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Whole-body Distribution of Radioactively Labelled Microspheres in the Rat during Anesthesia with Halothane, Enflurane, or Ketamine

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Cardiac output and distribution of blood flow using 15-μm radioactively labelled microspheres were determined in 25 Wistar rats. In seven awake control animals, first and second injections of microspheres did not change cardiac output (137 ± 8 ml/min) or result in alteration in apparent blood flow to the various organs studied. Halothane anesthesia (n = 6) (1.3 per cent inspired) resulted in a decrease in cardiac output, with increases in the percentages of cardiac output going to the brain, kidney, liver and large intestine. Enflurane anesthesia (n = 6) (2.2 per cent inspired) did not decrease cardiac output. The percentages of cardiac output going to the liver, lung, spleen, and large intestine increased. Both halothane and enflurane caused decreases in the percentages of cardiac output going to the heart and skeletal muscle. Ketamine anesthesia (n = 6) (125 mg/kg, im) differed from the other two agents in that few changes occurred from the awake state except in brain, lung and muscle. Microspheres that were trapped after the first injection were released from muscle and skin with ketamine anesthesia, resulting in an apparent decrease in the distribution of cardiac output to muscle in the controls and an apparent increase in "flow" to the lung. The microsphere method gives reliable information about cardiac output and distribution of flow in rats anesthetized with halothane or enflurane. Further studies are necessary to determine whether microsphere studies are valid indicators of organ flow during ketamine anesthesia in the rat. (Key words: Anesthetics, intravenous: ketamine. Anesthetics, volatile: halothane; enflurane. Heart: cardiac output. Measurement techniques: microspheres.)

THE LABORATORY RAT has frequently been used to investigate various actions of anesthetic agents. Whether commonly used anesthetic agents produce in the rat cardiovascular effects similar to those known to occur in man has not been studied. The use of radioactively labelled microspheres allows for the determination of cardiac output and the distribution of blood flow before and after drug treatment. We have used this technique to investigate three commonly used anesthetic agents and have compared these results with what is known to occur in other experimental animals and man.

Methods

Twenty-five fasted male Wistar rats (230–400 g) were anesthetized with diethyl ether, and PE 50 polyethylene tubing was passed through the right carotid artery and placed in the left ventricle using pressure monitoring. The neck incision was closed and a femoral artery was cannulated with PE 50 tubing as well. Both catheters were tunnelled subcutaneously, brought out through the skin over the back, and flushed with a solution of heparin and physiologic saline solution. The rats were then placed in restraining cages and allowed to awaken. Blood pressure was monitored continuously through the femoral-artery cannula by a Statham® P 23 Db pressure transducer using a Brush Mark 260® recorder.

The protocol consisted of a one-hour control period, a 20-min induction period, and a one-hour period of stable anesthesia. Anesthesia was established with one of the following agents: halothane 1.3 per cent (n = 6); enflurane, 2.2 vol per cent (n = 6); or ketamine, 125 mg/kg, intramuscularly (n = 6). A control group (n = 7) was treated identically but remained unanesthetized throughout. All animals breathed room air spontaneously throughout the experiment. Inhaled concentrations of the volatile agents were determined at 15-min intervals by gas chromatography.§ The inhaled concentrations represent approximately 1 MAC values for the volatile agents in young rats. Ketamine was supplemented with half of the initial anesthetic dose after half an hour of stable anesthesia. This was done to prevent purposeful movements that would normally occur approximately 40 min after the initial injection. All animals were placed under a heating lamp to maintain rectal temperatures at 37 C.

To determine cardiac output and distribution of blood flow, carbonized microspheres were used. Strontium-85 (^{85}SR)- and cerium-141 (^{141}Ce)-labelled microspheres (15 ± 1.1 μm)¶ with specific activities

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§ Gow-Mac Model 750 Flame Ionization Detector; 1.83 meters SS column containing 20 per cent SE 30 on Chromasorb W.

¶ Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

of 9.6 mCi/g for ^{85}Sr and 12.8 mCi/g for ^{141}Ce were used. The microspheres had been suspended in dextran, 10 per cent, containing Tween 80®, 0.05 per cent. The microspheres were agitated, drawn into a plastic syringe which had been modified to fit into a gamma counting vial, and counted in a Beckman Biogamma® at the appropriate energy spectrum for each isotope. After counting, the microspheres were again agitated, and 0.1–0.2 ml (40,000–60,000 microspheres) were injected into the left ventricular catheter over 20 sec and flushed with saline solution 0.4 ml. Ten seconds prior to the microsphere injection and for the following 60 sec, blood was withdrawn from the femoral artery by a constant-withdrawal Gilford® pump. The blood was then placed in a preweighed counting vial and the actual withdrawal rate, 0.755 ± .006 ml/min, was determined. The empty injection syringe was again counted. The above procedure was done for each isotope. The first injection (^{85}Sr) was made at the end of the awake control period. After one hour of stable anesthesia, the second isotope (^{141}Ce) was injected. Arterial blood for blood-gas analysis was obtained after this second injection as well. The animals were then sacrificed by giving potassium chloride through the ventricular catheter.

The organs of the body were removed, weighed, and placed in counting vials. The position of the left ventricular catheter was verified at this time. Samples of skin, muscle, liver, and small intestine were taken; otherwise, the whole organ was counted. The contribution to body weight for skin was taken to be 18 per cent and that for muscle, 45 per cent.[1] These values were used to determine the distribution of flow to skin and muscle, which were not weighed *in toto*. Total weights of the liver and small intestine were determined for each animal. The tissue and blood samples were then counted in the Biogamma for 5 min at the appropriate energy spectrum, allowing for overlap of strontium in the cerium window.

Cardiac output was determined by the formula: cardiac output = counts injected × reference sample withdrawal rate ÷ reference blood counts. Regional distribution of cardiac output was calculated by comparing the radioactivity in each organ with the total injected radioactivity. Organ flow was determined by multiplying the cardiac output by the fractional distribution of the cardiac output to the organ.

Because a large number of microspheres with the strontium label (first injection) appeared in the lung, after ketamine anesthesia with a proportionate decrease of microspheres in muscle, additional studies were done. Six animals were studied to see whether the initial injection of microspheres remained in the areas of original distribution or whether the microspheres could be displaced by drug treatment. These additional rats were anesthetized with diethyl ether and had a left ventricular catheter placed. A single isotope was injected while the animal was anesthetized. The skin over one side of the torso was removed, as well as the underlying muscle and the muscles of the hind leg. In four of these animals the depth of anesthesia was allowed to lighten and ketamine, 125 mg/kg, was injected intramuscularly into a foreleg. Half an hour later these animals were sacrificed and an equal portion of skin and muscle from the contralateral side was obtained, along with lung tissue. Two control rats were similarly treated but received intramuscular injections of saline solution and remained anesthetized throughout with diethyl ether. The sequence of left and right sides for dissection was randomized. The lung, muscle and skin samples were weighed and counted for 5 min in the gamma counter.

The data presented are the mean values ± standard errors of the mean. The data were analyzed using the Student *t* test for unpaired data for comparisons between groups and the Student *t* test for paired data for comparisons within groups. $P < 0.05$ was taken as significant.

Results

In the unanesthetized animals, there were no significant differences in cardiac outputs, percentages of cardiac outputs, or blood flows to organs using the two different microsphere labels given 90 min apart. The first injection, ^{85}Sr, resulted in a cardiac output of 135 ± 9 ml/min, and the second injection, ^{141}Ce, resulted in a cardiac output of 139 ± 15 ml/min. Since no difference was found, the values for cardiac output, flow as a percentage of cardiac output and absolute blood flows to various organs were combined (table 1), and these values compared with the awake values for the three anesthetized groups. There was no significant difference in these values in the awake state for all animal groups except for flows to lung and muscle, which were different in the rats that subsequently received ketamine anesthesia. By estimating the mass of muscle and skin,[1] we were able to account for 99 ± 7 per cent of the total counts injected.

After an hour of stable halothane anesthesia, cardiac output decreased significantly from 135 ± 13 to 100 ± 13 ml/min (table 2). Significant increases in per cent cardiac output were seen in brain, kidney, and large intestine, while decreases were seen in heart and skeletal muscle (fig. 1). Calculated changes in actual blood flow were similar, but were significant only for heart, muscle and stomach. Even though blood pressure decreased significantly from the awake value, cal-

TABLE 1. Fractional Flow, Total Blood Flow, and Blood Flow per Organ in Unanesthetized Control Rats

Organ	Weight (g)	Cardiac Output (Per Cent)	Flow (ml/g/min)	Blood Flow/Organ (ml/min)
Brain	1.7 ± 0.1	1.2 ± 0.2	0.9 ± 0.07	1.5 ± 0.2
Heart	1.2 ± 0.1	6.6 ± 0.4	7.6 ± 0.5	8.7 ± 0.3
Lung	1.8 ± 0.2	0.7 ± 0.1	0.6 ± 0.1	1.0 ± 0.1
Skin	60 ± 3*	8 ± 1	0.2 ± 0.03	10.9 ± 1.1
Right kidney	1.7 ± 0.04	6.2 ± 0.4	5.1 ± 0.5	8.6 ± 0.8
Left kidney	1.6 ± 0.1	6.4 ± 0.5	5.4 ± 0.6	8.9 ± 0.9
Muscle	143 ± 9*	54 ± 8	0.5 ± 0.1	71 ± 10
Liver	12.5 ± 0.8	3.3 ± 0.1	0.4 ± 0.3	4.5 ± 0.3
Spleen	0.7 ± 0.04	0.6 ± 0.1	1.4 ± 0.2	0.9 ± 0.1
Stomach	1.8 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	1.6 ± 0.2
Small intestine	11.2 ± 0.6	10.1 ± 1.4	1.4 ± 0.3	15 ± 3
Large intestine	4.1 ± 0.2	1.6 ± 0.2	0.6 ± 0.1	2.3 ± 0.5
TOTAL		99.6		136

* Estimated weight.

culated total peripheral vascular resistance did not change (table 2).

Unlike cardiac output during halothane anesthesia, cardiac output remained unchanged from the awake value in the rats anesthesized with enflurane (table 2). Since blood pressure decreased to 96 ± 2 torr, the major effect of enflurane was to cause a significant decrease in calculated total peripheral vascular resistance. Significant changes in flow as a percentage of cardiac output were seen in heart, lung, muscle, liver, spleen and large intestine (fig. 2), while actual blood flow changes were seen only in heart, lung, muscle, spleen, and large intestine.

Blood pressure and heart rate decreased significantly with ketamine anesthesia (table 2). Cardiac output appeared to decrease but the change did not reach statistical significance because of the large standard error seen during the awake measurement. There was a significant increase in the percentage of cardiac output going to the brain after ketamine anesthesia, while decreases in both percentage of output and actual blood flow were seen in skeletal muscle (fig. 3). More interesting was the finding that there were significant apparent increases in flow as a percentage of cardiac output and in actual blood flow in the awake state for lung, and decreases for muscle, as compared with the other group of animals. The additional experiments done with ether and ketamine anesthesia showed that the increase in the number of microspheres in the lung was due to release of microspheres from the skin and muscle. There was a 32 per cent loss of microspheres from muscle after ketamine anesthesia. The control experiments, in which only saline solution was injected, showed that the microspheres did not move from the muscle or skin when the two sides were compared. These additional experiments demonstrated that drug treatment altered the apparent distribution of microspheres even though the drug was given after the initial injection of the first dose of microspheres.

Discussion

In their classic paper, Rudolph and Heymann first showed that distribution of cardiac output could be accurately assessed through the use of radioactive

TABLE 2. Hemodynamic Data and Results of Arterial Blood-gas Analysis

	Awake (n = 7)	Halothane (n = 6)	Enflurane (n = 6)	Ketamine (n = 6)
Mean blood pressure (torr)	120 ± 2	84 ± 4*	96 ± 2*	107 ± 4*
Heart rate (beats/min)	462 ± 8	350 ± 12*	385 ± 18*	410 ± 15*
Cardiac output (ml/min)	137 ± 8	100 ± 13*	126 ± 7	99 ± 8†
Cardiac index (ml/kg/min)	424 ± 37	326 ± 47*	418 ± 40	326 ± 26
Stroke volume (ml)	0.28 ± 0.02	0.29 ± 0.04	0.33 ± 0.03	0.24 ± 0.02
Total peripheral vascular resistance (torr/ml/min)	0.93 ± 0.06	0.90 ± 0.10	0.78 ± 0.04*	1.08 ± 0.09
P_{O_2} (torr)	—	73 ± 3	78 ± 6	85 ± 4
P_{CO_2} (torr)	—	40 ± 2	37 ± 6	35 ± 1
*p*H	—	7.35 ± 0.06	7.38 ± 0.03	7.38 ± 0.03

* $P < 0.05$ by paired analysis.

† Not significantly different from paired control value because of large standard error in awake value.

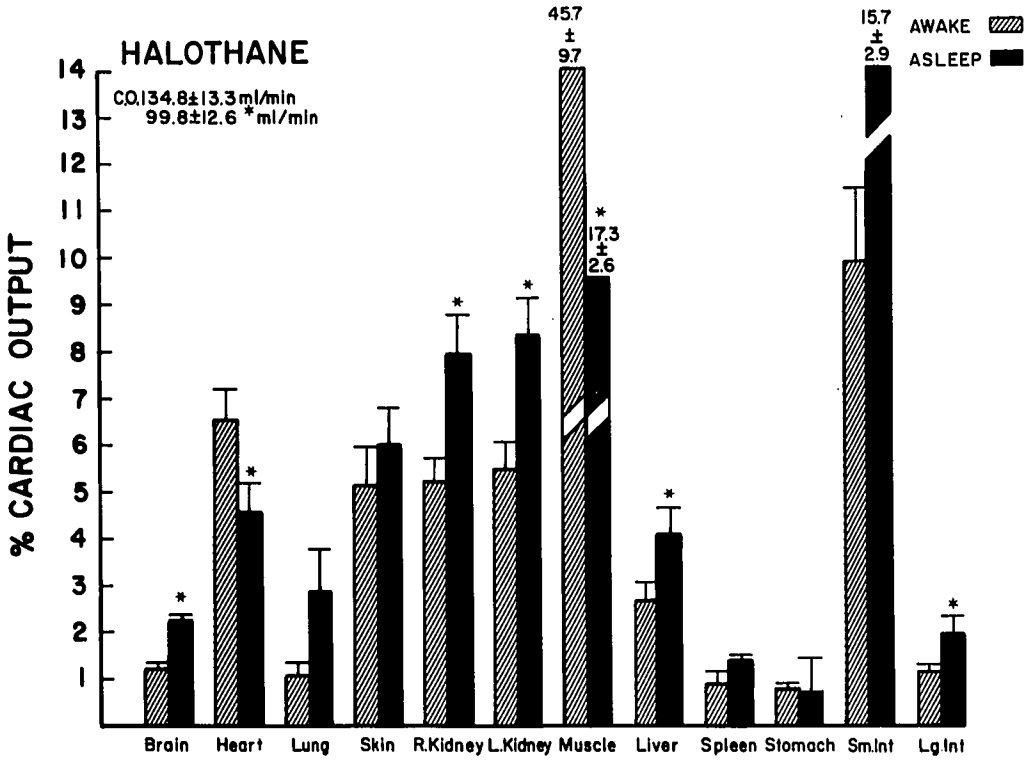

FIG. 1. Percentages of cardiac output before and during halothane anesthesia at 1.3 per cent inspired concentration. Skin, muscle, liver and small intestinal distribution estimated from analysis of aliquots. *$P < .05$ by paired analysis.

microspheres.[2] Since that time, several investigators have adapted this technique to examine distribution of blood flow in the rat. Buckberg *et al.*[3] advocated the use of 15-μm microspheres instead of larger spheres for measuring regional flows because the smaller spheres are more evenly distributed across the lumens of larger vessels due to axial streaming. Malik and co-workers,[4] using 15-μm microspheres, showed that

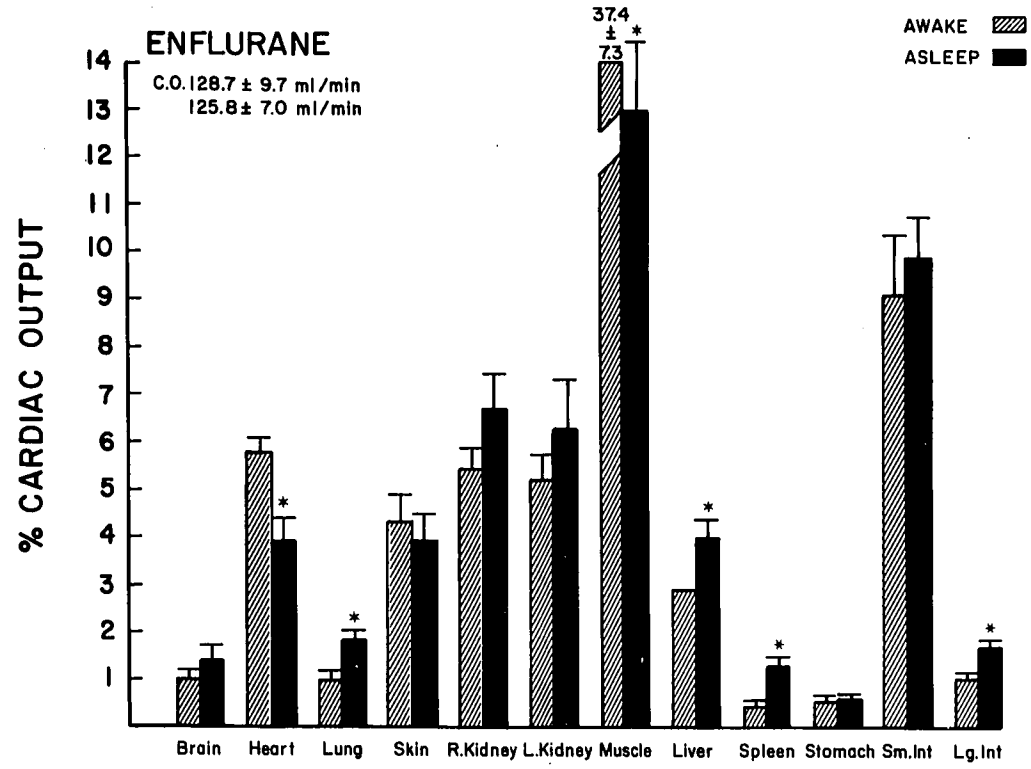

FIG. 2. Percentages of cardiac output before and during enflurane anesthesia 2.2 per cent inspired concentration. Skin, muscle, liver and small intestinal distribution estimated from analysis of aliquots. *$P < .05$ by paired analysis.

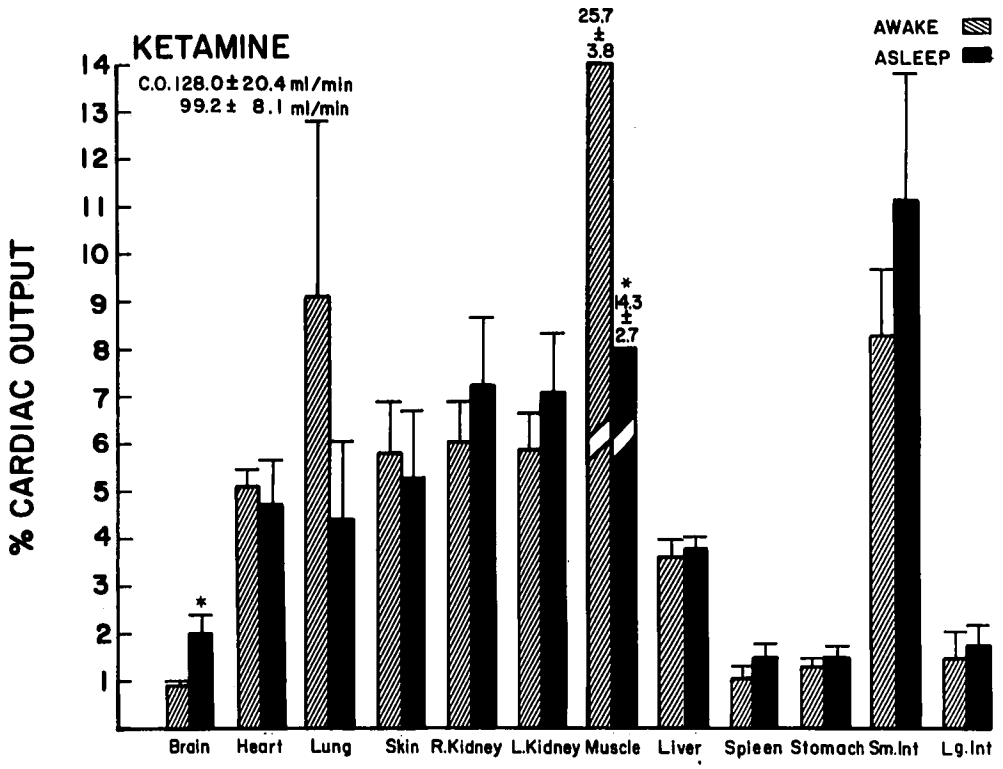

FIG. 3. Percentages of cardiac output before and after ketamine, 125 mg/kg, intramuscularly. Skin, muscle, liver and small intestinal distribution estimated from analysis of aliquots. The awake values for lung are higher and values for muscle are significantly lower than the awake values for the control experiments. *$P < .05$ by paired analysis.

by using a reference sample method, both cardiac output and regional blood flow could be determined in the rat. Tsuchiya and co-workers[5,6] have shown that when fewer than 100,000 15-μm microspheres are injected, there is no significant alteration in systemic hemodynamics. Our study used fewer than 100,000 microspheres, and our awake group showed no change in hemodynamic variables. The mean value of 137 ± 8 ml/min for cardiac output agrees well with the results of Tsuchiya and co-workers,[6] who obtained a cardiac output value of 119 ± 13 ml/min. That our cardiac output value is valid is also substantiated by the work of Snyder and co-workers,[7] who found a cardiac output of 119 ± 5 ml/min in the rat using a thermal dilution technique.

Before the microsphere technique can be adopted in our model, however, several important criteria must be met. First, adequate mixing of the microspheres in the left ventricle is necessary. Our data show relatively small standard errors for flow to the heart and equal distributions to right and left kidneys. Preliminary experiments showed equal distributions of flow to the testes as well, further supporting good mixing in the left ventricle. Second, there must be an adquate number of microspheres injected to give reliable results. Tsuchiya *et al.*[6] have shown that when 200–400 microspheres are present in the reference sample, cardiac output determinations are valid. Our samples contained about 300 microspheres per blood sample. Tissues with low blood flows, such as muscle and skin, did not contain as many microspheres, and therefore their absolute flows are open to question. This problem could have been alleviated with a larger sample size. Last, the microspheres must not cause appreciable alteration in hemodynamic variables. Our group of unanesthetized rats, which received both varieties of microsphere, showed no significant change in cardiac output or blood flow.

How anesthetic agents alter cardiac output and distribution of flow in the rat has not been studied extensively. Halothane is known to depress cardiac output in man without a significant change in peripheral vascular resistance,[8] which is what our study shows. The effect of enflurane in man remains controversial. Calverly *et al.*[9] showed a 26 per cent decrease at 1 MAC in man, while Rathod *et al.*,[10] using echocardiographic assessment of ventricular performance, concluded that pump performance and muscle function were maintained with 1 MAC enflurane. Our study shows no decrease in cardiac output and that the major effect of enflurane is to decrease total peripheral vascular resistance. Since arterial blood P_{CO_2} values were similar in enflurane- and halothane-treated animals, sympathetic stimulation due to hypercapnia with support of cardiac function does not seem a likely explanation for the differences seen. Ketamine anesthesia is known to increase cardiac output and blood pressure shortly

after administration in man.[11] Our method of administration (125 mg/kg followed half an hour later by half the dose) was necessary to maintain anesthesia in the rat. We could find no study examining changes in cardiac output in man after an hour of ketamine anesthesia. Whether the cardiovascular response in rats is significantly different from the response that might be seen in man when the drug is similarly administered cannot be determined from our study.

Distribution of blood flow to the brain was increased by halothane and ketamine, but not by enflurane. The insertion of a left ventricular catheter via the right carotid artery might be expected to alter blood flow to the brain. However, studies by Malik *et al.*[12] show that unilateral or bilateral carotid cannulation in the rat does not significantly affect cerebral blood flow or flows to other organs, suggesting that adequate blood flow must exist through the vertebral vessels and other anastomotic channels. The effects of these anesthetics on cerebral blood flow in the rat compare closely to those known to occur in man. Halothane consistently produces an increase in cerebral blood flow, as does ketamine.[13,14] Enflurane, in contrast, has been shown to produce no change in cerebral blood flow when used in inhaled concentrations from 0.85 vol per cent to 3.2 vol per cent.[15]

Blood flow and percentage of cardiac output supplying the myocardium were decreased in rats anesthetized with halothane and enflurane, as is known to occur in other species.[16] Such changes were not seen in animals anesthetized with ketamine. Ketamine is known to increase myocardial blood flow in man, which may be the result of an increase in cardiac output that was not seen in the rat.[17] Distribution of blood flow to the kidneys was consistently increased with halothane anesthesia. Enflurane and ketamine did not produce such an increase. Almost all human studies using clearance techniques have demonstrated a decrease in renal blood flow with halothane.[18] Using flow-probe techniques, however, Vatner *et al.*[19] found an increase in renal blood flow with halothane. Recently, Bastron *et al.*[20] have shown renal vasodilation with halothane in the isolated perfused kidney. A state of diuresis is necessary to measure renal blood flow by clearance techniques. Since our animals had been fasted but allowed water *ad libitum,* perhaps their normal state of hydration gives a more realistic indication of what halothane does to the kidney. Under the conditions of these studies, these three anesthetics did not decrease renal blood flow.

Arterial blood flow in the liver was increased with halothane or enflurane, but not with ketamine anesthesia. Since the blood supply to the liver is comprised of arterial and portal flow, and portal flow did not decrease, halothane and enflurane anesthesia do not appear to compromise the blood supply to the liver. The total estimated splanchnic blood flow to liver, spleen, stomach, small and large intestine was unaltered by any of the anesthetic agents studied. In man, splanchnic flow is decreased 30 per cent by halothane anesthesia due to a decrease in perfusion pressure.[21] Studies examining the effects of enflurane or ketamine on splanchnic blood flow in man are not available. This apparent discrepancy between rat and man is unexplained by our study.

Blood flow to the skin was unaltered by any of the anesthetics. However, our sample size was small, and therefore the number of microspheres trapped was small. Meaningful interpretations of changes in blood flow to the skin are therefore not accurate. The sample of tissue taken for skeletal muscle was also small, but large changes in flow were seen. When additional muscle was taken, these changes were substantiated. The three anesthetics studied all decreased muscle blood flow. Halothane is known to cause a dose-dependent decrease in skeletal muscle blood flow in human volunteers.[22] Ketamine anesthesia (2 mg/kg, iv) increases forearm muscle flow in man, but no change is seen in man simultaneously given nitrous oxide and oxygen.[23]

One striking finding in our study was the apparent decrease in the awake value seen for muscle in those animals subsequently receiving ketamine anesthesia. The awake control animals had a value for percentage of cardiac output to muscle of 54 ± 8 per cent; halothane awake, 46 ± 10 per cent; enflurane awake, 37 ± 7 per cent. The awake value for the ketamine-treated animals was only 26 ± 4 per cent. The corresponding increase in the number of microspheres seen in the lung for the first isotope suggested that the injection of ketamine was opening up arteriovenous fistulas in the muscle bed and allowing "trapped" microspheres to reach the lung. To test this hypothesis, additional experiments were done in which equal amounts of tissue were obtained before and after ketamine and only one injection of microspheres. Since the muscle mass constitutes 45 per cent of the body weight, the finding that the migration of microspheres to lung came from muscle was not surprising. However, other tissues such as skin probably also contribute to the microspheres found in the lung. The 15-μm microspheres lodge in vessels more than 15 μm in diameter because of the formation of microsphere chains.[24] Longnecker *et al.*[25] have shown that small arteries (20–65 μm) dilate with ketamine anesthesia, and this may explain the release of microspheres from muscle and other vascular beds.

The finding that microspheres can be released by

drug treatment necessitates that control experiments with no drug administration be included, using both microsphere labels. Furthermore, the use of the microsphere method to determine bronchial blood flow seems inappropriate, because a subsequent treatment might allow for release of microspheres and this might be interpreted as an increase in bronchial flow. Last, lungs must be analyzed in all experiments to rule out migration of microspheres.

In summary, injection of radioactively labelled 15-μm microspheres is a reliable method for studying cardiac output and distribution of blood flow in the rat during halothane and enflurane anesthesia. Ketamine anesthesia results in changes that are not always seen in man, which may be explained in part by differences in drug dosages, as well as different species responses to ketamine. Ketamine anesthesia also results in a release to lung of microspheres that were originally trapped in muscle and skin. By limiting the number of microspheres injected, use of proper awake controls, and meticulous attention to detail, the microsphere method can give important information about changes induced by anesthetic agents.

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