

Effects of Hypocarbica and Normocarbica on Cardiovascular Dynamics and Regional Circulation in the Hypothermic Dog

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The effects of carbon dioxide on the cardiovascular system, cerebral, mesenteric, and renal blood flows, and total-body oxygen consumption under surface-induced hypothermia to 24 C were evaluated in 12 dogs. In Group I (six dogs), P_{aCO_2} was allowed to decrease from 35 to 18 torr during cooling without the addition of CO_2 to the inspired gas mixture. In Group II (six dogs), CO_2 was added to the inspired gases to maintain P_{aCO_2} 34-38 torr during cooling. Arterial blood pH increased in Group I (7.39 to 7.50), while it decreased in Group II (7.35 to 7.27). Cardiac index decreased markedly with cooling in Group II, from 3.37 to 1.18 l/min/m², while it showed an initial increase in Group I at 34 C, followed by a decrease to 1.62 l/min/m² at 24 C. Stroke index did not change significantly, but heart rate decreased significantly in either group, with Group II showing a greater decrease. Mean arterial pressure was significantly decreased in either group from about 120 to 80 torr, but there was no significant differences in mean arterial pressures between groups at the same hypothermic temperatures. Mean pulmonary arterial and pulmonary capillary wedge pressures were essentially unchanged in both groups. Pulmonary vascular resistance showed significantly greater increases in Group II than in Group I. Internal carotid arterial blood flow was significantly greater in Group II than in Group I, but there was no difference in renal or superior mesenteric arterial blood flows between the two groups. Total-body oxygen consumption in either group decreased from about 127 ml/min/m² at 37 C to 41 at 24 C, and there was no significant difference between groups. These results suggest that adding CO_2 to the inspired gases to maintain normal P_{aCO_2} during hypothermia may be desirable for cerebral perfusion but harmful to the cardiovascular system. (Key words: Brain: blood flow. Carbon Dioxide: hypocarbica; tension. Heart: cardiac output; myocardial function. Carbon dioxide, vascular pressures. Hypothermia. Kidney: blood flow. Oxygen: consumption.

DEEP HYPOTHERMIA by surface-cooling is widely used to minimize the discrepancy between oxygen supply and demand in various organs of the neonate who needs open-heart surgery with total circulatory arrest. The effects of deep hypothermia on the cardio-

vascular system have been well documented.¹⁻⁴ Cardiac output and arterial blood pressure may transiently increase at temperatures between 34 and 30 C and then progressively decrease as temperature decreases. Heart rate also decreases markedly. Pulmonary vascular resistance increases more than systemic vascular resistance. Regional circulation also decreases markedly, and decreases in cerebral and renal blood flows are more profound than those in splanchnic blood flow. It has been postulated that these vascular constricting changes are augmented by hypocarbica from increased CO_2 solubility and decreased CO_2 production by cellular metabolism during hypothermia.⁵ Since hypocarbica causes vasoconstriction in certain vascular beds (especially in brain) and shifts the oxyhemoglobin-dissociation curve to the left, adding CO_2 to the anesthesia circuit to maintain normal P_{aCO_2} during hypothermia has been advocated.⁶ However, there is a surprising lack of data to describe the cardiovascular effects of CO_2 during hypothermia. The purpose of this study was to evaluate the effects of CO_2 on cardiovascular dynamics and regional circulation during surface-induced hypothermia.

Method

Twelve mongrel dogs each weighing 10-13 kg, were anesthetized with pentobarbital, 30 mg/kg, followed by a continuous infusion of 0.1 mg/kg/min. Lactated Ringer's solution, 20 ml/kg, was given intravenously over a 1½ hour period during cannulation and surgical preparation. The intravenous infusion was maintained at 2-3 ml/kg/hr during the rest of the experiment. The dogs were covered with a heating pad to maintain normal temperatures during the initial phase of the study. Following endotracheal intubation, the animals' lungs were ventilated with oxygen and nitrogen, 50 per cent each, through a closed anesthesia circle system which was connected to an oxiconsumeter. The oxiconsumeter has been described.⁷ Briefly, the oxiconsumeter monitors total-body oxygen consumption (\dot{V}_{O_2}) by a replenishment technique whereby the oxygen removed by the patient from a closed rebreathing circuit is replaced. This is accomplished with a feedback-controlled pump that adds oxygen at a rate necessary to maintain a constant

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inspired percentage of oxygen. The instrument responds to a step change in \dot{V}_{O_2} every 4 min. The system's accuracy has been shown to be ± 6 per cent in an *in-vivo* comparison; the major errors result from oxygen sensor or electronics drift or from leaks in the system or changes in residual volume. End-tidal CO_2 was continuously monitored with a Beckman infrared CO_2 analyzer. An arterial catheter was placed in the aorta through a right femoral artery and a Swan-Ganz (triple-lumen) catheter was inserted in the pulmonary artery through the right external jugular vein. Pressures were measured with the catheters attached to Microdot pressure transducers. The left internal carotid, left renal and superior mesenteric arteries were isolated and electromagnetic flow probes of appropriate size were placed around them. The probes were connected to a model BL-610 pulsed-logic flowmeter (Biotronics Laboratory, Inc.). Animals were each given an intravenous injection of pancuronium bromide, 0.2 mg/kg, and after their conditions had stabilized at 37 C, control measurements of \dot{V}_{O_2} , mean arterial pressure (MAP), heart rate, central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), arterial and mixed venous blood-gas values, hemoglobin, O_2 saturation, left internal carotid arterial blood flow, left renal blood flow, and superior mesenteric arterial blood flow were made. The animals were surface-cooled to 24 C by packing them with bags of crushed ice. Rectal and esophageal temperatures were continuously monitored with telethermometers. In Group I (six dogs, hypocarbic group), slight hypocarbia (32–37 torr) was established during

normothermia and ventilation was then maintained unchanged during cooling. In Group II (six dogs, normocarbic group), normocarbica was maintained throughout the study. As the temperature decreased, CO_2 was added to the inspiratory side of the closed circle to maintain an end-tidal CO_2 between 5 and 6 per cent. Blood-gas values were measured with an ABL-1 blood-gas analyzer. Arterial and mixed venous blood O_2 saturation and hemoglobin were measured with an IL co-oximeter. The *pH* and Pa_{CO_2} values were corrected for temperature using the nomogram of Kelman and Nunn.⁸ The values of \dot{V}_{O_2} were corrected for STPD. Cardiac index and stroke volume were calculated using the Fick equation and calculated surface area. The Student *t* test for paired samples or independent samples was used for statistical analysis of the data.

Results

The cooling times from 37 to 24 C were 110 ± 20 and 118 ± 16 min (mean \pm SD) in the hypocarbic and the normocarbic groups, respectively. In the hypocarbic group, Pa_{CO_2} s (corrected for temperature) decreased markedly as the temperature decreased, while Pa_{CO_2} s in the normocarbic group were maintained within the normal range of the euthermic standard (table 1). The slight metabolic acidosis at 37 C in both groups is normal at this altitude, where the barometric pressure is 640 torr. The metabolic acidosis became more profound as the temperature decreased to 24 C, as negative base excess increased from 3.6 to 8.4 mEq/l in the hypocarbic group and from 4.0 to 9.9 mEq/l in the normocarbic group. Mean arterial blood *pH* values

TABLE 1. Arterial Blood *pH*, P_{CO_2} , and Negative Base Excess in Hypocarbic and Normocarbic Dogs during Cooling*

	Temperature (C)						
	37	34	32	30	28	26	24
<i>pH</i>							
Hypocarbic dogs	7.39 ± 0.02	7.40 ± 0.03	7.41 ± 0.03	7.45† ± 0.03	7.48† ± 0.03	7.52† ± 0.03	7.52† ± 0.03
Normocarbic dogs	7.35 ± 0.01	7.33 ± 0.02	7.30† ± 0.03	7.30† ± 0.03	7.29† ± 0.03	7.30† ± 0.02	7.27† ± 0.03
P_{CO_2} (torr)							
Hypocarbic dogs	34.8 ± 2.0	32.2 ± 0.9	29.7† ± 0.9	26.5† ± 0.9	22.7† ± 1.2	20.3† ± 1.1	17.7† ± 1.0
Normocarbic dogs	37.5 ± 1.8	38.0 ± 2.3	38.0 ± 3.2	36.0 ± 3.1	35.6 ± 3.1	34.0 ± 3.1	36.0 ± 4.0
Negative base excess (mEq/l)							
Hypocarbic dogs	3.6 ± 1.5	4.5† ± 1.7	5.3† ± 1.9	5.7† ± 1.9	6.4† ± 1.9	6.4† ± 1.8	8.4† ± 1.2
Normocarbic dogs	4.0 ± 0.6	5.5† ± 0.9	6.6† ± 1.1	7.2† ± 1.1	7.7† ± 1.1	8.1† ± 1.1	9.9† ± 1.3

* Data represent means \pm SE (n = 6). *pH* and P_{CO_2} values were corrected for temperature.

† Significantly different from control (37 C), $P < 0.05$.

TABLE 2. Cardiovascular Dynamics in Hypocarbic and Normocarbic Dogs during Cooling*

	Temperature (C)						
	37	34	32	30	28	26	24
Mean arterial pressure (torr)							
Hypocarbic dogs	121 ± 6	120 ± 4	104 ± 9	103 ± 9	99 ± 10†	95 ± 9†	86 ± 10†
Normocarbic dogs	121 ± 4	117 ± 7	110 ± 10	109 ± 11	96 ± 13†	87 ± 12†	75 ± 12†
Heart rate (beats/min)							
Hypocarbic dogs	115 ± 6	102 ± 4†	92 ± 4†	80 ± 3†	67 ± 3†	55 ± 2†	44 ± 3†
Normocarbic dogs	123 ± 11	94 ± 5†	83 ± 5†	74 ± 4†	63 ± 3†	53 ± 2†	39 ± 5†
Mean pulmonary arterial pressure (torr)							
Hypocarbic dogs	17 ± 2	18 ± 3	17 ± 3	15 ± 2	15 ± 2	15 ± 2	16 ± 2
Normocarbic dogs	17 ± 2	19 ± 1	18 ± 2	18 ± 2	18 ± 2	18 ± 2	18 ± 2
Pulmonary capillary wedge pressure (torr)							
Hypocarbic dogs	11 ± 2	11 ± 2	11 ± 2	10 ± 2	11 ± 2	11 ± 2	12 ± 2
Normocarbic dogs	10 ± 1	11 ± 2	10 ± 2	10 ± 2	11 ± 2	11 ± 2	12 ± 1†

* Data represent means ± SE (n = 6).

† Significantly different from control (37 C), P < 0.05.

(corrected for temperature) in the hypocarbic group were 7.39 at 37 C and 7.52 at 24 C. In the normocarbic group, mean pH values were 7.35 at 37 C and 7.27 at 24 C. MPAP and PCWP (table 2) did not change significantly in either group during cooling, except that in the normocarbic group PCWP at 24 C was significantly higher than the control value at 37 C. MAP and heart rate decreased progressively during cooling (table 2). The decrease of heart rate in the hypocarbic group was less rapid to 34 C; below this temperature, the slopes of heart rates in the two groups were almost identical. The renal, superior mesenteric arterial, and carotid arterial blood flows showed progressive marked decreases during cooling (fig. 1). The carotid arterial and renal flows decreased very rapidly with temperature, while superior mesenteric arterial flow remained relatively constant at the lower temperature. Renal and superior mesenteric arterial blood flows in the normocarbic group were not significantly different from the corresponding values in the hypocarbic group. However, carotid arterial flow was significantly greater in the normocarbic group at 28 to 24 C. The cardiac index in the hypocarbic animals increased significantly at 34 C and decreased progressively during hypothermia (fig. 2). In the normocarbic group, the cardiac index did not show an initial increase, and the values at 34, 32, 26 and 24 C were significantly lower than those in the hypocarbic group. There was no statistically significant change in stroke index in either group or difference between groups. Systemic and pulmonary vascular resistances increased in both groups during cooling (fig. 3). In the hypocarbic dogs, systemic vascular resistance decreased slightly at 34 to 30 C and was consistently lower than the corresponding values in the normocarbic animals during cooling. Pulmonary vas-

cular resistance in the hypocarbic group was unchanged during hypothermia, while in the normocarbic group it showed progressive increases during hypothermia and was significantly greater at 26 and 24 C (fig. 3). \dot{V}_{O_2} decreased exponentially in both groups during hypothermia (fig. 4), and there was no significant difference between groups.

Hemoglobin concentration was 12.6 ± 1.7 g/dl (n = 12), and arterial O_2 saturation was 99.1 ± 0.9 per cent (n = 12) for both groups at normothermia, and there was no significant change of these values during hypothermia. Mixed venous blood O_2 saturation values were 87.6 ± 2.4 per cent (n = 6) and 83.5 ± 3.2 per cent (n = 6) for the hypocarbic and normocarbic groups, respectively; the corresponding values were 90.3 ± 2.1 per cent and 86.9 ± 3.7 per cent at 24 C, with no significant differences occurring.

Discussion

Our results are in general agreement with those in several previous studies,¹⁻⁴ where MAP, MPAP, heart rate, cardiac index and regional circulation all decreased markedly during cooling while systemic and pulmonary vascular resistance increased. Like us, Delin *et al.*² demonstrated that renal blood flow decreased more profoundly than superior mesenteric arterial blood flow. However, our data show that there is no difference between the decreases in blood flows in these two vascular beds with or without the addition of CO_2 , suggesting that hypothermia elicited the predominant vasoconstrictor response in both vascular beds.

The effects of carbon dioxide on the cardiovascular system are complex because the responses depend upon the summation of its direct effect which

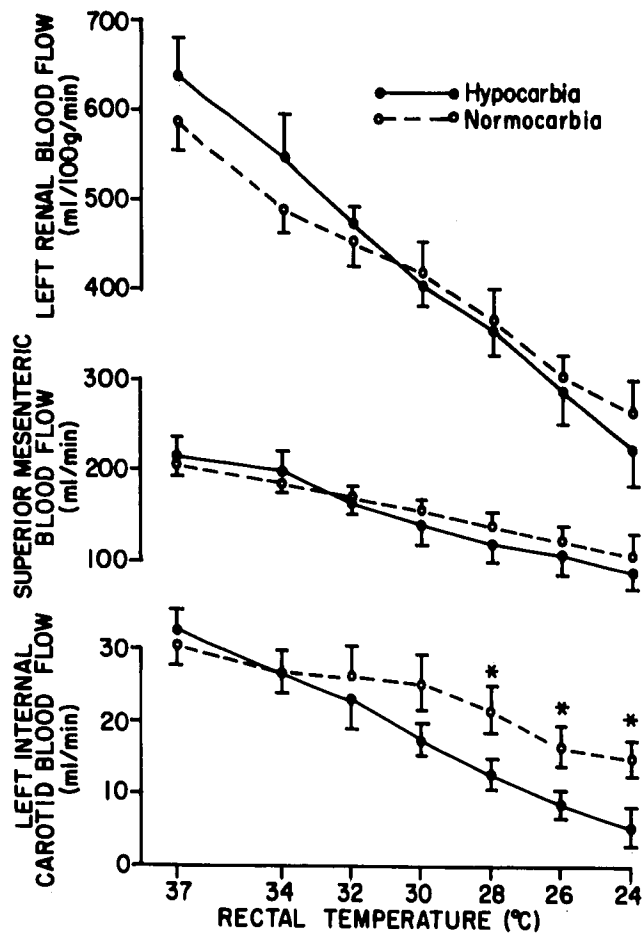


FIG. 1. Effects of hypocarbia and normocarbia on regional blood flows during hypothermia. Means \pm SE, $n = 6$. *Significant difference ($P < 0.05$) between hypocarbia and normocarbia.

is cardiac depression and vasodilation, and its indirect effect which is cardiac stimulation and vasoconstriction mediated via the sympathetic nervous system.⁹ Furthermore, all vascular beds do not respond in the same manner to the cardiovascular effects of CO_2 and catecholamines. Conflicting data in the medical literature may also represent differences in experimental designs and in animal models. The inhalation of CO_2 causes dose-related increases in heart rate, arterial pressure, and cardiac output, but a decrease in systemic vascular resistance, in conscious subjects.¹⁰ In anesthetized patients, however, these variables may increase slightly or decrease.^{11,12} Kittle *et al.*¹³ observed a decrease in systemic vascular resistance in lightly anesthetized dogs for the initial 30 min of CO_2 inhalation and then an increase to above the control level. The cerebrovascular bed responds poorly to sympathetic stimulation and shows marked vasodilation from hypercarbia.¹³ The coronary arterial and cutaneous blood flows also increase slightly with an increase in Pa_{CO_2} .¹⁴ However, the renal, splanchnic and skeletal

muscle blood flows seem to decrease from vasoconstriction in conscious or lightly anesthetized patients as Pa_{CO_2} increases.¹¹ Pulmonary vascular resistance also increases as Pa_{CO_2} increases.¹⁵ Nevertheless, these data do suggest that CO_2 produces vasodilation of cerebral as well as peripheral vasculatures during normothermia. Since CO_2 also stimulates catecholamine discharge from the adrenal medulla to produce cardiac stimulation and peripheral vasoconstriction, but not cerebral vasoconstriction, prolonged hypercarbia is expected to produce cerebral vasodilation and peripheral vasoconstriction.

Clinically, the addition of CO_2 to the inspired gas mixture during hypothermia has been advocated.^{5,6} This recommendation is based on several assumptions. 1) Hypocarbia under hypothermia augments peripheral vasoconstriction, thus further increasing systemic vascular resistance during cooling. 2) Pa_{CO_2} values during hypothermia are more physiologic when kept within the eutermic normal range when corrected for temperature. 3) The decrease in cerebral blood flow during hypothermia is augmented by hypo-

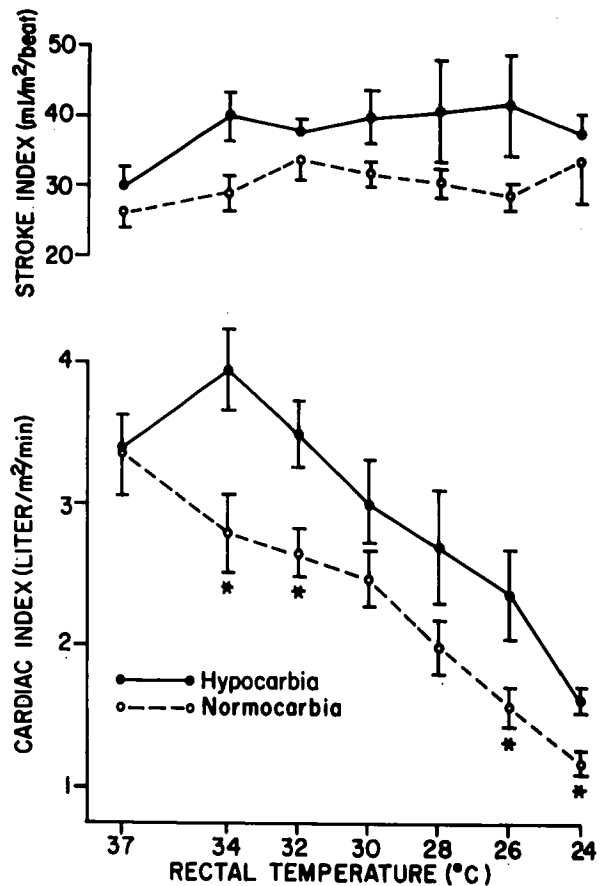


FIG. 2. Effects of hypocarbia and normocarbia on cardiac index and stroke index during hypothermia. Means \pm SE, $n = 6$. *Significant difference ($P < 0.05$) between hypocarbia and normocarbia.

carbia and may cause cerebral hypoxia and lead to brain damage. Published evidence does not support all of these assumptions. During normothermia, an increase in systemic vascular resistance from hypocarbia is not significant, because the response in the splanchnic, renal and skeletal muscle vascular beds to hypocarbia is negligible.¹³ It has been shown that the increased venous pressure associated with hyperventilation rather than hypocarbia itself is the cause of increased mesenteric vascular resistance.¹⁶ Using radiographic technique, Miller *et al.*¹⁷ observed severe vasoconstriction in non-anesthetized, spontaneously breathing mice cooled to 0 C. However, vasoconstriction did not begin above 20 C in the control animals. There is no general agreement as to what the normal Pa_{CO₂} values should be at lower than normal body temperatures since hypothermia itself is not a normal physiologic condition. Severinghaus¹⁸ proposed that normal ventilation during hypothermia "is that in which carbon dioxide elimination equals its rate of metabolic production as cooling progresses"; such that

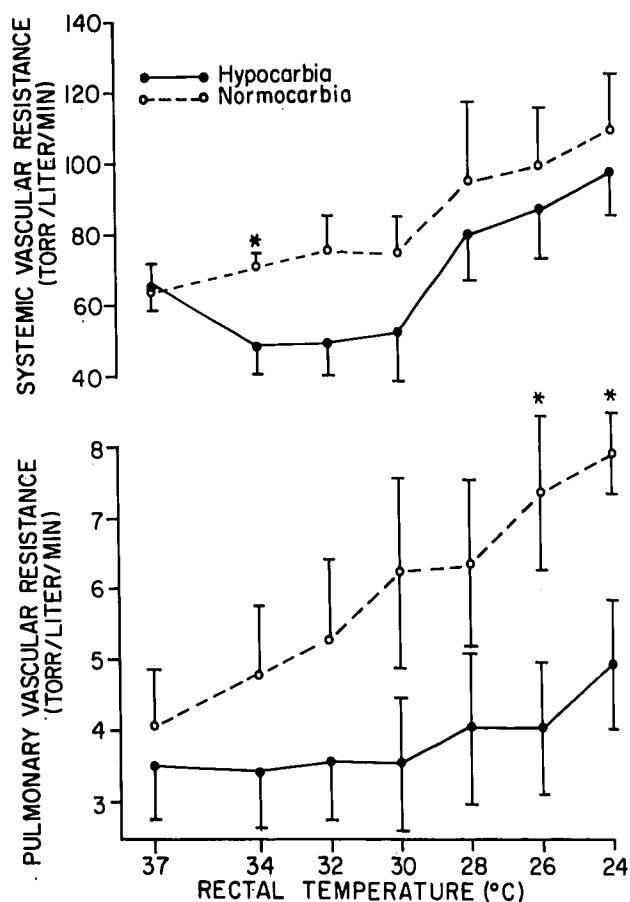


FIG. 3. Effects of hypocarbia and normocarbia on pulmonary vascular resistance and systemic vascular resistance during hypothermia. Means \pm SE, n = 6. *Significant difference ($P < 0.05$) between hypocarbia and normocarbia.

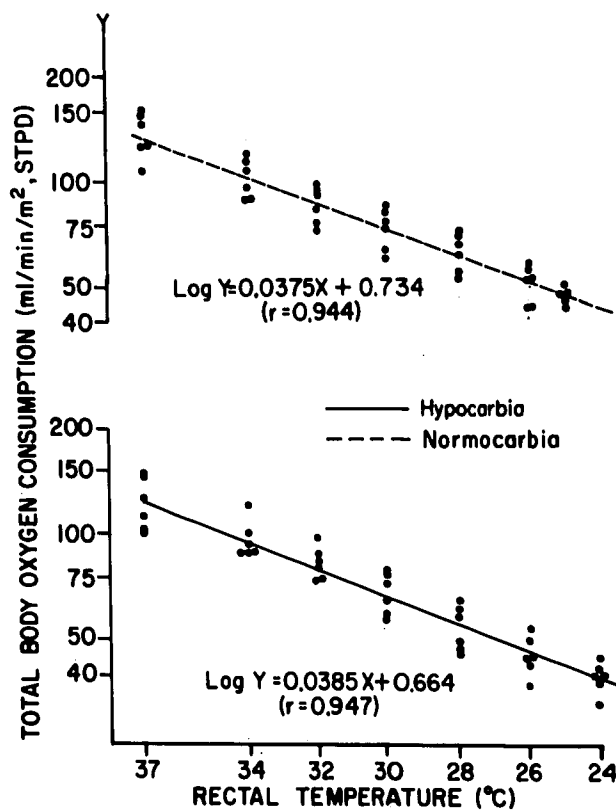


FIG. 4. Effects of hypocarbia and normocarbia on total-body oxygen consumption during hypothermia. There was no significant difference between the effects of hypocarbia and normocarbia on the rate or quantity of oxygen consumption at the temperatures examined.

blood CO₂ content remains unchanged, pH increases *in vivo* at the same rate as in blood cooled *in vitro*, and alveolar and arterial blood P_{CO₂}s decrease at the same rate as those of blood cooled *in vitro*. Hypercarbia increases cerebral blood flow and decreases cerebrovascular resistance and hypocarbia does the opposite,^{13,19} and hypothermia potentiates the cerebral vasoconstriction of hypocarbia.¹⁹

In our study, Pa_{CO₂}s (corrected for temperature) were maintained within normal limits in dogs in Group II (compared with the euthermic standard). Normocarbia during hypothermia caused a rapid decrease in the cardiac index and augmented the increases in pulmonary and systemic vascular resistance. Increases in these resistances can increase right and left ventricular work, thereby further promoting myocardial depression. The greater decrease of cardiac index in the normocarbic group was the result of a greater decrease in heart rate in the normocarbic animals (fig. 2). McConnell *et al.*²⁰ have also demonstrated, in dogs placed on cardiopulmonary bypass at 28 C, that increasing blood pH from 7.40 to 7.70 increased coronary arterial blood flow and myocardial lactate utilization and augmented left ventricular per-

formance. Nearly equal blood flows in the renal and superior mesenteric beds were observed in both groups in this study, while the cerebral blood flows were significantly greater in the normocarbic group at the lower temperatures.

Marked vasoconstriction during hypothermia is an important concern for anesthesiologists and cardiovascular surgeons, since it may produce hypoxia and brain damage. Various institutes, as well as ours,^{8,21} have been successfully using deep hypothermic anesthetic techniques without adding CO₂. These clinical experiences have demonstrated that at 20 C patients can tolerate circulatory arrest safely for as long as an hour without neurologic problems. Hägerdal *et al.*¹⁰ showed that decreasing PaCO₂ in the rat produced a more profound decrease in the cerebral blood flow at 22 C than at 27 C. However, they also observed that at a PaCO₂ of 15 torr there was no change in phosphocreatine, adenosine triphosphate, and adenosine diphosphate levels in brain cortical tissue at 22 C as compared with 37 C. The serum lactate level was also significantly less as compared with the level at 37 C. Based on these results, they concluded that a PaCO₂ of 15 torr did not cause any tissue hypoxia under hypothermia. We have recently shown that hypothermia to 20 C in infant lambs during controlled ventilation, without the addition of inspired CO₂, did not cause any derangement in cerebrospinal fluid (CSF) acid-base and electrolyte balance, even though in all animals arterial pressures and cardiac outputs were markedly decreased at 20 C.⁴ When their circulations were arrested beyond one hour, however, we observed rapid increases in CSF P_{CO₂} and potassium ion concentration and decreases in CSF pH and bicarbonate levels. It has been shown that circulatory arrest for a period of one hour at 20 C does not cause any neurologic damage or histologic change in the brains of Rhesus monkeys when ventilation is controlled and CO₂ is not added to the anesthetic circuit.²² These observations suggest that an uneventful recovery of a neonate undergoing open-heart surgery during hypothermia depends more on the duration of circulatory arrest and the smoothness of the rewarming process than on the cooling process itself. The present study has also demonstrated no difference in \dot{V}_{O_2} s between the two groups (fig. 4) during hypothermia. However, we cannot eliminate the possibility that adding CO₂ may improve cerebral circulation in clinical hypothermia, where circulation is maintained by a pump.

Our results suggest that adding CO₂ to an anesthesia circle system to maintain normal PaCO₂ during hypothermia below 28 C may be desirable for cerebral perfusion, but harmful to the cardiovascular system. The biochemical and physiologic effects of CO₂ during hypothermia need to be studied more extensively to avoid unnecessary iatrogenic complications.

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