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CORTISOL LEVELS AND ADRENAL RESERVE AFTER SUCCESSFUL CARDIAC ARREST RESUSCITATION

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ABSTRACT—The postresuscitation phase after out-of-hospital circulatory arrest shares similarities with severe sepsis. Corticosteroid replacement is beneficial in patients with septic shock and adrenal dysfunction. The goal of this study was to assess baseline cortisol and adrenal reserve of out-of-hospital circulatory arrest patients after recovery of spontaneous circulation. Thirty-three consecutive patients successfully resuscitated after cardiac arrest were prospectively included between March 2002 and June 2003. A serum cortisol assay and a corticotropin test (250 μg i.v.) were done 6 to 36 h after circulatory arrest. A cortisol increase smaller than 9 μg/dL after corticotropin (nonresponders) defined adrenal reserve insufficiency. Response status was compared in the three outcome groups: survival with full neurologic recovery (n = 4), early death from refractory shock (n = 10), or later death from neurologic dysfunction (n = 19). Patients who died of early refractory shock had lower baseline cortisol levels than patients who died of neurologic dysfunction (27 μg/dL [15–47] vs. 52 μg/dL [28-73], respectively; $P < 0.01$), suggesting an inadequate adrenal response to severe systemic inflammation. Corticotropin response status was not associated with standard severity markers and seemed uninfluenced by therapeutic hypothermia. In conclusion, patients who die of early refractory shock after cardiopulmonary resuscitation may have an inadequate adrenal response to the stress associated with this condition. Thresholds for cortisol levels at baseline and after corticotropin need to be determined in this clinical setting.

KEYWORDS—Shock, adrenal insufficiency, corticotropin, reperfusion, sepsis

INTRODUCTION

Out-of-hospital circulatory arrest (OHCA) results in some 250,000 deaths annually in the United States and Canada, with death rates ranging from 4% to 33%, depending on the organization of the chain of survival (1). The recovery of spontaneous circulation leads to a whole-body ischemia-reperfusion syndrome designated "postresuscitation disease" (2) and resembling severe sepsis (3, 4). The high blood cytokine levels, cytokine production dysregulation, and presence of endotoxin in plasma are reminiscent of the immunological profile in patients with sepsis (3). Recently, mild hypothermia was shown to increase survival rates after cardiopulmonary resuscitation (CPR) (5, 6), confirming that the outcome is determined, not only by the time to circulation recovery, but also by pathogenic processes that occur during the postarrest phase and lead to organ dysfunction, including neurologic deterioration.

In severe sepsis, the integrity of the hypothalamic-pituitary-adrenal axis can be impaired by multiple mechanisms (7–10), and the adrenal response to exogenous corticotropin has been found helpful in identifying patients at higher risk of death (11, 12). Relative adrenal insufficiency has also been found in patients with severe trauma in whom major tissue damage, hemorrhagic shock, and ischemia-reperfusion lead to a nonseptic inflammatory response (13, 14). Subsequently, Annane et al. (15) showed that replacement therapy with low-dose corticosteroids decreased mortality rates in patients with septic shock and adrenal insufficiency defined as failure to respond to a corticotropin injection by a cortisol increase ≥ 9 μg/dL. During and after cardiac arrest, Schultz et al. (16) found that serum cortisol levels, although high, were lower than expected after such a severe stress. Corticotropin induced no significant response when the mean group value was considered, but the study did not attempt to distinguish responders from nonresponders.

The goals of the present study were to determine whether serum cortisol and adrenal reserve were related to the severity of postresuscitation disease in patients who recovered spontaneous circulation after CPR. We used the threshold determined for severe sepsis to identify responders to a short corticotropin test and we then looked for a relationship between responder status and outcomes.

MATERIALS AND METHODS

Study population

All consecutive patients older than 16 years of age admitted to our intensive care unit (ICU) between March 2002 and June 2003 after successful OHCA resuscitation were included prospectively in the study, provided their hemodynamic condition was stable at ICU admission with or without vasopressor agents. The study was approved by the Ethics Committee of the French Society for Critical Care, and informed consent was obtained from the next-of-kin of each patient. Circulatory arrest was defined as absence of spontaneous respiration or heartbeat with unresponsiveness to stimulation. Patients with a history of corticosteroid therapy and those who had received the steroidogenesis-inhibiting agent etomidate were not eligible for the study.

Clinical evaluation

The Simplified Acute Physiology Score (SAPS II) (17) and the Sequential Organ Failure Assessment (SOFA) (18) score were calculated during the first 24 h. At ICU admission, all patients were mechanically ventilated via an endotracheal tube. The clinical and laboratory data obtained routinely in ICU patients were recorded for the

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study during the first 3 days. Starting in November 2002, patients admitted after ventricular fibrillation were treated with hypothermia (31°C–32°C) initiated as early as possible on admission and maintained for 24 h, using wet cold wraps and ice, together with neuromuscular blocking agents to prevent shivering. The use of hypothermia in patients admitted after asystole or pulseless circulatory arrest was left to the discretion of the attending physician. Central temperature was monitored using an anal probe.

Outcomes identified three groups of patients: survivors, all of whom had normal neurological function; patients who died within 4 days from early refractory shock with multiple organ failure; and patients who died later from neurologic dysfunction with or without the need for initial inotropic support (4).

Laboratory variables

Plasma lactate and total plasma proteins were measured using routine assay techniques. Lactate was used as a marker for ischemia and plasma total proteins were used as a marker for dilution. A short corticotropin stimulation test was performed between 6 and 36 h after the circulatory arrest. Tetracosactrin (250 mg, Synacthène; Ciba, Reuil-Malmaison, France) was given intravenously, and blood samples were taken immediately before and 30 and 60 min after the injection. Cortisol was measured using an immunoenzymetric assay (Vidas-cortisol; Biomérieux, Lyon, France) with a detection limit of 0.2 μL/dL. The cortisol response (Δmax) was defined as the difference between the baseline concentration and the concentration 30 or 60 min postinjection, whichever was highest. Nonresponders were defined as having a Δmax less than 9 μg/dL, which was taken as an indicator of impaired adrenal function reserve (7, 11, 12). The results of identical tests in patients admitted for septic shock during the study period were collected.

Statistical analysis

Data were expressed as medians with the interquartile range. Death was categorized as absent, early refractory shock, or neurologic dysfunction (4), and the relationship between numerical variables and death was analyzed using a nonparametric analysis of variance (Kruskal-Wallis test) followed by a Mann-Whitney *U* test for comparisons between two groups. Categorical variables were compared by the chi-square or Fisher's exact test. Relations between two continuous variables were analyzed using the Spearman's rank correlation test. Statistical tests were performed using Stata 7 software (Stata Inc., College Station, TX.).

RESULTS

Patient characteristics

Thirty-three patients were included, of whom 27 (82%) were men. The median age was 51 years (39–55), the median SAPS II was 65 (56–76), the median SOFA score was 10 (7–12), and the median Glasgow Coma Score (GCS) was 3 (3–3). Table 1 reports the main patient characteristics. Of the 33 patients, 29 (88%) died, 10 from early refractory shock and 19 later on from neurologic dysfunction. The four survivors recovered normal neurologic function. The time from cardiovascular collapse to first-response life support was longer and the use of epinephrine during resuscitation was more common in the group with fatal early shock than in the group with delayed death from neurological failure, whereas no difference was found for duration of resuscitation. Lactate levels were significantly higher on Day 1 in patients dying from early refractory shock (Table 1), indicating further hemodynamic deterioration in this group.

As a positive control group, 24 patients admitted to our ICU for septic shock underwent a short corticotropin test during this study. There were 18 men (75%), with a median age of 70 years (63–78), a median SAPSII score of 59 (41–71), and a median GCS of 14 (13–15). Of these 24 patients, 11 (46%) died.

Serum cortisol levels before and after corticotropin stimulation

All OHCA patients had high serum cortisol levels, with a median of 40 μg/dL (23–58) during the measurement period

TABLE 1. **Clinical characteristics of patients admitted to the ICU after out-of-hospital circulatory arrest**

Parameters	Survivors (n = 4)	Dead from early refractory shock (n = 10)	Dead from neurologic dysfunction (n = 19)	*P*
Age	58 [49–65]	51 [45–54]	48 [38–57]	0.38
SAPS II score	47 [44–57]†	77 [74–93]	64 [59–75]*	0.01
SOFA score	7.5 [5–8]†	12.5 [12–15]	8 [7–10]	0.03
Epinephrine (mg)	1 [0–2]†	6.5 [5–12]	4 [2–6]*	0.004
GCS on admission	4 [3–6]†	3 [3–3]	3 [3–3]	0.006
First cardiac rhythm				
Asystole/pulseless activity	1	8	15	0.09
Ventricular arrhythmia	3	2	4	
Witness	3	7	15	0.67
Interval from collapse to first-response life support (min)	4.5 [2–7]	12 [10–15]	8 [5–11]*	0.04
Duration of CPR (min)	10 [6–14]	17 [10–30]	17 [6–27]	0.21
Cardioversion (n)	2 [2–2]	1 [0–2]	1 [0–5]	0.62
Duration of vasopressor administration (h)	0 [0–9]	29 [17–40]	6 [0–48]	0.05
Hypothermia	2	2	8	0.07
Lactate (Day 0, mmol/L)	7.4 [3–11]	14 [8.5–16]	7.7 [4–11]	0.15
Lactate (Day 1, mmol/L)	1.6 [1–2]†	8.4 [5–15]	3.3 [2–5.2]*	0.004
Plasma total protein (Day 0, g/L)	60 [60–72]	61 [52–68]	67 [59–72]	0.35
Plasma total protein (Day 1, g/L)	60 [55–67]	52 [45–56]	63 [56–67]	0.09
PaO_2/FiO_2	197 [164–273]	218 [179–245]	381 [250–532]*	0.006
Creatinine (μmol/L)	78 [61–85]	139 [109–154]	108 [92–138]*	0.007
Cortisol (μg/dL)	19 [9.3–33]	27 [15–47]	52 [28–73]*	0.01
ΔCortisol (μg/dL) after corticotropin test	16 [6.1–21]	15 [6–21]	8 [1.3–19]	0.63
Relative adrenal insufficiency (nonresponders)	1	3	10	0.21
Interval from cardiac arrest to corticotrophin test (h)	19 [13.8–24.5]	21 [17–23.4]	22.2 [18.2–23]	0.96

Relative adrenal insufficiency was defined as a smaller than 9 μg/dL increase in serum cortisol 30 or 60 min after a corticotropin injection (7, 11).
*$P < 0.05$ between early refractory shock and neurologic dysfunction groups.
†$P < 0.05$ between survivors and nonsurvivors.
PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fractional concentration of inspired oxygen; ΔCortisol, plasma cortisol increase 30 or 60 min after a corticotropin injection (whichever was larger).

(6–36 h postarrest). There was a trend toward lower serum cortisol levels in survivors than in nonsurvivors ($P = 0.08$, Table 1). The group of patients who died of early refractory shock had a significantly lower median cortisol level at baseline than the group that died of neurologic dysfunction (27 μg/dL [15–47] vs. 52 μg/dL [28–73], respectively; $P < 0.01$). The serum cortisol Δmax after corticotropin was 10.8 μg/dL (1.7–18.8) with all patients pooled. Hypothermia seemed to have no influence on the baseline cortisol level or postcorticotropin Δmax. Values in the patients with septic shock were similar to those in the OHCA patients: baseline cortisol was 31 μg/dL (22–45), and the postcorticotropin Δmax was 10.5 μg/dL (0.6–15.2).

When defined as a Δmax smaller than 9 μg/dL, relative adrenal insufficiency was observed in 14 patients (42%), which was similar to the rate in the patients with septic shock (12/24, 50%) admitted to our ICU during the study period. However, relative adrenal insufficiency was not associated with mortality or with the cause of death in the OHCA patients. Furthermore, relative adrenal insufficiency was not associated with factors predicting poorer outcomes, such as asystole as the first rhythm cardiac recorded, absence of a witness, time from cardiovascular collapse to first-response life support, or total duration of cardiopulmonary resuscitation. Hypothermia had no influence on serum cortisol levels at baseline or after the corticotropin test. The interval from cardiac arrest to corticotropin test was identical in all the three groups.

DISCUSSION

We found that adrenal insufficiency was common in patients who recovered effective circulation after resuscitation for circulatory arrest. Patients who died of early refractory shock had lower plasma cortisol values than those who died later from neurologic dysfunction.

Postresuscitation disease, a condition described by Negosky (19) in patients with successfully resuscitated circulatory arrest, is associated with a systemic inflammatory response similar to the immunologic profile observed in patients with severe sepsis (3). In patients with sepsis, higher cortisol levels (11, 12) were associated with poorer outcome, and hydrocortisone and fludrocortisone therapy has been shown to decrease mortality in the subset with no response to a corticotropin test (cortisol increase <9 μg/dL). In our study, using the same criteria, we found relatively high baseline cortisol levels contrasting with a 42% prevalence of relative adrenal insufficiency defined as failure to respond to corticotropin. A similar prevalence of relative adrenal insufficiency was noted in patients with septic shock admitted during the study period. This further highlights some similarities observed in severe sepsis and postresuscitation disease, as already published elsewhere (3, 4). Several mechanisms may lead to adrenal insufficiency with extensive destruction of adrenal tissue, most notably in patients with an underlying coagulopathy (7). Furthermore, high levels of inflammatory cytokines can directly inhibit adrenal cortisol synthesis (7): for instance, in humans, exogenous interleukin 6 causes a dramatic and prolonged elevation in plasma ACTH and cortisol on the first day, followed by a blunted response to corticotropin (20). Inflammation and coagulopathy have been described after successful circulatory arrest resuscitation (3, 21, 22).

Although the correlation between cortisol levels and disease severity is well established, the magnitude of the cortisol response most likely to promote a favorable outcome in the critically ill patient remains undefined (23). Identification of a range below which adrenal insufficiency is likely and above which adrenal insufficiency is unlikely would be useful. Alternatively, adrenal function reserve can be evaluated based on the response to corticotropin. Many thresholds have been suggested. Adrenal insufficiency appears unlikely when a random serum cortisol level is above 34 μg/dL and likely when a random serum cortisol is below 15 μg/dL or the increase in response to corticotropin is less than 9 μg/dL (7, 11).

Schultz et al. (16) demonstrated that basal cortisol levels before and just after CPR did not discriminate between groups with or without recovery of spontaneous circulation. Of 205 patients who received cardiopulmonary resuscitation, 44 achieved a stable return to spontaneous circulation. However, an initial serum cortisol concentration below 30 μg/dL was associated with 100% mortality within 24 h, suggesting hemodynamic instability. Overall, there were only two survivors without neurologic dysfunction. In our study, we also found lower cortisol values in the group that died of early refractory shock than in the group that died later from neurologic dysfunction. Catecholamines and cortisol act synergistically to augment vascular tone. Inadequate circulating cortisol concentrations may compromise the effectiveness of endogenous or exogenous epinephrine, thus contributing to the occurrence of early refractory shock in patients with low cortisol levels. We also observed a trend toward lower serum cortisol levels in survivors than in nonsurvivors. However, because of the small number of survivors ($n = 4$), no definite conclusion can be drawn from this finding. Survivors are probably exposed to lower level of stress than nonsurvivors and, therefore, may have had cortisol levels appropriate for their needs. This may be explained by the cytokine levels in these patients, which are known to be related to the initial stress: the increase was higher in the nonsurvivors than in the survivors, and among the nonsurvivors, cytokines levels were higher in those who required vasopressors that in the hemodynamically more stable group. Conceivably, a small to moderate increase in plasma cytokine levels may adequately stimulate adrenal synthesis as observed in survivors and nonsurvivors without early refractory shock. A larger increase, as seen in the patients with early refractory shock, may inhibit cortisol synthesis, explaining the lower and inadequate levels of plasma cortisol observed in these patients (3, 20).

However, the response to corticotropin was not associated in our study with the usual markers of disease severity or the cause of death (early refractory shock or neurologic dysfunction). Hypothermia was used in our ICU starting in November 2002 and seemed to have no effect on cortisol levels under basal conditions or after the corticotrophin test. However, given the limited number of patients, we cannot exclude an effect of hypothermia on basal cortisol levels or the response to corticotropin. In 1955, Ganong et al. (24) showed that hypo-

thermia in a canine model decreased the 17-hydroxycorticosteroid output from the adrenal vein and inhibited the effect of a corticotropin bolus. In keeping with this finding, in humans with accidental hypothermia (mean core temperature of 32°C), the adrenal response to corticotropin was decreased or absent (25).

The difference between baseline cortisol levels between patients who died of early refractory shock and those who died of neurologic dysfunction may have important consequences because Laurent et al. (4) showed that hemodynamic instability, a common problem between 6 and 24 h after resuscitation, was not predictive of the neurologic outcome. This suggests that cortisol replacement therapy may help some patients recover from early refractory shock and perhaps also achieve a good neurologic recovery.

Our study has several limitations. The small sample size ($n = 33$) and very high mortality rate (88%) does not allow us to provide a reliable interpretation regarding mortality. The optimal timing for performing the corticotropin test is not known. Thresholds and criteria for adrenal insufficiency have been defined for patients with septic shock, but may not be applicable to patients with postresuscitation disease, most notably those treated with hypothermia.

In conclusion, adrenal insufficiency as assessed by corticotropin test is common after cardiac arrest, the rate of occurrence being similar to that in septic shock, but is not associated with severity. The lower cortisol levels in patients with early refractory shock suggest relative adrenal insufficiency. Definitions of adrenal dysfunction in postresuscitation disease need to be developed in larger studies.

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