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Altered immune parameters in chronic alcoholic patients at the onset of infection and of septic shock

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Abstract

Introduction Chronic alcoholic patients have a threefold to fourfold increased risk for developing a severe infection or septic shock after surgery, which might be due to altered immune response. The aim of this outcome matched study was to investigate proinflammatory and anti-inflammatory immune parameters during the course of infection and subsequent septic shock in chronic alcoholic patients, and to compare these parameters with those in nonalcoholic patients.

Methods Twenty-eight patients from a cohort of fifty-six with either pneumonia or peritonitis and subsequent septic shock were selected. Fourteen patients were chronic alcoholics whereas fourteen were nonalcoholic patients. Chronic alcoholic patients met criteria (*Diagnostic and Statistical Manual of Mental Disorders IV*, of the American Psychiatric Association) for alcohol abuse or dependence. Measurements were performed during the onset of infection (within 24 hours after the onset of infection), in early septic shock (within 12 hours after onset of septic shock) and in late septic shock (72 hours after the onset). Blood measurements included proinflammatory and anti-inflammatory cytokines.

Results Chronic alcoholic patients exhibited significantly lower plasma levels of IL-8 ($P < 0.010$) during the onset of infection than did matched nonalcoholic patients. In early septic shock, chronic alcoholic patients had significantly decreased levels of IL-1β ($P < 0.015$), IL-6 ($P < 0.016$) and IL-8 ($P < 0.010$). The anti-inflammatory parameters IL-10 and tumour necrosis factor receptors I and II did not differ between alcoholic and nonalcoholic patients.

Conclusion At the onset of infection and during early septic shock, chronic alcoholic patients had lower levels of proinflammatory immune parameters than did nonalcoholic patients. Therefore, immunomodulatory therapy administered early may be considered in chronic alcoholic patients at the onset of an infection because of their altered proinflammatory immune response.

Keywords: alcohol, altered immune response, cytokines, severe infection

Introduction

Chronic alcoholic patients have a twofold to fivefold increased risk for postoperative morbidity after surgery as compared with nonalcoholic patients [1,2]. As a result of this increased postoperative morbidity, intensive care treatment and overall hospital stay are prolonged [1,2]. Among all complications, infections are the most serious and are associated with a worse outcome [1-3].

Prolonged and excessive consumption of alcohol has been shown to predispose to a variety of infectious complications, which may be due, in part, to an inability to produce important cytokines [4]. In experimental settings, T-cell mediated

CAGE = Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers; CRP = C-reactive protein; IL = interleukin; TNF = tumour necrosis factor; TNF-R = tumour necrosis factor receptor.

immunity was found to be suppressed by ethanol [4,5], which was associated with altered cytokine production [6,7]. A significant suppression of tumour necrosis factor (TNF)-α, as well as of IL-6 and IL-10, in a model of chronic alcoholism was reported [8-10]. TNF-α and IL-1β plasma cytokine levels are induced early as the 'first hit' of infection, whereas IL-10 is the subsequent response to this first hit, stimulated by macrophages and monocytes [10]. In clinical studies the delayed-type hypersensitivity skin response was decreased in chronic alcoholic patients before surgery and was further impaired after surgery [2,11,12]. Immediately after surgery the IL-6/IL-10 ratio was found to be depressed in chronic alcoholic patients [13], and the subsequent rate of infection was elevated. Several controversal clinical studies evaluated the impact of inflammatory and mediator release on the development of severe infection and subsequent septic shock [14,15]. Elevated levels of IL-6 and IL-8 were associated with higher mortality rates [14,16].

To the best of our knowledge, no other studies have been reported that investigated the progression from infection to septic shock in terms of immune modulating cytokines in chronic alcoholic patients. The aim of the present study was to investigate whether chronic alcoholic patients differed from nonalcoholic patients with respect to plasma cytokine levels at the onset of infection and in early septic shock.

Methods

The patients or relatives gave written, informed consent to participate in this institutionally approved, case–control study. A total of 14 chronic alcoholic patients with septic shock were included, along with 14 control individuals (nonalcoholic patients with septic shock). These 28 patients were selected from a cohort of 56 with either pneumonia or peritonitis and who subsequently developed septic shock. Patients with nosocomial pneumonia met criteria given by the US Centers for Diseases Control and Prevention [17], and nosocomial peritonitis was diagnosed according to the Mannheimer Peritonitis Index [18]. Subsequent septic shock criteria were defined as outlined in the consensus conference of 1992 [19].

Patients were excluded if they were younger than 18 years, if they had a diagnosis of liver cirrhosis, if consent could not be ontained, or if they were considered 'social drinkers', with an ethanol intake of about 20–60 g/day [1]. Basic patient characteristics such as age, height, weight and Acute Physiology and Chronic Health Evaluation III score [20] were documented.

Diagnosis of chronic alcohol abuse and alcohol dependence

The history was recorded, and an alcoholism related questionnaire – the CAGE Questionnaire [21] – was administered to all patients. (The acronym CAGE stands for 'Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers'.) All chronic alcoholic patients met criteria for alcohol abuse or dependence (*Diagnostic and Statistical Manual of Mental Disorders IV*, from the American Psychiatric Association [22]), had a daily ethanol intake in excess of 60 g, and had a CAGE score of 3 or more. Patients with a daily ethanol intake below 25 g and a CAGE score of 1 or less were considered to be nonalcoholic. Conventional laboratory markers such as γ-glutamyl transferase and mean corpuscular volume were determined, in accordance with routine clinical practice. In addition, a marker of higher sensitivity and specificity, namely carbohydrate deficient transferrin, was measured.

Monitoring and management

A radial artery catheter and a central venous line were inserted for routine cardiovascular monitoring. A fibreoptic, pulmonary artery flotation catheter (Swan-Ganz Oximetry/TD-Catheter model 93A-741h-7.5F; Baxter Edwards Laboratories, Irvine, CA, USA) was inserted in all patients with sepsis. Fluids were administered to achieve optimal left ventricular filling pressure, reaching the plateau value for left ventricular stroke work. If the cardiac index was less than 2.5 l/min per m^2, then dobutamine was administered up to 20 μg/kg per min to maintain cardiac index between 3.0 and 3.5 l/min per m^2. Noradrenaline (norepinephrine) was administered to patients in whom mean arterial pressure was below 70 mmHg. All patients were mechanically ventilated and received continuous analgesic sedation.

Haemodynamic measurements included heart rate and cardiovascular pressures, as measured from the mid-axillary line. Also, cardiac output measurements (as measured using the thermodilution method with 10 ml iced physiological saline solution as injectate, employing a cardiac computer [SAT-2 Oximeter/Cardiac Output Computer; Baxter Edwards Laboratories]) were taken in triplicate, with results expressed as the mean value. Blood samples were drawn simultaneously, slowly and continuously over 30 s.

Arterial and mixed venous blood samples were analyzed for oxygen and carbon dioxide tensions (ABL 300; Radiometer Inc., Copenhagen, Denmark) and for their haemoglobin content and oxygen saturation (Hemoximeter OSM 3; Radiometer Inc.). Oxygen content, delivery and consumption were calculated according to the standard formulae.

Measurements

Measurements were performed within 24 hours after the onset of infection (peritonitis/pneumonia), within 12 hours after the onset of septic shock, and 72–96 hours after the onset of septic shock. With each measurement, haemodynamic and oxygen transport related measures were recored and blood samples were drawn.

Laboratory parameters

Blood samples were collected in sterile tubes and centrifuged at 1800 *g* for 10 min, and serum was stored at -80°C. All

mediators were analyzed at room temperature (i.e. 23°C). Measurements were done using commercially available enzyme-linked immunosorbent assay kits (Quantikine™ Immunoassay Kit; R&D Systems, Minneapolis, MN, USA) for the cytokines (TNF-α, TNF-receptors [TNF-Rs], IL-1β, IL-6 and IL-8). IL-10 was analyzed using a commercially available enzyme immunoassay (TiterZyme IL-10 enzyme immunoassay kit; Perseptive Diagnostic, Cambridge, MA, USA). Detection limits and variation coefficients were as follows: TNF-α, 4.4 pg/ml (5.1%); TNF-RI, 30.0 pg/ml (5.9%); TNF-RII, 10.0 pg/ml (3.2%); IL-1β, 1.0 pg/ml (5.2%); IL-6, 0.7 pg/ml (3.6%); IL-8, 10.0 pg/ml (6.7%); and IL-10, 1.0 pg/ml (5.8%). Routine laboratory markers, including leucocytes, lactate and C-reactive protein (CRP), were also determined.

Statistical analysis

Data are presented as median (range). The Wilcoxon matched pairs signed rank sum test was used to compare intergroup variables. The adjusted significance (Bonferroni method) for twice measured haemodynamic and oxygen transport parameters was $P/2 = 0.025$; the adjusted significance for the thrice measured parameters was $P/3 = 0.017$.

The Friedman test was used to identify significant intragroup differences from infection to early or late septic shock. If the global test revealed a significant difference, then the Wilcoxon test was used to define at which time point a significant change occurred. $P < 0.05$ was considered statistically significant. Correlation coefficients were calculated according to the Spearman rank correlation. The receiver operating characteristic curve was used to provide a presentation of the relationship between sensitivity and sensitivity of mediators that were found to be significantly different between groups, and possibly to provide diagnostic cutoff levels. The area under the receiver operating curve represents the probability of discrimination between chronic alcoholic patients and nonalcoholic patients [23].

Results

Basic patient characteristics did not differ significantly between groups (Table 1). There were significant differences with respect to alcoholism-related data and laboratory markers (Table 1).

Immune parameters

At the onset of infection IL-8 plasma levels were significantly lower in chronic alcoholic patients than in nonalcoholic patients (Fig. 1), whereas no differences between groups occurred with respect to plasma IL-1β and IL-6 levels (Figs 2 and 3). During early septic shock, IL-1β, IL-6 and IL-8 were significantly lower in chronic alcoholic patients (Figs 1, 2, 3). IL-1β significantly increased in nonalcoholic patients from the onset of infection to early septic shock (Fig. 2). Also, IL-1β and IL-6 significantly decreased in the nonalcoholic patients from early to late septic shock (Figs 2 and 3).

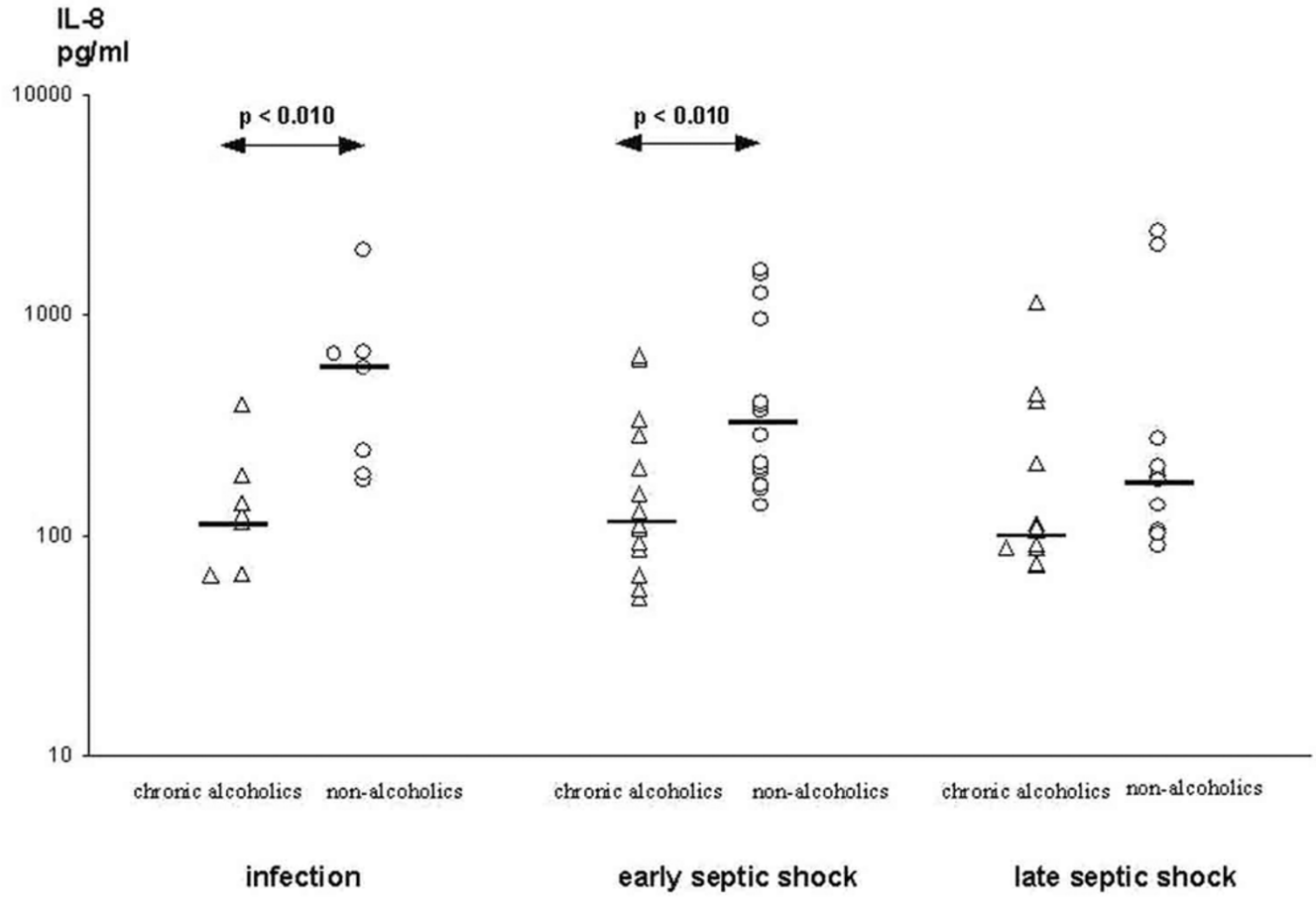
Table 1

Basic patient characteristics

Characteristic	Chronic alcoholic patients	Nonalcoholic patients	*P*
Age (years)	57 (24–72)	60 (23–74)	0.872
Body surface area (m^2)	1.87 (1.57–2.40)	2.08 (1.68–2.14)	0.174
Weight (kg)	74 (50–120)	85 (55–93)	0.210
Culture positive/culture negative (*n*)	4/14	3/14	>0.999
Peritonitis/pneumonia (*n*)	8/6	8/6	>0.999
Survivors/nonsurvivors (*n*)	6/8	6/8	>0.999
Nicotine abuse (*n* [%])	9/14 (64%)	6/14 (43%)	0.153
APACHE III score (admission)	40 (26–76)	27 (9–74)	0.107
Length of ICU stay (days)	16 (3–50)	19 (9–41)	0.397
CAGE score	4 (3–4)	0 (0–1)	<0.001
Ethanol consumption (g/day)	170 (60–380)	0 (0–20)	<0.001
CDT (mg/l)	17.2 (5.1–70.1)	3.2 (2.0–8.2)	<0.001
MCV (fl)	96.2 (77.2–106.0)	90.2 (78.3–102.3)	0.031
GGT (U/l)	31 (20–178)	20 (10–97)	0.074

Values are expressed as median (range), unless otherwise stated. APACHE, Acute Physiology and Chronic Health Evaluation; CAGE, alcohol-related questionnaire; CDT, carbohydrate-deficient transferrin; GGT, γ-glutamyl transferase; ICU, intensive care unit; MCV, mean corpuscular volume.

Figure 1



Interleukin (IL)-8 in the course of septic shock in chronic alcoholic patients and nonalcoholic patients.

In the chronic alcoholic patients significant increases occurred for soluble TNF-RI from infection to early septic shock (Table 2). However, no significant intergroup differences for soluble TNF-RI (Table 2) were found. In addition, IL-10 plasma levels did not differ between groups during infection to septic shock.

For the significant intergroup differences, receiver operating curves were calculated for the progression from infection to septic shock. The corresponding area under the curve values were 0.60 for IL-1β, 0.62 for IL-6, and 0.66 for IL-8.

Conventional laboratory markers

CRP was significantly increased in chronic alcoholic patients at the onset of infection as compared with non-alcoholic patients (Table 3). During early septic shock, leucocyte count was significantly increased in the chronic alcoholic patients (Table 3).

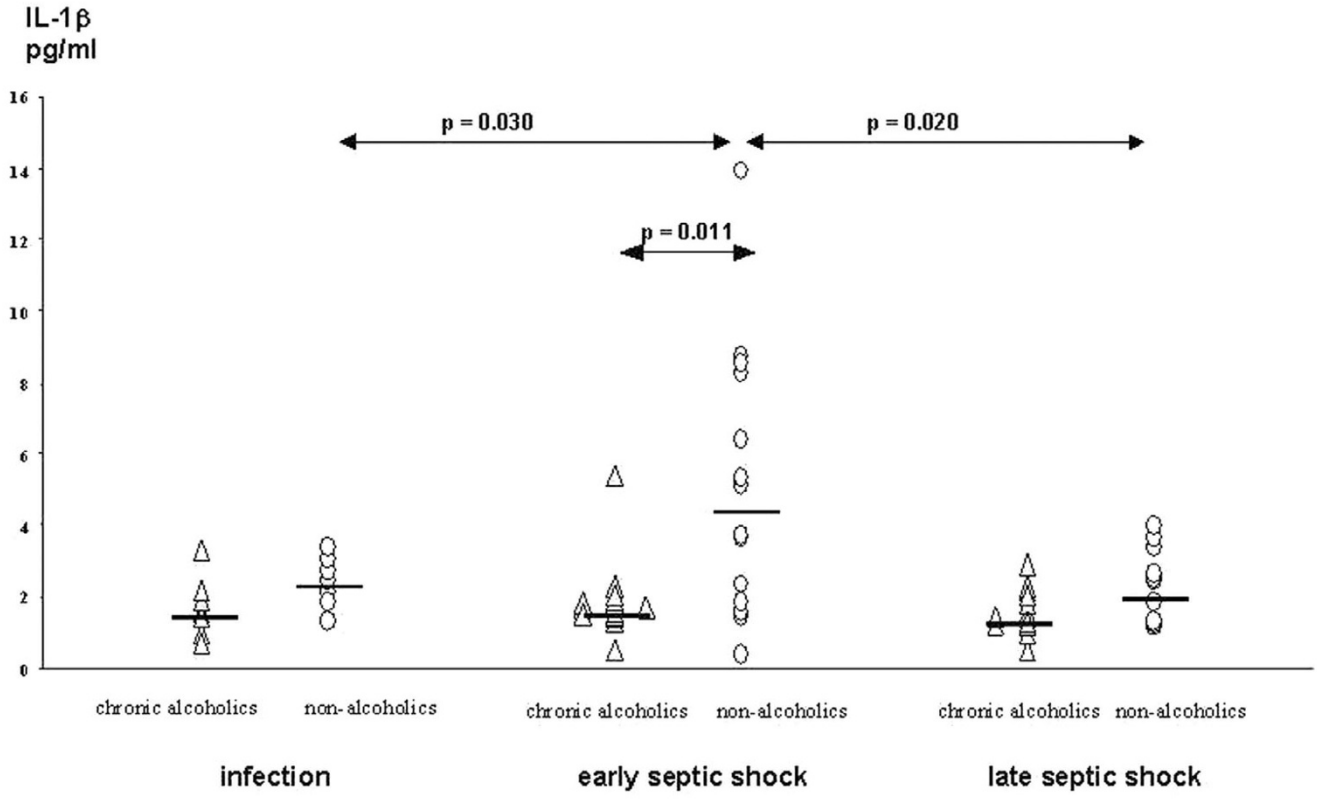
Chronic alcoholic patients had a significantly lower oxygenation index during early and late septic shock than did nonalcoholic patients (Table 4). The oxygenation index in chronic alcoholic patients with pneumonia was not statistically different from that in chronic alcoholic patients with peritonitis.

Outcome

In the present study the period between establishing infection and development of septic shock did not differ between chronic alcoholic patients (5 [2–10] days) and nonalcoholic patients (4 [1–129] days; $P < 0.171$). Numbers of culture-positive versus culture-negative samples did not differ between groups (Table 1). The identities of the positive cultures isolated from blood culture or peritoneal swab/histology were as follows: *Enterococcus faecium* ($n = 3$), *Streptococcus pyogenes* ($n = 2$), *Staphylococcus aureus* ($n = 1$) and *Enterococcus faecalis* ($n = 1$). All patients with peritonitis were surgical patients. All infections were hospital acquired.

The survival rate for nonalcoholic patients with septic shock was 53% (10/19), whereas only 43% (9/19) of the chronic alcoholic patients survived. With regard to mortality rates, 47% (9/19) of the nonalcoholic patients and 57% (12/21) of the chronic alcoholic patients died (Table 1).

Figure 2



Interleukin (IL)-1β in the course of septic shock in chronic alcoholic patients and nonalcoholic patients.

Discussion

The most important finding was that chronic alcoholic patients had lower plasma levels of cytokines at the onset of infection and in early septic shock, in particular IL-1β, IL-6 and IL-8.

Proinflammatory cytokines

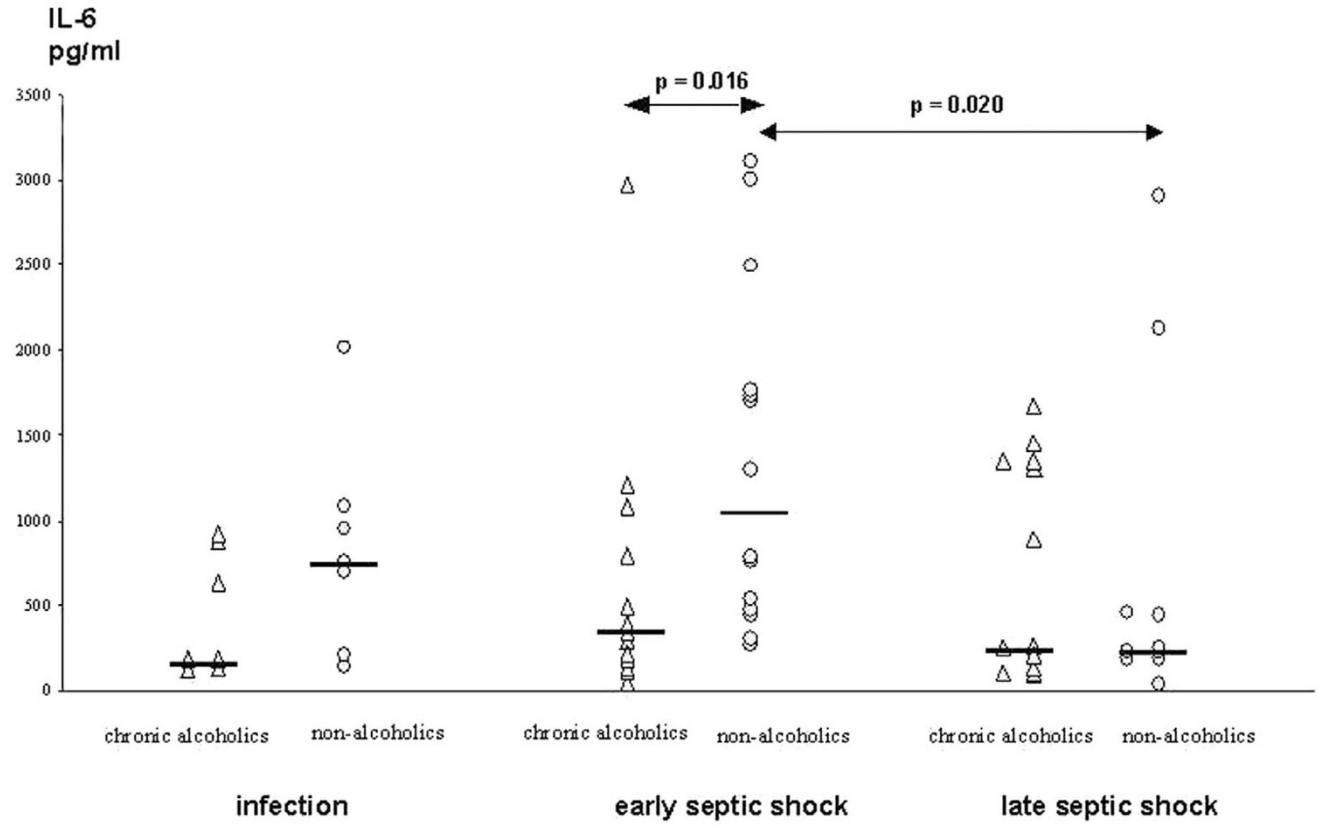
This is the first clinical study to demonstrate an altered plasma cytokine response in chronic alcoholic patients at the onset of infection and early septic shock.

Experimental studies have shown that ethanol modulates cytokine secretion and synthesis *in vivo* and *in vitro* [24]. *In vitro*, alcohol blunted the stimulation of cytokine production by lipopolysaccharide, and the alcohol induced decrease in cytokine synthesis was proportional to the level of alcohol consumption [6]. Also, levels of production of TNF-α and IL-8 in mast cells as well as in blood monocytes were downregulated by clinically relevant ethanol concentrations [25,26].

In a clinical study [27], alveolar macrophages and their ability to produce cytokines locally were studied because of the high risk for pneumonia associated with chronic alcoholism. *In vitro* stimulation of alveolar macrophages from chronic alcoholic persons resulted in significant suppression of TNF-α as compared with those from healthy control individuals. The local pulmonary suppressive effects of acute or chronic alcoholism have been described [8,10]. In chronic alcoholic patients, circulating IL-1β, IL-6 and TNF-α levels were significantly elevated as compared with nonusers of alcohol, and this elevation was correlated with liver disease [28]. In the present study, patients with active liver cirrhosis were excluded because of the different cytokine kinetics that occur in the presence of liver disease.

That levels of systemic proinflammatory cytokines were significantly lower in chronic alcoholic patients than in nonalcoholic patients in early sepsis is an important new finding. The proinflammatory response to invading micro-organisms might be fundamentally impaired in chronic alcoholism, and this may contribute to the clinically evident immune alteration in such patients. This is in contrast to a previous report that found that TNF-α is elevated in early infection in patients developing septic shock [29]. The latter may be the effect of a severe infection whereas the former may be the cause of progression of the disease. However, this remains speculative and requires further investigation.

Figure 3



Interleukin (IL)-6 in the course of septic shock in chronic alcoholic patients and nonalcoholic patients.

Anti-inflammatory cytokines

In the present study no differences with respect to IL-10 levels were found between groups either during the initial development of infection or in early septic shock.

In previous studies IL-10 was produced in large amounts during septicaemia and septic shock [30]. Increased IL-10 production by human blood monocytes was observed after acute ethanol treatment [31]. Considering the ability of IL-10 to inhibit monocyte function, it is likely that elevated IL-10 levels contribute to the disturbed cellular immune response observed after acute alcohol treatment. However, we did not find a difference in response of chronic alcoholic patients with respect to IL-10. The reasons for this might be, first, that elevated IL-10 levels occur earlier in the development of infection and may not be seen later in the course of the disease [13]. Second, the reduced proinflammatory response might have contributed to lower IL-10 levels [14], and therefore no difference was found between groups. In addition, no significant intergroup differences were found with respect to soluble TNF-RI and TNF-RII. A significant rise in soluble TNF-RI was noted from the onset of infection to early septic shock in the chronic alcoholic patients. High values of soluble TNF-Rs were reported during severe sepsis [32], which was confirmed by previous data. One study evaluated the *in vitro* expression of TNF-Rs on macrophages in response to ethanol exposure [33]; ethanol significantly reduced the expression of TNF-Rs on interferon-γ stimulated pulmonary macrophages. In the present study we found that levels of TNF-Rs were not suppressed, and so hypothetically chronic alcoholic patients have a preferentially anti-inflammatory immune response.

In particular, plasma levels of IL-6 were significantly lower in chronic alcoholic patients in our study. Although IL-6 was initially found to be proinflammatory, recent findings suggest that IL-6 has anti-inflammatory effects [34]. Therefore, IL-6 might contribute to the resolution of acute and chronic inflammatory processes by direct suppression of IL-1β and TNF-α [35].

Patient characteristics

In the present study CRP was significantly increased in chronic alcoholic patients during infection. This is in accordance with a previous study conducted in patients with a daily alcohol intake of more than 80 g [36]. Chronic alcohol consumption is associated with higher CRP concentrations. CRP is mainly regulated by proinflammatory cytokines [37]. Proinflammatory cytokines were significantly decreased in early septic shock and did not differ in late septic shock. Addition-

Table 2

Immune parameters at onset of infection, early and late septic shock

Parameter	Chronic alcoholic patients	Nonalcoholic patients	*P*
IL-10 (pg/ml)			
Infection	35 (2–37)	41 (12–392)	0.110
Early septic shock	37 (4–371)	66 (2–255)	0.590
Late septic shock	30 (2–118)	35 (0–81)	0.576
Soluble TNF-RI (pg/ml)			
Infection	3440 (1280–6680)*	4750 (3540–7880)	0.153
Early septic shock	10,860 (2260–16,670)*	7170 (3280–14,950)	0.622
Late septic shock	9410 (1240–15,940)	7920 (4130–15,000)	0.775
Soluble TNF-RII (pg/ml)			
Infection	7280 (3990–8500)	7180 (5930–8890)	0.668
Early septic shock	8070 (3500–8500)	7900 (5100–10,000)	0.895
Late septic shock	7980 (3050–8500)	8120 (5480–10,660)	0.567
TNF-α (pg/ml)			
Infection	10 (4–18)	19 (12–93)	0.048
Early septic shock	14 (1–56)	14 (3–29)	0.385
Late septic shock	10 (1–29)	10 (7–16)	0.723

Values are expressed as median (range). IL, interleukin; TNF, tumour necrosis factor; TNF-R, tumour necrosis factor receptor. *Significant changes from infection to early septic shock, and from early septic shock to late septic shock.

Table 3

Clinical and laboratory signs of infections

Sign	Chronic alcoholic patients	Nonalcoholic patients	*P*
Temperature (°C)			
Infection	37.2 (36.8–38.1)	37.5 (37.1–38.8)	0.851
Early septic shock	37.8 (36.2–39.8)	38.7 (37.6–39.9)	0.037
Late septic shock	38.1 (36.6–38.8)	37.2 (35.8–39.2)	0.413
Leucocytes ($\times 10^9$/l)			
Infection	8.9 (4.4–13.2)	10.2 (3.4–10.2)	0.663
Early septic shock	18.9 (6.5–45.8)	9.5 (3.5–13.9)	<0.010
Late septic shock	15.0 (9.8–39.2)	17.8 (12.3–33.2)	0.717
CRP (mg/l)			
Infection	110 (80–223)	54 (8–72)	<0.010
Early septic shock	203 (75–266)	144 (42–323)	0.162
Late septic shock	124 (44–210)	120 (90–258)	0.690
Lactate (mmol/l)			
Infection	1.6 (0.8–2.0)	1.9 (1.0–5.1)	0.174
Early septic shock	2.3 (1.4–3.2)	1.9 (1.0–5.1)	0.520
Late septic shock	2.0 (0.8–4.5)	2.0 (0.7–2.8)	0.702

Value are expressed as median (range). CRP, C-reactive protein.

Table 4

Haemodynamic and oxygen transport related data and catecholamines

Variables	Septic shock	Chronic alcoholic patients	Nonalcoholic patients	*P*
Heart rate (beats/min)	Early	104 (69–143)	122 (99–140)	0.048
	Late	111 (52–153)	106 (91–146)	0.696
MAP (mmHg)	Early	84 (69–112)	76 (59–94)	0.060
	Late	78 (68–113)	78 (61–101)	0.643
PCWP (mmHg)	Early	16 (9–19)	11 (8–15)	0.021
	Late	15 (8–20)	10 (8–15)	0.312
Cardiac index (l/min per m^2)	Early	5.1 (3.5–6.2)	5.0 (3.0–10.4)	0.940
	Late	4.6 (3.4–7.00)	4.0 (3.3–4.8)	0.196
DO_2 (ml/min per m^2)	Early	721 (489–888)	718 (408–1366)	0.870
	Late	693 (485–922)	580 (453–817)	0.366
VO_2 (ml/min per m^2)	Early	140 (114–237)	181 (49–330)	0.178
	Late	162 (95–263)	143 (33–253)	0.437
PaO_2/FiO_2 (mmHg)	Early	198 (110–256)	282 (188–320)	<0.010
	Late	193 (151–298)	291 (161–511)	0.020
Noradrenaline (μg/kg per min)	Early	0.3 (0.1–0.8)	0.5 (0.2–1.0)	0.112
	Late	1.3 (0.1–1.7)	1.1(0.1–2.4)	0.522

Values are expressed as median (range). DO_2, oxygen delivery; MAP, mean arterial pressure; PaO_2/FiO_2, arterial oxygen tension/fractional inspired oxygen ratio (oxygenation index); PCWP, pulmonary capillary wedge pressure; VO_2, oxygen consumption.

ally CRP might not be stimulated adequately in chronic alcoholic patients in early or late septic shock, which might be explained as an immune breakdown. There was a significant increase in leucocyte count in early septic shock. The leucocyte count has low predictive ability as a marker of infection [38]. A marked activation of the hypothalamic–pituitary–adrenal axis occurs during ethanol withdrawal, and this could result in an hypercortisolism mediated leucocytosis in early septic shock [39].

Chronic alcoholic patients had a significantly lower oxygenation index, which might be due to the higher number of smokers [40]. However, in the present study the percentage of smokers was not significantly different between the groups, and none of the patients were hypoxic because of a higher inspired oxygen fraction, indicating that these mechanisms were not relevant.

There were only a few significant differences in haemodynamic parameters. Chronic ethanol abuse can be associated with a variety of cardiovascular disorders, ranging from asymptomatic left ventricular dysfunction to hypertension, stroke, heart failure and sudden death from arrhythmias [2,41]. The higher pulmonary capillary wedge pressure could be interpreted as a result of a higher end-diastolic pressure leading to heart failure if there were normal ventricular compliance [41].

Because the number of patients with dual addiction (i.e. to both alcohol and nicotine) is more frequently seen than isolated or no addictions, we cannot totally exclude that the effects of ethanol on cytokine interactions were also influenced by nicotine. However, in the present study no significant difference between groups was seen. Spies and coworkers [42] examined patients with comorbid chronic alcoholism and nicotine abuse, and found that only TNF-α plasma levels were significantly higher in chronic alcoholic smokers than in chronic alcoholic nonsmokers.

Conclusion

In conclusion, chronic alcoholic patients exhibited lower levels of proinflammatory immune parameters and of IL-6 during infection and early sepsis, which might be due to an inhibitory effect on proinflammatory cytokine production induced by alcohol abuse and which might contribute to the clinically evident immune alteration. Therefore, chronic alcoholic patients may benefit from immune monitoring and early immune modulatory treatment at the onset of severe infections. However, this requires further investigation.

Competing interests

None declared.

Key messages

- At the onset of infection and during early septic shock, chronic alcoholic patients had lower levels of proinflammatory immune parameters than did nonalcoholic patients
- Immunomodulatory therapy administered early may be considered in chronic alcoholic patients at the onset of an infection because of their altered proinflammatory immune response

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