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Successful Cardiopulmonary Resuscitation After Cardiac Arrest as a “Sepsis-Like” Syndrome

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Background—We investigated the immunoinflammatory profile of patients successfully resuscitated after cardiac arrest, representing a model of whole-body ischemia/reperfusion syndrome.

Methods and Results—Plasma cytokine, endotoxin, and ex vivo cytokine production in whole-blood assays was assessed in 61, 35, and 11 patients, respectively. On admission, high levels of plasma interleukin (IL)-6, IL-8, IL-10, and soluble tumor necrosis factor (TNF) receptor type II could discriminate between survivors and nonsurvivors. Among nonsurvivors, the initial need for a vasopressor agent was associated with higher levels of IL-1 receptor antagonist, IL-10, and IL-6 on day 1. Plasma endotoxin was detected in 46% of the analyzed patients within the 2 first days. Endotoxin-induced TNF and IL-6 productions were dramatically impaired in these patients compared with healthy control subjects, whereas an unaltered production was observed with heat-killed *Staphylococcus aureus*. In contrast, IL-1 receptor antagonist productions were enhanced in these patients compared with healthy control subjects. The productions of T-cell–derived IL-10 and interferon- γ were also impaired in these patients. Finally, using in vitro plasma exchange between healthy control subjects and patients, we demonstrated that the endotoxin-dependent hyporeactivity was an intrinsic property of patients' leukocytes and that an immunosuppressive activity was also present in their plasma.

Conclusions—Altogether, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in these patients recall the immunological profile found in patients with sepsis. (*Circulation*. 2002;106:562-568.)

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ reperfusion ■ inflammation ■ interleukins

The prognosis of survival in patients with out-of-hospital cardiac arrest (OHCA) remains poor, ranging from 4% to 33%, essentially depending on the organization of the chain of survival.¹ During and after cardiopulmonary resuscitation, activation of blood coagulation,^{2,3} platelet activation with formation of thromboxane A₂,⁴ and an alteration of soluble E-selectin and P-selectin⁵ have been described. More challenging are the pathophysiological disturbances, described as “postresuscitation” disease⁶ (observed after the return to spontaneous circulation), such as hypovolemic shock, cardiogenic shock, and vasodilatory shock.⁷ Four phases after resuscitation are thought to occur depending on the degree and duration of organ ischemia⁷: (1) Within the first 24 hours after the event, a microcirculatory dysfunction from the multifocal hypoxia leads to rapid release of toxic enzymes and free radicals into the cerebrospinal fluid and blood; (2) over 1 to 3 days, cardiac function and systemic function improve, but intestinal permeability increases, predisposing the patient to sepsis syndrome and

leading to multiple organ dysfunction syndrome; (3) days after cardiac arrest, a serious infection may occur, and the patient declines rapidly; and (4) the patient eventually dies.

We hypothesized that postresuscitation disease may be related to an early systemic inflammatory response, leading to an exacerbation of the inflammatory balance,^{5,7} and may possibly be associated with an “endotoxin tolerance,” as observed in severe sepsis.⁸ In the present study, we investigated (1) the kinetics of plasma cytokines after a successfully resuscitated cardiac arrest, (2) the plasma endotoxin levels, and (3) the occurrence of dysregulation of the immune response assessed by ex vivo cytokine production by blood leukocytes.

Methods

Patients After OHCA and Healthy Control Subjects

The present study was performed according to the ethics rules of our institutions (Cochin Hospital and Delafontaine Hospitals), and informed consent was obtained from all patients' next of kin. Cardiac

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arrest was defined as the absence of spontaneous respiration or cardiac pulse and unresponsiveness. Patients aged >16 years successfully resuscitated after OHCA were prospectively included in the present study. Only those reaching the ICU with stable hemodynamic conditions were included whether or not catecholamines were required. Both the Simplified Acute Physiology Score (SAPS II score)⁹ and the Logistic Organ Dysfunction (LOD)¹⁰ score were calculated. These scores provide an accurate estimate of overall severity (SAPS II score) and organ dysfunction severity (LOD score) on the first day of the ICU stay and, thus, help to predict the probability of hospital mortality.

As a positive control group, patients with severe sepsis, as defined by a panel of experts from the American College of Chest Physicians/Society of Critical Care Medicine, were studied.¹¹ As a negative control group, we included healthy volunteers.

Cytokines and Soluble Receptor Kinetics

Blood samples (4 mL) were collected on sodium citrate and immediately centrifuged at 1500g for 10 minutes at 4°C, and then the plasma was stored at -80°C until analysis. Blood collection was performed on admission to the unit (day 0) and daily for the 7 following days (days 1 to 7).

Whole-Blood Cultures

Blood samples were diluted 1:5 in RPMI-1640 culture medium (BioWhittaker), and 0.5 mL was added per well. The cells were stimulated with *Escherichia coli* lipopolysaccharide (LPS, O111:B4) at 10 ng/mL or 1 µg/mL (Sigma Chemical Co), with heat-killed staphylococci (SAC) at 100 µg/mL (Calbiochem), with concanavalin A (ConA) at 10 µg/mL (ICN), or with phytohemagglutinin (PHA) at 10 µg/mL (DIFCO). Culture supernatants were harvested after a 24-hour incubation period with LPS or SAC and after a 48-hour incubation period with ConA or PHA.

Plasma and Cell-Exchange Experiments

The cell pellets were washed twice with endotoxin-free Dulbecco's PBS (BioWhittaker). Whole-blood cultures were performed before separation with reconstituted blood (washed cell pellet and plasma from the same person) and mixed cells and plasma (cell pellet from a patient with plasma from a healthy ABO/rh group compatible volunteer and vice versa). The final blood dilution was 1:5 in RPMI-1640. The cultures were stimulated with *E coli* LPS (O111:B4) at 1 µg/mL or with SAC at 100 µg/mL for 24 hours at 37°C.

Measurement of Cytokines and Soluble Receptor in Plasma and Culture Supernatants by ELISA

Interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, RANTES, and soluble TNF receptor type II (sTNFRII) concentrations were determined by using ELISA kits from R&D Systems; interferon (IFN)-γ was measured with an ELISA kit purchased from Becton Dickinson; IL-8 and IL-1 receptor antagonist (IL-1ra) ELISA were performed with the use of our own specific antibodies.

Endotoxin Detection

For endotoxin dosage, we used *Limulus* amebocyte lysate reagent water (BioWhittaker). To overcome the background absorbance of plasma, we used a diazo-coupling *Limulus* amebocyte lysate assay that yields a magenta coloration (Associates of Cape Cod Inc). To inactivate putative inhibitors, plasma was diluted 1:4 in *Limulus* amebocyte lysate reagent water and heated for 30 minutes at 65°C. The optical density was read at 570 nm, and the absorbance at 405 nm was subtracted to minimize the interference of plasma opalescence.

Statistical Analysis

Data were expressed as median (interquartile range) or mean ± SEM, as indicated. The value 0 was attributed when the result was below the detection limits of the assay. Because of the high mortality rate

on the first days after admission, we performed statistical analysis of circulating markers only on the first 2 days. Differences within and between groups were analyzed by Wilcoxon signed rank tests, Mann-Whitney *U* tests, Kruskal-Wallis tests, or χ^2 tests. The relationships between 2 continuous variables were analyzed by Spearman rank correlation tests. Variables found to be significantly associated with mortality on the basis of univariate analysis were then included in a stepwise multiple logistic regression model to identify independent factors. A value of $P < 0.05$ was the criterion for statistical significance. Statistical analysis was performed by using Stata 5.0 software (Stata Corp).

Results

Patients' Characteristics

Sixty-one patients fulfilling criteria of OHCA resuscitation were included in the present study from February 1999 to April 2000. There were 18 women and 43 men, with a median age of 59.5 (range 51 to 71) years, a SAPS II score of 64 (range 56 to 71), and Glasgow coma score of 3 (range 3 to 4) on admission (Table 1). All patients were intubated and mechanically ventilated. Thirty-four of 52 patients admitted to Cochin Hospital underwent an immediate coronary angiography, 29 of whom had coronary artery occlusion and 19 of whom were successfully dilated. The first blood sampling (day 0) was performed as early as 2 hours 58 minutes (range 2 hours 10 minutes to 4 hours 45 minutes) after the onset of cardiac arrest. Eighteen patients survived, of whom only 1 had severe disabilities. Forty-three patients died within a median of 5 (range 3 to 6) days. Twenty-four of the nonsurvivors (56%) died from early circulatory dysfunction. Thirty-one patients developed secondary infection: 12 among the 18 survivors and 19 of the 43 nonsurvivors (66% versus 44%, respectively; $P = \text{NS}$), with a median duration of 2 (range 1 to 3) days. Most of them exhibited pulmonary infection (28 of 31 [90%]); there was no bacteriological identification for 10 patients. We observed only 3 patients with bacteremia at day 3 (2 patients) and day 4 (1 patient).

We also included 5 patients with septic shock: 2 women and 3 men with a median age of 72 (range 64 to 75) years, a SAPS II score of 73.5 (range 50 to 80), and a LOD score of 9 (range 8 to 11). Three of them eventually died. Seven normal volunteers were also studied.

Plasma Cytokines and sTNFRII

Enhanced levels of circulating cytokines were observed in OHCA patients on admission and were comparable to those observed in severe sepsis (Tables 1 and 2). The levels of lactate, sTNFRII, IL-6, IL-8, and IL-10 on admission were significantly higher in nonsurvivors than in survivors (Figure 1, Table 1). We found a significant correlation between lactate levels and IL-6 ($r = 0.67$, $P < 10^{-4}$) or sTNFRII ($r = 0.55$, $P = 0.001$) on admission. Detectable levels of TNF-α were found within the first 2 days in only 33 patients (54%), with a median of 23 (range 11 to 31) pg/mL. However, the presence of TNF-α was significantly associated with a higher mortality rate ($P = 0.035$). Among the cytokines or soluble receptor, there was no independent variable predictive of death compared with the interval from collapse to basic life support and duration of cardiopulmonary resuscitation (receiver operating characteristic test 0.88). On day 1,

TABLE 1. Characteristics of OHCA Patients Successfully Resuscitated on Admission to Hospital

Parameters	All Patients (n=61)	Survivors (n=18)	Nonsurvivors (n=43)	P
Age, y	59.5 (51–71)	55 (51–69)	65.5 (51–73)	0.18
SAPS II score	64 (56–71)	51 (48–57)	67 (60.5–77.5)	<0.0001
LOD score	8.5 (7–11)	7 (6–8)	9 (8–12)	<0.0001
GCS score on admission	3 (3–4)	3 (3–6)	3 (3–3)	0.007
First cardiac rhythm, n				
Asystole	22	2	20	0.02
Ventricular arrhythmia	38	16	22	
Pulseless activity	1	0	1	
Interval from collapse to basic life support, min	5 (2–9)	2 (1–5)	5.5 (5–10)	<0.0001
Duration of CPR, min	15 (7–20)	6 (5–11)	15 (10–25)	0.0002
LVEF, %	32.5 (23–45)	32.5 (20–50)	32.5 (24–40)	0.6
	(n=34)	(n=14)	(n=20)	
Lactate, mmol/L	5.1 (2.5–7.9)	2.9 (1.7–4.9)	6.6 (3.5–10)	0.0006
Bicarbonate, mmol/L	19.8 (15.9–22.9)	22.3 (20.2–25.3)	18.4 (15–21.5)	0.0036
sTNFRII, pg/mL	5714 (3629–8350)	3685 (2690–5408)	6744 (4007–9463)	0.007
IL-1ra, pg/mL	13 972 (1947–40 319)	3603 (979–15 786)	14 560 (2865–40 972)	0.11
IL-6, pg/mL	177 (53–355)	55 (35–136)	287 (112–1001)	0.002
IL-8, pg/mL	67 (22–183)	32 (0–50)	108 (36–278)	0.002
IL-10, pg/mL	122 (41–250)	108 (36–278)	156 (51–293)	0.03
RANTES, pg/mL	7035 (3892–20 369)	7033 (2899–19 256)	7389 (4086–20 722)	0.58

LVEF indicates left ventricular ejection fraction; GCS, Glasgow Coma Score.

IL-1ra, IL-6, IL-8, and IL-10 were higher in nonsurvivor patients requiring vasopressor agents within the first day (Table 3).

Plasma Endotoxin Levels

Endotoxin was detected in the plasma of 46% of the patients analyzed on the first 2 days (n=35), and its concentration decreased over time (Figure 2). A decreased level was observed during the 3-day survey among 73% of the patients, whereas an increase was detected in 27% of them. The very first measurement was performed 2 hours 50 minutes (range 2 hours to 3 hours 32 minutes) after the onset of cardiac arrest, a timing similar to the one observed in the overall population. We observed higher levels of IL-6, IL-1ra and

IL-10 in these patients (Figure 3). However, there was no correlation between the presence of endotoxin and mortality.

Production of Cytokines in Whole-Blood Assays on In Vitro Stimulation

No or low spontaneous productions of TNF- α and IL-6 were noticed for patients (n=11) and healthy volunteers (n=7), whereas high amounts of IL-1ra were produced in vitro without any stimulation by the patients' leukocytes (Figure 4). LPS stimulation induced the production of high amounts of TNF- α and IL-6 in healthy volunteers, whereas no TNF- α and low levels of IL-6 were produced by the leukocytes of OHCA patients. Conversely, patients' leukocytes were responsive to SAC and produced amounts of TNF- α and IL-6

TABLE 2. Plasma Cytokine and sTNFRII Concentrations on Hospital Admission in OHCA Patients, in Patients With Sepsis (Positive Control Group), and in Healthy Volunteers (Negative Control Group)

Cytokines and Receptors, pg/mL	OHCA Patients (n=61)	Patients With Sepsis (n=5)	Healthy Volunteers (n=7)
TNF- α	16 (0–30)	16 (0–46)	0 (0–0)*
sTNFRII	5714 (3629–8350)	4000 (7021–12 656)	1458 (1589–3617)‡
IL-1ra	13 972 (1947–40 319)	72 897 (657–94 884)	46 (0–111)‡
IL-6	177 (53–355)	406 (390–4901)*	0 (0–0)‡
IL-8	67 (22–183)	399 (76–529)	0 (0–0)‡
IL-10	122 (41–250)	199 (160–1003)	0 (0–0)‡
RANTES	7035 (3892–20 369)	2021 (583–2184)†	11 957 (9527–12 817)

Data are median (25% to 75% quartile). OHCA patients had a plasma cytokine pattern similar to that observed in patients with sepsis.

* $P<0.05$, † $P<0.01$, and ‡ $P<0.001$ for patients with sepsis and healthy volunteers vs OHCA patients.

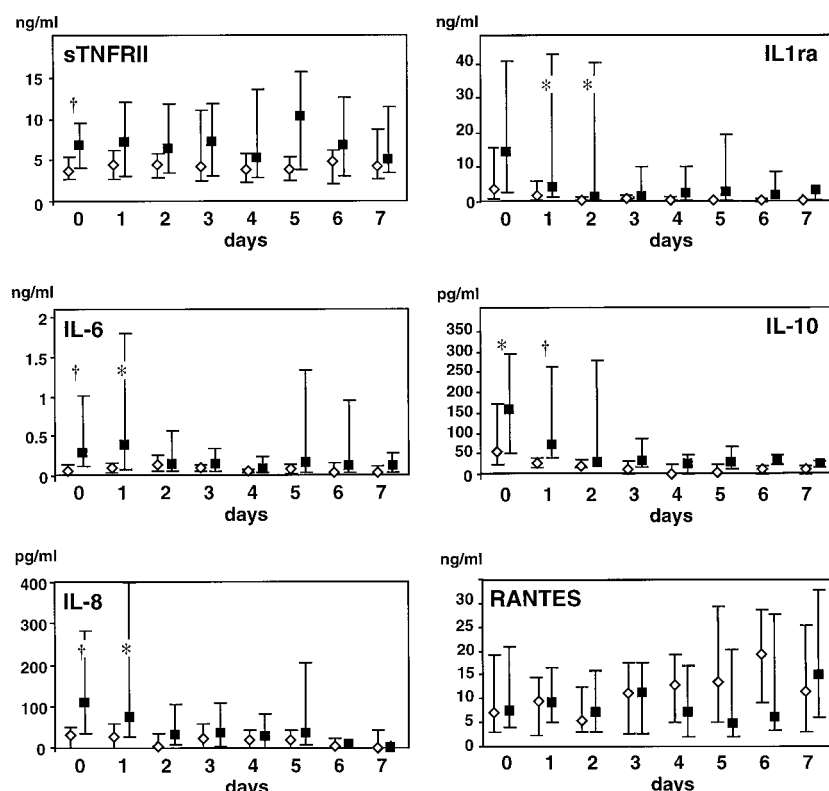


Figure 1. Kinetics of cytokines and sTNFRII levels on admission and over a 7-day period in 61 resuscitated survivors (n=18, open diamonds) and nonsurvivors (n=43, black squares) of OHCA. Two of them died within a few hours after admission, 5 were dead at day 1, 6 were dead at day 2, 15 were dead at day 3, 21 were dead at day 4, 30 were dead at day 5, and 37 were dead at days 6 and 7. Data are expressed as median (25% to 75% quartile). * $P<0.05$ and † $P<0.005$.

similar to those obtained from healthy control subjects. For IL-1ra, not only were the leukocytes from OHCA patients able to secrete this molecule in response to LPS or SAC, but the amounts were significantly higher than those found in healthy control subjects (Figure 4).

The ability of T lymphocytes from OHCA patients to produce cytokines in vitro was also impaired. ConA-induced IFN- γ and IL-10 productions were significantly reduced compared with production in healthy volunteers. IL-10 production in response to PHA was also reduced in patients, whereas PHA-induced IFN- γ was unaltered (data not shown).

We repeated this experiment on 7 of these patients surviving on day 3 with identical results (data not shown).

In Vitro Plasma Exchange Experiments

In vitro plasma exchange experiments were performed to determine whether the hyporeactivity observed in the patients' leukocytes (n=7) could be reversed by incubation with plasma from healthy control subjects (n=7). These experiments also tested the capacity of the plasma of OHCA patients to exert an inhibitory effect on cytokine production by leukocytes from healthy control subjects (data not shown). The effect of experimental procedures themselves on cellular reactivity was tested by mixing autologous cell pellets and plasma at the end of the washing steps, and in all cases, the production of TNF- α was compared with that obtained with whole blood without separation. As already reported, almost

TABLE 3. Plasma Cytokine and sTNFRII Levels in Survivors and Nonsurvivors Receiving and Not Receiving Catecholamines Within First 24 Hours (Day 1) After Hospital Admission

Cytokines and Receptors, pg/mL	Survivors Without Catecholamines (n=8)	Survivors With Catecholamines (n=10)	Nonsurvivors Without Catecholamines (n=18)	Nonsurvivors With Catecholamines (n=23)
TNF- α	0 (0–7.5)	12 (0–30)	12 (0–30)	17.5 (0–27)
sTNFRII	3790 (2927–5153)	5485 (2209–7400)	3325 (2801–7516)	8550 (5207–14 133)
IL-1ra	1172 (263–8021)	2656 (811–5890)	1603 (625–4144)	36 997 (1949–75 146)*
IL-6	114 (73–270)	88.5 (66–127)	148 (61–717)	2233 (247–4113)†
IL-8	15 (0–50)	26 (13–58)	27 (6–42)	322 (61–767)*
IL-10	32 (13–49)	27.5 (16–34)	48 (23–106)	193 (64–361)†
RANTES	3847 (2019–14 035)	10 924 (5508–14 621)	8588 (5023–17 264)	9194 (4929–15 625)

Data are median (25% to 75% quartile). On day 1, nonsurvivors receiving catecholamines had significantly higher levels of some plasma cytokines compared with levels in those not requiring vasopressor agents. Two patients receiving catecholamines were deceased before collection of blood samples at day 1.

* $P<0.01$ and † $P<0.001$ vs nonsurvivor group.

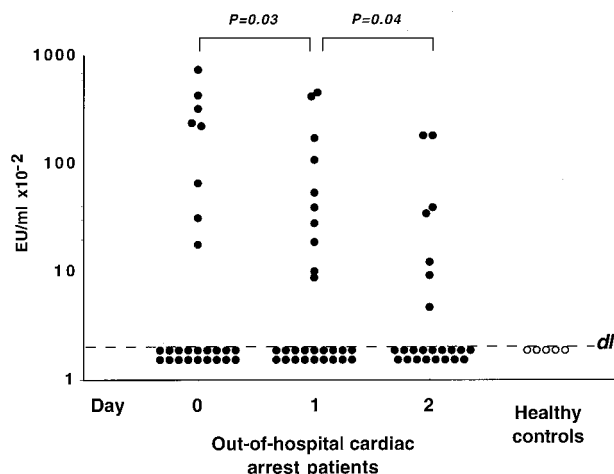


Figure 2. Measurement of endotoxin levels (endotoxin units [EU]/mL) in plasma of 35 resuscitated OHCA patients on admission (day 0) and the 2 days after (days 1 and 2). dl indicates detection limit (0.02 EU/mL).

no TNF- α was produced in the whole blood from OHCA patients in response to LPS, whereas leukocytes were responsive to SAC stimulation. When the cells from healthy control subjects were incubated with plasma from OHCA patients, a strong inhibition of TNF- α production was observed. The levels of TNF- α were significantly lower than those obtained before blood fractionation and also lower than those of reconstituted autologous blood. In addition, the hyporeactivity of leukocytes of OHCA patients revealed with LPS was not reverted when the cells were washed and incubated with plasma from healthy control subjects. In contrast, the *in vitro* plasma and cellular exchanges did not significantly affect the SAC-induced TNF production.

Discussion

In the present study, we showed that there is a “systemic inflammatory response syndrome” in patients who were

successfully resuscitated after cardiac arrest. There was an intense increase of various cytokines and sTNFRII within the blood compartment as early as 3 hours after cardiac arrest. Levels of IL-1ra, IL-6, IL-8, and IL-10 were higher in nonsurvivors, especially among those requiring vasopressors. Catecholamines are known to induce IL-10 release.¹² However, the higher levels of cytokines or soluble receptor in nonsurvivors requiring vasopressors at day 1 are likely to reflect the severity of shock rather than to be a consequence of the treatment, because there was no difference of circulating cytokines levels between survivors whether or not they received catecholamines. TNF- α was detectable in only 54% of our patients and was related to mortality. In sepsis, measurement of sustained plasma proinflammatory cytokines, such as TNF- α and IL-6, rather than their peak concentrations identifies those patients who develop multiple organ dysfunction and death.¹³ As opposed to findings for the patients with sepsis, we observed in OHCA patients that an early release of cytokines was the best predictor of mortality. Of note, in contrast to all chemokines studied so far, the levels of RANTES were not related to mortality in patients with sepsis¹⁴ or in OHCA patients.

Although it is well established that prolonged ischemia results in tissue and organ damage, the reperfusion-induced injury, defined as tissue damage occurring as a direct consequence of revascularization, may be more harmful.¹⁵ We found that lactate, which is known to be a marker of tissue hypoxia, was related to mortality. Moreover, there was a good correlation between lactate and some cytokines, such as IL-6, and sTNFRII on admission, suggesting a close relation between ischemia/reperfusion and inflammatory response. Moreover, ischemia/reperfusion of the gut, by resulting in endotoxin translocation, may further promote remote organ injury. Along this line, we found an increase in plasma endotoxin levels in OHCA patients, although there was no relation to mortality. There was up to 50% secondarily developed bacterial infection, mostly lung infection. Only 3 instances of bacteremia were observed in our follow-up at a

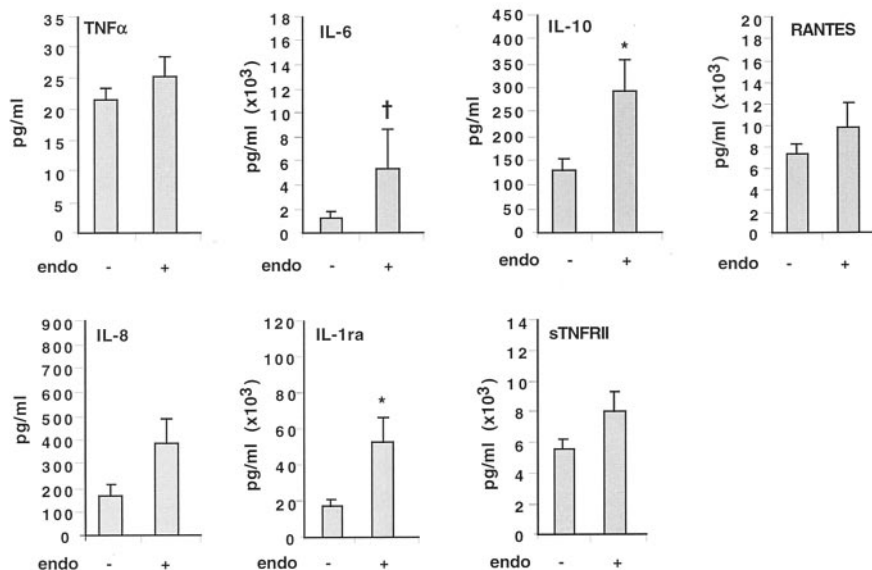


Figure 3. Cytokines and soluble receptor concentrations in plasma of resuscitated OHCA patients according to endotoxin detection in their plasma within first 2 days. endo+ indicates endotoxin detected (n=16 patients); endo-, endotoxin not detected (n=19). Data are mean \pm SEM. * P <0.05 and † P <0.005.

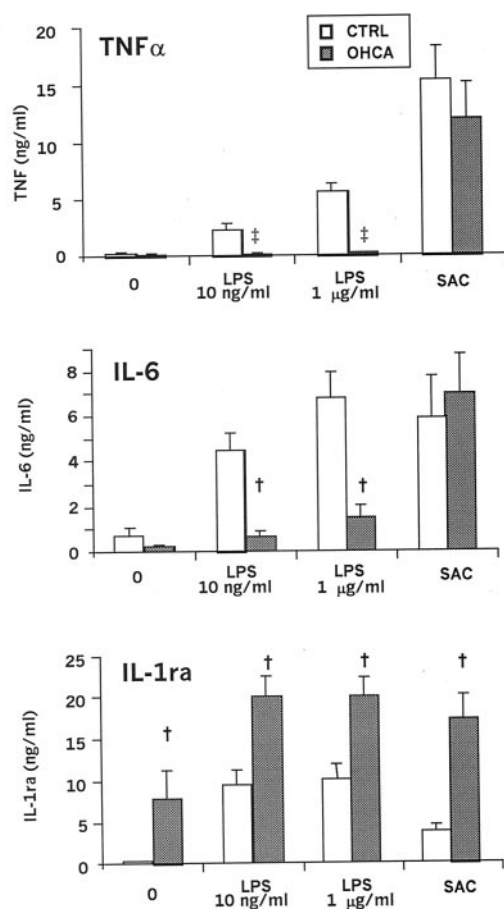


Figure 4. TNF- α , IL-6, and IL-1ra production in whole blood after a 24-hour incubation with LPS or SAC. Eleven resuscitated OHCA patients on day 1 were compared with 7 healthy control subjects (CTRL). Data are mean \pm SEM. † $P < 0.005$ and ‡ $P < 0.0005$.

late stage, between days 3 and 4. Our results support the 4 phases⁷ previously suggested but are in disagreement with a previous report showing frequent early bacteremia after cardiac arrest.¹⁶

Neither cytokines nor receptors were independently related to mortality. Because of the very high sensitivity and specificity of the variables already known to be related to mortality, such as interval time from collapse to basic life support and duration of cardiopulmonary resuscitation, it was very unlikely that one of the other parameters studied might improve them. However, these data are often missing in unwitnessed incidents or are not accurate in many others.¹

Hyporesponsiveness of circulating leukocytes, as assessed in terms of ex vivo cytokine production, has been extensively reported in septic patients and in patients with systemic inflammatory response syndrome.^{8,17} Although this phenomenon has been referred to as endotoxin tolerance, it appears to affect monocytes and neutrophils as well as lymphocytes and to be dependent on the nature of the activating signal.^{18,19} This may represent a protective response against an overwhelming dysregulation of the proinflammatory process, but on the other hand, it may induce a state of immune paralysis

(endogenous immunosuppression), leading to an increased risk of subsequent nosocomial infections.²⁰ In OHCA patients, we observed leukocyte dysregulation depending on the cytokines studied and the nature of the stimulating agent. The unaltered or enhanced response of leukocytes to SAC suggests that monocytes and neutrophils are viable and functional and that the LPS hyporesponsiveness is not due to necrosis or apoptosis of these cells. The responsiveness of T lymphocytes is also rapidly altered in OHCA patients, as evidenced by the marked reduction of the capacity of the cells to produce IFN- γ and IL-10 after activation with ConA. The capacity of plasma from OHCA patients to reduce in vitro the LPS-induced activation of leukocytes from healthy donors demonstrated that whole-blood hyporesponsiveness to endotoxin was caused by soluble serum factors systemically released after cardiac arrest. Furthermore, we established that the intrinsic leukocyte function appears also to be affected, inasmuch as in vitro exchange of healthy donors' plasma for patients' plasma did not restore TNF production of peripheral blood mononuclear cells from OHCA patients. These observations are in agreement with similar studies involving severe sepsis.^{8,21} The fact that SAC-induced TNF production by leukocytes from healthy donors was not affected by the addition of plasma from OHCA patients may indicate that this plasma contains large amounts of molecules able to specifically neutralize endotoxin.²²

In conclusion, we found a marked increase in plasma cytokines of patients successfully resuscitated after cardiac arrest, especially in nonsurvivors. Furthermore, we observed the presence of plasma endotoxin in $\approx 50\%$ of our patients and a dysregulation of cytokine production. All these features recall those observed in severe sepsis and might lead to new therapeutic approaches in postresuscitation care.

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