clinical investigations in critical care

Does N-Acetyl-L-Cysteine Influence Cytokine Response During Early Human Septic Shock?*

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Study objective: To assess the effects of adjunctive treatment with N-acetyl-L-cysteine (NAC) on hemodynamics, oxygen transport variables, and plasma levels of cytokines in patients with septic shock.

Design: Prospective, randomized, double-blind, placebo-controlled study.

Setting: A 24-bed medico-surgical ICU in a university hospital.

Patients: Twenty-two patients included within 4 h of diagnosis of septic shock.

Interventions: Patients were randomly allocated to receive either NAC (150 mg/kg bolus, followed by a continuous infusion of 50 mg/kg over 4 h; n=12) or placebo (n=10) in addition to standard therapy.

Measurements: Plasma concentrations of tumor necrosis factor-α (TNF), interleukin (IL)-6, IL-8, IL-10, and soluble tumor necrosis factor-α receptor-p55 (sTNFR-p55) were measured by sensitive immunoassays at 0, 2, 4, 6 and 24 h. Pulmonary artery catheter-derived hemodynamics, blood gases, hemoglobin, and arterial lactate were measured at baseline, after infusion (4 h), and at 24 h.

Results: NAC improved oxygenation (PaO2/FI赵2 ratio, 214±97 vs 123±86; p<0.05) and static lung compliance (44±11 vs 31±6 l/cm H2O; p<0.05) at 24 h. NAC had no significant effects on plasma TNF, IL-6, or IL-10 levels, but acutely decreased IL-8 and sTNFR-p55 levels. The administration of NAC had no significant effect on systemic and pulmonary hemodynamics, oxygen delivery, and oxygen consumption. Mortality was similar in both groups (control, 40%; NAC, 42%) but survivors who received NAC had shorter ventilator requirement (7±2 days vs 20±7 days; p<0.05) and were discharged earlier from the ICU (13±2 days vs 32±29 days; p<0.05).

Conclusion: In this small cohort of patients with early septic shock, short-term IV infusion of NAC was well-tolerated, improved respiratory function, and shortened ICU stay in survivors. The attenuated production of IL-8, a potential mediator of septic lung injury, may have contributed to the lung-protective effects of NAC.

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Key words: antioxidants; ARDS; cytokines; glutathione; hemodynamics; lung compliance; N-acetyl-L-cysteine; oxygenation; septic shock

Abbreviations: DO2= oxygen delivery; FIO2= fractional inspired oxygen; GSH= reduced glutathione; IL = interleukin; MOF= multiple organ failure; NAC= N-acetyl-L-cysteine; NS= not significant; O2ER= oxygen extraction ratio; OFR= oxygen free radical; PEEP= positive end-expiratory pressure; SLC= static lung compliance; sTNFR= soluble tumor necrosis factor-α receptor; TNF= tumor necrosis factor-α; VO2= oxygen consumption

S eptic shock remains a major cause of death in ICUs. Complications of septic shock have been related to an intense host response based on a delicate equilibrium between various pro- and anti-inflammatory mediators.1 Although essential for infection containment, an overwhelming production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and IL-8, may induce biochemical and cellular alterations ei-
ther directly or by orchestrating secondary inflammatory pathways. These include the recruitment and activation of granulocytes and macrophages, enhancement of cell adhesion, induction of nitric oxide synthase, and phospholipase activation. Activation of granulocytes and endothelial cells generates an "oxidative burst" with massive production of oxygen free radicals (OFRs). Endogenous antioxidant defense mechanisms are decimated in sepsis and fail to cope with this excessive release of OFRs. As a result, OFRs start causing indiscriminate structural and functional alterations of various cellular constituents, resulting in irreversible cellular damage.

N-acetyl-L-cysteine (NAC)—the N-acetyl derivative of the amino acid L-cysteine—has antioxidant, cytoprotective, and microcirculatory effects that could prove beneficial in septic conditions. Pharmacologic actions of NAC include the restoration of cellular antioxidant potential by replenishing depleted reduced glutathione (GSH) stores; the scavenging of OFRs both directly and as a precursor of GSH; the inhibition of neutrophil aggregation and TNF production; and the regeneration of nitric oxide, which is vital for organ perfusion during endotoxic shock and is inactivated readily by OFRs.

Extensive clinical experience with large IV doses of NAC has been accumulated as a consequence of its use in patients with hepatic failure due to acetaminophen overdose. Infusion of NAC in this patient population proved to be nontoxic and was well-tolerated. The potential benefit of NAC in clinical septic shock has received little attention and remains controversial. Therefore, we designed a randomized, prospective, double-blind, placebo-controlled study in patients with early septic shock to assess the effects of a short-term infusion of NAC on hemodynamics, oxygen transport variables, and plasma levels of pro- and anti-inflammatory cytokines.

**Materials and Methods**

**Patients**

The protocol was approved by the Committee for Ethics in Human Research of the University Hospital. Informed consent was obtained from the next of kin of each patient. Only patients in whom septic shock was diagnosed within 4 h of onset were enrolled in the trial. Septic shock was defined according to consensus guidelines as sepsis with hypotension unresponsive to fluid resuscitation and evidence of organ hyperperfusion or dysfunction. Patients were excluded from the study for the following reasons: age <18 years; suspected pregnancy or parturient state; treatment with IV, oral, or aerosolized NAC to fluidify tracheobronchial secretions; known allergy to NAC; history of severe asthma; hepatic or renal failure not due to septic shock; immunosuppressed state (ie, treatment with steroids within 1 month before study inclusion; bone marrow or organ transplant recipients; leukopenia [WBC <1,000/mm^3] or neutropenia [polymorphonuclear granulocyte count <500/mm^3]; hematologic malignancy and AIDS; treatment with nonsteroidal anti-inflammatory agents, immunoglobulins, monoclonal antibodies, or methylxanthine derivatives; lung injury score >2.0; patients whose medical condition was considered to be irreversible or in whom death was imminent within 24 h after admission. The acute physiology and chronic health evaluation (APACHE II) score was employed to determine the initial severity of illness. An "inotrope score" was used to adjust for relative catecholamine dependency. This score took into account the type of adrenergic agent used as well as its infusion rate, and scores were obtained for each patient at baseline and at 4 and 24 h. When a patient was receiving a combination of adrenergic drugs, the inotrope score was calculated as the sum of the scores for each individual agent.

If required, patients underwent surgical procedures before the start of the study. No invasive surgery or renal replacement techniques were performed during the 24-h study period. All patients were ventilated in volume-controlled mode (Servo 900C ventilator; Siemens Elema; Solna, Sweden) and received continuous analgesic sedation with midazolam and fentanyl. Ventilator settings, level of positive end-expiratory pressure, and fractional inspired oxygen (FIO_2) were kept constant during NAC or placebo infusion.

All patients received routine resuscitation therapy for septic shock, including fluid administration with crystalloids and colloids, dobutamine to maintain a cardiac index greater than 4 L/min·m^2; and dopamine and/or norepinephrine to maintain a mean arterial pressure above 65 mm Hg. RBC transfusion was allowed after the NAC or placebo infusion was ended. After blood cultures and sampling at different culture sites were performed, all patients initially received broad-spectrum antibiotics consisting of either a third-generation cephalosporin or ciprofloxacin and an aminoglycoside. Antibiotic treatment was adjusted according to culture results.

**Protocol**

Randomization was achieved according to a computer-steered permuted block design. Solutions were prepared in the central pharmacy of the University Hospital, delivered to the ICU, and further handled by a nurse who was unaware of the study protocol. The investigators did not know whether placebo or active drug was infused. NAC (Flumucil; Zambon; Amsterdam, the Netherlands) was administered in 5% dextrose (150 mg/kg in 250 mL over 15 min, followed by a continuous infusion of 50 mg/kg in 500 mL over 4 h). The placebo group received an equal amount of 5% dextrose during the same time period.

**Measurements**

All patients had radial arterial catheters (arterial line kit; Argon; Athens, Tex) in place. A pulmonary artery catheter (Edwards

**Table 1—Inotrope Score**

<table>
<thead>
<tr>
<th>Norepinephrine (µg/min)</th>
<th>Dopamine (µg/kg/min)</th>
<th>Dobutamine (µg/kg/min)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0-5</td>
<td>0-6</td>
<td>1</td>
</tr>
<tr>
<td>5-14</td>
<td>6-15</td>
<td>7-18</td>
<td>2</td>
</tr>
<tr>
<td>15-25</td>
<td>16-30</td>
<td>19-35</td>
<td>3</td>
</tr>
<tr>
<td>&gt;25</td>
<td>&gt;30</td>
<td>&gt;35</td>
<td>4</td>
</tr>
</tbody>
</table>

*Adapted from Peake et al.*
Swan-Ganz model 97-120-7F; Baxter Healthcare; Irvine, Calif) was also inserted. Heart rate, mean systemic and pulmonary arterial pressure, right atrial pressure, and pulmonary artery occlusion pressure were continuously monitored (Sirecust 1281; Siemens; Danvers, Mass). Cardiac output was measured in triPLICATE by the thermodilution technique. Standard formulas were used to calculate cardiac index, systemic vascular resistance index, pulmonary vascular resistance index, oxygen delivery (DO_{2}), oxygen consumption (VO_{2}), and oxygen extraction ratio (O_{2}ER). Static lung compliance (SLC) was calculated as the exhaled tidal volume divided by the difference between plateau airway pressure and positive end-expiratory pressure (PEEP). Plateau airway pressure and PEEP were read from the digital airway pressure display of the ventilator, after application of, respectively, a 10-s end-inspiratory and end-expiratory pause. Arterial and mixed venous blood samples were simultaneously withdrawn for measurements of PO_{2}, PCO_{2}, and pH (ABL 3; Radiometer; Copenhagen, Denmark). Hemoglobin and oxygen saturation were measured using a co-oximeter (OSM 3; Radiometer). Arterial lactate was measured by a colorimetric test method (Ektachem; Johnson & Johnson; Rochester, NY). All measurements were obtained at baseline (15 min before start of the study) and were repeated after 4 and 24 h.

Arterial blood was collected in sterile serum tubes before, during (at 2 h), and after (at 4, 6, and 24 h) the infusion of NAC or placebo. The samples were immediately centrifuged at 3,000 g for 10 min (Hettich Zentrifugen; Tuttinglen, Germany). Two aliquots of plasma were collected for each time point and stored at −80°C until analysis. Plasma concentrations of TNF-α, IL-6, IL-8, and sTNFR-p55 were measured by specific enzyme amplified immunoassays (Biosource; Fleurus, Belgium). Each immunoassay had demonstrated no measurable cross-reactivity to other assayed cytokines, as determined by the manufacturer. The sensitivities were 3 pg/mL for TNF-α, 2 pg/mL for IL-6, 0.7 pg/mL for IL-8, 1 pg/mL for IL-10, and 0.05 ng/mL for sTNFR-p55. Survival was defined as being alive at the end of hospital stay.

**Statistics**

Statistical analysis included a two-way analysis of variance for repeated measures followed by a Dunnett’s test. Intergroup comparisons relating to age, APACHE II score, duration of mechanical ventilation, and duration of ICU stay were analyzed by a Student’s t-test. Data are expressed as mean±SD unless otherwise indicated. Statistical significance was considered at a p value of <0.05.

**RESULTS**

**Patient Characteristics**

Table 2 lists the patients’ clinical and demographic characteristics. Twelve of 22 patients received NAC (NAC group) and 10 received placebo (control group). Patients in the NAC group were older than the controls (68±12 vs 57±17 years), but this difference did not reach statistical significance. Seventeen patients had septic shock on admission (11 in the NAC group, and 6 placebo-treated patients) and 5 died while hospitalized in the ICU for noninfection-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>APACHE II Score</th>
<th>Type of infection</th>
<th>Pathogen*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>20</td>
<td>Pneumonia</td>
<td>Pa, Ko</td>
<td>Survived</td>
</tr>
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<td>2</td>
<td>71</td>
<td>M</td>
<td>30</td>
<td>Pneumonia</td>
<td>Ni</td>
<td>Died (MOF)</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>F</td>
<td>22</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Died (MOF)</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>29</td>
<td>Pneumonia</td>
<td>Sa</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>M</td>
<td>24</td>
<td>Pneumonia</td>
<td>Sp</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>15</td>
<td>Peritonitis</td>
<td>Ec, Ef</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>20</td>
<td>Pneumonia</td>
<td>Sp</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>M</td>
<td>22</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Died (RS)</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>M</td>
<td>21</td>
<td>Pneumonia</td>
<td>Pm</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>93</td>
<td>F</td>
<td>32</td>
<td>Pneumonia</td>
<td>Ca</td>
<td>Died (CD)</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>F</td>
<td>19</td>
<td>Skin infection</td>
<td>Ni</td>
<td>Survived</td>
</tr>
<tr>
<td>12</td>
<td>82</td>
<td>M</td>
<td>27</td>
<td>Cholecystitis</td>
<td>Ni</td>
<td>Died (MOF)</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>17</td>
<td>Pneumonia</td>
<td>Ec, Ck</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>M</td>
<td>21</td>
<td>Peritonitis</td>
<td>Pa, Ef</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>32</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Died (MOF)</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>F</td>
<td>22</td>
<td>Pseudomonas aeruginosa</td>
<td>Pa</td>
<td>Died (MOF)</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>25</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Died (CD)</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>M</td>
<td>20</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>32</td>
<td>Peritonitis</td>
<td>Ni</td>
<td>Died (RS)</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>24</td>
<td>Pneumonia</td>
<td>Ni</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>17</td>
<td>Peritonitis</td>
<td>Ec</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>M</td>
<td>17</td>
<td>Pneumonia</td>
<td>Ec</td>
<td>Survived</td>
</tr>
</tbody>
</table>

*Pa=Pseudomonas aeruginosa; Ko=Klebsiella oxytoca; Ec=E coli; Sa=Staphylococcus aureus; Sp=Streptococcus pneumoniae; Ef=Enterococcus faecalis; Pm=Proteus mirabilis; Ca=Candida albicans; Ck=Citrobacter koseri; Ec1=Enterobacter cloacae.

1Isolated from blood.

NI=not identified; MOF=multiple organ failure; RS=refractory shock; CD=cardiac death.
related reasons. Baseline APACHE II (23±5 vs 23±6 NAC vs control) and inotrope scores (3.9±3.3 vs 3.8±3.7) were nearly identical; the differences were not significant (NS). Inotrope scores at 4 and at 24 h were also similar (4.1±3.1 vs 4.2±3.7 at 4 h; 4.0±3.2 vs 4.3±3.6 at 24 h; p=NS). Infection was documented in 9 NAC-treated patients and in 8 control patients. The NAC infusion was well-tolerated by all patients, and no adverse effects were noted. Patients in the two groups received a similar amount of fluid and RBCs (5.3±0.2 L vs 5.5±0.4 L, and 0.8±0.1 U vs 0.7±0.2 U, respectively; both p=NS).

**Hemodynamic Parameters, Oxygen Transport Variables, and Lung Compliance**

There was no significant difference between groups in PaO2/FIO2 ratio and SLC on admission, but both variables steadily increased in the NAC group to become significantly higher than in controls at 24 h (Fig 1). Systemic and pulmonary hemodynamic parameters, DO2, VO2, arterial lactate concentrations, and arterial pH followed a similar course in both groups (Table 3).

**Outcome**

Outcomes are listed in Table 2. The overall hospital mortality rate was similar in both groups (40%). All nonsurvivors in both groups died while being mechanically ventilated. Time from enrollment in the study until death was 6±2 days in the NAC group and 6±5 days in the control group. No difference between groups in duration of mechanical ventilation or ventilator-free days (calculated as the number of days a patient was alive and without mechanical ventilation at 28 days) was observed. In the NAC and placebo groups, respectively, ventilation duration was 7±1 vs 14±5 days; there were 12±3 vs 7±3 ventilator-free days; for both comparisons, p=NS. However, NAC-treated survivors had shorter duration of mechanical ventilation (7±2 vs 20±7 days; p<0.05) and a shorter ICU stay (13±2 vs 32±9 days; p<0.05).

**Plasma Cytokine Levels**

Plasma cytokine levels are illustrated in Figures 2 and 3. Cytokines were detectable in all patients but, as expected, showed marked interpatient variability. In an attempt to adjust for a 30% difference in absolute plasma levels of cytokines between groups at baseline (data not shown; p=NS), the evolution of cytokines was expressed as proportional changes from baseline. NAC administration did not influence plasma levels of TNF-α, IL-6, and IL-10, but acutely lowered sTNFR-p55 and IL-8 levels.

**DISCUSSION**

IV infusion of NAC has been shown to exert significant hemodynamic effects in experimental models of sepsis.\(^5\,8\,17\) NAC, administered before and during *Escherichia coli* endotoxemia or endotoxic shock, can protect sheep,\(^5\) dogs,\(^8\) and pigs\(^17\) from pulmonary hypertension and a fall in cardiac output. In human septic shock, Spies et al\(^13\) documented...
Table 3—Hemodynamic and Oxygen Transport Variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Immediately After NAC Infusion</th>
<th>24 h After NAC Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>122±29</td>
<td>119±28</td>
<td>96±11</td>
</tr>
<tr>
<td>NAC</td>
<td>111±17</td>
<td>116±14</td>
<td>114±16*</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>66.4±15.6</td>
<td>73.1±10.2</td>
<td>75.0±14.8</td>
</tr>
<tr>
<td>NAC</td>
<td>75.2±17.9</td>
<td>79.4±12.0</td>
<td>75.3±12.5</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>31.6±7.5</td>
<td>33.5±5.1</td>
<td>32.4±7.3</td>
</tr>
<tr>
<td>NAC</td>
<td>29.3±7.5</td>
<td>30.3±5.1</td>
<td>31.4±5.3</td>
</tr>
<tr>
<td>Cardiac index, L/kg·min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.9±1.2</td>
<td>4.9±1.6</td>
<td>4.9±1.6</td>
</tr>
<tr>
<td>NAC</td>
<td>4.7±1.3</td>
<td>5.0±1.2</td>
<td>4.3±0.7</td>
</tr>
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<td>Pulmonary artery occlusion pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>16.3±5.9</td>
<td>17.4±4.5</td>
<td>17.6±5.6</td>
</tr>
<tr>
<td>NAC</td>
<td>15.2±4.2</td>
<td>14.8±2.6</td>
<td>15.9±4.6</td>
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<td>Right atrial pressure, mm Hg</td>
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<tr>
<td>Control</td>
<td>13.8±5.4</td>
<td>14.9±3.0</td>
<td>15.2±5.1</td>
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<tr>
<td>NAC</td>
<td>11.9±5.1</td>
<td>13.0±3.6</td>
<td>13.3±4.9</td>
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<tr>
<td>Systemic vascular resistance index, dyne·s·cm⁻⁵·m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>936±387</td>
<td>1019±287</td>
<td>1026±344</td>
</tr>
<tr>
<td>NAC</td>
<td>1131±322</td>
<td>1073±274</td>
<td>1163±176</td>
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<td>Pulmonary vascular resistance index, dyne·s·cm⁻⁵·m⁻²</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>280±176</td>
<td>292±166</td>
<td>292±130</td>
</tr>
<tr>
<td>NAC</td>
<td>254±79</td>
<td>264±96</td>
<td>291±91</td>
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<tr>
<td>Arterial pH</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.33±0.12</td>
<td>7.35±0.16</td>
<td>7.37±0.05</td>
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<tr>
<td>NAC</td>
<td>7.36±0.09</td>
<td>7.33±0.05</td>
<td>7.39±0.04</td>
</tr>
<tr>
<td>Hematocrit, %</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>33.5±6.4</td>
<td>29.5±5.1</td>
<td>29.9±2.3</td>
</tr>
<tr>
<td>NAC</td>
<td>32.4±7.9</td>
<td>31.9±7.9</td>
<td>33.1±4.4*</td>
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<tr>
<td>Arterial lactate, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.5±2.0</td>
<td>2.5±1.6</td>
<td>2.0±1.5</td>
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<tr>
<td>NAC</td>
<td>3.9±3.4</td>
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<tr>
<td>$\text{DO}_2$, mL/min·m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>719±215</td>
<td>628±180</td>
<td>647±208</td>
</tr>
<tr>
<td>NAC</td>
<td>684±279</td>
<td>711±227</td>
<td>634±151</td>
</tr>
<tr>
<td>$\text{VO}_2$, mL/min·m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>172±57</td>
<td>167±48</td>
<td>148±61</td>
</tr>
<tr>
<td>NAC</td>
<td>140±49</td>
<td>147±56</td>
<td>132±49</td>
</tr>
<tr>
<td>$\text{O}_2$ER, %</td>
<td></td>
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<tr>
<td>Control</td>
<td>25.7</td>
<td>27.6</td>
<td>23.7</td>
</tr>
<tr>
<td>NAC</td>
<td>21.7</td>
<td>21.5*</td>
<td>21.7</td>
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*p<0.05 vs control.

improvement of cardiac function, tissue oxygenation, and survival in patients in whom NAC (150 mg/kg IV bolus, followed by 18.75 mg over 90 min) increased oxygen consumption. In contrast, Peake et al.14 treated patients with a different NAC infusion scheme (150 mg/kg IV bolus, followed by 50 mg/kg over 4 h, and then 100 mg/kg over 24 h for 44 h) and found significant depression of cardiovascular performance after 24 h together with increased mortality. These studies must be interpreted with caution. The mean terminal half-life of reduced NAC after IV bolus administration in healthy volunteers is 2 h.18

The hemodynamic effects of NAC in patients with fulminant hepatic failure are also related to the plasma levels of the drug and persist only during the hour following the 150-mg/kg loading dose.19 Thus, Spies et al.18 merely observed the acute effects of the NAC bolus on cardiovascular and oxygenation parameters, since the subsequent infusion contained only a low dose of NAC. In contrast, Peake et al.14 studied the effects of a continuous infusion of NAC over a longer period of time in severely ill patients (mean APACHE II score of 33) who already exhibited signs of cardiac depression and tissue hypoperfusion at study onset. We included patients whose severity of illness stood midway between those seen
These discrepancies may be explained by differences in patient population,20 dose and timing of intervention,13 and timing of the measurements.13,20

An important finding of our study was that NAC improved systemic oxygenation in association with an increase in lung compliance. This could explain why survivors who received NAC were more easily weaned from mechanical ventilation and could be discharged sooner from the ICU. Our results are in agreement with those of clinical trials evaluating the use of NAC in established ARDS.3,21,22 NAC improved lung compliance, chest radiograph edema score, and arterial oxygenation in postseptic ARDS patients.3 In patients with lung injury, of whom 45% had sepsis as a primary or complicating event, relatively low doses of NAC (40 mg/kg/d for 3 days) significantly improved systemic oxygenation and diminished the need for ventilatory support.21 Recently, a prolonged infusion of NAC (70 mg/kg/d for 10 days) was found to improve cardiac function and to attenuate lung injury in patients with ARDS of different etiology.22 Experimental studies in animals...
have also demonstrated beneficial pulmonary effects of NAC. In rodent models of acute lung injury, postinsult treatment with NAC was shown to decrease microvascular lung leak and pulmonary edema formation.\textsuperscript{23,24} NAC restored microvascular permeability, decreased lung edema, and ameliorated arterial oxygenation following \textit{E coli} endotoxic shock in sheep\textsuperscript{2} and pigs.\textsuperscript{17,25} A similar effect of NAC causing a decrease in lung microvascular permeability, with subsequent reduction of edema formation, could explain the improved lung compliance in our NAC-treated septic shock patients who did not have ARDS at study inclusion. The small sample size in this study does not allow us to establish a firm relationship between the rapid improvement of respiratory function in the whole group of NAC-treated patients and the shorter duration of ventilation and ICU stay observed in those who survived. However, accumulation of activated neutrophils in the pulmonary circulation followed by focal endothelial damage and development of interstitial edema can occur within 4 h after induction of experimental sepsis.\textsuperscript{26} Since NAC has been shown to prevent or to attenuate these microvascular and cellular alterations,\textsuperscript{3,23,34,27} its early administration may potentially counteract pulmonary dysfunction during the course of septic shock.

The beneficial pulmonary effects of NAC in septic shock may be imputed to the anti-inflammatory and antioxidative effects of the drug. NAC significantly reduced neutrophil recruitment\textsuperscript{23,24} and aggregation\textsuperscript{6} in experimentally injured lungs. However, NAC did not inhibit neutrophil degranulation, either in experimental endotoxin-induced lung injury\textsuperscript{5,6} or in patients with ARDS\textsuperscript{28} or at risk for ARDS.\textsuperscript{29} Preservation of the glutathione redox state by thiol donation may represent another mechanism of NAC-mediated pulmonary protection in sepsis. Tissue GSH levels are severely depleted in experimental endotoxic\textsuperscript{30} and septic\textsuperscript{31} shock. However, RBC and plasma GSH levels have been shown to rise only slowly after administration of NAC in postseptic ARDS patients.\textsuperscript{3} Finally, by scavenging hypochlorous acid, low concentrations of NAC were able to inhibit \textit{in vitro} inactivation of \textalpha\textsubscript{1}-antiproteases,\textsuperscript{4} restricting the deleterious effects of neutrophil-derived elastase on lung tissue.\textsuperscript{32} However, NAC did not limit spontaneous oxidant production in granulocytes from patients with early ARDS.\textsuperscript{28}

Taken together, these observations suggest that the acute effects of NAC may be attributed to a direct inhibitory effect on one or more factors that can modulate neutrophil activity in the lung. Such an anti-inflammatory effect has been demonstrated in endotoxin-shocked dogs, in which pretreatment with NAC attenuated the release of TNF-\alpha.\textsuperscript{8,33} NAC probably did not influence TNF levels in our patients with established septic shock because of the inherent difference in timing of clinical NAC administration compared to the experimental setting. Like TNF-\alpha, plasma levels of sTNFR-p55 are elevated in septic patients.\textsuperscript{34} Since this anti-inflammatory substance originates primarily from increased synthesis and shedding by activated neutrophils,\textsuperscript{35} the lower sTNFR-p55 levels in NAC-treated patients might reflect an effect of NAC on neutrophils. Another interesting finding is that treatment with NAC was associated with lower plasma IL-8 levels. IL-8 levels are often increased in septic patients, with the highest levels found in patients with shock.\textsuperscript{36,37} IL-8 promotes recruitment and activation of neutrophils\textsuperscript{38} and is recognized as an important mediator of systemic inflammation and, in particular, septic lung injury.\textsuperscript{37} Patients with ARDS that occurs in association with sepsis from a pulmonary or nonpulmonary source have been reported to have higher concentrations of IL-8 in plasma and BAL fluid than patients with ARDS of nonseptic origin.\textsuperscript{39} Plasma levels of IL-8 in clinical ARDS due to sepsis have also been found to correlate with lung injury score and oxygenation index.\textsuperscript{40} Finally, IL-8 blockade in experimental endotoxin shock resulted in hemodynamic improvement, attenuation of plasma leakage, reduced OFR production, and increased survival rate.\textsuperscript{41} NAC may influence the synthesis or the release of IL-8 by several intertwined mechanisms. NAC has been shown to attenuate lipopolysaccharide-induced IL-8 synthesis in human monocytes\textsuperscript{42} and endothelial cells\textsuperscript{43} by reducing the activity of the transcription factor NFkB. Monocytes secrete massive quantities of IL-8 in response to thrombin formation.\textsuperscript{44} Excessive generation of thrombin resulting in microvascular fibrin deposition is characteristic for ARDS and might be decreased by NAC.\textsuperscript{45} By offering either direct protection from oxidative damage\textsuperscript{46} or by enhancement of microcirculatory blood flow, NAC could also stabilize pulmonary endothelial cells, thereby resulting in less IL-8 release.

In conclusion, the present study demonstrated that a short-term infusion of NAC in patients with early diagnosed septic shock improves systemic oxygenation and SLC without influencing systemic and pulmonary hemodynamics. NAC-treated survivors had a less complicated weaning period and a shorter duration of stay in the ICU than the placebo-treated group. The decrease in plasma levels of IL-8 during NAC infusion may play a role in early lung protection in ongoing septic shock and merits further investigation. A larger clinical trial is needed to assess
whether a prolonged infusion of NAC can affect the
development of organ failure and outcome in severe
septic shock.

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