Effects of N-acetylcysteine on tissue oxygenation in patients with multiple organ failure and evidence of tissue hypoxia

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ABSTRACT: Covert tissue hypoxia, particularly of the splanchnic region, appears important in the pathogenesis of multiple organ failure (MOF). This investigation evaluates the effects of N-acetylcysteine (NAC) upon several measures of tissue oxygenation in 10 patients with severe MOF and evidence of splanchnic hypoxia (as suggested by a pathologically low value (<7.32) of the pH of the gastric mucosa (pHi)).

Patients were studied following a prospective, randomized, placebo-controlled, cross-over design. Measurements included pulmonary and systemic haemodynamics, cardiac output by thermodilution, arterial and mixed venous blood gas values, blood lactate concentration, whole-body oxygen uptake by analysis of the expired gases, and pHi by tonometry. A complete set of measurements was obtained before and 45 min after the infusion of NAC ($150 \text{ mg} \cdot \text{kg}^{-1}$ in 250 mL of saline) and, also, before and 45 min after the infusion of an equivalent volume of saline.

NAC increased the cardiac index and vasodilated the systemic circulation ($p < 0.01$). However, O_2 delivery to the tissues did not increase because the arterial oxygen content fell after NAC ($p < 0.01$). Mean O_2 extraction or lactate concentration did not change after NAC, and pHi fell slightly (from 7.11 ± 0.21 to 7.07 ± 0.21 ; $p < 0.05$). The infusion of saline did not modify any variable significantly. The O_2 extraction fraction increased exponentially in those patients with reduced O_2 transport to the tissues.

These results argue against a beneficial effect of N-acetylcysteine upon tissue oxygenation in patients with severe multiple organ failure and evidence of splanchnic hypoxia. Furthermore, they suggest that the mechanisms controlling the extraction of oxygen by the peripheral tissues in these patients were not impaired.

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Multiple organ failure (MOF) is frequent in critically ill patients and often determines their outcome [1]. A defect in peripheral tissue O_2 extraction can cause covert tissue hypoxia and seems important in the pathogenesis of MOF [2–4]. Studies in experimental animals suggest that N-acetylcysteine (NAC) can improve O_2 extraction and tissue oxygenation [5]. In humans, NAC appears to enhance tissue O_2 extraction in patients with fulminant hepatic failure due to acetaminophen overdose [6], but not in patients with sepsis [7].

Regional changes of tissue oxygenation, such as O_2 extraction defects, may not be evident from whole-body measurements [8–11]. Measurement of the gastric mucosal pH (pHi) by tonometry is an easy-to-obtain index of tissue oxygenation of the gastrointestinal tract [12], with potential prognostic implications [8]. The effects of NAC upon pHi are not well understood [7].

The aim of this investigation was to assess the effects of NAC upon several indices of tissue oxygenation in patients with MOF and some evidence of tissue hypoxia, such as a pathologically low pHi, at the inclusion

in the study. We reasoned that, if NAC was to enhance tissue oxygenation in these patients, they had to have some evidence of tissue hypoxia to begin with. The response of tissue oxygenation was assessed both at the whole body level (O_2 uptake, O_2 extraction and blood lactate concentration) and at the regional level (pHi). To avoid potential mathematical coupling of variables related to O_2 transport and utilization [10], cardiac output and O_2 uptake were measured using independent methods (thermodilution and metabolic chart, respectively).

Materials and methods

Study subjects

Ten consecutive patients with MOF and a pHi lower than 7.32, which is generally considered the lower limit of normality [13], were studied. Mean age ($\pm \text{SD}$) was 57 (± 13) yrs, range 41–74 yrs. The diagnostic criteria

of MOF were those of TRAN *et al.* [14]. All patients had a minimum of three failing organs. MOF was of septic origin (pneumonia, cholecystitis) in seven patients, one patient had cardiogenic shock after myocardial infarction, and two subjects had adult respiratory distress syndrome (ARDS) (one after surgery and the other after an episode of acute pancreatitis). None had had recent (<72 h) upper abdominal surgery and/or gastric haemorrhage, that might potentially interfere with measurements of pHi [13]. Seven patients required haemofiltration and/or vasoactive drugs (dopamine (10–20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and/or norepinephrine (0.2–1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to maintain diuresis and systemic haemodynamics. The dosage of the latter was not modified during the study in any patient. The investigation was approved by the Ethics Committee of the Hospital Universitari Son Dureta (Palma, Mallorca, Spain). The patient's next of kin signed the informed consent after being fully informed of the purpose, characteristics and nature of the study.

Study design

The study was designed as a prospective, randomized, placebo-controlled, cross-over investigation. Patients were studied within the first 72 h after establishing the diagnosis of MOF [14]. At the time of the study, all patients were clinically stable, mechanically-ventilated (Servo C; Siemens, Sweden), paralysed (pancuronium bromide, 4 $\text{mg}\cdot\text{h}^{-1}$), and sedated (midazolam, 7 $\text{mg}\cdot\text{h}^{-1}$). The inspiratory fraction of O_2 (F_{I,O_2} , 0.82 ± 0.24) (mean $\pm$ SD) and the initial ventilatory settings (tidal volume 10.2 ± 0.9 (range 8.5–11.7) $\text{mL}\cdot\text{kg}^{-1}$; respiratory frequency 19.5 ± 3.9 (range 14–27) $\text{breaths}\cdot\text{min}^{-1}$; positive end-expiratory pressure (PEEP) (three patients) 10 cmH_2O) were not modified during the study.

After a first set of measurements (see below), patients were randomly assigned to receive an *i.v.* infusion of either NAC or saline. NAC was given as a bolus (150 $\text{mg}\cdot\text{kg}^{-1}$ in 250 mL of saline) during 15 min, followed by a maintenance perfusion of 4 $\text{mg}\cdot\text{kg}^{-1}$ during a further 30 min (30 mL approximately); this dosage is the same as used in previous studies [6, 7]. An equivalent volume of saline was administered following an identical regimen. Forty five minutes after the start of the infusion, measurements were obtained again and the infusion stopped. Thirty minutes were then allowed for wash-out, and a new baseline set of measurements was obtained. Patients were then switched to receive the alternative medication (saline or NAC), which was administered following the same regimen outlined above, and final measurements were obtained 45 min later.

Methods

A complete set of measurements included systemic and pulmonary haemodynamics (Siemens 960; Sweden), arterial and mixed venous blood gas values (IL 1312; Izasa, Spain), haemoglobin and O_2 saturation (IL Co-Ox 282; Izasa, Spain), arterial lactate (Analox, UK), pHi (Tonometrics Inc., USA) and whole-body oxygen uptake (Calorimet, Sweden). All cardiovascular pressures were determined at end-expiration and referred to the

mid-axillary line. Cardiac output was measured using the thermodilution method at end-expiration. Results are expressed as the mean value of at least three different measurements with less than 10% variation between them. Cardiac output was normalized for body surface area (m^2) (cardiac index). The pHi was measured following standard recommendations [13]. Briefly, the gastric tonometer (Tonometrics, USA) was inserted nasogastrically and its correct positioning was confirmed by radiography. The silicone balloon of the tonometer was filled with 2.5 mL of 0.9% saline. The carbon dioxide tension (PCO_2) of the saline, measured with a standard electrode (IL1312; Izasa, Spain), was used to calculate pHi in combination with an equilibration factor provided by the manufacturer of the tonometer and the arterial bicarbonate measured simultaneously in the arterial blood [8, 13, 15]. To minimize the influence of the pH of the gastric juice on pHi, all patients received *i.v.* ranitidine (50 $\text{mg}\cdot 12\text{ h}^{-1}$). Oxygen uptake ($\dot{V}\text{O}_2$) was measured directly from the expired gases using a closed circuit method [16] (Calorimet, Sweden). The methodological validation of this technique has been published before by our group [16]. Arterial and mixed venous O_2 contents (Ca,O_2 , $\text{C}\bar{\text{v}},\text{O}_2$), O_2 transport to tissues (cardiac index $\times \text{Ca},\text{O}_2$) and the tissue O_2 extraction ratio ($(\text{Ca},\text{O}_2 - \text{C}\bar{\text{v}},\text{O}_2)/\text{Ca},\text{O}_2 \times 100$) were calculated using standard formulae.

Analysis

Results are presented as mean $\pm$ SD. Because a carry-over effect was ruled out [17], the order of treatment was not considered in the analysis. The statistical significance of differences was tested using analysis of variance (Friedman), followed by *post-hoc* contrasts (Wilcoxon). Potential relationships between variables of interest were investigated by regression analysis. A *p*-value of less than 0.05 was considered statistically significant.

Results

There were no major complications associated with the infusion of NAC or the use of the gastric tonometer. During the study, body temperature did not change in any patient by more than 0.2°C , as assessed by the pulmonary artery thermistor. Mortality rate was very high (nine patients died), probably reflecting the severity of MOF (mean Simplified Acute Physiological Score I (SAPS I) calculated on admission 4.6 ± 5.6 (range 8–24)) [14].

NAC did not modify right atrial pressure (P_{ra}), mean pulmonary artery pressure ($\bar{P}_{\text{pa}}$), capillary wedge pressure (P_{cw}) or mean systemic blood pressure (table 1). Cardiac index increased from 3.9 ± 1.4 to $4.4\pm 1.5\text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ($p<0.01$); because cardiac frequency (f_{c}) did not change (table 1), this was due to an increased stroke volume (34.3 ± 11.0 to $38.5\pm 9.8\text{ mL}\cdot\text{m}^{-2}$ ($p<0.01$)). Pulmonary vascular resistance (PVR) did not change (table 1) and systemic vascular resistance (SVR) decreased after NAC from 18.9 ± 8.2 to $14.8\pm 4.6\text{ mmHg}\cdot\text{L}^{-1}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ($p<0.01$). The infusion of saline did not significantly modify any of these haemodynamic measures (table 1).

Table 1. – Haemodynamic, gas exchange and tissue oxygenation measurements

	Baseline	NAC	Baseline	Saline	ANOVA
P_{ra} mmHg	8±4	10±4	8±4	9±4	NS
P_{pa} mmHg	29±5	29±5	28±4	29±6	NS
P_{cw} mmHg	11±5	11±3	11±4	11±5	NS
Mean systemic pressure mmHg	73±13	70±11	72±11	73±14	NS
f_c beats·min ⁻¹	116±29	114±24	114±28	113±27	NS
Cardiac index L·min ⁻¹ ·m ⁻²	3.9±1.4	4.4±1.5**	4.1±1.5	4.1±1.5	0.009
Stroke volume index mL·min ⁻¹ ·m ⁻²	34.3±11.0	38.5±9.8**	35.8±8.9*	36.2±10.2	0.02
PVR mmHg·L ⁻¹ ·min ⁻¹ ·m ⁻²	4.8±1.5	4.3±1.5	4.6±1.5	4.8±1.7	NS
SVR mmHg·L ⁻¹ ·min ⁻¹ ·m ⁻²	18.9±8.2	14.8±4.6**	17.3±6.0*	17.5±6.6	0.04
P_{a,O_2} kPa	11.7±4.0	10.7±3.8	11.1±4.0	11.2±4.3	NS
P_{a,CO_2} kPa	5.8±1.3	6.1±1.1	5.9±1.1	6.0±1.0	NS
Arterial pH	7.29±0.12	7.27±0.11	7.27±0.10	7.26±0.10	NS
Venous admixture %	37±15	40±15*	38±15	39±14	0.04
Haemoglobin g·dL ⁻¹	11.0±1.1	10.5±1.1	10.9±1.2	10.5±1.2	NS
S_{a,O_2} %	93±4	91±6*	92±5	92±5	NS
Ca_{a,O_2} vols %	14.6±1.9	13.5±2.2*	14.1±2.0*	13.7±1.9	0.03
O_2 delivery mL·min ⁻¹ ·m ⁻²	551±156	590±197	570±196	550±182	NS
$V'O_2$ mL·min ⁻¹ ·m ⁻²	126±24	135±24*	128±33	132±31	0.05
Extraction ratio %	30±9	30±10	30±8	30±9	NS
P_{v,O_2} mmHg	38.8±6.5	39.2±7.9	38.6±6.4	39.6±7.2	NS
Lactate mEq·mL ⁻¹	2.5±2.1	2.59±2.1	2.5±2.1	2.5±2.1	NS
Arterial bicarbonate	21.3±3.1	20.9±3.3	21.0±3.1	20.8±2.9	NS
Gastric PCO_2 kPa	8.4±5.9	8.8±5.5	8.6±5.5	8.9±5.8	0.04
Gastric mucosal pH	7.11±0.21	7.07±0.21*	7.09±0.20	7.07±0.21	0.009

Values are presented as mean±SD. NAC: N-acetylcysteine; P_{ra} : right arterial pressure; P_{pa} : pulmonary artery pressure; P_{cw} : capillary wedge pressure; f_c : cardiac frequency; PVR and SVR: pulmonary and systemic vascular resistance, respectively; P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; S_{a,O_2} : arterial oxygen saturation; Ca_{a,O_2} : arterial oxygen content; $V'O_2$: oxygen uptake; P_{v,O_2} : mixed venous oxygen tension; PCO_2 : carbon dioxide tension; ANOVA: analysis of variance; NS: non-significant. *: $p<0.05$; **: $p<0.01$, compared to the previous measurement. (1 kPa = 7.5006 mmHg).

Fig. 1. – Relationship between O_2 transport and: a) O_2 uptake; and b) tissue O_2 extraction in each patient (different symbols) throughout the study (four measurements per patient). Regression lines were fitted to all points shown in the graph using: a) a first; or b) a second order polynomial fitting algorithm that minimizes the residual sum of squares (Sigma Plot; Jandel Corp., USA). Oxygen uptake measurements were not available in two patients. For further explanation, see text.

After NAC, arterial oxygen tension (P_{a,O_2}) decreased ~ 0.9 kPa (7 mmHg) ($p=0.06$) due to an increase in venous admixture ($p=0.04$) (table 1). Accordingly, both arterial oxygen saturation (S_{a,O_2}) ($p=0.06$) and Ca_{a,O_2} decreased ($p=0.03$) (table 1). Oxygen transport to tissues was not significantly influenced by NAC because the effects of a lower O_2 content were balanced by a higher cardiac index. Oxygen uptake increased slightly after NAC from 126 ± 24 to 135 ± 24 mL·min⁻¹·m⁻² ($p<0.05$). This increase represents a 7% change, and is within the variability of the method [16].

Figure 1 shows the relationship between O_2 delivery to the tissues and O_2 uptake (fig. 1a) and the O_2 extraction fraction (fig. 1b) in each subject throughout the study (four measurements per patient). Overall, the mean values of O_2 extraction ratio, mixed venous oxygen tension (P_{v,O_2}) and blood lactate concentration did not change after NAC (table 1). By design, pH_i was

Fig. 2. – Effects of N-acetylcysteine (NAC) (and saline) on the pH of the gastric mucosa (pHi) in 10 patients. Bars indicate mean values. The asterisk indicates statistical significance ($p<0.05$) of changes. For further explanation, see text.

pathologically low (<7.32) in each patient, ranging 6.66–7.31 (fig. 2). After NAC, pH_i decreased in 7 of the 10 patients (fig. 2) and, as a result, mean pH_i decreased significantly (7.11 ± 0.21 to 7.07 ± 0.21 ; $p < 0.05$). This change was due to a minor increase in gastric PCO_2 , because the arterial bicarbonate concentration did not change after NAC (table 1). In absolute terms, the changes both of pH_i and gastric PCO_2 were very small. The infusion of an equivalent volume of saline did not have any significant effect in any measured variable (table 1).

Discussion

The main finding of the present study is that, in patients with severe MOF and some evidence of tissue hypoxia (pH_i <7.32), NAC does not enhance tissue O_2 extraction and/or pH_i (table 1 and fig. 2). Moreover, because O_2 extraction increased exponentially when O_2 delivery to the tissues was low (fig. 1b), the results suggest that the mechanisms controlling O_2 extraction by the tissues were not impaired in these patients [18].

An O_2 extraction defect has been identified in experimental models of sepsis [19–21]. Capillary obstruction (by activated inflammatory cells) and/or endothelial cell damage (by O_2 free radicals, among others) can cause such an O_2 extraction defect [18]. This is thought to play an important role in the development of MOF in critically ill patients [2–4, 22]. NAC decreases the neutrophil-aggregating activity, enhances nitric oxide release by the endothelium, and has important antioxidant properties [5]. Thus, in theory, NAC may improve O_2 extraction and tissue oxygenation. In septic dogs, ZHANG *et al.* [5] showed that pretreatment with NAC before the administration of endotoxin increased the O_2 extraction ratio. In patients with fulminant hepatic failure due to acetaminophen overdose, HARRISON *et al.* [6] reported that NAC enhanced tissue O_2 extraction. These observations suggest that NAC may facilitate a better matching between O_2 demand and supply [23]. We did not observe such an effect of NAC in patients with MOF. This is consistent with a recent report by SPIES *et al.* [7] in patients with sepsis, who also failed to identify any significant effect of NAC upon tissue O_2 extraction.

Several factors can contribute to the explanation of these discrepancies. Firstly, in the experimental study by ZHANG *et al.* [5], NAC was administered before endotoxin was given. In the present patients, the effects of NAC were studied as early as possible during the course of their disease, but certainly after the patient had developed a severe MOF [14]. Moreover, one of the inclusion criteria in the present study was the presence of an abnormally low pH_i (fig. 2). The reason for this approach was that, if NAC was to improve tissue hypoxia, patients had to have some evidence of it to begin with. Whether the administration of NAC before the development of MOF can be clinically useful in critically ill patients is a matter of speculation and cannot be answered from the present results.

Secondly, the improved O_2 extraction after NAC reported by ZHANG *et al.* [5] in septic dogs was evident only at very low levels of O_2 transport to the tissues. By contrast, the values of O_2 transport in the present patients (table 1) were much higher and well above the

critical O_2 transport value recently determined in patients by RONCO *et al.* [24]. Moreover, in the patients with fulminant liver failure reported by HARRISON *et al.* [6], the O_2 extraction values were much lower than those usually seen in critically ill patients (table 1), probably because of the hyperdynamic circulatory status characteristic of patients with liver failure [25]. It is conceivable that this difference in haemodynamic situation can explain, at least in part, the differences between their findings [6] and ours. We did not include patients with severe lactic acidosis in the present study. Therefore, the results cannot be readily extrapolated to such a population. However, we think that it is unlikely that NAC may have shown a different effect in these patients, because NAC showed no consistent effect even in patients with very high O_2 extraction (fig. 1b). In the present patients, the O_2 extraction fraction ranged from relatively low to moderately high values, and, interestingly, it shared the type of smooth exponential relationship with tissue O_2 transport (fig. 1b) predicted theoretically in healthy individuals and observed experimentally in animals [18].

Thus, the present results reinforce the idea that O_2 extraction by the tissues is not impaired in patients with MOF. Furthermore, as shown in figure 1a, O_2 uptake was related to O_2 delivery when all measurements were considered but, individually, these two variables were not consistently related. Collectively, our results are in keeping with recent publications, which tend to minimize the importance of a potential "pathological" dependence of O_2 uptake upon O_2 delivery to the tissues in critically ill patients [1, 24, 26].

Ischaemia of the gastric mucosa may be an early manifestation of impaired tissue perfusion in critically ill patients [15]. Several studies have indicated the clinical utility of monitoring pH_i in critically ill patients [8, 27]. In patients with sepsis, SPIES *et al.* [7] have shown that NAC can improve pH_i in only about half of the patients studied. Unfortunately, the authors were unable to find a parameter that can help in predicting which patient will respond positively to NAC [7]. In the present patients, pH_i decreased after NAC (fig. 2). Although this change was statistically significant, in absolute terms it was very small (table 1). Furthermore, changes of gastric PCO_2 were also of very small magnitude. Therefore, we believe that the clinical significance of the fall in pH_i seen after NAC in the present patients is, at least, questionable. However, from our results, it is clear that NAC does not improve pH_i in patients with MOF, once there is evidence of tissue hypoxia (low pH_i). Whether a more prolonged infusion of NAC and/or the administration of the drug earlier in the course of the disease (before pH_i drops below the normal limit) might show a positive therapeutic effect of the drug [7] will require further study.

It is interesting to note that the effects of NAC upon systemic haemodynamics were remarkably similar between all published studies [5–7] and our own. The cardiac index increased and systemic vascular resistance decreased significantly after NAC (table 1). The higher cardiac index after NAC was due to an increased stroke volume (table 1), which suggests that NAC may have increased myocardial contractility [5, 7]. The fall in arterial oxygenation after NAC has been observed before,

both in experimental animals [5] and in humans [28], and is explained by the increase of venous admixture (table 1) probably due to the effects of the increased pulmonary blood flow upon ventilation-perfusion relationships [29].

In summary, this investigation complements and extends previous investigations on the effects of N-acetylcysteine on tissue oxygenation in critically ill patients [6, 7, 28]. Our results show that, in patients with severe multiple organ failure and evidence of splanchnic hypoxia, N-acetylcysteine augments the cardiac index and vasodilates the systemic circulation, but fails to enhance tissue oxygen extraction or the pH of the gastric mucosa. Overall, our results argue against an oxygen extraction defect in patients with multiple organ failure.

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