The Effects of Halothane on Circulatory
Reflexes of the Dog

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The effects of halothane on pressor and depressor responses as well as on the arterial and venous components of these responses were studied in the dog. Halothane, 0.5–1.5 per cent, inspired, reduced arterial pressure and both pressor and depressor responses to central vagal stimulation. Using the major vessel occlusion (MVO) technique, 0.3–1 per cent halothane delivered to the entire animal depressed arterial and venous tone and the arterial and venous components of reflex responses to central vagal stimulation and carotid occlusion. Three to 10 per cent halothane administered for 1–2 minutes only during MVO, with its distribution limited to the cephalad circulation, did not affect arterial and venous tone and reflex responsiveness of the cædual circulation, but markedly reduced the cephalad arterial pressure and reflex responses. Thus, with the isolation of the cephalad circulation, halothane had no apparent effect on the central vasomotor control mechanisms at a time when its peripheral cardiovascular depressant action was evident.

Halothane is known to depress cardiovascular function, yet there is insufficient information to explain this effect. It has been ascribed to halothane's actions at many sites, including the myocardium,1,2 arterial smooth muscle,3–5 and sympathetic ganglia.6–9 In addition, while central vasomotor depression is generally accepted as a factor in the depression of cardiovascular function concomitant with deepening anesthesia, only two studies10,11 suggest that halothane causes central vasomotor depression. At this point the importance of the contribution of central vasomotor depression to the observed cardiovascular effects has not been established. Moreover, it is not known whether halothane suppresses the pressor and depressor responses equally, or differentially as is the case with cyclopropane.12,13 Finally, although the contribution of venous tone to hemodynamic integrity is recognized, there is little information regarding halothane's action on the venous system and its reflex responsiveness.

The purpose of this paper is to present data collected in an attempt to establish whether halothane suppresses pressor as well as pressor reflexes, to determine whether halothane depresses venous as well as arterial reflex responsiveness, and to assess the relative importance of the contributions of halothane's central and peripheral actions to the observed deterioration of cardiovascular function.

Methods

The experimental protocols required three experimental designs. Therefore, a section on procedures common to the three designs is included prior to detailing each.

Mongrel dogs of either sex, weighing between 11 and 17 kg., were used. Anesthesia was induced with intravenous sodium thiopental (25–30 mg./kg.) and the animal placed in the supine position. The trachea was intubated and the lungs ventilated with 70 per cent nitrous oxide in oxygen delivered from calibrated flowmeters in a nonrebreathing circuit. A Harvard respirator (Model 607) was
used. For eight animals the respirator was set to deliver a minute volume 50 per cent greater than that predicted from the data of Kleinman and Radford. For the other eight animals the respirator was adjusted to produce an arterial $P_{CO_2}$ of 30–35 mm. Hg (Astrup AME-1). In these animals, the arterial blood oxygen saturation also was determined (American Optical Oximeter) and was found always to be greater than 90 per cent.

During the surgical procedure, additional thiopental was administered when indicated. Afterwards, adequate anesthesia was achieved with nitrous oxide–oxygen alone. A continuous infusion of a low concentration of succinylcholine Cl (0.1 mg./minute) was given to abolish shivering and movement of the respiratory muscles. At least two hours elapsed between the last dose of thiopental and the collection of data.

In order to maintain adequate hydration over many hours, an infusion of dextrose (5 per cent) in saline solution (0.45 per cent) was administered at a rate of 50–75 ml./hour. In those animals in which base excess was determined (Astrup), NaHCO$_3$ was added to the infusion to maintain a base excess of −3 to −6 mEq./l. Blood loss during surgery was compensated by infusion of either heparinized dog blood or dextran (6 per cent). Body temperature was maintained between 37° and 39° C. (rectal) by means of an electric heating pad.

Arterial pressures sensed with Statham (P 23 A) transducers, and venous pressures sensed with Statham (P 23 B) transducers, were recorded on a Grass Model 5 or 7 polygraph.

Halothane vaporized in a Cooper Kettle which had been calibrated by gas chromatography (Perkin-Elmer Model 154 DG) was added to the nitrous oxide–oxygen mixture.

I. METHODS USED TO DETERMINE THE EFFECTS OF HALOTHANE ON PRESSOR AND DEPRESSOR REFLEX RESPONSIVENESS

After a midline incision the vagi were divided low in the cervical region. A Palmer bipolar electrode was placed on the central end of the cut nerve, which was bathed in mineral oil at 38° C. A polyethylene catheter was passed via a femoral artery into the abdominal aorta to measure the arterial pressure. Reflex responses were elicited by central vagal stimulation. The stimulus was derived from a Grass stimulator (Model S4) through a stimulus isolation unit. In each dog, stimulation parameters were selected to yield the largest reproducible pressor or depressor response. After control pressor and depressor responses to central vagal stimulation were established, halothane was added to the nitrous oxide–oxygen mixture and its effect on these responses was determined.

In two preparations, complete barostatic de-buffering was accomplished by crushing the sinus nerves and vagotomy. Completeness of debuffering was confirmed by the absence of the reflex response to carotid occlusion.

II. METHODS USED TO COMPARE THE EFFECTS OF HALOTHANE ON THE ARTERIAL AND VENOUS COMPONENTS OF THE RESPONSE TO CAROTID OCCLUSION AND TO CENTRAL VAGAL STIMULATION

Eight dogs were prepared as in Section I. The common carotid arteries were isolated in the neck. The animal was further prepared for major vessel occlusion (MVO). A detailed description of this technique has been published. Briefly, with the dog supine, the chest was opened in the midline. The azygos vein, the costocervical arteries and the internal mammary arteries and veins were ligated and divided. The descending aorta was isolated at a level just caudal to the left subclavian artery and just above the diaphragm. Modified Blalock-Niedler clamps were positioned on the aorta at these points. The inferior vena cava was isolated at the same level and another Blalock-Niedler clamp applied. Thus, during MVO, when the aorta and the inferior vena cava were occluded simultaneously, the body was divided functionally with respect to the circulation. The cephalad portion continued to be perfused by the heart, while the caudal portion was isolated effectively from the heart during the short interval of MVO. The cephalad arterial pressure was measured via a catheter placed in the internal mammary artery. Caudal arterial pressure was measured by means of a catheter inserted into a femoral artery and ending in the aorta just below the diaphragm. Caudal venous pressure was measured by a catheter inserted...
through a femoral vein into the inferior vena cava and ending just below the entry of the hepatic veins.

After these preparations were completed, a series of 30-second control MVO's was carried out to test the stability of the system and the completeness of circulatory isolation. (When the major vessels are occluded, venous pressure rises to a plateau which reflects the existing tone of the venous beds, and the caudal arterial pressure falls to a level dependent mainly upon the tone of the arterial beds.) Pressor responses to bilateral common carotid artery occlusion or central vagal stimulation then were elicited during MVO. As shown previously, the caudal arteries and venous beds are separated functionally and respond independently during MVO. The magnitude of the caudal circulatory changes was used as an index of the reflex responsiveness of the venous and arterial systems.

After establishment of control reflex responses during MVO, halothane (0.4–1 per cent) was added to the inspired mixture for ten to 20 minutes and MVO repeated at regular intervals. In this manner, changes in venous and arterial responsiveness could be studied when halothane was administered to the entire animal.

III. METHODS USED TO COMPARE THE CENTRAL AND PERIPHERAL EFFECTS OF HALOTHANE ON THE CARDIOVASCULAR RESPONSES TO CENTRAL VAGAL STIMULATION

Seven dogs were prepared for MVO and central vagal stimulation as described. In these experiments the MVO's were held for longer periods, 1–2 minutes, and pressor reflex responses during MVO induced by central vagal stimulation were studied. After establishment of control responses during nitrous oxide–oxygen anesthesia, MVO was executed and halothane (3–10 per cent) was added to the inspired mixture only during the MVO period. This was accomplished rapidly by switching to a second respirator prefilled with the selected anesthetic mixture. Thus, during MVO the cephalad circulation (the head, forelimbs, heart and lungs) was perfused with blood containing halothane. The caudal circulation, i.e., structures below the diaphragm,
Fig. 2. Effects of halothane on pressor and depressor responses to central vagal stimulation in a "debuffered" animal. Records as in Figure 1. Note the depression of both pressor and depressor responses. (Stimulus parameters, right vagus: 100 cps./2 msec./4 V.; left vagus: 20 cps./4 msec./4 V.)

including the splanchnic bed, remained free of halothane. With this method, simultaneous observations of the responses of the two functionally divided areas of the circulation could be made. Any effect of halothane on the reflex responses of the cephalad sections could be the result of both central and peripheral actions of the agent. However, alteration in the reflex responses of the caudal section of the dog could be due only to the central actions of halothane because the agent was not allowed to reach areas below the diaphragm.

Results

Effects of Halothane on Pressor and Depressor Reflex Responses

In four dogs inhaling nitrous oxide, stimulation of the central end of the sectioned vagus nerve produced either a rise or a fall in arterial pressure, depending upon stimulus parameters used. These pressor and depressor responses were reproduced in pairs at five-minute intervals. Halothane (0.5 to 1.5 per cent) was then added to the inspired mixture and the stimulations repeated. Halothane lowered the blood pressure and concomitantly reduced the magnitude of both the pressor and depressor responses (fig. 1). After withdrawal of halothane both responses returned to control values. In eight trials in four dogs, halothane reduced the mean arterial pressure from an average of $142 \pm 13.1^a$ to $68 \pm 10.7$ mm Hg. The pressor response was reduced from an average rise of $49 \pm 6.0$ to $18 \pm 5.0$ mm Hg, and the depressor response from an average fall of $46 \pm 7.2$ to $14 \pm 3.2$ mm Hg. Reduction of one response always was associated with the reduction of the other. In two animals, experiments were repeated after debuffering, to rule out any direct action of halothane on the carotid baroreceptors. In the debuffered animal, the effects of 1 per cent halothane on arterial pressure, pressor and depressor responses to central vagal stimulation were the same as in those with intact sinus nerves (see fig. 2).

Effects of Halothane on Arterial and Venous Components of the Response to Carotid Occlusion and Central Vagal Stimulation

In six animals, MVO was executed, and when the caudal venous and arterial pressures had stabilized, the common carotid arteries were occluded for 10–15 seconds. Carotid occlusion caused an increase in caudal venous and arterial pressures as well as an increase in cephalad arterial pressure. These

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*a This and subsequent values all denote average ± S.E.
findings confirmed the presence of both an arterial and a venous component in this reflex response, as was reported previously.\textsuperscript{15} This procedure was repeated at five-minute intervals with reproducible results. When halothane was added to the inspired mixture and the procedure repeated, the magnitudes of both the caudal venous and arterial pressor responses and the cephalad arterial response were reduced (fig. 3). In ten trials in six dogs, 0.3 to 1 per cent halothane reduced the carotid occlusion response within 10–20 minutes. The caudal mean venous pressure rise was reduced from 2.9 ± 0.4 to 0.9 ± 0.2 mm Hg, the caudal mean arterial pressure rise reduced from 9.1 ± 1.1 to 1.7 ± 1.1 mm Hg, and the cephalad mean arterial pressure rise reduced from 30 ± 3.1 to 15 ± 2.1 mm Hg.

In six trials in three dogs, MVO was executed, and when the caudal venous and arterial pressures had stabilized, central vagal stimulation for 10 seconds caused a rise in the caudal venous and arterial pressures and a rise in the cephalad arterial pressure (fig. 4). When the procedure was repeated during administration of 0.4 to 1 per cent halothane, the magnitudes of the caudal venous and arterial responses as well as the cephalad arterial response were reduced significantly (fig. 4). After 10–20 minutes of halothane administration, the mean increase in caudal venous pressure resulting from central vagal stimulation was reduced from 4.5 ± 0.4 to 2.1 ± 0.3 mm Hg, the mean increase in caudal arterial pressure rise was reduced from 16.0 ± 1.5 to 7.7 ± 0.9 mm Hg, and the mean increase in

**Fig. 3.** Effects of halothane on carotid occlusion responses executed during major vessel occlusion (MVO). Venous pressure on top trace has been set so that zero equals 0.0 mm Hg (indicated by \textsuperscript{**}). Caudal arterial pressure (second trace) is recorded in a scale of 0–200 (indicated by *) prior to MVO and 0–40 mm Hg during MVO. Mean cephalad arterial pressure was recorded in the bottom trace. Carotid occlusion (C. O.) for 15 seconds was performed during MVO after caudal venous pressure reached a plateau. Note the pressor responses to C. O. in all three control traces (left panel). After 1 per cent halothane had been inhaled for ten minutes and MVO repeated (middle panel), caudal venous and arterial and cephalad arterial pressor responses were reduced. Note also the reduction in arterial pressure and caudal venous pressure plateau level. Complete recovery was recorded 20 minutes after termination of halothane (right panel). Time signal: 1 and 5 seconds.
cephalad arterial pressure rise was reduced from 44 ± 7.0 to 23 ± 4.8 mm. Hg.

In four trials in two animals, stimulus parameters were selected so that central vagal stimulation during MVO caused a depressor response, i.e., a reduction in the caudal venous and arterial pressures and a fall in cephalad arterial pressure (see fig. 5). After 1 percent halothane had been added to the inspired mixture for 8–10 minutes, the mean decrease in caudal venous pressure was reduced from 1.1 ± 0.1 to 0.5 ± 0.1 mm. Hg, the mean decrease in caudal arterial pressure was reduced from 4.5 ± 0.7 to 1.5 ± 0.7 mm. Hg, and the mean decrease in cephalad arterial pressure was reduced from 30 ± 7.1 to 8 ± 3.5 mm. Hg.

The venous and arterial pressure levels produced by MVO alone in all of the above experiments were reduced by halothane also. In the 20 trials in the eight dogs described, halothane reduced both the level to which the venous pressure rose (from 5.0 ± 0.3 to 3.7 ± 0.4 mm. Hg) and the level to which caudal arterial pressure fell (from 19 ± 1.0 to 15 ± 1.0 mm. Hg). These reductions do not account for the decrease in the magnitude of the response to either carotid occlusion or central vagal stimulation during MVO. In four trials increasing blood volume restored the caudal venous and arterial pressure responses to MVO itself but did not alter the response to carotid occlusion or central vagal stimulation.

**Central and Peripheral Effects of Halothane on the Response to Central Vagal Stimulation**

In 13 trials in seven dogs, halothane was administered only during the MVO. With this design halothane reached the cephalad circulation only. In these experiments MVO was held for longer periods (1–2 minutes) and pressor responses to central vagal stimulation during MVO were elicited (figs. 6 and 7). When halothane was given during MVO, the caudal venous and arterial pressures either remained unchanged (fig. 7) or rose (fig. 6), while the cephalad arterial pressure fell moderately (fig. 6) or markedly (fig. 7). The caudal venous and arterial responses to central vagal stimulation were unaffected, while the cephalad arterial response was reduced markedly (fig. 6) or abolished (fig. 7). It appears that although halothane affected the cephalad circulation it did not do so by depressing central vasomotor areas. Had central depression occurred, the reflex responsive-

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**Fig. 4.** Effects of halothane on pressor responses to central vagal stimulation during MVO. Records as in figure 3 except that pulsatile cephalad arterial pressure was recorded. Stimulation of the central end of the cut left vagus nerve for 10 seconds resulted in rises of caudal venous, caudal arterial, and cephalad arterial pressures. Note that all three pressor responses, as well as the arterial pressure and caudal venous pressure plateau levels, were reversibly reduced by halothane. (Stimulus parameters: 15 cps./3 msec./10 V.)
Fig. 5. Effect of halothane on a depressor response to central vagal stimulation during MVO. Records as in figure 3. The central end of the cut right vagus nerve was stimulated to evoke a depressor response. All three components of the depressor response (caudad venous, caudad arterial and cephalad arterial) were reduced during halothane inhalation. (Stimulus parameters: 100 cps./2 msec./4 V.)

ness of the caudal circulation would have been obtunded.

Discussion

It is well known that circulatory homeostasis is altered by general anesthetic agents. This alteration may involve changes in arterial and venous tone, venous capacity, cardiac function, circulatory volume, and neural and hormonal control mechanisms. It is necessary to determine the effect of an anesthetic on each in order to evaluate fully the basis for the observed change in circulatory status occurring during anesthesia.

Since one of the primary determinants of cardiac output is venous return, the effects of anesthetic agents and anesthesia on venous tone and capacity warrant investigation. However, there is at this point little information on the effects of anesthetic agents on the venous system. Caffrey et al. studied the effect of halothane on the compliance of veins in the human forearm and found insignificant increases. It is difficult, however, to predict the nature of a drug's action on the whole venous system from data derived from an action on forearm veins only. The MVO preparation makes it possible to study simultaneously the tone and reflex responsiveness of both the venous and the arterial portion of the circulation below the diaphragm. Our data demonstrate that, when delivered to the whole animal, halothane depresses the venous as well as the arterial tone and the venous and arterial reflex responses to both central vagal stimulation and bilateral carotid occlusion. Thus, stimuli which normally would result in alterations of venous capacity could not be expected to induce the same degree of change under halothane anesthesia. Just after the start of a period of MVO, the level to which the inferior vena caval pressure rises is largely dependent upon the tone of the venous system when blood volume is relatively constant. Halothane decreased the height of the venous pressure plateau, indicating a decrease in venous tone. Therefore, by increasing the capacitance of the venous system, halothane decreases the effective circulatory volume by sequestering an aliquot proportional to the capacitance change. This alone can decrease both cardiac output and arterial blood pressure. Therefore, the fall in arterial pressure during halothane anesthesia may be due to increased venous capacitance and decreased venous bed responsiveness as well as to a decrease in arterial tone. If, in addition, halothane's negative inotropic action is consid-
Fig. 6. The effect of halothane on pressor responses to central vagal stimulation when administered for 60 seconds only during the MVO. Here the halothane reaches only structures perfused by the cephalad circulation. Records as in figure 4. Left panel, control 60 seconds MVO. The central end of the cut right vagus nerve was stimulated for 15 seconds during MVO to evoke pressor responses in all three tracings. In the right panel, 8 per cent halothane was inhaled at the start of MVO and was withdrawn when MVO was terminated. The venous component of the pressor response to central vagal stimulation was not altered. The caudal arterial component actually was increased while the cephalad arterial component was reduced markedly. Note also the small fall (right panel) in cephalad arterial pressure prior to the vagal stimulation and the concomitant reflex rise of caudal arterial and venous pressures. (The irregularity superimposed on the caudal venous pressure trace was an artifact due to the lungs touching the Blalock-Niedler clamp on the inferior vena cava.) (Stimulus parameters: 30 cps./4 msec./3 V.)

Fig. 7. Same as in figure 6, but MVO was maintained for 120 seconds and 5 per cent halothane was delivered only during the entire period of MVO. Note the marked decrease in cephalad arterial pressure and complete disappearance of cephalad arterial pressor response to central vagal stimulation, while caudal venous and arterial pressor responses are not diminished. (Stimulus parameters: 15 cps./1.5 msec./20 V.)
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It is not surprising that the arterial pressure decreases even though total blood volume may not change.

Previously, it has been widely held that, concomitant with deepening anesthesia, there is progressive depression of medullary function. The data presented here (figs. 6 and 7) demonstrate that invoking depression of central vasomotor function to explain changes of cardiovascular function accompanying anesthesia may be unwarranted. Under the conditions of our experiments, halothane has been shown to depress vascular reactions at a time when central vasomotor mechanisms are affected very little. With the MVO method it is possible to study the effects of a drug on the central nervous system by administering the drug to the cephalad circulation during the MVO period. When a drug is administered to the cephalad circulation, any effect on reflex responses of the caudal circulation can be due only to the action of the drug on central vasomotor areas and/or autonomic structures perfused by the cephalad circulation, since the drug does not reach the caudal circulation. It can be concluded, therefore, that halothane given only to the cephalad circulation during MVO has no effect on central vasomotor areas which are responsible for the caudal vascular responses to central vagal stimulation. The depression of cephalad vascular responsiveness must have been due to direct actions on structures peripheral to the central nervous system. Significant depression of spinal tracts responsible for the integrity of reflex pathways is ruled out by the experimental design employed, since halothane administered during MVO reached the cervical and thoracic spinal cord. The results of these experiments suggest that the depression of arterial and venous reflex responsiveness seen when halothane was given to the entire animal (figs. 3, 4, and 5) was due largely to the action of halothane at peripheral sites.

Data from the present study also demonstrated that both pressor and depressor reflex responses are depressed by halothane. This is in contrast to our previous finding that cyclopropane depresses the pressor but spares the depressor reflex response. Although the effects of cyclopropane on reflex responses are attributed to its central action, data presented here indicate that halothane acts peripherally to depress reflex responses. Interestingly, cyclopropane has little effect on arterial pressure, whereas halothane reduces it significantly. Thus, changes in central vasomotor function caused by an anesthetic may not be a significant determinant of arterial pressure during anesthesia.

To distinguish central from peripheral sites of action of halothane with the MVO preparation, the anesthetic can be administered only in high inspired concentrations for short periods of time. The present findings were confirmed in a subsequent study employing cross-circulation preparations.

Conclusions

Our findings indicate that halothane, in the dog, depressed vascular responsiveness by depression of responses to both depressor and pressor stimuli. The tone and reflex responsiveness of both the arterial and the venous compartments of the vascular beds below the diaphragm were reduced by halothane. It has been shown that central cardiovascular control mechanisms were not affected by inspired concentrations of halothane as high as 10 per cent for periods as long as two minutes. The circulatory depression produced by inhalation of halothane appears to be due to an action on structures peripheral to the central nervous system.

References


Watercolor of New England beach scene by R. Douglas Sanders, M.D., Wilmington, Del., which won first prize in watercolors at the annual meeting exhibit at the Las Vegas Convention Center.