS

Six rhesus monkeys, *Macaca mulatta*, were surgically prepared with a chronic stainless steel implant in the parietal area of the skull as described elsewhere [5]. This implant rests extradurally and has a 2 mm opening to allow insertion of the Teflon catheter through the dura and into the cerebrum. The catheter is held firmly in place by means of an "O" ring in the implant.

Each monkey was anesthetized on the day of the experimental procedure with ketamine hydrochloride (Vetalar) 25 mg/kg intramuscularly. A Teflon coated catheter of a medical mass spectrometer was inserted through the surgical implant into the cerebrum to a depth of 3 cm after the dura was penetrated with an 18-gauge needle. The mass spectrometer was the Medspect MS8 manufactured by Scientific Research Instruments, Baltimore, Maryland. The Teflon catheters were previously calibrated in an agitated saline bath at 37°C. All readings were corrected for water vapor pressure at 37°C.

The monkey was then placed in a comfortable restraint chair and allowed a minimum of 3 hr for recovery of full consciousness. The restraint chair was equipped with a sealed Plexiglas helmet into which controlled ambient gases were introduced at a constant flow of 20–22 liter per min. Each monkey was exposed sequentially to 5% carbon dioxide in air, 12% oxygen in nitrogen, and 12% oxygen with 5% carbon dioxide in nitrogen. Each exposure was for about 15 min followed by a 15 min rest period on compressed air. This was sufficient to allow cerebral gas tensions to stabilize.

RESULTS

Table 1 lists the steady-state intracerebral gas tensions in four monkeys and includes mean values for each experimental condition. The control values obtained with compressed air are pO_2 16.5 mm Hg and pCO_2 49.2 mm Hg. Previous work in this laboratory, including 11 procedures on five animals, demonstrated control values of pO_2 13.5 ± 3.5 mm Hg and pCO_2 50.4 ± 7.9 mm Hg.

The simple addition of 5% carbon dioxide to compressed air resulted in an increase in cerebral pO_2 to 23.5 mm Hg and increase in pCO_2 to 53.0 mm Hg. With removal of the CO_2, there is a residual effect upon cerebral pO_2 which decreased only to 19.2 mm Hg.

The 12% oxygen in nitrogen resulted in a profound effect upon cerebral pO_2 which dropped to 5.0 mm Hg. Both this value and the decreased pCO_2 are again consistent with previous results [6]. The addition of 5% carbon dioxide to the 12% oxygen mixture results in a remarkable amelioration of the effect upon cerebral pO_2. Instead of decreasing to 5.0 mm Hg, the pO_2 remains at 15.7 mm Hg, very close to the original control value on air. The cerebral carbon dioxide value of 50.2 mm Hg is also close to control.

In two other monkeys arterial and venous blood gas determinations were obtained during both hypoxic stress and hypoxia with hypercarbia. These data show the development of arterial hypocarbia in the hypoxic state, while 5% CO_2 resulted in a maintenance of normal arterial pCO_2. While relative hypoxia was present in both experimental circumstances, the pO_2 was higher in animals breathing supplemental CO_2.

DISCUSSION

The cerebrovascular response to hypercapnia, hypocapnia, and hypoxia has been extensively investigated, but questions concerning mechanism of response persist [9]. Cerebrovascular resistance is exquisitely sensitive to changes in arterial pCO_2, and mathematical models using arterial pCO_2 to predict cerebral blood flow have been developed in the rhesus monkey as well as other species. An eightfold change in cerebral blood flow occurs as arterial pCO_2 increases from 15 to 150 mm Hg in anesthetized monkeys [11].

In previously reported data [6] in five animals exposed to varying concentrations of oxygen in nitrogen, the cerebral pO_2 and pCO_2 averaged 13.5 ± 3.5 mm Hg (pO_2) and 50.4 ± 7.9 mm Hg (pCO_2) while breathing compressed air. With exposure to decreasing ambient oxygen the cerebral pO_2 decreased to a pO_2 of 2.5 ± 2.7 mm Hg at an ambient oxygen concentration of 10.7%. Cerebral pO_2 is almost linearly related to arterial and ambient pO_2. Cerebral pCO_2 progressively fell with increasing hypoxia secondary to hyperventilation in the spontaneously breathing animal.

Moderate changes in arterial pO_2 do not cause significant changes in cerebral blood flow; but more severe hypoxia, with arterial pO_2 less than about 50 mm Hg, results in increased blood flow [4, 8, 13]. Since this is the level at which progressive cerebral tissue lactic acidosis is reported to occur, the controlling factor is probably not the tissue pO_2 but tissue pH [4].

Thus, both arterial pCO_2 and, at low levels, pO_2 are important factors in determination of cerebral blood flow and these two seem to be additive [12].

In our study, arterial pCO_2 was not controlled in the simple hypoxic state and fell due to hyperventilation. With simple hypoxia and no supplemental carbon dioxide, the cerebral pCO_2 fell from 47.5 mm Hg to 43.2 mm Hg. Breathing a mixture of 5% carbon dioxide and 12% oxygen in nitrogen resulted in a cerebral pCO_2 of 50.2 mm Hg.

The reported restoration of task performance and electrical activity in hypoxemia by carbon dioxide administration is probably due to the maintenance of a relatively normal cerebral tissue pO_2 [3]. During hypoxia, cerebral oxygen consumption is relatively constant, but carbohydrate metabolism is altered and production of lactic acid by the brain increases [2]. This indicates an increase in anaerobic metabolism which is a much less efficient means of oxidative phosphorylation, and this, in turn, may be responsible for cerebral dysfunction.

Restoration of near normal cerebral pO_2 by carbon dioxide inhalation is demonstrated in this study; and this phenomenon, as a means of preserving aerobic me-

tabolism and normal pH, may well account for the protective effect of carbon dioxide.

It seems likely that the preservation of near normal tissue oxygen tension is mediated by the increased cerebral blood flow and improved arterial pO_2 due primarily to hypercapnia. Increased blood flow allows for a decreased arterial–venous oxygen difference and presumably then, a decreased arterial–tissue oxygen difference as demonstrated in this experiment.

SUMMARY

Cerebral tissue oxygen and carbon dioxide tensions were monitored continuously in six rhesus monkeys using a Teflon coated catheter and a medical mass spectrometer. The monkeys were exposed to several ambient gas mixtures in a sealed helmet. Gases included air, 12% oxygen in nitrogen, and 12% oxygen with 5% carbon dioxide in nitrogen. Twelve percent oxygen in nitrogen resulted in a marked decrease in tissue pO_2 to 5.0 ± 2.2 mm Hg from a control of 16.5 ± 2.9. The addition of 5% carbon dioxide to the 12% oxygen provided almost complete amelioration of the decline in tissue pO_2 with a mean value of 15.7 $\pm$ 0.5 mm Hg.

CONCLUSIONS

These results are demonstrated in diffusely ischemic cerebral tissue secondary to arterial hypoxemia. Such states may occur with shock, hypotension, and pulmonary insufficiency. Focal cerebral ischemia due to cerebrovascular insufficiency is frequently not improved or actually exacerbated by increased arterial pCO_2. Further study is indicated to define clinical conditions in which supplemental CO_2 might improve cerebral oxygenation.

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