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Cortisol Response to Corticotropin Stimulation in Trauma Patients

Influence of Hemorrhagic Shock

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Background: **An abnormal adrenocortical function and a vasopressor dependency have been demonstrated during septic shock. Because trauma and hemorrhage are the leading causes of noninfectious inflammatory syndromes, the goal of this study was to assess the adrenal reserve of trauma patients and its relation with clinical course.**

Methods: **Cortisol response to an intravenous corticotropin bolus was obtained in 34 young trauma patients (Injury Severity Score = 29.1 ± 7.3) at the end of the resuscitative period ("early phase") and at the end of the first posttraumatic week ("late period"). Cortisol response less than +9 g/dl defined an impaired adrenal function, and the corresponding patient was called a nonresponder. According to the early response, hemorrhagic shock, circulating interleukin-6, need for vasopressor therapy, subsequent organ dysfunction and infection, and outcomes were studied.**

Results: **Sixteen patients (47%) were nonresponders at the end of the early phase. Hemorrhagic shock was more frequent (69 *vs.* 28%; $P = 0.037$) and interleukin-6 concentrations were higher (728 ± 589 *vs.* 311 ± 466 pg/ml; $P = 0.048$) in these patients. The early cortisol responses were negatively correlated with the concomitant interleukin-6 serum concentrations ($r^2 = 0.298$; $P = 0.003$). Four early nonresponders (and shock patients) remained nonresponders during the late phase (25%). Morbidity and mortality were similar in early nonresponders and responders. The duration of norepinephrine treatment and the total amount of infused drug were significantly higher in early nonresponders.**

Conclusions: **A sustained impairment of adrenal reserve is frequently observed in trauma patients. This abnormal cortisol response to corticotropin stimulation is related with the inflammatory consequences of hemorrhagic shock and is followed by a prolonged vasopressor dependency.**

THE stress response is a complex adaptive phenomenon that allows the integration of the defense mechanisms directed against external and internal stressors. This coordinated response involves the nervous, endocrine, and immune systems.[1] Indeed, the immune system through the inflammatory mediators, especially cytokines, stimulates the release of corticotropin-releasing factor from hypothalamic neurons. This central activation of the hypothalamic–pituitary–adrenal (HPA) axis and the direct stimulation of adrenal glands by the sympathetic system may be a regulatory mechanism for preventing an excessive immune reaction. Major trauma is a leading cause of nonseptic inflammatory reaction through severe tissue injuries, hemorrhagic shock, and ischemia–reperfusion consequences. An uncontrolled inflammatory process may play a key role in the development of multiple organ dysfunction, resulting in an increase in posttraumatic delayed morbidity and mortality.[2]

As with septic patients,[3,4] abnormalities of adrenocortical function and vasopressor dependency have been occasionally reported in trauma patients.[5–7] A huge and sustained increase in interleukin-6 plasma concentrations is a characteristic feature of the trauma patients.[8,9] This cytokine represents a major determinant of the magnitude of HPA axis responses, especially cortisol secretion, to stressors.[10–12]

The goals of the current prospective and longitudinal study in severe trauma patients were therefore (1) to quantify adrenal reserve in relation with the injury severity, the hemodynamic status, and interleukin-6 early plasma concentrations, and (2) to evaluate the relation between an abnormal cortisol response to corticotropin stimulation, a possible vasodepressor dependency, and the clinical outcome of the patients.

Materials and Methods

Study Population

All consecutive trauma patients admitted in the surgical intensive care unit (ICU) between November 1, 2000, and January 31, 2001, were prospectively enrolled in the study if they met the following criteria: (1) age between 18 and 55 yr; (2) expected Injury Severity Score (ISS)[13] greater than 16; and (3) probability of survival greater than 48 h. Patients were not eligible if they had previous acute or chronic disease or treatment, especially those that may have disrupted the HPA axis. Pregnancy was also an exclusion criteria.

The protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (No 00/1829), and informed consent was obtained

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from the patient's next of kin. The care of the patients was directed by the same existing protocols and was not modified by the study. Volume loading was performed to obtain a mean arterial pressure 70 mmHg or greater, a hemoglobin concentration 8 g/dl or greater, a prothrombin time 16 s or greater, and a platelet count 75×10^9/l or greater. Norepinephrine was given when the volume status was considered as normal in the face of persistent hypotension or to maintain a cerebral perfusion pressure of 70 mmHg or greater.

Data Collection

Clinical Evaluation. Two periods were defined during the evolution of the patients: the early phase and the late phase. The early phase, from the trauma to the end of the resuscitative period, included the surgical procedures. At that time, hemodynamic stability of the patients was assessed by the absence of additional volume loading or increase in norepinephrine dosage during the last 12 h. The late phase corresponded to the end of the first posttraumatic week.[2] The ISS and Simplified Acute Physiology Score[14] were calculated during the early phase to assess the magnitude of the trauma and its general consequences. An Abbreviated Injury Scale for the Head of 3 or greater defined a severe brain injury.[13] A Shock Score of 3 or greater defined a significant hemorrhagic shock during the early phase.[15] A Multiple Organ Dysfunction score was calculated each day.[16] The Multiple Organ Dysfunction scores at the end of the early phase and during the late phase were reported. The total amount of fluids infused during the early phase was noted, and the rate of volume loading was calculated by dividing the total amount by the duration of the phase. The duration of norepinephrine infusion and the total amount of the drug infused were calculated. Each patient was examined daily for the presence of nosocomial infections (urinary tract, bloodstream, wound infection) according to the criteria established by the Centers for Disease Control.[17] A pulmonary infection was considered nosocomial if it manifested more than 48 h after hospital admission. Ventilator-associated pneumonia was defined as a pneumonia occurring after more than 48 h of mechanical ventilation. Pneumonia was suspected on the appearance of persistent pulmonary infiltrates on the chest radiograph and at least one of the following clinical and biologic findings: (1) purulent tracheal secretions; (2) body temperature greater than 38.5°C or less than 36.5°C; and (3) leukocyte count greater than 10×10^9/l or less than 4×10^9/l.[18] Confirmation of pneumonia was obtained by a positive plugged telescoping catheter ($\leq 10^3$ cfu/ml).[19] The diagnosis of pneumonia was also accepted in the presence of a microorganism in pleural effusion or isolation of the same microorganism (except coagulase-negative staphylococci or *Corynebacterium* spp.) from at least one blood culture as well as a respiratory tract specimen, in the absence of other foci of infection.[20] For each patient, the number of infectious episodes was noted. All patients were evaluated for the complete ICU stay, and outcome and length of stay in the ICU and hospital were reported.

Laboratory Variables. Plasma lactate and total plasma proteins were measured using routine assays. Lactate was used as a biologic marker of ischemia, and plasma proteins were used as an index of dilution.

A short corticotropin stimulation test was performed at the end of the early phase and during the late phase.[3] Tetracosactrin, 250 μg (Synacthène®; Ciba, Rueil-Malmaison, France) was given intravenously. Blood samples were taken immediately before the test and 30 and 60 min afterward. After centrifugation, plasma samples were stored at −20°C, and cortisol was measured by radioimmunoassay (CORT-CT2; Schering, Gif-sur-Yvette, France) with a detection limit at 0.2 μg/10 ml. Assuming that, in trauma patients as in septic patients, basal cortisol concentrations would be greater than 18 μg/dl, the cortisol response to corticotropin stimulation was defined as the difference between the basal concentration and the highest of the 30- and 60-min concentrations and not as the peak cortisol value after corticotropin. In these conditions, the diagnosis of impaired adrenal function reserve was established on the basis of a cortisol response less than 9 μg/dl, and the patient became a so-called nonresponder to the corticotropin stimulation.[3]

At the end of the early phase, the plasma sampled before the corticotropin stimulation was used to assay the plasma concentration of interleukin-6. Measurements were performed in duplicate using a solid-phase sandwich enzyme-linked immunosorbent assay (Immunotech®; Beckman Coulter, Marseille, France). For interleukin-6, the samples were incubated in microtiter plate wells, coated with a first monoclonal antibody in the presence of a second monoclonal linked to acetylcholinesterase. The assay detection limit was 3 pg/ml.

Statistical Analysis

Assuming that the incidence of abnormal cortisol response to corticotropin stimulation may be of the same magnitude for severely injured patients as for patients with septic shock (between 40 and 50%),[4] a sample size of at least 25 trauma patients was calculated to achieve a β error of 0.1 and an α error of 0.05 (one-sided test). Continuous variables were first checked for normality or nonnormality using a Shapiro-Wilk test. When a variable appeared log-distributed, the transformation was used for further comparison. Thereafter, variables were compared using the Fisher exact test for proportions, Mann–Whitney U test for nonnormally or nonlog-normally distributed continuous variables, and Student *t* test for normally or log-normally distributed variables. Correlations between log-cytokine concentrations in blood and changes in cortisol concentrations after the early corticotropin stimulation were performed using linear regres-

Table 1. Characteristics of the Patients and Results of the Two Corticotropin Stimulations

No.	Sex	Age (yr)	t_0	ISS	SAPS	Shock	t_1	$Cort_1$	$\Delta Cort_1$	t_2	$Cort_2$	$\Delta Cort_2$	S/NS
1	M	18	5.5	34	23	No	12.0	17.0	+8.2	127.5	14.3	+20.8	S
2	M	19	2.0	29	20	Yes	12.0	11.0	+3.0	130.0	22.6	+18.0	S
3	F	20	4.0	27	32	Yes	55.0	9.0	+7.0	170.5	19.4	+16.7	S
4	F	45	1.0	22	28	No	39.0	9.0	+12.2	180.0	24.3	+14.6	S
5	M	42	4.0	29	42	Yes	24.0	42.6	+2.5	166.0	5.8	+19.4	S
6	M	48	1.0	24	41	Yes	63.0	21.2	+15.9	255.0	22.0	+13.3	S
7	M	29	2.0	17	8	No	20.0	18.5	+12.9	71.0	15.4	+18.3	S
8	M	54	2.0	27	55	Yes	38.0	16.2	+8.9	158.0	13.2	+9.6	S
9	M	25	2.0	41	46	No	11.0	10.5	+2.7	—	—	—	NS
10	M	43	1.0	27	22	No	6.0	1.6	+25.4	118.0	19.0	+26.0	S
11	M	41	2.5	34	42	No	13.0	22.0	+15.0	132.0	16.0	+18.0	S
12	M	55	1.0	18	30	Yes	6.0	23.9	+3.3	248.0	26.0	+6.8	S
13	F	23	10.0	43	45	No	7.0	16.6	+12.3	127.0	16.0	+13.4	S
14	M	18	2.0	38	52	No	12.0	28.0	−0.1	185.5	8.6	+24.8	NS
15	M	41	2.0	29	63	Yes	30.0	16.7	−1.8	148.0	33.6	+7.8	NS
16	M	40	1.0	24	47	Yes	15.0	16.9	+14.0	135.0	18.0	+15.2	S
17	M	52	1.0	17	36	No	12.0	24.7	+18.2	57.0	18.7	+18.2	S
18	M	24	10.0	25	46	No	20.0	33.7	+18.5	140.0	12.2	+29.1	S
19	M	18	3.0	33	59	Yes	6.0	13.1	+5.9	—	—	—	NS
20	M	25	5.0	35	42	No	19.0	23.7	+9.2	131.0	18.2	+12.1	S
21	F	20	7.0	29	26	No	19.0	28.9	+23.1	59.5	18.7	+18.2	S
22	M	24	3.0	21	28	No	10.0	9.7	+2.3	124.0	24.0	+16.7	S
23	F	18	9.0	20	38	Yes	38.0	6.2	+16.8	135.5	4.7	+18.0	S
24	M	27	1.0	34	38	Yes	14.0	8.9	+7.7	127.5	19.3	+8.7	S
25	M	26	2.0	25	21	No	15.0	23.4	+5.7	220.5	25.9	+13.0	S
26	M	22	4.0	29	21	No	18.0	21.4	+9.9	278.5	18.4	+13.8	S
27	M	31	2.0	38	55	Yes	23.0	9.1	+12.6	249.0	19.3	+20.7	S
28	M	36	2.0	25	11	No	14.0	16.2	+9.7	187.0	15.0	+15.0	S
29	F	50	7.0	29	38	No	18.0	13.0	+9.2	111.0	28.0	+13.1	S
30	M	32	3.0	43	27	Yes	15.0	17.3	+8.2	185.0	22.0	+8.0	S
31	F	43	2.0	41	59	Yes	19.0	14.0	+7.0	158.0	31.0	+21.0	S
32	M	32	1.0	25	20	Yes	27.0	26.0	+4.0	122.5	9.0	+18.0	S
33	M	44	3.0	34	32	Yes	39.0	24.0	+15.0	152.5	23.0	+19.0	S
34	F	55	7.0	25	39	No	48.0	24.2	+9.0	218.0	18.1	+24.7	NS

Cortisol units are μg/dl.

t_0 = time to admission; ISS = Injury Severity Score; SAPS = Simplified Acute Physiology Score; t_1 = time to the first or "early" stimulation (h); $Cort_1$ = basal value during the first stimulation; $\Delta Cort_1$ = response during the first stimulation; t_2, time to the second or "late" stimulation (h); $Cort_2$ = basal value during the second stimulation; $\Delta Cort_2$ = response during the second stimulation; S = significant; NS = nonsignificant.

sions. Data are presented as the mean ± SD. $P < 0.05$ was considered as the minimum level of statistical significance.

Results

Sixty-one patients were admitted in the surgical ICU during the study period. Twenty-two patients were not eligible because of age older than 55 yr (n = 7), an ISS less than 16 (n = 4), a chronic disease (n = 7), or a recent steroid administration (n = 4). Five eligible patients were not included because of death within 48 h (n = 3) or technical problems with biologic analysis (n = 2). Thirty-four patients were therefore included (age, 34 ± 12 yr; male/female ratio, 26/8; table 1). They were admitted in the unit 3.4 ± 2.7 h after the trauma (vertical falls = 12, pedestrians = 8, motor vehicle accident = 14). Severity of injury was moderate or severe (ISS = 29.1 ± 7.3) with significant physiologic consequences (Simplified Acute Physiology Score = 21.7 ± 14.3).

The first corticotropin stimulation (early phase) was performed 21.7 ± 14.3 h after the trauma in the whole group (table 1). Nineteen patients (56%) had a basal cortisol plasma concentration less than 18 μg/dl. Sixteen patients had a cortisol response less than 9 μg/dl and were designed as early nonresponders (table 2 and fig. 1). The cortisol responses were not correlated with the basal cortisol concentrations, which were identical between nonresponders and responders (17.9 ± 9.0 *vs.* 18.4 ± 8.2 μg/dl, respectively; $P = 0.886$). As shown in table 2, early nonresponders and early responders were similar in terms of age, gender, time of admission, ISS, Simplified Acute Physiology Score, mechanical ventilation and subsequent sedation, and time to early corticotropin stimulation. Previous intravenous etomidate administration was similar in the two groups (0.5–0.6 mg/kg, 25.8 ± 12.0 and 23.8 ± 12.2 h before the stimulation in responders and nonresponders, respectively). The incidence of brain injury was not different between the two subgroups of patients (69 *vs.* 44%, respectively; P =

Table 2. Clinical and Biologic Characteristics of the Patients according to the Cortisol Response (ΔCort) to Corticotropin Stimulation at the End of the Early Phase

	Early Responder ΔCort ≥ 9 μg/dl	Early Nonresponder ΔCort < 9 μg/dl	*P* Value
Time to early stimulation (h)	23.9 ± 15.3	19.1 ± 13.0	0.333
n	18	16	
Age (yr)	35.9 ± 12.1	30.9 ± 12.6	0.244
Gender (M/F)	12/6	14/2	0.233
Time to admission (h)	2.5 ± 1.2	4.2 ± 3.3	0.057
Injury Severity Score	27.6 ± 7.1	30.9 ± 7.3	0.195
SAPS II	34.3 ± 12.7	39.4 ± 15.4	0.436
Etomidate administration	12	9	0.725
Hemorrhagic shock	5	11	0.037
Peak arterial lactate	2.2 ± 1.5	3.9 ± 1.7	0.003
Early MOD score	4.6 ± 2.7	7.6 ± 2.9	0.004
Total volume loading (ml)	8,011 ± 6,412	10,297 ± 7,600	0.349
Volume loading rate (ml/h)	409 ± 434	583 ± 344	0.022
Crystalloid volume (ml)	4,489 ± 3,194	4,066 ± 3,067	0.697
Colloid volume (ml)	1,975 ± 2,062	3,356 ± 1,724	0.043
No. of patients transfused	9	11	0.315
Blood product volume (ml)	1,547 ± 2,174	2,813 ± 3,297	0.191
Norepinephrine infusion	11	12	0.324
Mechanical ventilation	11	13	0.270
Plasma total proteins (g/l)	46.6 ± 11.5	44.1 ± 9.2	0.484
Interleukin-6 (pg/ml)	311 ± 466	728 ± 589	0.048

MOD = multiple organ dysfunction.

0.185) and the mean Abbreviated Injury Scale for the Head were similar (2.9 ± 1.8 *vs.* 2.4 ± 2.2, respectively; $P = 0.394$). Nonresponders and responders were significantly different in terms of incidence of hemorrhagic shock (69 *vs.* 28%, respectively; $P = 0.037$), early Multiple Organ Dysfunction score (7.6 ± 2.9 *vs.* 4.6 ± 2.7, respectively; $P = 0.004$), and peak arterial lactate (3.9 ± 1.7 *vs.* 2.2 ± 1.5, respectively; $P = 0.003$). The rate of volume loading and the volume of infused colloid solution (hydroxyethylstarch) were also significantly higher in the nonresponder group. However, neither the magnitude of the dilution nor the incidence of norepinephrine infusion was different between the two groups. Finally, the interleukin-6 concentrations were significantly higher in nonresponders.

The second corticotropin stimulation (late phase) was performed at a similar time in early nonresponders and early responders (table 3). Two patients died in the early nonresponders group before this second test. The four nonresponders at the second stimulation came exclusively from the early nonresponders group ($P = 0.028$; fig. 1). As shown in table 3, total number of infectious episodes, mortality, and lengths of stay were similar between early nonresponders and early responders. The main differences between these two subgroups of patients during the ICU stay were the duration of vasopressor therapy and the total amount of norepinephrine infused. Whatever the responses, patients were not given exogenous steroids throughout the study.

Figure 2 shows the relation between the hemorrhagic shock and the cortisol response to corticotropin stimulation. Despite similar mean basal cortisol concentrations before the two corticotropin stimulations between patients without or with shock, there was a trend toward a lesser response in shock patients, and the incidence of nonresponders was higher in this subgroup as compared with the patients without shock (69 *vs.* 28%, respectively; $P = 0.037$). As shown in figure 2, the cortisol response to corticotropin stimulation increased between the two periods of the study in the two sub-

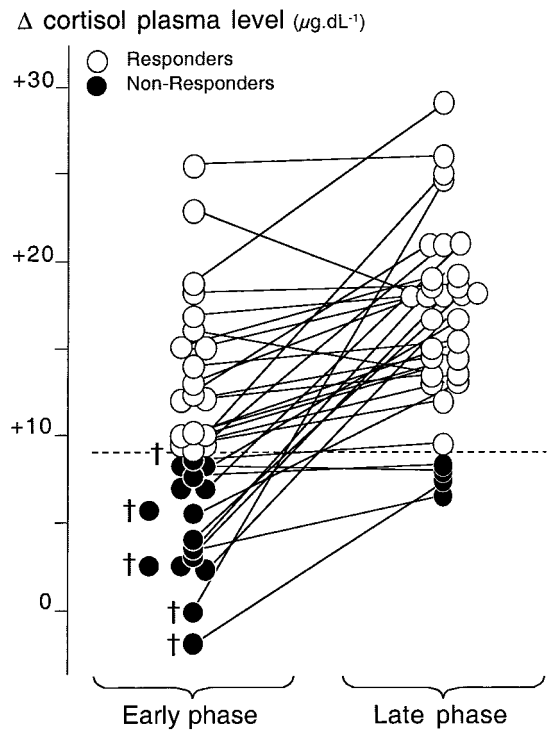

Fig. 1. Cortisol response to corticotropin stimulation at the end of the early phase (21.7 ± 14.3 h) and at the end of the first posttraumatic week (late phase; 156.5 ± 52.2 h). The dashed line represents the threshold of normal response (+9 g/dl), and daggers indicate the nonsurvivors.

Table 3. Influence of the Cortisol Response (ΔCort) to Corticotropin Stimulation during the Early Phase on the Response to the Second Stimulation (Late Phase) and the Overall Outcomes

	Early Responder ΔCort ≥ 9 μg/dl	Early Nonresponder ΔCort < 9 μg/dl	*P* value
Time to late stimulation (h)	152.1 ± 64.0	162.2 ± 37.9	0.607
Late MOD score	2.6 ± 2.5	3.4 ± 3.9	0.518
Plasma total proteins (g/l)	54.5 ± 5.5	52.9 ± 7.1	0.466
Basal cortisol value (μg/dl)	18.1 ± 5.0	19.6 ± 8.5	0.518
Δ Cortisol value (μg/dl)	+17.8 ± 4.8	+14.9 ± 5.9	0.138
No. of infectious episodes	1.9 ± 2.5	2.3 ± 2.6	0.660
Norepinephrine treatment			
Duration (h)	51.3 ± 112.0	84.6 ± 103.1	0.040
Total dose (mg)	30.0 ± 62.1	123.2 ± 245.2	0.038
ICU length of stay (days)	15.8 ± 11.7	18.0 ± 16.4	0.650
ICU death (mortality)	1 (6%)	4 (25%)	0.164
Hospital length of stay (days)	50.2 ± 44.0	47.7 ± 54.3	0.584

MOD = multiple organ dysfunction; ICU = intensive care unit.

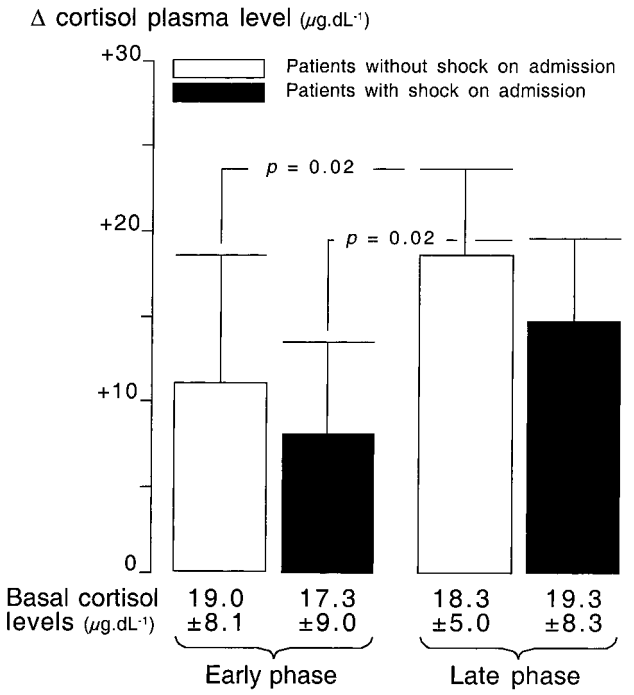

Fig. 2. Influence of hemorrhagic shock on the basal cortisol plasma concentrations and the cortisol response to corticotropin stimulation at the end of the early phase and at the end of the first posttraumatic week (late phase).

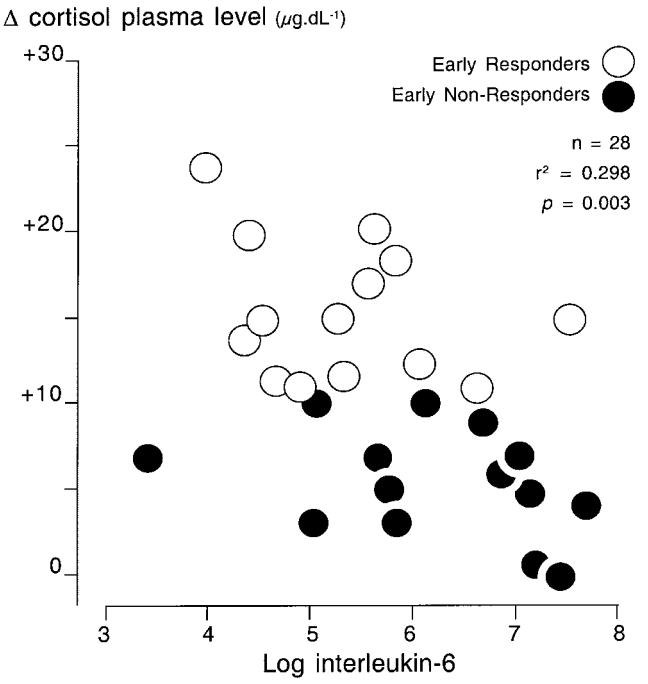

Fig. 3. Relation between interleukin-6 plasma concentrations and the cortisol response to corticotropin stimulation at the end of the early phase. Interleukin-6 plasma concentrations were not avilable in six patients.

groups, but four shock patients remained nonresponders at the second stimulation (29 *vs.* 0%; $P = 0.038$).

At the end of the early phase, before the first corticotropin stimulation, the interleukin-6 plasma concentrations were higher in shock patients than in the remaining patients (661 ± 549 *vs.* 383 ± 498 pg/ml, respectively; $P = 0.05$). As shown in figure 3, cortisol response after the early corticotropin stimulation was negatively correlated with concomitant interleukin-6 plasma concentrations.

Discussion

In the current study, a significant decrease in adrenal reserve was observed in 47% of trauma patients (ISS > 16) and was prolonged during at least 7 days in 25% of these nonresponders. This abnormal cortisol response to corticotropin stimulation was related with the inflammatory consequences of hemorrhagic shock and was followed by a prolonged vasopressor dependency.

Notwithstanding the fact that the short corticotropin stimulation test using 250 μg tetracosactin is widely used in ICU patients,[4,11] especially when basal cortisol concentrations are rather low,[21] its results were discussed because this supraphysiologic amount of exogenous corticotropin bypasses the brain–hypothalamus–pituitary portion of the HPA axis and tests directly the integrity of adrenal gland with a lower sensitivity than a low tetracosactin dose (1–2 μg).[21] Moreover, the results of the test were established in healthy subjects and in patients with absolute adrenal insufficiency and not in critically ill patients,[22] even if the prognostic value of the combination of basal cortisol concentrations with cortisol response was recently demonstrated in septic shock patients.[4] Nevertheless, we qualified our results as an impaired adrenal reserve and attributed such an abnormal response to hemorrhagic shock after consideration of the possible alternative role of anesthesia, volume loading, and brain injury. Indeed, etomidate reduces the adrenal reserve through an inhibition of steroidogenesis[23] in 88% of patients receiving a single dose of the drug.[24] However, this adrenocortical dysfunction appears to resolve within 12 h of a single bolus dose,[25] and this anesthetic was equally distributed between early nonresponders and responders in the current study. In the same way, plasma dilution following volume loading was similar in the two subgroups of patients and could only be involved in the high incidence of low cortisol concentrations in these patients, as previously suggested by Rydvall *et al.*[26] However, because a stable plasma osmolality was a standard of care for the trauma patients,[27] and a deleterious effect of hydroxyethyl starch on adrenal reactivity seems unlikely, a direct role of volume loading in the impairment of the cortisol response to corticotropin stimulation was not taken into account. Finally, isolated brain injury induces a biphasic pattern of neuroendocrine activity with an early sympathetic storm and an altered function of HPA axis, followed by a decrease in both responses[28] in such a way

that an hypopituitarism occurs in approximately 40% of the patients with moderate or severe head injury.[29] Even if more than one half of the multiple-injured patients suffered from a severe brain injury in the current study, the exclusive role of the head trauma in the reported decrease in adrenal reserve was excluded because the incidence and magnitude of brain injuries were similar between early nonresponders and responders, and because the HPA dysfunction is mainly observed in brain-injured patients with hypotensive or hypoxic insults.[29]

Hemorrhagic shock is the main factor of the posttraumatic inflammatory response, and the immunologic consequences of trauma are correlated with the severity of hemodynamic insult.[30] Experimental repeated or prolonged hemorrhage induces a delayed cortisol secretion,[31] and the basal cortisol concentrations are inversely correlated with the increase in interleukin-6 concentrations following experimental hemorrhage–reinfusion.[32] The association of hemorrhage–reperfusion with tissue injuries explains the magnitude of interleukin-6 expression following trauma.[8,9,33] In humans, exogenous interleukin-6 causes an impressive marked and prolonged elevation of plasma corticotropin and cortisol on the first day, followed by blunted corticotropin responses.[10] A continuous and sustained corticotropin secretion may therefore occur in trauma patients and might lead to a pituitary depletion over a period of time. Following experimental hemorrhage and resuscitation, a decrease in hepatic 11β-hydroxysteroid dehydrogenase activity leads to a sustained increase in plasma corticosterone concentrations, which regulate the corticotropin release, further reducing adrenal responsiveness.[34] A primary failure of pituitary function was observed in septic shock patients,[22,35] and the abnormal cortisol response to corticotropin stimulation has been attributed to a prolonged understimulated adrenal gland.[22]

The early adrenal dysfunction was clearly associated with an increased need for vasopressor therapy. Such a relation may be explain by a reduction of the well-known role of steroids in the regulation of adrenergic receptor numbers and responses.[3] The current results suggest an impaired pressor sensitivity to catecholamines in trauma patients, which has been demonstrated in animals[36] and warrants further clinical studies.

In conclusion, this study confirms the fact that a sustained inflammatory response from either infective or noninfective source results in cortisol deficiency in relation with a primary adrenal insufficiency or a loss of corticotropin secretion. A clinical exploration of HPA axis, using a measurement of corticotropin and cortisol concentrations before and after a stimulation by corticotropin or corticotropin-releasing hormone, may be indicated in trauma patients to identify the consequences of a possible modulation of HPA axis activity.

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