The Effects of Halothane and Cyclopropane on Skeletal Muscle Vessels and Baroreceptor Reflexes

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with the assistance of Richard A. Shaffer ‡

The effects of halothane anesthesia and cyclopropane anesthesia on vascular smooth muscle and reflex adjustments of peripheral vascular resistance were studied in the isolated innervated dog gracilis muscle cross-perfused with donor blood. Administration of halothane (1.5%) or cyclopropane (35%) to the donor animal resulted in vasocostriction in the gracilis muscle. Vasocostrictor responses to local injection of norepinephrine were unchanged by cyclopropane and depressed significantly by halothane. Vascular resistance in the muscle was not altered by administration of halothane or cyclopropane to the recipient animal. Reflex vasocostriction was depressed by halothane and by cyclopropane in the recipient animal, whereas reflex vasodilatation was unaffected by either agent. We conclude that both depression of vascular responsiveness to norepinephrine and interference with reflex vasocostriction contribute to the hypotension ordinarily observed with halothane anesthesia. No evidence was found for activation of the sympathetic nervous system or sensitization of vascular smooth muscle to norepinephrine by cyclopropane. The maintenance or slight elevation of blood pressure observed with cyclopropane anesthesia may well be related to the direct vascular smooth muscle-stimulating activity of this agent.

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Received from the Departments of Pharmacology and Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa. Accepted for publication July 25, 1967.

Portions of this work were presented at the meeting of the American Society for Pharmacology and Experimental Therapeutics, Mexico City, Mexico, July, 1966 (Pharmacologist 8: 181, 1966). Supported by USPHS grants NB-04889 and 5T1-HE557704.

There has been a great deal of investigation of the effects of anesthetics on neural vaso-regulatory mechanisms. Price et al. 3, 4 postulated that cyclopropane elicits arterial hypertension and increased plasma catecholamine concentrations in dogs by selectively depressing the vasodepressor center, pressor neurons being spared. Price et al. also postulated that halothane produces equal depression of both pressor and depressor areas in the medullary centers of the dog 5, 6 and in addition interferes with transmission in peripheral sympathetic ganglia. Markee et al. 7 and Bartstone et al. 8 using different experimental methods, failed to substantiate this concept of the action of cyclopropane and concluded that the pressor representations of the medulla are more depressed by cyclopropane than are the depressor areas. Recently, Ngai and Bulme, 9 utilizing chronically implanted blood-flow probes and indwelling arterial catheters, studied the cardiovascular effects of cyclopropane and halothane in dogs without basal narcosis. These experiments demonstrated that both cyclopropane and halothane depress the pressor responses to medullary stimulation and carotid occlusion.

In light of these discrepant observations, the present study was undertaken to examine further the effects of cyclopropane and halothane on cardiovascular reflexes. Attention was directed toward dissociating the effects of these agents on peripheral vessels from neurogenically mediated cardiovascular responses.

Methods

Experiments were performed on 15 pairs of mongrel dogs weighing 12–28 kg. The smaller member of each pair was designated the donor dog and the larger the recipient dog. The animals were anesthetized with intravenous
sodium pentobarbital, 30 mg./kg. The trachea was cannulated to facilitate intermittent positive pressure ventilation. The animals were immobilized with gallamine triethiodide in intermittent doses of 10–20 mg., given through a cannulated external jugular vein.

The gracilis muscle of the recipient dog, with its artery, vein, and nerve, was isolated completely from surrounding connective tissue. After administration of heparin sodium, 5 mg./kg., to both animals, a femoral artery of the donor dog was cannulated with tubing leading to a model T8 Sigma motor pump. The artery to the recipient’s gracilis muscle was then cannulated with tubing leading from the pump. All venous effluent from the gracilis vein was returned by gravity to an external jugular vein of the donor dog. Intraarterial injection of drugs was made into the tubing just proximal to entry into the artery of the muscle. Gracilis muscle perfusion pressure was monitored from the tubing leading away from the constant-flow pump. Systemic arterial blood pressure of each animal was obtained by cannulation of a femoral artery. Pressures were recorded on a Beckman-Offner direct-writing oscillograph with Statham arterial pressure transducers. With the pump providing constant flow to the gracilis muscle, changes in perfusion pressure were directly proportional to changes in vascular resistance.

Reflex vasodilatation in the gracilis muscle bed was produced by intravenous injection of norepinephrine, 1–3 μg./kg., to the recipient dog. Reflex vasoconstriction was evoked by intravenous injection of acetylcholine, 10 μg./kg., to the recipient animal. Norepinephrine, 0.025 and 0.05 μg., and histamine, 0.05 μg., were administered intraarterially to the muscle as tests for vasoconstrictor and vasodilator capacity, respectively. These procedures were carried out prior to and during administration of the anesthetic agent being investigated. The order of procedures was randomized.

The order of administration of either halothane or cyclopropane to either the donor or recipient animal was alternated. The animal to be given an anesthetic was ventilated with 100 per cent O₂ by means of a pressure-limited respirator. The other animal was then ventilated with a fixed-volume respirator supplied with either 100 per cent oxygen or room air. Halothane was administered in concentrations sufficient to reach an end-expired concentration of 1.5 per cent, and cyclopropane was administered in doses sufficient to reach an end-expired concentration of 35 per cent. End-expired samples of gas were obtained by means
of a Rahn end-tidal sampler. Halothane concentration was determined by means of an Analytic Systems model 10 halothane analyzer. Cyclopropane concentration was calculated by determining end-expired oxygen concentrations with a Beckman D-2 paramagnetic oxygen analyzer, carbon dioxide and water vapor having been previously absorbed. The calculation of cyclopropane concentration by determining oxygen concentrations was based on the observation that the lungs of the animals were for all practical purposes denitrogenated by ventilation with 100 per cent oxygen. In all experiments animals received anesthetics for periods not exceeding 20–25 minutes.

Arterial blood samples were obtained from each animal just prior to discontinuation of anesthetic administration. Arterial $P_{O_2}$, $P_{CO_2}$, and pH were determined either with an Astrup microelectrode or with an Instrumentation Laboratories model 113 pH and gas analyzer. All data were subjected to statistical analysis by paired Student's $t$ tests, or by the four-point bioassay technique of Finney.5

![Graphs](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931616/)

**Fig. 2.** Effect of cyclopropane, administered to the recipient dog, on vasoconstrictor and vasodilator responses in the cross-perfused gracilis muscle. Cyclopropane administered in amount sufficient to reach end-expired concentration of 35%. PP: perfusion pressure; BP: systemic blood pressure; IV: intravenous injection; LA: intra-arterial injection; NE: norepinephrine; ACH: acetylcholine; HIST: histamine. Note the change in scale of perfusion pressure in different segments of the experiment.

**Table 1.** Effect of Halothane (1.5%) and Effect of Cyclopropane (35%) on Blood Pressure and Gracilis Muscle Perfusion Pressure

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<th>Blood Pressure (mm. Hg)</th>
<th>Perfusion Pressure (mm. Hg)</th>
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<td>Halothane</td>
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<td>To donor (7)*</td>
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<td>68</td>
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<td>To recipient (8)</td>
<td>129</td>
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<td>Cyclopropane</td>
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<td>To donor (7)</td>
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<td>131</td>
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<td>To recipient (7)</td>
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* Numbers in parentheses refer to number of experiments.
† Mean arterial pressure of animal receiving anesthetic.
‡ Probability determined by $t$ test.
§ NS = not significant.
ability values at the 5 per cent level or less were considered significant.

**Results**

Figure 1 illustrates results from a typical experiment when halothane was administered to a donor animal. Control responses are shown at the left. Intravenous norepinephrine administered to the recipient dog raised systemic arterial pressure and evoked reflex vasodilatation in the cross-perfused recipient muscle. Conversely, intravenous acetylcholine lowered systemic arterial pressure and caused reflex vasoconstriction in the muscle. Vasoconstrictor and vasodilator responses were then produced by intra-arterial norepinephrine and histamine, respectively. Administration of halothane to the donor animal produced a typical hypotensive response. This resulted in the appearance of vasoconstriction in the recipient muscle now perfused with blood containing halothane. As shown in the right side of the figure, the only major effect of halothane on responses in the muscle was a marked reduction in the magnitude of vasoconstriction produced by intra-arterial norepinephrine.

Figure 2 illustrates a typical experiment in which cyclopropane was administered to a recipient. The same responses shown in figure 1 were studied. Administration of cyclopropane produced very little change in either systemic arterial blood pressure or muscle perfusion pressure. The only response which was altered by cyclopropane was reflex vasoconstriction produced by intravenous acetylcholine, which was reduced by approximately half.

A summary of changes in arterial pressure and perfusion pressure obtained with administration of halothane or cyclopropane to the donor or recipient dog is presented in table 1. With the administration of halothane to the donor animal (blood perfusing the muscle contained anesthetics), arterial pressure decreased significantly, while muscle perfusion pressure increased significantly. When halothane was administered to the recipient dog (no anesthetic reached the muscle), arterial pressure of the recipient dog was depressed, but there was no significant effect on muscle perfusion pressure. There was no significant change in arterial pressure with administration of cyclopropane to the donor dog. There was, however, a significant increase in perfusion pressure of the muscle. When cyclopropane was administered to the recipient animal there were no significant changes in either arterial pressure or perfusion pressure. The increases in muscle perfusion pressure elicited by administration to the donor of halothane and cyclopropane were not altered by acute denervation of the muscle.12

Table 2 summarizes effects of halothane and cyclopropane on vasodilator and vasoconstrictor responses in the cross-perfused gracilis muscle.
cyclopropane on changes in muscle perfusion, pressure produced by intra-arterial administration of histamine, reflex vasodilatation, and reflex vasoconstriction. With administration of halothane to the donor dog there was an average increase in dilator responses, not statistically significant. Reflex vasoconstriction was essentially unchanged. With administration of halothane to the recipient dogs the only significant difference from control was a decrease in reflex vasoconstriction. When cyclopropane was given to the donor animals reflex vasoconstriction was not changed, while dilator responses produced reflexly or with intra-arterial histamine were significantly increased. With administration of cyclopropane to the recipient dog the only significant change was a decrease in reflex vasoconstriction.

Figure 3 depicts changes in perfusion pressure obtained with intra-arterial administration of norepinephrine when cyclopropane or halothane were given to the donor animal. During cyclopropane administration there was no significant change in the response to intra-arterial norepinephrine. Halothane, however, produced a significant depression of the vasoconstrictor response to norepinephrine.

Table 3 summarizes the effects of halothane and cyclopropane on the stimuli for reflex vasoconstriction and vasodilatation, i.e., the blood pressure responses to norepinephrine and acetylcholine. The only significant effect was a reduction in the response to acetylcholine when halothane was administered to the recipient animal.

The mean arterial pH, P<sub>O₂</sub> and P<sub>CO₂</sub> values (blood samples taken just before anesthetic was discontinued) were as follows: animals given cyclopropane and oxygen, pH 7.36, P<sub>O₂</sub> 358 mm. Hg, P<sub>CO₂</sub> 32 mm. Hg; animals given halothane and oxygen, pH 7.38, P<sub>O₂</sub> 455 mm. Hg, P<sub>CO₂</sub> 34.3 mm. Hg; animals ventilated with room air, pH 7.43, P<sub>O₂</sub> 104 mm. Hg, P<sub>CO₂</sub> 26.4 mm. Hg; animals ventilated with 100 percent oxygen, pH 7.46, P<sub>O₂</sub> 475 mm. Hg, P<sub>CO₂</sub> 36.6 mm. Hg.

Discussion

The utilization of the cross-perfused gracilis muscle preparation provides an excellent means whereby neurogenically mediated vaso-motor effects of an anesthetic can be separated from peripheral vascular effects of the drug. When the drug is administered to the donor animal the direct effect of the agent on vascular responses in the muscle can be studied. Conversely, when the agent is limited to the recipient animal, and thus does not reach the muscle, neurogenically mediated vascular effects can be identified.

Halothane to Donor Animal

Administration of halothane to the donor animal produced significant depression of arterial blood pressure. This hypotensive effect has been reported previously by many investigators. The perfusion pressure of the muscle bed increased, signifying vasoconstriction. This increase in vascular resistance was totally unexpected with halothane, which has been considered a vascular smooth muscle depressant. The mechanism of this vasoconstriction, the subject of another communication from this laboratory, appears to be the release by halothane of vasopressin (antidiuretic hormone).

When halothane was present in the blood supplying the muscle, the vasoconstrictor response to intra-arterial norepinephrine was depressed. A similar depression of norepinephrine response by halothane has been observed.
TABLE 3. Effect of Halothane (1.5%\(^\text{a}\)) and Effect of Cyclopropane (35%) on Systemic Mean Arterial Blood Pressure Changes Produced in Recipient by Norepinephrine and Acetylcholine

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\(^*\) Numbers in parenthesis refer to number of experiments.

\(^f\) Mean arterial pressure.

\(^\text{f}\) Probability determined by t test.

\(\text{N.S.}\) = not significant.

in the human forearm.\(^{12}\) There was, however, no effect on reflexly evoked vasoconstriction in the muscle perfused with blood containing halothane. This differential effect suggests that halothane may exert only minimal effects on the vascular response to neurogenically released norepinephrine and yet depress the response to catecholamines in blood.

Emerson and Massion\(^{17}\) observed vasodilator responses with halothane (1–2 per cent) in the dog forelimb during the first few minutes of inhalation. We occasionally noted a similar early action, but this was always over-ridden by the later vasoconstrictor effect.

Cyclopropane to Donor Animal

The increase in perfusion pressure of the muscle observed when cyclopropane was administered to the donor dog was not unexpected in light of previous reports that cyclopropane increases blood levels of catecholamines.\(^{14–16}\) Further investigation revealed that the vasoconstriction seen in these experiments is not mediated by catecholamines but rather is the result of a direct stimulant action of cyclopropane on vascular smooth muscle.\(^{12}\) Such an effect could explain in part the maintenance of systemic arterial pressure during cyclopropane anesthesia. Emerson and Massion\(^{17}\) reported recently that cyclopropane (11–20 per cent) produced vasodilatation in the dog limb perfused naturally or at constant flow but not in the dog limb perfused with blood from a heart-lung system. The qualitatively different observation, i.e., vasoconstriction, noted in the present study is most likely a function of the higher concentration (35 per cent) of cyclopropane utilized. The possibility also remains that skin vessels (present in the dog limb as studied by Emerson and Massion but not involved in the isolated perfused gracilis muscle) may be more sensitive than skeletal muscle vessels to the vasodilator effect produced by low concentrations of cyclopropane.

Cyclopropane in blood had no effect on reflex vasoconstrictor responses or on vasoconstrictor responses produced by intra-arterial norepinephrine. The present experiments thus do not confirm previous reports that cyclopropane enhances sensitivity of vascular smooth muscle to norepinephrine.\(^{18–20}\) This difference in findings may perhaps be explained by the fact that different types of vessels have been examined in each study, e.g., rabbit nortic strip,\(^{16}\) rat.meso-appendix vessels,\(^{19}\) and human calf vessels.\(^{20}\) Pure skeletal muscle vessels may well participate in any increased reactivity to norepinephrine. On the other hand, the previous reports of the sensitizing
effect of cyclopropane should be examined critically. Increased responsiveness to norepinephrine was noted: (a) in tissue from a conducting vessel which has little functional importance in control of peripheral resistance; (b) in meso-appendicidal vessels perfused with an artificial medium, when norepinephrine was applied topically rather than through the vascular channels; and (c) in calf vessels of one human subject in which case a maximal dose of norepinephrine was administered. No data were presented for the second subject included in the latter study. It is obvious that additional studies are required in order to establish more firmly the validity of the proposed vascular-sensitizing action of cyclopropane.

An increase in the dilator responses produced both reflexly and by intra-arterial histamine was observed. These increased responses cannot be due to an effect of the anesthetic on neural pathways (since the anesthetic was limited solely to the donor dog) and are therefore probably the result of responses originating from an increased level of vasconstrictor tone. It would appear, therefore, that the peripheral effects of cyclopropane are limited to a direct vasoconstrictor effect.

**Halothane to Recipient Animal**

With administration of halothane to the recipient animal, systemic arterial pressure fell, while there was no significant effect of perfusion pressure. A significant decrease in reflex vasoconstriction was also observed. Because the animals were already hypotensive as a result of halothane anesthesia, the hypotensive stimulus which produced reflex vasoconstriction was significantly less than control (see table 3). In view of this, the reduction in reflex vasoconstriction was not clearly demonstrated. However, since muscle perfusion pressure did not increase with systemic hypotension, it may be concluded that halothane depresses reflex vasoconstriction. The results, therefore, confirm previous findings of Price et al., and Ngai and Bolme, of a reduction by halothane of reflex pressor responses.

The effect of halothane on baroreceptor reflexes was not uniform, since reflex vasoconstriction was depressed while reflex dilatation was unaffected. On the basis of reduction by halothane of depressor and pressor responses evoked by medullary stimulation, Price concluded that this anesthetic equally depresses medullary pressor and depressor vasomotor areas. The results of the present study suggest that if depression of depressor areas occurs, it is not manifested by reduction of reflex vasodilatation, which involves, in addition to the medullary areas, baroreceptors, and spinal and sympathetic pathways. It is entirely possible that there may not be a necessary relationship between threshold of the medullary depressor area to electrical stimulation and the integrity of the entire reflex vasodilator arc.

**Cyclopropane to Recipient Animal**

The only significant effect observed with administration of cyclopropane to the recipient was a reduction in reflex vasoconstriction. There was no effect of cyclopropane on reflex vasodilatation. These findings are compatible with the thesis that cyclopropane depresses pressor area representations in the vasomotor center, but do not support the postulate that cyclopropane “spares” medullary pressor representations. These conclusions are supported by the failure of the present experiments to demonstrate any significant activation by cyclopropane of the sympathetic nervous system, at least as represented by the innervation to skeletal muscle. If such an effect were present one would have anticipated a rise in perfusion pressure of the muscle due to liberation of catecholamines from the sympathetic nerves leading to the muscle. No such effect was seen. Indeed, all the peripheral effects noted can be ascribed to a direct vasoconstrictor effect of cyclopropane.

**Conclusions**

In the cross-perfused dog gracilis muscle preparation halothane and cyclopropane depress reflex vasoconstriction without altering reflex vasodilatation. Halothane also depresses the vasoconstrictor response to norepinephrine, whereas there is no significant change of this response with cyclopropane. The reduction of reflex vasoconstriction and depression of response to norepinephrine can explain in part the mechanism of the hypotension commonly
observed with halothane anesthesia. The findings with cyclopropane do not support the thesis that cyclopropane depresses inhibitory vasomotor mechanisms to a lesser extent than excitatory mechanisms. Cyclopropane produced vasoconstriction not mediated by sympathetic activation or by sensitization of vascular smooth muscle to norepinephrine. The vasoconstriction observed with cyclopropane, which appears to be a direct drug effect, could be a mechanism for the maintenance or elevation of arterial pressure observed with cyclopropane anesthesia.

References