

Central Sympathetic Excitation Caused by Cyclopropane

Henry L. Price, M.D.,* John C. Warden, M.B.,† Lee H. Cooperman, M.D.,‡
Ronald A. Millar, M.D., Ph.D., F.F.A.R.C.S.S

Cats anesthetized with chloralose were studied by recording electrical activity from cervical sympathetic nerves. Cyclopropane inhalation typically increased impulse frequency, this effect depending directly upon the alveolar concentration of the gas. Spinal-cord section at C1-2 reduced or abolished this action, but midcollicular decerebration did not. Baroreceptor denervation also abolished the sympathetic response at low, but not at high, cyclopropane concentrations, while baroreceptor reflexes were completely obtunded by intermediate concentrations. These results support the contention that cyclopropane increases sympathetic nervous activity and that this action could reflect a selective depression of certain medullary inhibitory neurons. In addition, we have found evidence for direct stimulation by cyclopropane of excitatory "pressor" neurons.

ONE OF US has proposed that cyclopropane causes sympathetic excitation in both man and dog, and that the mechanism of excitation involves the medullary vasomotor neurons.¹⁻³ We also suggested that sympathetic activation was at least partially responsible for a number

of circulatory changes during cyclopropane anesthesia, including the frequent occurrence of arterial hypertension and ventricular extrasystoles. Finally, we postulated that the coexistence of arterial hypertension and increased sympathetic nervous activity during anesthesia resulted from a paralysis of the barostatic "buffer" reflexes caused by actions of cyclopropane which selectively inhibit the "depressor" areas of the medulla oblongata.⁴

In recent years, results of studies utilizing nerve recordings^{5,6} have supported the validity of these hypotheses. However, in other more indirect, experiments⁷⁻¹⁰ they have been questioned. The present study attempts to investigate the problem further using direct methods.

Methods

The subjects of the experiments were 40 cats. They were anesthetized initially with 40 per cent halothane in oxygen delivered into a plastic bag enclosing a small animal cage. Inhalation anesthesia was continued during insertion of cannulae into the trachea, a femoral artery and a femoral vein. In all but two animals, chloralose, 40 mg/kg, was then injected intravenously, halothane administration stopped, and 100 per cent oxygen continued. The animals not given chloralose were decerebrated at the midcollicular level before discontinuation of halothane.

The left preganglionic cervical sympathetic nerve was approached by reflecting the larynx and pharynx from the midline; this also gave access to the carotid sinus, aortic depressor and vagus nerves. The cervical sympathetic nerve was cut close to the superior cervical ganglion, dissected free of surrounding tissue and placed on a metal backplate immersed in mineral oil. In three animals, the left aortic de

* Professor of Anesthesia, University of Pennsylvania.

† Recipient of a travel grant from the Postgraduate Medical Foundation, University of Sydney, Sydney, Australia.

‡ Assistant Professor of Anesthesia, University of Pennsylvania.

§ Consultant Anaesthetist, Addenbrooke's Hospital, Cambridge, England.

Received from the Departments of Anesthesia, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, Pennsylvania, and Addenbrooke's Hospital, Cambridge, England. Accepted for publication December 3, 1968. Supported (in part) by U. S. Public Health Service Grants 5-P01-GM-09070-06 and 1-P01-GM-15430-01 and Research Training Grant 2-T10-GM-215-11 from the National Institute of General Medical Science, National Institutes of Health. A preliminary report of these findings was given at the Federation of American Societies of Experimental Biology on April 20th, 1968, in Atlantic City, New Jersey.

pressor nerve was cut, together with the sympathetic, while in a further three cats, the aortic depressor nerve was found to be present within the sheath surrounding the sympathetic nerve, from which it was indistinguishable without recording from the fibers. The sympathetic nerve was dissected to obtain multifiber strands which had satisfactory signal-to-noise ratios. Recordings were made with bipolar platinum wire electrodes connected to a Grass preamplifier; a ground wire connected the metal backplate to the preamplifier, the output going to a Grass audioamplifier and to one channel of a Tektronix 565 oscilloscope, from which the sympathetic action potentials could be photographed by means of a Grass camera and Reflexor attachment. Time marks from a battery-operated neon timing circuit were displayed on the oscilloscope trace.

The signal from one vertical oscilloscope amplifier was fed to a pulse height selector. This comprised both discriminator and pulse-shaping circuits, by means of which nerve action potentials between selected upper- and lower-voltage limits were converted into square pulses, which were then counted on a Nuclear-Chicago ratemeter. Three counting ranges on the ratemeter were used: 0-30, 0-100, and 0-300 impulses/sec; these were frequently calibrated with a Hewlett-Packard signal generator and electronic counter; the ratemeter time constants could be varied widely. The ratemeter output was delivered to a Grass amplifier and multichannel recorder. The output of the pulse height selector was monitored continuously to ensure that a change in the signal-to-noise ratio did not affect the number of action potentials counted during an experimental sequence; this was done by using the pulse height selector output to trigger a Venner Electronics reset unit (TS 32), which caused the resetting to zero of a time scale which was displayed on the oscilloscope.⁵ Audiomonitoring of the sympathetic discharge was used continuously throughout every experiment.

In two cats, the left depressor nerve was divided low in the neck, freed from the vagus nerve, and placed across platinum electrodes for stimulation with a Grass stimulator and isolation transformer. Stimulus parameters were

1-10V, 100-microsec duration, 100 per second, maintained for 20 seconds.

Two cats were studied following midcollicular decerebration; 17 animals were studied before and an hour and a half after section of the spinal cord at C1. In the latter animals, a loose silk ligature was passed intradurally around the cervical cord at level C2, after which dissection of the sympathetic nerve was begun. Prior to cord section the normal response to cyclopropane was sought for comparison with that following division of the cord. The same sympathetic fibers were studied before and an hour and a half after slowly pulling the ligature tight.

Systolic, diastolic, and mean arterial pressures were displayed on a Grass recorder, using a Statham P-23d transducer. End-tidal carbon dioxide concentration was monitored continuously by means of a Beckman physiologic gas analyzer, model 160, or a Godart "Capnograph." Corrections were made for the collision-broadening effect of cyclopropane.¹¹

Prior to the start of nerve dissections and recording, mechanical ventilation was started using a Bird Mark 4 assister and Mark 7 ventilator; gallamine triethiodide, 20 mg, was given intravenously every 30 minutes throughout each experiment. Two-ml samples of arterial blood were withdrawn at intervals for measurement of pH, P_{CO_2} , P_{O_2} , and base deficit with an Instrumentation Laboratories assembly. The blood lost (6-8 ml) was replaced with dextran or physiologic saline solution. Metabolic acidosis was invariably present at the start of each experiment; appropriate injections of sodium bicarbonate were given then, and subsequently, on the basis of (base deficit \times body weight \times 0.3) milliequivalents.

End-tidal CO_2 concentration was maintained in the range 4.0-5.0 per cent. The measurements reported were obtained at a Pa_{CO_2} below 45 mm Hg and at Pa_{O_2} above 70 mm Hg. Mean Pa_{CO_2} values were 35.9 ± 4.4 (SD) mm Hg.

Rectal temperature of the animal was maintained at 37 C with a water-warmed rubber "K-pad" (Gorman-Rupp) and a Yellow Springs Thermister.

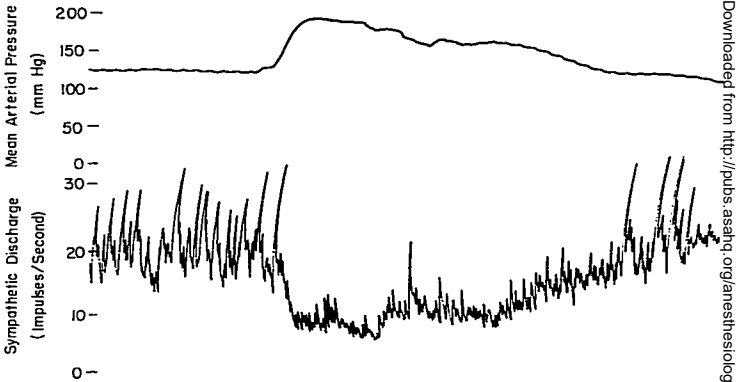


FIG. 1. Reflex inhibition of sympathetic activity caused by intravenous injection of 4 μ g epinephrine.

Intravenous injection of epinephrine hydrochloride (E), 1–4 μ g, were given early in each experiment to test the sympathetic response to raised arterial pressure. Only fibers showing conspicuous inhibition of the discharge were studied. Figure 1 shows an example of this response. In some animals, a continuous in-

fusion of norepinephrine (5 μ g per ml) was given intravenously to raise arterial pressure during administration of the inhalation anesthetic.

Cyclopropane in oxygen was administered by a nonbreathing technique using a total flow rate of 2.5–3.0 LPM for periods ranging

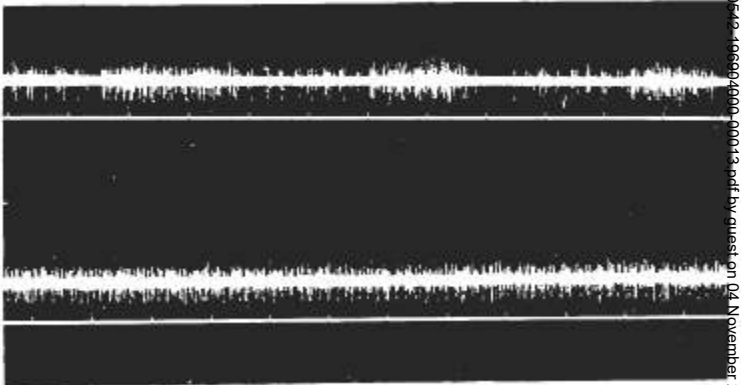
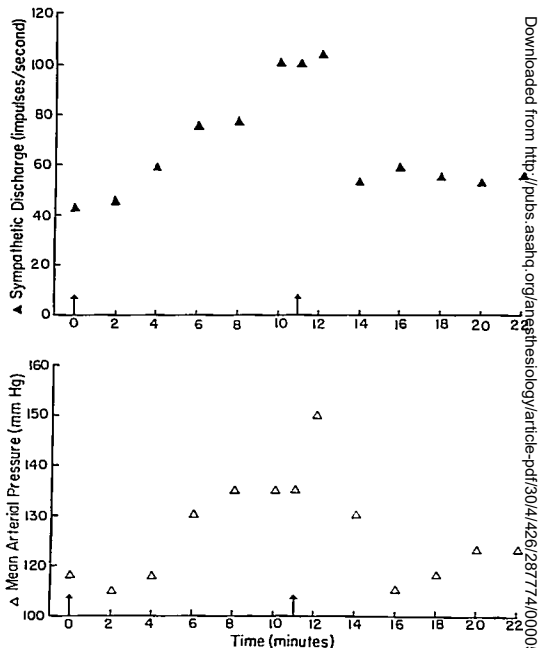


FIG. 2. Impulses recorded from a preganglionic cervical sympathetic nerve fiber before and at the end of a 12-minute exposure to cyclopropane (35 per cent end-expired concentration). Time marks = 1 sec.

FIG. 3. Time course of changes in sympathetic nervous activity and mean arterial pressure during and after exposure to cyclopropane (35 per cent end-expired concentration), administered between arrows.



from 11 to 16 minutes, by which time maximal responses were obtained. End-expired cyclopropane concentrations were measured by the method of Linde and Price.¹²

Results

INTACT ANIMALS

The multifiber cervical sympathetic nerve strands studied showed a respiratory rhythm, the peak discharge usually occurring early in the expiratory pause. Within a few minutes after inhalation of cyclopropane had begun this rhythm became disrupted, and the discharge assumed an increasingly continuous character (fig. 2). Initially (1-3 minutes) the mean rate of discharge either remained at the control level or fell below it. Arterial hypotension invariably occurred at this time. In the next 8 to 10 minutes arterial pressure and

sympathetic activity both increased, reaching maximum values after 10 to 12 minutes' exposure to cyclopropane. Cardiac rate showed variable responses.

Similar findings were observed in 23 of 29 intact cats. In the other six cats the first administration of cyclopropane either did not increase or reduced the sympathetic discharge rate. One unresponsive animal was not exposed to cyclopropane again. Two cats showed increases in sympathetic nervous activity on subsequent exposures although not on the first. The first, unresponsive, strands that occurred in two additional animals were discarded, and cyclopropane was found to increase sympathetic discharge in second, arbitrarily-selected, strands. One animal was unique in that testing of several strands failed to show any increase in activity on exposure to cyclopropane.

Downloaded from http://pubs.asahq.org/esthesiology/article-pdf/30/4/426/287774/0000542-10990400-0013.pdf by guest on 04 November 2024

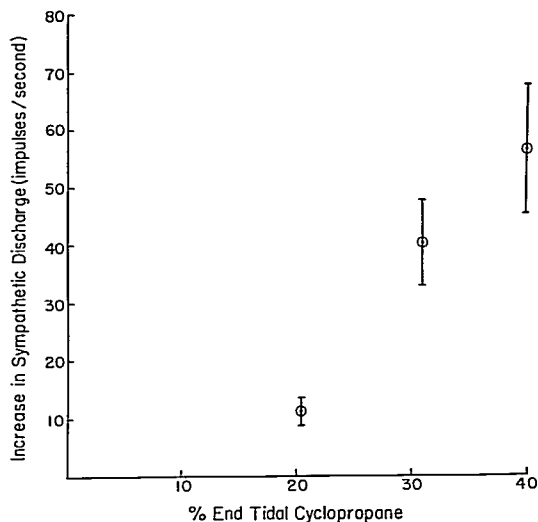


FIG. 4. Mean increase in sympathetic discharge in relation to cyclopropane concentration. Bars indicate one standard error.

Following substitution of oxygen for the cyclopropane-oxygen mixture, sympathetic activity declined towards (sometimes below) the initial levels, and the respiratory rhythm returned over a period of 4 to 8 minutes. In the initial 1 to 2 minutes after termination of cyclopropane the arterial pressure "overshot" (exceeded all previous levels), then returned toward normal. These findings from a single animal are illustrated in figure 3.

We attempted to construct dose-response curves relating increase in sympathetic nervous activity to end-expired concentration of cyclopropane. In several individual cases these were hyperbolic (cf fig. 7), but the mean response from a group of 12 cats, each exposed to three concentrations of cyclopropane, was nearly linear (fig. 4). The threshold concentration for sympathetic activation was approximately 15 per cent. An upper limit was not established. There was some evidence that the responses could increase with time and/or repeated exposure. Table 1 shows the findings

in a single animal exposed to cyclopropane on eight consecutive occasions separated by 15-20 minute washout periods. Of two other animals similarly exposed, one showed a much smaller increase on repeated administration, the other none.

The magnitude of the "overshoot" in arterial blood pressure following discontinuation of cyclopropane was also found to be related to the end-expired concentration achieved during administration of the anesthetic. The data from all 29 normal animals, shown in figure 5, have been grouped in four concentration ranges: 16-19, 25-29, 31-39 and 41-47 per cent. When more than one administration of cyclopropane in any concentration range was given to individual animals, the "overshoot" values were averaged and a single value entered for each animal. However, despite the similarity of figures 4 and 5, a significant correlation between increase in sympathetic activity and "overshoot" of arterial pressure in individual animals could not be established.

DEPRESSOR-NERVE STIMULATION

Electrical stimulation of the left aortic depressor nerve, with only one remaining baroreceptor nerve intact (either the right carotid sinus or depressor nerve), was found to cause a reduction in arterial pressure and cervical sympathetic discharge. In two cats it was possible to show that cyclopropane abolished the baroreceptor reflex rapidly (7-10 minutes) and almost completely at end-tidal concentrations of about 30 per cent. When this concentration of cyclopropane was inspired the increase in sympathetic nervous activity closely paralleled the inhibition of the reflex (fig. 6). However, when higher concentrations (40-50 per cent) were inspired sympathetic activity continued to increase with time after the reflex had disappeared completely.

TABLE 1. Effect of Repeated Exposure to Cyclopropane on Sympathetic Nervous Activity

Control†	Frequency* (Impulses/sec)		End-expired Cyclopropane Concentration (Volumes per cent)
	During Cyclopropane‡	Change§	
32	38	+6	33
26	51	+25	31
30	60	+30	33
33	82	+49	32
28	100	+72	33
{30	55	+25	22
{34	43	+9	17
42	123	+81	33

* Preganglionic cervical sympathetic nervous activity.

† Cyclopropane absent.

‡ After 11-minute inhalation of cyclopropane.

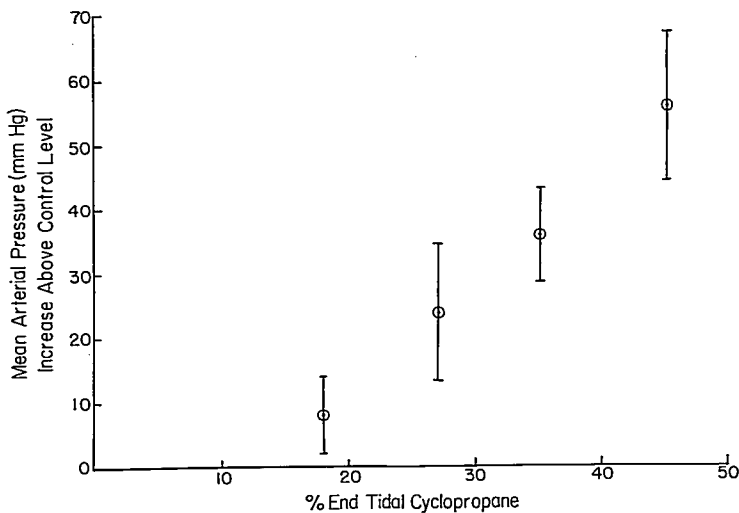


FIG. 5. Mean increase in arterial pressure (above control) following discontinuation of cyclopropane (overshoot) in relation to cyclopropane concentrations attained during exposure. Bars indicate one standard error.

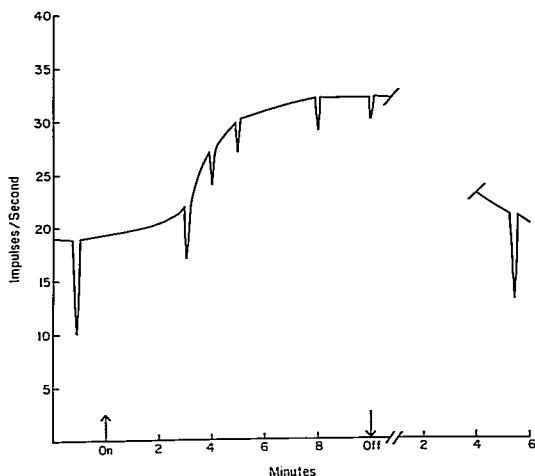


FIG. 6. Temporal relation between inhibition of the response to stimulation of the left aortic depressor nerve and the level of sympathetic nervous activity during exposure to cyclopropane (between arrows) in a single animal. Ordinate, sympathetic discharge in impulses/sec. Sharp inhibitions of the discharge are caused by repeated standard 20-second electrical stimulations of the nerve.

DECEREBRATED ANIMALS

Both animals were exposed to 45 per cent cyclopropane (end-tidal), and both showed increases in cardiac rate, mean arterial blood pressure and sympathetic nervous activity. The actual changes in impulse rate were from 2 to 32 and from 30 to 210 impulses/sec.

BARORECEPTOR-DENERVATED ANIMALS

In 12 animals response curves relating sympathetic discharge to end-tidal cyclopropane concentration were obtained following division of both vagi and the carotid sinus, aortic depressor and the contralateral cervical sympathetic nerves. In seven of these experiments response curves were obtained both before and after buffer nerve section. Figure 7 illustrates such a comparison in one animal. Before denervation, concentrations of cyclopropane below 20 per cent caused significant increases in sympathetic activity. After denervation the same concentrations were ineffective in increasing activity above the control level. However, still higher concentrations did increase the discharge, although not as much as before denervation. In table 2 are presented the data from all seven cats in which both "intact"

and "buffer-denervated" measurements were made; comparisons are at end-tidal concentrations which agreed within 2 volumes per cent, only a single pair of measurements from each animal being included. Increases in sympathetic discharge, expressed in impulses/sec, are seen to be greatly reduced by baroreceptor denervation. It should be pointed out, however, that denervation greatly increased the "resting" level of sympathetic discharge and that this fact may invalidate any attempt to compare the responses in terms of magnitude.

Figure 8 considers *directional* changes in sympathetic activity in 11 of the 12 experiments in which cyclopropane was given to animals subsequent to baroreceptor denervation. One animal was excluded because the background level of sympathetic activity fell away rapidly and progressively after section of the nerves, preventing a valid assessment of the effect of cyclopropane. The figure shows increases and decreases in activity in the 11 denervated animals 11 minutes after the start of cyclopropane administration and expresses these changes as percentage of control level immediately before cyclopropane was given. A wide variation among experiments is obvi-

ous, as is the fact that pronounced and consistent increases in sympathetic activity could be obtained only at cyclopropane concentrations greater than 45 per cent. The effects of lower concentrations, including those in the clinical range, were inconsistent.

Arterial pressure responses in the buffer-denervated group were distinctly abnormal, the early increase in arterial pressure during the first 5 to 10 minutes of cyclopropane administration being replaced by a progressive decline, while the "overshoot" following discontinuation of the anesthetic was absent.

In view of the close reciprocal relationship between alterations in arterial pressure and sympathetic discharge in spinal animals (see below), and the possibility that arterial hypo-

TABLE 2. Effect of Buffer Deafferentation on Sympathetic Response to Cyclopropane

	Frequency* (Impulses/sec)			End- expired Cyclo- propane Concen- tration (Volumes per cent)
	Intact	Denervated†	Difference	
	+53	+13	-40	46
	+21	+7	-14	42
	+2.5	+0.5	-2	39
	+58	+35	-23	27
	+15	+7	-8	35
	+32	-19	-51	28
	+8	+7	-1	38
Mean Change	+27.1	+7.2	-19.9	
SE	±8.2	±6.1	±7.3	

* Preganglionic cervical sympathetic nervous activity.

† After baroreceptor denervation.

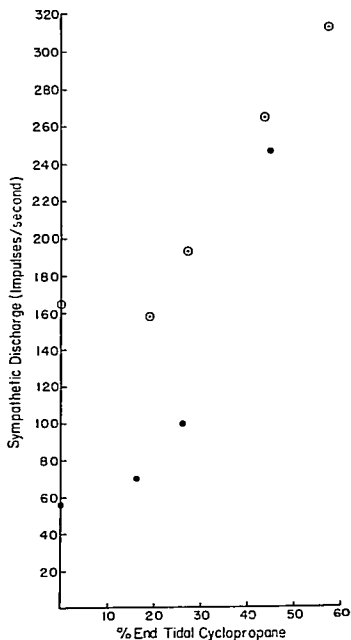


FIG. 7. Effect of cyclopropane on sympathetic discharge before (●) and after (○) baroreceptor denervation.

tension was wholly or in part responsible for the increase in sympathetic discharge associated with administration of high cyclopropane concentrations in baroreceptor-denervated animals, intravenous infusions of norepinephrine were given in three experiments. In these it was found that raising arterial pressure to or above the control level did not reduce sympathetic activity either before or during cyclopropane administration, and, therefore, that stimulation of such activity by high concentrations of cyclopropane in baroreceptor-denervated animals was not attributable to the coincident production of arterial hypotension.

SPINAL ANIMALS

In initial experiments examining the effects of various anesthetics on preganglionic sympathetic discharge one to three hours following spinal-cord transection, an extremely sensitive inverse relationship between the discharge and arterial pressure was not appreciated since perfusion pressure was maintained at levels which are not ordinarily considered to cause tissue ischemia. However, it was subsequently found that pressure variations within the range 50-120 mm Hg conspicuously altered the level of sympathetic activity in spinal animals. Figure 9 illustrates an extreme example of reciprocating waves in arterial pressure and pregangli-

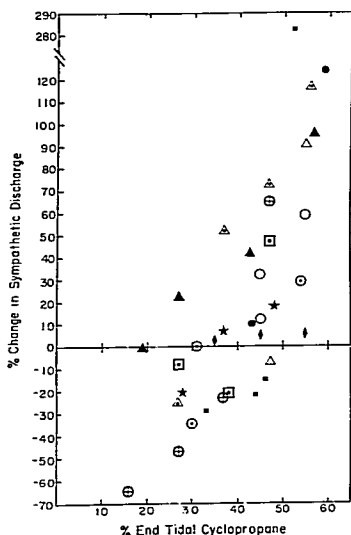


FIG. 8. Changes in sympathetic discharge during exposure to cyclopropane in 11 animals after baroreceptor denervation. Individual symbols are used for each animal's responses to various concentrations of cyclopropane.

onic discharge, about 40 minutes following cord transection and in the absence of cyclopropane. Therefore, these initial experiments, in which cyclopropane invariably reduced arterial pressure and increased sympathetic discharge, were discarded and the procedure was repeated in an additional group of seven animals whose arterial pressures could be controlled by intravenous infusion of norepinephrine.

Satisfactory control of arterial pressure during the administration of cyclopropane was possible in all seven animals. Table 3 lists the results of cyclopropane inhalation in the six experiments in which identical concentrations were given both before and 1-3 hours after cord section. Since the "resting" level of sympathetic activity was declining slowly with time in several preparations, the arithmetic mean of two control levels of sympathetic ac-

tivity (one just before cyclopropane was given, the other 15 minutes following its discontinuation) was used to compute the change caused by cyclopropane. It can be seen that a large increase in sympathetic activity occurred during cyclopropane administration in the intact animals, whereas erratic changes occurred after cord section, the mean change in the spinal animals being insignificantly different from zero. A similar analysis including data from all seven animals exposed to still higher concentrations of cyclopropane (36-47 percent) also failed to attain significance, although there were small increases in four of the animals.

Discussion

The present study had three major aims: to document the occurrence of increased sympathetic nervous activity during cyclopropane administration, to examine the means by which this action is exerted, and to determine whether there is a relation between sympathetic excitation and hemodynamic changes during cyclopropane anesthesia.

The evidence on the first point is quite plain. Previous studies by direct methods,^{5,6} together with the present work, have now established sympathetic excitation as a characteristic effect of cyclopropane inhalation in both cats and rabbits. Indirect methods have provided strong evidence that the same response occurs in dog and man. In fact, the data relating sympathetic activation to cyclopropane concentration obtained in the present study (fig. 4) bear a remarkable resemblance to the early indirect results derived from plasma norepinephrine levels in man (fig. 1).

Since only cervical sympathetic fibers were examined in the present study, we have no internal evidence that the increase in sympathetic nervous activity was generalized, but it seems clear from previous work^{5,6} that the response to cyclopropane is a general one and that the cervical sympathetic fibers are representative in their behavior. Both recent and previous data derived from measurements of plasma catecholamine concentrations suggest that the sympathetic response in man is also generalized, except that it probably does not involve the adrenal medulla.¹

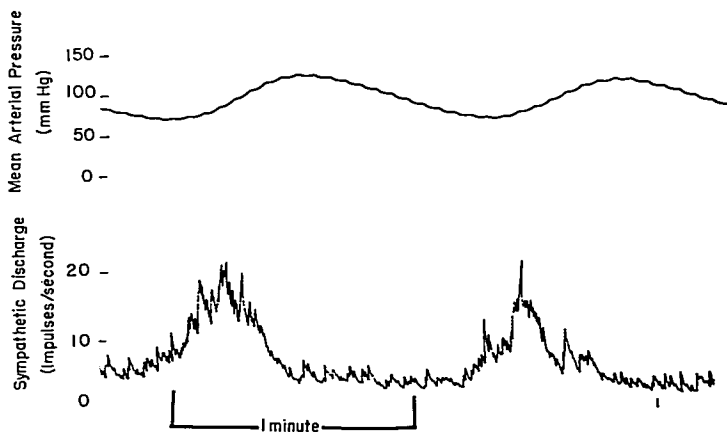


FIG. 9. Spontaneous reciprocal changes in mean arterial pressure and sympathetic nervous activity in a single spinal animal in the absence of cyclopropane.

The mode of action of cyclopropane was examined by measuring the effects of mid-colicular decerebration, spinal cord section and buffer deafferentiation upon the response to the anesthetic. Although the response ap-

parently was normal after decerebration, section of the spinal cord at C1-2 abolished it in most animals. In the few cases where sympathetic activities still occurred after spinal section, it was greatly reduced. These results

TABLE 3. Effect of Spinal-Cord Section on Sympathetic Response to Cyclopropane

Frequency* (Impulses/sec)						End-expired Cyclopropane Concentration (Volumes per cent)
Intact			Spinal‡			
Control†	During Cyclopropane‡	Change	Control	During Cyclopropane	Change	
35	215	+180	41	38	-3	41
24	72	+48	16	36	+20	40
26	96	+70	34	34	±0	35
23	51	+28	11	22	+11	40
29	42	+13	126	115	-11	27
22	45	+25	93	93	±0	37
Mean +60.7			Mean +2.8			
SE ±25.3			SE ±4.5			

* Proganglionic cervical sympathetic nervous activity.

† Cyclopropane absent.

‡ After 11-minute inhalation of cyclopropane.

§ After cord section.

suggest that the main locus of action is within the medulla oblongata, and presumably in the vasomotor center.

The vasomotor center is thought to contain two major types of neurons responsible for the regulation of sympathetic discharge at the spinal level. The more numerous "pressor" neurons are tonically active and fire into descending pathways, thus causing excitation of spinal vasomotor neurons. The "pressor" neurons are held in check by medullary "depressor" neurons which are not tonically active but which are excited by incoming impulses originating in peripheral baroreceptors and running centrally in the ninth and tenth cranial nerves. The inhibition caused by these afferents occurs at the medullary,¹² and possibly also at the spinal, level. When the baroreceptor afferent nerves are cut the medullary vasomotor neurons are uninhibited and discharge at an elevated rate.

In a buffer-denervated preparation the response to cyclopropane indicates effects upon the "pressor" neurons; the "depressor" cells, having no input, are inactive, and the level of sympathetic outflow is determined by the unrestrained activity of the pressor elements. Our results suggest that there is no effect on the "pressor" neurons until relatively high cyclopropane concentrations (30-50 per cent) are attained, when sympathetic activity increases. The data are consistent with the view that cyclopropane in clinically useful anesthetic concentrations does not depress the "pressor" neurons, while in high concentrations it excites them. By the process of elimination, then, the response to cyclopropane at moderate concentrations in normal animals presumably depends upon inhibition of the inhibitory neurons, as we have previously proposed.³

Consistent with this view is the observation that the response to stimulation of the aortic depressor nerve is essentially abolished by concentrations of cyclopropane approximating 30 per cent, and that, when the gas is administered, sympathetic activation begins with and essentially mirrors the developing inhibition of the reflex (cf fig. 6). It is also conceivable that the reflex is inhibited not merely because of depression of "depressor" neurons, but be-

cause the "pressor" elements are directly excited by cyclopropane. We cannot rule out this possibility; however, the buffer-deafferented animals failed to show any excitation at this concentration of cyclopropane.

A contrary view has been taken by Ngai and Bolme,¹⁰ who found in the dog that cyclopropane depressed the circulatory response to electrical stimulation of the hypothalamus and concluded that the "excitatory vasomotor mechanisms (adrenergic)" were "depressed" by this agent. No explanation for sympathetic activation was found by these authors. Previously, Bartlestone, Katz and Ngai⁸ had found that pressor responses to stimulation of the central end of the divided ulnar nerve were more quickly abolished by cyclopropane than were depressor responses to stimulation of the central vagus. They interpreted this and their other findings to mean that cyclopropane obtunds the activity of those central functions responsible for increasing vascular tone in response to afferent stimulation. Unfortunately for this argument, responses to pain (ulnar nerve stimulation) are not a part of the normal mechanism of blood pressure regulation, and could be expected to be easily abolished by anesthesia for reasons advanced by Ranson over fifty years ago.¹⁴ Also, central stimulation of the vagus cannot be considered to be a specific stimulus or an interpretable test since it contains several different kinds of afferent fibers. Finally, Markee and her co-workers⁹ examined the responses of arterial pressure to electrical stimulation of the medulla. They concluded that "depressor" representations were more resistant to cyclopropane than "pressor" ones. Their work, in turn, was stimulated by an earlier report by one of us³ in which we reached exactly opposite conclusions, later confirmed in still another study.⁴ It seems fair to conclude this discussion by stating that many methods used in the past are of dubious value because they are indirect, and because the experimental results are modified by so many extraneous factors that they are open to a number of interpretations.

Another problem is the use of different analytical criteria by various investigators. For example, Markee *et al.*⁹ used the maximum change in arterial pressure in response to elec-

trical medullary stimulation as a criterion; we² used the threshold for the response. It is conceivable that the findings in the two studies were quite similar, but the interpretation would vary according to the criteria employed.

The behavior of arterial pressure, cardiac rate and cardiac rhythm in these experiments indicates that sympathetic activation has important circulatory consequences both during and after administration of cyclopropane. As has been mentioned, the first few minutes of cyclopropane inhalation were frequently marked by arterial hypotension, which was antagonized or reversed as sympathetic activity began to increase. In animals in which the enhanced sympathetic response did not occur (spinal animals, buffer-sectioned animals, and some intact animals) this behavior of arterial pressure was not observed and marked hypotension persisted throughout the period of cyclopropane administration. Similarly, the overshoot of arterial pressure which occurred shortly after terminating cyclopropane inhalation was proportional to the concentration of anesthetic which had been breathed and did not occur in any animal whose sympathetic activity had not been elevated during administration of cyclopropane. This response, earlier reported in man by one of us,¹⁵ is believed to reflect an increase in cardiac output occurring as the anesthetic diffuses out of the myocardium in the presence of a still-elevated level of sympathetic nervous activity. It can be viewed as supporting the belief that increased sympathetic activity during anesthesia antagonizes the myocardial depression which is so prominent a feature of the actions of cyclopropane in the heart-lung preparation.¹⁶ Other evidence for this view has been presented previously.¹⁷

Cardiac rate often increased during the administration of cyclopropane, possibly reflecting an increased sympathetic effect, but rhythm usually remained normal until shortly after discontinuation of cyclopropane, when the "overshoot" occurred. Ventricular extrasystoles were frequent at this time, presumably because of the combined influences of cyclopropane, elevated sympathetic nervous activity and arterial hypertension.¹⁸

Summary and Conclusions

Cyclopropane increased the firing rates of preganglionic cervical sympathetic nerve fibers in 27 of 29 cats. Where examined, this effect was found to be proportional to the end-expired cyclopropane concentration.

Midcollicular decerebration did not appear to affect the response to cyclopropane. After spinal cord section at C1-2 cyclopropane still increased sympathetic activity in some animals, but it reduced it in others, and the mean response in the group studied was insignificantly different from zero. Buffer denervation abolished the sympathetic response to low and moderate concentration of cyclopropane, but not that to higher ones. Cyclopropane rapidly and completely abolished the reflex response to electrical stimulation of the left aortic depressor nerve at concentrations approximating 30 per cent.

These observations suggest that cyclopropane inhibits the "depressor" neurons of the medulla oblongata while sparing the "pressor" representation. At high concentrations cyclopropane stimulates the "pressor" neurons by a direct action. An additional excitatory action at the spinal level cannot be excluded, although it appears relatively unimportant.

References

1. Price, H. L., Linde, H. W., Jones, R. E., Black, G. W., and Price, M. L.: Sympathoadrenal responses to general anesthesia in man and their relation to hemodynamics. *ANESTHESIOLOGY* 20: 563, 1959.
2. Deutsch, S., Linde, H. W., and Price, H. L.: Circulatory and sympatho-adrenal responses to cyclopropane in the dog. *J. Pharmacol. Exp. Ther.* 135: 354, 1962.
3. Price, H. L., Cook, W. A., Jr., Deutsch, S., Linde, H. W., Mishalove, R. D., and Morse, H. T.: Hemodynamic and central nervous actions of cyclopropane in the dog. *ANESTHESIOLOGY* 24: 1, 1963.
4. Price, H. L., Price, M. L., and Morse, H. T.: Effects of cyclopropane, halothane and propane on the vasomotor "center" of the dog. *ANESTHESIOLOGY* 26: 55, 1965.
5. Millar, R. A., and Biscoe, T. J.: Post-ganglionic sympathetic discharge and the effects of inhalation anesthetics. *Brit. J. Anaesth.* 38: 92, 1966.
6. Biscoe, T. J., and Millar, R. A.: The effect of cyclopropane, halothane and ether on cen-

- tral baroreceptor pathways, *J. Physiol.* 184: 535, 1966.
7. Millar, R. A., and Biscoe, T. J.: Pre-ganglionic sympathetic activity and the effects of anaesthetics, *Brit. J. Anaesth.* 37: 804, 1965.
 8. Bartlestone, H. J., Katz, R. L., and Ngai, S. H.: Effect of cyclopropane on reflexly induced circulatory responses in the dog, *ANESTHESIOLOGY* 27: 756, 1966.
 9. Markee, S., Wang, H. H., and Wang, S. C.: Effects of cyclopropane on the central vasomotor mechanism of the dog, *ANESTHESIOLOGY* 27: 742, 1966.
 10. Ngai, S. H., and Bolme, P.: Effects of anesthetics on circulatory regulatory mechanisms in the dog, *J. Pharmacol. Exp. Ther.* 153: 495, 1966.
 11. Smith, T. C., Colton, E. T., and Dripps, R. D.: Mixed venous-arterial carbon dioxide difference in anesthetized man, *Fed. Proc.* 6: 333, 1967.
 12. Linde, H. W., and Price, H. L.: Gas analyzer for rapid estimation of cyclopropane, *ANESTHESIOLOGY* 19: 757, 1958.
 13. Kahn, N., and Mills, E.: Centrally evoked sympathetic discharge: A functional study of medullary vasomotor areas, *J. Physiol.* 191: 339, 1967.
 14. Ranson, S. W., and Billingsley, P. R.: Afferent spinal paths and the vasomotor reflexes. Studies in vasomotor reflex arcs, VI. *Amer. J. Physiol.* 42: 16, 1916.
 15. Price, H. L., King, B. D., Elder, J. D., Libien, B. H., and Dripps, R. D.: Circulatory effects of raised airway pressure during cyclopropane anesthesia in man, *J. Clin. Invest.* 30: 1243, 1951.
 16. Price, H. L., and Helrich, M.: The effects of cyclopropane, diethyl ether, nitrous oxide, thiopental and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation, *J. Pharmacol. Exp. Ther.* 115: 206, 1955.
 17. 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.
 18. Moe, G. K., Malton, S. D., Rennick, B. E., and Freyburger, W. A.: The role of arterial pressure in the induction of idioventricular rhythms under cyclopropane anesthesia, *J. Pharmacol. Exp. Ther.* 94: 319, 1948.

Drugs

MAO INHIBITORS Monoamine oxidase inhibitors potentiate the effects of dietary and injected tyramine and other sympathomimetic amines. Studies in various rat and cat preparations have indicated that MAO inhibitors act by retarding the binding and/or breakdown of these sympathomimetic amines by liver microsomal enzyme systems, allowing higher blood levels of these amines. This leads to the release of more endogenous catecholamines from storage sites. Other enzymes (diamine oxidase, choline oxidase) are also inhibited, thus potentiating the action of barbiturates, amphetamine, and morphine and its congeners. Since destruction by catechol-o-methyltransferase and uptake into storage sites terminate catecholamine action, MAO inhibitors do not potentiate the action of exogenous adrenalin or noradrenalin. (Rand, M. J., and Trinker, F. R.: *The Mechanism of the Augmentation of Responses to Indirectly-acting Sympathomimetic Amines by Monoamine Oxidase Inhibitors*, *Brit. J. Pharmacol.* 33: 287 (June) 1968.)