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Anesthetic Influences on Regional Hemodynamics in Normal and Hemorrhaged Rats

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Forty-six male Sprague–Dawley rats were divided in five groups: awake animals and those receiving ketamine, halothane, enflurane, or isoflurane anesthesia. Cannulae were inserted into the left femoral artery and vein and the left ventricle. Inspired concentrations of the volatile anesthetics were adjusted to achieve the minimal alveolar concentration (MAC) of each drug. Ketamine, 125 mg·kg^{-1}, was injected intraperitoneally and then infused at a rate of 1 mg·kg^{-1}·min^{-1}. All animals breathed spontaneously throughout the experiment ($F_{I_{O_2}}$ = 0.3). Following a 2-h stabilization period, 30% of estimated blood volume was withdrawn gradually over 10 min. Immediately before and 20 min after hemorrhage, cardiac output and regional blood flows were measured by the microsphere method (^{85}Sr, ^{141}Ce-labeled 15-μm microspheres, respectively). Arterial blood samples were analyzed for P_{O_2}, P_{CO_2}, *p*H, lactate, and pyruvate at these times also. Prior to hemorrhage, cardiac output (CO) values were similar in awake rats and those receiving ketamine or isoflurane, but CO was reduced moderately by enflurane and to a greater extent by halothane. After hemorrhage, CO was greatest in awake animals and those receiving isoflurane, and awake rats tended to have the greatest organ blood flows. Values of lactate/pyruvate and excess lactate were least in awake animals. Overall results suggested that, in terms of cardiac output and regional blood flows, ketamine approximates the awake state most closely in normovolemic animals, whereas isoflurane anesthesia is most like the awake condition after hemorrhage. (Key words: Enflurane. Halothane. Hemodynamics. Hemorrhage. Isoflurane. Ketamine. Microspheres. Regional blood flow.)

GENERAL ANESTHETICS alter both cardiac function and peripheral circulatory control, resulting in significant changes in cardiac output and/or organ blood flows in resting animals[1] and humans.[2] Anesthetics also influence cardiovascular responses to stresses such as hemorrhage.[3]

Although several studies have addressed questions relating to the peripheral circulatory actions of the anesthetics, most have measured organ blood flows in only a few organs and many have emphasized a single organ only. Others have compared several anesthetics but have not reported results for awake animals, so that comparisons to the awake state are not always possible.

In the present investigations, we determined cardiac output and regional blood flows in 20 tissues of awake rats and those anesthetized with either halothane, enflurane, isoflurane, or ketamine. Hemodynamic measurements were obtained in normovolemic animals to determine the influences of anesthetics on the unstressed cardiovascular system and measurements were repeated after hemorrhage in order to determine whether anesthetics altered the cardiovascular responses to stress. We asked two major questions in these studies: 1) in terms of cardiac output and regional blood flows, which anesthetic was most like the awake state in normovolemic animals, and 2) which anesthetic was most like the awake state after hemorrhage?

Materials and Methods

Forty-six male Sprague–Dawley rats (mean body weight 348 ± 4 g) were used to determine the influences of anesthetics on regional hemodynamics both before and after hemorrhage. Animals were divided into five groups based upon anesthetic exposure. Those anesthetized received either halothane (n = 9), enflurane (n = 8), isoflurane (n = 11), or ketamine (n = 9), while awake (n = 9) animals were studied after brief diethyl ether anesthesia in order to obtain vascular access. The volatile anesthetics were delivered in amounts sufficient to prevent purposeful movement during surgical preparation and thereafter the inspired concentration was adjusted to achieve the minimal alveolar concentration for that agent in rats (enflurane, 2.2 vol%[4]; halothane, 1.2 vol%; isoflurane, 1.4 vol%[5]), corrected for animal age and inspired to alveolar differences according to data reported by White *et al.*[5] Ketamine, 125 mg/kg, was administered intraperitoneally initially and supplemented with 60 mg/kg intraperitoneally 30 min later. Thereafter, ketamine was infused at a rate of 1 mg·kg^{-1}·min^{-1} throughout the experiment. All animals breathed oxygen enriched air ($F_{I_{O_2}}$ = 0.3) throughout. Those anesthetized breathed via a tracheostomy tube, while tracheostomy was not performed in the unanesthetized animals.

Polyethylene cannulae (PE-50) were inserted into a femoral artery and vein for arterial pressure and blood sampling and for the intravenous infusion of fluids and/or drugs respectively. Saline (containing heparin, 2 U/ml) was infused at the rate of 1.5 ml/hr in all animals (ketamine was added to the saline solutions in those receiving this drug). A polyethylene catheter (PE-50), which had been tapered to a tip diameter approximately

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that of PE-10 tubing, was inserted into the left ventricle through the right carotid artery, and the position was verified by pressure monitoring. Awake animals were treated identically to those anesthetized, except the cannulae were tunneled subcutaneously and exteriorized through the back and the wounds were covered with 2% lidocaine gel. The unanesthetized animals were restrained gently in a commercially available rat-restraining cage that was designed specifically for this purpose. The femoral arterial and left ventricular cannulae were connected to standard pressure transducers,‡ and arterial pressure was recorded continuously.

The protocol consisted of a 2-h period of stable anesthesia (or no anesthesia in the awake animals) after surgical preparation and thereafter 30 per cent of the estimated blood volume (shed blood volume = 1.8 ml/100 g of body weight) was withdrawn gradually over 10 min. The following were measured immediately before and 20 min after the end of hemorrhage: arterial P_{O_2}, P_{CO_2}, and *p*H, hematocrit, lactate, pyruvate, heart rate, cardiac output, and regional blood flows. Blood gas measurements were performed by a standard blood gas analyzer.§ Hematocrit was determined by the micromethod, and lactate and pyruvate were determined by an enzymatic method.[6] Cardiac output and regional blood flows were determined using the microsphere method.[1] Strontium-85 (^{85}Sr) or cerium-141 (^{141}Ce) labeled microspheres (15 ± 1 μm) were injected into the left ventricle, and the catheter was flushed with 0.4 ml saline. Approximately 40,000 microspheres were injected immediately before and again 20 min after hemorrhage. Cardiac output and regional blood flows were measured using the reference sample technique. Arterial blood was removed by a constant withdrawal pump (withdrawal rate 0.01 ml/s) for 10 s before and 60 s after the injection of microspheres. The rats were killed with intravenous KCl after the ^{141}Ce labeled microspheres had been injected and the organs were removed, blotted on filter paper, weighed, and placed in counting tubes. Radioactivity was determined in the following tissues: brain (subdivided into left cerebral hemisphere, right cerebral hemisphere, and cerebellum), heart, lungs, right kidney, left kidney, stomach, small bowel, cecum, large bowel, spleen, liver, diaphragm, cremaster muscle, rectus abdominus muscle, gastrocnemius muscle, tibialis anterior muscle, psoas muscle, and skin (aliquots of skin and liver were sampled due to the size of the organs). The injected radioactivity was determined by subtracting residual activity in the catheter and syringe from the initial activity. Radioactivity of the reference samples and organs was measured in a well-type gamma counter that corrected for overlap among isotopes.¶ Cardiac output (CO) was determined by the equation: CO = total injected activity × reference sample flow ÷ reference sample activity. Cardiac output was expressed as absolute flow in $ml \cdot min^{-1}$. Regional blood flow (QR) was determined by the equation: QR = organ activity × reference sample flow ÷ reference sample activity. QR was expressed as absolute flow in $ml \cdot min^{-1} \cdot 100\ g^{-1}$.

Portal venous blood flow was estimated as proposed by Ross and Daggy.[7] Organ vascular resistances were calculated as the quotient of mean arterial pressure and organ blood flow ($mmHg \cdot ml^{-1} \cdot min \cdot g$). Central venous pressure was assumed to be zero, and portal venous pressure was assumed to be 10 mmHg for these calculations.[8]

Statistical analyses were performed using Students *t* tests for paired data to compare values before and after hemorrhage within each group. One-way analysis of variance and Duncan's multiple range tests were used for multiple comparisons among groups before hemorrhage or after hemorrhage.[9] Cluster analysis was used to estimate the overall similarity of each treatment to the awake state.[10] All data are presented as the mean ± the standard error of the mean (SEM). Statistical significance was presumed to be present when there was no more than one chance in 20 that the null hypothesis had been rejected by chance alone ($P < 0.05$).

Several predetermined criteria were used to eliminate experiments that were considered unsuccessful because of technical difficulties. These included arterial oxygen tension values of less than 60 mmHg, non-uniform distribution of microspheres manifested by differences between left and right kidney blood flows of greater than 20% or evidence of shunting or migration of microspheres as indicated by the presence of increased radioactivity in the lungs.

Results

Results for systemic hemodynamics, calculated cardiac values and arterial blood values are summarized in table 1. Those for organ blood flows and regional vascular resistances are summarized in table 2.

Prior to hemorrhage the mean arterial pressure was similar in awake animals and those receiving ketamine, whereas this value was reduced significantly in those breathing isoflurane, halothane, or enflurane. Twenty

‡ Gould Statham Corporation, Hato Rey, Puerto Rico.

§ Radiometer BMS 3, PHM73, Radiometer America, Cleveland, Ohio.

¶ CompuGamma 1282-002, LKB Instruments Incorporated, Gaithersburg, Maryland.

TABLE 1. Hemodynamic and Arterial Blood Values

Variable	A	K	H	E	I	DMRT
MAP (mmHg)						
N	125 ± 4	119 ± 4	91 ± 3	82 ± 3	98 ± 2	AKIHE
HE	109 ± 5*	53 ± 2*	56 ± 2*	52 ± 1*	84 ± 3*	AIHKE
CO ($ml \cdot min^{-1}$)						
N	117 ± 7	126 ± 5	75 ± 4	97 ± 3	119 ± 5	KIAEH
HE	72 ± 6*	44 ± 3*	42 ± 2*	51 ± 3*	69 ± 3*	AIEKH
HR (min^{-1})						
N	465 ± 15	400 ± 20	344 ± 9	323 ± 6	380 ± 11	AKIHE
HE	486 ± 15	285 ± 15*	318 ± 8*	303 ± 7*	330 ± 11*	AIHEK
SV (ml)						
N	0.25 ± 0.01	0.32 ± 0.02	0.22 ± 0.01	0.28 ± 0.01	0.32 ± 0.01	IKEAH
HE	0.15 ± 0.01*	0.16 ± 0.01*	0.13 ± 0.01*	0.16 ± 0.01*	0.21 ± 0.01*	IEKAH
SVR (mmHg · $ml^{-1} \cdot min$)						
N	1.10 ± 0.08	0.95 ± 0.02	1.23 ± 0.07	0.86 ± 0.04	0.84 ± 0.04	HAKEI
HE	1.57* ± 0.11	1.26* ± 0.10	1.37 ± 0.08	1.05* ± 0.06	1.24* ± 0.07	AHKIE
RPP · 10^{-3} (beats · min^{-1} × mmHg)						
N	74.5 ± 4.0	59.1 ± 4.3	37.1 ± 1.8	33.1 ± 2.4	50.6 ± 2.2	AKIHE
HE	70.6 ± 4.3	18.9 ± 1.4*	22.2 ± 1.0*	21.3 ± 1.2*	41.9 ± 2.6*	AIHEK
Pa_{O_2} (mmHg)						
N	118 ± 3	102 ± 5	86 ± 6	82 ± 7	99 ± 5	AKIHE
HE	119 ± 4	116 ± 7*	110 ± 8*	87 ± 8	100 ± 6	AKHIE
Pa_{CO_2} (mmHg)						
N	28 ± 1	37 ± 2	44 ± 1	44 ± 2	32 ± 1	EHKIA
HE	24 ± 1	29 ± 3*	44 ± 1	39 ± 1*	30 ± 2*	HEIKA
H^+ (nEq/l)						
N	37.7 ± 1.0	44.2 ± 0.9	48.5 ± 1.6	44.5 ± 1.7	40.1 ± 1.1	HEKIA
(*p*H)	(7.42)	(7.35)	(7.31)	(7.35)	(7.40)	
HE	37.9 ± 1.1	43.1 ± 2.1	49.7 ± 1.6	43.8 ± 1.1	40.5 ± 1.2	HEKIA
(*p*H)	(7.42)	(7.37)	(7.30)	(7.36)	(7.39)	
Hct						
N	45 ± 0.4	44 ± 0.8	43 ± 1.0	43 ± 0.3	45 ± 0.7	AIKEH
HE	34 ± 0.7*	35 ± 0.8*	35 ± 0.8*	34 ± 0.5*	34 ± 0.5*	HKAEI
L/P						
N	12.4 ± 0.9	14.3 ± 1.3	15.6 ± 1.2	15.2 ± 1.0	18.3 ± 1.3	IHEKA
HE	16.6 ± 1.5	32.2 ± 5.1*	34.7 ± 6.1*	23.8 ± 0.4*	26.4 ± 1.7*	HKIEA
Excess lactate (mmol/l)						
HE	0.4 ± 0.2	1.5 ± 0.2*	1.5 ± 0.4*	1.1 ± 0.3*	1.0 ± 0.2*	HKEIA

Values are mean ± SEM.

* $P < 0.05$ *versus* normovolemic values.

A = awake; K = ketamine; H = halothane; E = enflurane; I = isoflurane; N = normovolemia; HE = 20 min after hemorrhage. Groups underlined by the same line are not significantly different from each other ($P > 0.05$) by Duncan's Multiple Range Test (DMRT). Groups are ordered from left to right in decreasing order of magnitude or alphabetical order when values are identical.

minutes after hemorrhage the mean arterial pressure was reduced significantly in all groups, but the values were greatest in those awake or breathing isoflurane, while arterial pressure was significantly less in those receiving halothane, ketamine, or enflurane. Prior to hemorrhage, cardiac output values were similar in awake animals and those treated with ketamine or isoflurane, but these values were reduced moderately by enflurane and to a greater extent by halothane. Hemorrhage reduced cardiac output in all groups, but cardiac output after hemorrhage was greatest in the awake animals and those breathing isoflurane, whereas it was reduced to similar values in those receiving enflurane, ketamine, or halothane. The anesthetics altered heart rate significantly both before and after hemorrhage. Prior to bleeding, there were individual variations among groups, but the overall net effect was a significant decrease in heart rate produced by both ketamine and the inhalation anesthetics. Hemorrhage tended to increase heart rate in awake animals, although this tendency did not reach statistical significance. In contrast, heart rate slowed in response to hemorrhage in all those anesthetized. During normovolemia, the stroke volume values were different among the various treatment groups, but the overall interpretation was for stroke volume to be greatest in animals receiving isoflurane or ketamine anesthesia as compared with awake animals or those breathing halothane. Stroke volume was reduced significantly in all groups after hemorrhage, but the value for stroke volume was significantly greater in those receiving isoflurane as compared with all others. Prior to hemorrhage, systemic vascular resistance was reduced significantly in animals receiving enflurane or isoflurane but was not different from awake in those receiving ketamine or halothane. After hemorrhage, systemic vascular resistance increased significantly in awake animals and those receiving ketamine, enflurane, and isoflurane. Before hemorrhage, the rate-pressure product (the product of heart rate and systolic arterial pressure) was greatest in awake animals and was reduced significantly by each of the anesthetics, although the reduction was greatest in those receiving halothane or enflurane. The rate-pressure product was not altered after hemorrhage in awake animals but it was decreased significantly by each of the anesthetics. Among the anesthetics, the rate-pressure product was greatest in those receiving isoflurane and reduced to similar values (approximately one-half of the isoflurane value) by halothane, enflurane, or ketamine.

Values for the various measurements that were performed on arterial blood are summarized in the lower part of table 1. In general, arterial oxygen tension was greatest in awake animals and least in those receiving halothane or enflurane. After hemorrhage, there was an increase in arterial oxygen tension in those anesthetized with ketamine or halothane. Before hemorrhage, arterial P_{CO_2} values were similar in awake animals and those receiving isoflurane. Arterial P_{CO_2} was increased by each of the other anesthetics, with the greatest values occurring in animals receiving halothane or enflurane. In general, the trend was for a reduction in arterial P_{CO_2} after hemorrhage, and this decrease was statistically significant in those receiving ketamine, enflurane, or isoflurane. After hemorrhage, animals receiving halothane and enflurane demonstrated significantly increased arterial P_{CO_2} values as compared with those receiving ketamine or isoflurane or those awake. The hydrogen ion concentrations tended to vary directly with the P_{CO_2} values before hemorrhage, with the greatest hydrogen ion concentrations occurring in animals receiving halothane and enflurane and the least occurring in awake animals. Hydrogen ion concentration was unchanged 20 min after hemorrhage in all groups. Hematocrit values were generally similar both before and after hemorrhage, with the major impact being a significant reduction in hematocrit in all groups after bleeding. The lactate/pyruvate ratios were generally similar prior to hemorrhage, although the value for isoflurane was significantly greater than that in awake animals. The lactate/pyruvate values increased in all anesthetized animals after hemorrhage, whereas this value did not change in awake animals. The values for excess lactate were significantly greater, as compared with those in awake rats, in animals receiving halothane or ketamine.

Regional Blood Flow and Vascular Resistance

Results for measured regional blood flows and calculated vascular resistances are summarized in table 2. Values for the brain are reported only for the left cerebral hemisphere and the cerebellum, because the values for the right hemisphere were altered significantly by the presence of the catheter in the carotid artery (table 3).

Prior to hemorrhage, blood flow to the left cerebral hemisphere was similar in awake animals and those receiving ketamine, but this value was increased by enflurane, halothane, or isoflurane. After hemorrhage, left hemispheric blood flow was unaltered in awake animals but was reduced significantly in those receiving ketamine, halothane, or enflurane, and there was a trend for a reduction in those receiving isoflurane, although this value did not reach statistical significance. Although the absolute values for flow were somewhat greater in the cerebellum as compared with the left hemisphere, the general trend of responses was similar for both regions. In both cerebellum and cerebrum, the patterns for vascular resistance were similar both before

TABLE 2. Organ Blood Flows (ml·min^{-1}·100 g^{-1}) and Organ Vascular Resistances (mmHg·ml^{-1}·min·g)

Organ	A	K	H	E	I	DMRT
Cerebrum						
Flow						
N	90 ± 5	113 ± 11	186 ± 23	150 ± 14	194 ± 17	IHEKA
HE	100 ± 8	64 ± 7*	131 ± 12*	106 ± 8*	160 ± 17	IHEAK
Resist						
N	142 ± 7	112 ± 7	48 ± 3	60 ± 9	55 ± 5	AKEIH
HE	112 ± 7*	91 ± 8	46 ± 5	52 ± 5	58 ± 8	AKIEH
Cerebellum						
Flow						
N	101 ± 5	91 ± 9†	227 ± 37	208 ± 27†	266 ± 22†	IHEAK
HE	122 ± 12‡	69 ± 6*	158 ± 18	142 ± 10*‡	241 ± 26‡	IHEAK
Resist						
N	126 ± 4	139 ± 12	47 ± 6	46 ± 8	44 ± 4	KAHEI
HE	96 ± 8*	82 ± 9*	38 ± 4	38 ± 3	45 ± 7	AKIEH
Heart						
Flow						
N	501 ± 47	290 ± 30	197 ± 26	224 ± 21	437 ± 47	AIKEH
HE	758 ± 126*	176 ± 20*	163 ±14	145 ± 13*	436 ± 69	AIKHE
Resist						
N	27 ± 2	45 ± 5	51 ± 6	36 ± 2	26 ± 4	HKEAI
HE	19 ± 4*	35 ± 7*	36 ± 3*	40 ± 6	22 ± 3	EHKIA
Kidney						
Flow						
N	710 ± 42	674 ± 25	551 ± 54	505 ± 30	584 ± 32	AKIHE
HE	438 ± 33*	275 ± 16*	267 ± 17*	246 ± 10*	350 ± 19*	AIKHE
Resist						
N	18 ± 1.2	17 ± 0.4	18 ± 1.9	17 ± 1.1	17 ± 0.9	AHEIK
HE	26 ± 2.1*	20 ± 1.8	21 ± 1.1	22 ± 1.1*	25 ± 1.8*	AIEHK
Stomach						
Flow						
N	97 ± 11	166 ± 14	44 ± 4	73 ± 4	92 ± 7	KAIEH
HE	42 ± 5*	34 ± 3*	27 ± 2*	30 ± 1*	37 ± 3*	AIKEH
Resist						
N	136 ± 20	68 ± 5	198 ± 22	101 ± 4	104 ± 11	HAIEK
HE	253 ± 24*	134 ± 14*	180 ± 11	144 ± 8*	214 ± 22*	AIHEK
Small bowel						
Flow						
N	306 ± 16	387 ± 28	188 ± 17	267 ± 16	268 ± 21	KAIEH
HE	163 ± 16*	147 ± 11*	133 ± 7*	159 ± 6*	174 ± 7*	IAEKH
Resist						
N	38 ± 3	29 ± 2	47 ± 5	27 ± 1	35 ± 3	HAIKE
HE	67 ± 11*	31 ± 3	35 ± 2	27 ± 1	43 ± 3*	AIHKE

TABLE 2. (*Continued*)

Organ	A	K	H	E	I	DMRT
Cecum						
Flow						
N	261 ± 29	252 ± 29	147 ± 11	198 ± 11	257 ± 21	AIKEH
HE	132 ± 25*	102 ± 17*	72 ± 8*	111 ± 9	149 ± 15*	IAEKH
Resist						
N	48 ± 5	48 ± 6	60 ± 7	37 ± 3	37 ± 3	HAKEI
HE	95 ± 21*	50 ± 8	70 ± 9	40 ± 4	55 ± 7*	AHIKE
Large bowel						
Flow						
N	138 ± 19	108 ± 11	76 ± 8	101 ± 15	130 ± 16	AIKEH
HE	88 ± 12*	44 ± 4*	56 ± 5*	58 ± 7*	85 ± 9*	AIEHK
Resist						
N	100 ± 17	108 ± 10	116 ± 12	84 ± 14	79 ± 10	HKAEI
HE	125 ± 13	107 ± 16	87 ± 8	92 ± 23	95 ± 11*	AKIEH
GI tract						
Flow						
N	232 ± 14	279 ± 17	131 ± 10	187 ± 11	208 ± 13	KAIEH
HE	123 ± 13*	101 ± 8*	90 ± 3*	108 ± 4*	129 ± 7*	IAEKH
Resist						
N	51 ± 4	40 ± 2	65 ± 6	39 ± 2	45 ± 4	HAIKE
HE	89 ± 13*	45 ± 5	52 ± 2	40 ± 2	59 ± 5*	AIHKE
Spleen						
Flow						
N	92 ± 16	173 ± 25	122 ± 19	169 ± 24	126 ± 16	KEIHA
HE	42 ± 5*	31 ± 4*	51 ± 7*	77 ± 6*	124 ± 22	IEHAK
Resist						
N	153 ± 25	73 ± 8	79 ± 11	50 ± 8	86 ± 14	AIHKE
HE	267 ± 36*	151 ± 18*	103 ± 13*	57 ± 6	74 ± 13	AKHIE
Portal vein						
Flow						
N	118 ± 8	157 ± 10	80 ± 6	107 ± 4	120 ± 7	KIAEH
HE	62 ± 7*	53 ± 4*	55 ± 2*	61 ± 2*	77 ± 4*	IAEHK
Hepatic art.						
Flow						
N	30 ± 4	8 ± 1	30 ± 5	17 ± 1	31 ± 4	IAHEK
HE	40 ± 4*	16 ± 2*	17 ± 3*	16 ± 2	34 ± 3	AIHEK
Resist						
N	411 ± 51	1,760 ± 317	353 ± 49	499 ± 34	358 ± 46	KEAIH
HE	271 ± 42*	335 ± 43*	384 ± 49	361 ± 43*	260 ± 16*	HEKAI
Total hepatic						
Flow						
N	151 ± 8	165 ± 10	111 ± 11	124 ± 5	152 ± 6	KIAEH
HE	102 ± 9*	70 ± 5*	72 ± 5*	77 ± 3*	111 ± 4*	IAEHK

TABLE 2. (*Continued*)

Organ	A	K	H	E	I	DMRT
Skin						
Flow						
N	11 ± 0.9	17 ± 1.9	7 ± 1.0	12 ± 0.7	15 ± 1.1	KIEAH
HE	5 ± 0.5*	3.0 ± 0.5*	3 ± 0.4*	4 ± 0.3*	3 ± 0.7*	AEHIK
Resist						
N	1,216 ± 119	755 ± 66	1,436 ± 232	679 ± 49	694 ± 84	HAKIE
HE	2,342 ± 184*	1,719 ± 183*	1,931 ± 175*	1,405 ± 123*	2,070 ± 239*	AIHKE
Diaphragm						
Flow						
N	98 ± 22	47 ± 7	28 ± 4	32 ± 3	32 ± 3	AKEIH
HE	72 ± 9	36 ± 4	34 ± 3*	39 ± 4*	34 ± 4	AEKHI
Resist						
N	176 ± 33	291 ± 31	377 ± 50	271 ± 25	324 ± 34	HIKEA
HE	166 ± 17	158 ± 15*	175 ± 14*	144 ± 14*	271 ± 32	IHAKE
Cremaster M.						
Flow						
N	6 ± 1.9	7 ± 1.2	3 ± 0.6	7 ± 1.0	8 ± 1.3	IEKAH
HE	4 ± 0.4	4 ± 0.4*	3 ± 0.3	3 ± 0.4*	3 ± 0.4*	AKEHI
Resist						
N	3,510 ± 822	2,330 ± 453	4,853 ± 1359	1,530 ± 247	1,777 ± 335	HAKIE
HE	2,672 ± 322	1,563 ± 160	2,076 ± 200	1,724 ± 221	2,767 ± 306*	IAHEK
Rectus abdom. M.						
Flow						
N	13 ± 2.5	6 ± 0.7	3 ± 0.4	4 ± 0.6	5 ± 0.8	AKIEH
HE	6 ± 0.9*	4 ± 0.5*	3 ± 0.2	5 ± 0.5*	8 ± 2.2	IAEKH
Resist						
N	1,386 ± 363	2,267 ± 378	3,972 ± 536	2,209 ± 285	2,327 ± 352	HIKEA
HE	1,988 ± 277	1,366 ± 192	1,873 ± 274*	1,044 ± 90*	1,399 ± 258*	AHIKE
Gastrocnemius M.						
Flow						
N	8 ± 1.4	11 ± 2.0	3 ± 0.4	5 ± 0.9	6 ± 0.9	KAIEH
HE	5 ± 0.5*	7 ± 1.6*	5 ± 0.5*	6 ± 0.8	8 ± 0.9	IKEAH
Resist						
N	2,944 ± 1,129	1,452 ± 367	3,189 ± 395	1,806 ± 252	2,270 ± 549	HAIEK
HE	2,308 ± 226	1,734 ± 865	1,091 ± 117*	1,040 ± 131*	1,198 ± 170	AKIHE
Tibialis M.						
Flow						
N	17 ± 3.5	16 ± 2.2	3 ± 0.5	4 ± 0.5	5 ± 1.1	AKIEH
HE	7 ± 1.0*	7 ± 1.8*	6 ± 0.7*	6 ± 1.2*	7 ± 1.5	AIKEH
Resist						
N	1,086 ± 264	882 ± 113	3,501 ± 570	2,586 ± 327	2,360 ± 411	HEIAK
HE	1,708 ± 239	1,477 ± 698	917 ± 170	1,044 ± 209*	1,402 ± 226	AKIEH

TABLE 2. (*Continued*)

Organ	A	K	H	E	I	DMRT
Psoas M.						
Flow						
N	20 ± 3.2	13 ± 1.9	5 ± 0.7	5 ± 0.8	7 ± 1.1	AKIEH
HE	12 ± 1.6*	6 ± 0.9*	6 ± 0.4	7 ± 0.8*	9 ± 1.3	AIEHK
Resist						
N	923 ± 242	1,113 ± 230	1,994 ± 286	1,971 ± 264	1,711 ± 202	HEIKA
HE	1,011 ± 105	936 ± 106	983 ± 89*	880 ± 130*	1,047 ± 123	IAHKE

Values are mean ± SEM.
* $P < 0.05$ *versus* normovolemic values.
† $P < 0.05$ cerebrum *versus* cerebellum in normovolemic state.
‡ $P < 0.05$ cerebrum *versus* cerebellum after hemorrhage.
A = awake; K = ketamine; H = halothane; E = enflurane; I = isoflurane; N = normovolemia; HE = 20 min after hemorrhage. Groups underlined by the same line are not significantly different from each other ($P > 0.05$) by Duncan's Multiple Range Test (DMRT). Groups are ordered from left to right in decreasing order of magnitude or alphabetical order when values are identical.

and after hemorrhage. Regional vascular resistances were reduced significantly by the inhalation anesthetics both before and after hemorrhage, whereas these values were similar in awake animals and those receiving ketamine.

Myocardial blood flow was greatest in awake animals and those receiving isoflurane, and it was reduced progressively by ketamine, enflurane, or halothane in normovolemic rats. After hemorrhage, myocardial blood flow increased in awake animals, was unchanged in those receiving isoflurane or halothane, and decreased in animals anesthetized with ketamine or enflurane. In general, myocardial vascular resistance tended to decrease after hemorrhage, although no distinct patterns were present either before or after blood loss.

Before hemorrhage, renal blood flow was least in animals breathing enflurane, but the values were similar in all other groups. Hemorrhage resulted in significant reductions in renal blood flow in all groups, but the values in anesthetized rats were significantly less than those in awake animals. Among the anesthetics, renal blood flow after hemorrhage tended to be greatest in those receiving isoflurane and least in those anesthetized with enflurane. Renal vascular resistance was unaltered by the anesthetics either before or after hemorrhage. The trend was for increased renal vascular resistance after hemorrhage, but significant changes occurred only in awake animals and those receiving enflurane or isoflurane.

Individual values for the splanchnic viscera and for the gastrointestinal tract (stomach, small bowel, cecum, and large bowel) are reported in the tables, and only the overall responses will be summarized here. Halothane was associated with reduced blood flow to the gastrointestinal tract, both before and after hemorrhage, as compared with that in awake rats, whereas gastrointestinal tract flows were unchanged by the other anesthetics. Blood flow to the gastrointestinal tract was reduced markedly after hemorrhage in all groups. Before hemorrhage, regional vascular resistance values were greatest in those receiving halothane. After hemorrhage, the value was greatest in awake rats. Gastrointestinal vascular resistance increased after hemorrhage in awake animals and those receiving isoflurane.

Liver blood flow is comprised of both the portal venous and the hepatic arterial circulations. Estimated portal venous flow was greatest in animals anesthetized with ketamine and least in those receiving halothane, whereas the value was intermediate for those awake or receiving isoflurane or enflurane. Portal venous flow was reduced in all groups after hemorrhage, but the absolute value of flow was greatest in those receiving isoflurane as compared with the other anesthetics. He-

TABLE 3. Blood Flow in Each Cerebral Hemisphere
($ml \cdot min^{-1} \cdot 100\ g^{-1}$)

Organ	A	K	H	E	I
R. Hemisph. N	86 ± 4	105 ± 9	136 ± 13	110 ± 10	137 ± 12
L. Hemisph. N	90 ± 5	113 ± 11	186 ± 23*	150 ± 14*	194 ± 17*
R. Hemisph. HE	90 ± 8	55 ± 6	83 ± 12	69 ± 5	126 ± 17
L. Hemisph. HE	100 ± 8	64 ± 7*	131 ± 12*	106 ± 8	160 ± 17*

Means ± SEM.
* $P < 0.05$ paired *t* test, right (R) *versus* left (L) hemisphere during normovolemia (N) or 20 min after hemorrhage (HE).

patic arterial flow was altered by the anesthetics and by hemorrhage also. Hepatic arterial flow was reduced significantly by enflurane or ketamine anesthesia, but it was not altered from that in awake animals by halothane or isoflurane. After hemorrhage, hepatic arterial flow was greatest in the awake animals and those receiving isoflurane, but it was significantly less in those receiving the other anesthetics. Hepatic arterial flow increased after hemorrhage in awake rats and those receiving ketamine, but it decreased in those anesthetized with halothane. Before hemorrhage, hepatic arterial vascular resistance was similar in all groups except those receiving ketamine, in which the value was increased markedly. After hemorrhage, hepatic arterial resistance decreased in awake animals and in those receiving ketamine, enflurane, or isoflurane, whereas this value was unchanged in those receiving halothane. The values for hepatic arterial vascular resistance were similar in all groups after hemorrhage. Before hemorrhage, total hepatic blood flow (the sum of portal venous flow and hepatic arterial flow) was less than that in awake animals only in those receiving halothane. Total hepatic flow decreased significantly in all groups after hemorrhage, but the values were greatest in awake animals and those receiving isoflurane, and they were significantly less in those receiving enflurane, halothane, or ketamine.

Before hemorrhage, cutaneous blood flow was greatest in those receiving ketamine, least in those receiving halothane and intermediate in those awake or receiving enflurane or isoflurane. Skin blood flow was reduced markedly after hemorrhage in all groups. Before hemorrhage, cutaneous vascular resistance was greatest in animals receiving halothane and least in those receiving isoflurane or enflurane. Cutaneous vascular resistance was increased significantly in all groups following hemorrhage.

Blood flow to the muscles may be considered in two general categories: that to the diaphragm and that to all other muscles. Diaphragmatic flow was greater than that to other muscles, presumably because the diaphragm represented the most intense working muscle of the muscles that we sampled in these animals. Before hemorrhage, the diaphragmatic blood flow was greatest in awake animals and it was reduced to similar values in all those anesthetized. Diaphragmatic vascular resistance tended to deccrease following hemorrhage, although this change reached statistical significance only in those receiving ketamine, halothane, or enflurane anesthesia. After hemorrhage, diaphragmatic vascular resistance was greatest in animals receiving isoflurane, and the values were similar in all other groups. Among the other muscles, the values for muscle blood flow before hemorrhage were greatest in awake animals and those receiving ketamine and least in those receiving halothane. After hemorrhage, muscle blood flows decreased in awake animals and those receiving ketamine, while the responses were variable in those receiving the other anesthetics. After hemorrhage, vascular resistance values were generally unchanged in awake animals and those receiving ketamine, but they tended to decrease in those receiving the volatile anesthetics.

Discussion

These studies provide data for anesthetic influences on regional blood flows in both normovolemic and hypovolemic rats. While it is obviously tenuous to transfer results from one species to another, it is appropriate to question whether the rat is a reasonable model of the hemodynamic influences of anesthetics in humans. In humans, halothane, enflurane, and isoflurane produce relatively comparable reductions in arterial pressure, but they act by different hemodynamic mechanisms. Halothane has a predominant effect on cardiac output,[2] isoflurane acts predominantly by decreasing systemic vascular resistance,[11] and enflurane decreases both factors.[12,13] Our results for mean arterial pressure, cardiac output, and systemic vascular resistance in normovolemic rats are generally similar to those observed in humans, although the mechanism for the changes in cardiac output appears to be different in rats. In adult humans, cardiac output is decreased primarily by changes in stroke volume, whereas heart rate was primarily responsible for the changes in cardiac output in these adult rats. An infusion of ketamine did not alter cardiac output, mean arterial pressure, or systemic vascular resistance as compared with those values in awake animals, and these results are in general agreement with the effects observed during continuous infusion of this drug in humans also receiving nitrous oxide.[14]

Hemorrhage resulted in significant reductions in mean arterial pressure and cardiac output in all animals, whether awake or anesthetized. However, the greatest cardiac output values after hemorrhage occurred in awake animals and those receiving isoflurane, while cardiac outputs were significantly less in those receiving enflurane, ketamine, or halothane. Isoflurane appeared to have little or no effect on cardiac output either before or after hemorrhage, whereas ketamine did not alter cardiac output before hemorrhage but reduced it markedly after bleeding. Indeed, cardiac output values after hemorrhage were similar in animals receiving ketamine or halothane. These results are similar to those reported by Weiskopf *et al.*,[3] who observed similar

reductions in cardiac output in hemorrhaged dogs receiving either halothane or ketamine anesthesia.

All of the anesthetics except isoflurane increased Pa_{CO_2} values, as compared with those in awake animals. The absence of increased Pa_{CO_2} in rats receiving isoflurane is surprising because halothane,[15] isoflurane,[16] and enflurane[12] each decreased ventilation and increased Pa_{CO_2} (to values of 47, 55, and 61 mmHg, respectively) in healthy human volunteers who breathed approximately the minimal alveolar concentration of these anesthetics. The values for Pa_{CO_2} may appear to be unusually low in our awake animals, but the resting Pa_{CO_2} in awake rats is not well established. Reports of Pa_{CO_2} values in awake rats range from 22 to 40 mmHg, with several investigators reporting values of 30 mmHg or less.[17-19] Our awake animals had undergone operation only a few hours previously, but we do not believe the Pa_{CO_2} values can be attributed to postoperative discomfort only. The wounds were coated with lidocaine gel prior to closure to provide postoperative analgesia (plasma lidocaine values of 0.37 μg/ml were measured in one animal in order to document the blood levels associated with this technique). We also measured Pa_{CO_2} values in chronically instrumented rats, and the values were approximately 30 mmHg even while the animals were asleep.

Hematocrit values decreased similarly in all animals after hemorrhage, confirming that similar amounts of blood loss were present in all groups. Lactate/pyruvate values and excess lactate increased in all anesthetized animals after hemorrhage, but these values did not change in awake animals. Both excess lactate and lactate/pyruvate have been used as indices of the severity of shock, and the relationship between the cardiac output values after hemorrhage and the increases in these indices is apparent here (*i.e.*, halothane and ketamine were associated with the least cardiac output values and the greatest L/P or excess lactate values after hemorrhage).

Before hemorrhage, ketamine did not alter cerebral or cerebellar blood flows as compared with those in awake animals. Ketamine is reported to increase cerebral blood flow (CBF) in other species, including dogs[20] and humans.[21] Idvall *et al.*[22] reported a 20% increase in total CBF in rats receiving ketamine anesthesia for 30 min. In normovolemic rats, we observed a 25% increase in cerebral blood flow ($P = 0.075$), but this was countered by a tendency for decreased cerebellar flow. In both studies, Pa_{CO_2} values were increased during ketamine anesthesia. It should be emphasized that our animals were not ventilated and the brain hemodynamic values represent the net effects of the anesthetics themselves and their indirect cerebrovascular effects resulting from changes in Pa_{CO_2}. However, cerebral and cerebellar vascular resistances were reduced markedly in animals receiving isoflurane despite Pa_{CO_2}values, which were similar to those in awake animals, suggesting that isoflurane is a potent dilator of the cerebrovasculature in rats even in the absence of major changes in Pa_{CO_2}. Isoflurane has been shown to increase cerebral blood flow in dogs[23] and swine[24] also, but 1 MAC of isoflurane apparently does not increase cerebral blood flow in humans.** In general, the trend was for cerebellar blood flows to exceed cerebral blood flows in awake rats and those receiving the volatile anesthetics, although such apparent differences were statistically significant only in those receiving enflurane or isoflurane before hemorrhage or in awake animals or those receiving enflurane or isoflurane after hemorrhage.

Comparisons of right *versus* left cerebral blood flow values indicated that the presence of the cannula in the right carotid artery significantly reduced blood flow to the right hemisphere in normovolemic rats receiving the potent vapors and in all anesthetized rats after hemorrhage. We would recommend that others consider this finding when reporting global cerebral blood flow values in anesthetized rats that have a ligated carotid artery.

Coronary artery blood flow was reduced significantly by ketamine, enflurane, and halothane anesthesia, as compared with the value in awake normovolemic rats. The value in our awake animals is similar to that reported by Idvall *et al.*[22] but less than that previously reported by Miller *et al.*[1] Coronary artery blood flow responses to hemorrhage were quite variable among groups. Myocardial blood flow increased significantly after hemorrhage in awake animals, but it decreased in those receiving ketamine or enflurane and remained unchanged in those receiving halothane or isoflurane. Regression analysis demonstrated a significant positive correlation between the rate-pressure product and myocardial blood flow both before and after hemorrhage (r values of 0.69 and 0.86, respectively; $P < 0.05$), although the slope of the regression line was increased after hemorrhage as compared with that before (1.20×10^{-2} *vs.* 6.54×10^{-3}), $P < 0.05$). While we recognize the limitations of the rate-pressure product as an index

** Murphy FL Jr, Kennell EM, Johnstone RE, Lief PL, Jobes DR, Tompkins BM, Gutsche BB, Behar MG, Wollman H: The effects of enflurane, isoflurane and halothane on cerebral blood flow and metabolism in man. ASA Annual Meeting, Abstracts of Scientific Papers, pp 61-62, 1974.

of myocardial oxygen consumption, we also recognize the potential value of an indirect index of myocardial blood flow for other investigations in rats, and a correlation between flow and this product was present in awake and anesthetized rats both before and after hemorrhage.

Although there appeared to be a trend toward decreased renal blood flow in anesthetized normovolemic rats, this trend reached statistical significance only in those receiving enflurane, and renal vascular resistance values were similar in all normovolemic animals. The reported data are contradictory regarding the influences of anesthetics on renal hemodynamics in animals and humans. Vatner and Smith[25] and Priano[26] reported that halothane did not alter renal blood flow in dogs, but Deutsch *et al.*[27] and Mazze *et al.*[28] observed decreased renal blood flow and increased renal vascular resistance in humans receiving halothane. Isoflurane did not alter renal blood flow in dogs[29] or swine,[24] but this drug reduced renal blood flow in humans.[30] Cupples *et al.*[31] observed no change in renal blood flow in rats anesthetized with ketamine. Thus, our results for anesthetic influences on renal hemodynamics in rats appear to be similar to those reported for dogs and swine, but the human responses appear to be different from any of these animals (although it should be emphasized that the measurement techniques were quite different in the animal *vs.* the human studies). Renal blood flow was reduced after hemorrhage in all groups, and renal vascular resistance tended to increase, although this trend reached significance only in those awake or receiving enflurane or isoflurane. Renal blood flow after hemorrhage was reduced significantly in all anesthetized animals as compared with the value in awake rats, indicating that some impairment of renal blood flow after hemorrhage occurred with all anesthetics. These results differ from those of Priano, who reported that 30% blood loss did not reduce renal blood flow in dogs anesthetized with ketamine or halothane.[32] However, direct comparisons are difficult because of differences in species, measurement technique, and experimental protocol.

The estimated portal venous flow (table 2) includes blood flow data for the spleen as well as the digestive tract organs. Since the digestive tract organs would appear to be the more critical organs in terms of blood flow and organ ischemia, we analyzed the data for the gastrointestinal tract separately also. Digestive tract blood flow was greatest in normovolemic animals receiving ketamine and least in those receiving halothane. After hemorrhage, flow to the digestive tract was significantly greater in those awake or receiving isoflurane as compared with that in animals receiving halothane. These results may be of importance in explaining the overall cardiovascular responses to hemorrhage, since splanchnic and/or intestinal ischemia may be associated with the release of a cardiodepressor substance after hemorrhage.[33,34] While we have no direct evidence to support or refute this hypothesis, there was a strong direct linear correlation ($P < 0.01$) between gastrointestinal blood flow and cardiac output in these studies. Of course, correlation does not imply causality, nor does it indicate which is the dependent variable. Before hemorrhage, total hepatic blood flows were similar in awake rats and those receiving ketamine, isoflurane, or enflurane, but total hepatic flow was significantly less in those anesthetized with halothane. Hepatic arterial flow was similar in awake animals and those receiving halothane or isoflurane, but this value was significantly less in those receiving enflurane or ketamine. Portal flow was similar in awake animals and those receiving isoflurane or enflurane, but this value was increased in rats anesthetized with ketamine and decreased in those receiving halothane. In all groups, portal venous and total hepatic blood flows were decreased significantly after hemorrhage. The results for hepatic arterial resistance and portal venous flow are consistent with the physiologic principle of "reciprocity of total hepatic flow" for all conditions except halothane anesthesia. Reciprocity of flow is demonstrated by a direct relationship between portal venous flow and hepatic arterial resistance, so that increases in portal flow result in increased hepatic arterial resistance and a consequent reduction in hepatic arterial flow. This mechanism acts to maintain a relatively constant total hepatic blood flow despite changes in portal venous flow. This general relationship appeared to be intact after hemorrhage in all animals except those receiving halothane when hepatic arterial resistance did not decrease to compensate for the reduced portal flow. Both Andreen *et al.*[35] and Hughes *et al.*[36] reported that halothane inactivates this important control mechanism in dogs also. While our study did not address this issue specifically, it is interesting to speculate that the inactivation of this compensatory mechanism may play a role in the development of hepatic dysfunction after halothane anesthesia, especially since an animal model of halothane-induced hepatic dysfunction is the rat that is pretreated with pentobarbital and then exposed to halothane and reduced oxygen in the breathing mixture.

Cutaneous blood flow, as compared with that in awake rats, was increased in normovolemic animals receiving ketamine, but this value was unchanged by the other anesthetics. Hemorrhage resulted in marked reductions in skin flow and increases in skin vascular resistance in all animals, presumably as a compensatory mechanism to direct blood flow to more essential organs.

This well-established physiologic response to hemorrhage does not appear to be impaired by the anesthetics studied here.

Regional hemodynamics among the various muscles will be pooled for purposes of this discussion, but it should be emphasized that these muscles were selected to include a working muscle (the diaphragm) and several other types of muscles as well. The muscles were selected to include those composed of different fibers, because differences in fiber type probably account for differences in flows among the various muscles.[37] In general, awake animals and those receiving ketamine had the greatest muscle blood flows prior to hemorrhage. Muscle blood flow values were reduced by hemorrhage and, surprisingly, the trend was for reduced vascular resistance in most muscles of those receiving inhalation anesthetics. Thus, the muscle vasculature, unlike the cutaneous circulation, apparently did not participate in a redistribution of blood flow to more vital organs.

The results for both the systemic and regional hemodynamics reported here may be influenced by the varying Pa_{CO_2} values that occurred in these spontaneously breathing rats. Pa_{CO_2} was increased in those receiving enflurane or halothane and unchanged from the awake value in those breathing isoflurane, and these relationships were present both before and after hemorrhage. Ketamine was associated with moderately increased Pa_{CO_2} values before hemorrhage, but the Pa_{CO_2} after hemorrhage was similar to that in awake animals. In general, increased Pa_{CO_2} is associated with increases in cardiac output[38] and regional blood flows to the brain,[39] heart,[40,41] and splanchnic viscera.[42,43] On this basis alone, halothane and enflurane, as compared with isoflurane, would be expected to provide greater cardiac output and blood flow to vital organs both before and after hemorrhage. However, this was not the case for CO, myocardial blood flow, and splanchnic blood flow. Therefore, it would appear that the pharmacologic effect of these agents, and not the Pa_{CO_2} value was the dominating factor responsible for the observed hemodynamics in animals receiving halothane or enflurane.

Is a single ideal or preferred anesthetic defined by these studies? This is a qualitative evaluation at best, but one might define the preferable anesthetic in normovolemic animals as the one that produced the fewest alterations in cardiac output and regional blood flows, as compared with those in awake rats. Similarly, one might define the preferable anesthetic for hemorrhage as the one that resulted in responses that were similar to those in awake animals. We attempted to approach these questions by intuitive analysis of the data and by the statistical technique of cluster analysis. This technique does not produce a result that is associated with a specific probability, but it provides an overall impression of which condition most closely approximates that of the awake state, either before or after hemorrhage. Such evaluations lead us to conclude that, in terms of cardiac output and regional blood flows, ketamine anesthesia in normovolemic rats most closely approximated the values that were obtained in awake animals. Isoflurane was intermediate in this regard, while enflurane and halothane resulted in the greatest alterations from the awake state. After hemorrhage, isoflurane anesthesia most closely approximated the awake state, while enflurane, halothane, and ketamine resulted in progressively greater alterations. These interpretations give an overall impression of the extent to which the anesthetics altered the cardiovascular responses to hemorrhage, but they do not necessarily imply that a single anesthetic is preferable in the presence of hemorrhage. Nevertheless, most efforts are directed toward improving cardiac output and reducing vascular resistance in order to improve regional blood flows to vital organs during hypovolemia, and the present results would suggest that isoflurane may be especially helpful in achieving these goals.

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