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Effects of L-arginine and *N*-Nitro-L-arginine treatment on hemodynamics, DO_2, VO_2, and extravascular lung water in a dog endotoxin shock model

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Abstract: To verify the effect of nitric oxide pathway modification during sepsis, experiments were conducted in four groups of anesthetized dogs which received lipopolysaccharide (LPS) intravenously (group 1), 300 mg·kg^{-1} of L-arginine plus LPS (group 2), 20 mg·kg^{-1} of *N*-nitro-L-arginine plus LPS (L-*N*NA, group 3), and normal saline as the control group. Hemodynamic and oxygenation data as well as extravascular lung water (EVLW) were measured or calculated. The results showed that L-arginine increased cardiac output index (CI) and decreased the peripheral vascular resistance index (PVRI) without a significant influence on oxygen extraction ratio (O_2ER), oxygen delivery (DO_2), or oxygen consumption (VO_2). All of the untoward hemodynamic effects of LPS were exacerbated by the addition of L-*N*NA. Therefore, as DO_2 was significantly decreased by L-*N*NA, and although O_2ER was increased (insufficiently), VO_2 was still decreased significantly. EVLW was markedly increased by L-*N*NA. These results support the hypothesis that inhibition of nitric oxide synthesis may exacerbate hemodynamic and oxygenation consequences in septic shock.

Key words: L-arginine, *N*-nitro-L-arginine, Endotoxin shock

Introduction

Nitric oxide (NO) plays an important physiologic and pathophysiologic role in the regulation of vascular tone [1] and in the mediation of vascular abnormalities during sepsis [2,3]. Inhibition of nitric oxide synthesis has been noted to ameliorate the altered hemodynamics during endotoxin shock in animals [4]. However, recent experimental results [5], which show that inhibition of nitric oxide synthesis further decreased cardiac output (CO) via vasoconstriction, challenge the use of nitric oxide synthesis inhibitors for improvement of hemodynamics during septic shock.

Over the last 5 years, there have been great efforts to demonstrate the necessity of increasing oxygen delivery to match a large increment in oxygen demand during sepsis in order to limit organ ischemia and dysfunction [6]. Therefore, the effects of inhibition of nitric oxide synthesis, focusing not only on perfusion flow but also on oxygenation, need to be clarified.

To investigate the role of nitric oxide in altered pulmonary hemodynamics and oxygenation, the present study examined the effects of an inhibitor of nitric oxide synthesis and of a precursor of nitric oxide generation on systemic and pulmonary hemodynamics, oxygen delivery (DO_2), oxygen consumption (VO_2), and extravascular lung water (EVLW) in a dog model of endotoxin shock.

Materials and methods

Short-term experiments were conducted in four groups of anesthetized dogs (weighing 13–16 kg). The dogs were anesthetized with sodium pentobarbital (25 mg·kg^{-1}), providing additional doses if necessary. Endotracheal intubation was performed, and throughout the experiment spontaneous respiration with room air was kept. The femoral arteries and veins were cannulated for monitoring mean arterial pressure (MAP) and for intravenous administration of lipopolysaccharide (LPS), L-arginine, and *N*-nitro-L-arginine (L-*N*NA).

A Swan-Ganz catheter (5F, American Edwards Laboratories, Irvine, CA, USA) was inserted via the isolated right external jugular vein and positioned in the pulmonary artery for measurement of central venous (CVP), pulmonary arterial (MPAP), and pulmonary arterial wedge pressures (PAWP). CO was determined as an average of three measurements

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by the thermodilution technique with a CO computer (SL Monitor, SpaceLab, Redmond, WA, USA). Continuous electrocardiographic monitoring was performed throughout the experiment for measurement of heart rate (HR).

Blood specimens were taken from the femoral artery and pulmonary artery for determination of oxygen pressure (PO_2), carbon dioxide pressure (PCO_2), hemoglobin concentration, and oxygen saturation using a blood gas analyzer (ABL3, Radiometer, Copenhagen, Denmark) and for calculation of DO_2, oxygen extraction ratio (O_2ER), and VO_2.

The dogs were allowed to stabilize for 30 min after cannulation before any other experimental manipulation, and were then randomly assigned to one of four experimental protocols. None of the dogs received any fluids except for a small solution of LPS, L-arginine, and L-*N*NA.

Group 1 (n = 8): endotoxin shock

After baseline hemodynamic parameters and blood samples had been obtained, 2 mg·kg^{-1} of LPS (*Escherichia coli* serotype O55:B5, Sigma Chemical, St. Louis, MO, USA) was infused intravenously over 5 min. Hemodynamic measurements and blood samples were obtained at 30, 60, 120,180, and 240 min thereafter.

Group 2 (n = 8): endotoxin shock treated with L-arginine

Three hundred mg·kg^{-1} of L-arginine (Sigma Chemical) dissolved in sterile saline was administered intravenously 30 min prior to infusion of LPS. Hemodynamic measurements and blood samples were also obtained at 30, 60, 120, 180, and 240 min after LPS administration.

Group 3 (n = 8): endotoxin shock treated with L-NNA

The experimental protocol for this group was the same as that of group 2, except that 20 mg·kg^{-1} of L-*N*NA (Sigma Chemical) dissolved in sterile saline was administered intravenously instead of L-arginine. Hemodynamic observations and blood samples were also

Table 1. Hemodynamic variables in the three groups treated with endotoxin (group 1) and pretreated with L-arginine (group 2) or L-*N*NA (group 3) in addition to endotoxin

					Minutes after administration of LPS				
		n	Baseline	0#[a]	30	60	120	180	240
MAP (mmHg)	Group 1	8	136.6 ± 11.6		75.6 ± 22.7**	68.9 ± 17.5**	70.6 ± 15.4**	82.6 ± 12.9**	90.3 ± 14.3**
	Group 2	8	132.6 ± 10.0	123.0 ± 16.0	76.9 ± 9.5**	79.9 ± 17.9**	80.1 ± 20.0**	87.8 ± 16.4**	92.3 ± 16.0**
	Group 3	8	134.4 ± 11.6	146.4 ± 12.1	89.5 ± 22.3**	96.5 ± 23.5*,**	100.6 ± 22.8*,**	107.5 ± 24.1*,**	110.8 ± 26.9**
MPAP (mmHg)	Group 1	8	14.0 ± 0.9		10.1 ± 0.3**	9.5 ± 1.8**	11.3 ± 1.7**	11.6 ± 1.8**	12.5 ± 1.9**
	Group 2	8	14.7 ± 1.8	11.5 ± 3.3**	10.0 ± 4.1**	10.5 ± 3.2**	10.6 ± 3.6**	10.7 ± 3.2*,**	11.3 ± 2.9**
	Group 3	8	16.1 ± 2.4	17.3 ± 2.1	11.6 ± 2.1**	12.9 ± 1.9*	12.6 ± 1.4	14.5 ± 1.8*	14.9 ± 1.8**
HR (bpm)	Group 1	8	189.9 ± 15.0		155.6 ± 29.7**	148.3 ± 30.4**	159.0 ± 22.3**	156.3 ± 12.3**	153.1 ± 19.4**
	Group 2	8	180.2 ± 25.3	172.0 ± 21.4	141.4 ± 26.1**	147.3 ± 28.9**	145.3 ± 23.8**	145.6 ± 27.7**	148.3 ± 31.5**
	Group 3	8	180.4 ± 31.1	169.4 ± 24.6	157.1 ± 47.8**	175.5 ± 38.1	170.4 ± 37.2	159.6 ± 29.1**	169.2 ± 36.2
PCWP (mmHg)	Group 1	8	3.3 ± 1.2		2.5 ± 1.5	2.3 ± 1.4	2.4 ± 1.5	2.1 ± 1.6	2.3 ± 1.5
	Group 2	8	4.1 ± 1.1	4.0 ± 1.0	3.3 ± 2.1	3.5 ± 2.3	3.3 ± 1.9	3.2 ± 1.9	3.3 ± 1.8
	Group 3	8	4.8 ± 1.4	4.2 ± 1.2	3.5 ± 1.4	4.3 ± 1.1	3.3 ± 1.4	3.7 ± 1.1	4.0 ± 1.1
CVP (mmHg)	Group 1	8	4.1 ± 0.9		2.5 ± 0.6**	2.1 ± 0.8**	2.6 ± 0.4**	2.2 ± 1.1**	2.7 ± 0.9**
	Group 2	8	4.5 ± 0.3	3.8 ± 0.4	2.0 ± 1.0**	2.2 ± 0.9**	2.6 ± 0.4**	2.2 ± 1.1**	2.7 ± 0.9**
	Group 3	8	3.9 ± 0.6	3.6 ± 0.6	1.0 ± 0.7**	1.8 ± 1.2**	1.1 ± 0.8*,**	1.6 ± 1.1**	2.0 ± 0.5**
CI (L·m^{-1}·m^{-2})	Group 1	8	3.8 ± 0.2		2.1 ± 0.4**	2.2 ± 0.5**	2.2 ± 0.4**	2.4 ± 0.5**	2.5 ± 0.6**
	Group 2	8	3.9 ± 0.1	4.0 ± 0.3	2.6 ± 0.8**	2.7 ± 0.7*,**	2.8 ± 0.9*,**	2.7 ± 0.8**	2.8 ± 0.8*,**
	Group 3	8	3.9 ± 0.3	3.8 ± 0.1	1.8 ± 0.8**	1.8 ± 0.6*,**	1.4 ± 0.5*,**	1.3 ± 0.4*	1.2 ± 0.5*
SI (ml·beats^{-1}·m^{-2})	Group 1	8	20.5 ± 1.9		13.8 ± 2.5**	15.3 ± 3.2**	14.4 ± 2.9**	15.6 ± 3.6**	17.6 ± 4.8**
	Group 2	8	21.9 ± 3.6	23.4 ± 1.1	17.8 ± 4.5**	19.4 ± 4.9*	18.8 ± 4.6*	19.1 ± 3.8*	19.0 ± 3.5
	Group 3	8	22.3 ± 3.8	24.4 ± 2.8	12.5 ± 6.2**	10.3 ± 2.9*,**	8.3 ± 2.3*,**	8.0 ± 1.9*,**	7.4 ± 2.2*,**
SVRI	Group 1	8	2785 ± 384		2708 ± 570	2466 ± 658	2402 ± 566	2704 ± 801	2801 ± 768
(dynes·s·cm^{-5}·m^{-2})	Group 2	8	2676 ± 298	2412 ± 279	2698 ± 665	2495 ± 642	2354 ± 523	2551 ± 426	2706 ± 409
	Group 3	8	2662 ± 372	3101 ± 297**	4320 ± 1177*,**	4451 ± 962*,**	5844 ± 1344*,**	6554 ± 1137*,**	7574 ± 1561*,**
PVRI	Group 1	8	238.1 ± 30.7		325.5 ± 38.9**	258.3 ± 39.3	320.1 ± 85.8**	332.8 ± 114.9**	329.5 ± 95.3**
(dynes·s·cm^{-5}·m^{-2})	Group 2	8	230.4 ± 47.1	174.6 ± 51.7	225.3 ± 87.6*	207.8 ± 61.5*	210.6 ± 87.2*	213.7 ± 87.8	235.0 ± 95.7
	Group 3	8	233.6 ± 44.3	301.1 ± 30.3**	374.4 ± 104.6*,**	411.1 ± 141.9*,**	549.9 ± 192.9*,**	693.3 ± 250.2*,**	754.1 ± 240.3*,**

MAP, mean arterial pressure; MPAP, mean pulmonary pressure; HR, heart rate; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

[a] 30 min after administration of L-arginine and L-*N*NA in groups 2 and 3, respectively.

Data are given as mean ± SD.

* $P < 0.05$ *vs* group 1. ** $P < 0.05$ *vs* baseline.

obtained at 30, 60, 120, 180, and 240 min following infusion of LPS.

Group 4 (n = 6): control

The dogs in this group received only an equivalent volume of normal saline instead of LPS, L-arginine, or L-*N*NA. The observed variables were as same as those in the above three groups.

Hemodynamic data included MAP, CVP, MPAP, PAWP, and CO. The calculated parameters included cardiac index (CI), SVRI = (MAP − CVP)/CI, and PVRI = (PAP − PAWP)/CI. Gravimetric analysis [7], with modifications in ultracentrifugation [8], was used for determination of EVLW.

Statistical analysis was performed using analysis of variance (ANOVA) to compare the differences between two groups at corresponding time points. Data are expressed as means ± SD. Significance was accepted when $P < 0.05$.

Results

Table 1 and Table 2 present the data relating to hemodynamics and oxygen transport in the three groups. Table 3 presents the measurements of EVLW.

All of the animals survived the observation period.

The pure effects of L-arginine and L-*N*NA on hemodynamics were very mild, as indicated by the small changes in MAP, HR, PCWP, CVP, CL, and SI by 30 min after the two agents had been administered prior to endotoxin challenge. Only MPAP was significantly reduced by L-arginine, while SVRI and PVRI were markedly elevated by L-*N*NA.

Treatment with LPS caused a significant increase in PVRI (+38.0%), and a decrease in MAP and MPAP, while pretreatment of LPS with L-*N*NA was followed by a more significant increase in PVRI (+222.8%) and SVRI (+184.5%), but there were no significant changes in SVRI by pretreatment of LPS with L-arginine, which also decreased PVRI significantly (−52.0%) compared with the endotoxin shock group. Administration of LPS resulted in a significant decline in CI (3.8 ± 0.2 to 2.2 ± 0.5 l·min^{-1}·m^{-2}), and this decline was very marked (2.2 ± 0.5 *vs* 1.4 ± 0.5 l·min^{-1}·m^{-2}) in the endotoxic dogs pretreated with L-*N*NA. In contrast, a significant increase in CI (2.2 ± 0.5 *vs* 2.8 ± 0.9 l·min^{-1}·m^{-2}) was found in the endotoxic dogs pretreated with L-arginine.

LPS reduced DO_2 significantly (−35.0%), but as there was a significant increase in O_2ER (+81.5%), LPS affected VO_2 little throughout the experiment. Pretreatment of LPS with L-arginine did not affect DO_2, VO_2, or O_2ER at any time points throughout the experiment. As DO_2 was significantly decreased (−58.2%) in the pretreatment of LPS with L-*N*NA, although O_2ER was increased (insufficiently), VO_2 was still decreased significantly (−18.3%).

Table 3. Extravascular lung water (g·g^{-1} dry weight) in the four groups treated with normal saline (control), endotoxin (group 1), and pretreated with L-arginine (group 2) or L-*N*NA (group 3) in addition to endotoxin

Control ($n = 6$)	Group 1 ($n = 8$)	Group 2 ($n = 8$)	Group 3 ($n = 8$)
3.64 ± 0.53	5.35 ± 0.97*	5.69 ± 0.38*	6.23 ± 0.68*,**

Data are given as mean ± SD.
* $P < 0.05$ *vs* control; ** $P < 0.05$ *vs* group 1.

Table 2. Oxygen transport data in the three groups treated with endotoxin (group 1) and pretreated with L-arginine (group 2) or L-*N*NA (group 3) in addition to endotoxin

				Minutes after administration of LPS		
		n	Baseline	60	120	240
DO_2 (ml·min^{-1}·m^{-2})	Group 1	8	686.1 ± 108.1	445.9 ± 122.0	490.1 ± 108.9	533.7 ± 103.8
	Group 2	8	683.4 ± 105.9	511.3 ± 101.2	534.3 ± 177.2	525.5 ± 139.8
	Group 3	8	716.1 ± 50.8	412.7 ± 96.3	335.5 ± 84.5*,**	299.6 ± 90.1*,**
O_2ER (%)	Group 1	8	18.9 ± 1.4	34.3 ± 7.1	37.0 ± 7.5	28.0 ± 8.8
	Group 2	8	18.1 ± 3.2	26.3 ± 8.2	28.8 ± 8.5	24.3 ± 7.4
	Group 3	8	19.4 ± 4.0	33.6 ± 10.4**	38.8 ± 9.3**	39.5 ± 10.0*
VO_2 (ml·min^{-1}·m^{-2})	Group 1	8	129.3 ± 20.3	149.8 ± 37.8	174.2 ± 38.8	145.9 ± 57.9
	Group 2	8	136.1 ± 45.3	117.4 ± 19.6	146.5 ± 51.7	120.1 ± 16.8
	Group 3	8	140.6 ± 36.9	132.4 ± 56.8	120.0 ± 41.1*	114.9 ± 37.9*

DO_2, oxygen delivery; O_2ER, oxygen extraction ratio; VO_2, oxygen consumption.
Data are given as mean ± SD.
* $P < 0.05$ *vs* group 1; ** $P < 0.05$ *vs* group 2.

EVLW in the LPS group was significantly higher than in the control group (3.64 ± 0.53 *vs* 5.35 ± 0.97 $g \cdot g^{-1}$ dry weight). Pretreatment of LPS with L-*N*NA further significantly increased EVLW (5.35 ± 0.97 *vs* 6.23 ± 0.68 $g \cdot g^{-1}$), but it changed little in the endotoxic dogs pretreated with L-arginine.

Discussion

Treatment of septic shock remains a therapeutic challenge. A current focus of shock research is on the controversial role of nitric oxide in the pathogenesis of septic shock.

Particular interest has been aroused by the notion that nitric oxide may be a kind of "terminal mediator of sepsis." The products of both Gram-negative bacteria (such as endotoxin or LPS [1]) and Gram-positive bacteria [9] as well as cytokines such as tumor necrosis factor (TNF-α), interleukin-1, and interferon-γ [10] can all activate calcium-independent nitric oxide synthase in both endothelium and vascular smooth muscle.

The important question is whether the inhibition of nitric oxide synthesis is indeed desirable in the treatment of sepsis. Many studies have reported beneficial effects from inhibition of nitric oxide synthesis. For example, studies in sheep receiving live *Escherichia coli* [2] or in pig given a continuous infusion of endotoxin [11] showed that many of the hemodynamic changes were caused by excess nitric oxide production, and that they could be improved by inhibitors of nitric oxide synthesis such as *N*-mono-methyl-L-arginine (L-*N*MMA). In mice given intraperitoneal *E. coli* and antibiotics, L-*N*MMA also improved the outcome [12]. However, in our dogs, except for the improved MAP, the LPS-induced increases in systemic vascular resistance, MPAP, and PVRI were not improved but worsened by L-*N*NA administration. This improvement in MAP was obtained at the expense of CI, which fell significantly below the control level. Meadow et al. [13] noted that despite improved MAP, L-*N*NA administration caused acidosis to persist and kept urine output low. These results may be attributed to the decrease in CI due to nitric oxide synthesis inhibition. Working with a different pig model, inhibition of nitric oxide synthesis initiated LPS-induced pulmonary hypertension [14]. Pastor et al. [5] suggested from their results in rabbits that inhibition of nitric oxide synthesis may have a limited role in the treatment of septic shock. In mice given intravenous endotoxin, *N*-nitro-L-arginine methyl ester (L-*N*AME) increased mortality [15]. Petros et al. [16] reported the effects of L-*N*MMA on two septic adult patients. One patient appeared to benefit from L-*N*MMA infusion (both arterial pressure and CO increased concurrently), while the other patient experienced a 40% reduction in CO after L-*N*MMA.

Such variability may be attributable to many factors such as differences in experimental protocols, in the types of endotoxin challenged, or in the responsiveness of animal to LPS. The most probable factor may be, as proposed by Nava et al. [17] and others [3], that endotoxin appears to affect different isoforms of nitric oxide synthase in very different ways with very different time constants. The constitutive form of nitric oxide synthase is inhibited by endotoxin in the early stage (early response), whereas the inducible form of nitric oxide synthase appears to be stimulated by endotoxin in the late stage (late response). Recently, dose-specific and time-specific effects of nitric oxide synthesis inhibition during septic shock have been proposed [17].

Because our model was short-term, it is very unlikely that in such a short-duration experiment LPS would activate the inducible form of nitric oxide synthase. Therefore, in the case of increases in both systemic and pulmonary vascular resistance, the administration of L-*N*NA, a nitric oxide synthesis inhibitor, might have been predicted to have serious adverse hemodynamic consequences.

The mechanism of decreased CI after L-*N*NA is unclear. In our dogs, such a reduction was not associated with any clinically important increases in either central venous pressure or left atrial pressure. A combination of left ventricular afterload increase, cor pulmonale, increase in resistance to venous return, or decrease in pulmonary perfusion and coronary perfusion could all be envisioned as a result of L-*N*NA administration. For example, Chu et al. [18] showed that epicardial coronary artery vasoconstriction was increased in dogs given a nitric oxide synthesis inhibitor.

The endothelium has been shown to play an important regulatory role in the pulmonary vasculature tone [19]. Elevation of pulmonary vascular resistance occurs frequently in patients with septic shock. The increase in pulmonary vascular resistance can lead to right ventricular dysfunction and CO reduction, producing an insufficient systemic oxygen delivery and thereby increasing mortality. In the lung, nitric oxide may play a more dominant role in lowering vascular tone under basal conditions, especially in the regulation of pulmonary vascular resistance in acute hypoxia and pulmonary hypertension during septic shock [20]. Our results support this finding that L-*N*NA further increased pulmonary arterial pressure, PVRI, and EVLW following LPS administration.

Similar findings were noted following single-dose and continuous infusion of L-*N*AME administration in a sheep and swine model during continuous infusion of *E. coli* endotoxin [21,22]. Meadow et al. [13] ob-

served that L-*N*NA preferentially constricted the pulmonary circulation to a greater extent than it did the systemic circulation. These findings suggest that nitric oxide production may have a protective function by limiting LPS-induced pulmonary hypertension and reducing pulmonary microcirculatory dysfunction during septic shock.

The mechanism of the increase in EVLW by inhibition of nitric oxide synthesis during septic shock remains uncertain. In vivo measurements of EVLW did not demonstrate any significant differences between two control groups and one with inhaled nitric oxide [22]. This suggests that the primary effect of inhaled nitric oxide consists of controlling vasomotion rather than causing any changes in the permeability of the alveolar-capillary membrane. The elevation of pulmonary vascular resistance may lead to pulmonary hypertension and finally to right ventricular dysfunction, which is a common cause for most pulmonary edema. It has been reported that reducing pulmonary vascular resistance by nitroprusside depleted EVLW in experimental pulmonary edema [23]. Minnard et al. [15] reported that inhibition of nitric oxide synthesis diminished the protective effects of nitric oxide, enhancing neutrophil infiltration, adhesion, and release of cytotoxic mediators such as superoxide which may cause deleterious histologic changes in the lungs of animals treated with L-*N*AME, finally resulting in profound hypoxia as an inflammatory response.

We observed that at this dose of L-*N*NA, DO_2 was severely reduced. Even though oxygen extraction increased by +40%, such an increase was still insufficient to keep VO_2 at a level similar to the pre L-*N*NA values. Given a longer experimental duration, the exacerbated hemodynamics and oxygenation by L-*N*NA might have caused metabolic acidosis. Little is known about the effects of L-arginine on the prognosis of septic shock. In the present model, L-arginine with LPS administration did not cause significant changes in SVRI, MAP, MPAP, DO_2, O_2ER, VO_2, or EVLW, but decreased PVRI (−34%) and increased CI (−26%). These results suggests a beneficial effect of L-arginine on systemic blood flow, peripheral perfusion, and oxygenation.

In summary, this study adds to the growing volume of evidence that systemic inhibition of nitric oxide production in septic shock may be potentially detrimental to hemodynamics and oxygenation. LPS-induced decreased CI, DO_2, VO_2, elevated pulmonary vascular resistance, and EVLW were all enhanced by L-*N*NA administration, indicating a limited role of inhibition of nitric oxide synthesis in the treatment of septic shock. To permit extrapolation of these findings to the clinical setting, further work will be necessary to characterize the individual nitric oxide synthesis inhibitors regarding their potential benefits and adverse effects, especially in a longer-duration model of septic shock.

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