Effect of Cyclopropane on Reflexly Induced Circulatory Responses in the Dog

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The present study was undertaken because of previously published divergent conclusions regarding the action of cyclopropane on vasomotor control mechanisms. The magnitude of reflexly-induced pressor and depressor responses elicited by carotid occlusion or stimulation of afferent nerves was used on an index of the reactivity of vasomotor mechanisms. Cyclopropane, in the dog, decreased the magnitude of reflexly-induced venous and arterial pressor responses, but did not alter significantly reflexly-induced depressor responses. These results were obtained whether cyclopropane was allowed to reach the whole animal or its distribution was limited to the cephalad portion of the circulation during periods of major vessel occlusion. It is concluded that in the dog, cyclopropane obtunds the activity of those central functions responsible for increasing both venous and arterial vascular tone in response to afferent stimulation. Contrarily, the function of central pathways which mediate reflexly-induced reductions in peripheral venous and arterial tone are not depressed by cyclopropane.

The results of previous studies of the effect of cyclopropane on cardiovascular control mechanisms have differed markedly.1 2 3 Price et al.1 found that cyclopropane in dogs selectively inhibits the excitability of the medullary depressor neurons with a lesser effect on the pressor neurons. These results were extrapolated to explain the arterial hypertension observed during cyclopropane anesthesia. However, Markee and Wang2 and more recently Markee et al.,3 also using dogs, found that cyclopropane markedly suppressed the pressor response to medullary stimulation with a lesser decrease in the depressor response. The present study was undertaken in an attempt to resolve the problem posed by these conflicting reports. Changes in the magnitude of reflexly induced pressor and depressor circulatory responses were used as indicators of the effect of cyclopropane on the integrated output of the central nervous system mechanisms which regulate the circulation. In lightly anesthetized dogs, changes in the arterial pressure induced by bilateral common carotid artery occlusion and afferent vagal and uhar nerve stimulation were measured before, during, and after cyclopropane inhalation. The results of these experiments, contrary to those of Price et al.,1 indicate that cyclopropane acting on the central nervous system depresses the reflex pressor responses, but spares the reflex depressor responses.

Methods

Dogs weighing between 11 and 16.5 kg. were used. The animals were anesthetized with 10 mg./kg. of thiamylal sodium given intravenously. A tracheostomy was rapidly performed and the tracheal cannula connected through a non-rebreathing valve to a Mark 4 Bird respirator or a Frumin-Lee respirator. Artificial ventilation with constant tidal volume and frequency was continued for the duration of the experiment. A nitrous oxide (80 per cent) and oxygen (20 per cent) mixture was delivered to the animal except when selected concentrations of cyclopropane were used. Succinylcholine chloride (0.1–0.2 per cent solution) was continuously infused at a
low rate (0.1 mg./minute) in order to diminish reflex skeletal muscle movement in response to nerve stimulation.

The vagus nerves were isolated and sectioned at the cervical level. Bipolar electrodes were applied to the central cut ends of these nerves. One of the ulnar nerves was also sectioned and a stimulating electrode applied to its central cut end. These nerves were electrically stimulated, in sequence, with currents derived from a Grass S4C stimulator through a stimulus isolation unit. The stimulating currents were square waves of 1 millisecond duration with varying frequency and intensity chosen to elicit either a pressor response or a depressor response. The common carotid arteries were isolated and prepared for subsequent occlusion. The arterial pressure was measured through one of the femoral arteries with a Statham P23A transducer and recordings made on a Grass 5B polygraph.

One hour or more after the induction of anesthesia, a series of control pressor and depressor responses were obtained by stimulation of the ulnar or the vagus nerve. Then cyclopropane was introduced into the system in increasing concentrations from 5 to 30 per cent. Each concentration was maintained for at least 10 minutes. During periods of 5 and 10 per cent cyclopropane inhalation, nitrous oxide was continued, but its concentration reduced in a corresponding amount. During periods of 20 and 30 per cent cyclopropane inhalation, nitrous oxide was discontinued. During cyclopropane inhalation, ulnar and vagus nerve stimulation was repeated and the cyclopropane-induced changes in the pressor and depressor responses were recorded. The same procedure was repeated during the recovery periods after cyclopropane had been discontinued for at least 10 minutes.

In order to limit the distribution of cyclopropane to the cephalad portion of the animal, major vessel occlusion (MVO) was carried out in 6 animals. Detailed description of this technique has been published previously. Briefly, with the dog lying supine, the chest was opened in the midline. The descending aorta was isolated at levels just caudal to the left subclavian artery and just cephalad to the diaphragm. Blalock-Niedler clamps were positioned at these points on the aorta. The inferior vena cava was also isolated cephalad to the diaphragm and another Blalock-Niedler clamp similarly applied. The azygos vein, the costo-cervical arteries and the internal mammary arteries and veins were ligated and cut. Thus, when the aorta and the inferior vena cava were occluded simultaneously, the body was functionally divided with respect to the circulation. The cephalad portion continued to be perfused by the heart's action while the caudal portion was effectively cut off from the heart during the short interval of MVO. A catheter placed in the internal mammary artery and connected to a Statham transducer sensed the cephalad arterial pressure. The caudal arterial and vena caval pressures were sensed with appropriate transducers (P23B, venous).

After these preparations were completed, a series of 2 minute control MVO's were carried out to test the stability of the system and the completeness of circulatory isolation. Subsequently, reflex circulatory responses were elicited during MVO's. Bilateral common carotid artery occlusion and afferent ulnar or vagal stimulation were used as stimuli, as described above. Reproducible changes in cephalad and caudal arterial and caudal venous pressures were recorded in response to these stimuli. The magnitude of the circulatory changes were used to indicate the reflex responsiveness of central vasomotor mechanisms before and during the administration of cyclopropane to the cephalad part of the dog.

In 36 instances, cyclopropane, in concentration of 25, 50, or 75 per cent, was introduced into the anesthetic reservoir in place of nitrous oxide after the aorta and the inferior vena cava were occluded. These concentrations were used because of the very short time interval (50-60 seconds) between the execution of MVO with concurrent administration of cyclopropane and the application of test stimulus. In this manner cyclopropane distribution was limited to the cephalad portion of the circulation. In addition, in other experiments, cyclopropane was allowed to reach the whole animal and the effect on reflex circulatory responses again observed.

In 5 animals, the carotid sinuses were de-
Depressor response to vagus nerve stimulation was not reduced. Ten minutes after stopping the cyclopropane and reinstituting nitrous oxide-oxygen, the pressor response had not quite recovered, while the depressor response was still essentially unchanged. Similar results were observed in six experiments on these dogs.

To rule out the possible direct influence of cyclopropane on the carotid sinus baroreceptors, the experiment was repeated on three debuffered animals. In six experiments on these three debuffered dogs, substitution of 20 to 30 per cent cyclopropane for nitrous oxide-oxygen depressed the reflex pressor response to ulnar nerve stimulation, but did not reduce the reflexly-induced depressor response to vagus nerve stimulation (fig. 2).

Cyclopropane (5 per cent) was added to nitrous oxide-oxygen (75:20) in 2 dogs to determine whether nonanesthetic concentrations of cyclopropane could selectively depress reflex pressor responses while sparing depressor functions. In figure 3, it can be seen that 15 minutes after adding the 5 per cent cyclopro-

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931615/)
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Fig. 3. Debuffered dog. Pairs of ulnar (pressor) and then vagus (depressor) nerve stimulations produced reproducible changes in pulsatile and mean pressure (left panel). Cyclopropane diminished the pressor response but did not alter the depressor response (middle panel). Partial recovery after ten minutes (right panel).

Cyclopropane, the reflex pressor response was diminished, while the reflex depressor response was not at all reduced.

Figure 4 illustrates a typical response to bilateral carotid occlusion during inhalation of nitrous oxide-oxygen (80:20) mixture in a vagotomized dog both during MVO and after release of MVO. This response pattern can be repeated every 15 minutes over many hours with almost superimposable pressure curves resulting from each period of carotid occlusion. In six experiments on three dogs substitution of 25 per cent cyclopropane for the nitrous oxide resulted in a marked reduction in the caudal venous and arterial, and cephalad arterial responses to carotid occlusion performed.

Fig. 4. Major vessel occlusion (MVO) method. Venous pressure on top trace has been set so that zero equals 5.5 mm Hg (indicated by **). Caudal arterial pressure is recorded on a scale of 0–200 mm Hg (indicated by *) prior to MVO and 0–40 mm Hg during MVO. Cephalad arterial pressure (internal mammary artery) is recorded as a mean. Carotid occlusion (CO) was executed during MVO and again just after the MVO was released. Cyclopropane reduced both caudal venous, and arterial pressure responses to CO executed during MVO. Cephalad pressor responses were diminished as well. The response to CO after release of MVO was also depressed by cyclopropane.
during the MVO period. The magnitude of the response to the carotid occlusion performed after release of MVO was also reduced.

The MVO method was then employed to determine whether or not cyclopropane might be acting peripherally to influence the responses to reflex pressor and depressor activity already noted. Cyclopropane was administered after the MVO was established. The total period of cyclopropane administration was confined to 120 seconds, corresponding to the duration of the MVO period. In figure 5 it can be seen that caudal arterial and venous responses to carotid occlusion were reduced by inhalation of as little as 9 inspirations (tidal volume, 300 ml.) of 25 per cent cyclopropane. This depression of the reflex pressor response of the caudal circulation to carotid occlusion could not have been influenced by direct peripheral action of cyclopropane. Depression of the cephalad arterial pressure response to carotid occlusion was also produced by the short period of cyclopropane administration. Similar results were observed with the inhalation of 25, 50, and 75 per cent cyclopropane in 36 experiments on 6 dogs.

The MVO method was also used in experiments analogous to those described previously, i.e., as in figures 1 and 2. The animals were vagotomized and debuffered and then reflexly-induced pressor and depressor responses were elicited by appropriate nerve stimulation during periods of MVO. In some animals it was found that high frequency stimulation of the central end of the cut vagus elicited reproducible depressor responses, while stimulation of the other vagus nerve at lower frequencies produced reproducible pressor responses. The MVO period was started and, after 50 seconds, first the depressor response was invoked for 20 seconds, and then, after a 20 second delay, the pressor response was elicited (fig. 6, first panel). The MVO was repeated and 10 per cent cyclopropane added to the nitrous oxide-oxygen mixture during the MVO. The caudal depressor remained unchanged, but the pressor response was reduced. Increasing the cyclopropane concentration to 30 per cent during a successive MVO period still did not reduce the reflex depressor response, but markedly reduced both the caudal and cephalad pressor responses. When the order of induction of pressor and depressor responses was reversed during the MVO period, cyclopropane still reduced the pressor response, but did not influence the depressor response. These results were observed in 9 experiments on 3 dogs.

Because it can be assumed that the magnitude of a cardiovascular reflex response may be the resultant of an algebraic sum of pressor
and depressor activity, the experiment illustrated in figure 7 was conducted. Fifty seconds after MVO, simultaneous stimulation was induced in two nerves, individual stimulation of which was previously shown to be effective in producing either pressor or depressor reflex responses. The pressor response predominated and the caudal venous and arterial pressure rose. When the pressor stimulus was stopped, but the depressor stimulus continued, the caudal pressure fell; following a rest period of 20 seconds, the pressor reflex was again elicited alone, and then all stimulation was stopped and MVO released. When this was repeated after the animal had inhaled 30 per cent cyclopropane for 10 breaths (tidal volume, 210 ml.), the combined response was diminished, the depressor response was unaffected, and the terminal pressor response was markedly diminished. Recovery was complete as depicted in the right panel of figure 7. These responses in the caudal circulation of a debuffered dog could not be due to direct peripheral action of cyclopropane and are assumed to be central. Again, cyclopropane has depressed the pressor function and spared the depressor function.

Discussion

It is clear from the present studies that, in the dog, cyclopropane depresses reflexly induced pressor responses while sparing reflexly induced depressor responses. In preference to electrical stimulation of specific sites within the central nervous system alteration in the magnitude of reflexly induced vascular changes was chosen as a method which would indicate the effect of cyclopropane on cardiovascular control mechanisms of the central nervous system. Afferent nerve stimulation, or carotid occlusion produces vascular responses which are the resultant of the integration of activity of various central pathways. The results of experiments using direct electrical stimulation of the central nervous system ^3^ needed corroboration: (1) since the effects of cyclopropane may not be manifest equally at all points of the central pathways mediating changes in peripheral pressure, and (2) since electrical stimulation of discrete areas of the central nervous system may not involve the same potential pathways utilized for the regulation of the circulation. Therefore, the use of afferent nerve stimulation, or carotid occlusion, exposes
to the action of cyclopropane a more complete gamut of potentially vulnerable points actively involved in central cardiovascular control mechanisms. This approach appeared to be necessary because of the divergent opinions as to the effects of cyclopropane held by Markee et al. and Price et al. and which were obtained using electrical stimulation of the central nervous system as the means of invoking centrally mediated vascular responses.

The debuffed preparation was used in several experiments because of the possible direct action of cyclopropane on the carotid sinus to increase firing along the sinus nerve. Any direct activation of carotid sinus receptors by cyclopropane would limit the interpretation of direct central actions of cyclopropane by reinforcing depressor responses and reducing pressor tone. The results of our experiments on debuffed dogs indicate that if there was any direct effect of cyclopropane on carotid sinus activity, it did not significantly influence the magnitude of the reflex changes induced by afferent nerve stimulation serving either the depressor or pressor functions of reflex arcs.

It was also necessary to rule out any direct peripheral action of cyclopropane on efferent neural or vascular smooth muscle mechanisms. The MVO method divides the dog's circulation into two zones. This functional division of the dog's circulation during short periods of MVO permitted the introduction of cyclopropane into the cephalad circulation without the gas reaching and directly influencing the responses of the caudal part of the circulation. Cyclopropane does reach the forelimbs, the central nervous system, the heart and the lesser circulation when inhaled during MVO. But changes in caudal vascular responses to reflex stimulation cannot be due to direct peripheral action of cyclopropane. The caudal circulatory changes induced by cyclopropane could not have been influenced by the effect of cyclopropane directly on the heart since the caudal circulatory responses are momentarily independent of cardiac functions during MVO.

In addition, the effect of cyclopropane on reflexly induced venous pressure changes can be seen to parallel the reflex arterial pressure responses. This experimental design is analogous to the cross-circulation concept, but is conducted in a single animal.
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The fact that during MVO, inhalation of cyclopropane for only 9 to 12 breaths was sufficient to produce significant reductions in reflexly-induced pressor responses is indicative of the extreme sensitivity of central pressor mechanisms to cyclopropane action. The depressor functions of the central nervous system are certainly not affected similarly.

Our results confirm those of Markee et al., and do not support the contentions of Price et al. as to the actions of cyclopropane on central mechanisms which control arterial blood pressure. In addition, our results cannot explain the sustained elevation of arterial pressure sometimes seen with cyclopropane as reported by Price et al. However, this rise may be due to a separate peripheral action rather than to cyclopropane's central action. Cyclopropane increases the magnitude of pressor responses produced by norepinephrine in, for example, the pithed rat (Ngai, S. H., unpublished data). Cyclopropane also increases the magnitude of contraction to norephinephrine of both the rabbit aorta in vitro and the nictitating membrane in vivo. It is possible that while the central pressor mechanisms are depressed by cyclopropane, the relative effectiveness of any given amount of catecholamine released peripherally might be enhanced. This peripheral action may account in part for the occasional sustained mild increase in arterial blood pressure seen with cyclopropane.

Summary

The inhalation of cyclopropane decreased reflexly induced pressor responses but spared reflexly induced depressor responses in the dog. These results were observed whether cyclopropane was allowed to reach the whole animal or was limited to the cephalad portion of the circulation during major vessel occlusion.

References


MUSCLE RELAXANT Diallyl-nor-toxiferin was used in 1200 patients. The onset of action is between that of succinylcholine and d-tubocurarine. It does not liberate histamine and even in paralyzing doses has no influence on transmission in autonomic ganglia, thus explaining the absence of circulatory effects. No laryngospasm, bronchospasm or postoperative muscle pain has been observed. Neostigmine antagonizes this relaxant promptly and recurarization following use of neostigmine has not been observed. (Drost, R., Böhmert, F., and Henschel, W. F.: Clinical Observations with Diallyl-Nor-Toxiferin (German), Der Anesthesist 15: 79 (March) 1966.)