The Effect of Hyperventilation on Subsequent Cerebral Infarction

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To evaluate the effect of lowered Pa_{CO_2} on the size of subsequent cerebral infarction in the dog, the middle cerebral artery was occluded at its origin and the internal carotid artery occluded between the posterior communicating artery and the anterior cerebral artery. Following occlusion, Pa_{CO_2} was maintained at 38 mm. Hg for two hours in the control group (four animals), and kept at 25 mm. Hg for two hours in the experimental group (five animals). In the control (normocarbic) group all animals showed extensive cortical damage as well as infarction in the lenticular nuclei, internal capsule and thalamus. In the experimental (hypocarbic) group only 60 per cent developed infarction, this being limited to the cortical area only, with no deeper structures involved. The average area of infarct in the control group was 612 $mm.^2$, in contrast to 15 $mm.^2$ in the experimental group.

HYPERVENTILATION with resultant hypocarbia is used to reduce brain volume and to improve intracranial exposure for the neurosurgeon. This phenomenon is believed to result from a significant reduction of the cerebral blood volume directly related to the lowering of the tension of CO_2. Reduction in cerebral blood flow associated with hyperventilation in man [1-6] and in the dog [7-9] has been documented repeatedly.

Concern that the decrease in cerebral blood flow accompanying hyperventilation can produce cerebral hypoxia has been expressed.[10-12] Since several neurosurgical procedures may require occlusion of major components of the cerebral circulation (*e.g.*, aneurysm clipping, arteriovenous malformation resection), cerebral infarction might result. The combination of hyperventilation and the occlusion of a major cerebral vessel might be expected to increase the likelihood of cerebral infarction, and to result in a greater degree of infarction than occlusion of the vessel alone. This could present a problem to the neurosurgeon wishing to gain exposure and minimize infarction.

The present study measures the effect of lowered Pa_{CO_2} on the size of a subsequent experimental cerebral infarct. If significant ischemic cerebral hypoxia were produced by hyperventilation with hypocarbia, the area of infarct should be greater in a hypocarbic than in a normocarbic group.

Methodology

The experimental animals were divided into two groups: a control group (four animals) in which the internal carotid and the middle cerebral arteries were clipped while Pa_{CO_2} was maintained at 38 mm. Hg for two hours following occlusion; and an experimental group (five animals) in which the internal carotid and middle cerebral arteries were clipped while Pa_{CO_2} was maintained at 25 mm. Hg for two hours following occlusion utilizing hyperventilation.

Mongrel dogs weighing from 10 to 15 kg. were used. Anesthesia was induced with sodium pentobarbital, 25 mg./kg., injected intravenously. The tracheas were intubated with a cuffed endotracheal tube and the lungs ventilated with 100 per cent oxygen via a Bird Mark VIII respirator with a Q circle adapter.

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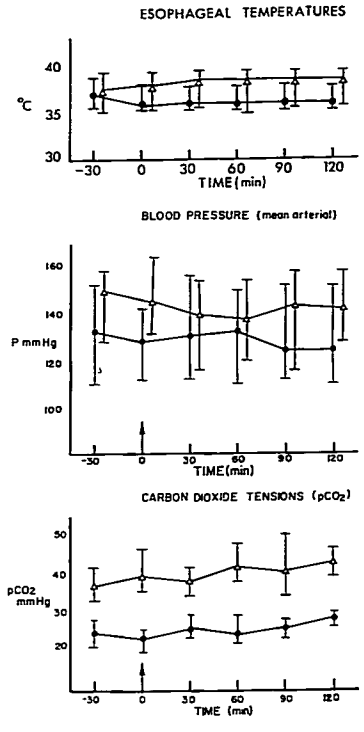

FIG. 1. Composite flowsheet of esophageal temperatures at 30-minute intervals preceding and following occlusion of the internal carotid and middle cerebral arteries, arterial carbon dioxide tension (P_{CO_2}) and mean arterial blood pressure. The moment of occlusion is indicated by the arrow at each abscissa at zero time. Open triangles indicate the normocarbic control group; solid circles indicate the hyperventilated experimental group. The bars at each reading indicate the range of values within the respective groups, as each triangle or circle represents the average value of the group.

A temperature probe was introduced into the midesophagus for continuous monitoring of body temperature. Blood pressure was monitored with a catheter introduced into a femoral artery connected to a strain gauge and a Grass polygraph.

SURGICAL TECHNIQUE

Using strict aseptic technique, a burr hole was made in the temporal bone and enlarged. The dura was then opened and reflected. The pyriform lobe was elevated and the internal carotid, middle cerebral, posterior communicating, and anterior cerebral arteries were identified. The internal carotid and middle cerberal arteries were clipped. The internal carotid artery was occluded between the posterior communicating artery and the anterior cerebral artery. The middle cerebral artery was clipped at its origin; 150 ml. of 5 per cent dextrose and water were injected intravenously during this procedure. Arterial blood was sampled anaerobically every 30 minutes in heparinized syringes. Pa_{CO_2} and *p*H were determined by the Astrup technique. The Bird respirator was adjusted to maintain Pa_{CO_2} at the desired level. In the experimental animals hyperventilation was initiated about 60 minutes before arterial clipping so that the desired Pa_{CO_2} would be assured when the clips were applied. O_2 saturation was measured with an A.O. oximeter.

POSTOPERATIVE CARE

Immediately after the operation the animals were placed on courses of treatment with penicillin, streptomycin, and chloromycetin. Until sacrifice, one week after surgery, the animals were provided with veterinary care and given daily neurologic examinations. At sacrifice they were given intravenous pentobarbital and exsanguinated. The brain was quickly removed, examined, and kept in 10 per cent formalin for two weeks.

EVALUATION OF LESION

Each brain was placed under a dissecting microscope to check the location and closure of the clips. The brains were then sectioned coronally in five-mm. slices in a specially-designed slicing apparatus. The slices were photographed, then traced on ruled graph paper. The delineation of the infarct was done by one of us (R. J. W.) who did not know whether the animal had been in the control or experimental group. The area of infarct was obtained by summing the infarcted areas of six consecutive slices. The difference between

the average areas of infarction of the control and hyperventilated groups was evaluated by Student's t test. The assumptions of the two-tailed test of significance were used.

Results

Pa_{CO_2}, blood pressure, and temperature values of the control and experimental groups are shown in figure 1. The groups differed in no important way except for the carbon dioxide tensions, which remained at the appropriate levels for two hours after occlusion. The desired Pa_{CO_2} was assured in the hypocarbic group by initiating hyperventilation approximately 60 minutes prior to arterial clipping. The desired Pa_{CO_2} was established 30 minutes prior to clipping in all animals (fig. 1). The mean Pa_{CO_2} of the hyperventilated animals was significantly different from that of the normocarbic controls at every time and at a confidence level of at least 0.001.

All body temperatures remained above 35° C. The differences in temperature between the normocarbic and hyperventilated groups were evaluated statistically and the mean temperatures from the two groups compared. The null hypothesis that the mean temperatures represented the same rather than two separate samples could not be rejected at the 0.10 confidence level at any time.

TABLE 1. Differences in Areas of Infarction in the Control (Normocarbic) and Experimental (Hyperventilated) Groups

Location	Control (per cent)	Hyperventilated (per cent)
Cortex	100	60
Lenticular nuclei	100	0
Internal capsule	100	0
Thalamus	100	0
Amygdala	50	0
Caudate nucleus	50	0

All animals had mean arterial blood pressures greater than 100 mm. Hg throughout the operation. O_2 saturation was always between 98.5 and 100 per cent, with no significant or systematic difference between control and hyperventilated animals.

Average initial pH values of control and hyperventilated animals were 7.36 and 7.34, respectively. At the time of occlusion the average pH of control was 7.35; that of hyperventilated animals, 7.44. At termination of blood gas monitoring two hours after occlu-

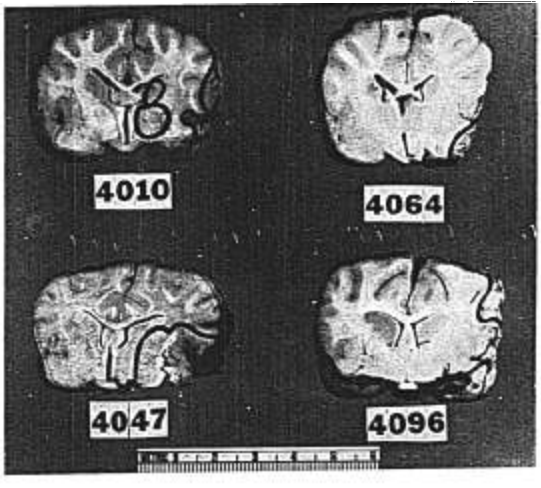

FIG. 2. Direct photographic comparison of representative sections from control (left) and hyperventilated (right) brains. Areas of infarction are outlined in black ink, showing that in the hyperventilated animals only cortical damage resulted, whereas extensive involvement of deep structures is the rule in the normocarbic animals.

sion, the *p*H of controls was 7.37; that of hyperventilated animals 7.48.

Table 1 lists the sites and incidences of infarction in the control and hyperventilated groups. It is apparent that cerebral infarction in the normocarbic group not only occurred more often but was more extensive. Only 60 per cent of the hyperventilated animals had any cortical infarction, 40 per cent entirely escaping damage. None of the hyperventilated animals had infarcts involving the deep structures.

Representative sections from control and hyperventilated brains are shown in figure 2. There was only cortical damage in hyperventilated animals, whereas extensive involvement of deep structures was the rule in normocarbic animals.

In comparing the sizes of infarctions, a clear difference was demonstrated between control and hyperventilated animals. The average area of infarction in the normocarbic group was 612 sq. mm., with a standard deviation of 563 sq. mm. The average area of infarction in the hyperventilated animals was 15 sq. mm., with a standard deviation of 21.6 sq. mm. The difference between the means was significant at the 0.02 confidence level.

Neurologic findings paralleled the differences in pathologic data. All hyperventilated dogs walked on the first postoperative day, whereas no controls walked until the third postoperative day. All hyperventilated dogs had rear-limb placing on the first postoperative day; 60 per cent had forelimb placing at this time, the others regaining it by the third postoperative day. Only one control animal regained placing, on the third postoperative day.

Discussion

We have produced cerebral infarction under optimal surgical and anesthetic conditions, in an attempt to simulate the conditions of a neurosurgical operation. Our purpose was to determine whether cerebral ischemic hypoxia was produced by the decrease in cerebral blood flow caused by hyperventilation.

The control and experimental groups were identical in all parameters (blood pressure, temperature, O_2 saturation, operating time, and postoperative care) except Pa_{CO_2} and *p*H. It should be noted that mean temperatures in the hyperventilated group were slightly lower than those in the control group. No temperature was lower than 35° C. Although at these temperatures there is a small reduction in cerebral oxygen consumption,[15] we do not believe that the difference in average temperatures of the two groups accounts for the large difference in extent of cerebral infarction. In addition, the animal with the lowest temperature during the two-hour postocclusion period was in the control group. The area of infarction was substantially smaller in the hyperventilated animals (15 sq. mm.) than in the normocarbic animals (612 sq. mm.), suggesting an apparent protective effect of hyperventilation under these circumstances.

Ever since establishment that hyperventilation reduces cerebral blood flow, controversy has existed as to whether cerebral ischemic hypoxia is produced. The present study tends to support the investigators who have maintained that cerebral ischemic hypoxia does not result from hyperventilation. Kety and Schmidt found that the cerebral metabolic rate of oxygen (CMR_{O_2}) was not altered during passive hyperventilation to a P_{CO_2} of 23 mm. Hg.[6] Other investigators[1-3] also demonstrated that in man there was no change in the CMR_{O_2} with hyperventilation. Alexander *et al.*[15] found that below a Pa_{CO_2} of 18.3 mm. Hg hypocarbia in man led to a decrease in aerobic utilization and an increase in anaerobic utilization of glucose. At an average Pa_{CO_2} of 18.3 the CMR_{O_2} was not altered, but cerebral metabolism changed in a direction indicative of an increase in anaerobic metabolism. The question is raised whether marked hypocarbia results in cerebral ischemia.

Our results clearly indicate that cerebral ischemic hypoxia occurred to a lesser degree in the hypocarbic than in normocarbic animals following experimental infarction. While the physiologic explanation of this protection is not obvious and clearly does not rest in the overall decreased cerebral blood flow, some recent observations shed light on the protection from ischemia afforded by hyperventilation. A recent article by Brawley, Strandness and Kelly[16] lends support to our findings. They found that "carbon dioxide inhalation produced a decrease in blood flow through an

area of cortex made ischemic by occlusion of the primary vessel of supply; whereas before occlusion, it had produced an increase in flow through the same area." They speculated that in the presence of ischemia the precapillary arterioles are maximally dilated, probably due to an increased tissue carbon dioxide tension, thus, an increase in Pa_{CO_2} will not cause further dilatation. The increase in Pa_{CO_2} would serve only to dilate arterioles in the surrounding nonischemic brain and cause a pressure drop in the collateral circulation and a fall in flow through the ischemic cortex. They speculate that hyperventilation with hypocarbia might increase flow in the ischemic region by increasing peripheral resistance in the normal brain, thus improving collateral perfusion to the ischemic area.

Hoedt-Rasmussen and his coworkers,[17] in their study of regional blood flow in patients with acute apoplexy, demonstrated abolition of the normal regulation of cerebral blood flow to the affected area. They believe the use of CO_2 as a cerebral vasodilator may be therapeutically harmful, since the CO_2 response was effective only in the nonfocal areas and not in the focus of vasomotor paralysis; thus, the use of CO_2 might tend to deviate blood away from an ischemic focus. Hoedt-Rasmussen and coworkers also indicated that hyperventilation with resulting hypocarbia would improve collateral blood flow to an ischemic area by causing cerebral vasoconstriction in the normal collateral areas, the increased local blood pressure improving blood flow to the area of ischemia.

Lassen [18] has recently proposed that hyperventilation with concomitant systemic alkalosis would be beneficial in local cerebral ischemia by counteracting the harmful effects of acute local metabolic acidosis. He theorizes that the local acidosis leads to cerebral edema either by alteration in cellular membrane properties or by an increase in capillary pressure. He believes the latter is due to vasomotor paralysis found in this ischemic area. This would result in a blood flow which exceeds the decreased local oxygen demand; he called this phenomenon the "luxury perfusion" syndrome. Lassen believes this loss of autoregulation is due to the local metabolic acidosis.

These hypotheses are attempts to explain the finding that in a carefully-controlled experimental design hyperventilation seemed to have a protective effect on subsequent cerebral infarction. Such an observation would not be expected if only the effect of hyperventilation on overall cerebral blood flow were considered.

Summary

This study was designed to evaluate the effect of hyperventilation with hypocarbia on the size of subsequent experimental cerebral infarction in the dog. Cerebral infarction was produced by occlusion of the internal carotid artery between the posterior communicating artery and the anterior cerebral artery and by occlusion of the middle cerebral artery at its origin. In the control group (four animals) Pa_{CO_2} was maintained at 38 mm. Hg for two hours following occlusion, and in the experimental group (five animals) Pa_{CO_2} was kept at 25 mm. Hg for two hours following occlusion. In both groups mean arterial blood pressure and body temperature showed no significant differences. In the control (normocarbic) group all animals had infarctions in the lenticular nuclei, internal capsule, and thalamus, as well as extensive cortical damage; half of the control animals also developed infarction in the amygdala and caudate nucleus.

In the experimental (hypocarbic) group, 60 per cent developed infarction, limited to the cortical area with none of the deeper structures involved. The average area of infarction in the normocarbic group was 612 sq. mm., compared with 15 sq. mm. in the hypocarbic group. It is possible that hyperventilation with hypocarbia exerts its protective effect on subsequent cerebral infarction by allowing more adequate perfusion of the ischemic area.

Mr. Soloway and Mr. Nadel participated in this study to fulfill thesis requirements for the M.D. degree.

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Muscle

ATYPICAL PSEUDOCHOLINESTERASE A screening method for separation of the plasmas of normal individuals from those of individuals homozygous and heterozygous for atypical pseudocholinesterase has been developed. This method allows the delineation of the three groups, using only 0.2 ml. of serum or plasma, three reagents, and no special equipment. One person can perform 75 tests in a day. (*Morrow, A. C., and others: Rapid Screening Method for the Common Atypical Pseudocholinesterase Variant, J. Lab. Clin Med. 71: 350 (Feb.) 1968.*)