Korean J Physiol Pharmacol
Vol 2: 345−351, June, 1998

Nitric Oxide Impairs the Recovery from Hemorrhagic Hypotension in Conscious Rats

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The role of nitric oxide (NO) in the hemorrhagic hypotension was examined using a NO synthase inhibitor, N^{ω}-nitro-L-arginine methyl ester (L-NAME), in conscious rats. The rats were bled at a constant rate (2 ml/kg/min) through a femoral arterial catheter until the mean arterial pressure (MAP) was reduced by 50 mmHg. We studied the responses to hemorrhage under normal condition (Control) and after the pretreatment with 3 doses of L-NAME (1.6, 8, 40 mg/kg i.v. of NOX1.6, NOX8, and NOX40, respectively). Intravenous bolus injection of L-NAME produced a sustained increase in MAP and decrease in heart rate (HR). During hemorrhage, the MAP fell faster in the NOX8 and NOX40-treated groups than in Control group, but the control group showed same response to NOX1.6. HR greatly increased in NOX groups. The recovery from hemorrhagic hypotension was slowed in the control group, which was not treated with L-NAME. In comparison with the control group, NOX8 and NOX1.6-treated groups registered a significant recovery in MAP during the 15 min recovery period, but NOX40 brought about only a slight increase in MAP. NO precursor, L-arginine (150 mg/kg i.v.), produced significant bradycardic responses before and after hemorrhage and significant depressor response only after hemorrhagic hypotension regardless of pretreatment with L-NAME. These data suggest that the role of NO in blood pressure regulation is greater after hemorrhagic hypotension than basal condition, but the effect of NO can be detrimental to the recovery from hemorrhagic hypotension. In addition, the bradycardic response of L-arginine provides indirect evidence that NO may inhibit sympathetic activity, especially after hemorrhagic hypotension.

Key Words: hemorrhagic hypotension, nitric oxide, L-NAME, L-arginine

INTRODUCTION

Nitric oxide (NO), which accounts for endothelium-dependent vasodilation, is synthesized from L-arginine in the presence of its synthetic enzyme NO synthase (NOS) (Palmer et al, 1988). N^{ω}-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor, increases arterial pressure (Sakuma et al, 1992; Koch et al, 1995). The increase in arterial pressure is primarily due to vasoconstriction (Koch et al, 1995) and can be at least partially reversed by using L-arginine. These indicate that NO can tonically dilate peripheral blood vessels under basal conditions.

NO release has been implicated in the hypotension associated with hemorrhagic shock (Liberthal et al, 1991; Thiemermann et al, 1993) and endotoxic shock (Szabo et al, 1993).

Park et al (1995) demonstrated that the maintenance of arterial pressure during hemorrhage was mediated almost entirely by the autonomic neural functions. In addition, the tachycardic response being attenuated in hypotensive period was observed. Schadt & Ludbrook's study (1991) supports our findings. Severe hemorrhage produces widespread vasodilation and sympathetic inhibition rather than activation. NO induced vascular hyporeactivity to vasoconstrictors in hemorrhagic shock (Thiemermann et al, 1993), and the compensatory effect of increased

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humoral agents can be diminished by vasodilator effect of increased NO. Kanagy (1997) recently reported increased vasoconstrictor response to norepinephrine during NOS inhibition-induced hypertension. Therefore, the inhibition of NO production may enable greater expression of vasoconstrictor influences and improve the therapeutic outcome from hemorrhagic shock.

It has been documented that the baroreceptor reflex is the most powerful and rapidly acting autonomic mechanism in maintaining blood pressure (Korner et al, 1990; Park et al, 1995). Scrogin et al (1998) showed that NO decreasing baroreflex gain but not affecting cardiac sympathetic tone. However, others reported that NO decreased baroreflex gain (Minami et al, 1995; Liu et al, 1996). Matsumura et al (1998) also noted that the central L-NAME produced pressor response due to the increased sympathetic outflow. In short, the effects of NO on the baroreceptor reflex or sympathetic activity are yet to be defined.

Accordingly, we examined the role of NO during acute hemorrhage and recovery from hemorrhagic hypotension in the conscious rats. With the NOS inhibitor L-NAME, we compared the circulatory responses to acute hemorrhagic hypotension with and without pretreatment.

METHODS

Animals and operations

The experiments were performed in conscious male Sprague-Dawley rats. Under anesthesia with pentobarbital sodium (50 mg/kg, i.p.), polyethylene catheters (PE-50, Clay Adams) filled with heparinized saline (50 U/ml) were inserted into the femoral vein for drug injection. Cannulae were also inserted into the abdominal aorta via both femoral arteries for hemorrhage and for the measurement of arterial pressure. After the surgery, the rats were allowed to regain consciousness for about 3 hours because the anesthetics attenuates baroreceptor reflex (Stornetta et al, 1987) and can alter compensatory responses to hemorrhage (Zimpfer et al, 1982). The arterial catheter was connected to a pressure transducer (model P23XL, Ohmeda) linked to a polygraph (Model 79, Grass Instruments, Quincy, MA). Electronically damped mean arterial pressure (MAP) and heart rate (HR) were continuously recorded throughout the experiment. Drugs for i.v. injection were dissolved in 0.9% NaCl.

Cardiovascular responses to different degrees of hemorrhagic hypotension

Rats were divided into two groups and were given an intravenous injection of saline or N^{ω}-nitro-L-arginine methyl ester (L-NAME; Sigma Chemicals, St. Louis, MO). In saline control group, the rats were randomly subdivided into 2 groups to compare the cardiovascular responses to hemorrhagic hypotension of 2 different degrees. Fifteen minutes after i.v. injection of saline (1 ml/kg), arterial blood was withdrawn into a syringe at a constant rate of 2 ml/kg /min, using an infusion/withdrawal pump (Model 55-2226, Harvard Apparatus) until MAP was reduced by 30 (Control-30) or 50 mmHg (Control). After hemorrhage, we continuously recorded the spontaneous recovery from hemorrhagic hypotension for 15 min.

Effects of NO synthase inhibitor on cardiovascular responses to hemorrhagic hypotension

In another series of experiments, we studied the role of NO on hemorrhagic hypotension, using 3 different doses of L-NAME (1.6, 8, and 40 mg/kg i.v.; NOX1.6, NOX8, and NOX40 group, respectively). Fifteen minutes after i.v. injection of L-NAME, hemorrhage was induced by aforementioned method until MAP was reduced by 50 mmHg. During hemorrhage, the duration of hemorrhage or blood loss required to reach the target MAP varied among rats. Therefore, hemorrhage data were normalized to the percentage of total blood loss to allow statistical comparisons at similar points, as Koch et al (1995) did. Total blood loss necessary to reduce MAP by 50 mmHg was considered as 100%.

Effects of NO precursor on cardiovascular responses after hemorrhage

We examined the role of NO in the recovery of hemorrhagic hypotension in 3 different conditions. To compare the cardiovascular responses of NO precursor treatment before and after hemorrhagic hypotension, L-arginine (150 mg/kg, i.v.; Sigma Chemicals, St. Louis, MO) was injected to a basal condition without any treatment and 15 min after hemorrhage

with saline- or NOX8-pretreatment.

Statistical Analysis

All data are presented in mean±SE. Unpaired t-test was used to make comparisons between groups, and paired t-test was used for paired observations within a group. Probability levels of less than 0.05 were considered statistically significant.

RESULTS

Effect of NO synthase inhibition on MAP and HR

Baseline values of MAP and HR before experiment are presented in Table 1. Values of all groups were similar before the experiment. Effects of intravenous bolus injection of L-NAME on MAP and HR are summarized in Table 2. L-NAME injection produced a significant increase in MAP and a decrease in heart rate. At large doses (NOX8 and NOX40), pressor and bradycardic responses were greater than at a small dose (NOX1.6), but the responses caused by NOX8 and NOX40 were not different. In control groups, however, the same volume of saline injection did not produce any changes in MAP and HR (Data not shown).

Effects of NO synthase inhibition on cardiovascular responses to hemorrhage

Cardiovascular responses during hemorrhage are presented in Fig. 1. In control groups (Control-30 and Control), the overall hypotensive response pattern was similar in spite of the differences in the amount of blood lost. Control-30 showed a slower fall than Control because of our normalization method (see methods). The total hemorrhage time spent to reduce MAP by 30 mmHg was not different between them (5.81±0.78 vs. 6.44±0.62 min in Control-30 and Control, respectively). HR increased according as MAP decreased, but the increase was mitigated and even reduced at the end of hemorrhage. The re-

Table 1. Basal values of mean arterial pressure (MAP), heart rate (HR), and body wt

	Control-30	Control	NOX1.6	NOX8	NOX40
MAP (mmHg)	115±2	108±2	112±1	113±2	115±3
HR (beats/min)	422±4	425±9	423±8	446±13	399±12
wt (g)	345±16	357±15	363±16	344±13	361±9
n	5	7	6	8	6

Values are mean±SE.
Control-30, reduction of MAP by 30 mmHg with no pretreatment; NOX, pretreatment with nitric oxide synthase inhibitor (L-NAME; 1.6, 8, 40 mg/kg i.v.); n, number of rats.

Table 2. Effects of L-NAME on mean arterial pressure (MAP) and heart rate (HR)

L-NAME (mmHg)	1.6			8			40		
	Before	After	Change	Before	After	Change	Before	After	Change
MAP (mmHg)	111±1	124±3**	14±3	112±2	133±5**	21±5	116±2	143±5***	27±4$^{\#}$
HR (beats/min)	430±8	403±7***	−27±3	449±12	394±8**	−55±12	400±12	350±19*	−49±12
n		6			8			6	

Values are mean±SE, n indicates number of rats.
Before and After indicate values before and maximal changes after L-NAME injection, respectively.
$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ compared with corresponding Before values
$^{\#}p<0.05$ compared with Change values in NOX1.6 group

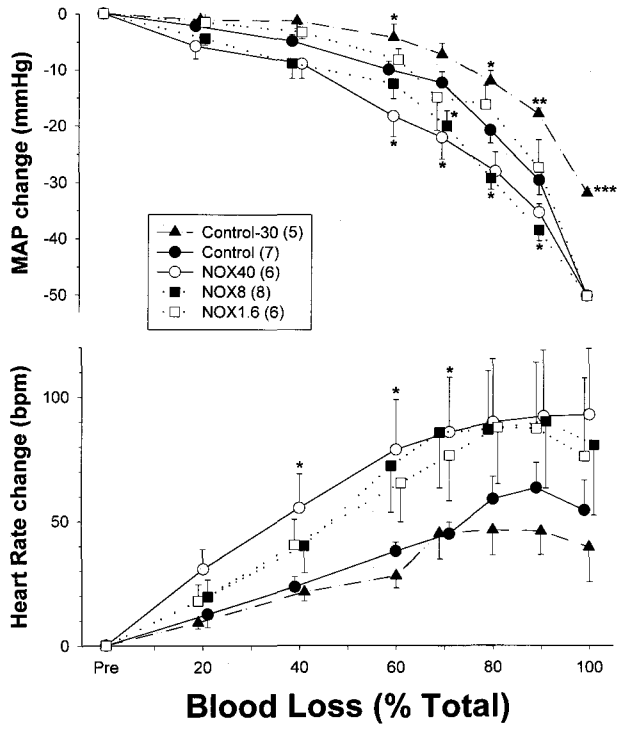

Fig. 1. Effects of L-NAME on cardiovascular responses to hemorrhagic hypotension. Values are mean±SE; numbers in the parentheses indicate number of rats. Normalization method of total hemorrhage time and the abbreviations for each group are shown in the text. *p< 0.05, **p<0.01, ***p<0.001 compared with corresponding Control values.

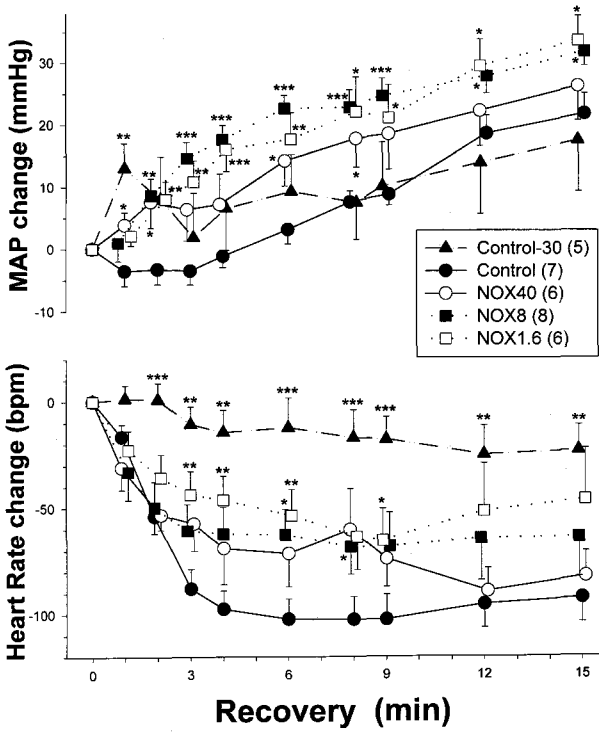

Fig. 2. Effects of L-NAME on cardiovascular responses during recovery period after hemorrhagic hypotension. Values are mean±SE; numbers in the parentheses indicate number of rats. Abbreviations for each group are shown in the text. *p<0.05, **p<0.01, ***p<0.001 compared with corresponding Control values.

sponses in L-NAME-treated groups were different from that of the Control. The total hemorrhage time was not significantly different among them (Data not shown), but L-NAME treated groups except NOX1.6 showed a faster fall than Control, especially after 60% of total hemorrhage time. HR responses of all L-NAME treated groups were greater than Control.

Effects of NO synthase inhibition on cardiovascular responses during recovery period

Fig. 2 shows the recovery from hemorrhagic hypotension for 15 min. In Control, the MAP recovery from hemorrhagic hypotension was attenuated compared with other groups and was even more decreased during first 4 min. NOX8 and NOX1.6 produced a significant enhancement of recovery of MAP compared to Control throughout the recovery period for 15 min, but NOX40 showed a slight enhancement. Elevated HR during hemorrhage was generally decreased to their prehemorrhage values, but Control showed a significant decrease and even below the prehemorrhage level. HR of NOX groups still remained elevated compared to Control.

Effects of NO precursor on cardiovascular responses before and after hemorrhage

In Table 3, the cardiovascular responses of L-arginine before and after hemorrhage are summarized. In prehemorrhage condition, L-arginine did not change MAP, but HR was significantly decreased. After 15 minutes of recovery period, administration of L-arginine caused a marked decrease in MAP and an increase in HR compared to prehemorrhage values, but the responses were not significantly different between Control and NOX8.

DISCUSSION

In this study, the inhibition of NOS produced a

Table 3. Effects of L-arginine (15 mg/kg) on mean arterial pressure (MAP) and heart rate (HR) before and after hemorrhage

	Before Hemorrhage			After Hemorrhage					
				Control			NOX8		
	Before	After	Change	Before	After	Change	Before	After	Change
MAP (mmHg)	111±2	108±1	−4±2	92±7	72±8***	−21±1$^{\#\#\#}$	114±3	95±4***	−19±2$^{\#\#}$
HR(beats/min)	405±16	388±16*	−17±6	393±20	351±17***	−41±5$^{\#}$	414±8	371±7***	−43±3$^{\#\#\#}$
n		5			8			15	

Values are mean±SE.
Before and After indicate values before and maximal changes after L-arginine injection (150 mg/kg i.v.), respectively.
$^{*}p<0.05$, $^{***}p<0.001$ compared with corresponding Before values
$^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ compared with Change values in Before Hemorrhage.

significant increase in MAP under basal condition, and also the hypotensive action of L-arginine, NO precursor, is greatly expressed after hemorrhagic hypotension compared with the basal condition. These findings provide that NO plays an hypotensive role after hemorrhage as well as under resting condition. In addition, the present study provides evidence that NOS improves the recovery from hemorrhagic hypotension in the conscious rat.

This study confirms earlier work on the pressor effects of intravenous administration of L-NAME, which indicated that continuous release of endogenous NO maintains a vasodilator tone under basal conditions (Sakuma et al, 1992; Koch et al, 1995; Chen & Hu, 1997). However, two larger doses (8 and 40 mg/kg) used did not show dose-dependent manner. Chen & Hu (1997) also reported this finding (10 and 30 mg/kg) in conscious normotensive and hypertensive rats. This finding had led to a hypothesis that NOS inhibitor has a maximal pressor limit probably due, at least in part, to other counterregulatory mechanisms.

There is another consideration required to evaluate the role of NO in the regulation of blood pressure. In the present study, L-arginine, a precursor of NO, produced a significant depressor response only after hemorrhagic hypotension. We supposed that under resting condition the basal vasoconstrictor tone counteracts the vasodilator action of exogenous L-arginine, and it is possible that the dose that was used was insufficient to express further vasodilation. In contrast, L-arginine produced significant bradycardic responses before and after hemorrhagic hypotension. It was very unprecedented finding because depressor response generally elicits baroreflex-mediated tachycardia. These findings have never been described previously, but it provides very limited indirect evidence that NO contributes sympathoinhibition during hemorrhagic hypotension. Other studies partially support our result; central and peripheral NOS inhibition increased MAP due to an increased sympathetic outflow (Sakuma et al, 1995; Matsumura et al, 1998), but Scrogin et al (1998) failed to reveal any change in sympathetic activity. Therefore, the reason is not clear at present, and additional studies may be required to explain these questions.

In the conscious animals, the maintenance of arterial pressure early in hemorrhage is primarily due to increased sympathetic nervous system activity resulting from unloading of arterial baroreceptors (Burke & Dorward, 1988; Korner et al, 1990; Schadt & Ludbrook, 1991; Park et al, 1995). MAP decreased abruptly during the late hemorrhage and decreased further in the beginning of recovery period. HR greatly decreased in spite of sustained hypotension during recovery period. Major determinant of these findings is thought to be withdrawal of sympathetic vasoconstrictor drive and subsequent peripheral vasodilation (Burke & Dorward, 1988; Schadt & Ludbrook, 1991). We observed that NOX8 and NOX40 showed slightly faster fall in MAP than Control during hemorrhage, but total hemorrhage time were not significantly different among them (data not shown). It is probably due to an inhibition of the blood pressure buffering action of NO (Just et al, 1994; Nafz et al, 1997).

Recent studies have reported that NOS inhibition increased MAP during hypovolemic shock (Liberthal et al, 1991; Koch et al, 1995), and it might be due to excessive NO production and/or release. In this experiment, L-NAME pretreatment increased MAP more than saline at the start of hemorrhage. Faster recovery in L-NAME-treated rats might be due to an elevated baseline pressure, but Koch et al (1995) reported that the effect of L-NAME was not due to the resetting of baseline hemodynamics in conscious rabbits. In their study, infusion of phenylephrine did not prevent or limit the increase in vascular conductance after hemorrhagic hypotension, although phenylephrine and L-NAME produced similar hemodynamic changes. They also suggested that NO release increased more after blood pressure fall than under basal conditions or during normotensive period of hemorrhage. Therefore, we may explain that the hemorrhagic hypotension with peripheral vasodilation is due to the combined effects of decreased sympathetic activity and increased release of NO.

On the other hand, the decrease in MAP and the increase in vascular conductance after hemorrhagic hypotension occur despite increased release of vasopressor agents such as angiotensin II, arginine vasopressin, and epinephrine (Schadt & Gaddis, 1990; Schadt & Hasser, 1991; Park et al, 1995). Interestingly, arginine vasopressin and epinephrine also release NO from endothelial cells in cerebral and pulmonary arteries (Katusic, 1992; Russ & Walker, 1992). The pressor effects of these humoral agents may be hindered by their release of NO. In other words, NOS inhibitor can potentiate pressor responses to other vasoconstrictors (Conrad & Whittemore, 1992). Another possible explanation for the rapid recovery associated with L-NAME pretreatment is the failure of sympathoinhibitory mechanisms after hemorrhagic hypotension. Sakuma et al (1992) reported that N-methyl-L-arginine, another NOS inhibitor, stimulated renal sympathetic nerve activity in the anesthetized rats. It suggests that NO may act centrally to inhibit sympathetic tone. HR increased greatly during hemorrhage and slightly decreased during recovery period in spite of the same degrees of hemorrhagic hypotension in L-NAME-treated groups. It may also be due to suppression of sympathoinhibitory mechanisms. In other words, when NOS is inhibited, sympathetic activities continue even when they are otherwise depressed.

Although NOS inhibitor improves the recovery of arterial pressure from hemorrhagic hypotension, it is still debated whether the NOS inhibitor contribute to the long-term recovery or survival from hemorrhagic hypotension. Vromen et al (1996) suggested that NOS inhibitor in severe hemorrhagic shock might have beneficial effects on blood pressure and survival, while Mellander et al (1997) reported that NO was essential for survival after acute hemorrhage. According to the studies of Yao et al (1996), low dose of NOS inhibitor increased survival rate after hemorrhagic shock, but high dose increased damage to various organs. Taken all these together, we suggest that the therapeutic dose range of NOS inhibitor is narrow; administration of higher doses of the NOS inhibitors increases mortality despite the recovery of arterial pressure, presumably resulting from widespread vasoconstriction (Koch et al, 1995). However, we did not assess the long-term survival and/or organ function. Certainly, additional studies are required to elucidate potential adverse effects of NO synthase inhibition during the treatment of several types of severe hypotension.

In conclusion, NO plays a more important role in blood pressure regulation after hemorrhagic hypotension than basal conditions, but the effect of NO might be detrimental to the recovery from hemorrhagic hypotension.

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