Temperature Dependence of Halothane and Cyclopropane Anesthesia in Dogs: Correlation with Some Theories of Anesthetic Action

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The minimum alveolar concentration of anesthetic (MAC) necessary to prevent movement in response to a painful stimulus was found to vary directly and linearly with temperature (°C) in dogs anesthetized with halothane or cyclopropane. Halothane MAC fell by half as body temperature decreased from 38° C. to 30° C. Cyclopropane MAC fell by a quarter for the same temperature change. The heat changes (enthalpies) calculated from these data correlated well with enthalpies of absorption of anesthetics to lipoprotein films. In the case of cyclopropane they also correlated well with the enthalpies found for hydrate formation from ice.

A PREVIOUS study demonstrated that the minimum alveolar concentration of anesthetic (MAC) required to prevent gross muscular movement in response to a painful stimulus was relatively constant in dogs.[1] There was little difference between *MAC* for different dogs or for the same dog tested on different days or for the same dog tested on one day over periods greater than 8 hours. Hypocarbia, hypercarbia, hypoxia to a Pa_{O_2} of 30 mm. of mercury, or hypertension did not change MAC. Hemorrhagic hypotension, or metabolic acidosis induced with ammonium chloride produced a 10–20 per cent reduction in MAC. Hypoxia below a Pa_{O_2} of 30 mm. of mercury produced a 25 to 50 per cent reduction in MAC. Thus, despite varying circumstances and stresses, MAC remained relatively stable except as the stresses became extreme.

One parameter which was deliberately held constant in all these studies was body temperature. This is one factor which is said to markedly affect anesthetic requirement. With few exceptions,[2, 3, 4] the evidence for this is to be found mainly in clinical observations. Recently, Cherkin and Catchpool gave direct evidence in studies on goldfish to substantiate these observations.[5] They determined the partial pressure of methoxyflurane, chloroform, diethyl ether, and halothane required to prevent movement in 50 per cent of goldfish stimulated electrically. As temperature increased, the anesthetic partial pressure required rose exponentially. We sought to confirm their findings in the dog using halothane. In addition, we studied the influence of temperature on cyclopropane anesthesia.

Methods

Anesthesia was induced and maintained with halothane or cyclopropane. The dog was prepared as in the previous study.[1] MAC was determined in triplicate, using tail clamp as the stimulus. Halothane concentrations were determined with an infrared analyzer, end-tidal samples being obtained from a nylon catheter inserted to the tracheal end of the endotracheal tube. Cyclopropane was sampled from the inspiratory limb of the circle

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system and analyzed by oxygen difference with a Model D Beckman-Pauling meter. Entrainment of air which would give an erroneous reading due to dilution with nitrogen was prevented by maintaining a constant positive pressure of 2 to 4 cm. of water within the system. Initial nitrogen washout from the system was accomplished with 5 liters/minute flows for at least 10 minutes (total gas system volume approximately 6 liters). A 1 liter/minute total flow was maintained throughout the remainder of the experiment. Alveolar cyclopropane values were calculated as the inspired values diluted by water vapor at body temperature. Since one and one-half to two hours usually elapsed between induction and the first readings, we have ignored the effect of uptake which would be minimal at this time [6] and which would also be balanced partially by a respiratory quotient of less than one.

Procedures and Results

Five dogs were anesthetized with halothane. Following induction of anesthesia esophageal temperature ranged from 38° to 40° C. Initial temperatures were held at about 39° C. (range 38.1° to 40.3°) while MAC was determined. Body temperature was then lowered by surface cooling to approximately 36° then 32° and then 28° C., MAC being determined at each temperature. MAC determinations were not made at any temperature until at least 20 minutes after the removal of the surface ice. In two of
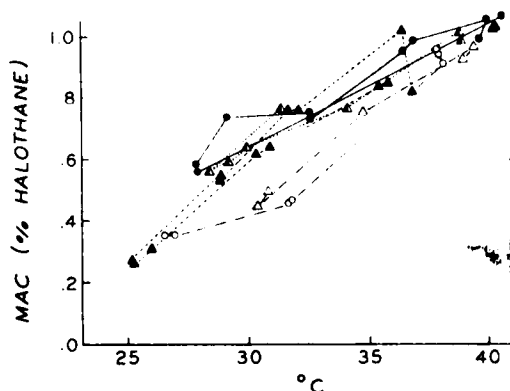

Fig. 1. Relation between esophageal temperature and halothane MAC for 5 dogs. Individual MAC's for each dog are identifiable as the points connected by the lines unique to that dog. The mean MAC's and temperatures at various ranges as recorded in table 1 are taken from the individual values shown here.

the dogs the process was then reversed (*i.e.*, the dog rewarmed) and MAC measured at points of ascending temperature. Within the error of the technique, in neither of these cases was an hysteretic phenomenon seen. Figure 1 shows the results obtained. Table 1 lists the mean results from the individual dogs far various temperature ranges.

A second group of 4 dogs was anestheized with cyclopropane. It was difficult to obtain a stable MAC with cyclopropane at temperatures above 39° C. For this reason the initial temperature at which MAC's were determined was about 38° C. Temperature was then lowered to about 32° C., then to

TABLE 1

Dog Number	Temperature Range ° C.							
	26–30		30–34		34–38		38–42	
	Temp	MAC	Temp	MAC	Temp	MAC	Temp	MAC
1	29.2	0.60	31.4	0.77	34.2	0.77	38.8	1.00
2	28.3	0.63	32.6	0.74	36.4	0.96	40.1	1.03
3	27.2	0.42	31.3	0.70	36.1	0.88	40.3	1.02
4	26.8	0.35	31.8	0.46	37.9	0.95	38.1	0.92
5	28.0	0.33	30.6	0.47	34.8	0.76	39.2	0.94
Average	27.9	0.47	31.5	0.63	35.9	0.86	39.3	0.98

MAC is minimum alveolar concentration of halothane in volumes per cent. Temp is temperature in degrees centigrade.

TABLE 2

Dog Number	Temperature Range ° C.									
	40–35		35–30		30–25		30–35		35–40	
	Temp	MAC	Temp	MAC	Temp	MAC	Temp	MAC	Temp	MAC
1	38.1	27.5	31.2	19.8	27.0	13.9	32.0	19.0	37.9	21.8
2	37.5	19.5	31.7	18.1	27.1	17.1	32.8	17.2	37.6	20.9
3	37.6	16.7	31.3	16.4	27.3	13.2	32.6	15.2	37.7	17.2
4	37.6	18.9	32.0	17.5	27.4	16.5	33.8	21.1	37.7	22.0
Average	37.7	20.6	31.6	18.0	27.2	15.2	32.8	18.1	37.7	20.5

MAC is minimum alveolar concentration of cyclopropane in volumes per cent. Temp is temperature in degrees centigrade.

27° C. then raised to 32° C. and to 38° C., MAC determinations being made at each temperature. Again at least 20 minutes elapsed between removal of ice or cessation of heating during the rewarming process and subsequent stimulation. The data are tabulated in table 2 and figure 2. As with halothane, no consistent hysteresis was seen on return to 32° or 38° C. after cooling. The average values from tables 1 and 2 are plotted in figure 3.

Oil/gas and water/gas partition coefficients for halothane and cyclopropane were determined at approximately 37°, 30°, and 24° C. The technique for the halothane determinations has been described.[7] The method of analysis for cyclopropane utilizes the Scholander gas analyzer.[8] The solvent (water, olive oil) is contained in the side arm and 100 per cent cyclopropane is introduced into the reaction chamber. The solvent is then introduced into the reaction chamber and cyclopropane uptake and solvent volume measured in the usual manner. Uptake/solvent volume gives the partition coefficient. The technique will be described in detail elsewhere. The results are illustrated in figure 4.

Discussion

Change in body temperature exerted a significant influence on MAC. A 10° C. decrease in temperature from 38° C. diminished cyclopropane MAC by a quarter and halothane MAC by half (fig. 3). In general, these results are in accord with the impression that hypothermia reduces the anesthetic requirement, although they indicate that hypothermia to 27° C. does not afford complete anesthesia, at least in dogs. This is in contrast to the report that anesthesia is not required for surgical procedures in dogs below 28° C.[4] The latter study, however, utilized mainly fixed agents which would still be effective, although to a diminished extent, as time progressed and temperature fell. The results of this study for halothane are in close agreement with those found by Cherkin and Catchpool in their experiment with a dissimilar species, the goldfish. Despite the dissimilarity, "MAC" for goldfish was 1.8 per cent at 37° C. (extrapolated value) and fell by half to 0.9 per cent at 27° C.

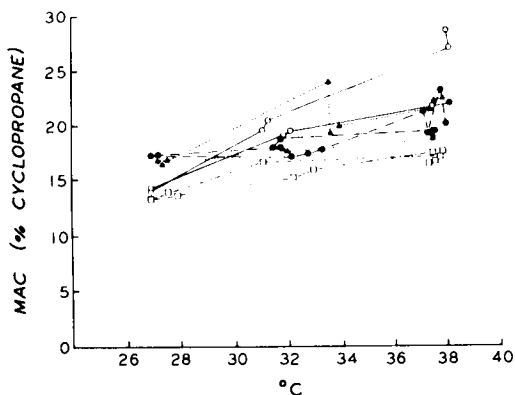The temperature data also permit specula-

Fig. 2. Relation between esophageal temperature and cyclopropane MAC for 4 dogs. MAC values for each dog are connected by lines unique to that dog. Table 2 is derived from the individual values shown here.

tion as to the site of action of anesthetics. For example, from the temperature data, the ΔH or change in heat or change in enthalpy found in the absorption* of one mole of gas into the "material" constituting the site of anesthetic action may be calculated from the integrated Clausius-Clapeyron equation [9, 10]:

$$\log \frac{MAC_1}{MAC_2} = \frac{\Delta H}{2.3R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

where MAC_1 is the MAC concentration at T_1 temperature absolute and similarly, MAC_2 is the MAC concentration at T_2 temperature absolute, and R is the gas constant (1.99 calories per mole per ° C.). This assumes that (1) there is essentially no interaction among the anesthetic molecules in the gaseous state (i.e., the anesthetics act like perfect gases) and (2) at the two temperatures, the concentration of anesthetic dissolved in the "material" constituting the site of anesthetic action is the same and produces a constant depth of anesthesia. The second assumption may be open to question since it is known that cold itself can produce anesthesia.[5] However, the effect of cold on anesthetic requirement apparently is a dual one. Over the range of reversible temperature change (5–30° C. in goldfish and 25–40° C. in dogs) cold appears to multiply the effect of the anesthetic without being an anesthetic itself. For example, if Cherkin and Catchpool's data for goldfish between 5 and 30° C. are extrapolated to lower temperatures, anesthetic requirement continues to decrease but never reaches zero. However, experimentally, below 5° C. there is an abrupt fall in anesthetic requirement to a zero requirement at a temperature immediately above 0° C. These data suggest that above 5° C., cold does not act independently as an anesthetic but only as it affects the interrelationship between anesthetic agent and the material constituting the site of anesthetic action. Further evidence suggesting such a role for cold may be taken from our data. If the decreased anesthetic requirement with

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* The sign obtained should actually be negative since in absorption heat is given off. However, rearranging to account for this does not change the absolute figure obtained and it is this figure with which we are primarily concerned.
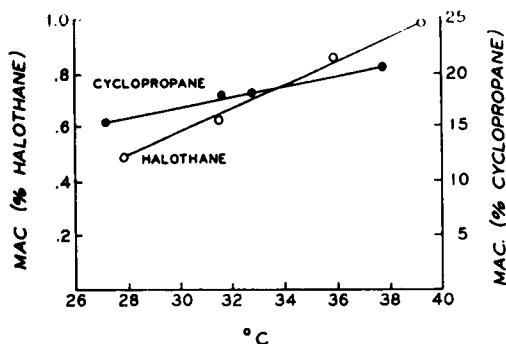

FIG. 3. A summation of the effect of temperature change on the MAC for halothane and for cyclopropane. The MAC scale for halothane is on the left while that for cyclopropane is on the right.
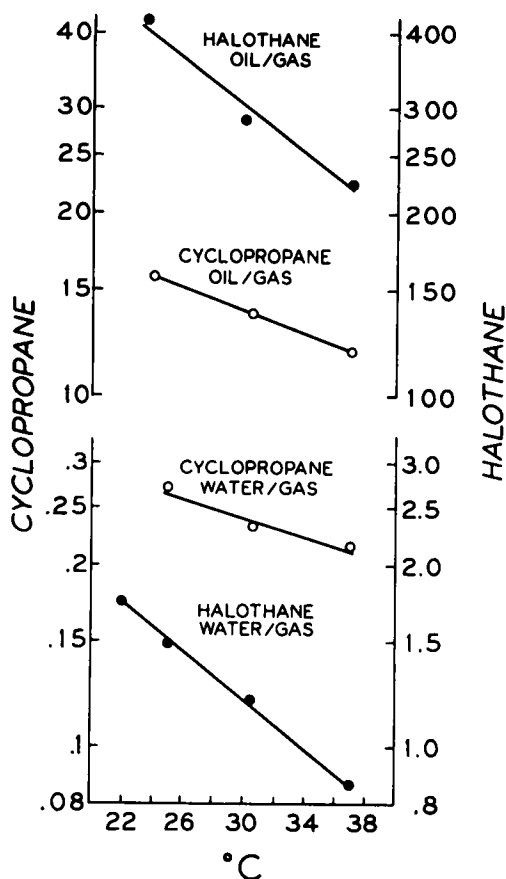

FIG. 4. Change in water and olive oil solubility for cyclopropane and for halothane with change in temperature. Solubility, as expressed by the water/gas or oil/gas partition coefficient, is on the Y-axis as logarithmic scale. The scale is broken at mid-point to permit the inclusion of all values on one graph. The solubility scale for halothane is on the right.

hypothermia were due to cold alone, then the decrease in requirement per decrease in temperature should be the same for all anesthetics. This is not what we have found. Instead, for a 10° C. decrease from 38° C., the cyclopropane requirement fell by 25 per cent and the halothane requirement by 50 per cent. Even if the 25 per cent reduction in cyclopropane requirement were achieved by cold alone it would leave unexplained the additional 25 per cent reduction seen with halothane. If the latter is explained by an interaction between halothane, site of anesthetic action, and cold, it would be difficult to understand why some similar interaction would not apply to cyclopropane, thus further reducing the 25 per cent decrease in requirement which might be attributed to cold alone.

Further evidence that it is the number of anesthetic molecules at the site of anesthetic action which determine the presence or absence of anesthesia is the correlation between MAC and solubility in oil at various temperatures. That is, as temperature and MAC fall, solubility rises (vide infra) and the number of molecules dissolved in a lipid phase remains roughly constant. If a lipid (or lipoprotein) is the site of anesthetic action, then assumption 2 above is valid. Actually, this argument also holds if water is the site of anesthetic action, since changes in solubility in water with temperature parallel those occurring in lipid (vide infra). It might be noted that assumption 2 is also made by authors of the hydrate theory of anesthesia [9, 11] and of the theory of anesthesia involving absorption into cellular or subcellular membranes.[12, 13]

In disagreement with the above comments one may argue from our data that some direct effect of cold probably does occur in homeotherms. The plot of MAC versus temperature is rectilinear on arithmetic coordinates (fig. 3), but curvilinear downward on semilogarithmic coordinates. A rectilinear graph on semilogarithmic coordinates is what would be anticipated if cold affected the relationship between anesthetic gas and site of anesthetic action (that is, if as temperature fell there was a proportionate increase in anesthetic effect). This is actually found in poikilotherms.[5] However, there is considerable

scatter in our data and the better fit to an arithmetic plot may be coincidental.

Assuming the validity of the above equation, a ΔH of 5.5 ± 2.9 kcal./mole (kilocalories per mole) may be calculated for cyclopropane. This is arrived at by determining the mean ΔH for all 4 dogs (the 5.5 figure is the mean of these 4 figures). The mean is the same whether the temperature is being lowered (5.6 kcal./mole) or raised (5.3 kcal./mole).

Similarly, a ΔH value of 14.8 ± 4.6 kcal./mole may be calculated for halothane. Again, the mean figures are much the same when ΔH is calculated from MAC's determined as temperature was decreased (13.5 kcal./mole) or increased (17.1 kcal./mole). The change in enthalpy of 14.8 kcal./mole for halothane in dogs correlates reasonably well with the value of 12.5 cal./mole obtained by Cherkin and Catchpool in goldfish.[5] If only the extreme points of temperature and MAC from our data are used (MAC 0.98 per cent at a temperature of 312.3° K. and MAC 0.47 per cent at 300.9° K.; an enthalpy of 12.0 cal./mole is found for halothane (see figure 3 and table 1). The reason for suspecting this may be a more accurate approximation to the true value is that measurement of MAC is susceptible to a 10 per cent experimental erorr. The greater the difference between two MAC values, the greater the relative accuracy of the determination of the difference. Hence, the MAC values at the extremes are most likely to be correct.

Enthalpies from our in vivo MAC data may also be obtained by making an Arrheneus plot as did Cherkin and Catchpool for their data. A visual fit to our data on such a plot gives values of 4.7 ± 2.5 kcal./mole for cyclopropane and 11.9 ± 3.4 kcal./mole for halothane.

These enthalpy values for dog and goldfish may be compared with those predicted by various theories of anesthesia. Hafemann, D. F. and Miller, S. L. (personal communication) have found two cyclopropane hydrates with ΔH values 7.4 and of 6.3 kcal./mole. These values apply to the formation of hydrate from ice. They should be compared with ΔH determinations of 18.6 and 30.7 kcal./mole by the same workers for hydrate

formation from liquid water. These values are not comparable to the *in vivo* value of 5.5 kcal./mole. Since water adjacent to a membrane is already structured, the enthalpy value for formation of hydrate from ice (7.4 or 6.3 kcal./mole) is thought to be more appropriate.[9]

Miller[9] and Pauling[11] would classify the halothane molecule as fitting only into structure II hydrates since the molecular length is greater than 6 Å. The enthalpy for formation of the structure II hydrate from water would be approximately 31 kcal./mole. Again, this figure is far in excess of the 14.8 kcal./mole we obtained. However, Miller suggests that the use of these enthalpy values is inappropriate[9] (*vide supra*) and that the enthalpy obtained for the ice-hydrate-gas equilibrium would approach that found *in vivo*.

Our data are in close agreement with Clements and Wilson's findings for the heat of absorption of cyclopropane (7.9 kcal./mole)[12, 13] and of halothane (11.7 kcal./mole) (John Clements, personal communication) in surface lipoprotein films at varying temperatures. They have shown that absorption of anesthetics in such films increases surface pressure of the film. If this occurs in cellular or subcellular membranes it would perhaps tend to tighten the films and to prevent the increase in permeability to passage of ions that normally accompanies excitation. This stabilization of the ionic composition within and without may be the means by which anesthesia is produced.[13]

Change in enthalpy of halothane or cyclopropane on their absorption to oil or water may also be calculated from the integrated Clausius-Clapeyron equation where the MAC values are replaced by solubility values obtained at temperatures T_1 and T_2. A small temperature correction must also be introduced. The final equation is written as

$$\Delta H = \frac{2.3\ T_1 T_2 R}{T_2 - T_1} \log \frac{\lambda_2 T_1}{\lambda_1 T_2}$$

where λ_1 and λ_2 are the solvent/gas partition coefficients at absolute temperatures T_1 and T_2, respectively. The close agreement between Cherkin and Catchpool's and our data and between our data and the heat of halo-

thane absorption in lipoprotein films found by Clements is not as good for heat of absorption in water or olive oil. For example, our data for halothane as illustrated in figure 4, give ΔH's of 9.0 kcal./mole for water and 9.0 kcal./mole for oil. These are lower than the 14.8 kcal./mole derived from MAC data. Similarly a ΔH of 4.1 kcal./mole for water and 4.6 kcal./mole for oil is obtained from the cyclopropane solubility data. These are both lower than the 5.5 kcal./mole derived from MAC data.

The changes in MAC are inversely proportional to the changes in oil/gas or water/gas partition coefficients. The increase in solubility of halothane is greater than that of cyclopropane over the same temperature range and similarly, the decline in the halothane MAC with temperature is greater than that of cyclopropane. The proportionate change in solubility with temperature for either anesthetic is identical for that anesthetic regardless of whether the solvent phase is water or olive oil.

The results obtained quantitate the reduction in halothane or cyclopropane requirement that accompanies a decrease in body temperature. This is not to say that anesthetic input from the machine must be reduced accordingly. The increase in anesthetic solubility that accompanies a fall in temperature would result—if considered alone—in a greater anesthetic uptake. Since solubility increases approximately as much as MAC decreases, this suggests that uptake, and hence the required anesthetic input, should remain relatively constant (or not decrease as much as the MAC indicates). However, with hypothermia there is also a concomitant decrease in cardiac output. This results in a decrease in uptake which probably balances the effect of increased solubility.

The effect on MAC of temperature reductions beyond those given by this paper are not certain. Cherkin and Catchpool's report for goldfish suggests a continuing exponential decline in MAC down to 5° C., whereafter there appears to be an abrupt fall in anesthetic requirement to zero at 1.6° C. Our attempts to study MAC in dogs at lower temperatures have thus far been frustrated by

the ventricular fibrillation that occurs at temperatures between 20 and 23° C.

Summary

Decrease in dog temperature produces a rectilinear fall in MAC for both halothane and cyclopropane. The halothane MAC is decreased by half by a fall from 38° C. to 28° C., while the cyclopropane MAC is decreased by a quarter over the same temperature range. From these data, enthalpies of absorption of these anesthetics were calculated for whatever material constitutes their site of anesthetic action. For halothane the enthalpy equalled 14.8 ± 4.6 kcal./mole and for cyclopropane equalled 5.5 ± 2.9 kcal./mole. These enthalpies correlate well with those found for absorption in lipoprotein surface films, or with those found for cyclopropane for hydrate formation from ice.

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METHOXYFLURANE Decreased blood pressure and narrowed pulse pressure were frequently noted during the early period of maintenance with methoxyflurane as commonly seen with halothane. Caution has to be taken concerning the use of d-tubocurarine chloride when blood pressure is decreased in the early stages of maintenance with methoxyflurane as it may cause profound hypotension. Twenty milliliters of epinephrine solution 1:10,000 was administered intramuscularly during methoxyflurane anesthesia with no appreciable change in the electrocardiogram. During recovery from methoxyflurane, nausea was noted in 32 per cent of the patients which is a higher incidence than with halothane, and vomiting in 27 per cent of the patients which is about the same as with halothane. Both nausea and vomiting were less than with ether. (*Shiozawa, S., Kaido, K., and Harano, M.: Clinical Experiences of Methoxyflurane Anesthesia. Comparison of Methoxyflurane and Halothane Anesthesia (Japanese), Jap. J. Anaesth. 13: 655, 1964.*)