The Effects of Halothane on Peripheral and Central Vasomotor Control Mechanisms of the Dog

Hsueh-hwa Wang, M.B., Ralph A. Epstein, M.D.,† Shirley J. Markee, M.D.,‡ Herbert J. Bartelstone, D.D.S., Ph.D.§*

This report presents additional data supporting the conclusion from a previous publication that in the dog, halothane produces its hypotensive effect by peripheral rather than central actions. Cardiovascular responses evoked by reflex vagal stimulation and by direct medullary stimulation were used to test the effects of halothane. Two types of cross-circulation design were employed. Halothane was delivered to the head or to the body of the recipient animal. Halothane given to the head of the recipient caused little or no reduction of the vasomotor responses. However, when halothane was delivered to the recipient's body only, marked reduction of vasomotor responses was observed. It is concluded that there is no significant centrally mediated depression of cardiovascular function during halothane anesthesia.

WE HAVE DEMONSTRATED[1] that halothane caused a striking depression of vascular reflex responsiveness by perpiheral actions at a time when no central depression was evident. Using the major vessel occlusion (MVO) technique, halothane in high concentrations (3–10 per cent) administered to the cephalad portion of the circulation (above the diaphragm) for a short period of time (1–2 minutes), did not affect the vascular reflex responsiveness of the caudad portion of the animal. Such a finding is surprising in view of the obvious central nervous system depressant actions of general anesthetics. The present study was undertaken to explore further whether halothane has any effect on central vasomotor control mechanisms. Using cross-circulation preparations, halothane was administered either to the vascular isolated head or to the remaining portion of the animal. This preparation permitted the administration of halothane in low concentrations for long periods of time. Results of these experiments confirm and extend our previous findings, and indicate that the central vasomotor control mechanisms are not affected by halothane.

Methods

Thirteen pairs of mongrel dogs of either sex were used. Each donor animal weighed between 16 and 24 kg., and each recipient between 11 and 16 kg. In each experiment, the donor animal was at least 2 kg. heavier than the recipient.

Two types of basal anesthesia were used. In six experiments the donor and recipient animals were given a hypnotic dose of sodium thiopental (25–30 mg./kg., i.v.). After tracheal intubation the lungs were ventilated with 70 per cent nitrous oxide in oxygen, with a nonrebreathing system using a Harvard respiratory pump (Model 607). The animals then were immobilized with a slow intravenous infusion of succinylcholine HCl (0.1 mg./minute). In the remaining seven experiments, the basal anesthetic was sodium pentobarbital, 30 mg./kg., i.v.; no succinylcholine was given. The trachea of each animal was intubated and the animal ventilated weith 100 per cent oxygen. Ventilation was adjusted to maintain essentially the same Pa_{CO_2} (generally 30–35

* Assistant Professor of Pharmacology.
† Postdoctoral trainee, Department of Anesthesiology. Present address: Department of Anesthesiology, The Clinical Center, National Institutes of Health, Bethesda, Maryland 20014.
‡ Assistant Professor of Anesthesiology.
§ Associate Professor of Pharmacology.

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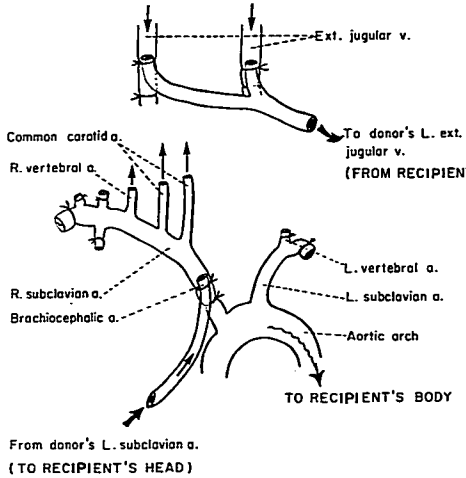

FIG. 1. Perfusion circuit diagram of recipient's head in "Type I cross" preparations.

mm. Hg) in both donor and recipient animals. Either Pa_{CO_2} was determined by the Astrup technique (Astrup AMEI) or the end-tidal P_{CO_2} was monitored continuously with an infrared detector (Beckman LB-1). The animals were given intravenous infusions of 5 per cent dextrose in saline, administered at a rate of 50–75 ml./hour. Blood loss was replaced with 6 per cent dextran in saline or with dog's blood.

Cross-circulation was carried out in one of two ways, described below.

"TYPE I CROSS" PREPARATIONS

In eight experiments in which central vagal stimulation was employed, the vagi of the recipient animals were isolated in the lower neck, and the central end of one severed nerve was placed on a Palmer bipolar electrode and bathed in mineral oil at 38° C. The stimulus was derived from a Grass Stimulator (Model S4) through a stimulus isolation unit. The cervical muscles were either cut or compressed with a tourniquet. All vascular and neural pathways in the neck were interrupted except the common carotid arteries, the vertebral arteries, the external jugular veins, the vessels within the spinal column and the spinal cord. The chest was then opened through a midline sternotomy and the brachiocephalic trunk isolated. Both common carotid and the right vertebral arteries were identified and preserved. All branches of the right subclavian artery other than the right vertebral (omocervical, costocervical, internal mammary and axillary) were identified and ligated. The left vertebral artery was isolated and ligated after cross circulation had been established. The donor animal's neck and chest were opened in the midline and the left external jugular vein and left subclavian artery were isolated. Cross circulation was effected by connecting the proximal end of the donor's left subclavian artery to the distal end of the recipient's brachiocephalic trunk and by connecting the distal ends of both of the recipient's external jugular veins to the proximal end of the donor's left external jugular vein (fig. 1). Tygon tubing was used for the vascular connections, and heparin (50 mg., i.v.) was used as the anticoagulant. Thus, after cross-circulation had been established, the recipient's head was perfused through both common carotid arteries and the right vertebral artery.

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"Type II Cross" Preparations

In five experiments in which direct stimulation of the medullary vasomotor center was carried out, cross-circulation was established using a method previously described,[2] with modifications. Briefly, all cervical structures of the recipient animal were ligated or divided except the common carotid artery, external jugular veins and vascular elements of the spinal column. The vertebral arteries were ligated as they emerged from the transverse foramina of the second cervical vertebra.* Cross-circulation was accomplished by anastomosing the corresponding carotid arteries and jugular veins of the recipient and donor, using Payr's cannulae. No anticoagulant was used. The head of the recipient was placed in a stereotaxic instrument, and after an occipital craniotomy, the medullary pressor area was stimulated using a bipolar coaxial electrode. The stimulus was derived from a Grass S-4 stimulator via a stimulus isolation unit. Reproducible pressor responses were elicited by stimulating areas 3–5 mm. rostral to the obex, 2–3 mm. lateral to the midline and 1–2 mm. below the dorsal surface.

In both cross-circulated preparations the recipient's femoral arterial pressure (recipient body pressure) and the donor's femoral arterial pressure (recipient head pressure) were measured by Statham 23 AC transducers and recorded on a Grass Model 7 polygraph. In some experiments the recipient's heart rate was measured by a Grass tachograph triggered by the pulse wave.

Halothane was added to the nitrous oxide–oxygen mixture when the latter was used as the basal anesthetic, or to oxygen when pentobarbital was the basal anesthetic. Halothane was vaporized either in a calibrated Copper Kettle or in a calibrated Fluotec vaporizer. In three experiments the end-tidal concentrations of halothane for both animals were mea-

* In one experiment the anterior spinal artery of the recipient animal was ligated intradurally after a partial laminectomy of C_2. The results from this experiment were identical with the others. This was done to rule out the possibility that when halothane was given to the donor, the concentration of halothane reaching the recipient's medulla might be lowered by blood of the anterior spinal artery of the recipient, which contained no anesthetic.

Table 1. Effect of Halothane on Arterial Pressure and Pressor Response to Central Vagal Stimulation of the Recipient in "Type I Cross" Experiments

Exp.	Basal Anesthesia	Per Cent of Halothane	Body Arterial Pressure (mm. Hg)				Pressor Response of Body to Central Vagal Stimulation (mm. Hg)			
			Control	After Halothane		Recovery	Control	After Halothane		Recovery
				2′	10′			2′	10′	
To body										
H28	N_2O-O_2	2.0	162	123	45	170(10′)	+60	+15	+18	+60(10′)
H30	N_2O-O_2	1.0	162	120	88	155(20′)	+35	+25	0	+30(20′)
H32	N_2O-O_2	0.5	155	120	108	152(20′)	+55	+45	+25	+55(20′)
H33	N_2O-O_2	1.0	125	90	20†	122(5′)	+70	+65	+ 5	+70(5′)
H34	N_2O-O_2	0.5	160	135	100	145(10′)	+50	+40	+15	+50(10′)
H44	N_2O-O_2	1.0	140	75	45	125(20′)	+70	+65	+35	+70(20′)
H45	Pentobarbital	3.0	145	80	40	140(25′)	+45	+30	+15	+40(25′)
H49	Pentobarbital	2.0	125	65	40	145(18′)	+40	+25	+15	+40(18′)
		Mean±S.E.	148	101±9.4	60±11.6		+53±4.8	+13±5.7	+17±4.0	
		MPD±S.E.	±4.9	−47±5.9***	−88±8.6***			−10±1.2***	−36±4.5***	
To head										
H28	N_2O-O_2	2.0	175	175	120	150(20′)	+55	+50	+55	+55(20′)
H30	N_2O-O_2	1.0	172	165	125	165(13′)	+30	+32	+30	+30(13′)
H32	N_2O-O_2	0.5	150	130	130	155(20′)	+75	+80	+75	+75(20′)
H33	N_2O-O_2	1.0	175	175	175	175(20′)	+60	+65	+55	+65(20′)
H34	N_2O-O_2	0.5	110	115	78	110(14′)	+60	+55	+52	+62(14′)
H44	N_2O-O_2	1.0	125	138	65	125(20′)	+75	+70	+65	+75(20′)
H45	Pentobarbital	3.0	145	115	65	140(20′)	+65	+95	+60	+60(20′)
H49	Pentobarbital	2.0	145	115	65	140(18′)	+65	+95	+62	+65(18′)
		Mean±S.E.	149	147±10.5	102±14.4		+60±5.0	+68±7.8	+57±4.6	
		MPD±S.E.	±8.5	−2±7.7	−47±10.0**			+8±5.7	−3±1.4	

MPD = mean paired differences (from control values). ***$P < 0.001$; **$P < 0.005$; *$P < 0.05$ (Student's t tests). Numbers in parentheses indicate minutes to the time the recovery readings were made. †In this experiment arterial pressure declined rapidly between 6 and 8 minutes. Halothane was discontinued and cardiac massage performed for 30 sec. Recovery was complete.

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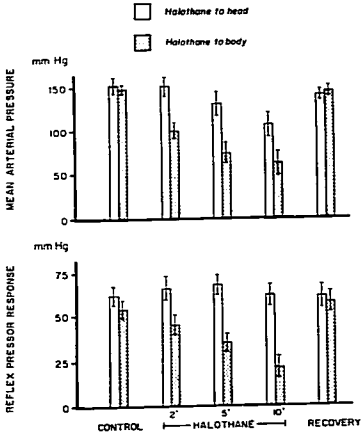

FIG. 2. (Upper) comparison of the effects of halothane on the arterial pressure of the body of the recipient animal when the same concentration of halothane was administered to the head and then to the body, or *vice versa;* (lower) comparison of the effects of halothane on the magnitude of the pressor response of the recipient's body to central vagal stimulation when halothane was administered as above. These data are from eight "Type I cross" experiments; all values are mean ± S.E.

sured by gas chromatography. After 1 per cent halothane had been given to the recipient for 30 minutes, the end-tidal concentration was 0.70–0.75 per cent; that in the donor was always less than 0.0015 per cent. The reverse was found when the same concentration was given the donor for the same period of time. In four experiments in which pentobarbital basal anesthesia was used,† the end-tidal halothane concentrations in the animal receiving the anesthetic were monitored continuously by means of an infrared detector (Beckman) to determine whether the anatomical differences in the two animals of a crossed pair, *i.e.*, in effect a "two-headed" donor and a "headless" recipient had an effect on the end-tidal halothane concentrations. End-tidal concentrations of halothane were found to have the same time course (within 0.05 per cent) whether delivered to donor or recipient.

† The basal anesthesia was changed from nitrous oxide–oxygen to pentobarbital to facilitate the determination of halothane concentrations by infrared analysis.

Results

Peripheral and Central Effects of Halothane on Arterial Pressure

The data from "Type I" and "Type II" cross experiments are presented separately because of differences in experimental design. "Type I cross" preparations underwent thoracotomy whereas "Type II cross" preparations did not, hence the degree of surgical trauma was less in the latter. While most "Type I cross" preparations were under nitrous oxide–oxygen basal anesthesia and immobilized with succinylcholine, "Type II cross" preparations all were anesthetized with pentobarbital. "Type I cross' preparations received halothane in inspired concentrations varying from 0.5–3 per cent, while "Type II cross" preparations all received 1 per cent halothane.

"Type I Cross" Experiments

When halothane (0.5–3 per cent) was delivered to the recipient animal, it was distributed only to the body of the animal and not to the head. Thus, changes in the arterial pressure during halothane administration resulted from peripheral actions of this agent. Under these conditions the arterial pressure of the recipient (body pressure) began to fall within 30 seconds, and continued to decline throughout the ten minutes of administration. As can be seen in Table 1, the mean body pressure decreased, on the average, 47 and 88 mm. Hg after two and ten minutes of halothane administration, respectively, from a control value of 148 mm. Hg. After discontinuation of halothane, the body pressure recovered to control values within 25 minutes.

When the same concentration of halothane was delivered to the donor, and thus reached the head but not the body of the recipient, changes in arterial pressure in the recipient's body would suggest a central action of halothane. Under these conditions, body pressure did not change after two minutes of halothane administration. After five minutes there was a small decrease, and after ten minutes mean body pressure fell an average of 47 mm. Hg from a control value of 149 mm. Hg (table 1).

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After ten minutes the donor's arterial pressure (recipient's head pressure) had decreased an average of 45 mm. Hg (range 27–55) from a control of 107 mm. Hg (range 75–137). After discontinuation of halothane, both the donor's and the recipient's arterial pressure returned to control levels within 20 minutes.

Figure 2 is a comparison of changes in body pressure occurring after halothane had been administered to the head and to the body. After ten minutes of halothane administered to the recipient (body), body pressure fell to a much lower level than when halothane in the same concentration was administered to the donor (head of the recipient). In fact, after two minutes of halothane delivered to the body, body pressure had decreased as much as it had after ten minutes of halothane administered to the head.

When halothane was delivered to the recipient's head, it was often noted that the body pressure rose initially, and in three animals (H 32, H 34, and H 44) this rise persisted for as long as two minutes (fig. 3). In spite of

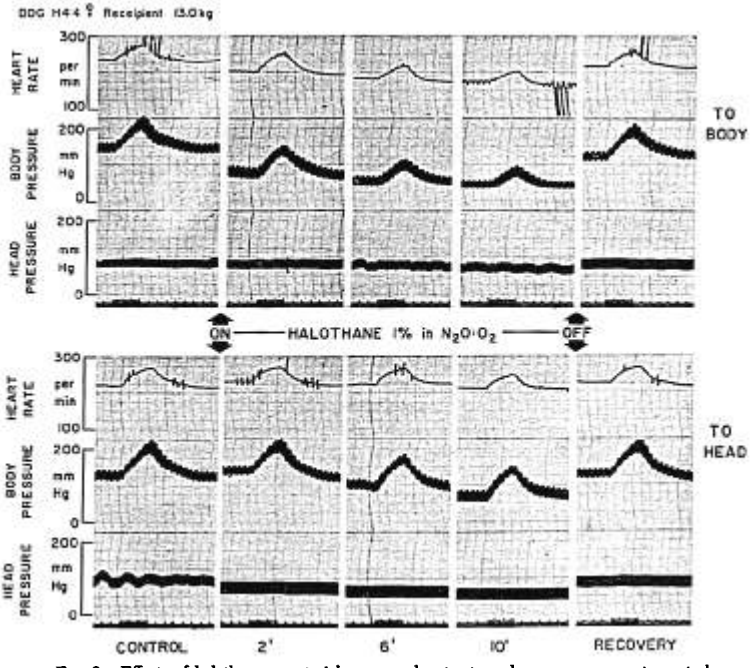

FIG. 3. Effects of halothane on arterial pressure, heart rate and pressor response to central vagal stimulation in a "Type I cross" experiment. Top trace, recipient's heart rate, mid trace, recipient's body pressure; lower trace, donor's head pressure. At each signal the central end of the recipient's cut right vagus nerve was stimulated for 15 seconds. Upper panels: halothane administered to the body. Note the marked fall in body arterial pressure and heart rate and the decrease in magnitude of the pressor and heart rate changes to central vagal stimulation after only two minutes of halothane. Lower panels: halothane administered to the head. Note the rise in body arterial pressure followed by a smaller fall. The pressor and heart rate responses to central vagal stimulation are essentially unchanged after ten minutes. Time signal: 1 and 5 seconds.

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the presence of halothane in the circulation to the head, this rise may have been a barostatic response to the decrease in the head pressure. This could occur, since the carotid sinus of the recipient was included in the circulation to the head. To test this hypothesis, in one experiment (H 44) in which halothane administered to the head had elevated the body pressure during the first two minutes (fig. 3), halothane administration was repeated, but this time the donor's arterial pressure was not allowed to fall. This was accomplished by manipulating an adjustable occlusive clamp placed on the descending aorta of the donor. Under these conditions, with the perfusion pressure to the head maintained constant, the early rise in the body pressure no longer occurred (fig. 4). After two minutes the body pressure just began to fall.

"Type II Cross" Experiments

In this group of five experiments, 1 per cent halothane was administered. When halothane was delivered to the recipient animal, thus reaching only its body, body pressure began to fall within 30 seconds, as in the "Type I cross" experiments. However, at the end of ten minutes of administration, the average decrease was only 40 mm. Hg, compared with a decrease of 88 mm. Hg in "Type I cross" preparations. Control arterial pressures of the two groups were similar (table 2).

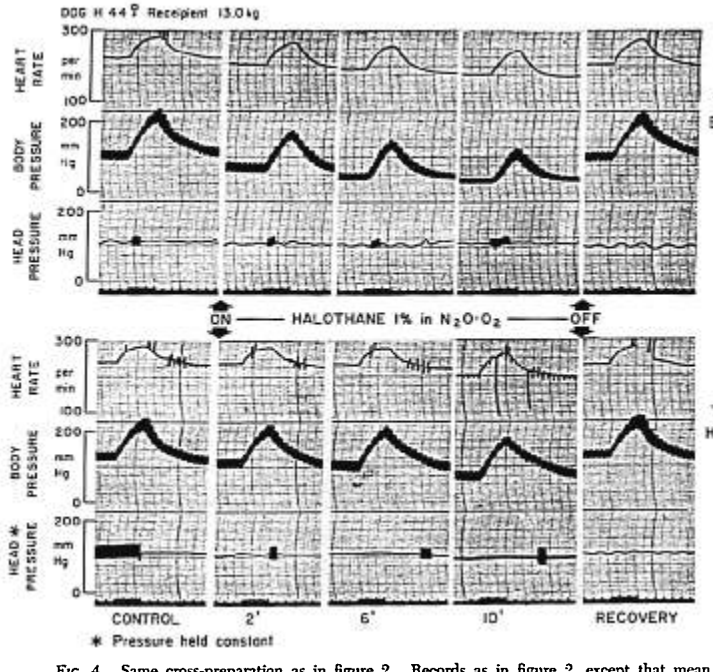

FIG. 4. Same cross-preparation as in figure 2. Records as in figure 2, except that mean and pulsatile head pressures were recorded alternately. Halothane administration was repeated while the head pressure was held constant. Changes were essentially the same as in figure 2, except that rise in body pressure for the first two minutes was no longer present.

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TABLE 2. Effect of Halothane on Arterial Pressure and Pressor Responses to Medullary Stimulation of the Recipient in "Type II Cross" Experiments

Exp.	Basal Anesthesia	Per Cent of Halothane	Body Arterial Pressure (mm. Hg)				Pressor Response of Body to Medullary Stimulation (mm. Hg)			
			Control	After Halothane		Recovery	Control	After Halothane		Recovery
				2′	10′			2′	10′	
To body										
H50	Pentobarbital	1	145	130	110	135(18′)	+60	+10	+15	+50(16′)
H51	Pentobarbital	1	135	120	95	125(15′)	+50	+40	+25	+15(5′)
H52	Pentobarbital	1	140	105	80	130(25′)	+75	+45	+15	+50(25′)
H55	Pentobarbital	1	180	150	145	175(12′)	+50	+20	+15	+50(10′)
H56	Pentobarbital	1	145	125	115	150(10′)	+70	+45	+35	+70(15′)
		Mean±S.E.	149	126±7.3	109±10.9		+61±5.1	+38±4.6	+21±4.0	
		MPD±S.E.	±8.0	−23±4.0***	−40±5.2***			−23±3.7***	−40±5.9***	
To head										
H50	Pentobarbital	1	150	145	140	145(15′)	+55	+50	+45	+55(12′)
H51	Pentobarbital	1	135	155	135	135(20′)	+60	+60	+50	+50(20′)
H52	Pentobarbital	1	150	160	155	155(20′)	+75	+75	+75	+75
H55	Pentobarbital	1	180	200	170	180(14′)	+65	+60	+55	+65(25′)
H56	Pentobarbital	1	130	140	135	135(14′)	+70	+70	+55	+65(14′)
		Mean±S.E.			147±6.8		+65±3.5	+63±4.4	+56±5.1	
		MPD±S.E.			−2±3.8			−2±2.1	−9±2.8*	

MPD = mean paired differences (from control values). ***$P < 0.001$; **$P < 0.005$; *$P < 0.05$ (Student's t tests). Numbers in parentheses indicate minutes to the time the recovery readings were made.

However, when halothane was delivered to the donor, thus reaching only the head of the recipient, the latter's body pressure remained essentially at control level after ten minutes of halothane. An initial rise persisting for two minutes or more was seen in four of the five experiments. The donor's arterial pressure (head perfusion pressure) averaged 120 mm. Hg (range 75–190) under control conditions and decreased on an average of 21 mm. Hg (range 10–40) after ten minutes of halothane administration. Generally, the donor's arterial pressure was higher than that of the animals of "Type I cross" preparation, and decreased less during halothane inhalation.

PERIPHERAL AND CENTRAL EFFECTS OF HALOTHANE ON PRESSOR RESPONSES TO CENTRAL VAGAL STIMULATION

The pressor response to central vagal stimulation was studied in eight "Type I cross" experiments. The central end of a cut vagus nerve of the recipient animal was stimulated electrically for 10–15 seconds to evoke a reproducible pressor response. This was repeated every two to three minutes throughout the experiment.

When halothane was administered to the recipient, *i.e.*, to only its body, the magnitude of the evoked pressor response was reduced within two minutes. This response continued to decrease with time and by ten minutes it was reduced to about a third of the control value. On the other hand, when halothane was administered to the donor, *i.e.*, to the head of the recipient, reflex response was unchanged or increased after two and five minutes, and was essentially unchanged after ten minutes (table 1 and fig. 3).

The reduction in reflex responsiveness when halothane was delivered to the body was not related to the concomitant fall in the recipient's body pressure. As shown in figure 2 and table 1, halothane administered to the head for ten minutes decreased body pressure by 47 mm. Hg but caused no change in the reflex response. However, halothane administered to the body for only two minutes also decreased the body pressure by 47 mm. Hg. Here the reflex response definitely was reduced. Maintenance of reflex responsiveness throughout the ten-minute period of halothane administration only to the head, as contrasted with the progressive reduction of this response when halothane was administered to the body, is illustrated in figure 2. In four of the eight experiments, the period of halothane administration to the head was extended to 20–30 minutes. The pressor response to central vagal stimulation remained unchanged.

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Peripheral and Central Effects of Halothane on Pressor Responses to Medullary Vasomotor Area Stimulation

In each of the five "Type II Cross" experiments, the medullary vasomotor area of the recipient animal was stimulated electrically for 6–10 seconds to evoke a reproducible pressor response. The duration and stimulus intensity were chosen to evoke a reproducible and submaximal pressor response. Tachycardia of varying degrees always accompanied the pressor response to medullary stimulation. The stimulus was repeated every two to three minutes throughout the experiment.

When halothane was administered to the recipient for ten minutes, there was a progressive reduction of both pressor response and tachycardia (table 2 and fig. 5). After ten minutes the pressor response was only 21 mm. Hg (control response, 61 mm. Hg). The magnitude and time of reduction were in the same range as with central vagal stimulation in the "Type I cross" experiments. Recovery of the pressor response to control levels took place within 25 minutes. This was similar to the recovery patterns seen in "Type I cross" experiments.

When halothane was administered to the donor (or head of the recipient), the response to medullary stimulation remained unchanged after two minutes, and was reduced slightly after ten minutes (table 2 and fig. 5). The average pressor response, after ten minutes of halothane administration, was 56 mm. Hg; control response, 65 mm. Hg. This decrease was much less than that seen when halothane was delivered to the body for the same period.

Discussion

Although two types of basal anesthesia were employed (nitrous oxide–oxygen or pentobarbital), both animals of any crossed pair received the same basal anesthetic. The results were not dependent upon the basal anesthetic used. Halothane concentrations varied from 0.5 to 3 per cent, but the same inspired concentration always was administered alternatively to the head and the body in a given experiment. To reduce trauma, minimize blood loss and maintain the stability of the preparations, absolute vascular isolation of the head was not attempted. Spinal extradural sinuses were not ligated, and rather than dividing the posterior cervical muscles, they were compressed with a tourniquet. The modified procedure was deemed adequate because the small amount of halothane reaching the body from the head, or *vice versa*, would be eliminated rapidly via the lungs. In fact, only trace amounts of halothane (less than 0.0015 per cent) could be detected in the lungs of the animal not receiving halothane, compared with 500 times this concentration (0.75 per cent) in the lungs of the animal receiving it.

Delivery of halothane to the donor involved the distribution of halothane in a "two-headed dog," whereas delivery to the recipient involved that to a "headless dog." Therefore, it was necessary to ascertain whether this anatomical difference could influence the arterial concentration of halothane significantly. Continuous monitoring of end-tidal concentration of halothane of the animal receiving the anesthetic demonstrated that the halothane concentration in the lungs and its time course were the same whether it was inhaled by the donor ("two heads") or the recipient ("headless") of a crossed pair. This made it possible to make quantitative comparisons of the effects of halothane on the vascular responses of the recipient's body when it was delivered to either the body or the head.

Halothane administered to the vascularly isolated head, had little or no effect on the reflex responses to central vagal stimulation or the response to direct stimulation of the medullary pressor area. It could be argued that, since the response to central vagal stimulation may be maximal, a reduction in reflex responsiveness might not be revealed. However, direct medullary stimulation which elicited only submaximal control responses was equally unaffected. These results confirm the findings of our previous report [1] that the central vasomotor control mechanisms are not affected significantly by halothane. A peripheral site of action appears more likely, since when halothane was delivered to the body alone, responses obtained with both types of stimulation were reduced markedly and promptly. While these data exclude halothane's central actions and place its vasomotor effects at the periphery, the particular peripheral sites involved were not investigated in the present study.

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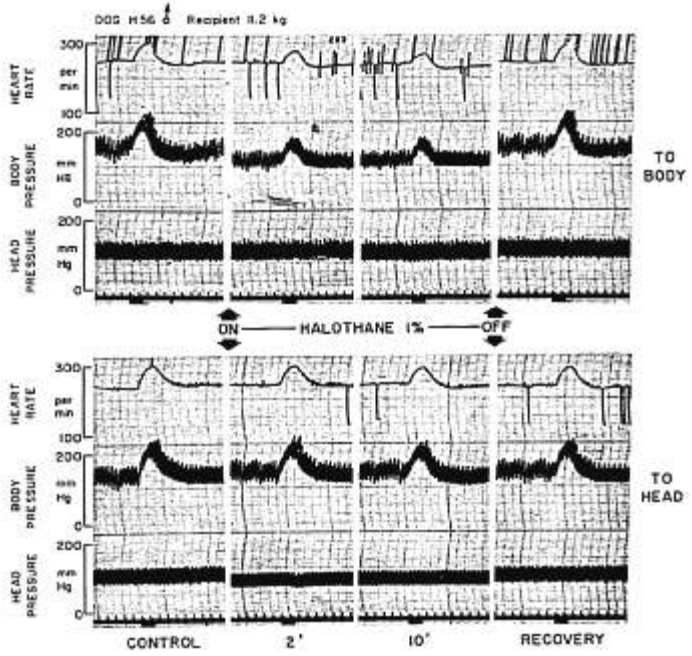

FIG. 5. Effects of halothane on arterial pressure, heart rate and pressor response to medullary pressor area stimulation in a "Type II cross" experiment. Records as in figure 2. At each signal the medullary pressor area of the recipient animal was stimulated for six seconds. Upper panels: halothane administered to the body. Note decreases in body pressure, pressor and heart rate responses to medullary stimulation after only two minutes of halothane. Lower panels: halothane administered to the head. Note that the body pressure remains the same and the pressor response is unchanged at two, and only slightly decreased at ten, minutes. Artifacts in tachograph recordings are due to fluctuations of arterial pressure waves from which the tachograph was triggered.

Some comments are necessary in regard to the effect of halothane on arterial blood pressure *per se*. In the "Type I cross" experiments, when halothane was administered to the donor (the head of the recipient), the recipient's body pressure decreased after five to seven minutes. This did not occur in the "Type II cross" experiments. This difference could be explained, to a large extent, by the physiologic states of the animals. In the "Type I cross" preparations, both donor and recipient had undergone thoracotomy and extensive dissection, and central cardiovascular compensatory mechanisms may have been functioning above normal. It has been shown by Biscoe and Millar [7] that carotid sinus baroreceptors are sensitized by halothane. Thus, with high existing vasomotor center activity, an increased firing of sinus nerves could result in the observed decrease in body pressure. On the other hand, in the "Type II cross" preparations, where the dissection and blood loss had been minimized, the animals were in better condition. A similar increase in sinus nerve firing would not be expected to affect the recipient's vasomotor center activity as much

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as in the "Type I cross" preparations. The finding that in the "Type II cross" experiments halothane delivered to the head did not cause a fall in the body arterial pressure strongly suggests that halothane does not have a significant central depressant action.

Central vasomotor depression during halothane anesthesia has been questioned by Beaton,[3] and by Millar and Biscoe.[4] On the contrary, Price *et al.*,[5, 6] while demonstrating various peripheral sites of halothane's cardiovascular depressant actions, also considered "central autonomic paresis" an important cause of cardiovascular depression. Their conclusion implicating a central site of action for halothane was based upon data obtained from two types of experiments. In the "cephalic bypass" preparations, Price *et al.*[6] perfused the head of the dog with blood containing halothane, via a pump-oxygenator, and found a decrease in arterial pressure in the body and also decreases in heart rate, myocardial contractile force and carotid occlusion response. However, these authors stated that the perfusion system was not very efficient in the removal of halothane, so that recovery was not obtained in the majority of their animals. Furthermore, the observed decrease in the response to carotid occlusion could have been the result of an increased sinus nerve firing rate induced by halothane [7] and not that of central depression. Price *et al.*[8] also found that halothane depressed the pressor response to medullary stimulation when the anesthetic was injected directly into the area to be stimulated. With this method, the concentration of halothane around the cells stimulated cannot be assessed. In the experiments reported here, when anesthetic concentrations of halothane were inhaled by the donor animal and distributed to the medullary area of the recipient, pressor response to direct central stimulation was not depressed.

The finding that halothane, in anesthetic concentrations, depresses cardiovascular function by peripheral rather than central action is not unique to this agent. Preliminary data from this laboratory indicate that two other general anesthetic agents, thiopental and chloroform, also have little or no action on central vasomotor mechanisms, while markedly depressing cardiovascular function by their peripheral action. By contrast, it has been shown in previous reports from our laboratories [9, 10] that cyclopropane markedly depresses the medullary vasomotor center and reflex responses. However, cyclopropane does not produce hypotension, whereas halothane does. It is interesting that a normotensive state is preserved in the presence of an agent shown to depress the central vasomotor mechanisms while hypotension occurs with an agent sparing the vasomotor center function. Thus, it is the peripheral rather than central action of anesthetics that has a significant influence on circulatory status. Alterations in cardiovascular function, therefore, may not be related directly to the degree of central nervous system depression occurring during general anesthesia. From our studies involving four agents, it would appear that cardiovascular changes during anesthesia depend primarily on the specific action of the general anesthetic agent at peripheral sites.

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