

Systemic and Regional Blood Flow Changes during Halothane Anesthesia in the Rhesus Monkey

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The radioactive microsphere technique was used to determine regional blood flow concurrently with other hemodynamic measurements before and during halothane anesthesia in monkeys. Eleven monkeys were studied during both spontaneous and controlled respiration at 0.8 and 1.2 per cent end-tidal halothane concentrations; seven other monkeys served as controls. Halothane caused a significant decrease in arterial blood pressure due to decrease in both cardiac output and total peripheral resistance; pulse rate was also significantly decreased. At both levels of halothane anesthesia, significantly increased percentages of the cardiac output were delivered to the kidneys, lungs (bronchial artery), adrenals, and bone at the expense of the heart, skeletal muscle, chest wall, pancreas, and fat. There was little change in calculated resistance or proportions of the cardiac output delivered to the brain and skin at 0.8 per cent halothane, but at 1.2 per cent the vasculature of the brain dilated while that of the skin constricted. Relatively few hemodynamic differences between spontaneous and controlled respiration were observed. Four of the eleven experimental monkeys, whose body temperatures

were not maintained, had more severe decreases in arterial pressure and cardiac output; regional values in the hypothermic monkeys were similar to those in the monkeys whose temperatures were maintained, except that cutaneous vessels in the former showed marked vasoconstriction at both halothane concentrations. (Key words: Circulatory effects of anesthesia; Halothane; Radioactive microspheres; Cardiac output; Blood pressure; Regional blood flow; Peripheral resistance.)

MEASUREMENTS of blood flow to an organ or tissue of the body usually necessitate placement of a flowmeter, plethysmograph, or similar device around the organ or a major blood vessel supplying it, or the determination of the arteriovenous difference for oxygen, dye, or another tracer using the Fick principle. Measurement of clearance rates of injected indicators has also been a useful technique. These methods have the disadvantage of measuring blood flow to a few areas of the body only.

A relatively new technique for measuring blood flow in many organs and tissues simultaneously has been reported.^{1,2} It has the limitation of being restricted to use in experimental animals, and only intermittent, rather than continuous, measurements can be obtained. The technique consists of injecting nonrecirculating plastic microspheres labeled with different gamma-emitting radioactive nuclides into the left ventricle of the heart and, later, measuring the radioactivity in various organs and tissues. Using different isotopic labels at various intervals permits repeated measurements of regional blood flow in the same animal, uncomplicated by recent surgery or anesthesia. Recent studies by Forsyth *et al.*³ and Hoffbrand and Forsyth⁴ have validated these methods in the unanesthetized rhesus monkey.

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This investigation examines the effects of two concentrations of halothane-oxygen anesthesia and compares the effects of spontaneous and mechanically controlled ventilation on the regional distribution of the blood flow and other cardiovascular variables in the monkey.

Methods

Subjects of the study were 18 male monkeys (*Macaca mulatta*) weighing 3.7 to 8.8 kg. Using sodium pentobarbital anesthesia (30 mg/kg iv), polyvinyl catheters were placed aseptically into the inferior vena cava and abdominal aorta via the left iliac vessels, and into the left ventricle through the left common carotid artery. All catheters were brought out through the skin near the umbilicus, and were continuously flushed (0.5 ml/hr) with heparinized (5 units/ml) 0.9 per cent NaCl solution to maintain patency. After recovery the monkeys were placed in primate-restraining chairs, modified to allow tilting to the supine position, inside sound-protected booths. Three to seven days were allowed for recovery from surgery, and during this period the 11 experimental animals were placed supine for several hours each day with their heads enclosed in a plexiglass box through which room air was pumped. This procedure was followed by a food reward, and by the day of the experiment the animals had adapted to this manipulation without undue excitement.

One hour before the experiment, each monkey was tilted to a supine position in the chair. The catheters were connected to P23Cb Stat-ham strain gauges placed at the midthoracic level outside the booth; thus, all measurements, infusions, and blood sampling could be performed without disturbing the animal. Arterial, central venous and left ventricular end-diastolic pressures were continuously recorded on a Beckman type R recorder. Heart rate was also recorded with a cardi tachometer couple. Cardiac outputs were determined in duplicate by the dye-dilution technique of Hamilton. Indocyanine green was injected into the left ventricle and blood withdrawn at a constant rate with a Harvard pump from the catheter in the abdominal aorta and passed through a Waters X-302 densitometer. All blood was returned after the dye curve had been obtained. Immediately before each cardiac output determination and microsphere in-

jection, arterial blood samples were analyzed for pH, P_{CO_2} , and P_{O_2} with Radiometer electrodes. Blood withdrawn was replaced with 0.9 per cent NaCl. Rectal temperature was monitored continuously with a Yellow Springs thermistor probe.

After baseline measurements had been obtained, 3 to 4 per cent halothane in oxygen was passed through the plexiglass box enclosing the monkey's head. A Foregger anesthesia machine utilizing a Copper Kettle for vaporization of halothane was used. When a sufficient depth of anesthesia had been achieved, the box was removed; the trachea intubated and the endotracheal tube was connected to a Summers T nonbreathing system. Heating pads were placed under the backs of seven of the monkeys (average weight 5.7 kg) to maintain rectal temperatures of 37.5 C; the other four experimental monkeys (average weight 4.4 kg) were not heated.

End-expired halothane concentration was continuously monitored with a Beckman LB-1 infrared analyzer. All experimental measurements were taken 45 minutes after the desired alveolar halothane concentrations had been achieved to insure that steady states had been reached. The second series of measurements followed the maintenance of 0.8 per cent end-tidal halothane during spontaneous ventilation. During the next experimental period, ventilation was controlled with a Harvard animal ventilator. The volume was adjusted to maintain P_{aCO_2} close to 40 mm Hg. Following the third set of regional blood flow measurements, anesthesia was increased to 1.2 per cent end-tidal halothane; mechanical ventilation was continued. After the fourth series of regional measurements, each monkey was allowed to breathe spontaneously at 1.2 per cent halothane, and then the last set of measurements was made (see table 1).

Identical control studies were performed using seven monkeys (average weight 4.4 kg), with the animals supine. Four or five injections of microspheres were made, cardiac outputs were determined, and blood samples were taken at similar time intervals as with the 11 experimental monkeys, without any other manipulations.

The distribution of blood flow was determined by injecting a suspension of nuclide-labeled microspheres (50 μ in diameter) through

TABLE 1. Hemodynamic Values before Each of Five Microsphere Injections of the Seven Control and Seven Anesthetized Monkeys

	Group*	Spontaneous Ventilation				Controlled Ventilation				Spontaneous Ventilation	
		First Microsphere (Baseline)		Second Microsphere (0.8 per cent halothane)		Third Microsphere (0.8 per cent halothane)		Fourth Microsphere (1.2 per cent halothane)		Fifth Microsphere (1.2 per cent halothane)†	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mean arterial pressure (mm Hg)	C	114	16	121	17	124	21	118	21	54‡	15
	H	103	14	67‡	11	68‡	13	52‡	17		
Heart rate (beats/min)	C	182	10	191	21	197	11	188	24	144‡	18
	H	170	22	157‡	10	161‡	13	146‡	21		
Cardiac output (ml/min ⁻¹ kg ⁻¹ body weight)	C	316	70	301	64	312	65	283	73	190‡	31
	H	354	90	246	53	236‡	44	191‡	58		
Stroke volume (ml/kg body weight)	C	1.7	0.4	1.6	0.4	1.6	0.3	1.6	0.4	1.3‡	0.1
	H	2.1	0.3	1.6	0.3	1.5‡	0.2	1.3‡	0.3		
Total peripheral resistance (mm Hg/l ⁻¹ /min/kg body weight)	C	377	101	417	98	409	93	436	105	289	84
	H	312	110	284‡	80	294‡	76	281‡	65		
Left ventricular work (mm Hg/l/min ⁻¹ kg ⁻¹)	C	36	10	37	11	39	13	35	15	10‡	4
	H	36	8	16‡	4	16‡	4	11‡	5		
Arterial P _O ₂ (mm Hg)	C	95	11	91	12	90	6	93	8	307‡	137
	H	93	11	338‡	163	290‡	141	317‡	152		

* C = Seven control monkeys; H = seven halothane-treated monkeys.

† Values compared with those of the fourth microsphere infusion of the control group for significance tests.

‡ Significantly different ($P < 0.05$, t test) from the control group.§ Significantly different ($P < 0.01$, t test) from the control group.

the left ventricular catheter. The suspensions, containing 5,000 to 15,000 microspheres ($1-3 \times 10^6$ counts/min of isotope) are mixed with blood in the left ventricle and are distributed to each organ and tissue in direct proportion to its blood flow. The microspheres are trapped in the organ arterioles. Recent studies by Hoffbrand and Forsyth⁴ have verified the sensitivity and reliability of this technique, and have estimated that only about 0.1 per cent of the arteriolar tree of the monkey is embolized per infusion. The following nuclide-labeled microspheres were used: ¹²⁵I, ¹⁴¹Ce, ⁵¹Cr, ⁸⁵Nb, and ⁸⁶Sr, thus enabling five separate blood flow determinations in the same animal. Cardiac output was measured before each microsphere injection, so that absolute determinations of regional blood flow and resistance could be calculated.

At the end of each experiment the animal was sacrificed with an injection of sodium

pentobarbital and 26 organs and tissues were removed, weighed, and placed in glass vials. The radioactivity of each vial was counted for four minutes using a Nuclear Chicago well-type scintillation counter. The radioactivity present in all of the tissues of major organs was counted, but only that in portions (20 to 25 per cent of total weight) of skeletal muscle, limb bone, skin, chest wall, skull, and spine was counted. The remaining tissues (about 2 per cent of the total body weight) were also counted, so that total-body radioactivity could be calculated. The amounts of calculated total-body radioactivity agreed well (± 10 per cent) with the measured amounts injected.

Energy distribution patterns were recorded on a pulse-height analyzer set to divide the output of the scintillation counter into 100 channels of 10 keV each. Since each of the nuclides used has a gamma emission spectrum

with a characteristic peak within the 0–1,000 keV range, the amount of radioactivity for each organ could be determined. The counts from each channel were recorded on paper punch tape and subsequently transferred to magnetic tape to enable the calculations of the amounts of each nuclide in each tissue to be performed with an IBM 360 computer. Corrections were made for those isotopes that have known "spill-over" into other channels. The percentage of cardiac output to each organ was calculated as the amount of each nuclide's radioactivity in that organ, divided by the total body count of that nuclide. Flow to each organ was the percentage of the cardiac output times the cardiac output calculated from dye-dilution curves.

Organ resistance was calculated as the mean driving pressure (mean systemic arterial pressure minus central venous pressure) divided by the flow (liters/min) to that organ. Thus, the calculations of organ resistance assume that the arterial-venous pressure gradient in each organ is similar to that of the systemic measurements. While this assumption should be valid in most organs, the calculated resistance values in the coronary bed and in those organs contributing to portal-vein flow will be less valid.

The baseline regional values in the experimental and control groups were very similar to those previously reported by Hoffbrand and Forsyth,⁴ and are not repeated here. Changes in the proportion of the cardiac output, blood flow, and resistance/100 g tissue in each organ for each monkey during halothane anesthesia were expressed as percentages of the baseline values. These changes were compared with similarly calculated changes in the control group with the nonparametric Mann-Whitney U test.⁵ The mean values of the systemic measurements before each microsphere infusion were compared directly with those of the control group using the *t* test.

Results

The hemodynamic values in the seven control and seven normothermic experimental monkeys are shown in table 1. There were no significant changes in central venous and left ventricular end-diastolic pressures during anesthesia. Hematocrit values in both experimental and control groups were lower than

normal, ranging from 25 to 35 per cent. However, there was no significant difference between the two groups. Arterial P_{CO_2} , pH, and body temperature were maintained at values comparable to the animals' baseline values, thereby eliminating any influences of these variables on blood flow. Mean values of P_{CO_2} ranged from 36 to 40 mm Hg, while arterial pH values were between 7.42 and 7.46 in both control and experimental groups. There was a nonsignificant decrease in spontaneous respiratory rate, from a mean baseline value of 32/min to 27/min during 1.2 per cent halothane.

The regional blood flow values, expressed as percentages of the values obtained at the first microsphere injection, are shown for those major organs that had significant changes in the proportions of cardiac output delivered to them (table 2). The eyes and stomach received significantly less of the cardiac output and had increased resistance throughout anesthesia. The mesentery showed little change at 0.8 per cent halothane but received a significantly smaller proportion of cardiac output during both spontaneous and controlled ventilation at 1.2 per cent halothane. The other 11 organs had no significant changes in the proportions of cardiac output they received or their resistances, so their blood flows decreased in proportion to the decrease in cardiac output. These organs were the duodenum, jejunum, ileum, large intestine, cecum, spleen, liver (hepatic artery), spine, diaphragm, thyroid, and samples of lymph nodes.

At both levels of halothane anesthesia there were parallel decreases in percentages of cardiac output and blood flow to the heart and increases in coronary resistance. Subdivisions of the heart (atria, left and right ventricles, and septum) showed similar distributional alterations and, therefore, blood flow and resistance changes. Different subdivisions of limb, bone, skin, and skeletal muscle were similarly affected. However, in the brain the proportions of cardiac output and blood flow to the cerebellum and brain stem were consistently higher (and never significantly less than baseline values) throughout anesthesia, compared with the right and left hemispheres and the diencephalon. Although insertion of the left ventricular catheter through the left carotid artery necessitated tying off the latter, no

TABLE 2. Mean Regional Circulatory Changes in Organs Showing Most Significant Changes in Seven Monkeys Compared with Baseline Values during Halothane Anaesthesia*

	Group†	Cardiac Output (Per Cent)		Flow/ml/100 g		Resistance/100 g	
		Mean	SD	Mean	SD	Mean	SD
Heart	0.8 S	71§	15	51§	18	143	64
	0.8 C	70§	17	49§	19	147†	50
	1.2 C	61§	23	37§	22	171†	66
	1.2 S	65§	63	39§	17	148†	45
Brain	0.8 S	92	16	64§	9	105	27
	0.8 C	95	16	65§	18	104	21
	1.2 C	151§	25	89	40	64§	20
	1.2 S	123	27	71§	15	76§	14
Kidney	0.8 S	146§	25	106	33	68†	31
	0.8 C	143§	35	101	44	72§	24
	1.2 C	162§	35	92	46	60§	19
	1.2 S	144§	38	87	40	67§	21
Skin	0.8 S	118	25	86	27	90	59
	0.8 C	110	21	76	19	94	41
	1.2 C	65§	24	38§	20	167†	77
	1.2 S	85	27	51§	21	113	29
Skeletal muscle	0.8 S	49§	12	34§	12	208§	74
	0.8 C	48§	19	33§	17	233§	102
	1.2 C	47§	12	25§	11	211§	57
	1.2 S	59§	12	34§	10	157§	30
Limb bone	0.8 S	170†	65	124	57	64†	34
	0.8 C	153	67	107	50	76†	38
	1.2 C	144	63	83	49	76†	31
	1.2 S	180§	52	105	32	53§	15
Lungs (bronchial artery)	0.8 S	324§	216	223§	122	40§	30
	0.8 C	491§	522	300§	259	41§	35
	1.2 C	404§	216	221†	125	31§	23
	1.2 S	359§	275	202†	130	35§	20
Pancreas	0.8 S	71§	9	49§	6	134	27
	0.8 C	67§	11	45§	7	146	23
	1.2 C	52§	11	29§	12	186†	51
	1.2 S	58§	11	34	10	158†	21
Adrenals	0.8 S	141†	62	105	57	83	55
	0.8 C	185†	76	136	78	72	65
	1.2 C	257†	118	156	112	52†	50
	1.2 S	194†	99	117	68	65†	55
Chest wall	0.8 S	41§	13	29§	9	250§	111
	0.8 C	47§	11	32§	7	212§	37
	1.2 C	37§	9	20§	5	261§	56
	1.2 S	48§	17	28§	9	200§	54
Skull	0.8 S	223§	110	155	80	51§	20
	0.8 C	200§	88	135	53	56§	21
	1.2 C	145†	77	82	48	80†	42
	1.2 S	203§	86	117	44	51§	21
Fat	0.8 S	51§	9	35	5	186§	35
	0.8 C	46§	19	31§	14	238§	84
	1.2 C	27§	11	15§	7	389§	147
	1.2 S	37§	15	21§	8	285§	135

* Values are percentages of baseline values.

† 0.8 and 1.2 = per cent end-expired halothane; S = spontaneous ventilation; C = controlled ventilation.

‡ Significantly different ($P < 0.05$, Mann-Whitney U test) from control group changes.§ Significantly different ($P < 0.01$, Mann-Whitney U test) from control group changes.

preferential flow to the right hemisphere, compared with the left hemisphere was observed.

The data from four monkeys (not included in table 1) indicated that when rectal temperature was not maintained, the average decrease was 0.75 C/hour, resulting in more than a 2-C decrease by the end of the experiment. These monkeys had initial values similar to those in the temperature-maintained group, but arterial pressure and cardiac output progressively decreased, compared with the temperature-maintained group, during the course of the experiment. At 1.2 per cent halothane mean arterial pressures averaged 24 mm Hg, cardiac output values 89 ml/min/kg, and heart rates 75 beats/min in the hypothermic animals. The very severe decrease in systemic pressure and cardiac output in these monkeys indicate the necessity of maintaining body temperature, especially during deeper halothane anesthesia. There were similar changes in the redistribution of cardiac output. However, because output decreased much more drastically, particularly at 1.2 per cent halothane in this group, the reductions in regional blood flow were correspondingly greater. In contrast to the temperature-maintained group, in the hypothermic group proportion of output to skin decreased to 45 per cent of the baseline value at the second microsphere infusion and remained at 41 to 57 per cent of baseline throughout anesthesia.

There were no significant changes in the distribution of cardiac output in the control group during the course of the experiment. The largest change in distribution to the organs receiving more than 1 per cent of the cardiac output was an increase of 14 per cent to limb bone at the third microsphere injection. For those organs receiving less than 1 per cent of the cardiac output, the largest change was a 27 per cent increase to the adrenals at the fourth microsphere injection. These changes have been reported previously.⁴

Absolute values of blood flow/100 g tissue in some of the major organs at the first and second (0.8 per cent halothane, spontaneous ventilation) microsphere injections of the seven control and seven normothermic monkeys are shown in table 3. The values for the halothane group tended to start at higher levels, due to the initially higher cardiac output.

Discussion

The radioactive microsphere method used in this report has the advantage of permitting quantitative serial determinations of blood flow to organs and tissues simultaneously in awake as well as anesthetized animals. This method, however, does not allow continuous measurements in any one organ, as do electromagnetic flowmeters and plethysmography. Thus, the data in this study do not measure any early or fluctuating changes that may occur during anesthesia.

The duration of anesthesia, which in this study lasted three hours, may also affect the interpretation of results, since the anesthetic levels were administered in a fixed order. Several studies⁶⁻⁸ have indicated that there are time-dependent hemodynamic changes during halothane-oxygen anesthesia. One of these studies⁷ noted that major time-dependent changes occurred only after five hours of anesthesia; thus, it seems unlikely these influences were a major factor in our results.

Although arterial P_{CO_2} and pH values were not significantly affected by halothane, the very high P_{O_2} levels resulting from the oxygen administered cannot be completely dissociated from the changes produced by halothane. The inhalation of 100 per cent O_2 has no effect on hepatic flow,⁹ but does reduce renal blood flow somewhat.¹⁰ Cerebral circulation is not affected by the inhalation of 100 per cent O_2 provided P_{aCO_2} remains normal. Reivich¹¹ saw no effect on cerebral blood flow in monkeys over a wide P_{aO_2} range (60-380 mm Hg). Similar results were obtained by Lambertsen in man.¹² The concentrations of halothane employed in most studies are inspired concentrations, whereas we measured end-expired halothane concentrations. The latter method is believed to reflect more accurately a constant depth of anesthesia,¹³ but introduces another variable in attempts to compare the results of this study with those of other studies.

The various hemodynamic effects of halothane compiled in table 1 have been well established and have been the subject of a recent review.¹⁴ The decreases in systemic blood pressure, cardiac output, and total peripheral resistance, as well as a negative chronotropic effect, have been observed in

TABLE 3. Absolute Values of Blood Flow (ml/100 g) in Some Organs in Response to 0.8 Per Cent Halothane during Spontaneous Ventilation

	Group*	Baseline		Halothane, 0.8 Per Cent	
		Mean	SD	Mean	SD
Heart	C	366	142	340	195
	II	477	174	245	129
Brain	C	75	19	74	19
	II	98	16	63	13
Kidney	C	1,121	544	1,129	526
	II	1,731	374	1,770	473
Skin	C	25	5	23	4
	II	27	9	22	9
Skeletal muscle	C	29	10	27	9
	II	19	5	6	2
Gastrointestinal tract†	C	78	30	76	32
	II	93	24	59	13
Total splanchnic bed‡	C	134	32	130	28
	II	142	45	98	28
Liver (hepatic artery)	C	41	37	52	34
	II	69	14	44	19
Lung (bronchial artery)	C	34	31	33	26
	II	25	12	49	20
Adrenals	C	267	104	308	37
	II	222	86	225	157
Chest wall	C	28	9	25	10
	II	28	6	9	4

* C = Seven control monkeys; II = Seven monkeys anesthetized with halothane.

† Includes stomach, small intestine, large intestine, and cecum.

‡ Includes gastrointestinal organs, spleen, pancreas, and mesentery.

both man and animals. That left-ventricular end-diastolic pressure is not altered by halothane has also been observed by Hamilton *et al.*¹⁵ in dogs. Our findings in the monkey are consistent with these previous studies.

In studies of the effects of halothane upon myocardial perfusion,^{16, 17} there is general agreement that coronary blood flow is reduced. Our results concur with these findings. At all levels of anesthesia, regardless of the type of ventilation employed, consistent significant decreases in the proportion of cardiac output and coronary flow were observed, along with an increase in coronary resistance. The percentage decrease in coronary blood flow at each level of anesthesia was very simi-

lar to the percentage decrease in left ventricular work.

At 0.8 per cent halothane there was little change in the proportion of the cardiac output received by the brain; thus, blood flow decreased in proportion to the decrease in cardiac output. The decrease in cerebral blood flow was most marked at the lower (0.8 per cent) halothane concentration. This finding is in agreement with the work of Wollman *et al.*,¹⁸ which showed a consistent pattern of decreased cerebral blood flow in man during light anesthesia and increasing cerebral perfusion as anesthesia deepens. Cerebral vascular resistance decreased at 1.2 per cent halothane. It is unclear whether this resulted from auto-

regulatory mechanisms or from a direct vasodilating effect of halothane.^{14, 19-21} When blood flow to the brain was decreased, the cerebral hemispheres and the diencephalon were affected most, while the brain stem and the cerebellum continued to be perfused normally. In humans, a decrease in hemispheric blood flow with a concurrent decrease in vascular resistance has been shown.²²

Deutsch *et al.*,²³ using a para-aminohippurate clearance method, found a 38 per cent reduction in effective renal blood flow and a calculated 69 per cent increase in resistance when 1.5 per cent (inspired) halothane was administered to healthy men. Their results suggested that some vasoconstriction occurred in the efferent arterioles. Westermark and Wahlen²⁴ measured renal venous flow in the cat by means of a drop-recording technique. With few exceptions, halothane caused a reduction of renal vascular resistance during increasing anesthetic depth, and they ascribe this to autoregulation and depression of sympathetic activity. Our results, similarly, showed renal blood flow to be well maintained as a result of decreased vascular resistance and a marked increase in the proportion of cardiac output received. Hoffbrand and Forsyth⁴ recently showed that microspheres in the descending aorta do not preferentially stream past the orifices of the renal artery, since after left ventricular injection there were very similar concentrations of microspheres in renal and femoral arterial blood.

Total hepatic blood flow (hepatic artery and portal vein) in humans^{25, 26} and in animals²⁷⁻²⁹ is reduced by halothane. In this study splanchnic blood flow (portal vein) was decreased without a significant change in calculated vascular resistance. From similar findings in humans, Epstein and co-workers²⁵ concluded that the reduction in the blood flow is due to a decline in perfusion pressure secondary to arterial hypotension. These investigators also found that controlled respiration caused a significant reduction in flow and an increase in vascular resistance. This phenomenon was not manifested in the monkey. Dogs under halothane anesthesia and monitored by electromagnetic flowmeters have shown reduced hepatic arterial flow and resistance.^{24, 29} However, we found reductions

in blood flow which were proportional to the decreases in cardiac output and, thus, resistance remained unchanged.

We found little change in blood flow to the skin at the lower halothane concentration and a marked decrease in flow at the higher concentration. This finding is somewhat in agreement with results reported by Westermark,²⁹ who recorded an initial increase in cutaneous flow in the cat, which decreased to below the control level as depth of anesthesia was increased. As might be expected, we found that core temperature plays an important role in regulation of blood flow to the skin. The four monkeys in which body temperatures were allowed to fall had significant vasoconstriction and decreased flow with 0.8 per cent halothane; further vasoconstriction occurred with a 1.2 per cent concentration.

Westermark²⁹ also found increased resistance and decreased blood flow in muscle at every level of anesthesia. He proposed that the increased vascular resistance in muscle is possibly a reflexly-induced compensation for falling blood pressure. Lindgren *et al.*³¹ and Ngai and Bolme³² also found increased vascular resistance in cat and dog limbs, respectively. Brody and co-workers^{33, 34} demonstrated, in the dog, that the halothane-induced increase in vascular resistance in muscles resulted indirectly from liberation of the anti-diuretic hormone, vasopressin. Two studies in man^{25, 26} using plethysmographic measurements on intact limbs disagree as to the direction of the change in blood flow. Our study indicates there are decreases in blood flow and increases in vascular resistance in all skeletal muscle, and in the chest wall, at both levels of anesthesia.

No previous studies of the influence of halothane on bronchial arterial flow have been reported. Silber³⁷ noted an increase in regional pulmonary blood flow during spontaneous respiration with ether and nitrous oxide anesthesia; the flow decreased during controlled respiration. A change from spontaneous to controlled respiration caused no alteration in bronchial arterial blood flow in our study. Halothane has been shown to produce an increased blood flow in the pulmonary circulation.²⁸ In the monkey there was an increase in bronchial arterial flow to the lungs and a

decrease in vascular resistance. However, caution must be exercised in interpreting these results, as the lungs via the bronchial artery receive only a small proportion of cardiac output (about 0.9 per cent in the monkey⁴). Thus, the blood flow is low and the number of microspheres passing to the lungs is small, rendering these measurements less reliable than those of well-perfused organs. Similar considerations apply to other organs reported in this study, such as the adrenals, thyroid, and collected samples of fat and lymph nodes.

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Obstetrics

HYDRALAZINE, MATERNAL BLOOD PRESSURE AND FETAL CIRCULATION Hydralazine (Apresoline) is used therapeutically in toxemia of pregnancy to lower arterial blood pressure. The hypotensive effect has been reported to be associated with increases in cardiac output and in renal, cephalic, femoral, and splanchnic blood flows. The effects on uteroplacental and fetal circulations of hydralazine injected either into the mother or into the fetus or the neonate were investigated in near-term normotensive pregnant sheep. Intravenous doses of 0.2-0.5 mg/kg given to the mother decreased maternal arterial pressure and uterine blood flow to equivalent degrees; uterine vascular resistance did not change. Although fetal cardiovascular function was not appreciably affected, fetal blood P_{O_2} decreased significantly in the face of no change in maternal arterial P_{O_2} . When injected directly into the fetal circulation, hydralazine reduced fetal arterial pressure only after the administration of a dose 10 to 15 times that given to the mother; no alterations occurred in the fetal blood flow measured in the ascending aorta, the ductus, or the main pulmonary artery; fetal blood gases and pH remained unchanged. The lack of responsiveness of the fetus at term to direct administration of hydralazine suggests that the receptors acted upon by this drug may be incompletely developed (at least in the sheep) or that the magnitude of the placental circulation (a low-resistance system which contains the major portion of fetal blood volume) masks the magnitude of the vascular response within the fetus proper. Evidence for this is suggested by the fact that injection of hydralazine into the fetal circulation after the cord is clamped does produce a modest, albeit measurable, rise in blood pressure. (Larner, C. N., Weston, P. V., Brinkman, C. R., III, and Assali, N. S.: *Effects of Hydralazine on Uteroplacental and Fetal Circulation*, *Amer. J. Obstet Gynec.* 108: 375-381 (Oct.) 1970.) EDITOR'S COMMENT: This represents a valuable study toward a fundamental understanding of differences between the responses of maternal and fetal circulations to hypotensive drugs. Caution must be exercised when transferring these data obtained in normotensive animals to the hypertensive pregnant subject. The authors do indicate that such studies in hypertensive animals and patients are presently under way. We look forward to these data with great interest.