The Effects of Halothane on Arterial Pressure, Preganglionic Sympathetic Activity and Barostatic Reflexes

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The effects of halothane on arterial pressure and preganglionic sympathetic activity and the responses of these to stimulation of the aortic depressor nerve were studied in cats. When the end-expired concentration of halothane was 1.15 per cent, sympathetic activity was reduced only slightly, whereas blood pressure was markedly depressed. The magnitude of the sympathetic response to baroreceptor nerve stimulation was unaffected at this concentration, although the response of arterial pressure was reduced. Even when the end-expired concentration was 1.65 per cent, when baroreceptor nerve stimulation produced hardly any change in arterial pressure, the sympathetic nervous response was relatively little affected. The authors conclude, therefore, that halothane produces only slight depression in sympathetic activity and does not extinguish barostatic reflexes, and that the cardiovascular depression produced is largely, although not entirely, due to an action peripheral to the central nervous system. (Key words: Halothane; Sympathetic nervous activity; Barostatic reflexes; Arterial pressure.)

HALOTHANE (Fluothane) depresses cardiovascular function. Among the possible explanations are direct myocardial depression,[1-3] ganglionic blockade,[4,5] direct action on vascular smooth muscle,[6,7] and central sympathetic depression.[8,9] Only three studies[10-12] have employed direct measurement of sympathetic nervous activity. In one of these, in which the subjects were rabbits,[10] there was an increase in sympathetic activity which is now believed to have been due to a species difference. Results of a study of cats[11] anesthetized with chloralose, a basal anesthetic which interacts with halothane[12] in this species, indicate severe depression. Halothane has been found in some studies to depress barostatic reflexes[9,12] and in others to have no effect on them.[14,15] In only two previous studies has the sympathetic nervous response to baroreceptor nerve stimulation been measured directly,[12,13] again with divergent results. The present study, employing direct measurements of sympathetic nervous activity, is an attempt to investigate further the effects of halothane on sympathetic nervous activity and baroreceptor reflexes.

Methods

Experiments on 23 cats weighing 1.5 to 3.9 kg are reported. Each animal was initially anesthetized with 4 per cent halothane in O_2, which was led into a plastic bag enclosing the cage. Anesthesia was continued by mask while a femoral artery, vein, and the trachea were cannulated. Halothane was then discontinued and 20 mg gallamine (Flaxedil) given intravenously at 30-minute intervals while respiration was maintained with a Harvard animal pump delivering 50 per cent nitrous oxide and 50 per cent oxygen. Total flow to the respirator was 4 l/min. A 5-l reservoir bag with a pop-off valve was interposed in front of the Harvard respirator to prevent back-pressure on the anesthesia machine and to permit escape of excess gas. The esophagus and trachea were divided low in the neck. Both were tied together over a metal rod, after which the pharynx and larynx were pulled out through the mouth to give access to the cervical sympathetic trunks, vagi, aortic depressor and carotid sinus nerves.

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Received from the Department of Anesthesia, University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. Accepted for publication August 19, 1969. Supported (in part) by U.S.P.H.S. Grants GM-15430-02 and 2G-215-11 from the National Institute of General Medical Sciences, National Institutes of Health.

The left cervical sympathetic trunk was divided just below the superior cervical ganglion, dissected free of surrounding tissue, placed on a metal backplate and immersed in mineral oil. Multifiber strands were dissected free and placed on bipolar platinum wire electrodes connected to a Grass P-5 amplifier. The output was led to one channel of a Tektronix 565 oscilloscope and to a Grass audio-amplifier. The signal from one vertical oscilloscope amplifier was fed to a pulse-height selector, which comprised both discriminator and pulse-shaping circuits, so that action potentials between upper and lower voltage limits could be selected, converted into square-wave pulses, and counted on a Nuclear Chicago ratemeter. The ratemeter was calibrated with a Hewlett-Packard signal generator over the range of 0–300 cps. The ratemeter's output was delivered to a Grass amplifier and to a multichannel recorder. The output of the pulse-height selector was monitored continuously to insure that a change in the signal-to-noise ratio did not affect the number of action potentials counted during an experimental sequence. This was accomplished 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. Audio-monitoring of the sympathetic discharge was used continuously throughout the experiment.

To test the barostatic reflex initially an intravenous injection of epinephrine (1–5 μg) was used. Only fibers which were inhibited during the increase in arterial blood pressure were studied further.

The left aortic depressor nerve was divided low in the neck, dissected free, placed on platinum electrodes, and stimulated at intervals with an AEL stimulator and a Grass isolation transformer (0.05 to 1.5 volts, 0.1- to 5-msec pulses, 200 cps, 15-sec duration). If the left aortic depressor nerve could not be located or did not respond to stimulation, the right was used, but in all animals considered "normal" the vagi and sinus nerves were left intact. In the animals described as denervated the carotid sinus nerves were dissected free and cut, together with both vagi and the right aortic depressor nerve. Barostatic reflexes were recorded before and after division of the nerves, to insure that we were recording from sympathetic nerves and that denervation produced complete disappearance of the reflex.

Three cats were studied after midcollicular decerebration, performed with the animals' heads in a stereotaxic frame, under halothane anesthesia. When the typical decerebrate rigidity had occurred, halothane was discontinued and gallamine given intravenously as described previously.

In each of four cats a cervical laminectomy was performed and the spinal cord cut under direct vision at C1. Mean arterial blood pressure in these animals was maintained above 75 mm Hg with the aid of continuous infusion of norepinephrine (5 μg/ml of 5 per cent glucose solution) delivered by a Harvard infusion pump at a rate of 0.076 to 1.91 ml/min.

Arterial pressure was sensed by a Statham P-23D transducer and recorded on a Grass recorder. Mean pressures were obtained by electrical damping. Cardiac rate was recorded using a Grass tachograph triggered by the arterial pulse.

End-tidal CO_2 was measured continuously by a Godart Capnograph (corrections were made for the spectral absorption caused by N_2O) and kept as close as possible to 5.4 per cent.

Arterial blood samples (3 ml) were drawn at 100–120-minute intervals and analyzed in an Instrumentation Laboratory assembly for *p*H, P_{CO_2} and, occasionally, P_{O_2}. Blood withdrawn was replaced with an equal volume of physiologic saline solution.

Metabolic acidosis invariably was present before the start of each experiment and was corrected before the administration of halothane with $NaHCO_3$ on the basis of (base deficit × body weight × 0.3) mEq.

Rectal temperature was measured with a Yellow Spring thermistor and maintained at 37–38 °C with the aid of a "K-pad" (Gorman Rupp).

Protocol

The 23 cats were treated as follows.

Six "normal" animals (one aortic depressor nerve divided) were anesthetized with halothane delivered from a calibrated Fluotec va-

TABLE 1. Effects of Halothane on Sympathetic Discharge and Mean Arterial Blood Pressure in Normal Cats

	Initial Value	15-Min Value	Per Cent Depression from Control	30-Min Value	Per Cent Depression from Control	45-Min Value	Per Cent Depression from Control	60-Min Value	Per Cent Depression from Control	Final Value
Sympathetic Discharge Frequency (impulses/sec)										
Cat 1	20	20	0	20	0	25	−25	21	−5	16
Cat 2	70	50	28.6	38	45.7	28	60	28	60	66
Cat 3	31	9	71.0	16	48.4	13	58.1	15	51.6	50
Cat 4	55	25	54.5	29	47.7	26	52.7	23	58.2	50
Cat 5	35	35	0	34	2.9	16	54.3	9	74.3	54
Cat 6	40	18	55.0	17	57.5	10	75.0	13	67.5	35
MEAN $\bar{X}$	41.8	26.2	34.8	25.7	33.7	19.7	45.9	18.2	51.1	45.2
SE	7.3	5.9	12.3	3.8	10.0	3.1	14.5	2.9	11.7	7.1
Mean Arterial Blood Pressure (mm Hg)										
Cat 1	130	70	46.2	62	52.3	50	61.5	45	65.4	127
Cat 2	170	96	43.5	80	52.9	55	67.6	58	65.9	165
Cat 3	152	98	35.5	86	43.4	65	57.2	75	50.7	135
Cat 4	138	64	53.6	60	56.6	51	63.0	54	60.9	150
Cat 5	117	65	44.4	57	51.3	50	57.3	53	54.7	118
Cat 6	138	70	49.3	64	53.6	56	59.4	56	59.4	125
MEAN $\bar{X}$	140.8	77.2	45.4	68.2	51.7	54.5	61.0	56.8	59.5	136.7
SE	7.5	6.4	2.5	4.9	1.8	2.4	1.6	4.1	2.4	7.2

Mean and standard error of end-expired halothane concentrations
15 minutes 1.16 ± 0.03 per cent
30 minutes 1.20 ± 0.03 per cent
45 minutes 1.63 ± 0.05 per cent
60 minutes 1.73 ± 0.04 per cent
Horizontal brackets indicate significant change.

porizer. An inspired concentration of 3 per cent was given for two minutes, 2 per cent for two minutes, and 1.5 per cent then continued for 30 minutes. End-expired halothane concentrations were measured by gas chromatography after 15 and 30 minutes. Sympathetic activity (S.A.), mean arterial blood pressure (MABP) and heart rate (HR) also were measured at these times. At the end of 30 minutes the inspired halothane concentration was raised to 3 per cent for two minutes, then lowered to 2.5 per cent for two minutes and maintained at 2 per cent for an additional 30 minutes. Measurements of end-expired halothane, MABP and SA were made after 15 and 30 minutes (*i.e.*, 45 and 60 minutes after the start of halothane).

The six baroreceptor-denervated and three decerebrated animals were treated in the same manner, but halothane was discontinued after 15 minutes of exposure.

The same procedure was followed for the four spinal animals, except that mean arterial pressure was maintained at pre-halothane levels by increasing the norepinephrine infusion rate as needed.

The seven animals in which good responses to baroreceptor nerve stimulation were obtained included Nos. 4, 5, and 6 (in the "normal" series) and an additional four cats prepared in the same way as the "normal" cats except that they had been anesthetized 40 minutes previously with cyclopropane. These animals were anesthetized with a 1.5 per cent

inspired concentration of halothane for 15 minutes, followed by a 2 per cent concentration for an additional 15 minutes.

Since the aortic depressor nerve in the cat contains chemoreceptor fibers which have a higher threshold than the baroreceptor fibers with the lowest threshold,[16] the stimulation voltage was increased gradually to obtain a maximal response in each animal and maintained at this level throughout the study. The sensitivity of the barostatic reflex has been expressed as a maximal percentage depression of mean arterial blood pressure (MABP) and heart rate (HR) in the 15-sec stimulation period. The reduction in sympathetic activity has been calculated somewhat differently, namely, as the percentage of impulses deleted by the stimulus—in other words, as the area of the sympathetic activity–time curve carved out from the curve observed prior to stimulation. This is more representative than the peak response, since the sympathetic activity often failed to remain inhibited during the entire stimulation, and measuring peak change only would give undue weight to the first few seconds of the response. All initial and final recorded responses are taken as a mean of two values.

Results

All variations are expressed as standard errors of the mean. All statistical analyses were performed using paired t tests. A P value below 0.05 was considered statistically significant. "Initial" control values were obtained just before beginning the administration of halothane, final control values 30 minutes after discontinuation of halothane.

Intact Animals

Results from the six "normal" cats are presented in table 1. Mean arterial blood pressure (MABP) was reduced progressively as the level of anesthesia deepened. After 15 minutes (end-expired halothane concentration 1.16 ± 0.03 per cent) a 45.2 ± 2.5 per cent depression had occurred ($P < 0.001$). After 30 minutes (end-expired halothane concentration 1.20 ± 0.03 per cent) a 51.6 ± 1.8 per cent depression was observed ($P < 0.05$). After 45 minutes (end-expired halothane 1.63 ± 0.05 per cent) a 61.0 ± 4.1 per cent depression resulted ($P < 0.05$). After 60 minutes (end-expired halothane concentration $1.73 \pm .04$ per cent), the MABP depression was not significantly different from that found at 45 minutes. In general, very little individual variation was found in the progressive depression of mean arterial blood pressure as halothane concentration was increased.

The responses of sympathetic activity were much less uniform. Although the mean level of activity after 15 minutes of halothane had decreased 34.8 ± 12.3 per cent, a significant decline ($P < 0.05$), the activity of some fibers (in cats 1 and 5) had not declined. Although a decline in mean activity occurred as anesthesia deepened (to an end-expired concentration of 1.73 ± 0.04 per cent), this did not reach the level of statistical significance when compared with the results after 15 minutes of exposure.

Results after Denervation, Decerebration or Spinal Section

The results from the six baroreceptor-denervated cats, the three decerebrated cats and the four spinal cats are presented in table 2. In the six baroreceptor-denervated animals a 15-minute exposure to halothane (end-expired concentration 1.13 ± 0.03 per cent) decreased mean arterial blood pressure 51.4 ± 4.1 per cent ($P < 0.001$) and decreased sympathetic activity 33.9 ± 11.9 per cent ($P < 0.05$), changes similar in magnitude to those in the "normal" animals.

In the decerbrated cats also both sympathetic activity and MABP were depressed within the ranges found in "normal" cats, as was the change in sympathetic activity found in the spinal cats. However, in the spinal cats MABP was maintained as close as possible to the initial level with norepinephrine.

The effect of halothane on the sensitivity of the response to stimulation of the aortic depressor nerve is reported in table 3. At an end-expired halothane concentration of 1.13 ± 0.04 per cent there was a significant decrease (26.3 to 16.0 per cent) ($P < 0.05$) in the blood pressure response, whereas neither the response of SA nor that of HR changed significantly. Deepening anesthesia to an end-

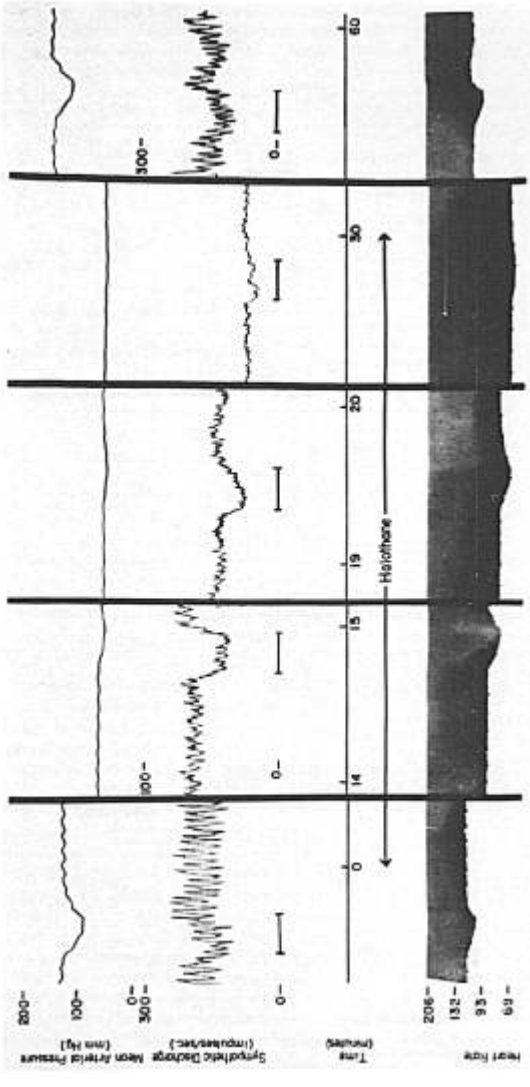

FIG. 1. Effects of increasing depths of halothane anesthesia on arterial pressure, sympathetic discharge frequency and heart rate and on the responses of these to a 15-sec period of aortic depressor nerve stimulation.

Inspired halothane concentration was 1.5 per cent during the time interval 0–15 min and 2 per cent during the time interval 15–30 min.

The horizontal bar indicates a 15-sec nerve stimulation. The sympathetic impulses before and after halothane administration occurred in bursts, giving the curve a saw-toothed appearance. During administration of halothane the pattern of impulse discharge changed to one of continuous firing. The curve is taken from an animal which had a somewhat exaggerated depression in sympathetic frequency (note change in scale from 0–300 to 0–100 to the right of the first vertical bar) but it clearly demonstrates that even though the sympathetic frequency is diminished aortic depressor nerve stimulation will depress it further without causing any conspicuous change in arterial pressure.

TABLE 2. Effects of Halothane on Sympathetic Discharge and Mean Arterial Blood Pressure in Baroreceptor-denervated Decerebrate, and Spinal Cats*

	Sympathetic Discharge Frequency			Mean Arterial Blood Pressure		
	Control (impulses/sec)	15-Min (impulses/sec)	Per Cent Depression from Control	Control (mm Hg)	15-Min (mm Hg)	Per Cent Depression from Control
Baroreceptor-denervated						
Cat 1	50	60	−20	150	89	40.7
Cat 2	28	11	60.7	155	52	66.5
Cat 3	60	28	53.3	132	70	47.0
Cat 4	10	7.5	25.0	142	55	61.3
Cat 5	24	14	41.7	113	59	47.8
Cat 6	35	20	42.9	140	77	45.0
MEAN $\bar{X}$	34.5	23.4	33.9	138.6	67.0	51.4
SE	7.4	7.9	11.9	6.1	5.8	4.1
Decerebrated						
Cat 1	20	14	30.0	150	72	52.0
Cat 2	50	25	50.0	135	105	22.2
Cat 3	18	11	61.1	86	44	48.8
MEAN $\bar{X}$	29.3	16.7	47.0	123.7	73.7	41.0
SE	10.4	4.3	9.1	19.3	17.6	9.4
Spinal Cats						
Cat 1	20	7	65.0	86	80	7
Cat 2	9	4	55.6	90	75	−7.1
Cat 3	27	14	48.1	95	95	0
Cat 4	21	11	47.6	80	70	12.5
MEAN $\bar{X}$	19.3	9.0	54.1	82.8	75.0	3.1
SE	3.8	2.2	4.1	5.3	2.0	4.3

* End-expired halothane concentrations: baroreceptor-denervated animals after 15 minutes' halothane, 1.13 ± 0.03 per cent; decerebrated animals after 15 minutes' halothane, 1.01 ± 0.11 per cent; spinal animals after 15 minutes' halothane 1.05 ± 0.05 per cent.
Horizontal brackets indicate significant change.

TABLE 3. Effects of Halothane on the Responses of Sympathetic Discharge, Mean Arterial Blood Pressure, and Heart Rate to Aortic Depressor Nerve Stimulation*

	Initial Control	At 1.13 ± 0.04 Per Cent Halothane	At 1.64 ± 0.04 Per Cent Halothane	Final Control
Frequency response	28.9 ± 3.0	27.1 ± 4.9	18.7 ± 4.9	30.5 ± 5.9
Mean arterial pressure response	26.3 ± 5.9	16.0 ± 2.9	7.0 ± 1.7	24.3 ± 4.1
Heart rate response	11.4 ± 2.2	8.2 ± 1.7	3.8 ± 0.7	8.2 ± 1.2

* All values are means from seven animals expressed as percentage reductions (see text) ± standard errors.
Horizontal brackets indicate significant change.

expired concentration of 1.64 ± 0.04 per cent depressed the responses of both HR (11.4 to 3.8 per cent) and MABP (26.3 to 7.0 per cent) significantly ($P < 0.02$), but the response in sympathetic activity, although depressed on the average, was not significantly different from the control level.

Discussion

It has been found that administration of halothane uniformly produces a depression in MABP which increases with increasing depths of anesthesia. Although the mean sympathetic frequency declined moderately (and significantly), the variations were so great (even including an increase in activity in one animal) that decreased activity cannot be considered a major cause of the hypotension observed. The response to baroreceptor nerve stimulation presented a similar picture, decreased responses in MABP and HR with deepening of anesthesia, but an essentially unchanged response in sympathetic activity. This suggests that the vascular response to changing sympathetic activity levels is blocked peripherally to the site of measurement.

To analyze the central actions of halothane we have adopted the concept of Alexander,[18] who proposed that the sympathetic outflow is largely controlled by two opposing cell populations in the medulla oblongata, a tonically-active pressor representation and a depressor area excited only on receipt of impulses from peripherally-located baroreceptors. Both centers act via descending pathways upon the vasomotor neurons in the spinal cord. Since the three decerebrate cats reacted to halothane in a way not obviously different from the "normal" cats, we suggest that halothane acts at the medullary level or below.

The depression in sympathetic activity in spinal animals was similar to that found in "normal" cats exposed to halothane, but to demonstrate this blood pressure had to be maintained at the preanesthetic level, because the spontaneous sympathetic output of the spinal cord is inversely dependent upon the level of arterial pressure.[11] However, that the spontaneous sympathetic output of the spinal cord can be depressed by halothane does not necessarily mean that the depression observed in intact animals stemmed entirely from this action. One finding suggests that the spinal cord is not the prime locus of halothane's action. If the declining sympathetic activity in normal animals were the result of block at the cord level one would expect the preanesthetic pattern of impulse activity, large spiking waves (seen in normal but not in spinal animals), to continue in a somewhat diminished form. This does not happen. Soon after exposure to halothane the sympathetic rhythm becomes disrupted to almost continuous firing. This we take as an indication that the prime site of action of halothane may be above the spinal cord.

The response in decerebrated animals was normal, again suggesting a medullary site of action. After baroreceptor denervation the medullary pressor neurons are uninhibited and fire at an elevated rate. The response to halothane in such a preparation, therefore, represents the effect of the anesthetic on the pressor elements alone. From our data we conclude that these elements are depressed by halothane. If at the same time the depressor elements were unaffected, one would expect an enhanced sympathetic response to depressor nerve stimulation; this we did not find. Therefore, we conclude that the depressor elements also must be depressed, although probably not to the same degree as the pressor elements since the sympathetic activity in normal cats declines in a manner similar to that in denervated cats. This analysis leaves unanswered the question why, if central barostatic mechanisms are really unaffected, the presence of arterial hypotension during the administration of halothane does not evoke a reflex increase in sympathetic nervous activity. One possibility —that halothane is acting to suppress sympathetic nervous activity by sensitizing the baroreceptors[17]—apparently can be ruled out by the observation that there was no significant difference in the levels of sympathetic firing during halothane anesthesia when comparing normal and buffer-denervated animals. A more likely supposition is that the barostatic reflexes are not functionally normal during halothane anesthesia despite the fact that stimulation of the aortic depressor nerve still depresses sympathetic activity. It should be remem-

bered that the convention used to express the reflex response is the percentage depression of sympathetic frequency (or arterial pressure or heart rate) observed during stimulation of the depressor nerve. In the presence of halothane the prestimulus frequency is already reduced because the spinal vasomotor neurons and (probably) the medullary "pressor" neurons are depressed. Under these conditions a further reduction in sympathetic activity may be abnormally easy to effect by activation of the medullary "depressor" neurons (*i.e.*, by depressor nerve stimulation). Conversely, the release of medullary inhibition which occurs when arterial pressure declines may be insufficient to increase "pressor" neuron activity because of simultaneous direct depression of these elements by halothane.

The authors wish to acknowledge the able technical assistance of Mr. Leo Davidson.

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Erratum

An error appeared in the article, "Diffusion Anoxia: A Critical Reappraisal," by M. Jack Frumin and Gerald Edelist, in the September issue of the Journal (ANESTHESIOLOGY 31: 243, 1969). The sentence which starts in the twelfth line of the right-hand column on page 248 should begin, "For example, a 50 per cent alveolar dilution . . . ."