

Influence of Ketamine Anesthesia on Cardiac Output and Tissue Perfusion in Rats Subjected to Hemorrhage

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Ketamine anesthesia has been considered suitable for use in patients suffering from acute hypovolemia. Using a microsphere technique, fractional distribution of cardiac output and tissue perfusion were determined in rats subjected to moderate (10 ml/kg), or severe (bled to 60 torr systolic arterial pressure) hemorrhage. In the moderate bleeding experiments, rats under ketamine anesthesia were compared to awake rats as well as to awake normovolemic rats. In the severe bleeding experiments, rats under ketamine anesthesia were compared to rats under barbiturate anesthesia. Following moderate bleeding the ketamine group had a significantly larger cardiac output and higher arterial pressure than the unanesthetized group. There were no major differences in the fractional distribution of cardiac output, although tissue perfusion in the ketamine group was significantly larger in heart, kidneys, skin, and small intestine. The shed blood volume necessary to reach 60 torr in systolic arterial pressure was 36 per cent of normal blood volume in the ketamine group, and 23 per cent in the barbiturate group. In spite of the greater blood loss, rats under ketamine anesthesia displayed significantly larger cardiac output and a higher elevation of arterial pressure 20 min after the hemorrhage. In the ketamine group, fractional distribution of cardiac output favored the internal organs as opposed to an increase in the carcass in the barbiturate group. The ketamine anesthetized rats had a significantly larger perfusion to most organs, including heart, kidneys, and brain. It is concluded from this study that in rats experiencing acute hypovolemia blood flow to vital organs and cardiac output are well maintained under ketamine anesthesia. (Key words: Anesthetics, intravenous: ketamine; pentobarbital. Blood: loss. Blood pressure: hypotension. Heart: cardiac output. Hemorrhage: tissue perfusion. Measurement techniques: microspheres. Shock: tissue perfusion.)

IN SEVERAL CLINICAL REPORTS, ketamine has been claimed to be a useful anesthetic drug for patients with large blood losses or hypovolemic hypotension.¹⁻⁵ Aquado-Matorras *et al.*⁶ found improved peripheral circulation in patients in shock following ketamine administration using a plethysmographic technique. In an experimental study, Longnecker and Sturgill⁷ observed higher survival rates and fewer pathologic changes in the splanchnic organs in hemorrhaged rats anesthetized with ketamine than with pentobarbital, halothane, or fluoroxene. These findings suggest that tissue perfusion under hypovolemia is better preserved with ketamine anesthesia than with

the other anesthetic techniques. However, there have been no investigations where tissue perfusion has been studied in hypovolemic animals under ketamine anesthesia.

The present study was undertaken to determine cardiac output and regional tissue perfusion, with the aid of microsphere technique, in hemorrhaged rats under ketamine anesthesia. Comparisons have been made with unanesthetized and barbiturate-anesthetized hypovolemic rats.

Material and Methods

Fifty male Wistar SPF rats (260-310 g) were cannulated under light ether anesthesia 24 h prior to the hemodynamic experiments. A specially prepared polyethylene tubing, PE-10,⁸ was passed into the left ventricle of the heart via the right carotid artery. Both femoral arteries and veins were exposed, and PE-90 tubings were inserted into the abdominal aorta and caval vein, respectively. These catheters had been elongated to a 40-mm tip. All catheters were exteriorized at the tail, flushed with heparinized saline, and clamped.

Following cannulation, the rats were kept in special Plexiglas[®] cages with the tail and catheters outside the wall. Water and food were supplied *ad libitum*.

The rats were randomly divided, into five experimental groups with ten animals in each group:

- Group I: Unanesthetized normovolemic rats served as controls in the moderate bleeding experiments;
- Group II: Unanesthetized rats subjected to moderate hemorrhage;
- Group III: Rats under ketamine anesthesia subjected to moderate hemorrhage;
- Group IV: Rats under barbiturate anesthesia subjected to severe hemorrhage; and
- Group V: Rats under ketamine anesthesia subjected to severe hemorrhage.

Ketamine anesthesia was induced with an iv bolus injection of 30 mg/kg and maintained with a continuous iv infusion of 1.5 mg·kg⁻¹·min⁻¹.⁹ In the barbiturate group, sodium pentobarbital was used. The dosage was 30 mg/kg for induction, given as an iv bolus injection, and for maintenance, 20 per cent of the initial dose per hour as a continuous iv infusion was ad-

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Received from the Departments of Anesthesiology, Experimental Research and Nuclear Medicine, Malmö General Hospital, University of Lund, Malmö, Sweden. Accepted for publication March 2, 1981.

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ministered. With both ketamine and pentobarbital anesthesia, the volume of the induction dosage was 0.5–1.0 ml, and maintenance dosage was always given as 0.036 ml/min via an infusion pump (syringe pump model 351, Sage Instruments). With both anesthetic techniques, the rats spontaneously breathed room air and no supplementary drugs were given.

In a previous study,⁹ ketamine anesthesia was evaluated by determination of plasma concentrations of the anesthetic drug. A similar study to determine pentobarbital levels was undertaken in 10 Wistar SPF rats (265–300 g). One femoral artery and vein were cannulated under light ether anesthesia 24 h prior to the experiment. During the pentobarbital anesthesia arterial blood samples were collected in heparinized tubes at 5 or 30 min after induction for determination of the plasma concentration of the anesthetic drug. As each sample was large (4 ml), only one could be obtained from each animal. The tubes were centrifuged at $1000 \times g$ for 10 min. After extraction of the plasma sample (adjusted to pH 4.6 with phosphate buffer) into chloroform and re-extraction into 12.5 mM aqueous sodium hydroxide and adjustment with borate buffer to pH 10, the optical density was determined at 240 nm. After acidification of the sample with sulphuric acid to pH 1, another reading at 240 nm was performed. The concentration of pentobarbital was calculated from the difference in absorption.[†]

For the hemodynamic experiments the following measurements were performed: 1) arterial blood pressure, continuously recorded with a microtip transducer (Millar Instruments Inc., Houston, Texas). This technique has previously been described in detail by Idvall *et al.*¹⁰ 2) pH, PaCO₂, PaO₂, and base excess were determined on 0.5 ml of arterial blood (acid-base analyzer, ABL 1, Radiometer®, Copenhagen, Denmark). The blood-gas tensions were corrected to rectal temperature of the rats. 3) Hematocrit was determined using 20 μ l of blood. Heparinized capillary tubes were centrifuged at $1000 \times g$ for 10 min. 4) Determinations of cardiac output and regional blood flow were performed using a microsphere technique described in a previous work.¹¹ In this study, 15 μ m carbonized microspheres labeled with ⁴⁶Sc or ⁸⁵Sr (3M Company, St. Paul, Minnesota) were injected into the left ventricle of the heart. Each microsphere injection, 25 μ l, contained at least 4.5×10^5 microspheres. All volume losses due to blood sampling were compensated with three times the volume of normal saline.

[†] Standard method of the Section of Toxicology, Department of Clinical Chemistry, Malmö General Hospital, Malmö, Sweden.

In Group I, unanesthetized normovolemic rats, measurements 1–4 were made only once. In Group II, unanesthetized rats were bled 10 ml/kg via one of the arterial catheters. The hemodynamic measurements were performed 5 and 20 min after bleeding was finished. The rats in Groups I and II were kept in their cages during the experiments with the cages covered by a dark cloth to avoid undue disturbance. In Group III, the same protocol was followed as in Group II, but the rats were under ketamine anesthesia, which had been induced at least 15 min before bleeding was begun. In Group IV, barbiturate anesthesia was given, and hemodynamic measurements were made during steady-state anesthesia 20 min after induction. The rats were then hemorrhaged via an arterial catheter to a reservoir to achieve an arterial systolic blood pressure of 60 torr. When the pressure was stable, the catheter was clamped and the shed blood volume was determined. Twenty minutes after this hemorrhage measurements 1–4 were made. For rats in Group V, the same protocol was followed except that the rats were under ketamine anesthesia. Throughout the experiments, body temperature was maintained with a heating lamp at 36.5–37.5° C.

Finally, normal blood volume was determined in ten unanesthetized Wistar SPF rats (270–310 g). Cannulation of one femoral artery and vein was done under light ether anesthesia the day prior to the experiment. Human serum albumin labeled with ¹³¹I corresponding to 40 kBq in a volume of 0.5 ml was administered intravenously as a tracer substance. Arterial blood samples of 0.5 ml were collected 5, 15, 30, and 60 min after injection of the radioactive label. The radioactivity of the injected dose, blood samples and a standard sample were determined in an automatic well-counter (2 \times 2 inch well crystal, Nuclear Chicago) connected to a gamma spectrometer (Ultrascaler® 2, Nuclear Chicago). The blood concentration of ¹³¹I at zero time was obtained by semilogarithmic extrapolation. The blood volume was calculated as the ratio of the injected amount of radioactivity to the concentration of radioactivity at zero time.

The mean and standard deviation (SD) were calculated for each group. The significance of the difference between two means was estimated with Student's *t* test for paired observations. *P* < 0.05 was regarded as significant.

Results

Both ketamine and pentobarbital anesthesia offered stable conditions with loss of corneal and righting reflexes. Plasma concentration of pentobarbital was found to be 112 ± 9 μ mol/l at 5 min and 102 ± 9 μ mol/l at 30 min postinduction. Normal blood

volume of the rats was found to be 7.00 ± 0.45 ml/100 g body weight.

In the hemodynamic study there were no important differences between the findings obtained 5 and 20 min after hemorrhage in Groups II and III, and therefore only measurements made at 20 min will be discussed further and are presented in table 1 and figures 1 and 2. Cardiac output was significantly reduced in rats hemorrhaged 10 ml/kg in both the unanesthetized and the ketamine-anesthetized group as compared to the controls (table 1). In the ketamine group, however, cardiac output was significantly larger than in the group of unanesthetized hemorrhaged rats. Further comparison between the two hemorrhaged groups showed that systolic blood pressure and Pa_{O_2} were significantly higher in the ketamine group than in the awake group.

Fractional distribution of cardiac output in Groups I–III is shown in figure 1. After bleeding, the fractions were significantly increased to the heart, adrenals, and brain in both unanesthetized and ketamine-anesthetized rats as compared to the controls. The fractions were not significantly elevated to the lungs and splanchnic organs, while carcass fractions were significantly reduced. Comparison between the two hemorrhaged groups showed that the heart fraction in the ketamine group was significantly larger while fractions to liver, spleen, adrenals, and brain were significantly smaller than in the awake group.

Figure 2 shows the corresponding organ blood flow values in the Groups I–III. Following hemorrhage, perfusion was reduced in all organs and tissues compared to the controls with the exception of the heart in the ketamine group. Comparison of the two hemorrhaged groups revealed significantly larger blood flow in the ketamine group to the heart, small intestine, kidneys, and skin.

Table 2 shows measurements made during barbiturate and ketamine anesthesia, respectively. Under both normovolemic and severe hypovolemic conditions cardiac output was significantly larger in the ketamine group. With both anesthetics, however, there was a significant reduction of cardiac output measured 20 min after hemorrhage. In the hemorrhaged groups arterial pressure at that time was found to be significantly higher in the ketamine group while there was no difference in heart rate. In both anesthetic groups, the rats became acidotic after bleeding with significant falls in base excess, and there was no difference between the two hypovolemic groups in this respect. After bleeding, reduction in hematocrit was more pronounced in the ketamine group. To obtain a systolic arterial pressure of 60 torr the shed blood volume in the ketamine group was 25.0 ± 2.7 ml/kg,

TABLE 1. Measurements in Normovolemic Unanesthetized Rats, and Rats Subjected to Hemorrhage, 10 ml/kg

	Controls	Rats Hemorrhaged 10 ml/kg*	
		Unanesthetized	Ketamine-Anesthetized
Cardiac output (ml/min)	69.0 ± 10.2	39.1 ± 6.6	53.2 ± 7.7
Heart rate (beat/min)	403 ± 23	454 ± 31	461 ± 30
Systolic BP (torr)	129 ± 6	119 ± 7	128 ± 4
Diastolic BP (torr)	75 ± 6	72 ± 7	76 ± 6
pH	7.47 ± 0.04	7.39 ± 0.04	7.41 ± 0.03
Pa_{CO_2} (torr)	30 ± 5	35 ± 4	33 ± 4
Pa_{O_2} (torr)	104 ± 12	94 ± 10	106 ± 10
Base excess (mmol/l)	+0.1 ± 1.6	-2.1 ± 2.5	-1.9 ± 2.7
Hematocrit (Per cent)	40 ± 2	35 ± 1	35 ± 1

Values are means ± SD.

* The hemorrhaged groups consisted of unanesthetized rats and those subjected to ketamine anesthesia. The following measurements showed significant differences between the two hemorrhaged groups: cardiac output, systolic blood pressure, and Pa_{O_2} .

and in the barbiturate group 16.1 ± 3.0 ml/kg. The difference is significant.

Figure 3 illustrates the fractional distribution of cardiac output in Groups IV and V. Under both normovolemic and hypovolemic conditions the fractions to the heart, kidneys, and brain were larger in the ketamine group as compared to corresponding situations in the barbiturate group. Carcass fractions in the ketamine group were smaller in both conditions.

The corresponding organ and tissue blood flow values are shown in figure 4. Under conditions of severe hypovolemia, perfusion was significantly larger in the rats in the ketamine group to brain, tongue, heart, kidneys, adrenals, intestine, liver (a hepatica), and skin as compared to rats in the barbiturate group. The difference in organ perfusion between the two groups was similar under normovolemic conditions.

Discussion

In this study two different methods were used to create a condition of acute hypovolemia; moderate bleeding was accomplished by withdrawal of a fixed volume of blood, and a more severe bleeding was initiated by withdrawal of blood to be fixed systolic arterial pressure. In a pilot study with unanesthetized rats a fixed volume bleeding was well-tolerated, but the larger blood loss needed to achieve a fixed arterial systolic pressure of 60 torr gave an unacceptably high mortality rate. In these awake rats arterial pressure was maintained at a higher level even at larger blood

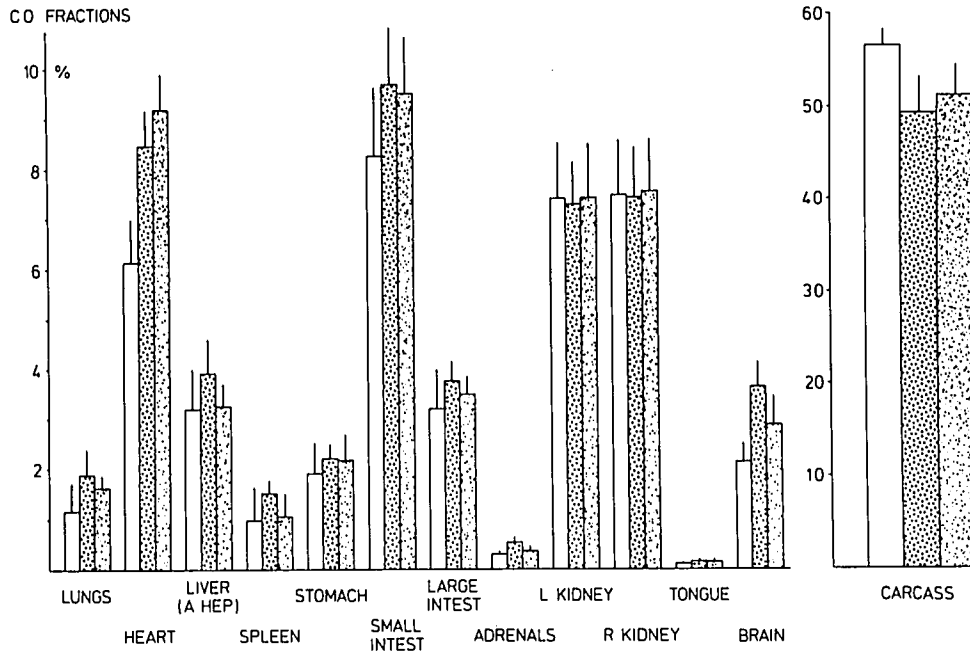


FIG. 1. Fractional distribution of cardiac output in percentage shown as the mean \pm SD ($n = 10$). In each group of bars, the first refers to unanesthetized normovolemic rats (Group I), the second to unanesthetized rats bled 10 ml/kg (Group II), and the third to ketamine-anesthetized rats bled 10 ml/kg (Group III). Measurements made 20 min after hemorrhage in Groups II and III are presented. Significant differences between fractions in Groups II and III appeared in the following organs: heart, liver, spleen, adrenals, and brain.

losses which finally resulted in circulatory collapse. When the rats were anesthetized, however, bleeding gave a gradual reduction in arterial pressure, and a systolic arterial pressure of 60 torr could be achieved without immediate mortality. Thus, to study the hemodynamic effects of severe hemorrhage, rats under ketamine anesthesia were compared to rats under barbiturate anesthesia. Barbiturate anesthesia

was chosen as it is widely used and well established in hemodynamic experiments. In the clinical situation barbiturates are often used for induction of anesthesia.

In order to calculate the percentage of blood loss obtained by the different bleeding procedures, normal blood volume was determined. Our value of 7.00 ml/100 g was consistent with the findings of others¹²⁻¹⁴

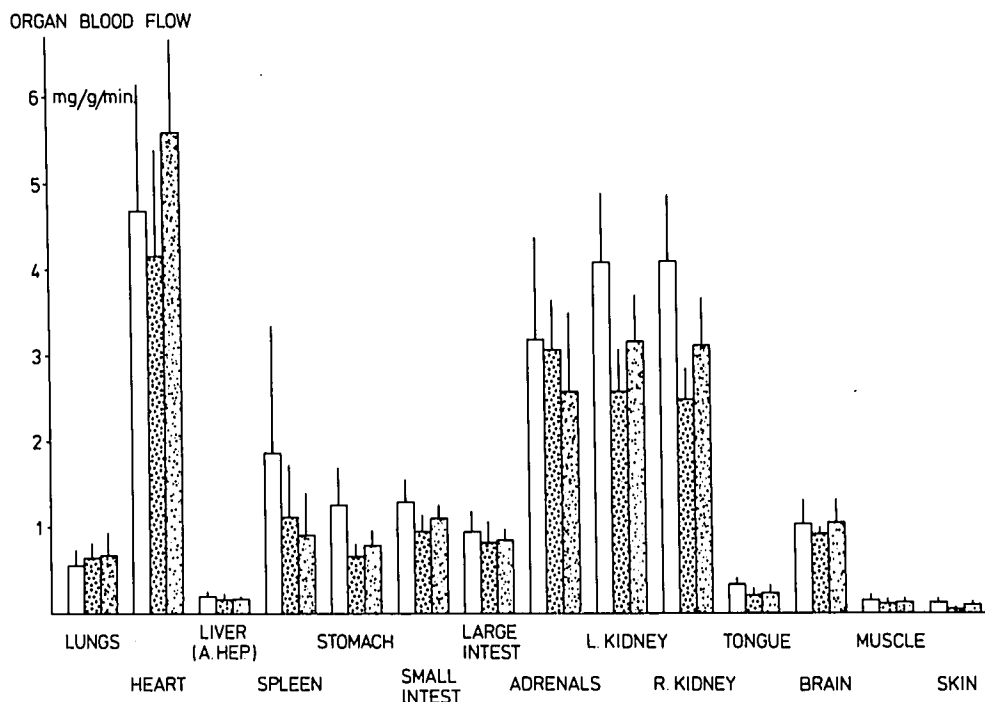


FIG. 2. Individual organ blood flows expressed as $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ shown as mean \pm SD ($n = 10$). In each group of bars, the first refers to unanesthetized normovolemic rats (Group I), the second to unanesthetized rats bled 10 ml/kg (Group II), and the third to ketamine-anesthetized rats bled 10 ml/kg (Group III). For Groups II and III measurements made 20 min after hemorrhage are shown. Significant differences in organ blood flows between Groups II and III were found in: heart, small intestine, kidneys, and skin.

TABLE 2. Measurements From Experimental Groups IV and V

	During Barbiturate Anesthesia		During Ketamine Anesthesia	
	Normovolemia	Hypovolemia	Normovolemia	Hypovolemia
Cardiac output (ml/min)	58.5 ± 4.7	38.8 ± 3.7	74.4 ± 5.4	49.2 ± 4.3
Heart rate (beat/min)	361 ± 14	457 ± 44	411 ± 20	477 ± 19
Systolic BP (torr)	121 ± 6	69 ± 9	131 ± 4	91 ± 6
Diastolic BP (torr)	78 ± 3	47 ± 6	85 ± 6	67 ± 5
pH	7.37 ± 0.04	7.29 ± 0.04	7.42 ± 0.07	7.30 ± 0.04
P _{aCO₂} (torr)	42 ± 3	34 ± 5	33 ± 7	31 ± 5
P _{aO₂} (torr)	97 ± 10	113 ± 19	107 ± 18	113 ± 9
Base excess (mmol/l)	-1.1 ± 2.2	-9.5 ± 3.3	-1.9 ± 2.2	-9.2 ± 3.6
Hematocrit (per cent)	40 ± 3	31 ± 3	39 ± 2	27 ± 4

Values are means ± SD.

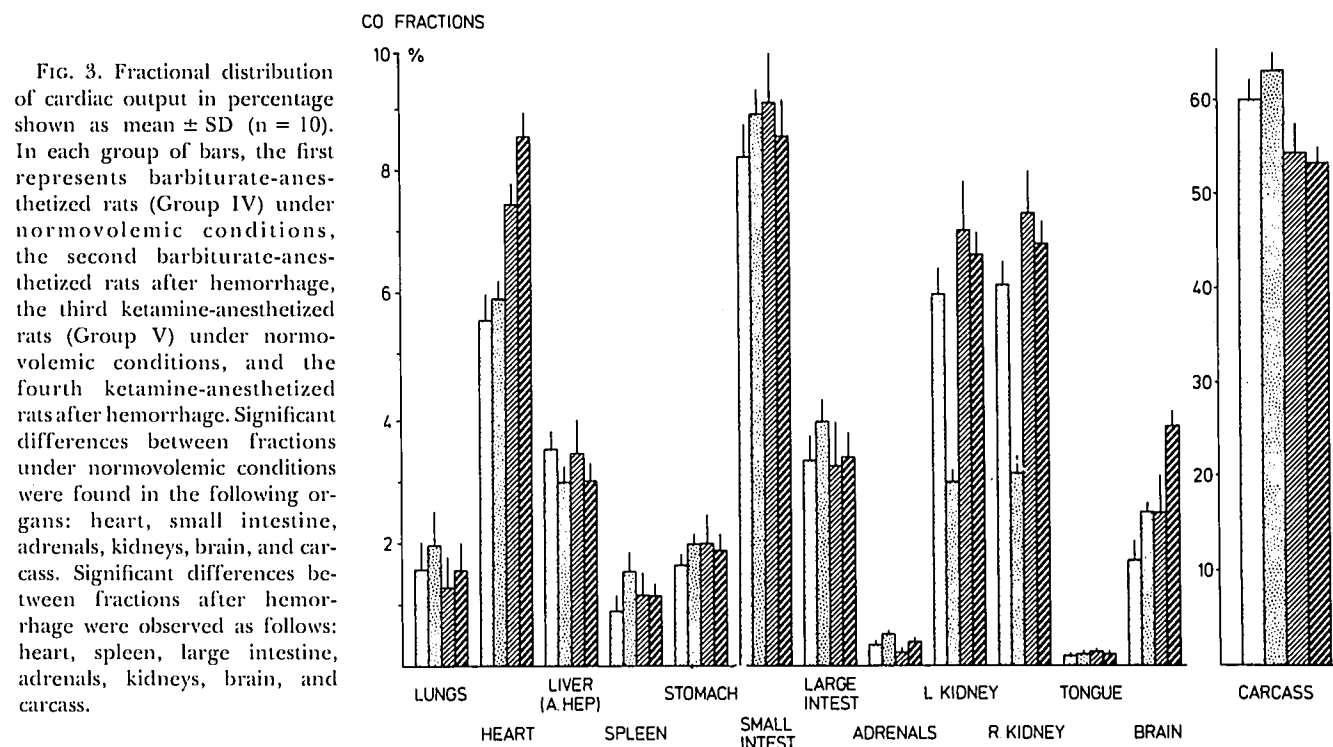
* The following significant differences were found between the groups during normovolemic conditions: cardiac output, heart rate, systolic and diastolic blood pressure, and P_{aCO₂}. Under hypo-

volemic conditions significant differences appeared in the following measurements: cardiac output, systolic and diastolic blood pressure, and hematocrit.

obtained by different techniques. We used an ¹³¹I albumin technique since it is simple and easily reproducible, and no correction was made for the difference between peripheral and whole body hematocrit. Thus, in this investigation the fixed volume loss represented approximately 14 per cent of the normal blood volume. The fixed pressure hemorrhages represented losses of 23 per cent, in the barbiturate group, and 36 per cent, in the ketamine group, of the normal blood volume. Obviously, a significantly larger blood loss was tolerated by rats anesthetized with ketamine. This agrees with the findings of Longnecker and Sturgill⁷ who hemorrhaged rats to a mean pressure of 40 torr.

Variations in depth of anesthesia may induce hemodynamic changes. To exclude this possibility the anesthetic used was administered as a continuous iv infusion. In a previous study where the infusion technique was applied, determinations of plasma concentrations of ketamine showed steady state conditions.⁹ Consistent results were obtained with pentobarbital in this investigation.

When using the microsphere technique, measurements can be subjected to large random errors in hypovolemic animals with a reduced cardiac output and low tissue perfusion rates. However, to avoid this effect large injections of microspheres were given,



ORGAN BLOOD FLOW

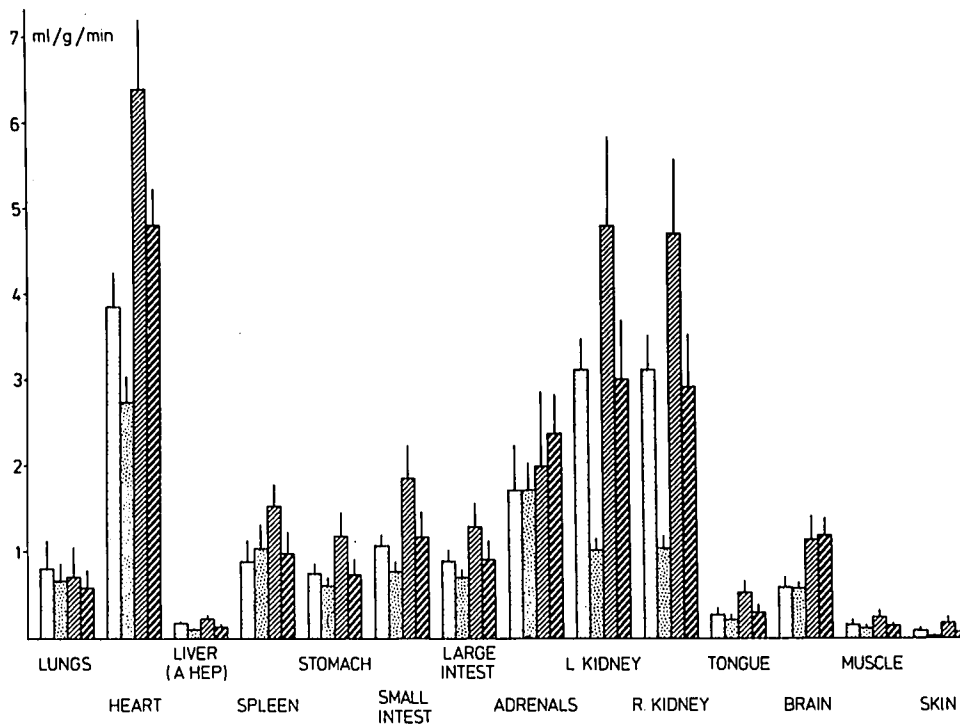


FIG. 4. Individual organ blood flows expressed as $\text{ml}\cdot\text{g}^{-1}\cdot\text{min}^{-1}$ shown as mean \pm SD ($n = 10$). In each group of bars, the first refers to barbiturate-anesthetized rats (Group IV) under normovolemic conditions, the second to the situation after hemorrhage, the third to ketamine-anesthetized rats (Group V) under normovolemic conditions, and the fourth to the situation after hemorrhage. Significant differences in organ blood flows between the two normovolemic groups were noted in the following organs: heart, stomach, small and large intestine, kidneys, tongue, and brain. After hemorrhage significant differences in organ blood flows between the two groups were observed in the following organs: heart, liver, small and large intestine, adrenals, kidneys, tongue, brain, and skin.

providing at least 400 spheres in the least perfused tissue specimen.¹⁵ On the other hand, it is also known that large numbers of microspheres might induce systemic hemodynamic effects such as decreased cardiac output and arterial pressure and increased heart rate. These effects have been described by Tsuchiya *et al.*¹⁶ However, in a methodological study¹¹ we have shown that 4.5×10^5 microspheres could be injected in unanesthetized rats without adverse circulatory effects. The same kind of microspheres, 15 μm carbonized spheres, were used in both these studies, but in the present study we used only one single thin cardiac catheter (PE-10) and dispersed the microspheres in a smaller volume (25 μl) of saline. Moreover, the blood sample following the reference sample collected for determination of cardiac output contained no radioactivity. This indicated that no microspheres had transit times beyond the time used for collection of the reference sample.

With moderate hemorrhage, cardiac output and arterial pressure were significantly reduced in awake rats. This change was associated with a diversion of blood from the carcass to the internal organs, especially the heart, lungs, adrenals, and brain. Increases in cardiac output fractions to the splanchnic organs were less pronounced, while there were no changes in fractions to the kidneys. These results are in good agreement with those of Sapirstein *et al.*,¹⁷

who studied rats under light barbiturate anesthesia with the aid of a soluble indicator, and those of Gregg *et al.*,¹⁸ who studied unanesthetized rats with the same technique.

In rats anesthetized with ketamine, moderate bleeding also induced a diversion of blood from the carcass to the internal organs. Blood flow was generally well maintained in the ketamine group due to an augmented cardiac output, and coronary blood flow was larger than in the controls. Cardiac workload and myocardial oxygen consumption are normally increased during ketamine anesthesia.¹⁹ Extraction of oxygen by the heart is nearly maximal under basal conditions, and an increase in oxygen requirement due to an increase in cardiac work can be satisfied mainly by an increase in coronary blood flow.²⁰ Presumably, this demand is fulfilled by ketamine, at least in the normal heart without coronary disease. Ketamine anesthesia was shown to produce a favorable effect on tissue perfusion in rats subjected to a 14 per cent blood loss.

In the severe bleeding experiments, arterial blood pressure was significantly better in the ketamine group 20 min after the hemorrhage. Elevation of systolic arterial pressure was 52 per cent, while in the barbiturate group it was only 15 per cent. At that time cardiac output was also significantly larger in the ketamine group.

After severe hemorrhage rats anesthetized with pentobarbital received an increased carcass fraction at the expense of the internal organs. This distribution of cardiac output following a severe bleeding was also found by Sapirstein *et al.*¹⁷ Liver (a hepatica) and kidneys were found to have especially reduced fractions, which agrees with the results of Takács *et al.*²¹ Warren and Ledingham²² have shown that pentobarbital anesthesia *per se* causes a fall in renal blood flow in the rabbit. The increase in cardiac output fraction to the carcass could indicate a relative vasodilation due to the effect of local metabolites,²³ blockade of vasoconstrictor reflexes,²⁴ or it could depend on the pentobarbital *per se* initiating dilation of peripheral small arteries and veins.²⁵

With ketamine, on the other hand, the carcass fraction was reduced following severe hemorrhage, while the fractions were preserved or increased to internal organs. Thus the compensatory mechanism seen in the moderate bleeding experiments, with increased vascular resistance of the carcass favoring blood flow to the internal organs, was maintained during severe hemorrhage by the ketamine group. Tissue perfusion of the internal organs was further enhanced by a significantly higher cardiac output in the ketamine-anesthetized rats as compared to the barbiturate-anesthetized rats. These findings are in agreement with the results of Longnecker and Sturgill⁷ who found fewer pathologic lesions resulting from splanchnic ischemia in rats anesthetized with ketamine than with other anesthetics studied. They also found a higher survival rate in ketamine-anesthetized rats. Theoretically, these beneficial effects following hemorrhage cannot be explained solely by an increased sympathetic discharge due to ketamine.²⁶ Excessive sympathetic activity has been shown to be harmful in hemorrhagic shock.²⁷ Ketamine might have other effects on the intestinal and renal vascular beds which resemble the vasodilation seen after low dose administration of dopamine.^{28,29}

After severe hemorrhage there was no significant difference in PaO₂ or PaCO₂ between the two anesthetic groups, and the rats in both groups displayed a minor increase in respiratory drive.

Rats anesthetized with either barbiturate or ketamine developed metabolic acidosis after severe hemorrhage, with reductions in pH and base excess which could result from a disturbance in the microcirculation and tissue oxygenation. Although the carcass fraction increased in the barbiturate group, blood flow in the muscle and skin specimens was reduced. In the ketamine group, the reduced carcass fraction especially affected muscle perfusion, while cutaneous blood flow was relatively well maintained.

However, these reductions in peripheral tissue perfusion may help explain the occurrence of anaerobic metabolism.

In conclusion, ketamine anesthesia in rats subjected to acute hemorrhagic hypotension, supported arterial blood pressure and cardiac output, and diverted blood to vital organs, especially heart, kidneys, and brain. The exact mechanisms responsible for these circulatory effects have not been elucidated by the present investigation, but apparently the sympathetic response to hemorrhage is affected in a favorable way by ketamine.

The applicability of these conclusions to the clinical situation has yet to be proven, although several reports advocate the beneficial effects of ketamine anesthesia in the acutely hypovolemic patient.

The author thanks Doctor Arne Hanson, Section of Toxicology, Department of Clinical Chemistry, for his help with the barbiturate assays.

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