Venodilator Effects of Adenosine Triphosphate and Sodium Nitroprusside; Comparisons during Controlled Hypotension

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Adenosine triphosphate as well as sodium nitroprusside has been used for hypotensive anesthesia. The purpose of this study was to examine the possibility that two hypotensive drugs may exert different effects on venous capacitance during controlled hypotension. In rats anesthetized with ketamine, mean arterial pressure was lowered to 50 mmHg by intravenous infusion of adenosine triphosphate or sodium nitroprusside. Venous capacitance was assessed before and during induced hypotension by measuring the mean circulatory filling pressure (MCFP). MCFP was measured after briefly arresting the circulation by inflating an indwelling balloon in the right atrium. MCFP was lower during adenosine triphosphate-induced as well as sodium nitroprusside-induced hypotension as compared with the respective value at control ($P<0.01$ for adenosine triphosphate and sodium nitroprusside). However, the decrease in MCFP by adenosine triphosphate (0.8 ± 0.1 mmHg) was less ($P<0.01$) than that by sodium nitroprusside (2.3 ± 0.3 mmHg). These results suggest that at a comparable level of arterial hypotension venodilator effect of adenosine triphosphate was less than that of sodium nitroprusside. Less venodilatation during adenosine triphosphate-induced hypotension may contribute to the maintenance of cardiac output during hypotensive anesthesia. (Key words: induced hypotension, mean circulatory filling pressure, adenosine triphosphate, sodium nitroprusside, vein)

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It is known that adenosine triphosphate causes vasodilatation and hypotension as administered intravenously[1–3]. Adenosine triphosphate as well as sodium nitroprusside has been used for hypotensive anesthesia[4,5]. Several studies have examined the hemodynamic changes during controlled hypotension caused by adenosine triphosphate or sodium nitroprusside[3,6]. At a comparable level of hypotension, adenosine triphosphate increases cardiac output and myocardial blood flow and decreases heart rate whereas sodium nitroprusside dose not alter cardiac output or myocardial blood flow and increases heart rate[3].

However, the effect of adenosine triphosphate on veins during hypotensive anesthesia is not known. The venous system contributes importantly to the control of circulation. A small change in venous capacitance significantly alters venous return to the heart and thus cardiac output[7]. The known difference in the effect on cardiac output between adenosine triphosphate and sodium nitroprusside might be due to the difference in the effect on venous capacitance between two drugs.

The effect of drugs on venous capacitance

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can be assessed by measuring mean circulatory filling pressure (MCFP)[7,8]. 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, since arterial capacitance is quantitatively insignificant as compared with venous capacitance[7,9], it is generally accepted that, at any given blood volume, MCFP is a reliable index of venous capacitance.

In this study, we examined the effect of adenosine triphosphate or sodium nitroprusside on MCFP under ketamine anesthesia. Ketamine was used as an anesthetic drug in this study since it has been previously shown that ketamine does not alter venous capacitance[10].

Methods

Surgical Preparation

Male Wistar rats (n=23), weighing 350–430g, were used in this study. Rats were anesthetized with ketamine 125 mg/kg given intraperitoneally, and added 10 mg/kg every 30 min. The femoral artery and vein were cannulated. The arterial catheter was advanced to the iliac bifurcation, and the venous catheter was positioned in the thoracic inferior vena cava. The catheters were connected to P23ID Statham transducers for recording arterial and central venous pressure, respectively. The left external jugular vein was cannulated for the route of drug infusion. A balloon-tripped catheter was placed in the right atrium through the right external jugular vein, and the proper location was tested by injection of air (0.3 ml) into the balloon to stop the circulation completely. If a smooth increase in venous pressure and a simultaneous decrease in arterial pressure to less than 30 mmHg were not observed, the balloon was repositioned.

Tracheostomy was done and the rat was ventilated with a mixture of oxygen and room air using a Harvard small animal respirator. Blood gases and pH were measured at the end of study (Corning 168, Blood Gas system).

Measurements of MCFP

The mean circulatory filling pressure (MCFP) was measured using the technique of Yamamoto et al.[11]. Immediately after the balloon was inflated, arterial pressure decreased and venous pressure increased and reached a plateau within 4–5 seconds. Since in this method arterial and venous pressure did not completely equilibrate during circulatory arrest, MCFP was calculated according to the following equation[8,11]:

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

where VPP is the venous plateau pressure, and FAP is the final arterial pressure during circulatory arrest, and K is the arterial-to-venous compliance ratio. Following the report by Yamamoto et al.[11], a K value of 1/60 was used in this study.

Protocol

MCFP was measured at a control state as well as during hypotension produced by adenosine triphosphate or sodium nitroprusside. Each rat received either adenosine triphosphate or sodium nitroprusside. The order of the experiments with adenosine triphosphate or sodium nitroprusside was randomized. MCFP during hypotension was determined during a steady-state hypotension at the mean arterial pressure of about 50 mmHg, which was obtained 8 to 10 min after the beginning of the infusion of either drug. The drugs were diluted in physiological saline. Using a microinfusion pump (Truth, model III), adenosine triphosphate was infused intravenously at a rate of 7.5±1.5 mg/min per kg and sodium nitroprusside at a rate of 40±13 μg/min per kg. The total volumes of infusion were less than 300 μl and not different between rats receiving adenosine triphosphate and those receiving sodium nitroprusside. In order to examine the effect of blood volume expansion made by infusion on MCFP, MCFP was measured before and after infusion of physiological saline of 400 μl in other five rats.

Statistical analysis

Data are expressed as mean ± SEM. Student's unpaired t-test was used for comparisons of results between adenosine

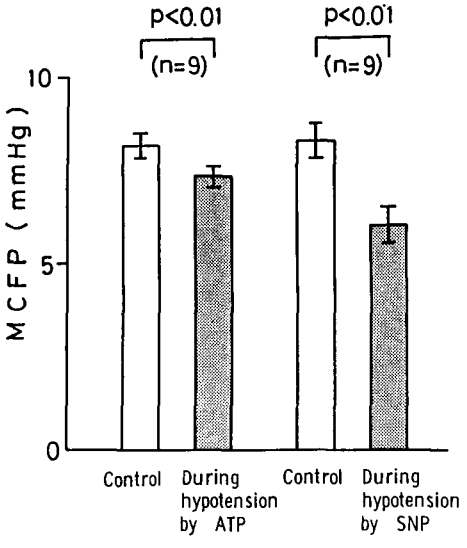

Fig. 1. The mean circulatory filling pressure (MCFP) at control and during drug-induced hypotension. Adenosine triphosphate as well as sodium nitroprusside decreased MCFP as compared with the respective value at control. However, MCFP by adenosine triphosphate (0.8±0.1 mmHg) was less than that by sodium nitroprusside (2.3±0.3 mmHg) ($P<0.01$).

triphosphate and sodium nitroprusside, and a paired t-test was used for comparisons between the control state and during drug-induced hypotension. $P<0.05$ was considered as significant.

Results

Table 1 summarizes values for mean arterial pressure, central venous pressure, and heart rate at a control state as well as during hypotension in rats treated with adenosine triphosphate or sodium nitroprusside. Mean arterial pressure, central venous pressure and heart rate at a control state were not different between rats treated with adenosine triphosphate and those with sodium nitroprusside. The drugs were infused until a steady-state hypotension at the mean arterial pressure of about 50 mmHg was achieved so that mean arterial pressure during hypotension was not different between two groups. Central venous pressure was decreased ($P<0.05$) by sodium nitroprusside but increased ($P<0.05$) by

Table 1. Mean arterial pressure, heart rate and central venous pressure at control and after adenosine triphosphate or sodium nitroprusside

	n	MAP (mmHg)	HR (beats/min)	CVP (mmHg)
Control	9	124±3	397±14	2.5±0.2
Adenosine triphosphate	9	53±2**	187±22**,&&	3.2±0.3*,&
Control	9	127±4	399±19	2.7±0.2
Sodium nitroprusside	9	49±1*	406±19	2.2±0.3*

MAP: mean arterial pressure, HR: heart rate, CVP: central venous pressure

* $P<0.05$ control vs drug-induced hypotension

** $P<0.01$ control vs drug-induced hypotension

& $P<0.05$ adenosine triphosphate vs sodium nitroprusside

&& $P<0.01$ adenosine triphosphate vs sodium nitroprusside

adenosine triphosphate during drug-induced hypotension. Heart rate was not altered by sodium nitroprusside but decreased ($P<0.01$) by adenosine triphosphate. During drug-induced hypotension sodium nitroprusside as well as adenosine triphosphate decreased MCFP as compared with the respective value at control ($P<0.01$ for both drugs) (fig. 1). However, the decrease in MCFP by adenosine triphosphate (0.8±0.1 mmHg) was less ($P<0.01$) than that by sodium nitroprusside (2.3±0.3 mmHg).

MCFP was not altered by infusion of physiological saline of 400 μl (before infusion 8.3±0.2 mmHg and after infusion 8.3±0.2 mmHg).

The Pao_2 during adenosine triphosphate-induced hypotension (230±30 mmHg) was not different from that (190±27 mmHg) during sodium nitroprusside-induced hypotension. Arterial pH, $Paco_2$ and base excess were 7.34±0.03, 35±3 mmHg, −4.2±1.5 mEq/l during adenosine triphosphate-induced hypotension and were 7.30±0.03, 36±2 mmHg and −5.0±1.8 mEq/l during sodium nitroprusside-induced hypotension, respectively. There were no difference in these values between the two groups.

Discussion

The major finding of this study is that during controlled hypotension, the decrease in MCFP by adenosine triphosphate was less than that by sodium nitroprusside in rats anesthetized with ketamine. Since MCFP largely reflects venous capacitance at a given blood volume, these results suggest that the venodilator effect of adenosine triphosphate was less than that of sodium nitroprusside at the doses to produce comparable decreases in arterial pressure.

The validity of this method for the measurements of MCFP has been discussed in the previous reports[10,11]. It has been shown that MCFP obtained by this method is not different from MCFP obtained by the classical method using blood transfer from the arterial to venous system after circulatory arrest[11]. This method has been used to examine the effect of various vasoactive drugs[11] or anesthetic agents on veins[10] and to examine the venous changes in hypertension[12].

We should consider the possibility that mechanisms other than the changes in venous capacitance had influenced MCFP during induced hypotension. In particular, we should consider the effects of fluid infusion, an anesthetic agent or possible alteration of cardiac function on MCFP.

First, adenosine triphosphate and sodium nitroprusside were given by intravenous infusion so that the resulted increase in blood volume could have altered MCFP. However, the infused volumes were less than 300 μl and were not different between adenosine triphosphate and sodium nitroprusside. Furthermore, an infusion of physiological saline of 400 μl did not alter MCFP. Thus it is unlikely that the difference between adenosine triphosphate and sodium nitroprusside in their effects on MCFP was caused by the difference in the infused volume.

Second, the study was done under ketamine anesthesia since the stable measurement of MCFP during hypotension was technically difficult to obtain in conscious rats. However, we consider it unlikely that ketamine anesthesia has altered the effects of adenosine triphosphate or sodium nitroprusside on veins. It has been shown that ketamine does not alter MCFP at the control state as well as following hemorrhage[10].

Third, despite of decreased MCFP, central venous pressure was higher during adenosine triphosphate-induced hypotension than that at control. One may consider the possibility that adenosine triphosphate might have depressed myocardial function so that central venous pressure was higher during induced hypotension. However, this possibility is unlikely since previous studies have shown that adenosine triphosphate does not suppress the myocardium and cardiac output increases during adenosine triphosphate-induced hypotension but not during sodium nitroprusside-induced hypotension[3]. We consider that the increase in central venous pressure during adenosine triphosphate-induced hypotension must have resulted from redistribution of cardiac output from splanchnic to peripheral circulation[13]. It has been shown that adenosine triphosphate causes vasodilatation powerfully in skeletal muscle and myocardium[14] in which the venous time constant is fast, and that blood flow distribution to the fast venous time constant compartment from the slow venous time constant compartment would result in a rise in the total venous return, leading to the increase in central venous pressure[15,16].

Based on these considerations we interpret the results to suggest that the venodilator effect of adenosine triphosphate is less than that of sodium nitroprusside at the doses to produce a comparable level of hypotension. It should be noted that we did not compare the dose-response curve of adenosine triphosphate with that of sodium nitroprusside. However, in the clinical use of these drugs for hypotensive anesthesia, adenosine triphosphate or sodium nitroprusside is given to obtain controlled hypotension at a certain level. Therefore, it is clinically important to know the relative strength of the venodilator effect of these drugs at the doses to produce a comparable

level of hypotension.

The results of this study may have an important clinical implication. Less venodilatation produced by adenosine triphosphate would beneficial because it would contribute to maintaining venous return and thus cardiac output. Previous studies have shown that adenosine triphosphate increases but sodium nitroprusside does not alter cardiac output when comparable levels of hypotension were achieved[3]. The difference in the effect on cardiac output between the two drugs could be accounted for in part by the difference in their effects on veins.

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