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Effects of N-Acetyl-*L*-Cysteine on Regional Blood Flow during Endotoxic Shock

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Abstract

We previously reported that N-acetyl-*L*-cysteine (NAC), an oxygen free-radical scavenger, can increase the oxygen extraction capabilities during endotoxic shock when blood flow is progressively reduced. In the present study, we investigated whether the protective effects of NAC are related to an improvement in regional blood flow following endotoxemia. Fourteen anesthetized, saline-infused and ventilated dogs were divided into two groups: 7 dogs received NAC (150 mg/kg, followed by a 20 mg/kg·h infusion), and the other 7 dogs served as a control time-matching group. Thirty minutes later all the dogs received *Escherichia coli* endotoxin (2 mg/kg) i.v. A saline infusion was started 30 min after endotoxin challenge to restore pulmonary artery occlusion pressure to baseline and maintain it constant. Regional blood flow was measured by ultrasonic volume flowmeter. In the control group, arterial pressure, left ventricular stroke work index and systemic vascular resistance remained lower than baseline. Mesenteric, renal and femoral arterial blood flow increased but only femoral blood flow returned to baseline levels. In the NAC group, cardiac index and left ventricular stroke work index remained higher and systemic and pulmonary vascular resistance were lower than in the control group. Blood flow in mesenteric, renal and especially femoral arteries was higher than in the control group. Fractional blood flow increased only in the femoral artery. PaO_2 and PvO_2 had similar courses in the two groups. A higher venous admixture was associated with a higher cardiac index and a lower pulmonary vascular resistance in the NAC group. Oxygen delivery and oxygen uptake were higher in the NAC-treated than in the control animals throughout the study. Oxygen extraction ratio was higher in the NAC group at the end of the study. We conclude that NAC can increase blood flow in the mesenteric, renal and femoral beds in endotoxic shock and this may be associated with a higher oxygen availability in the tissues.

Key Words
Regional blood flow
Oxygen delivery
Oxygen extraction
Oxygen free radicals
Antioxidant

Introduction

Septic shock is characterized by decreased blood pressure and systemic vascular resistance [1–4]. Despite a usually well-maintained cardiac output, maldistribution of blood flow associated with alteration in oxygen extraction can account for an inadequate perfusion of most organs [1–3, 5–8].

When fluid resuscitation alone fails to increase arterial pressure, pressor agents such as norepinephrine are frequently used to improve

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organ perfusion. However, the vasoconstrictive effects of these agents could be detrimental to the function of vital organs unless the vasoconstriction occurs selectively in nonvital organs. During endotoxic shock in animals, the oxygen extraction capabilities were not significantly increased with norepinephrine or dobutamine [9] and renal, splanchnic, and skeletal muscle blood flow was not improved by either norepinephrine, dopamine, or phenylephrine [1, 6]. In contrast, agents with some vasodilating properties such as prostaglandin E_1 may increase organ blood flow and enhance oxygen extraction in these conditions [10].

N-Acetyl-*L*-cysteine (NAC), an oxygen free-radical scavenger, has been reported to markedly reduce pulmonary hypertension and vascular permeability and significantly increase cardiac output and oxygen delivery (DO_2) by its vasodilating and myocardial protective effects in ischemic and in endotoxic animals [11–16]. NAC exerts also important anti-inflammatory effects on neutrophils and monocytes [17] and inhibits the production of tumor necrosis factor in septic conditions [16, 18], and protects against the tissue damage induced by interleukin-1 (IL-1) [19]. In a previous study on a canine model of endotoxic shock when blood flow was progressively reduced by cardiac tamponade [16], we observed that prior administration of NAC not only increased cardiac index and DO_2 but also decreased critical DO_2 and increased critical oxygen extraction ratio (O_2ER). Several mechanisms could account for these beneficial effects by NAC. One is an improvement in organ blood flow associated with increased nitric oxide availability [20] and the others are anti-inflammatory action [17, 18] and scavenging effect on oxygen free radicals [16], which are implicated in the tissue damage after endotoxic shock. These mechanisms may be interrelated, since tumor necrosis factor and oxygen free radicals can prevent the synthesis or destroy the biological activity of the constitutive nitric oxide [21–24].

Some clinical trials have examined the effects of NAC in patients with the adult respiratory distress syndrome (ARDS) [25–28] and sepsis. In a preliminary trial in 30 patients with sepsis-induced ARDS, Bernard [26] reported that intravenous administration of NAC markedly increased plasma cysteine as well as plasma and red cell glutathione levels which were initially decreased in these patients, and increased cardiac output, DO_2 and oxygen uptake (VO_2). In septic shock patients. NAC administration has been found to improve tissue oxygenation as indicated by an increase in VO_2, O_2ER and gastric intramucosal pH [27].

However, there are no data to show the regional effects of NAC during septic conditions. The present study was therefore performed to examine whether NAC can alter regional blood flow in the mesenteric, renal and femoral vasculatures during endotoxic shock.

Materials and Methods

Experimental Preparation

Fourteen mongrel dogs weighin 28 ± 1 kg were anesthetized with pentobarbital sodium (30 mg/kg bolus followed by 4 mg/kg·h i.v.) and paralyzed with pancuronium bromide (0.15 mg/kg bolus followed by 0.075 mg/kg·h i.v.). Each dog was mechanically ventilated with room air (Servo ventilator 900B, Siemens-Elema, Stockholm, Sweden). Respiratory rate was 12 breaths/min and tidal volume was adapted to keep end-tidal carbon dioyxide tension (47210A Capnometer, Hewlett-Packard, Waltham, Mass., USA) between 28 and 38 mm Hg. The left forepaw vein was catheterized to infuse pentobarbital sodium and pancuronium bromide, and the right forepaw vein to give fluids and NAC. The right femoral artery was cannulated for monitoring of arterial blood pressure and withdrawal of blood samples. A balloon-tipped pulmonary artery catheter (model 93A-131-7F, Baxter Healthcare, Irvine, Calif., USA) was inserted under guidance of pressure waves (monitor Sirecust 302A, Siemens, Erlangen, Germany) via the

Table 1. Cardiac filling pressures, arterial and venous PO_2, venous admixture, lactate and hematocrit

		Baseline 1	Baseline 2	30 min	60 min	90 min	120 min	150 min	180 min	210 min
PAOP	control	5.0±1.0	4.9±1.3	5.0±1.4	5.0±1.7	5.3±1.6	5.3±1.7	5.6±1.7	6.7±2.9	6.7±2.0
mm Hg	NAC	5.7±1.1	5.9±1.6	5.3±1.4	5.3±1.0	5.7±1.1	5.7±0.8	6.0±1.3	6.4±1.7	7.0±2.0
RAP	control	3.4±1.4	3.3±1.3	3.3±1.8	3.6±2.2	3.9±2.0	4.1±2.0	4.3±1.6	5.7±2.3	5.7±1.3
mm Hg	NAC	3.7±1.8	3.7±1.7	2.9±1.3	3.0±1.4	3.9±1.1	3.9±1.0	4.4±1.0	5.9±1.1	6.3±1.1
PaO_2	control	86±7	83±10	62±10	72±8	74±6	76±8	78±9	80±7	81±7
mm Hg	NAC	90±8	86±10	68±10	73±10	72±9	74±8	76±7	76±7	77±7
PvO_2	control	47±8	46±9	34±7	45±8	49±4	49±5	50±6	51±4	52±4
mm Hg	NAC	45±4	46±4	39±4	47±5	51±4	51±3	52±3	52±4	53±4
Qva/Qt	control	22±15	23±11	18±7	23±13	27±13	27±11	27±7	29±5	26±9
%	NAC	20±8	24±9	27±10*	33±7*	38±8*	34±8	32±8	33±8	33±10
Hematocrit	control	52±6	52±5	58±8	54±8	51±6	50±6	49±6	48±7	47±6
%	NAC	55±7	54±7	56±7	53±8	50±6	48±6	47±6	45±6	44±6
Lactate	control	2.0±0.8	2.1±0.8	5.6±2.2	4.2±1.7	3.5±1.3	3.1±1.2	3.0±1.1	2.7±0.9	2.6±0.9
mmol/l	NAC	2.0±0.6	2.2±0.6	5.2±1.8	4.3±0.9	3.9±0.9	3.7±0.8	3.4±0.8	3.1±1.0	3.0±1.0

Data are shown as mean ± SD; * $p < 0.05$ vs control. PAOP = Pulmonary arterial occlusion pressure; RAP = Right atrial pressure.

right external jugular vein. A splenectomy was performed through a midline laparotomy. Flow probes of an ultrasonic volume flowmeter (model T208, Transonic Systems Inc., Ithaca, N.Y., USA; calibrated by the manufacturer) were placed around the superior mesenteric, left renal and left femoral arteries, respectively.

Experimental Protocol

After surgical preparation, the dogs were allowed to stabilize for 30 min before baseline measurements (baseline 1). The dogs were randomly divided into two groups. In the NAC group (n = 7), NAC was administered as a bolus of 150 mg/kg followed by a constant infusion of 20 mg/kg·h. The other dogs (n = 7) served as a time-matching control group. Thirty minutes later, a second set of measurements (baseline 2) was obtained. Then each dog received *Escherichia coli* endotoxin (lipopolysaccharide *E. coli* 055:B5, No. 3120-10-7, Difco, Detroit, Mich., USA) as a slow intravenous bolus of 2 mg/kg over 2 min to produce an acute endotoxic shock. Saline infusion at 20 ml/kg·h was started 30 min after endotoxin administration to restore pulmonary artery occlusion pressure to baseline and maintain it constant. A heating blanket and warming lamps maintained core temperature constant.

Measurements

Pressures from femoral arterial and pulmonary arterial lines were monitored continuously using pressure transducers (series 966020-01, Baxter Healthcare) with amplifiers (Hellige Servomed, Freiburg, Germany) and a pen recorder (model 2600S Gould, Inc., Instruments Div., Cleveland, Ohio, USA). All pressures were determined at end-expiration. Cardiac index (liters/min·kg) was measured by the thermodilution technique (COM-2, Baxter) using three to five 5-ml bolus injections of cold 5% dextrose in ice water at end-inspiration. Blood flow of superior mesenteric, left renal and left femoral arteries was simultaneously measured.

Expired gases were directed through a mixing chamber for collecting expired oxygen fractions (P.K. Morgan Ltd., Chatham, Kent, UK). Minute volume was measured with a spirometer (Haloscale Wright Respirometer, Edronton, London, UK) over a 2-min period. Arterial and mixed venous blood samples were simultaneously withdrawn for immediate determinations of blood gases (analyzer Stat Profile 7, NOVA Biomedical, Waltham, Mass., USA), oxygen saturations (SaO_2, SvO_2) and total hemoglobin (OSM™ 3 Hemoximeter®, calibrated for dog blood, Radiometer, Copenhagen, Denmark). Hematocrit was determined by capillary method (Hettich Haematokrit, Tuttlingen, Germany). Blood lactate concentration was determined by a glucose/lactate analyzer (2300 Stat Plus, Yellow Spring Incorporation, Ohio, USA).

Venous admixture (Qva/Qt) was calculated by the formula:

$$Qva/Qt\ (\%) = (Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2)$$

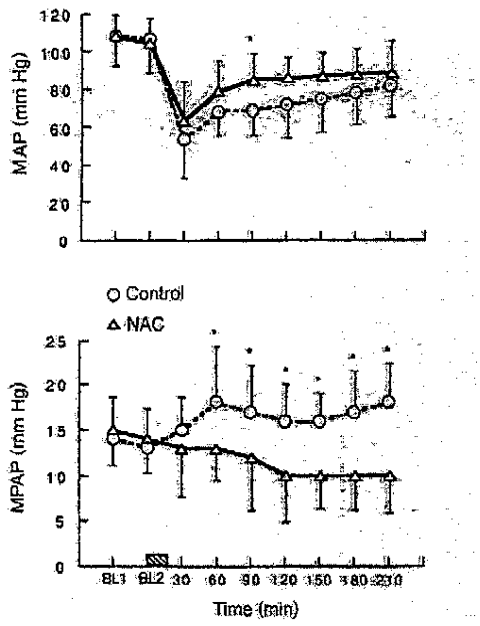

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Fig. 1. Time course of changes in mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP) in the two groups. The rectangle indicates the time of endotoxin administration. Data are shown as mean ± SD. BL1 = Baseline 1, BL2 = baseline 2. * $p < 0.05$ between the NAC-treated and the control group.

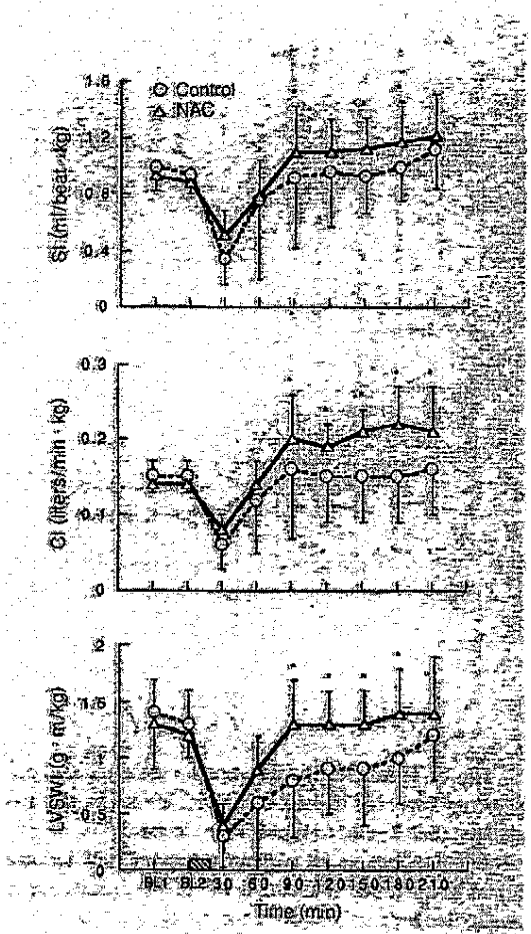

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Fig. 2. Time course changes in stroke index (SI), cardiac index (CI), and left ventricular stroke work index (LVSWI) in the two groups. (See legend to figure 1 for details.)

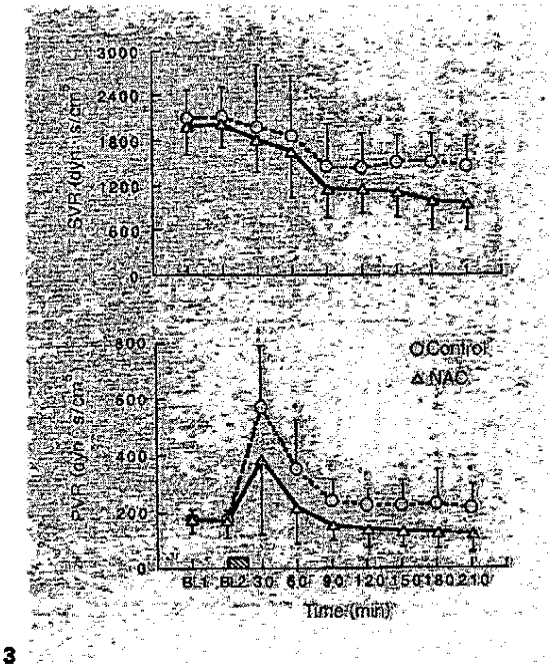
where $Cc'O_2$, CaO_2 and CvO_2 are the oxygen contents of pulmonary capillary, arterial and mixed venous blood, respectively. VO_2 was determined from the expired gases as previously described [4]. DO_2 was calculated by the product of cardiac index and arterial oxygen content. O_2ER was derived from the ratio of VO_2/DO_2.

Statistics

An ANOVA followed by a multiple comparison (Dunnett) test was used. A p value <0.05 was considered statistically significant. All values are expressed as mean ± SD.

Results

The results are shown in table 1 and figure 1–6. In all animals, endotoxin administration was followed by decreases in mean arterial pressure, cardiac index and left ventricular stroke work index, and an increase in pulmonary vascular resistance. Blood flow was significantly decreased in the superior mesenteric, renal and femoral arteries. Arterial and mixed venous oxygen tensions (PaO_2 and PvO_2) fell. DO_2 decreased, but VO_2 was pre-



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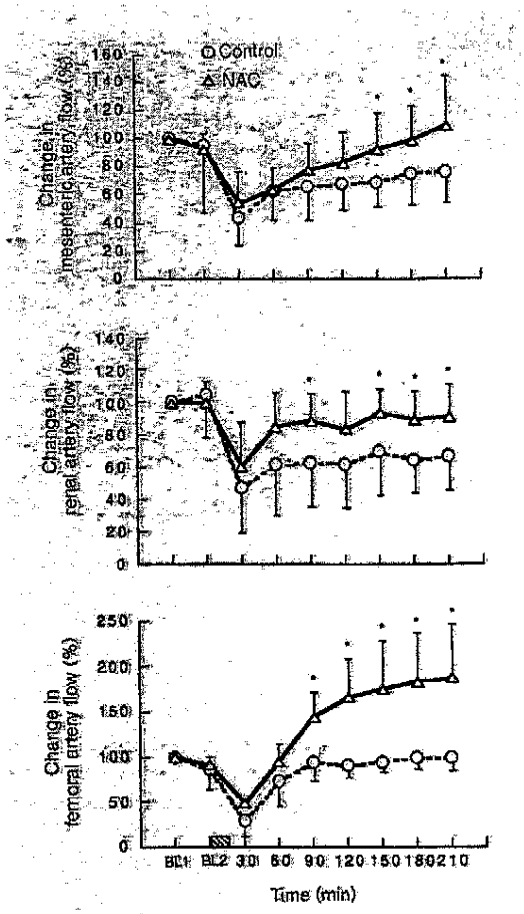

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Fig. 3. Time course of changes in systemic and pulmonary vascular resistance (SVR, PVR) in the two groups. (See legend to figure 1 for details.)

Fig. 4. Changes in mesenteric, renal and femoral blood flow during time course in the two groups of animals. (See legend to figure 1 for details.)

served by an increase in O_2ER. Blood lactate increased. However, NAC pretreatment significantly attenuated the increase in pulmonary vascular resistance and resulted in a higher Qva/Qt than in the control group.

After fluid administration in the control group, arterial pressure, left ventricular stroke work index and systemic vascular resistance remained lower than at baseline. Mesenteric, renal and femoral arterial blood flow increased but only femoral blood flow returned to baseline levels.

In the NAC group, mean arterial pressure followed a similar course as in the control group despite a decline in systemic vascular resistance. Pulmonary arterial pressure and pulmonary vascular resistance were significantly lower than in the untreated animals. Cardiac index and stroke index significantly increased but heart rate remained stable in both groups (data not shown). Left ventricular stroke work index was significantly higher in the NAC-treated than in the control group. Blood flow in mesenteric, renal and femoral arteries was consistently higher than in the control group. Mesenteric and femoral blood flow was higher than at baseline and renal blood flow returned to near baseline levels.

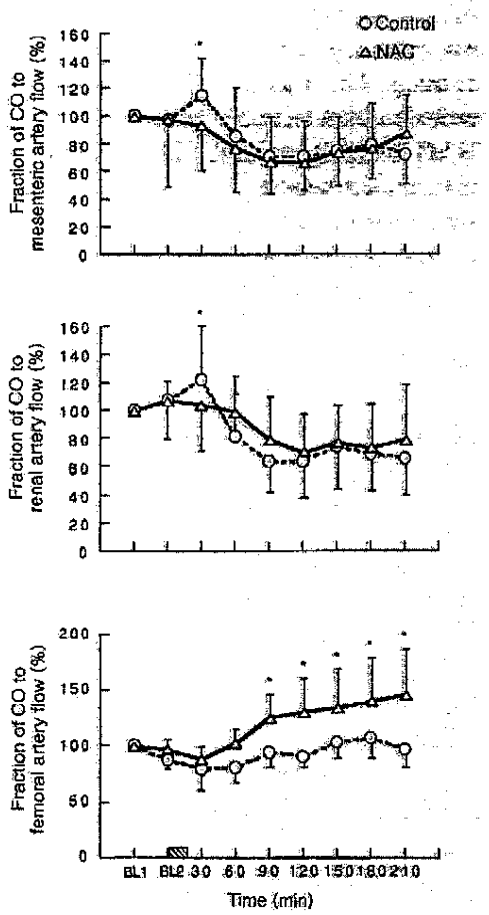

Fig. 5. Blood flow indexed to the cardiac output in mesenteric, renal and femoral vasculatures in the two groups of animals. (See legend to figure 1 for details.)

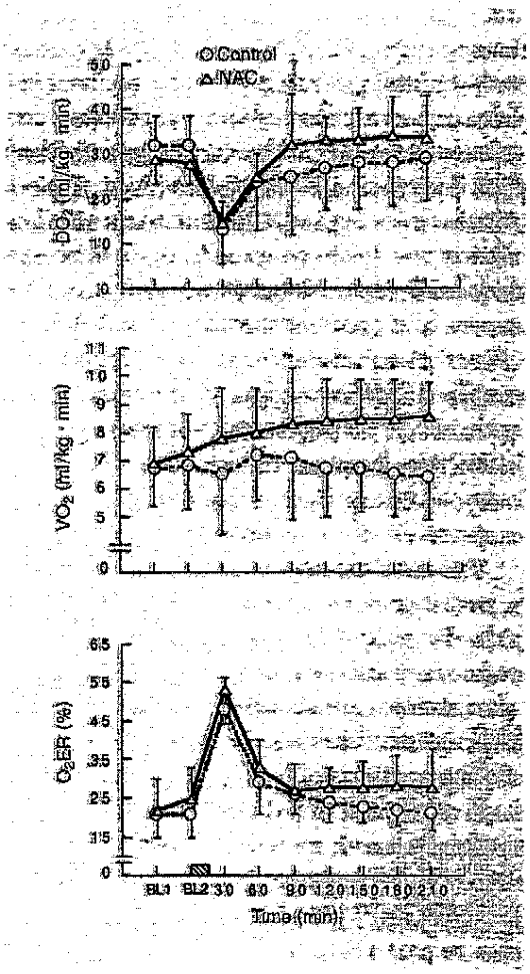

Fig. 6. Time course changes in DO_2, VO_2, and O_2ER in the two groups. (See legend to figure 1 for details.)

Fractional blood flow increased significantly only in the femoral vasculature.

PaO_2 and PvO_2 and similar courses in the two groups. Qva/Qt transiently increased in the NAC group. DO_2 and VO_2 were higher in the NAC-treated than in the control animals throughout the study. O_2ER was higher in the NAC group at the end of the study. Blood lactate and hematocrit progressively decreased in both groups.

Discussion

The canine endotoxic shock model employed in the present study is characterized by marked hypotension associated with peripheral vasodilation, but a well-maintained cardiac index. This hemodynamic pattern similar to the one found during human sepsis was obtained by a large fluid infusion to keep pulmonary artery occlusion pressure constant

and thereby avoid a fall in venous return following endotoxin administration. Despite the well-maintained cardiac index, regional differences in vascular responsiveness could contribute to the development of organ dysfunction by causing a maldistribution of blood flow between organs [29]. Endotoxin administration was followed by a decrease in mesenteric and renal blood flow, as it has been reported in previous studies [5, 29, 30]. However, femoral blood flow, which reflects primarily the blood supply to the muscle, was maintained in our study. Although femoral blood flow has been reported to be decreased in hyperdynamic septic pigs [1], it can be well maintained in septic dogs [31, 32].

The NAC-treated dogs maintained a lower systemic and pulmonary vascular resistance than the control animals. Also the increase in pulmonary arterial pressure typically observed after endotoxin challenge was blunted in the NAC-treated animals. These well-known vasodilating effects of NAC [11, 15, 16, 33] have been attributed to a direct relaxing action on vascular smooth muscle by an enhanced production of guanosine 3′-5′-cyclic monophosphate (cGMP) [34]. These effects are at least also in part related to the action of endothelium-derived relaxing factor/nitric oxide, an endogenous vasodilator that relaxes vascular smooth muscle and inhibits the aggregation and adhesion of platelets [19, 35]. Nevertheless, other mechanisms may be involved, since Sunman et al. [34] recently showed a direct endothelium-independent relaxing effect of NAC on vascular smooth muscle in isolated rat and human endothelium-denuded arteries. An inhibitory effect of NAC on the release of thromboxane A_2 has also been shown [11].

In these endotoxic shock conditions where systemic vascular resistance is already reduced, a lower systemic vasomotor tone may have detrimental effects by decreasing the tissue perfusion pressure. This was not observed in the present study. On the contrary, the mean arterial pressure in the NAC-treated was even somewhat higher than in the control animals. This was related to a higher cardiac index and stroke index under the influence of NAC. Since the cardiac filling pressures were maintained constant, the greater left ventricular stroke work index reflected an improved cardiac function in the NAC-treated group. Several mechanisms may account for this phenomenon, including an increase in coronary blood flow, a higher calcium gradient from sarcoplasmic reticulum to cytosol [12–14], and a protective effect against the oxygen free radical-mediated myocardial depression following endotoxemia [36].

Oxygen free radicals have been implicated in the organ damage secondary to endotoxic shock [20, 37]. NAC, a low molecular weight precursor to glutathione, can cross the cell membrane and thereby replenish intracellular glutathione stores [11, 17, 38] which are reduced during severe sepsis [39]. We recently reported that NAC administration can increase the plasma glutathione peroxidase levels, which are considered to reflect the tissue antioxidant activity [40] and to be tightly coupled to the cellular concentrations of glutathione [38]. NAC treatment has also been reported to increase blood-soluble sulfhydryl levels, to limit the increase in oxidized glutathione in the lung, and decrease breath H_2O_2 levels following IL-1 administration in rats [19]. Another important protective mechanism of NAC may be the inhibition of xanthine oxidase activity [11], which is also involved in the endotoxin-induced organ damage [37]. Our study indicated that NAC can significantly increase blood flow to the mesenteric, renal and femoral vascular beds. The fractional blood flow increased only to femoral artery. Thus the greater oxygen extraction capabilities under the influence of NAC can be attributed to an improvement in microvas-

cular blood flow within the organ rather than to an improvement in blood flow among the organs. The antioxidant effects of NAC are likely to play an important role in this process. Leff et al. [19] recently demonstrated that the administration of NAC immediately before or 2.5 h after intratracheal administration of IL-1 in rats decreased endothelial damage, neutrophil influx into lung lavage fluid, and edema. In a recent study we evaluated the effects of NAC on histological changes induced by endotoxin, but these were relatively limited in this acute model [41].

The higher Qva/Qt in the NAC-treated animals was related to the pulmonary vasodilating effects of NAC, later magnified by a higher cardiac index in this group. The lack of decrease in PaO_2 may be related to some (although nonsignificant) increase in PvO_2. Our study focused on the short-term effects of NAC, but some clinical studies evaluating the effects of NAC in patients with ARDS suggested that NAC can improve gas exchange [26, 28], increase static compliance [26] and reduce the duration of ventilatory support [28]. NAC-treated dogs had higher VO_2 than the controls, probably because they had a higher oxygen availability. A direct stimulating effect of NAC on cellular metabolism is unlikely and would be expected to be associated with a higher O_2ER.

We conclude that NAC administration prior to endotoxin can increase blood flow to the mesenteric, renal and femoral vasculatures and increase oxygen availability to these tissues. NAC does not improve the distribution of blood flow to the organs studied. Thus the greater oxygen extraction capabilities under the influence of NAC are likely due to an improvement in microvascular blood flow within the organ rather than to a distribution of blood flow among the organs. Whether NAC administration can also have protective effects when administered after endotoxin administration must be explored in further studies.

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