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Hemodynamic and Central Nervous Actions of Cyclopropane in the Dog

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ALTHOUGH it has been known for years that the administration of cyclopropane to man is frequently attended by increased arterial blood pressure, it is only recently that this effect has been recognized as a pharmacological action of the drug itself, distinct from other potential causes of hypertension during anesthesia such as hypercarbia, anoxia, delirium, or stimuli incident to operative or anesthetic maneuvers.[1] It has also been determined that arterial hypertension does not occur in man in response to cyclopropane inhalation when efferent sympathetic pathways are blockaded and that a normal response to the drug involves liberation of substantial quantities of the sympathetic mediator norepinephrine.[2] Recent evidence indicates that cardiac sympathetic nerves become hyperactive during cyclopropane inhalation in man and that liberation of norepinephrine from these nerves directly into the myocardium is responsible for the preservation of essentially normal cardiac contractility during light levels of anesthesia.[3] Knowledge of the human response ceases at this point, not from want of interest, but from inability to perform crucial experiments in man.

The experiments to be reported were performed in dogs, a species in which the response to cyclopropane closely resembles that observed in man. The results indicate that cyclopropane causes arterial hypertension and increased sympathetic nervous activity in dogs by selectively inhibiting the activity and excitability of medullary vasodepressor neurones.

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Methods

Results from 49 mongrel dogs are reported. In 23 animals chloralose (50–100 mg./kg.) was given intravenously prior to study; 18 animals whose brains were sectioned were given either halothane or diethyl ether during this procedure but were subsequently ventilated with oxygen in order to remove the anesthetic; 8 dogs were studied initially under light cyclopropane anesthesia. In all cases cyclopropane in oxygen was subsequently administered, using a technique previously described,[4] in order to test the response to moderate (30–40 per cent) concentrations of the drug. Respirations were maintained at constant rate and volume with a Bird or Palmer respirator and P_{CO_2} remained essentially constant throughout each study. Analyses of end-expired air for cyclopropane and carbon dioxide were made as in the study cited above. Femoral arterial pressure and lead 2 electrocardiogram were recorded as in the previous study. In 12 animals plasma catechol amine concentrations were determined by the method of Price and Price.[5]

Data were analyzed statistically using Student's t test. P values below 0.05 were regarded as significant.

Special procedures were as follows:

(1) *Perfusion of the Head.* In 5 animals anesthetized with chloralose the head was perfused with oxygenated blood via the right common carotid artery. Blood was drawn from a donor dog into a beaker containing heparin to supply a Sigmamotor pump which generated flow at rates ranging from 180 to 260 ml./minute. The blood was oxygenated in a de Wall oxygenator through which gas flowed at rates exceeding 2 liters/minute. A water bath maintained the temperature of blood entering the head at 37 ± 0.5° C. During perfusion of the head the left common carotid and both vertebral arteries were occluded and a garrotte was applied tightly around the neck, excluding the arterial inflow, external jugular veins, vagus nerves, and trachea. The external jugular veins were cannulated low in the neck in order to secure a venous return equal in volume to that infused by the pump. Cyclopropane 35 per cent, CO_2 5 per cent, O_2 60 per cent was delivered to the oxygenator when the effects of the anesthetic were to be tested. Otherwise 5 per cent CO_2 in O_2 was administered to the pump. Analyses of end-expired air for cyclopropane were used to test for the presence of significant contamination (above 1 volume per cent) of the alveolar air with cyclopropane.

(2) *Brain Stem Sections.* These were performed, following craniotomy and removal of the overlying cortex with suction, by gentle insertion of a scalpel handle. The level and completeness of section were verified post mortem.

(3) *Stimulation of the Cervical Vagus Nerve.* Electrical stimulation of the central end was effected, following section of the nerve, by a Tektronix pulse generator supplying 1 msec. square wave pulses at a frequency of 100 c.p.s. and e.m.f. ranging from 2 to 4 v.

(4) *Carotid Sinus Distension and Perfusion.* All visible branches of the right common carotid artery proximal to the sinus were ligated, as were the occipital and internal carotid arteries. When the sinus was to be distended with static pressure the external carotid artery was also tied; otherwise it was cannulated and connected to a Starling resistance so that pressure within the sinus could be abruptly increased by raising that within the resistance. During perfusions of the sinus, oxygenated blood was supplied by the pump-oxygenator mentioned above. Flow rate through the sinus was approximately 50 ml./minute. Static pressure was supplied by applying air pressure to blood contained in an inverted Erlenmeyer flask of 250-ml. volume. The pressure supplied was measured with an aneroid manometer which had previously been calibrated against a mercury column.

(5) *Brain Stem Stimulation.** Five of the six animals studied were decerebrated (by sections passing through or below the inferior colliculus) under ether anesthesia, and the anesthetic then discontinued. The sixth animal (20) was given chloralose; its brain was not sectioned. In all cases the head was fixed by ear pins in a dog sterotaxic instrument, and the cerebellum was unroofed and partially ablated in order to give access to the medulla 1 cm. rostral to the obex. A pair of concentric round or flat-tipped bipolar electrodes 0.7 mm. in diameter were loaded in the carriers and sunk within the brain substance at depths ranging from 0.5 to 5 mm. The depth attained was the minimum giving the desired response. In each of six preparations two stimulating electrodes were introduced into the medulla. They were positioned so that stimulation through one gave consistent pressor responses and stimulation through the other gave consistent depressor responses. Once these positions had been established a pair of curves (one pressor and one depressor) relating stimulus intensities and arterial pressure responses was constructed. In defining the curves all measured parameters of stimulation except voltage remained constant† once the optimal stimulus characteristics had been found. Duration of stimulation was invariably 10 seconds; frequency ranged, in various experiments, from 50 to 200 c.p.s.; all pulses

* These experiments were performed at the University of Oregon in the laboratory of Dr. J. M. Brookhart. Facilities for analyzing end-expired air samples for cyclopropane were not available during these experiments. Concentrations of cyclopropane in the inspired atmosphere were estimated from flowmeter readings; the flow rate supplied was 1.5 liters/minute.

† In preliminary experiments these electrodes were found to deliver current flows proportional to voltage over a range of conditions larger than that encountered in the present study.

TABLE 1

(A) Hemodynamic Effects of Administering Cyclopropane to the Head Alone in Five Animals (Means ± S.D.)

	Control Before	Response During	Control After	Significance of Response
M.A.B.P., mm. Hg	95.0 ± 16.6	+40.4 ± 21.2	+ 8.0 ± 4.1	$P < 0.01$
P.P., mm. Hg	52.6 ± 19.6	+22.0 ± 7.4	− 4.8 ± 9.1	$P < 0.01$
H.R./minute	175.6 ± 56.8	+ 7.2 ± 10.3	+11.0 ± 17.9	none

(B) Hemodynamic Effects of Administering Cyclopropane to the Trunk Alone in Five Animals (Means ± S.D.)

	Control	Response During	Control After	Significance of Response
M.A.B.P., mm. Hg	114.9 ± 29.1	−51.8 ± 39.2	−32.8 ± 24.0*	$P < 0.05$
P.P., mm. Hg	53.8 ± 14.7	−17.6 ± 15.7	− 1.5 ± 12.8*	none
H.R./minute	198.3 ± 71.3	− 6.5 ± 10.4	− 0.3 ± 6.4*	none

* Responses in four surviving dogs. The fifth animal did not recover following administration of cyclopropane to the trunk. M.A.B.P. = mean arterial blood pressure; P.P. = pulse pressure; H.R. = heart rate; S.D. = standard deviation.

were square waves of 1 msec. duration. The time between stimulations was uniformly 1.5 minutes. Since bradycardia or cardiac arrest often resulted from brain stem stimulation, the vagus nerve was divided in the neck in most (four) animals, while an additional one received 1.2 mg. atropine sulfate intravenously before study began. In the sixth animal (20) bradycardia did not occur, possibly because of actions of the muscle relaxant (gallamine) which was used. The carotid arteries were ligated bilaterally in all animals whose brains were sectioned. In 3 animals stimulation caused large respiratory movements and torsion of the neck which could have altered, respectively, intrapleural pressure and the position of the electrodes within the medulla. For this reason a muscle relaxant (gallamine, 2–4 mg./kg.) was given these animals prior to definitive study.

(6) *Evaluation of Effects Exerted Peripherally.* In the stimulation experiments it was impossible to limit distribution of cyclopropane only to the areas which were stimulated electrically. As a control an attempt was made in six animals to evaluate peripheral actions of autonomic mediators in the presence and absence of cyclopropane. If these actions were unchanged by systemic administration of the drug, it could be argued that changes in the response to central nervous system stimulation were less likely to be peripheral than central. For this purpose the following substances were given intravenously in repeated doses: phentolamine, 1.0 mg.; trimethaphan, 1.0 mg.; norepinephrine, 40–60 μg. Only agents affecting sympathetic nervous function were employed because, as stated previously, parasympathetic nervous activity had been blocked prior to studies involving electrical stimulation of the central nervous system. The animals studied were anesthetized with chloralose during control measurements, and received 1–1.5 mg. atropine sulfate intravenously in order to block vagal efferent activity. Concentrations of cyclopropane in end-expired air varied from 18 to 23 volumes per cent (v/v) among the animals studied by this technique.

Results

Perfusion of the Cephalic Circulation. Before these data are presented it should be emphasized that the responses observed did not result from changes in the P_{CO_2} of blood perfusing the head, because the gas tensions supplied to the oxygenator were so adjusted so that P_{CO_2} remained constant. Equally, they did not result from contamination of the systemic circulation with cyclopropane, since in no case could the gas be detected in the end-expired air.

TABLE 2. Responses to Cyclopropane Following Brain Section

Animal	Level of Section	A. P. After Section (mm. Hg)	A. P. Response to C_3H_6	E., N. Conc. During C_3H_6 (μg./liter)
60-14	Inferior to optic chiasm	140/104	++	—
60-64	Mid collicular	160/80	++	—
60-05	Mid collicular	140/94	++	—
60-1	Mid collicular	240/135	±	0.9, 0.3
60-66	Mid-pontine	142/76	+	—
60-65	Trapezoid body and inferior pons	170/79	++	1.0, 1.0
60P11	Upper edge of trapezoid body	180/60	+	—
60-09	Trapezoid body, inferior to pons	230/100	±	0.0, 0.3
60-69	Rostral medulla (acoustic tubercles)	190/132	—	0.0, 0.0
60-71	Obex	67/33	—	0.2, 0.2
60-68	C_1	167/113	—	0.2, 0.2
60-04	C_2	110/64	—	0.4, 0.3
60-66	C_1	128/67	—	—

A.P. = Arterial pressure; E. = epinephrine; N = norepinephrine.

The principal results are shown in table 1. Administration of cyclopropane to the pump-oxygenator supplying the head resulted, in every animal studied, in a substantial increase in mean arterial blood pressure, pulse pressure, and plasma catechol amine concentrations. Heart rate was inconsistently altered.

Administration of cyclopropane to the body (by inhalation) when the head was not exposed caused a small decrease in heart rate, a moderate fall in pressure in four of the five animals, and marked arterial hypotension in every case. Catechol amine concentrations consistently declined. One dog died exhibiting severe arterial hypotension. These results were not attributable to deterioration of the preparation since the measured variables tended in four of the five cases to return toward normal after cyclopropane was discontinued, and since they occurred in each of two animals whose trunks received cyclopropane initially, followed later by exposure of the head to the gas.

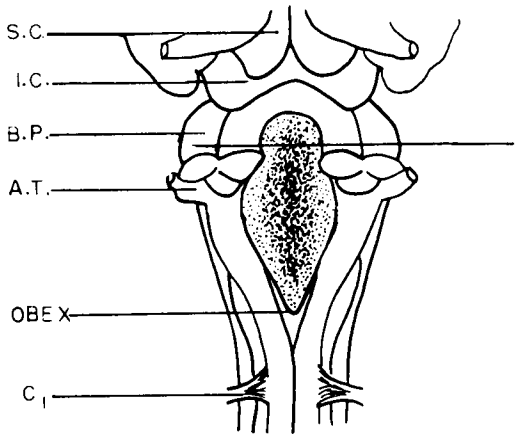

FIG. 1. Critical level of brain stem section for preservation of arterial hypertensive response to cyclopropane. Sections caudal to the horizontal line abolished the response. S.C. = superior colliculus; I.C. = inferior colliculus; B.P. =brachium points; A.T. = acoustic tubercle; C_1 = first cervical nerve. Stippled area indicates floor of fourth ventricle.

Carotid Sinus Perfusion. Since, in the head perfusion studies, cyclopropane reached and could have affected function in carotid sinus baroreceptors, it was essential to determine whether such an action could have resulted in systemic arterial hypertension. For this purpose carotid perfusion was used. Cyclopropane 35 per cent, CO_2 5 per cent, O_2 60 per cent was administered via the oxygenator. This procedure did not alter arterial pressure in any of four animals. Also, studies which were completed subsequently [6] showed that the action of cyclopropane on carotid sinus baroreceptors (sensitization) was opposite in direction to that which could account for the systemic hemodynamic effects of head perfusion.

Brain Stem Sections. Since the results obtained pointed toward a cephalic site of action,

an attempt was made to localize this site. Brain sections in 13 animals showed that arterial hypertension and increased catechol amine concentrations in arterial plasma still occurred in response to cyclopropane inhalation after progressively lower sections including classical decerebration; they were reduced or destroyed together by lesions within or just rostral to the medulla oblongata. Data are given in table 2, and the critical level of section is shown in figure 1.

Carotid Sinus Reflexes. One possibility which could explain these findings is that arterial hypertension during cyclopropane administration results from a lack of central responsiveness to impulses from peripheral baroreceptors.

Carotid sinus reflexes were studied in six animals. In two animals a carotid sinus was distended with pulsatile pressure; in four static pressure was used. In both cases mean intrasinusal pressure was raised abruptly from approximately 40 mm. of mercury to 180–250 mm. of mercury, while changes in systemic pressure were measured. A typical result, using static pressure, is shown in figure 2. The figure shows the depressor response progressively reduced during inhalation of cyclopropane. Concentrations (end-expired) of cyclopropane causing a 50 per cent reduction in the response averaged 20 volumes per cent (range 16 to 24) in the six dogs studied. The response was essentially abolished at cyclopropane concentrations ranging from 40 to 50 per cent. Vagal section did not alter these results in either of two animals, and there was no obvious difference between the results obtained using pulsatile and static pressure.

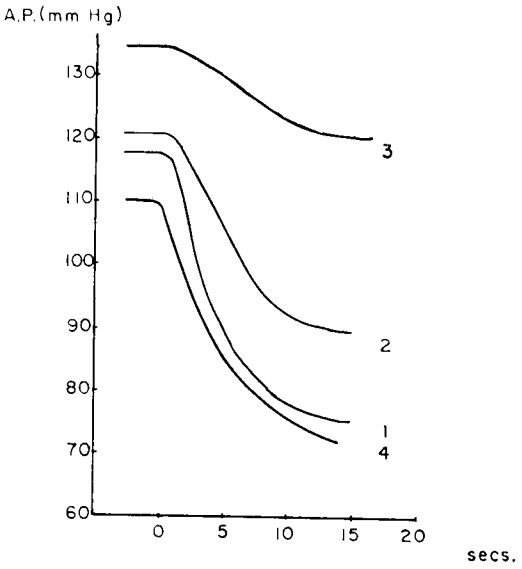

FIG. 2. Effect of cyclopropane on carotid sinus depressor responses: (1) Control (chloralose anesthesia); (2) 12 per cent cyclopropane; (3) 26 per cent cyclopropane; (4) Control after cyclopropane washout; A.P. = mean femoral arterial blood pressure; O (on time axis) = time right carotid sinus distended by 250 mm. of mercury static pressure. Note progressively greater level of systemic arterial pressure and progressively smaller response to sinus distension as cyclopropane concentration is increased.

TABLE 3. Electrical Thresholds for Medullary Stimulation

Animal	Condition	Cyclopropane Concentration	Threshold During (per cent of control)	Threshold After (per cent of control)
P 10	Vagotomized, Decerebrated	"Light"	P + 10 D + 160	*
Same	Vagotomized, Decerebrated	"Deep"	P + 70 D + 340	*
P 13	Vagotomized, Decerebrated	25%	P − 16 D + 230	−16 +20
P 14	Atropine, Decerebrated	25%	P + 12 D + 450	−25 +40
P 15	Vagotomized, Decerebrated	25%	P + 67 D + 143	+15 −50
P 16	Vagotomized, Decerebrated	†	P 0 D 0	0 0
P 20	Chloralose-Gallamine	25%	P + 33 D + 155	+22 +22
		Mean Changes	P + 25.2 D + 211.5	− 0.9 + 6.4

* Animal's condition deteriorated following exposure to cyclopropane.

† Suspected leak in equilibrating system; weak cyclopropane smell in breathing bag at end of equilibration period. P = pressor; D = depressor.

Electrical Stimulation of the Central Part of Divided Vagus Nerve. Four animals anesthetized with chloralose were studied. In two the response was erratic and not susceptible

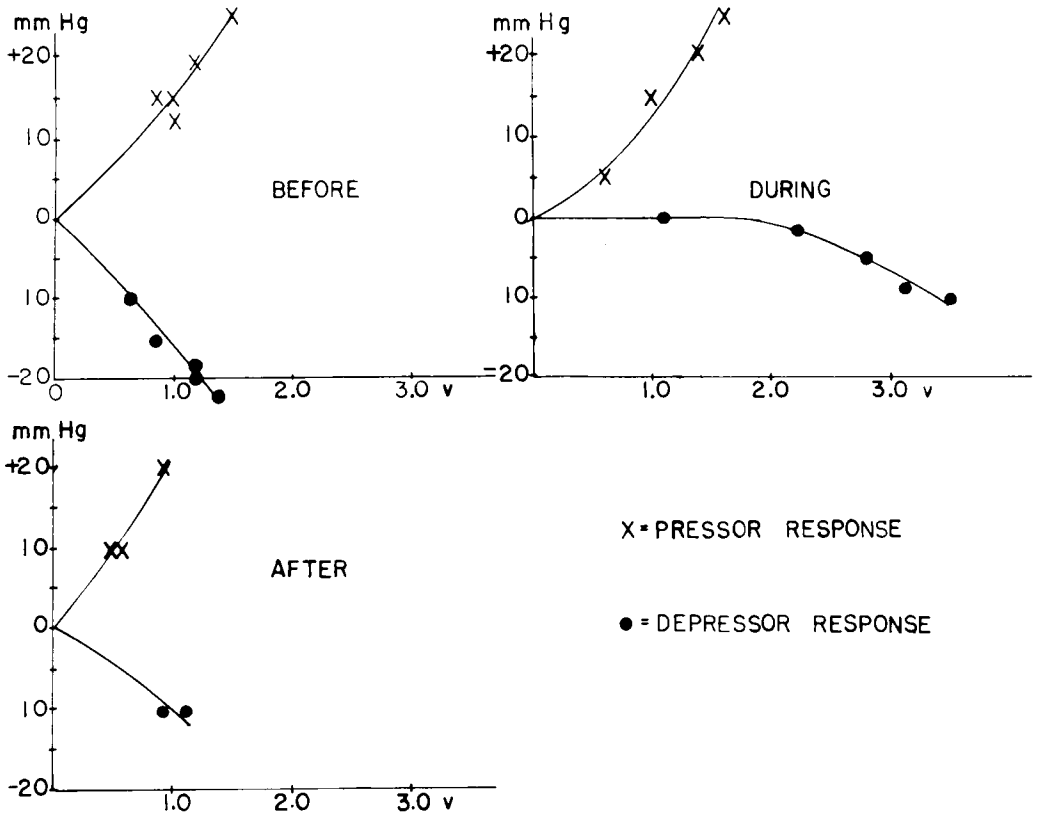

FIG. 3. Response of systemic arterial blood pressure to electrical stimulation of the medulla oblongata in a decerebrated dog. X = pressor response = increase in mean femoral arterial presssure during stimulation of "pressor area" with a fixed electrode. ● = depressor response = decrease in arterial pressure during stimulation in a discrete area associated with hypotensive responses. Responses shown are before cyclopropane administration, during inhalation of 25 per cent cyclopropane, and after cyclopropane washout. Stimulus strength (volts) shown on the abscissae.

to analysis; in the other two electrical stimulation of the central end of the divided vagus nerve consistently reduced systemic arterial pressure and heart rate. These responses were also reduced by cyclopropane administration; concentrations necessary for half-reduction in the two animals were 20 and 23 volumes per cent in end-expired air. These results, and those just described, made it likely that cyclopropane interfered centrally with the excitability of vasodepressor mechanisms. A direct test of this hypothesis was carried out by stimulating the brain stem electrically.

Electrical Stimulation of the Brain Stem. A typical result is shown in figure 3; more complete data appear in table 3. In table 3 electrical "thresholds" are arbitrarily defined as voltages necessary to cause a 10 mm. of mercury change in mean arterial pressure. It can be seen that administration of cyclopropane increased the threshold for depressor responses markedly without affecting thresholds for pressor responses to so marked a degree. The difference is statistically significant ($P < 0.05$).

Evaluation of Effect Exerted by Cyclopropane in the Periphery. In the stimulation experiments it was impracticable to restrict cyclopropane to the central nervous system. Consequently, further study was needed to rule out the possibility that the effects observed were exerted below the area which was stimulated, *i.e.*, in autonomic efferent nerves, ganglia, adrenal medulla, blood vessels, or heart.

Administration of norepinephrine caused arterial pressure to increase on the average as much in the presence of cyclopropane as in its absence; there was one significant increase and one significant reduction in the response, while three animals showed no change. In one of two animals phentolamine caused a significantly greater reduction in arterial pressure during cyclopropane administration than either before or after administration of the anesthetic. In the other animal the response was unaltered by cyclopropane. Standard doses of trimethaphan reduced arterial pressure to a greater degree, in each of three cases, in the presence of cyclopropane than in its absence. The change was statistically significant in two experiments, while in the third failure to show a significant difference was perhaps attributable to the limited number of observations available. Data are summarized in table 4.

TABLE 4. Responses of Mean Arterial Blood Pressure to Intravenous Administration of Norepinephrine, Trimethaphan, and Phentolamine

Animal	Agent	Change in M.A.B.P. During:		No. Obs.	Significance of Difference
		Control Periods	Cyclopropane Inhalation		
D 61-6	Norepinephrine	+56	+58	14	None
D 61-5	Norepinephrine	+31	+52	8	$P < 0.01$
D 61-9	Norepinephrine	+26	+27	11	None
D 61-8	Norepinephrine	+17	+22	16	None
D 61-7	Norepinephrine	+34	+27	14	$P < 0.05$
D 61-7	Trimethaphan	−10	−16	18	$P < 0.01$
D 61-5	Trimethaphan	−30	−33	5	None
D 61-6	Trimethaphan	−23	−37	14	$P < 0.01$
D 61-9	Phentolamine	−14	−11	11	None
D 61-8	Phentolamine	−9	−14	15	$P < 0.01$

M.A.B.P. = mean arterial blood pressure.
Obs. = number of observations.

These results are interpreted to mean that, while pressor responses caused by brain stem stimulation are unlikely to be changed by peripheral actions of cyclopropane, depressor responses so elicited may be exaggerated.

Discussion

The discussion is organized to deal with the following questions: what is the mechanism whereby cyclopropane causes arterial hypertension in dogs, what is the physiological significance of such a response, and what are the chances that actions similar to those hypothesized in dogs can account for responses observed in man?

The results of experiments extending over nearly a century indicate that the medulla oblongata contains two major cell populations which subserve vasomotor function.[7-13] The more numerous "pressor" neurones occupy sites in areas rostral and lateral to the obex, are tonically active, and directly excite spinal vasomotor neurones via pathways which descend in the ventrolateral portion of the spinal cord. Depressor representations are less numerous, tend to occur medially near the level of the obex, and are believed incapable of spontaneous activity. They are excited by afferent impulses from baroreceptors, and are essential for depressor reflexes.[13] Pathways descend in the cord from the depressor area which can suppress activity in spinal vasomotor neurones; it is not known whether brain stem depressor areas can directly affect medullary pressor neurones. Activation of the "depressor" area, however evoked, is believed to result in central inhibition of the prevailing vasoconstrictor discharge; vasodilator nerves do not appear to be involved.[14] Depressor reflexes can survive chronic infracollicular decerebration,[15] indicating that the medulla oblongata is an authentic integrating "center," and not a mere collection of pathways.

Investigations of central nervous cardiovascular representations have not yet established an anatomy of cardiac vagal regulation, and nervous control of cardiac activity is less well understood than is that of the blood vessels. It is known that carotid sinus reflexes normally affect myocardial contractility,[16] but it has not been shown whether this action is integrated in the medulla. In cats, reflex cardioaccelerator responses are said to be represented at higher levels.[17]

Viewed against a still incomplete background, the findings of the present study are most plausibly explained by supposing cyclopropane to inhibit selectively the excitability of the medullary depressor neurones. This action, in addition to explaining the present findings, would theoretically result in the hemodynamic and sympathoadrenal effects which cyclopropane has already been shown[4] to produce in the intact dog.

A physiological equivalent of the action proposed for cyclopropane can be elicited by carotid artery occlusion. In conscious dogs bilateral carotid occlusion (the arteries made chronically available by the construction of skin tunnels) increased systolic, diastolic, pulse and mean arterial pressures, and heart rate.[18] In dogs anesthetized with morphine and chloralose carotid occlusion could also be shown to increase cardiac output and total peripheral resistance [19] and the adrenal output of catechol amines, principally epinephrine.[20] Tachycardia during occlusion is thought to be largely attributable to decreased vagal tone.[21]

All of these canine responses to carotid occlusion have been demonstrated to accompany cyclopropane administration. The changes in arterial pressure and heart rate found by Deutsch and his associates [4] to accompany the administration of high concentrations of cyclopropane were quantitatively similar to, although somewhat greater than, those caused by carotid occlusion. Subsequent studies showed that tachycardia and hypertension could be dissociated by giving atropine. In atropinized animals administration of cyclopropane changed heart rate inconsistently, but the hypertensive response was not prevented. It therefore appears that a large part of the heart rate response to cyclopropane in the dog results from suppression of normal vagal tone, but that this action has little significance for the effect of the drug on the blood pressure; the pressor response is sympathetic in origin. The similarity between responses to cyclopropane and carotid occlusion therefore includes more than a superficial resemblance; it extends to mechanism.

It should be stated explicitly here that the proposed medullary action of cyclopropane, even assuming it to be proved rather than postulated, does not necessarily account for all of the autonomic circulatory responses to cyclopropane which have been observed in the intact dog. Indeed, such a specificity of action would be surprising.

The type of action proposed for cyclopropane in the dog is interesting in principle. It is commonly recognized that the induction of anesthesia may be attended by various manifestations indicating a release of lower parts of the nervous system from cortical control. It has not previously been shown that a steady state of general anesthesia can be associated with analogous changes in neuronal activity, nor that the areas involved may lie not only below the cortex, but as far caudally as the lowest part of the brain stem. Unlike any mechanism previously set forth to explain hemodynamic actions of an anesthetic drug, the action now proposed is not a reflex consequence of peripheral circulatory depression, nor is it attributable to direct stimulation of sympathetic representations within the central nervous system. It apparently represents a relatively specific inhibition of a normal inhibitory mechanism.

The existence of contrasting central nervous and peripheral actions of cyclopropane makes it likely that transient and steady-state responses to the drug will be different to the extent that local differences in blood flow can affect tissue equilibration rates. For example, if arterial baroreceptors equilibrate with cyclopropane before significant saturation of the medullary apparatus has occurred, arterial hypotension and bradycardia might be expected during the induction of anesthesia or whenever anesthetic depth is increased rapidly from a "light" to a "deeper" level. An exaggerated instance of this difference in sites of action is illustrated by the results obtained when cyclopropane was administered to the body but was prevented from entering the brain. The result of this—pronounced systemic arterial hypotension—seems most plausibly explained as resulting from aortic baroreceptor sensitization combined with direct actions of cyclopropane on the heart.

Human and canine responses to cyclopropane may next be compared. Both species exhibit arterial hypertension, at least in most cases; both experience an increase in cardiac output at low concentrations of cyclopropane, while decreased or normal cardiac output together with increased peripheral resistance typifies the response to high concentrations[1,22]; and both species exhibit an increase in plasma concentrations of catechol amines.[2,4] Points of difference follow: cardiac rate typically increases during cyclopropane inhalation in dogs, while in man heart rate may increase, decrease, or remain constant; in dogs mean arterial blood pressure tends to increase with

increasing cyclopropane concentration,[4] while in man the existence of this relation has not been demonstrated [1, 23] (and may not have been adequately tested); epinephrine appears to be the principal catechol amine secreted by dogs in response to cyclopropane, while in man norepinephrine predominates [2, 4]; and finally, it has been reported [24] that forearm blood flow increases during "light" cyclopropane anesthesia in man, whereas the mode of action currently proposed would seem to require vasoconstriction, and preliminary results in dogs indicate an increase rather than a decrease in peripheral vascular tone.

Some of these differences can be reconciled. To begin with the most serious one, it now appears that the earlier finding of forearm vasodilatation during "light" anesthesia in man [24] is to be attributed to coincident painful stimulation from surgical operations rather than to actions of cyclopropane. Studies made in man in the absence of surgical intervention indicate that vascular resistance increases with increasing cyclopropane concentration and that dilatation does not occur at any anesthetic concentration.[25]

The difference in the identity of the predominant catechol amine liberated by the two species is, to an extent, reassuring rather than worrisome. Dogs liberate epinephrine under a wide variety of conditions, particularly those involving circulatory "stress," which evoke norepinephrine secretion in man.[20, 26] In both dog and man therefore, the response to cyclopropane is that characteristic of the species. The fact that epinephrine and norepinephrine have peripheral actions which are different must be considered in comparing human and canine responses, as well as the fact that norepinephrine typically reaches cardiovascular effectors via sympathetic nerves while epinephrine arrives in arterial blood.

The fact that heart rate increases relatively little during exposure to cyclopropane in animals previously given atropine indicates that the tachycardia observed in normal animals results largely from a diminution in vagal restraint of the pacemaker. In man vagal "tone" is either normal or greater than normal during cyclopropane administration, and individuals given atropine during anesthesia attain cardiac rates substantially greater than normal as the result, apparently, of a marked increase in the activity of sympathetic nerves supplying the heart.[3] Thus, sympathetic nervous responses to cyclopropane in the two species appear basically similar. Parasympathetic actions are at least quantitatively different.

Summary and Conclusions

Studies of autonomic and circulatory actions of cyclopropane in mongrel dogs have been reported. Perfusion of the head alone with blood containing cyclopropane increased both systemic arterial mean and pulse pressures and catechol amine concentrations, but exposure of the body alone to the anesthetic had effects which were diametrically opposite in direction. Arterial hypertension and increased plasma catechol amine concentrations were both prevented by brain sections which involved any part of the medulla oblongata; sections above this level did not appreciably alter measured responses to cyclopropane. Various autonomic nervous stimuli which ordinarily cause arterial hypotension in dogs were shown to be ineffective during the administration of cyclopropane. It was concluded that cyclopropane elicited arterial hypertension and increased plasma concentrations of catechol amines in dogs by selectively depressing "depressor" neurones in the medulla oblongata; "pressor" neurones apparently were affected to a lesser degree. The relevance of these findings to results previously obtained in dog and man was discussed.

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References

1. Jones, R. E., Guldman, N., Linde, H. W., Dripps, R. D., and Price, H. L.: Cyclopropane anesthesia; effects of cyclopropane on respiration and circulation in normal man, ANESTHESIOLOGY 21: 380, 1960.
2. Price, H. L., Linde, H. W., Jones, R. E., Black, G. W., and Price, M. L.: Sympatho-

adrenal responses to general anesthesia in man and their relation to hemodynamics, ANESTHESIOLOGY 20: 563, 1959.
3. Price, H. L., Jones, R. E., Deutsch, S., and Linde, H. W.: Ventricular function and autonomic nervous activity during cyclopropane anesthesia in man, J. Clin. Invest. 41: 604, 1962.
4. Deutsch, S., Linde, H. W., and Price, H. L.: Circulatory and sympathoadrenal responses to cyclopropane in the dog, J. Pharmacol. Exp. Ther. 135: 354, 1962.
5. Price, H. L., and Price, M. L.: The chemical estimation of epinephrine and norepinephrine in human and canine plasma; a critique of the trihydroxyindole method, J. Lab. Clin. Med. 50: 769, 1957.
6. Price, H. L., and Widdicombe, J.: Actions of cyclopropane on carotid sinus baroreceptors and carotid body chemoreceptors, J. Pharmacol. Exp. Ther. 135: 233, 1962.
7. Dittmar, C.: Ein neuer Beweis für die Reizbarkeit der centripetal en Fasern des Rückenmarks, Ber. Sächs. Ges. Wiss., mat.-phys. Kl. 22: 18, 1870.
8. Ranson, W. S.: New evidence in favor of a chief vaso-constrictor center in the brain, Amer. J. Physiol. 42: 18, 1916.
9. Owsjannikow, P.: Die tonischen und reflectorischen Centren des Gefässnerven, Ber. Sächs. Ges. Wiss., mat.-phys. Kl. 23: 135, 1871.
10. Dittmar, C.: Über die Lage des sogenannten Gefässzentrums in der Medulla oblongata, Ber. Sächs. Ges. Wiss., mat.-phys. Kl. 25: 449, 1873.
11. Wang, S. C., and Ranson, W. R.: Autonomic responses to electrical stimulation of the lower brain stem, J. Comp. Neurol. 71: 437, 1939.
12. Amoroso, E. C., Bell, F. R., and Rosenberg, H.: The relationship of the vasomotor and respiratory regions in the medulla oblongata of the sheep, J. Physiol. 126: 86, 1954.
13. Alexander, R. S.: Tonic and reflex functions of medullary sympathetic cardiovascular centers, J. Neurophysiol. 9: 205, 1946.
14. Frumin, M. J., Ngai, S. H., and Wang, S. C.: Evaluation of vasodilator mechanisms in the canine hind leg; question of dorsal root participation, Amer. J. Physiol. 173: 428, 1953.
15. Lindgren, P.: Localization and function of the medullary vasomotor center in infracollicularly decerebrated cats, Circulat. Res. 9: 250, 1961.
16. Sarnoff, S. J., Gilmore, J. P., Brockman, S. K., Mitchell, J. H., and Linden, R. J.: Regulation of ventricular contraction by the carotid sinus. Its effect on atrial and ventricular dynamics, Circulat. Res. 8: 1123, 1960.
17. Peiss, C. N.: Central control of sympathetic cardioacceleration in the cat, J. Physiol. 151: 225, 1960.
18. Armstrong, G. G., Jr., Porter, H., Jr., and Langston, J. B.: Common carotid artery occlusion reflex in unanesthetized dogs, Amer. J. Physiol. 200: 741, 1961.
19. Leusen, I., Demeester, G., and Bouckaert, J. J.: Influence des presso-recepteurs des sinus-carotidiens sur le debit cardiaque, Arch. Int. Physiol. 64: 489, 1956.
20. De Schaepdryver, A. F.: Physio-pharmacological effects on suprarenal secretion of adrenaline and noradrenaline in dogs, Arch. Int. Pharmacodyn. 121: 222, 1959.
21. Heymans, C., and Neil, E.: Reflexogenic Areas of the Cardiovascular System. Boston, Little, Brown & Co., 1958.
22. Robbins, B. H., and Baxter, J. H.: Studies of cyclopropane IV. Cardiac output in dogs under cyclopropane anesthesia, J. Pharmacol. Exp. Ther. 62: 179, 1938.
23. Li, T. H., and Etsten, B.: Effect of cyclopropane anesthesia on cardiac output and related hemodynamics in man, ANESTHESIOLOGY 18: 15, 1957.
24. Kitchin, A. H., Sanger, C., de Wardener, H. E., and Young, I. M.: The blood flow in human muscle during cyclopropane anaesthesia, Clin. Sci. 12: 361, 1953.
25. Black, G. W.: Personal communication.
26. Walker, W. F., Zileli, M. S., Reutter, F. W., Shoemaker, W. C., Friend, D., and Moore, F. D.: Adrenal medullary secretion in hemorrhagic shock, Amer. J. Physiol. 197: 773, 1959.