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Laboratory Report

Hyperthermia and Halothane MAC in the Dog

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To evaluate the effect of hyperthermia on anesthetic requirement, the changes in minimum alveolar concentration (MAC) of halothane which accompanied increases in esophageal temperatures from 37.3 to 45.9 C were determined in eight spontaneously-breathing dogs. MAC increased linearly by 27 per cent as temperature rose to 40.7 C (*i.e.*, 8 per cent per degree C). At temperatures above 42 C MAC decreased. Death occurred at a mean temperature of 45.9 C. (Key words: Anesthetics, volatile: halothane; Potency, anesthetic: MAC; Hyperthermia: MAC.)

MODERATE HYPOTHERMIA reduces anesthetic requirements of homeotherms such as the dog[1,2] and the rat.[3] The effect of an increase in temperature has not been measured. To evaluate this effect, we determined the effect of hyperthermia on the minimum alveolar concentration (MAC) of halothane required to eliminate movement in response to a painful stimulus.

Materials and Methods

Eight healthy, unpremedicated, spontaneously-breathing dogs of various ages, breeds, sexes, and weights (14.4 kg ± SE 1.0; range 10.0–18.6 kg) were studied. Anesthesia was induced and maintained with halothane in oxygen. A cuffed endotracheal tube was introduced without the use of muscle relaxants. Intermittent end-tidal gas samples were obtained from a nylon catheter inserted through the endotracheal tube to within 1–3 cm of the endotracheal tube end. Halothane was analyzed with a Beckman LB-1 infrared gas analyzer frequently calibrated against a known halothane concentration. MAC was determined[4,5] as temperature slowly increased (approximately 1 C/45–60 minutes) from 37 to 46 C. All measurements were made after at least 15 minutes of a constant end-tidal halothane concentration. During periods of rapid respirations (as frequently occurred from 41 to 43 C), a gas sample was obtained at expiration by firmly compressing the animal's chest and clamping the endotracheal tube with a large hemostat just proximal to the sampling catheter. After sampling, the dog's lungs were re-expanded by two or three maximal inflations (to 30 cm H_2O airway pressure).

Hyperthermia was produced by insulating the animals with blankets and exposure to a heating lamp and/or heating blankets positioned above and below the body. Esophageal temperature was measured with a thermistor-probe electrode and a Yellow Springs telethermometer previously calibrated against a Bureau of Standards mercury thermometer or directly with the Bureau of Standards thermometer.

Blood for blood-gas, microhematocrit, and arterial blood glucose analyses was drawn from catheters positioned in the proximal aorta and right atrium via a femoral cutdown. We measured arterial and mixed venous (right atrium) oxygen and carbon dioxide partial pressures and *p*H using electrodes. Arterial carbon dioxide tensions and *p*H were corrected to the temperatures of the animals at the time of sampling, assuming reliability

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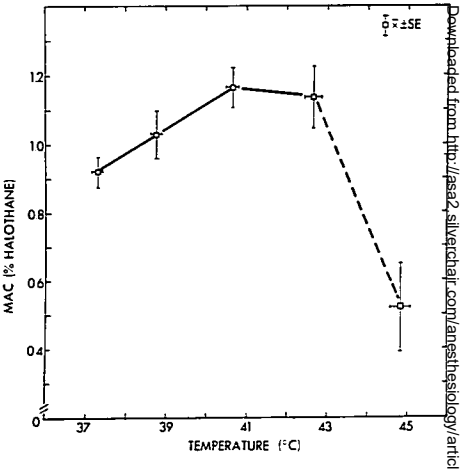

FIG. 1. The effect of hyperthermia on halothane MAC. Death occurred at a mean temperature of 45.9 C.

of correction factors at temperatures above 38 C.[6] We calculated arterial and mixed venous oxygen content at 37 C from blood-gas, *p*H, and hematocrit values. Aortic blood pressure and heart rate were recorded on a Beckman polygraph. Mean pressures were determined electrically.

In three dogs we measured oxygen uptake with a Tissot spirometer. All volumes were corrected to STPD, but no correction was made for the slight error produced by continued halothane uptake.

Individual experiments lasted 8–12 hours during which time the animals received

TABLE 1. Halothane Concentration at MAC vs. Temperature

	36–38 C		38–40 C		40–42 C		42–44 C		44 C		Death
	Temp. (C)	MAC (Per Cent)	Temp. (C)	MAC (Per Cent)	Temp. (C)	MAC (Per Cent)	Temp. (C)	MAC (Per Cent)	Temp. (C)	MAC (Per Cent)	Temp. (C)
Dog 1	37.4	0.94	—	—	40.5	1.08	42.0	1.27	—	—	46.0
Dog 2	37.0	0.79	38.8	0.94	40.8	1.09	43.3	1.31	45.5	0.45	46.0
Dog 3	37.3	1.01	39.1	1.17	41.0	1.28	42.3	1.33	—	—	45.8
Dog 4	37.2	1.06	38.8	1.17	40.2	1.23	—	—	45.2	0.33	45.9
Dog 5	37.6	0.89	38.8	0.91	41.0	1.14	42.7	1.18	44.9	0.32	45.2
Dog 6	37.3	1.10	38.5	1.28	40.2	1.45	43.0	1.01	44.1	0.95	46.8
Dog 7	37.3	0.92	38.4	0.94	40.9	1.15	—	—	—	—	—
Dog 8	37.4	0.67	39.0	0.79	40.7	0.91	42.8	0.72	44.4	0.57	—
Mean	37.3	0.92	38.8	1.03	40.7	1.17	42.7	1.14	44.8	0.52	45.9
SE	0.1	0.05	0.1	0.07	0.1	0.06	0.2	0.10	0.3	0.13	0.4

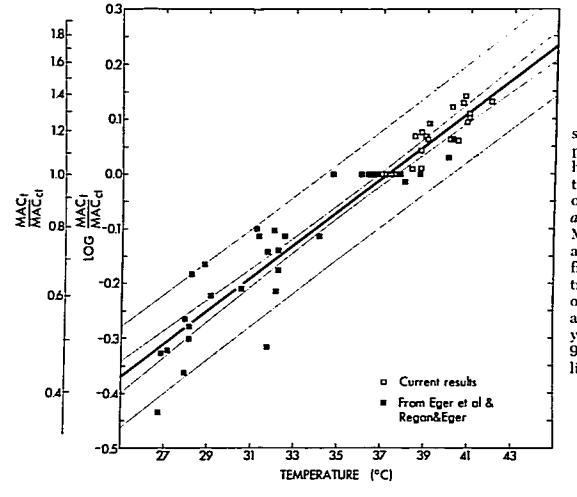

FIG. 2. The relationship of esophageal temperatures from 26–42 C to halothane MAC. Information on hypothermia was obtained from Eger *et al.*[1] and Regan and Eger.[2] MAC values are plotted as fractional changes from normothermic (control or MAC CT) values on logarithmic (right y axis) and arithmetic (left y axis) coordinates. The 95 per cent confidence limits are shown.

continuous intravenous infusion of 1 to 2 liters of 5 per cent dextrose in Ringer's lactate solution. During periods of hypoventilation (usually at temperatures greater than 44 C), breathing was manually assisted or controlled by compression of the rebreathing bag.

A linear regression relating the arithmetic and logarithmic changes in halothane concentrations at MAC produced by a rise in temperature was determined by the method of least squares. A similar statistical analysis was performed with a composite of previously published hypothermia data in dogs[1,2] and our current findings.

Results

In all dogs MAC increased as temperatures rose from 37 to 42 C (fig. 1, table 1). At temperatures above 42 C, MAC declined. Death occurred at a mean temperature of 45.9 C. The change in MAC from control (approximately 37 C) with progressive hyperthermia to 42 C fit arithmetic ($r = 0.910$) and logarithmic ($r = 0.915$) coordinates equally well. The equations were $Y = 0.079X - 1.956$ ($n = 24$) and $\log Y = 0.030X - 1.115$ ($n = 24$), where Y was change in MAC from control (value at 37 C) and X was temperature in degrees C. Analyses of composite data for hyperthermia to 42 C and hypothermia[1,2] to 26.8 C also showed similar likenesses for arithmetic ($r = 0.959$) and logarithmic ($r = 0.953$) plots (fig. 2). The equations were $Y = 0.057X - 1.088$ ($n = 59$) and $\log Y = 0.030X - 1.128$ ($n = 59$), where X and Y again denote temperature and change in MAC from control (37 C value), respectively.

Except for heart rate and oxygen uptake, all variables remained relatively constant to about 42 C (table 2). Above 42 C, hematocrit and arterial oxygen content increased slightly, while mean arterial pressure and Pa_{CO_2} decreased. Heart rate and oxygen uptake progressively increased directly with temperature.

Discussion

Our finding that hyperthermia to 42 C increased the halothane MAC about 8 per cent per degree C is in accord with the clinical impression that hyperthermia increases anesthetic requirement. The 8 per

TABLE 2. Summary of Results* of Increasing Temperature in Dogs

	Temperature (C)				
	36–38	38–40	40–42	42–44	>44
Temperature (C)	37.3 ± 0.1 (8)	38.8 ± 0.1 (7)	40.7 ± 0.1 (7)	42.7 ± 0.2 (7)	44.8 ± 0.3 (5)
Mean aortic pressure (torr)	88 ± 6 (8)	89 ± 8 (7)	94 ± 9 (7)	95 ± 9 (7)	70 ± 11 (5)
Heart rate (beats/min)	100 ± 9 (8)	117 ± 13 (7)	125 ± 8 (7)	171 ± 17 (7)	264 ± 10 (5)
Glucose (mg/100 ml)	129 ± 15 (4)	131 ± 16 (2)	115 ± 1 (2)	112 ± 12 (4)	— —
Pa_{CO_2} (torr)	48 ± 4 (8)	51 ± 2 (7)	51 ± 2 (7)	43 ± 4 (7)	39 ± 13 (3)
pH_a	7.31 ± 0.02 (8)	7.29 ± 0.02 (7)	7.30 ± 0.01 (7)	7.33 ± 0.03 (7)	7.35 ± 0.0 (3)
Arterial oxygen content (vol. per cent)	17.2 ± 0.7 (6)	17.3 ± 0.6 (6)	17.2 ± 0.8 (5)	18.6 ± 0.4 (5)	19.1 (1)
Mixed venous oxygen content (vol per cent)	15.0 ± 0.9 (6)	14.7 ± 0.8 (6)	14.5 ± 0.9 (5)	15.0 ± 0.4 (5)	15.3 (1)
Oxygen uptake (ml/min)	78 ± 6 (3)	97 ± 5 (3)	99 ± 10 (2)	134 ± 9 (3)	145 ± 20 (2)
Hematocrit (per cent)	34.8 ± 4.6 (6)	36.2 ± 3.7 (6)	36.0 ± 4.0 (5)	39.6 ± 2.1 (5)	40 (1)

* $\bar{X}$ ± SE; the number of observations is in parentheses (N).

cent change per degree C is somewhat greater than earlier reports of a 5 per cent reduction in MAC per degree C during hypothermia in dogs.[1,2] These previous data also suggested that MAC change with temperature more closely followed a rectilinear plot on arithmetic coordinates, whereas our data, alone or combined with those of the earlier results, fit arithmetic and semilogarithmic coordinates equally well. A semilogarithmic fit has been found in goldfish[7] for a wide range of temperatures. Such a fit suggests that temperature changes do not alter the basic mode of action of anesthetic on its site of action and that temperature changes per se do not impose a secondary (independent) effect on MAC.

However, we see such a secondary effect at temperatures above 42 C, which suggests that brain function deteriorates at higher temperatures. Deteriorating brain function was not associated with reductions in arterial blood glucose, arterial or venous oxygen content, or pH. The lack of change in these indices of nutritional adequacy indirectly suggests that brain damage resulted directly from the elevated temperatures. Such an influence is supported by previous reports of cerebral metabolic dysfunction at temperatures greater than 42 C.[8–10]

The increase in MAC imposed by the hyperthermia is inversely related to changes imposed on lipid solubility.[1,2] That is, although the partial pressure required for anesthesia increases, the concentration of anesthetic this produces in a lipid phase remains relatively constant. Although this relationship may be fortuitous, it does support the lipid theories of narcosis.

If these results in dogs apply to man, they

suggest that in hyperthermic patients the concentration of halothane needed to maintain anesthesia might be increased. It is unlikely that MAC's for other agents will be equally affected, since previous reports have shown marked differences between agents in the effects of hypothermia on anesthetic requirements.[1,2,3] However, since our data suggest that the results obtained with halothane during hypothermia can be extrapolated to the hyperthermic state (fig. 2), perhaps similar extrapolations may be made with other agents. If so, then methoxyflurane MAC[2] and isoflurane MAC[11] would show changes with hyperthermia similar to halothane MAC changes, whereas changes with ether and fluroxene MAC's would be less, and changes with cyclopropane MAC would be least of all.[1,2]

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Neonatology

BLOOD CLOTTING FACTOR LEVELS Fibrinogen and factors V, II, and VII + X were assayed on the first, second, third and tenth days of life in 96 premature infants. "Sick" premature infants, most with respiratory distress syndrome (RDS) were compared with "thriving" premature infants. In the "thriving" infants, the mean clotting factor level appeared independent of gestational age. Fibrinogen and factor V levels correlated well in thriving as well as sick infants, and were significantly decreased in sick infants. Factors II and VII + X were consistently low on the first day of life in both groups. They increased progressively but had not reached adult levels by the tenth day of life despite routine vitamin K_1 administration. Overall mortality and hemorrhagic manifestations related inversely to the blood clotting factor levels.

The source of the diminished concentrations of blood clotting factors, *i.e.*, diminished production (immaturity, toxicity, etc.) or increased consumption (*i.e.*, disseminated intravascular coagulation) is not apparent. *(Jensen, A.H., Josso, F., Zamet, P., and others: Evolution of Blood Clotting Factor Levels in Premature Infants during the First 10 Days of Life. Pediatr Res 7: 638–644, 1973.)*