

Protective Effect of Hypothermia in Cerebral Oxygen Deficiency Caused by Arterial Hypoxia

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To study the cerebral protective effects of hypothermia in arterial hypoxia, anesthetized (70 per cent N_2O), mechanically ventilated rats were cooled to a body temperature of 27°C. Hypoxia was induced by decreasing the oxygen content in the inspired gas mixture either to 6–7 per cent or to 2.5–3 per cent. This reduced mean P_{aO_2} to about 25 and 11–12 torr, respectively. At P_{aO_2} 25 torr, there was no change in cerebral blood flow (CBF), cerebral oxygen consumption (CMR_{O_2}), or labile tissue metabolites. The absence of signs of cerebral hypoxia could be attributed to an effect of temperature and pH on the hemoglobin–oxygen dissociation curve. Thus, at 27°C with a P_{aO_2} of 25 torr the total oxygen content (T_{O_2}) of arterial blood remained >15 ml (100 ml) $^{-1}$, about three times the value obtained at this P_{aO_2} in normothermic rats. At P_{aO_2} 11–12 torr, arterial T_{O_2} was reduced to about 5 ml (100 ml) $^{-1}$. The hypoxia induced no change in CMR_{O_2} , a threefold increase in CBF, a moderate lactacidosis in the tissue, and a small decrease in phosphocreatine content, but no change in ATP, ADP, or AMP. These changes are less marked than those occurring at the same arterial T_{O_2} in normothermic rats. It is concluded that hypothermia exerts a pronounced protective effect on the brain in hypoxic hypoxia, and that two mechanisms are involved. First, since hypothermia shifts the oxy-hemoglobin-dissociation curve towards the left, and prevents or minimizes a rightward shift due to acidosis, it maintains a high T_{O_2} in arterial blood at a given P_{aO_2} . Second, by reducing

CMR_{O_2} , and thereby presumably also cellular energy requirements, hypothermia exerts a protective effect at the cellular level. (Key words: Brain hypoxia; Hypoxia, cerebral; Hypothermia, hypoxia.)

IT IS GENERALLY ASSUMED that the brain can be protected against the harmful effects of a reduced oxygen supply by hypothermia,^{1–3} as well as by certain anesthetic drugs, notably the barbiturates.^{3,6} With one exception,⁴ the protective effects have been tested either during complete ischemia or in experimental situations the clinical validity of which is unclear. There is thus a need for further studies of potentially protective measures that can be instituted in clinical conditions of cerebral hypoxia.

Very little is known about possible protective measures in hypoxic hypoxia. In this condition, the oxygen supply to the brain is endangered because there is a reduction in the arterial oxygen tension (P_{aO_2}) and content (T_{aO_2}). It is now well established that even a pronounced hypoxic (or anemic) hypoxia can be tolerated without causing a reduction in cerebral oxygen consumption (CMR_{O_2}) or a major derangement in cerebral energy state.^{7–15} It has recently been shown that CMR_{O_2} is maintained at normal values even if P_{aO_2} is reduced to 20–25 torr, and that the increase in cerebral blood flow (CBF) represents the main, if not sole, mechanism that prevents energy failure.^{16–18} This conclusion is supported by experiments showing that conditions that interfere with the compensatory increase in CBF, such as a fall in blood pressure or ligation of a carotid artery, also lead to energy failure at the tissue level.^{11,19,20}

In the present experiments, we have studied the effect of hypothermia (reduction in body temperature by 10 degrees C) on the circulatory and metabolic responses of the brain to hypoxic hypoxia. To allow comparison with previous laboratory experiments per-

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formed at normal temperature,¹²⁻¹⁵ P_{aO_2} was reduced during hypothermia to 25 torr for maximally 30 minutes. However, since this did not induce any measurable change in CBF or cerebral metabolites, and since hypothermia did not cause a pronounced decrease in arterial T_{O_2} , P_{aO_2} was reduced further so as to induce a fall in T_{aO_2} to about 5 ml·(100 ml)⁻¹, the approximate value that normothermic animals reached at P_{aO_2} 25 torr. It is shown below that hypothermia exerts a pronounced protective effect on the brain under the conditions of the experiments.

Methods and Materials

Since the experimental techniques and methods used in the present study have been described in previous communications from the laboratory,^{14,15,21,22} only the general outlines are given here. All experiments were performed on unstarved male Wistar rats (300–400 g) anesthetized with 2–3 per cent halothane, tracheotomized, and immobilized with tubocurarine chloride (0.5 mg·kg⁻¹, intravenously). Halothane was then discontinued and the animals ventilated with 70 per cent N₂O and 30 per cent O₂ until hypoxia was induced. One femoral artery was cannulated for blood pressure recording and for sampling of blood. Rectal temperature was reduced to 27°C over a period of 30 minutes, ventilation being adjusted to maintain arterial blood pH close to 7.4. The animals were then allowed a stabilizing period of 30 minutes at the reduced temperature before hypoxia was induced. This was achieved by reducing the oxygen concentration of the insufflated gas mixture, keeping the nitrous oxide concentration constant at 70 per cent. There were three series of experiments, and these are described separately.

SERIES A

In this series both femoral arteries and one femoral vein were cannulated. Furthermore, the caudal part of the superior sagittal sinus was exposed by means of a small burr hole for sampling of cerebral venous blood. At the end of the 30-minute stabilizing period (at 27°C body temperature), the oxygen supply was reduced to give either a P_{aO_2} of about 25 torr or an arterial T_{O_2} of about

5 ml·(100 ml)⁻¹. During the last 20 minutes of the 30-minute hypoxic period, ¹³³xenon was added to the insufflated gas mixture. At the end of the saturation period, arterial and cerebral venous blood were sampled for ¹³³xenon and T_{O_2} . Then ¹³³xenon administration was discontinued, and samples were again taken from artery and vein during desaturation. After 5 minutes of desaturation, a further determination of cerebral arteriovenous oxygen differences (a-vD_{O₂}) was made. These experiments thus served to measure CBF and CMR_{O₂} after 30 minutes of hypoxia. During the measurements, blood from a donor rat was slowly infused intravenously to avoid a decrease in blood pressure due to blood loss. (For method, see Norberg and Siesjö, 1974.²³)

SERIES B

In this series, the animals were prepared as in series A. However, ¹³³xenon was not used to measure CBF; instead, arteriovenous oxygen content differences were measured 1, 2, 5, 15, and 30 minutes after induction of hypoxia (reduction of T_{aO_2} to about 5 ml·(100 ml)⁻¹). CBF changes were calculated from a-vD_{O₂}, assuming constant CMR_{O₂}. CBF is inversely proportional to a-vD_{O₂} according to the equation

$$CBF = \frac{CMR_{O_2}}{a-vD_{O_2}} \cdot 100$$

In addition, cerebral venous P_{O_2} was measured after 5 and 30 minutes of hypoxia.

SERIES C

In these animals, only one femoral artery was cannulated and the superior sagittal sinus was not exposed. Instead, preparations were made for freezing the tissue *in situ*.²⁴ At the end of the 30-minute hypoxic period, arterial blood was collected and the tissue was frozen for subsequent measurements of glucose, lactate, and pyruvate (arterial blood) or glucose, lactate, pyruvate, phosphocreatine (PCr), creatine (Cr), ATP, ADP, and AMP (tissue).

Arterial blood P_{O_2} , P_{CO_2} , and pH were measured at 27°C using microelectrodes. Arterial and venous T_{O_2} were measured according to the method of Fabel and Lübbers.^{25,26} CBF was measured with the modi-

TABLE 1. Rectal Temperatures, Mean Arterial Blood Pressures, and Blood Gases in Hypothermic Rats at Two Hypoxic Levels and in Hypothermic, Normoxic Rats

	Number of Rats	Temperature (C)	MABP (torr)	P _{aO₂} (torr)	P _{aCO₂} (torr)	pH
Hypothermia-normoxia	6	27.1 ± 0.2	127 ± 5	113.0 ± 17.0	28.7 ± 0.9	7.341 ± 0.011
Hypothermia-hypoxia P _{aO₂} ≈ 25 torr	6	26.7 ± 0.1	127 ± 3	25.8 ± 0.7	27.6 ± 0.8	7.401* ± 0.004
P _{aO₂} ≈ 12 torr	6	26.8 ± 0.1	111* ± 2	10.8 ± 0.9	27.1 ± 0.4	7.345 ± 0.012

Values are means ± SEM. Statistical differences were calculated between the hypoxic groups and the normoxic group.

Data for normoxic, hypothermic rats taken from Hägerdal *et al.*²¹

* P < 0.01.

fication of the Kety and Schmidt²⁷ method described by Norberg and Siesjö,²⁸ using a partition coefficient for ¹³³xenon of 0.70 as determined by Hägerdal *et al.*²¹ CMR_{O₂} was calculated as the product of CBF and a-vD_{O₂}, the latter taken as the mean of the two determinations.

Statistical differences were calculated by means of Aspin-Welch's test.²⁸

Results

SERIES A

As stated, two groups of rats were studied. In one, the P_{aO₂} was reduced to about 25 torr (steady-state value), and in the other, the oxy-

gen concentration was further reduced to give an arterial blood T_{O₂} of about 5 ml·(100 ml)⁻¹. Table 1 compares the data obtained in these groups with those previously published from this laboratory for normoxic, hypothermic rats.²¹ During hypothermia (and before hypoxia was induced), P_{aCO₂} was adjusted to about 30 torr, to give an arterial pH of about 7.4. The results show that moderate hypoxia (P_{aO₂} about 25 torr) did not induce a change in blood pressure, but that severe hypoxia (P_{aO₂} about 11 torr) gave rise to moderate hypotension. There was no significant decrease in pH in any of the hypoxic groups (see, however, below).

Table 2 contains the values for arterial and cerebral venous T_{O₂}, cerebral a-vD_{O₂}, CBF

TABLE 2. Arterial and Cerebral Venous Total Oxygen Content, Cerebral Arteriovenous Differences for Oxygen, Cerebral Blood Flow and Cerebral Oxygen Consumption in Hypothermic, Hypoxic Rats and Hypothermic, Normoxic Rats

	Number of Rats	T _{AO₂}	T _{VO₂}	a-vD _{O₂}	CBF	CMR _{O₂}
		ml · (100 ml) ⁻¹			ml · (100 g) ⁻¹ · min ⁻¹	
Hypothermia-normoxia	6	26.90 ± 0.70	19.60 ± 0.80	7.30 ± 0.90	82 ± 11	5.6 ± 0.1
Hypothermia-hypoxia P _{aO₂} ≈ 25 torr	6	15.74† ± 0.65	10.14† ± 1.24	5.66 ± 1.02	112 ± 27	5.1 ± 0.3
P _{aO₂} ≈ 12 torr	6	4.48† ± 0.35	2.18† ± 0.27	2.32† ± 0.20	248* ± 38	5.4 ± 0.3

Values are means ± SEM.

Data for normoxic, hypothermic rats taken from Hägerdal *et al.*²¹

* P < 0.01.

† P < 0.001.

TABLE 3. Changes in Rectal Temperature, Mean Arterial Blood Pressure, Arterial Blood pH, and Arterial and Cerebral Venous Blood P_{CO_2} and P_{O_2} with Time after Induction of Hypoxia (Six Rats)

	Temperature (C)	MABP (torr)	pH _a	P_{aO_2} (torr)	P_{cO_2} (torr)	P_{aO_2} (torr)	P_{cO_2} (torr)
Just before induction of hypoxia	26.9 ± 0.1	141 ± 2	7.419 ± 0.016	28.9 ± 0.3	32.2 ± 2.2	123 ± 7	31.6 ± 1.0
After induction of hypoxia							
1 min	26.7 ± 0.1	144 ± 3				20.6† ± 1.0	
2 min	26.7 ± 0.1	124† ± 3				14.9† ± 0.9	
5 min	26.6 ± 0.2	119† ± 1	7.432 ± 0.021	28.2 ± 1.2	28.7 ± 0.7	13.0† ± 0.6	11.6† ± 0.6
15 min	26.5 ± 0.2	120† ± 2				11.9† ± 0.8	
30 min	26.6 ± 0.2	114† ± 4	7.367* ± 0.006	28.0 ± 0.7	28.5 ± 1.0	11.0† ± 0.7	7.9† ± 0.5

Values are means ± SEM.

* $P < 0.05$.† $P < 0.01$.‡ $P < 0.001$.

and CMR_{O_2} for the groups in table 1. At P_{aO_2} 25 torr (inspired oxygen concentration 6–7 per cent), arterial T_{O_2} was reduced to $16 \text{ ml} \cdot (100 \text{ ml})^{-1}$. At the same P_{aO_2} , normothermic rats show a reduction of T_{aO_2} to 4–5 $\text{ml} \cdot (100 \text{ ml})^{-1}$, as previously reported from this laboratory.^{16–18} In the hypothermic animals, P_{aO_2} had to be reduced to 11 torr (inspired oxygen concentration 2.5–3 per cent) to obtain such low values for T_{aO_2} . There was no change in CMR_{O_2} during hypoxia. At P_{aO_2} 25 torr, a-v D_{O_2} and CBF were not significantly altered from normal, but at P_{aO_2} 11 torr there was a threefold increase in CBF.

SERIES B

In this series, arterial and cerebral venous blood was sampled just before and 1, 2, 5, 15 and 30 minutes after induction of hypoxia (final P_{aO_2} about 11 torr). Table 3 illustrates values obtained for body temperature, mean arterial blood pressure, arterial blood pH, and arterial and venous blood P_{CO_2} and P_{O_2} . Temperature was maintained at 26.5–26.9 C. Mean arterial blood pressure fell by 20 torr after 2 minutes and remained significantly reduced during the hypoxic period. After 30 minutes of hypoxia there was a small but significant

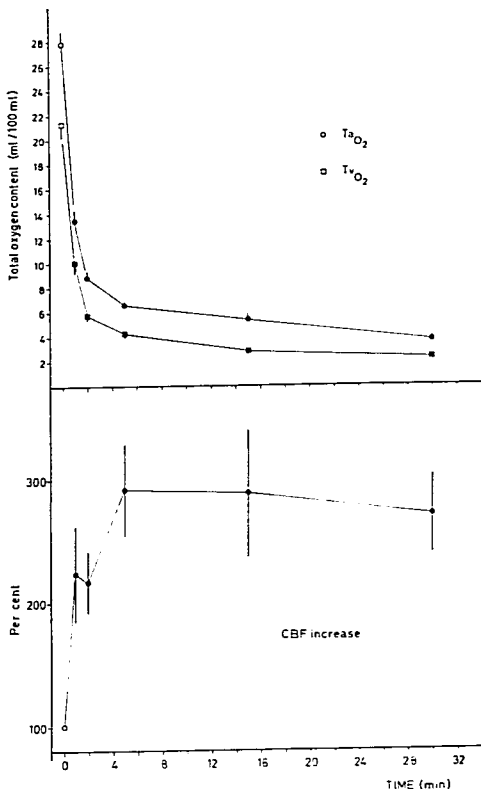
decrease in arterial blood pH. P_{aCO_2} remained 28–29 torr. During hypoxia, the cerebral arteriovenous P_{CO_2} difference was close to zero. The P_{aO_2} values show that arterial hypoxia developed gradually. However, after the first 2 minutes of hypoxia, P_{aO_2} was below 15 torr, and after 15 minutes the value was close to that observed after 30 minutes. Cerebral venous P_{O_2} was below 10 torr in all animals after 30 minutes.

In figure 1 arterial and venous blood T_{O_2} values have been plotted against time of hypoxia. Also shown are the CBF changes calculated from a-v D_{O_2} on the assumption of constant CMR_{O_2} . The results indicate that CBF approximately doubled during the first 1–2 minutes, and that the full CBF response (threefold increase: cf. table 2) was obtained within the first 5 minutes.

SERIES C

In these animals, the physiologic changes were similar to those of series A and B. Thus, at the end of the 30-minute hypoxic periods, mean P_{aO_2} values were 24.2 ± 0.6 and 12.3 ± 0.3 torr, and arterial T_{O_2} values were 17.10 ± 1.20 and $4.36 \pm 0.16 \text{ ml} \cdot (100 \text{ ml})^{-1}$, respectively. Metabolite concentrations

FIG. 1. Changes in arterial and cerebral venous total oxygen content, and cerebral blood flow, with time after induction of hypoxia to T_{aO_2} about $5 \text{ ml} \cdot (100 \text{ ml})^{-1}$. Solid symbols indicate significant differences from control, $P < 0.05$, and vertical bars, $\pm \text{SEM}$.



in blood and tissue were compared with those previously reported from this laboratory for normoxic animals maintained at 27°C body temperature.²²

Table 4 shows the lactate and pyruvate concentrations of arterial blood, and the calculated lactate/pyruvate (La/Py) ratios. At P_{aO_2} 24 torr, neither the lactate concentration nor the La/Py ratio had changed significantly. At P_{aO_2} 12 torr, there was a three- to fourfold increase in lactate, and a significant increase in La/Py ratio.

Tissue metabolites are shown in table 5. Since the brains of the (previously described^{21,22}) control groups were not extracted and analyzed simultaneously with those of the hypoxic groups, minor differences in metabolite concentrations should be ignored. In general, though, there was satisfactory agreement between the control groups and that representing mild hypoxia (P_{aO_2} about 24 torr). Since animals maintained at P_{aO_2} 24 torr had an arterial blood T_{O_2} exceeding $15 \text{ ml} \cdot (100 \text{ ml})^{-1}$ and did not show an in-

TABLE 4. Arterial Concentrations of Lactate and Pyruvate and Calculated Lactate/Pyruvate Ratios in Hypothermic Hypoxic Rats and Hypothermic Normoxic Rats

	Number of Rats	Lactate	Pyruvate	Lac/Py
		mmol · kg ⁻¹		
Hypothermia-normoxia	6	2.20 ± 0.29	0.154 ± 0.014	14.5 ± 1.1
Hypothermia-hypoxia P _a O ₂ ≈ 24 torr	6	2.91 ± 0.10	0.173 ± 0.012	17.2 ± 1.3
P _a O ₂ ≈ 12 torr	6	7.64† ± 0.24	0.226† ± 0.010	34.1† ± 1.2

Values are means ± SEM.

Data for normoxic, hypothermic rats taken from Hägerdal *et al.*²²† *P* < 0.001.

crease in CBF (table 2), the metabolite values obtained may be provisionally regarded as representing a normal state. Differences between the two hypoxic groups were therefore calculated statistically. The results show that pronounced hypoxia (PaO₂ about 12 torr) gave rise to a two- to three-fold increase in lactate concentration, as well as to a significant increase in Lc/Py ratio and decrease in phosphocreatine concentration. However, there was no change in ATP, ADP, or AMP and thus no sign of energy failure in spite of the pronounced reductions of PaO₂ and TlO₂ (see Discussion).

Discussion

When discussing the present results, it is essential to define the term "protection." In cerebral oxygen deficiency, whether it is caused by arterial hypoxia or by ischemia, there may be changes in function, metabolism or structure, each of which can be reversible or irreversible. In practice, a prophylactic and therapeutic measure could be defined as protective if it prevented or minimized functional, metabolic or structural changes that would occur in its absence. From a clinical point of view, it would be desirable to evaluate the final results of a hypoxic or ischemic insult, and thereby also the efficiency of prophylactic and therapeutic measures, from functional signs and symptoms. However, such indices are not easily studied in experimental animals and, in acute experiments,

it seems preferable to use biochemical indices of tissue hypoxia. There is evidence that unless tissue hypoxia gives rise to changes in adenine nucleotide levels, neuronal cellular damage does not usually result.^{19,29} When no change in ATP, ADP, or AMP is observed, one can tentatively conclude that any oxygen deficiency present is too moderate to induce neuronal damage. At such moderate levels of tissue hypoxia, the amount of lactate accumulated in the tissue and the magnitude of decrease in phosphocreatine may serve as provisional measures of severity of hypoxia.

In hypoxic hypoxia, physiologic "protection" is provided by an increase in CBF. The mechanisms of this increase have not been clarified. However, there are reasons to believe that hypoxia, at least when severe, leads to maximal vasodilatation and that, accordingly, CBF varies passively with the perfusion pressure. It follows from this that prophylactic and therapeutic measures could be protective if they either improve tissue perfusion or reduce the metabolic requirements of the tissue. Since cerebral vasodilatation may be maximal, improvement of CBF should occur mainly via an effect on perfusion pressure.

The present results should be considered in relation to those obtained during hypoxia in normothermic animals. At a body temperature of 37°C, reduction of PaO₂ to 25 torr gives rise to an increase in CBF to about 500 percent of normal, an increase in tissue lactate content to 8–10 mmol·kg⁻¹, a decrease of

phosphocreatine by about $1 \text{ mmol} \cdot \text{kg}^{-1}$, and a small increase in ADP.^{14,15,16-18} At this PaO_2 , arterial TO_2 falls gradually during the course of the 30-minute hypoxic period to reach values of $4-5 \text{ ml} \cdot (100 \text{ ml})^{-1}$. This gradual reduction of TaO_2 can be related to a progressive plasma acidosis with pH values approaching 7.1 at 30 minutes.

In the hypothermic animals, reduction of PaO_2 to 25 torr did not induce an increase in CBF, nor was there any change in tissue metabolites indicative of tissue hypoxia. Undoubtedly, this "protective" effect was partly due to the fact that, in hypothermia, the arterial blood TO_2 did not fall below $15 \text{ ml} \cdot (100 \text{ ml})^{-1}$, i.e., TaO_2 values were about three times as high as those observed in normothermic animals at the same PaO_2 . This can be attributed to two factors. First, a decrease in temperature will by itself cause a shift to the left of the oxyhemoglobin-dissociation curve.²⁰ Second, hypothermia prevented the development of plasma acidosis and, thereby, the rightward shift of the curve that occurs at normal body temperature.

Evidently, if the hypoxic load is defined in terms of PaO_2 , hypothermia has a pronounced protective effect. Since this does not necessarily reflect any protective effect at tissue level, PaO_2 was reduced further to yield an arterial TO_2 of about $5 \text{ ml} \cdot (100 \text{ ml})^{-1}$. Even at this PaO_2 level (11–12 torr), the plasma acidosis was less pronounced than at PaO_2 25 torr in normothermic animals, and it must be concluded that hypothermia efficiently minimizes anaerobic production of lactate in peripheral tissues. At PaO_2 11–12 torr, the hypothermic animals showed a threefold increase in CBF (from 82 ± 11 to $248 \pm 38 \text{ ml} \cdot (100 \text{ g})^{-1} \cdot \text{min}^{-1}$), i.e., there was a less marked increase in CBF than in normothermic animals at comparable arterial TO_2 values (from 114 ± 6 to $516 \pm 41 \text{ ml} \cdot (100 \text{ g})^{-1} \cdot \text{min}^{-1}$, see Jöhanesson and Siesjö¹⁷). In itself, this does not prove that hypothermia is associated with less marked tissue hypoxia. Thus, hypothermia might well limit the circulatory response to hypoxia, e.g., by its influence on blood viscosity, and the low venous blood PO_2 values obtained suggest that tissue hypoxia might have been present. However, the tissue analyses demonstrate that the hypothermic animals had metabolic changes

TABLE 5. Brain Tissue Values of Glucose, Lactate, Pyruvate, Phosphocreatine, Creatine and Adenylates ($\text{mmol} \cdot \text{kg}^{-1}$), and Calculated Lactate/Pyruvate Ratios

Number of Rats	Glucose	Lactate	Pyruvate	Lactate/Pyruvate	PCr	Cr	ATP	ADP	AMP
6	5.64 ± 0.14	1.86 ± 0.08	0.137 ± 0.004	13.9 ± 0.5	4.86 ± 0.04	5.82 ± 0.12	3.06 ± 0.02	0.240 ± 0.003	0.032 ± 0.001
6	5.07 ± 0.19	1.62 ± 0.09	0.101 ± 0.005	15.6 ± 0.9	5.23 ± 0.06	5.54 ± 0.10	3.15 ± 0.02	0.245 ± 0.004	0.031 ± 0.001
6	4.08 ± 0.12	1.90 ± 0.04	0.135 ± 0.004	14.1 ± 0.3	5.14 ± 0.05	5.55 ± 0.05	3.02 ± 0.04	0.274 ± 0.020	0.035 ± 0.002
6	$4.58^* \pm 0.16$	1.061 ± 0.08	0.1981 ± 0.003	20.51 ± 0.3	4.711 ± 0.04	5.971 ± 0.09	2.98 ± 0.03	0.255 ± 0.003	0.032 ± 0.001

The values hypothermic hypoxic groups are compared with values for normothermic and hypothermic normoxic groups from Hagerdal et al.¹⁷ The values hypothermic hypoxic groups are compared with values for normothermic and hypothermic normoxic groups from Hagerdal et al.¹⁷ The values hypothermic hypoxic groups are compared with values for normothermic and hypothermic normoxic groups from Hagerdal et al.¹⁷

* $1.070 > d$
 $0.05 > d$
 $0.05 > d$

that were decidedly less pronounced than those observed at normothermia. This was evident in that, in hypothermia, only about half as much lactate accumulated as in normothermia, the decrease in phosphocreatine concentration was smaller, and no increase in ADP was observed. Therefore, it must be concluded that the smaller increase in CBF reflects more moderate tissue hypoxia, rather than inability for further dilatation. This conclusion is supported by the fact that during hypercapnia hypothermic animals show increases in CBF to higher values than those presently observed.²¹

It should be emphasized that the present results were obtained in animals anesthetized with 70 per cent nitrous oxide. Although there is the theoretical possibility that the anesthetic may influence the response of the normothermic or hypothermic animal to hypoxia, two observations indicate that the effect, if any, should be small. Thus, 70 per cent N₂O does not significantly decrease CMR_{O₂} in the rat (Carlsson, Hägerdal and Siesjö, 1975, in press²²). Furthermore, at 22°C the presence of 70 per cent N₂O does not significantly alter the changes in intermediary metabolites induced by the hypothermia.²²

In conclusion, the present results show that hypothermia exerts a pronounced protective effect on the brain in hypoxic hypoxia. This effect seems to involve two mechanisms. First, since hypothermia shifts the oxyhemoglobin-dissociation curve towards the left, and prevents or minimizes a rightward shift due to acidosis, it maintains a high total oxygen content in arterial blood at a given P_{aO₂}. Second, by reducing CMR_{O₂}, and thereby presumably also cellular energy requirements, hypothermia exerts a protective effect at the cellular level.

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Alpha-adrenergic Blockade

PHENTOLAMINE AND MYOCARDIAL INFARCTION Acute myocardial ischemia was produced by ligation of the left anterior descending coronary artery in 19 dogs. After the development of sustained ST segment elevation and arterial hypotension (systolic pressure less than 80 torr for 30 minutes), phentolamine (2 µg/kg/min) was administered intravenously for 20 minutes. Data were obtained after myocardial infarction and 15 minutes after phentolamine administration. Comparison was made with 11 dogs with similarly produced myocardial ischemia receiving only saline treatment. Acute myocardial ischemia resulted in reductions of heart rate, stroke index, cardiac index, stroke work index, arterial blood pressure, dP/dt, coronary-artery blood flow, coronary vascular resistance, and myocardial oxygen uptake. Left ventricular end-diastolic pressure (LVEDP), systemic vascular resistance, and myocardial A-V O₂ difference increased. Phentolamine administration was accompanied by an increased mean cardiac index without change in LVEDP

or heart rate. Mean systemic vascular resistance decreased while mean arterial pressure increased. With improved cardiac performance, coronary blood flow increased by 41 per cent and myocardial oxygen uptake by 21 per cent. Similar changes were not observed in control animals. The authors suggest that phentolamine decreased myocardial oxygen requirements by: 1) decreasing systemic vascular resistance and afterload; 2) antagonizing venous constriction, thereby decreasing left ventricular end-diastolic volume (a decrease in heart size reduces myocardial oxygen needs). The authors suggest that the cautious use of alpha-adrenergic blockade can increase cardiac output without decreasing arterial pressure. They further indicate that the enhanced coronary blood flow and decreased oxygen requirements may be advantageous clinically. (Nagasawa K, Vyden JK, et al: Effect of Phentolamine on Cardiac Performance and Energetics in Acute Myocardial Infarction. *Circ Shock* 2: 5-11, 1975.)