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N-acetylcysteine decreases lactate signal intensities in liver tissue and improves liver function in septic shock patients, as shown by magnetic resonance spectroscopy: extended case report

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Abstract

Background *N*-acetylcysteine (NAC) has been shown to improve splanchnic blood flow in experimental studies. This report evaluates the effects of NAC on liver perfusion and lactate signal intensities in the liver tissue of septic shock patients using proton magnetic resonance imaging and spectroscopy. Furthermore, the monoethylglycinexylidide (MEGX) test was used to investigate hepatic function.
Methods Five septic shock patients received 150 mg/kg body weight NAC as an intravenous bolus injection over 15 min. Lidocaine was injected both prior to and following NAC administration in order to determine MEGX formation. Measurements (hemodynamics, oxygen transport-related variables, blood samples for lactate, liver-related markers) were performed 1 hour before and 1 hour after NAC injection. In addition to the proton magnetic resonance imaging patients received two proton magnetic resonance spectra, one prior to and one 30 min subsequent to the onset of the NAC infusion at a 1.5 Tesla clinical scanner, for measurement of liver perfusion and liver lactate signal intensity.
Main findings Following NAC infusion, the lactate signal intensity in the liver tissue showed a median decrease of 89% (11–99%), there was a median increase in liver perfusion of 41% (–14 to 559%), and the MEGX serum concentration increased three times (1.52–5.91).
Conclusions A decrease in the lactate signal intensity in the liver tissue and an increase in the MEGX serum concentration and in liver perfusion might indicate improved liver function as a result of NAC administration. Patients with compromised hepatosplanchnic function, such as patients with septic shock due to peritonitis, may therefore benefit from NAC therapy.

Keywords lactate, liver perfusion, monoethylglycinexylidide, *N*-acetylcysteine, proton magnetic resonance imaging, septic shock

Introduction

In septic shock, the vasoconstriction in splanchnic vessels is disproportionally greater than in other vascular beds and may persist despite the presence of normal systemic hemodynamic measurements [1]. Takala and Ruokonen found, in spite of normal global cardiopulmonary physiology, that

[1]H-MRS = proton magnetic resonance spectroscopy; MEGX = monoethylglycinexylidide; MR = proton magnetic resonance; NAC = *N*-acetylcysteine; PaO_2/FiO_2 = partial arterial oxygen tension/inspirator oxygen fraction.

inadequate perfusion and oxygenation of the splanchnic region increases the risk of Multiple Organ Dysfunction Syndrome [2]. The gut is described as the 'motor' of Multiple Organ Dysfunction Syndrome [3].

N-acetylcysteine (NAC), a precursor of glutathione synthesis, can exert important antioxidant cytoprotective effects and anti-inflammatory effects [4–8]. When endotoxic shock occurred, there was a significant increase in the absolute mesenteric blood flow but not in the fractional blood flow (i.e. hepatic flow index/cardiac index) following NAC administration [4,9]. In patients, NAC has been shown to increase the cardiac index and oxygen delivery in fulminant hepatic failure and in septic shock [4,6,10]. Devlin and colleagues showed in a recent study that the indocyanine green elimination in patients with hepatic dysfunction increased after NAC administration [11]. It is not clear, however, whether the increase in elimination rate is related to an increased hepatosplanchnic perfusion or to a better hepatic function [12].

The aim of this report was therefore to investigate whether the administration of NAC improves liver function and liver blood flow in septic shock patients. Owing to the fact that splanchnic dysoxia is usually presumed in sepsis [13], we focused on the measurement of lactate in the liver tissue accumulating following cell dysfunction [14]. Furthermore, the monoethylglycinexylidide (MEGX) test was used to investigate hepatic function.

Materials and methods

All patients were included after written informed consent of legislative and ethical committee approval. For continuous cardiovascular monitoring a fiber optic, pulmonary artery flotation catheter (Baxter Swan-Ganz® Intelicath™ continuous cardiac output thermodilution catheter 139H – 7.5 French; Baxter/Edwards Critical-Care, Irvine, California, USA) and a radial artery catheter were inserted. After adequate fluid resuscitation, norepinephrine was titrated to maintain the mean arterial pressure between 70 and 90 mmHg. All patients were mechanically ventilated and received a continuous infusion of the analgesic sedatives fentanyl and flunitrazepam. The mechanical ventilation was pressure controlled (Servo 900 C; Siemens, Solna, Sweden), and ventilator settings were not altered during the study period. All patients were normoventilated (arterial carbon dioxide tension = 35–45 Torr). None of the patients had a change in body temperature > 0.5°C during the study period, as documented by continuous monitoring of a catheter thermistor.

Blood was collected and hemodynamic measurements were performed 1 hour before and 1 hour after NAC injection. Patients received 150 mg/kg body weight NAC as an intravenous bolus injection over 15 min. Each hemodynamic measurement included the heart rate and cardiovascular pressures with reference to the midaxillary line. The hemodynamic measurements were immediately followed by the withdrawal of mixed venous and radial artery blood samples. Part of each sample was immediately analyzed for arterial and mixed venous oxygen and carbon dioxide tensions (ABL 300; Radiometer, Copenhagen, Denmark), along with arterial and mixed venous hemoglobin content and oxygen saturation (Hemoximeter OSM-3; Radiometer).

An intravenous bolus of 1 mg/kg body weight lidocaine was injected 1 hour before and 1 hour after NAC administration. Blood samples to determine the MEGX test were taken before and 15 min after lidocaine injection. The serum concentration of the lidocaine metabolite MEGX was determined by means of a fluorescence polarization immunoassay (Abbott GmbH, Wiesbaden, Germany). MEGX concentration values measured before lidocaine administration were subtracted from concentrations measured after 15 min, and the results were reported as serum MEGX concentrations (ng/ml). Blood samples were centrifuged at 4650 × *g* for 10 min, and serum was stored at –80°C until analysis.

The measurements of bilirubin, aspartate aminotransferase, alanine aminotransferase and serum lactate were analyzed as part of the clinical routine (Clinical Chemistry Department).

Proton magnetic resonance spectroscopy (^{1}H-MRS) measurements for measurement of lactate liver intensities were acquired at a 1.5 Tesla clinical scanner (Magnetom Vision; Siemens) with a stimulated echo acquisition mode sequence. A fast imaging procedure was performed prior to spectroscopy using a technique involving a gradient echo sequence, fast low angle shot (FLASH 2D), while the breath was held for several seconds. In these images a volume of interest of 64 ml resolution was positioned in the liver parenchyma of the right lobe. A localized shimming procedure was performed. The number of acquisitions was 256. We used echo times of 135 ms and 270 ms, respectively, to differentiate between the fatty acid signal and the lactate signal at 1.35 ppm. This was necessary as both signals consist of almost identical resonance frequencies but have different phase angles at varied echo times. Evaluation of the spectra was performed by means of the LC Model program [15] and data are expressed in arbitrary units that correspond to micromoles per liter. The liver perfusion measurement was performed with the gadolinium-enhanced proton magnetic resonance (MR) imaging method [16,17].

Results

Five septic shock patients were evaluated. Septic shock was defined according to the criteria for septic shock of the American College of Chest Physicians Consensus Conference [18]. All patients were studied within the first 24 hours of the onset of sepsis. Acute Physiology and Chronic Health Evaluation II [19] and Multiple Organ Dysfunction [20] scores were recorded. Basic patient characteristics, scores, outcome data, laboratory parameters and hemodynamic-related and ventilator-related data for each patient are

Table 1

Patient data: basic patient characteristics, scores, hemodynamic-related parameters, and laboratory parameters

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
Sex	Male		Male		Female		Male		Male	
Age (years)	66		74		84		61		47	
Sepsis source	Pneumonia		Pneumonia/urosepsis		Peritonitis		Peritonitis		Peritonitis	
Survivor	Yes		Yes		No		Yes		Yes	
N-acetylcysteine	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
APACHE II (points)	27	24	26	23	24	22	26	21	22	20
MOD score (points)	9	11	11	9	11	11	9	9	7	5
HR (beats/min)	121	122	100	102	116	118	119	100	62	76
MAP (mmHg)	98	90	86	83	88	74	71	83	80	74
CI (l/min/m^2)	3.4	3.8	3.7	4.3	3.0	3.8	4.2	4.5	7.0	6.1
NE (μg/kg/min)	0.09	0.14	0.47	0.47	0.64	1.27	0.48	0.48	0.05	0.00
PaO_2/FiO_2 (Torr)	307	217	260	151	314	266	172	179	218	236
Lactate (mmol/l)	1.0	1.7	1.6	1.6	3.5	2.5	1.9	1.2	1.3	0.9
ALAT (U/l)	16	38	17	39	15	14	5	5	16	8
ASAT (U/l)	19	48	20	49	22	18	6	8	12	9
Bilirubin (μmol/l)	40	44	15	13	58	83	20	17	54	38

ALAT, alanine aminotransferase; APACHE II, Acute Physiologic and Chronic Health Evaluation; ASAT, aspartate aminotransferase; CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; MOD, Multiple Organ Dysfunction; NE, norepinephrine; PaO_2/FiO_2, partial arterial oxygen tension/inspirator oxygen fraction.

presented in Table 1. The results for liver perfusion, liver lactate signal intensity and MEGX serum concentrations are shown in Figs 1–3, respectively.

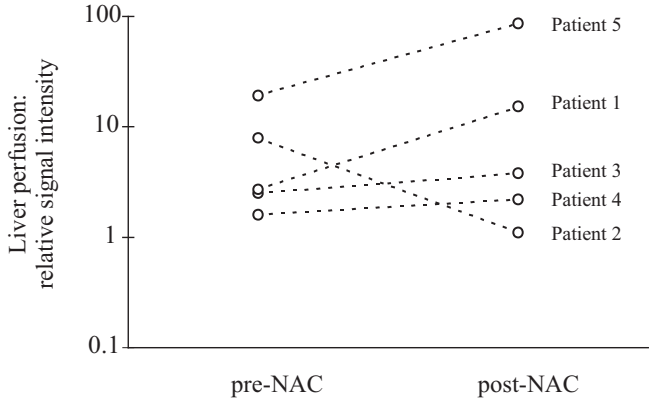
Discussion

The most important results of this report were threefold. There was a median decrease of 89% in lactate signal intensities in liver tissues, although the plasma lactate did not change markedly. Second, there was an increase in liver perfusion after NAC application and, finally, there was an improvement in liver function measured by the MEGX plasma concentration.

Liver function test and MEGX formation

All patients had MEGX concentrations lower than 50 ng/ml prior to administration of NAC (i.e. hepatic dysfunction was manifest) [21,22], without remarkable elevation in conventional routine parameters such as aspartate aminotransferase, alanine aminotransferase, bilirubin or serum lactate. After the treatment with NAC the 15 min MEGX concentration showed an increase up to 4.6-fold. The rate of hepatic uptake of lidocaine and MEGX elimination depends primarily on the hepatic blood flow, while MEGX is formed by P-450 in hepatic microsomes [4,22–24]. Cytochrome P-450 is predominantly localized in zone 3 of the hepatic lobule. In a nonseptical setting, MEGX formation increased due to an improved blood flow [23,25]. NAC may enhance zone 3 perfusion by increasing sinusoidal blood flow, since zone 3 misdistribution may exist in septic shock patients [21,22,26].

Figure 1

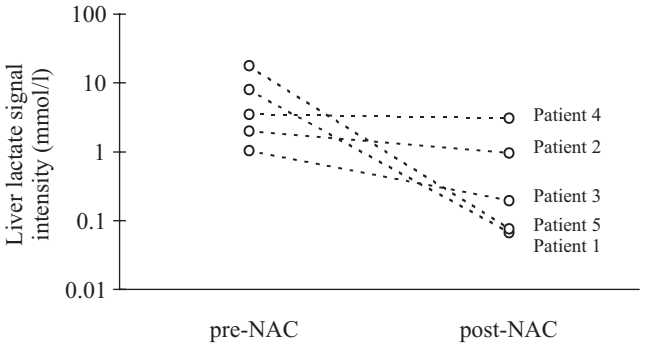


Liver perfusion: liver signal intensity before (pre) and after (post) *N*-acetylcysteine (NAC) application in the five patients.

Liver lactate and MR spectroscopy

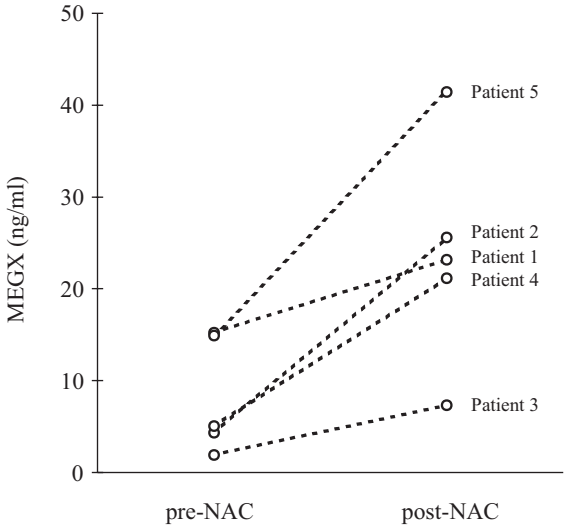
All patients showed a decrease in the lactate signal intensities in their liver tissue. In an animal study, Salzman and colleagues showed a significant transmesenteric lactate

Figure 2



Liver lactate signal intensity before (pre) and after (post) *N*-acetylcysteine (NAC) application in the five patients.

Figure 3



Monoethylglycinexylidide (MEGX) measurements before (pre) and after (post) *N*-acetylcysteine (NAC) application in the five patients.

concentration (lactate between arterial and mesenteric venous blood) increase after a 90 min ileal hypoxic period [27]. An *in vitro* study has shown that cell dysfunction leads to the inhibition of pyruvate dehydrogenase within minutes, thus leading to a pyruvate and lactate accumulation in the cell [14]. Accordingly, the decrease in liver lactate signal intensities identified in the present report could be due to a decreased splanchnic lactate production as a result of a NAC-induced increase in regional perfusion with improvement in microcirculation. The improvement in liver perfusion in four patients could be directly associated with the decrease in liver lactate signal intensities. This assumption is supported by the fact that MEGX formation increased after NAC application as a sign of an improved hepatic oxidative metabolism. The beneficial effects of NAC on tissue perfusion have already been shown in animal and clinical studies [10,26]. Blood lactate levels did not change. In order to cause a significant increase in blood, the rate of lactate production must exceed skeletal muscle, renal and hepatic uptake [28]. Since we did not measure hepatic lactate uptake or release to plasma it is difficult to say what should be expected.

We chose ^{1}H-MRS to determine biochemical changes in hepatic tissue. To the best of our knowledge, no studies have been published concerning ^{1}H-MRS determination of lactate signal intensities in liver tissue *in vivo*. Only one previous paper exists, which describes *in vivo* ^{1}H-MRS of the liver, assigning the peaks of carnitin, taurine, glutamate and glutamin [29]. Studies have been carried out on human bile and cerebral samples and on animals referring to lactate signal intensities in liver tissue [30–32]. ^{1}H-MRS is often used to determine lactate in other tissues (e.g. cerebral tissue) [33]. The technical advantage of ^{1}H-MRS is its increased sensitivity; with an equal quantity of nuclei, it is approximately 15 times more sensitive than ^{31}P-MR spectroscopy.

Furthermore, the effects of respiratory motions complicate liver studies. We decided against respiration synchronization, as this would have required three times as much measuring time. We used the stimulated echo acquisition mode in conjunction with water suppression techniques [34]. Spectral evaluation and quantification of metabolite concentrations was based on a fully automated program [31]. The spectra, however, have to be regarded critically. The resonance sequences can only be identified with an optimal signal/noise ratio. Therefore, the quantity of acquisitions is important. Acquisitions, similar to respiration synchronization, lead to a time problem. At a later stage, the signal/noise ratio depends on the coil. We used the body coil; however, a local surface coil would have optimized the signal/noise ratio.

Liver blood flow and MR imaging

In order to measure the liver perfusion, we selected gadolinium-enhanced MR imaging as a noninvasive assessment [16,17]. To the best of our knowledge, liver blood flow measurements have not been performed to date in humans, but portal venous flow, azygos venous blood flow and focal liver lesion blood flow measurements have been carried out in previous studies [35–37]. Our measurements were taken in the manual expiration hold at the respirator. Otherwise noise, which can worsen the signal/noise ratio, and the respiratory motions would lead to an inconsistent slice position and reproduction. The MR imaging in our study showed a median improvement of 41% in liver perfusion in our patients associated with a decrease in lactate signal intensities in liver tissue, and an increase in four patients in the cardiac index. The increase in cardiac index after NAC administration has already been shown in clinical studies [6,10]. These results suggest that NAC may have a beneficial effect on regional perfusion, which has already been shown in clinical and

Key messages

- N-acetylcysteine decreases liver lactate signal intensities in magnetic resonance spectroscopy
- N-acetylcysteine increases liver perfusion measured by magnetic resonance imaging
- N-acetylcysteine improves MEGX formation

experimental studies [4,9]. The decrease in pulmonary vascular and systemic vascular resistance has been illustrated in some studies on endotoxemia in animals [9,38].

The vasodilating effects of NAC may be caused by a direct relaxing action on vascular smooth muscle or by modulation of nitric oxide, which activates guanylate cyclase, leading to an increase in cyclic guanosine monophosphate accumulation and smooth muscle relaxation [4,39]. This vasodilating property could have been the cause of the decrease in the PaO_2/FiO_2 ratio seen in three of the five patients and of the increase in the norepinephrine dose seen in two of the five patients after NAC application, with a consecutive improvement in the PaO_2/FiO_2 ratio several hours after the intervention.

Conclusions

This report has shown, for the first time, that NAC decreases liver lactate signal intensities and increases perfusion measured by MR imaging and spectroscopy. The MEGX formation improved in all patients, probably due to a NAC-induced improvement in regional perfusion.

Competing interests

None declared.

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