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The Relationship among Canine Brain Temperature, Metabolism, and Function during Hypothermia

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Cerebral protection by hypothermia is commonly attributed to cerebral metabolic suppression. However, at temperatures below 28° C, the relationship of temperature to cerebral metabolic rate of oxygen consumption (CMR_{O_2}) has not been well characterized. Accordingly, the relationship between brain temperature and CMR_{O_2} was determined in eight dogs during cooling from 37 to 14° C while the EEG was continuously monitored. Cardiopulmonary bypass was initiated and control measurements were made at 37° C during anesthesia with nitrous oxide 50–60% inspired and morphine sulfate 2 $mg \cdot kg^{-1}$ intravenously (iv). Upon cooling to 27° C, the nitrous oxide was discontinued and the morphine was antagonized with naloxone 2 mg iv. Measurements were repeated at 27, 22, 18, and 14° C and in four dogs again at 37° C after nitrous oxide 50–60% had been reestablished at 27° C along with administration of morphine sulfate 2 $mg \cdot kg^{-1}$. For each temperature interval, the temperature coefficient (Q_{10}) for CMR_{O_2} was calculated (Q_{10} = CMR_{O_2} at x° C ÷ CMR_{O_2} at [x−10]° C). Between 37 and 27° C the Q_{10} was 2.23, but between 27 and 14° C the mean Q_{10} was doubled to 4.53. With rewarming to 37° C, CBF and CMR_{O_2} returned to control levels, and brain biopsies revealed a normal brain energy state. During cooling, the EEG developed burst suppression at or below 22° C. With further cooling, the periods of suppression increased; however, burst activity continued in seven of eight dogs even at 14° C. We conclude that the relationship of CMR_{O_2} to brain temperature is variable depending on the functional state of the brain; below 27° C progressive functional depression presumably accounts for the unexpectedly high Q_{10} values for CMR_{O_2}. (Key words: Brain: blood flow; electroencephalography; metabolism; temperature. Hypothermia.)

THE POTENTIAL for cerebral protection by profound hypothermia is well established and is commonly used clinically, particularly for open heart surgery to repair congenital defects. Thus, it is common for total circulatory arrest to be induced in patients for 60 min or more at 15–18° C without any subsequent cerebral dysfunction.[1] It is classically assumed that such protection is accounted for primarily by a temperature-induced decrease in cerebral oxygen demands sufficient to permit tolerance for such prolonged periods of absent oxygen delivery, although other mechanisms also may be operative.[2,3] Thus, an understanding of the relationship of temperature to the cerebral metabolic rate of oxygen consumption (CMR_{O_2}) is critical to an understanding of the protection that can be anticipated at any given temperature. For this purpose it is helpful to use the temperature coefficient (Q_{10}) for CMR_{O_2}. The Q_{10} for CMR_{O_2}, simply defined, is the ratio of two CMR_{O_2} values (higher divided by lower) over a 10° C range; it assumes a constant exponential function over a clinically relevant temperature range (38–14° C).

Though somewhat controversial, the Q_{10} for CMR_{O_2} is often stated to be between 2.0 and 3.0, which is also the Q_{10} for most biologic reaction rates.[4] Such a Q_{10} value for CMR_{O_2} has been reported in two *in vivo* canine studies for temperatures between 37 and 27°C[5,6] and also in *in vitro* brain slices.[7]

Another common assumption is that the normal human brain will withstand up to 5–6 min of circulatory arrest at 38° C without permanent cerebral injury. This figure, taken with an assumed Q_{10} of 2.5, will not explain, on a metabolic basis, the proven human tolerance for 60 min or more of circulatory arrest at 18° C.[1] Instead, it would predict that the brain's tolerance at 18° C would be little more than 30 min (5.5 min × 2.5 × 2.5 = 34 min).

There are three possible explanations for this apparent contradiction: 1) the Q_{10} for the human brain between 38 and 18° C is considerably greater than 2.5; 2) the brain's tolerance for circulatory arrest at 38° C is considerably greater than 5–6 min; or 3) the basis for protection during profound hypothermia depends on something more than just metabolic suppression.

In a previous canine study from our laboratory, Steen *et al.*[6] reported CMR_{O_2} values consistent with a Q_{10} value of 2.0–3.0 at temperatures between 37 and 28° C. However, at temperatures less than 28° C (18 and 14° C), the reported CMR_{O_2} values yielded a calculated Q_{10} approximately double that at the higher temperatures. If correct, this would explain the apparent contradiction above (5.5 min × 2.5 × 5.0 = 69 min).

The current study was designed to examine these relationships in more detail in order to 1) confirm (or refute) the results reported by Steen *et al.*[6]; 2) if the latter results were confirmed, to attempt to relate cerebral metabolic effects to functional (EEG) effects; and 3) also if the latter results were confirmed, to determine if these observations

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are possibly artifactual, secondary to deterioration of the preparation with time.

Materials and Methods

The protocol was reviewed and approved by the Institutional Animal Care and Use Committee. Eight unmedicated, fasting adult mongrel dogs, weighing 17.5 ± 0.7 kg (mean ± standard error of the mean [SEM]) were studied. With the dog in a Plexiglas® box, anesthesia was induced with halothane 3 to 4% inspired. Following the onset of anesthesia, muscle relaxation was produced with pancuronium 0.2 $mg \cdot kg^{-1}$ iv, and the trachea was intubated. Ventilation was controlled with a Harvard® pump set to maintain arterial carbon dioxide tension (Pa_{CO_2}) at 35–40 mmHg. Anesthesia was maintained with halothane 1% expired (Perkin Elmer mass spectrometer) in nitrogen and oxygen adjusted to maintain arterial oxygen tension (Pa_{O_2}) at 100–150 mmHg. Muscle paralysis was maintained by administering pancuronium 0.05 $mg \cdot kg^{-1}$ iv as needed.

Cannulas were inserted in a femoral artery for mean arterial blood pressure (MAP) measurements and blood sampling and in a femoral vein for drug and fluid administration. After anticoagulation with heparin (300–400 units $\cdot kg^{-1}$ iv), the sagittal sinus was exposed, isolated, and cannulated as described previously[8,9] for direct measurements of cerebral blood flow (CBF) from the anterior, superior, and lateral portions of both hemispheres (in normal brains this is equal to approximately 54% of the total brain weight[8,9]). Flow was recorded continuously with a flow-through electromagnetic flow probe (Carolina Medical Electronics, Inc., King, NC). CMR_{O_2} was calculated as the product of CBF and arterial − sagittal sinus blood oxygen content differences. A standard, nonprocessed, four-lead, two-channel EEG (bifrontal, biparietal) was recorded from electrodes glued to the skull. Body temperature was measured with an esophageal thermistor and brain temperature with a parietal epidural thermistor. Both had been calibrated previously with a mercury thermometer for the temperature range of 37–14° C.

To enable cardiopulmonary bypass, a left-sided thoracotomy was performed and the azygos vein ligated. For venous drainage to the extracorporeal circuit, cannulas were placed in the superior vena cava, inferior vena cava, and right ventricle *via* the right atrial appendage. The blood circulated through an oxygenator (Temptrol Pediatric Q110) and through a water bath for temperature control and was returned *via* a cannula (8 mm ID) in the root of the aorta. The bypass machine was primed with blood (about 1 l) from a donor dog and with saline (about 500 ml). During bypass, volume was added (300–600 ml saline) as needed. In individual dogs bypass flows were adjusted between 1.5 and 3.0 $l \cdot min^{-1} \cdot m^{-2}$ in order to maintain MAP between 60 and 100 mmHg throughout the period of hypothermic bypass. Sodium bicarbonate was administered as needed to maintain buffer base near 40 $mEq \cdot l^{-1}$.

After completion of the surgical preparation and the establishment of cardiopulmonary bypass, the halothane was discontinued; nitrous oxide (50–60%) replaced the nitrogen in the inspired gases; and morphine sulfate 2 $mg \cdot kg^{-1}$ iv was given. Twenty to thirty minutes after the discontinuation of halothane, duplicate control cerebral and systemic measurements were obtained at 37° C. Thereafter, the dogs were cooled to 27° C (requiring a mean time of 14 min), and duplicate measurements were repeated. Nitrous oxide was then replaced with 100% oxygen, and naloxone 2 mg iv was administered. Duplicate measurements were repeated 5 min later. Thereafter, the dogs were cooled to 22, 18, and 14° C and duplicate measurements repeated at each step (requiring a mean time of 55 min).

In four dogs the experiments were then terminated by circulatory arrest. In the other four dogs cardiopulmonary bypass was continued and the animals were rewarmed to 37° C (requiring a mean time of 41 min). At 27° C, 50–60% nitrous oxide was again introduced, and morphine sulfate, 2 $mg \cdot kg^{-1}$ iv was administered. At 37° C, duplicate measurements were again taken. Thereafter, the cerebral hemispheres were exposed by incising the dura, and bilateral brain biopsies were taken using a vacuum device that deposits a brain sample (approximately 200 mg) into liquid nitrogen in less than 1 s.

The animals then were killed with intravenous potassium chloride and termination of bypass. The total time of cardiopulmonary bypass was less than 2.5 h. Because the blood donor dogs had been anesthetized with pentobarbital a single sample was taken (at 22° C) for determination of the serum pentobarbital concentration by gas chromatography.

Carbon dioxide was added to the oxygenator gas mixture to keep Pa_{CO_2} at 35–40 mmHg during normothermic control measurements. Thereafter, no adjustment in the carbon dioxide gas flow rate was made during cooling or rewarming. For samples taken at 37 and 27° C, blood oxygen contents were calculated from oxyhemoglobin concentrations (IL 282 CO-oximeter) and oxygen tensions measured on IL electrodes maintained at 37° C. At 22° C carbon dioxide tensions were measured on IL electrodes maintained at 19° C. At 18 and 14° C, sagittal sinus blood was nominally saturated, and oxygen content differences were calculated only from oxygen tensions as measured on IL electrodes maintained at 19° C. These measurements were corrected to 37°C[10] prior to calculating oxygen content differences. Measurements at 19° C were necessary since samples taken at and below 22° C formed macrobubbles when measurements were attempted at 37°

C but not at 19° C. None of the tabulated blood gas or *p*H values was temperature-corrected; they are reported as measured at either 37 or 19° C. Brain biopsies were analyzed by an enzymatic fluorometric method to determine concentrations of phosphocreatine, adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), lactate, pyruvate, and glucose.[11] The energy charge (EC) was calculated using the following equation[12]:

$$EC = \frac{ATP + 0.5\ ADP}{ATP + ADP + AMP}$$

All tabulated values are reported as mean ± SEM. Selected measurements (see Results) at each temperature were compared by analysis of variance and the least significant difference procedure if the F value achieved a significant level. Q_{10} values for each temperature interval were calculated by plotting the measured CMR_{O_2} values on semilog paper and extrapolating over 10° C intervals (Q_{10} = CMR_{O_2} at x° C ÷ CMR_{O_2} at [x−10]° C). The Q_{10} values were then compared by analysis of variance and the least significant difference procedure.

Results

As anticipated, progressive cooling from 37 to 14° C was accompanied by a significant progressive decrease in CMR_{O_2} (table 1 and fig. 1) and a significant decrease in CBF at all hypothermic levels (table 1) compared to that at 37° C. The replacement of nitrous oxide with oxygen and the administration of naloxone 2 mg iv at 27° C during cooling had no effect on CMR_{O_2} or CBF (table 1). There was a transient increase in MAP and the expected increase in Pa_{O_2}. MAP did not otherwise significantly change during cooling. Blood gas and *p*H values were not compared statistically because of the temperature measurement variables (see Materials and Methods); however, buffer base values were normal and were not different during cooling and rewarming (table 1). In the four animals that were rewarmed to 37° C, both the mean CMR_{O_2} and the CBF returned to near mean control (precooling) levels (3.90 *vs.* 3.94 ml · 100 g^{-1} · min^{-1} for CMR_{O_2}, and 55 *vs.* 61 ml · 100g^{-1} · min^{-1} for CBF). The only significant change between rewarmed values and precooled values was in MAP (131 *vs.* 89 mmHg) due to a significant increase in systemic vascular resistance (mean cardiac index was unchanged: 2.37 *vs.* 2.34 l · min^{-1} · m^{-2}). During cooling the mean cardiac index was likewise unchanged (not tabulated; mean range: 2.22–2.41 l · min^{-1} · m^{-2}).

The magnitude of change in CMR_{O_2} during cooling as reflected by the calculated Q_{10} values at each temperature

TABLE 1. Brain Temperature, $CMRO_2$, CBF, MAP, and Blood Gas Values

n	8	8	8*	7	8	8	4
Brain temperature (° C)	37.0 ± 0.1	26.9 ± 0.1	26.8 ± 0.1	22.1 ± 0.0	17.9 ± 0.1	14.0 ± 0.0	37.1 ± 0.0
$CMRO_2$ (ml · 100 g^{-1} · min^{-1})†	3.89 ± 0.20	1.75 ± 0.10	1.75 ± 0.09	0.92 ± 0.09	0.47 ± 0.04	0.27 ± 0.03	3.90 ± 0.33
CBF (ml · 100 g^{-1} · min^{-1})	74 ± 10‡	40 ± 6	36 ± 5	30 ± 5	43 ± 8	31 ± 5	55 ± 8
MAP (mmHg)	85 ± 6	67 ± 5	92 ± 7	81 ± 9	78 ± 7	66 ± 4	131 ± 9
Pa_{O_2} (mmHg)	122 ± 12	304 ± 22	533 ± 24	467 ± 14	479 ± 16	513 ± 21	155 ± 21
Pa_{CO_2} (mmHg)	38 ± 1	48 ± 1	45 ± 2	26 ± 1	28 ± 2	31 ± 2	34 ± 1
*p*H	7.32 ± 0.02	7.22 ± 0.02	7.25 ± 0.03	7.45 ± 0.01	7.41 ± 0.03	7.35 ± 0.04	7.34 ± 0.01
Buffer base (mEq · l^{-1})	40 ± 1	38 ± 1	39 ± 1	41 ± 1	39 ± 1	39 ± 1	39 ± 1

Values are mean ± SEM.
Blood gas values at 37 and 27° C were measured at 37° C and are uncorrected. Blood gas values at 22, 18, and 14° C were measured at 19° C and are uncorrected.
CMR_{O_2} = cerebral metabolic rate for oxygen; CBF = cerebral blood flow; MAP = mean arterial pressure.

* These measurements were made 5 min following replacement of N_2O with O_2 and administration of naloxone, 2 mg.
† At the different temperatures (37, 27, 22, 18, and 14° C) the CMR_{O_2} values differed significantly from one another, $P < 0.05$.
‡ Significantly different from all hypothermic CBF values, $P < 0.05$.

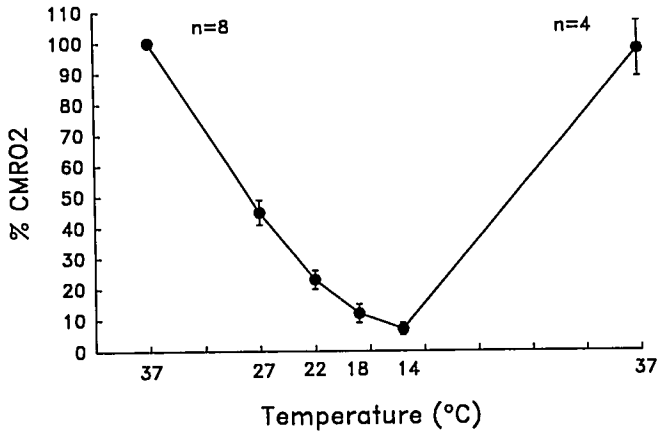

FIG. 1. Effect of temperature on CMR_{O_2}. The change in CMR_{O_2} with change in temperature is plotted as a percent of control (±SD). The relationship is neither linear nor exponential. With rewarming CMR_{O_2} returned to control. On the abscissa each temperature interval equals 5° C.

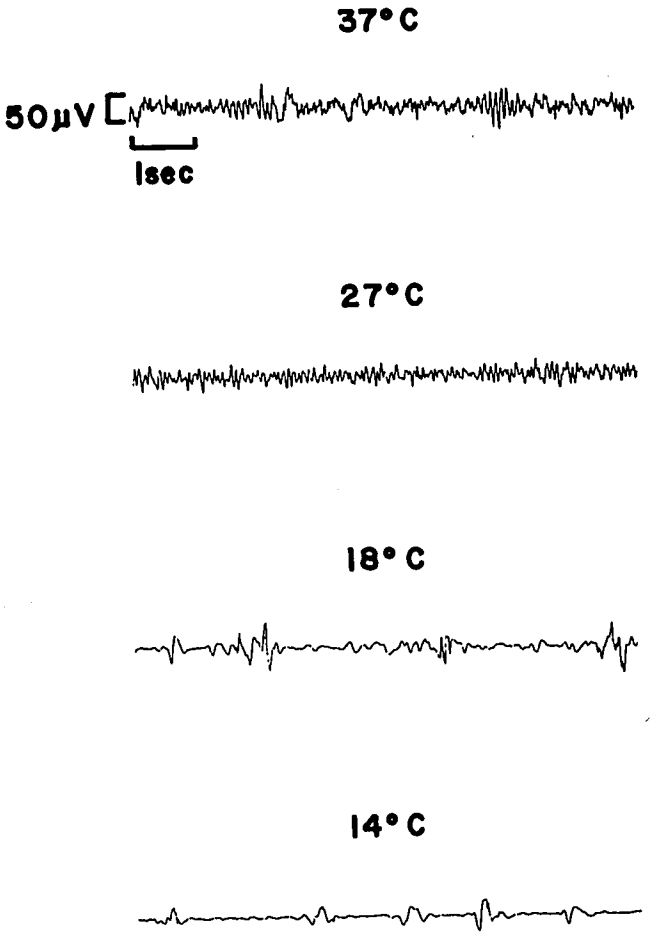

FIG. 2. Representative EEG tracings from a dog taken at 37, 27, 18, and 14° C.

interval was not constant (table 2). Between 37 and 27° C a mean Q_{10} value slightly greater than 2.0 (2.23) was again observed, as previously reported.[6-8] With decreases in temperature below 27° C to as low as 14° C, the mean Q_{10} was doubled to 4.53, a significant increase. There were no significant differences between Q_{10} values at different temperature intervals below 27° C. Clearly the relationship of temperature to CMR_{O_2} during cooling from 37 to 14° C was neither linear (fig. 1) nor exponential. The increased rate of decline in CMR_{O_2} below 27° C also could not be accounted for by deterioration in the preparation, since with rewarming, CMR_{O_2} returned to control values, with an overall Q_{10} (14–37° C) of 3.27.

During cooling there were progressive changes in the EEG (fig. 2). Between 37 and 27° C there were no consistent changes in frequency, but there was a consistent modest decrease in mean amplitude. Below 27° C a progressive pattern of decreasing frequency and increasing amplitude was observed with onset of burst suppression at or below 22° C. At 14° C only one animal was completely isoelectric; the remaining dogs continued to show burst activity of variable frequency (every 2–6 s).

After rewarming, in addition to a return to control CMR_{O_2} and CBF values, the brain energy state was normal as reflected by the concentrations of ATP and phosphocreatine and the energy charge (table 3). Brain glucose, lactate, and pyruvate concentrations after rewarming were increased relative to normal laboratory values. Blood glucose concentrations were above normal but did not change during cooling and rewarming (mean range: 164–181 $mg \cdot dl^{-1}$); blood lactate levels were also increased throughout the period of cardiopulmonary bypass (mean range: 4.5–4.9 $\mu mol \cdot ml^{-1}$). The latter is probably accounted for primarily by the use of 2–4-day-old donor blood for priming the bypass machine, in which lactate levels ranged from 4.0–8.0 $\mu mol \cdot ml^{-1}$. The serum pentobarbital concentrations that were obtained during bypass (at 22° C) yielded a mean value of only 1.3 ± 0.1 $\mu g \cdot ml^{-1}$, insufficient to affect CMR_{O_2} values.[13]

TABLE 2. Calculated CMR_{O_2} Q_{10} Values for Different Temperature Intervals during Cooling and Rewarming

	Temperature Interval (° C)	n	Q_{10}
Cooling	37–27	8	2.23 ± 0.06*
	27–22	7	3.76 ± 0.39
	22–18	7	5.87 ± 1.01
	18–14	8	5.00 ± 1.16
Rewarming	14–37	4	3.27 ± 0.21

Values are mean ± SEM.
* Significantly different from all other values during cooling, $P < 0.05$.

TABLE 3. Cerebral Metabolites after Rewarming

	N	ATP ($\mu mol \cdot g^{-1}$)	Phosphocreatine ($\mu mol \cdot g^{-1}$)	EC	Glucose ($\mu mol \cdot g^{-1}$)	Lactate ($\mu mol \cdot g^{-1}$)	Pyruvate ($\mu mol \cdot g^{-1}$)
Experimental	4	2.10 ± 0.05	3.22 ± 0.06	0.90 ± 0.00	4.32 ± 0.42	5.04 ± 2.05	0.18 ± 0.02
Laboratory normals*	6	2.01 ± 0.01	2.99 ± 0.12	0.87 ± 0.00	2.46 ± 0.18	1.23 ± 0.04	0.12 ± 0.00

Values are mean ± SEM.
* From Roald *et al.*[21]
ATP = adenosine triphosphate; EC = energy charge.

Discussion

In a previous study from our laboratory, Steen *et al.*[6] reported the effects of profound hypothermia on canine CMR_{O_2} with and without the addition of thiopental. One conclusion from that work was that although the relationship of temperature to CMR_{O_2} was exponential in the absence of EEG activity (as produced by large doses of thiopental), in the presence of EEG activity the relationship was a complex one, neither linear nor exponential. Q_{10} is an expression commonly used to describe the metabolic rate changes that occur with temperature alterations, and the expression assumes an exponential function. In the current study, in the study by Steen *et al.*,[6] and in an earlier canine study (using surface cooling),[5] we reported CMR_{O_2} values between 37 and 27° C that yielded consistent Q_{10} values of 2.23, 2.45, and 2.23, respectively for the three studies. If such a Q_{10} value is also applicable at lower temperatures, it implies a 55–60% reduction in CMR_{O_2} for every 10° C reduction in temperature. Such a reduction cannot explain the proven tolerance of the human brain for periods of circulatory arrest of 60 min (or more) at 18° C,[1] at least on a metabolic basis alone. Thus, even if one assumes that the human brain can tolerate as much as 8 min of circulatory arrest at 38° C, a Q_{10} of 2.23 would predict only a 40-min period of tolerance at 18° C (8 min × 2.23 × 2.23 = 40 min). This again assumes that cerebral protection by hypothermia is secondary solely to a decrease in CMR_{O_2}.

This apparent contradiction leads to the conclusion either that the Q_{10} for canine brain differs from that of human brain or that the Q_{10} below 27° C is much greater than 2.23. Otherwise, the basis for brain protection during profound hypothermia must be more than just cerebral metabolic suppression. In the study by Steen *et al.*, CMR_{O_2} was measured at 37, 28, 18, and 14° C.[6] From their reported CMR_{O_2}, the calculated Q_{10} for the temperature interval of 37–28° C was 2.45, whereas for the interval of 28–18° C the Q_{10} was 4.95. If these relationships are correct and applicable to the human brain, then even if one chooses a more realistic time of 5–6 min for human brain tolerance for circulatory arrest at 38° C, a tolerance for 60 min of circulatory arrest at 18° C is explainable on a metabolic basis alone (5.5 min × 2.45 × 4.95 = 67 min). Steen *et al.* also reported that at 18–17° C, the EEG was isoelectric in all dogs.[6] Also, Steen *et al.* did not return their dogs to control CMR_{O_2} values with rewarming because the design of that study superimposed the metabolic effects of high-dose thiopental during rewarming.[6] These facts suggest two possible explanations for their observed increase in the Q_{10} value at temperatures below 28° C: either a major neurofunctional (and hence metabolic) change occurred between 28 and 18° C or the observed decrease in CMR_{O_2} at these temperatures was artifactual, secondary to deterioration of the preparation with time. If the explanation is based on a neurofunctional effect, then it is important to determine whether this is a step change (*e.g.*, with onset of an isoelectric EEG) or a progressive change between 28 and 18° C. The current study was designed to address these issues. We measured CMR_{O_2} at 37, 27, 22, 18, 14, and again at 37° C in the absence of thiopental. Differences in anesthetic management between this study and the study by Steen *et al.*[6] at temperatures above 27° C preclude meaningful comparisons. However, below 27° C there should have been no meaningful anesthetic effects in either study (at 27° C, in humans, sensorium is markedly depressed, as seen by loss of response to verbal commands[14,15]; accordingly, anesthesia was discontinued in this study at 27° C), and comparisons are appropriate. Steen *et al.*[6] reported a mean CMR_{O_2} at 18° C of 0.45 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, as compared to 0.47 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ in the current study. At 14° C, the CMR_{O_2} values for the two studies were 0.35 and 0.27 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively. Such close agreement underlines the validity of the method used in the current study for measuring blood oxygen content differences at these low temperatures. Steen *et al.*[6] measured oxygen contents directly by the Van Slyke method, whereas in the current study we relied on oxygen tension measurements made at 19° C and corrected to 37° C.

The possibility that the low CMR_{O_2} values reported at 18 and 14° C in these two studies (and hence the similar high Q_{10} below 28° C) were secondary to deterioration

of the preparation can be clearly rejected. In the current study, rewarming returned both CBF and CMR_{O_2} to control levels, and the brain energy state was normal. Furthermore, in Steen *et al.*'s study,[6] CMR_{O_2} did return to the expected level with rewarming (approximately 50% of control), based on the known effects of a large dose of thiopental on CMR_{O_2} at normothermia.[16]

We conclude that the marked increase in canine Q_{10} between 28 and 18° C, as reported in both the current study and that by Steen *et al.*,[6] is real and must be explained on a neurofunctional basis. There were differences between the two studies in regard to the EEG effects of profound hypothermia. Steen *et al.* reported an isoelectric EEG in six of six dogs at 18–17° C,[6] whereas in the current study we observed continual burst activity in seven of eight dogs, even at 14° C. Such variability in the EEG effects of profound hypothermia has been reported by others[1,14,17,18] and in different species (including humans). In Steen *et al.*'s study, temperature was abruptly decreased from 28 to 18° C,[6] whereas in the current study we cooled in stages, first to 22° C and then to 18° C. Possibly some accommodation occurs, and staged cooling accounts for the differences. In any case, in the current study there clearly was not a step change in CMR_{O_2} to correlate with any EEG change between 27 and 14° C. Rather, the Q_{10} values at each temperature interval below 27° C were similarly increased to near 4.50, as compared to that of 2.23 between 37 and 27° C.

In humans it has been reported that cooling to 34–33° C produces an apparent cerebral stimulatory effect, as reflected by arousal in patients with depressed sensoria, increased amplitude in evoked potentials, and hyperresponsive reflexes.[14] Below 32° C this apparent stimulation is replaced by progressive functional suppression, which becomes marked below 27° C.[14,15] These biphasic functional observations presumably are paralleled by metabolic changes and are consistent with the increased Q_{10} values observed in the current study and in Steen *et al.*'s study[6] at temperatures below 27° C.

These relationships are readily understandable once it is accepted that the primary effects of hypothermia on integrated neuronal function (and the EEG) occur between 27 and 17° C. It is known that at normothermia complete suppression of integrated neuronal function (*e.g.*, an isoelectric EEG produced by thiopental) causes an approximate 50% reduction in CMR_{O_2}.[16] If one accepts the "true" Q_{10} for the brain to be 2.3 in the absence of any neurofunctional interaction, then the following must be true. At 27° C the CMR_{O_2} will be decreased to 43% of normal, due primarily to the temperature effect alone; theoretically, at 17° C it would be further decreased by the temperature effect to 19% of normal. However, the 43% value at 27° C will be decreased by about 50% at 17° C secondary to the neurofunctional suppression alone ("functional Q_{10}" = 2.0). This, combined with the temperature effect alone (Q_{10} = 2.3), results in a final decrease in CMR_{O_2} to 9–10% of control and a calculated Q_{10} between 27 and 17° C of 4.5.

The high brain concentrations of glucose, lactate, and pyruvate after rewarming might be explained, in part, by disruption of the blood–brain barrier. It has been reported that nonpulsatile cardiopulmonary bypass in dogs disrupts the blood–brain barrier and thus allows larger molecules to more readily enter into the brain tissue.[19,20] Thus, with increased blood concentrations of glucose and lactate during bypass, as occurred in the dogs of the current study, increased brain concentrations might also occur.

In conclusion, the relationship between brain temperature and CMR_{O_2} is a complex one that involves an interaction between temperature effects on rates of biochemical reactions and, in turn, on cerebral function. A Q_{10} slightly greater than 2.0 between 37 and 27° C is consistent with the expected Q_{10} for most biologic reactions and implies little functional interaction. Below 27° C, major functional effects are known to occur and presumably account for a marked increase in Q_{10} to near 4.5. These relationships have major implications for the potential brain protective effects provided by profound hypothermia.

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