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The Effects of Ketamine on Venous Capacitance in Rats

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The purpose of this study was to examine the effects of ketamine and pentobarbital on venous capacitance in rats. Venous capacitance was assessed by measuring the mean circulatory filling pressure (MCFP) at three levels of blood volume in conscious rats as well as during anesthesia with ketamine (125 mg/kg, ip) or pentobarbital (50 mg/kg, ip). MCFP was measured during brief periods of circulatory arrest produced by inflating an indwelling balloon in the right atrium. MCFP was maintained during ketamine anesthesia at a level similar to that measured in conscious animals, while it was decreased ($P < 0.01$) during pentobarbital anesthesia both at normal blood volume and following hemorrhage. These results suggest that ketamine did not alter but pentobarbital increased venous capacitance. The slope of the regression line relating MCFP and blood volume was not altered by ketamine but was increased ($P < 0.05$) by pentobarbital, which suggests that ketamine did not alter but pentobarbital decreased total vascular compliance. These results suggest that ketamine maintains but pentobarbital decreases venous tone. (Key words: Anesthetic, intravenous: ketamine; pentobarbital. Hemorrhage. Veins: compliance.)

THE VENOUS SYSTEM is necessary for control of circulation. A small change in venous capacitance significantly alters venous return to the heart and thus affects cardiac output.[1] It is therefore important to know the effects of anesthetic drugs on venous capacitance, particularly in a hypovolemic state.

It has been suggested that ketamine may be the drug of choice for anesthesia during hypovolemia, since it does not suppress sympathetic nervous activity.[2–5] However, the effects of ketamine on venous capacitance have not been examined.

An alteration in venous capacitance can be assessed by measuring mean circulatory filling pressure (MCFP).[1,6] MCFP is the equilibrium pressure between the veins and arteries during circulatory arrest. Thus, MCFP is a function of total vascular capacitance and blood volume. However, the capacitance of the arteries is minimal as compared with that of the veins.[1,7] Therefore, at a given blood volume, MCFP is determined largely by venous capacitance.

In this study, we examined the effect of ketamine or pentobarbital anesthesia on MCFP at a normovolemic, hypovolemic, and hypervolemic state. To examine the effects of ketamine and pentobarbital on venous capacitance, MCFP during anesthesia was compared with that in conscious animals at three levels of blood volume.

Methods

Surgical Preparation

Male Wistar rats (n = 20), weighing 380–430 g, were used for the study. With the rats under ether anesthesia, the femoral artery and vein were cannulated. The arterial catheter (Argyle cath. ID 0.053) was advanced to the iliac bifurcation, and the venous catheter (Argyle cath. ID 0.053) was positioned in the thoracic inferior vena cava. The catheters were connected to P231D Statham® transducers for recording arterial and venous pressures, respectively. A balloon-tipped catheter was placed in the right atrium through the right external jugular vein, and the proper location was tested by injecting 0.3 ml of air into the balloon to stop circulation completely. If a smooth increase in venous pressure and simultaneous decrease in arterial pressure to less than 30 mmHg were not observed, the balloon was repositioned. In preliminary studies, the position of the balloon in the right atrium was verified at the end of each experiment by inspection after thoracotomy. All catheters were tunneled subcutaneously to the back of the neck, exteriorized, and secured by sutures. After closure of the wounds, the rat was allowed to recover. Approximately 3 h after surgery, the rat was placed in a plastic box (22 × 8 × 8 cm) and left for 20–30 min to become accustomed to the experimental settings.

During experiments, rats breathed room air supplemented with oxygen. Blood gases and *p*H were measured at the end of the study (Corning® 168, Blood Gas System).

Measurements of MCFP

The mean circulatory filling pressure (MCFP) was measured by the method introduced by Yamamoto *et al.*[8] During circulatory arrest induced by balloon inflation in the right atrium, arterial and venous pressures were recorded as shown in figure 1. Immediately after the balloon was inflated, arterial pressure decreased and venous pressure increased. Venous pressure plateaued

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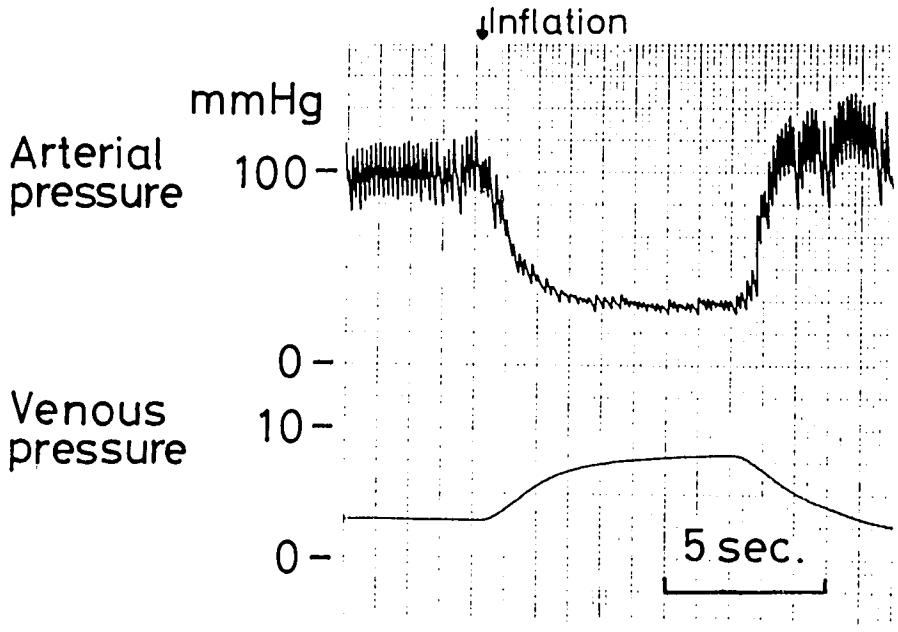

FIG. 1. Recording of arterial and venous pressure during inflation of the right atrial balloon. Arterial pressure decreased suddenly, and venous pressure increased and plateaued about 5 s after inflation.

about 5 s after inflation. MCFP was calculated from the following equation,[6,8]

$$MCFP = VPP + K(FAP - VPP)$$

where VPP is the venous plateau pressure and FAP is the final arterial pressure during circulatory arrest. K is the ratio of the arterial to venous compliance. Following the report by Yamamoto *et al.*,[8] a K value of 1/60 was used in this study.

PROTOCOL

MCFP was measured first in conscious rats at three levels of blood volume. Initially, MCFP at the baseline or normal blood volume was determined. Subsequently, blood volume was increased or decreased by 7.5 ml/kg by rapidly infusing fresh blood, which was obtained from a donor rat or removing blood through the arterial catheter, respectively. The order of transfusion and hemorrhage was randomized, and an interval of 10 min was allowed between each procedure. The rats then were divided into two groups of 10 each. One group of rats were anesthetized with ketamine 125 mg/kg intraperitoneally and the other group with pentobarbital 50 mg/kg intraperitoneally. The response to tail pinch was examined. If there was a response, a small supplemental dose of the anesthetic agent was given. Ten minutes after the administration of the anesthetic agent, by which time hemodynamic variables had stabilized, MCFP again was determined at three levels of blood volume, as was done in conscious rats. The dose of ketamine or pentobarbital was selected on the basis of previous studies by Longnecker and his colleagues.[9-11]

TABLE 1. Blood Pressures (BP), Central Venous Pressure (CVP), and Heart Rate (HR)

	n	BP (mmHg)	CVP (mmHg)	HR (beats/min)
Conscious	10	123 ± 4	3.1 ± 0.4	399 ± 12
Ketamine	10	120 ± 7†	3.0 ± 0.4	368 ± 7*
Conscious	10	119 ± 3	3.3 ± 0.2	401 ± 12
Pentobarbital	10	83 ± 3‡	3.1 ± 0.3	371 ± 15*

Mean ± SE.
* $P < 0.05$ conscious *versus* during anesthesia.
† $P < 0.01$ ketamine *versus* pentobarbital.
‡ $P < 0.01$ conscious *versus* during anesthesia.

DATA ANALYSIS AND STATISTICAL EXAMINATIONS

The slope of the MCFP-blood volume relationship was determined by regression analysis with the use of the method of least squares. Total vascular compliance was assessed from the slope of the MCFP–blood volume relationship (Δ blood volume/ΔMCFP). Student's unpaired *t* test was used for comparisons of results between ketamine and pentobarbital, and a paired *t* test was used for comparisons between the conscious state and during anesthesia. $P < 0.05$ was regarded as significant. Data are expressed as mean ± SE.

Results

Table 1 summarizes values for mean arterial pressure, central venous pressure, and the heart rate in conscious rats and during anesthesia with ketamine and pentobarbital. Ketamine did not alter but pentobarbital significantly decreased ($P < 0.01$) arterial pressure. Central

TABLE 2. Mean Circulatory Filling Pressure (MCFP) and Vascular Compliance

	n	MCFP, Normal Blood Volume (mmHg)	MCFP, Following Hemorrhage (mmHg)	MCFP, Following Infusion (mmHg)	Vascular Compliance ($ml \cdot kg^{-1} \cdot mmHg^{-1}$)
Conscious	10	7.5 ± 0.2	5.8 ± 0.2	9.9 ± 0.2	3.73 ± 0.30
Ketamine	10	7.6 ± 0.2*	5.7 ± 0.2*	9.5 ± 0.3	4.11 ± 0.33†
Conscious	10	7.6 ± 0.2	5.9 ± 0.2	9.6 ± 0.3	4.07 ± 0.29
Pentobarbital	10	6.1 ± 0.3‡	3.9 ± 0.2‡	8.8 ± 0.3	3.14 ± 0.30§

Mean ± SE.
* $P < 0.01$ ketamine *versus* pentobarbital.
† $P < 0.05$ ketamine *versus* pentobarbital.
‡ $P < 0.01$ conscious *versus* during anesthesia.
§ $P < 0.05$ conscious *versus* during anesthesia.

venous pressure was not changed by ketamine or pentobarbital. As compared with the conscious state, the heart rate was significantly slower ($P < 0.05$) during anesthesia with ketamine and pentobarbital.

Ketamine did not alter but pentobarbital significantly decreased ($P < 0.01$) MCFP at normal blood volume (Table 2, fig. 2). During ketamine anesthesia, MCFP after hemorrhage was maintained at a level similar to that in conscious rats, while during pentobarbital anesthesia it was decreased by 2.0 ± 0.2 mmHg, as compared with the conscious value ($P < 0.01$). The slope of the MCFP–blood volume relationship was steeper ($P < 0.05$) during pentobarbital anesthesia ($P < 0.05$) but was not changed significantly by ketamine anesthesia.

The Pa_{O_2} was higher than 100 mmHg in every rat. Arterial *p*H, Pa_{CO_2}, and base excess were 7.36 ± 0.03, 38 ± 3 mmHg and −3.0 ± 1.5 mEq/l, respectively, during ketamine anesthesia and were 7.35 ± 0.05, 40 ± 2 mmHg and −2.3 ± 3.3 mEq/l, respectively, during pentobarbital anesthesia. There were no differences in these values between the two groups.

Discussion

The principal finding of this study was that MCFP at normal blood volume as well as following hemorrhage was maintained during ketamine anesthesia at a level similar to that observed in the conscious state. By contrast, during pentobarbital anesthesia, MCFP significantly was decreased. These results suggest that pentobarbital increases venous capacitance, but ketamine does not alter it. This lack of effect of ketamine on MCFP and venous capacitance should contribute to maintaining venous return, thus, cardiac output, since venous return to the heart is proportional to the difference between MCFP and right atrial pressure.[1]

In this study, MCFP was calculated from venous plateau pressure and final arterial pressure during circulatory arrest produced by balloon inflation in the right atrium, using a K value of 1/60. The validity of this method for the measurement of MCFP has been discussed previously by Yamamoto *et al.*[8] They demonstrated that MCFP obtained by this method was not

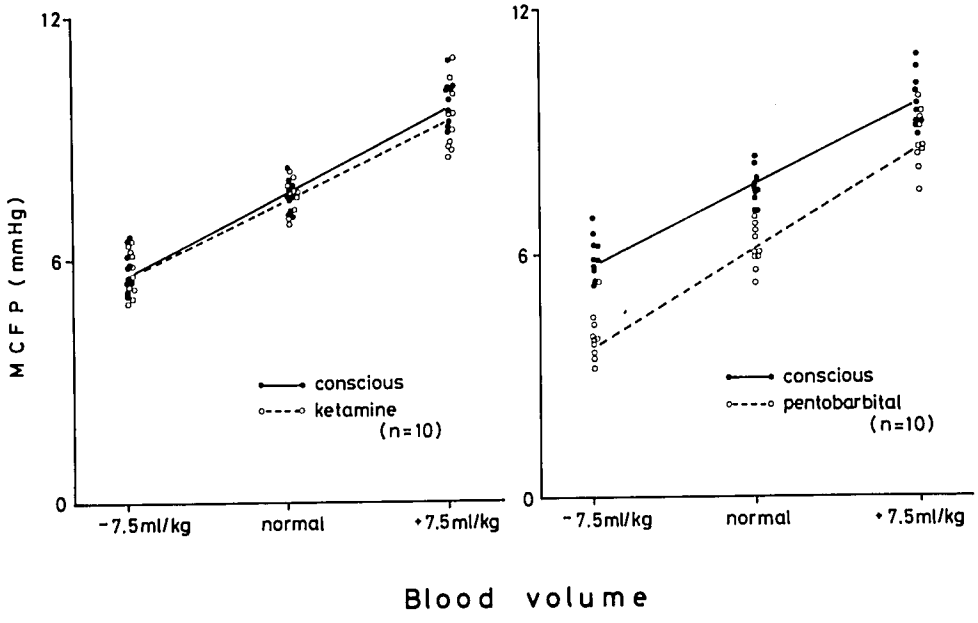

FIG. 2. The mean circulatory filling pressure (MCFP)–blood volume relationship in conscious and anesthetized rats with ketamine (left) or pentobarbital (right). Closed circles represent values in conscious rats and open circles those in anesthetized rats. MCFP at normal blood volume as well as following hemorrhage was maintained with ketamine but decreased ($P < 0.01$) with pentobarbital. Venous compliance, which is the inverse of the slope of the MCFP–blood volume relationship, decreased ($P < 0.05$) with pentobarbital but did not change significantly with ketamine.

different from MCFP obtained by the classical method using blood transfer from the arterial to venous system after circulatory arrest. The MCFP of 7.6 ± 0.2 mmHg obtained in this study at normal blood volume in conscious rats was consistent with the MCFP values reported by Yamamoto *et al.*[8] in conscious rats, as well as by Samar and Coleman,[6] who employed pulmonary artery occlusion instead of balloon inflation in the right atrium as a means to arrest circulation. Guyton *et al.*[1] also reported an MCFP value of 7.0 mmHg, using the method of artery-to-vein blood transfer in dogs in which the heart was stopped by fibrillation.

We should consider the possibility that venomotor reflexes provoked by circulatory arrest might have influenced the measurements of MCFP. However, this possibility is unlikely because reflex venoconstriction occurs 10–13 s after balloon inflation.[8] In this study the venous plateau pressure and the final arterial pressure obtained at 5 s after balloon inflation were used for calculation of MCFP.

Venous capacitance is determined by the unstressed volume and compliance of the veins.[7,12] Unstressed volume is the maximal volume of blood in the veins at zero transmural venous pressure.[12] Venous capacitance would be increased if unstressed volume or compliance of the veins is increased. Unstressed volume and compliance can be assessed from the MCFP–blood volume relationship. Venous compliance (Δ blood volume/ΔMCFP) is the inverse of the slope (ΔMCFP/Δ blood volume) given in figure 2. The unstressed volume can be assessed by extrapolating the slope of MCFP to 0 mmHg.[12] It is apparent from the slopes shown in figure 2 that pentobarbital increased unstressed volume and slightly decreased venous compliance. Ketamine had no significant effect on both unstressed volume and compliance. Thus, increased venous capacitance by pentobarbital was due to increased unstressed volume.

Several studies have shown that changes in venous tone alter unstressed volume but affect little venous compliance.[12,13] For example, intense neurogenic venoconstriction evoked by carotid sinus hypotension decreases unstressed volume to a great extent but alters little venous compliance.[13] Constricted veins exhibit decreased unstressed volume and dilated veins the reverse.[14] Thus, the results suggest that venous tone was not altered and maintained at a level similar to that in conscious state during ketamine anesthesia but was decreased during pentobarbital anesthesia. These effects of ketamine might be related to its stimulatory effects on the sympathetic nervous system.[3,4,15,16] It is suggested that pentobarbital suppresses sympathetic activity[17] which may result in decreased venous tone.

Several reports[2,9,11,18] have suggested that ketamine may be the drug of choice for anesthesia during hypovolemia. Longnecker and Sturgill[9] showed higher survival rates and fewer pathologic changes in the splanchnic organs in hemorrhaged rats anesthetized with ketamine than with pentobarbital or halothane. Idvall[18] showed that cardiac output was maintained and redistributed to the vital organs in hypovolemic rats anesthetized with ketamine. The maintenance of venous tone by ketamine may contribute significantly to these beneficial effects of ketamine on the circulation during hypovolemia, since it should contribute to maintaining venous return, thus cardiac output.

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