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Sympathoadrenal and Hemodynamic Effects of Isoflurane, Halothane, and Cyclopropane in Dogs

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The sympathoadrenal response and its relation to the hemodynamic effects of isoflurane, halothane, and cyclopropane were studied in ten dogs. Each animal was used as its own control. At weekly intervals, the changes in plasma epinephrine and norepinephrine concentrations and in cardiac output ($\dot{Q}$), whole-body oxygen consumption ($\dot{V}O_2$), arterial blood pressure, and heart rate at MAC-1 concentrations of isoflurane, halothane, and cyclopropane were determined. The sympathoadrenal activity, as reflected by plasma values for epinephrine, norepinephrine, and total catecholamines, was the same for isoflurane and halothane, whereas cyclopropane was associated with significant increases in these levels compared with the other two agents. Values reflecting cardiovascular function were also the same for isoflurane and halothane, although $\dot{Q}$ was significantly lower for halothane than for isoflurane. Cyclopropane was associated with significant increases in cardiovascular function and $\dot{V}O_2$. (Key words: Anesthetics, gases: cyclopropane; Anesthetics, volatile: halothane; Anesthetics, volatile: isoflurane; Sympathetic nervous system: volatile anesthetics; Heart: cardiac output; Oxygen: consumption.)

THE SUGGESTION of Price and associates[1,2] that the hemodynamic responses to anesthetic agents can be correlated roughly with their effects upon sympathetic nervous function has not been universally supported by the findings of others.[3-6] We believe these divergent results are related largely to differences in methods and, in particular, to shortcomings in the methods of determining plasma levels of epinephrine (E) and norepinephrine (NE). The trihydroxyindole (THI) method of catecholamine (CA) analysis, introduced by Lund[7] in 1949, has been modified and improved by others.[8-11] It is limited by errors originating in technical difficulties, and often by a lack of sufficient sensitivity for the detection of small, but physiologically significant, changes occurring in plasma. Recent technical refinements have made the THI method more sensitive and accurate at subnanogram concentrations and have permitted a high degree of reproducibility and reliability of results.[12-14]

We accordingly decided to reinvestigate the suggestion of Price and associates,[1,2] using modern methods of CA analysis. With each animal as its own control, we determined plasma E and NE concentrations, hemodynamic responses, and whole-body oxygen consumption ($\dot{V}O_2$) during isoflurane (Forane), halothane, and cyclopropane anesthesia.

Material and Methods

At weekly intervals, ten unpremedicated and fasted dogs (mean weight, 17.3 ± 0.8 kg) had their tracheas intubated with the aid of succinylcholine (20 mg) and were anesthetized in random sequence with MAC-1 concentrations of isoflurane, halothane, or cyclopropane in O_2 and N_2, administered through a nonrebreathing system. In addition, a final "awake study" was carried out with the aid of minimal amounts of thiopental 1 hour after completion of the third week of study with an anesthetic agent in each dog. F_{IO_2} was adjusted to maintain Pa_{O_2} at 150 ± 5 mm Hg, and use of a ventilator (Bird Mark IV/VIII) maintained Pa_{CO_2} at 40 ± 2 mm Hg. Body temperature was maintained at 37.0 ± 0.5 C by external means. Intravenous fluids (5 per cent glucose in distilled water) were given continuously (rate, 4 ml/kg/h).

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TABLE 1. Comparison of Hemodynamic and Catecholamine Data at Equivalent (MAC-1) Concentrations of Cyclopropane (C), Halothane (H), and Isoflurane (I) and in the "Awake" (A) State

Variable	Cyclopropane		Difference*			Halothane		Difference*			Isoflurane		Difference*			"Awake"		Difference*		
	Mean	SE	A	H	I	Mean	SE	A	I	C	Mean	SE	A	H	C	Mean	SE	H	I	C
$\dot{Q}$ (l/min)	4.09	0.44		x	x	2.38	0.29	x	x	x	3.22	0.36		x	x	4.15	0.53	x		
$\dot{V}_{O_2}$ (ml/min)	143	9		x	x	100	3	x	x	x	101	3		x	x	181	18	x		x
Arterial pressure (mean, mm Hg)	132	3		x	x	82	4	x	x	x	82	4		x	x	138	9	x		x
Heart rate (beats/min)	133	12		x		97	6	x	x		105	7		x		149	12	x		x
Epinephrine (ng/ml plasma)	0.85	0.14		x	x	0.44	0.06	x		x	0.43	0.08	x		x	0.80	0.14	x	x	
Norepinephrine (ng/ml plasma)	0.22	0.03		x	x	0.08	0.03	x		x	0.11	0.04	x		x	0.20	0.04	x	x	
Catecholamines (total, ng/ml plasma)	1.07	0.15		x	x	0.52	0.07	x		x	0.55	0.11	x		x	1.01	0.17	x	x	

* x in A, H, I, or C column indicates statistically significant difference ($P < 0.05$) between this value and corresponding one in "awake," halothane, isoflurane, or cyclopropane situation, respectively.

Catheters were placed in the carotid and pulmonary arteries for measurement of pressures, determination of cardiac output ($\dot{Q}$), and sampling of arterial and mixed venous blood. Pressures were transduced by strain gauge. Blood gases were measured by electrodes at 37.0 C. Blood O_2 content was calculated from Po_2 and oxyhemoglobin concentration (IL CO-Oximeter). Cardiac output was determined by the dye-dilution method, indocyanine green having been injected into the pulmonary artery and sampled from the carotid artery. Whole-body $\dot{V}o_2$ was calculated from measurements of $\dot{Q}$ and $(A\text{-}V)o_2$ by means of the Fick equation. Halothane and isoflurane concentrations were determined by infrared analysis of expired air. Cyclopropane concentrations were estimated from flow rates through calibrated flowmeters. MAC-1 concentrations observed by others[15,16] in the dog for halothane, isoflurane, and cyclopropane, 0.87, 1.48, and 17.5 per cent, respectively, were established and maintained for at least 30 minutes prior to and throughout the period of study. The condition of the "awake" study differed from the above only in that ventilation was spontaneous and the gas mixture was room air.

In each dog during each of the four situations, arterial blood pressure, blood gas concentrations, and heart rate were determined in duplicate, and $\dot{Q}$ and $(A\text{-}V)o_2$ were determined in triplicate. Following these procedures, two 25-ml samples of arterial blood were removed and centrifuged for 3 minutes in a precooled centrifuge (4 C) after 12.5 mg of sodium metabisulfite had been added. The supernatant plasma was removed, frozen in Dry Ice and acetone, and analyzed for E, NE, and total CA content within 24 hours. Studies in this laboratory have demonstrated no significant change in CA content in plasma samples collected and preserved in this manner and frozen for periods as long as 3 weeks.

Our method of CA analysis was that proposed by Valori and co-workers,[13,14] as modified by G.M. Tyce§ (personal communication). This variant of the THI method involves the separation and purification of catecholam-

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TABLE 2. Differences in Hemodynamic Variables and Catecholamines among Cyclopropane (C), Halothane (H), and Isoflurane (I) (mean ± SE)

Variable	C–H	C–I	I–H
$\dot{Q}$ (l/min)	1.71 ± 0.38	0.87 ± 0.38	0.84 ± 0.13
$\dot{V}o_2$ (ml/min)	42.9 ± 9.2	41.9 ± 8.3	1.20 ± 0.47
Arterial pressure (mean, mm Hg)	50.0 ± 6.2	49.9 ± 6.2	0.40 ± 6.2
Heart rate (beats/min)	35.5 ± 18.7	27.5 ± 12.9	9.0 ± 6.6
Epinephrine (ng/ml)	0.41 ± 0.14	0.42 ± 0.17	0.01 ± 0.07
Norepinephrine (ng/ml)	0.13 ± 0.03	0.10 ± 0.04	0.03 ± 0.02
Catecholamines (total, ng/ml)	0.54 ± 0.15	0.52 ± 0.20	0.03 ± 0.02

TABLE 3. Significance of Differences in Hemodynamic Variables and Catecholamines among Cyclopropane (C), Halothane (H), and Isoflurane (I)

Variable	C–H vs. C–I	C–H vs. I–H	C–I vs. I–H
$\dot{Q}$ (l/min)	1.563*	2.166†	0.075*
$\dot{V}o_2$ (ml/min)	0.081*	4.036‡	4.267‡
Arterial pressure (mean, mm Hg)	0.011*	5.657‡	5.645‡
Heart rate (beats/min)	0.352*	1.336*	1.277*
Epinephrine (ng/ml plasma)	0.045*	2.562†	2.236†
Norepinephrine (ng/ml plasma)	0.600*	2.777‡	1.566*
Total catecholamines (ng/ml plasma)	0.080*	2.973‡	2.280†

* Not significant.
† Significant ($P < 0.05$).
‡ Highly significant ($P < 0.01$).

ines from plasma by adsorption with alumina and cation-exchange resin, oxidation with ferricyanide at pH 6.5, tautomerization with NaOH and mercaptoethanol, and fluorimetric separation of E and NE by an Aminco-Bowman spectrophotofluorometer. This method is sensitive enough to detect concentrations of E or NE as low as 0.05 ng/ml, and to measure accurately concentrations of each CA as low as 0.10 ng/ml. By analysis of duplicate samples it has been established that the average deviation of single samples from the mean of their pair is 10 per cent. This figure is larger for concentrations less than 0.30 ng/ml, but for higher values the average deviation is reduced to about 2 per cent. Mean recovery of both catecholamines is 58 ± 11 per cent. Reported values are uncorrected for the percentage recovery.

Results

Observations pertinent to the four situations studied are summarized in table 1. Data from the "awake" study have been included for completeness despite our reservations as to whether these data are meaningful. It is of interest, however, that the data for the "awake" state were not significantly different from those for cyclopropane; they were, however, almost always significantly different from those for halothane and isoflurane. With cyclopropane, as compared with both halothane and isoflurane, $\dot{Q}$, $\dot{V}o_2$, and arterial pressure were greater, and these values were associated with larger values for plasma E, NE, and total CA. Although the increase in E accounted for the major portion of the difference, both CA's increased by approximately the same relative amount. The findings with halothane and isoflurane were generally similar; the only significant difference was a smaller cardiac output with halothane.

These data were also analyzed by comparing the differences between cyclopropane and halothane, cyclopropane and isoflurane, and isoflurane and halothane. Tables 2 and 3 show the actual differences between groups, and

TABLE 4. Correlation Coefficients (r) of Relationship Between Total Plasma Catecholamines and Hemodynamics for Each of Three Anesthetics, and for the Differences Between Them

	$\dot{Q}$	Arterial Pressure	Heart Rate
Anesthetic			
Cyclopropane	0.30	−0.15	−0.75*
Halothane	0.52	0.34	0.01
Isoflurane	0.75*	0.36	0.53
Differences			
C–H	0.38	0.30	−0.63*
C–I	0.20	0.10	−0.41
I–H	0.31	0.26	0.07

* Significant, $P < 0.05$.

their statistical significance. These data again show the similarity between isoflurane and halothane, and the significantly higher values for most parameters associated with cyclopropane.

The relationships between each of the hemodynamic variables and plasma catecholamines were sought by determining the correlation coefficients for each anesthetic, and for the differences between anesthetics. No remarkable relationship was found. The few significant correlations were outweighed by the many relationships that were weak or absent (table 4). Although a better correlation between total catecholamines and cardiac output might have been expected, closer examination did not confirm this (fig. 1).

Of particular interest is the wide range in catecholamine concentrations among individual dogs for each anesthetic (table 5).

Discussion

Interest in the sympathoadrenal response to general anesthesia has persisted since Brewster and associates[17] demonstrated that the hemodynamic effects of diethyl ether in intact dogs could be duplicated by means of an intravenous infusion of epinephrine (1 μg/kg/min). Since then, many investigators have used various analytical techniques and experimental designs to study the sympathoadrenal response to anesthesia.

Deutsch and associates[18] studied the effects of cyclopropane in dogs, and found significant increases (0.7 μg/l) in the concentration of E without similar increases in NE. Neither Millar and Morris[3] nor Dobkin and associates[4] however, found significant changes in the concentration of E or NE with cyclopropane in dogs. The differences in results may, perhaps, be due to differences in experimental design, as the latter two groups induced anesthesia with thiopental before administering cyclopropane. Deutsch and associates[18] believe this procedure suppresses the sympathoadrenal response. Our "awake" data are of interest in apparently not supporting this contention, at least with the small doses of thiopental used (mean dose, 100 mg).

TABLE 5. Concentrations (ng/ml) of Free Catecholamines in Arterial Plasma in Response to Isoflurane, Halothane, and Cyclopropane

	Epinephrine			Norepinephrine		
	Isoflurane	Halothane	Cyclopropane	Isoflurane	Halothane	Cyclopropane
Dog 1	0.28	0.30	1.07	0.00	0.02	0.20
Dog 2	0.51	0.39	1.35	0.02	0.06	0.14
Dog 3	1.00	0.63	0.69	0.29	0.16	0.19
Dog 4	0.39	0.38	0.28	0.19	0.16	0.13
Dog 5	0.29	0.21	1.24	0.11	0.11	0.26
Dog 6	0.36	0.88	1.53	0.00	0.08	0.30
Dog 7	0.32	0.39	0.49	0.03	0.03	0.12
Dog 8	0.69	0.51	0.56	0.33	0.21	0.39
Dog 9	0.17	0.32	1.02	0.10	0.03	0.18
Dog 10	0.33	0.42	0.30	0.08	0.00	0.26
MEAN	0.43	0.44	0.85	0.11	0.08	0.22

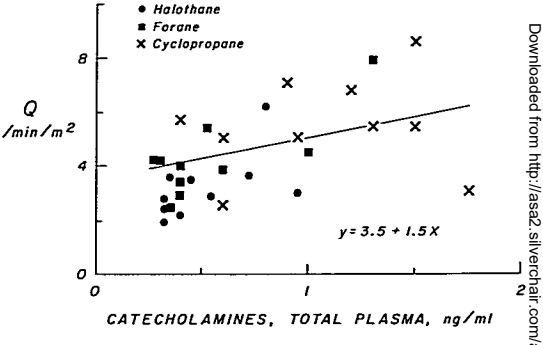

FIG. 1. Relation of concentration of total catecholamines to cardiac output.

The response of man to cyclopropane apparently differs from that of the dog, in that the sympathoadrenal response consists of an increase in NE concentration with little change in E. Price and associates[1,2] demonstrated a significant increase (> 0.5 μg/l) in NE concentrations in most of 13 subjects studied, without a similar increase in the concentrations of E. This increase in NE concentration could be duplicated by an infusion of exogenous NE (rate, 5 to 10 μg/min), which was also shown to be physiologically significant. However, Millar and Morris[3] found that in man the effects of cyclopropane ranged from producing no change to a significant increase in total CA concentration without a significant change in either E or NE concentrations. The degree to which anesthetic depth influences the sympathoadrenal response is unclear, though it may well be an important variable, as intimated by Hamelberg and associates.[19]

Investigations of the sympathoadrenal effects of halothane have yielded more uniform findings in both dog and man. These studies have demonstrated that no significant change occurs in plasma E, NE, or total CA concentrations.[1,3,4] Studies on the hemodynamic effects of halothane over a longer period, however, have demonstrated a recovery of $\dot{Q}$ toward normal and a possible β-stimulating effect.[20] The relation of plasma CA levels to these data is as yet unknown.

At present, there are few data on the sympathoadrenal response to isoflurane. Byles and associates[21] demonstrated that in dogs there was no change in plasma CA concentrations during isoflurane anesthesia. Dobkin and co-workers[22] found that in man there was a 50 per cent increase in total CA concentration, mostly in the NE fraction.

Our findings in dogs have shown that the sympathoadrenal responses to MAC-1 concentrations of halothane and isoflurane are similar. Cyclopropane is associated with a significant increase in plasma catecholamines. The hemodynamic data in general correspond well with the sympathoadrenal responses. We believe that the results of this study agree with, and support, the findings of Price and associates.[1,2] We believe also that our inability to correlate plasma catecholamine values with the hemodynamic responses by means of correlation coefficients does not alter the significance of our data.

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