Adrenal Dysfunction in Hemodynamically Unstable Patients in the Emergency Department

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Abstract. **Objective:** Adrenal failure, a treatable condition, can have catastrophic consequences if unrecognized in critically ill ED patients. The authors' objective was to prospectively study adrenal function in a case series of hemodynamically unstable (high-risk) patients from a large, urban ED over a 12-month period. **Methods:** In a prospective manner, critically ill adult patients presenting to the ED were enrolled when presenting with a mean arterial blood pressure ≤60 mm Hg requiring vasopressor therapy for more than one hour after receiving fluid resuscitation (central venous pressure of 12–15 mm Hg or a minimum of 40 mL/kg of crystalloid). Patients were excluded if presenting with hemorrhage, trauma, or AIDS, or if steroids were used within the previous six months. An adrenocorticotropic hormone (ACTH) stimulation test was performed and serum cortisol was measured. Treatment for adrenal insufficiency was not instituted. **Results:** A total of 57 consecutive patients were studied. Of these, eight (14%) had baseline serum cortisol concentrations of <20 μg/dL (<552 nmol/L), which was considered adrenal insufficiency (AI). Three additional patients (5%) had subnormal 60-minute post-ACTH-stimulation cortisol responses (<30 μg/dL) and a delta cortisol ≤9 μg/dL, which is the difference between the baseline and 60-minute levels. This is functional hypoadrenalism (FH). There were no laboratory abnormalities that distinguished patients with AI or FH from those with preserved adrenal function (PAF). Rates of survival to discharge did not differ between the AI group (7 of 8) and PAF patients (21 of 46; p = 0.052). **Conclusions:** Adrenal dysfunction is common in high-risk ED patients. Overall, it has a frequency of 19% among a homogeneous population of hemodynamically unstable vasopressor-dependent patients. The effect of physiologic glucocorticoid replacement in this setting remains to be determined. **Key words:** adrenal insufficiency; adrenal dysfunction; hypotension; shock; emergency; functional hypoadrenalism; adrenal crisis; hypoadrenalism. ACADEMIC EMERGENCY MEDICINE 1999; 6:626–630

CORTISOL is a major stress response hormone that has metabolic, catabolic, anti-inflammatory, and vasoactive properties on cardiac muscle and the peripheral vasculature. Cortisol mediates maintenance of peripheral vasomotor tone by facilitating catecholamine-induced vasoconstriction and it has a permissive effect on synthesis of catecholamines and vasoactive peptides.[1,2] In addition, cortisol has inotropic effects[3] and acutely influences fluid distribution, favoring accumulation in the vascular compartment.[3]

In response to external or internal stress, the neuronally stimulated release of corticotropin-releasing factor from the hypothalamus induces an increase in adrenocorticotropic hormone (ACTH) secretion by the anterior pituitary gland. This response overrides the normal diurnal pattern of secretion. The adrenal cortex responds to ACTH by increasing cortisol secretion. Prolonged elevation of serum cortisol triggers a negative feedback inhibition loop that results in subsequent decreases in ACTH and cortisol release.[4]

Patients with normal hypothalamic–pituitary–adrenal (HPA) axis function are consistently found to have elevated circulating cortisol concentrations during periods of stress or serious illness.[5–8] Numerous studies of HPA axis function in seriously ill patients have shown that total serum cortisol is increased, from two to ten times the upper limit of normal.[9–12] While the general incidence of overt adrenal insufficiency is extremely low,[13] occult or un-

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recognized adrenal dysfunction (AD) has a high prevalence among seriously ill patients.[14,15]

The purpose of this study was to examine the incidence of adrenal hypofunction in hemodynamically unstable (high-risk) patients presenting directly to the ED.

METHODS

Study Design. This was a prospective evaluation of adrenal function in critically ill hypotension ED patients. This study was approved by the Henry Ford Hospital Institutional Review Board (IRB) for Human Research in 1994, with waiver of consent. The committee believed that the clinical indication for assessing adrenal function in critically ill patients was no inordinate risk, but rather, a standard of care, although it had been understudied in this environment. Furthermore, cortisol levels were available to treating clinicians to guide subsequent patient management. The project was not begun until 1995 because of funding issues. The IRB renewed approval in 1995.

Study Setting and Population. For a 12-month period (October 1, 1995, to October 1, 1996), adult patients presenting in shock to the ED who required vasopressor therapy after adequate fluid resuscitation were entered into the study. Hypotension or shock was defined as mean arterial blood pressure $\leq$ 60 mm Hg. Adequate fluid resuscitation was defined as a central venous pressure (CVP) of 12–15 mm Hg or consisting of a minimum replacement of 40 mL/kg of volume resuscitation. Patients were excluded if they reported steroid use within six months, hemorrhage, trauma, or AIDS.

Study Protocol. The patients were managed solely by the emergency physicians. After baseline laboratory tests were obtained, the ACTH stimulation test was performed. Baseline cortisol and ACTH levels were obtained and synthetic ACTH 0.25 mg (Cortrosyn, Organon, NJ) was administered IV over 2 minutes; subsequent cortisol levels were obtained at 30 and 60 minutes postinjection.

In normal subjects, cortisol concentrations range from 5 to 20 μg/dL (138 to 552 nmol/L), being higher at 7 to 9 AM; plasma ACTH has a normal range from 10 to 130 pg/mL (2 to 29 pmol/L). The response to ACTH stimulation in healthy subjects is defined as an increase of 50% or more in serum cortisol concentration, or of at least 9 μg/dL, by 60 minutes posts-ACTH injection of cosyntropin. However, in critically ill patients, adrenal dysfunction has been defined as the presence of random serum cortisol <20 μg/dL (<552 nmol/L).[16–21] An additional category, functional hypoadrenalism (FH), has been defined as the combination of random serum cortisol $\geq$20 μg/dL, and a serum cortisol level at 60 minutes post-ACTH stimulation of <30 μg/dL or delta cortisol (60-minute level minus baseline) of $\leq$9 μg/dL.[22–25]

Blood for cortisol measurement was collected in glass tubes; the serum was separated and stored at −20°C until assayed. A commercial radioimmunoassay (RIA) kit was used for the quantitative measurement of cortisol in serum (Amerlex Cortisol RIA Kit, Amersham, Arlington Heights, IL). Blood for ACTH measurement was collected in siliconized glass ethylenediamine tetraacetic acid (EDTA) tubes. The plasma was separated and transferred into polypropylene tubes and frozen for storage within 15 minutes, and stored at −70°C until assayed. A commercially available immunoassay was used for the quantitative determination of ACTH in plasma (Allegro HS-ACTH, Nichols Institute, San Juan Capistrano, CA).

Data Analysis. All results are reported as the mean and the standard deviation. Analysis of variance (ANOVA) was used with Tukey's method of multiple comparisons. The Kruskal-Wallis test and the Wilcoxon nonparametric test were used to identify differences in the ranks of data between the three groups studied. Statistical significance was defined by a p-value less than 0.05 and an alpha-level of 0.017.

RESULTS

A total of 68 consecutive patients were originally enrolled: 11 of them were subsequently excluded because they did not meet the inclusion criteria. Of the 57 patients, eight (14%) had a baseline cortisol less than 20 μg/dL and these patients were therefore classified as adrenal insufficient (AI). Of the 49 patients with a baseline cortisol of $\geq$20 μg/dL, an additional group of three patients (5%) had a post-ACTH cortisol level <30 μg/dL, demonstrat-

TABLE 1. Serum Cortisol Concentrations and Adrenocorticotropic Hormone (ACTH) Stimulation Test

Adrenal Functional Status	*n* (%)	Serum Cortisol (μg/dL) ± SD		
		Baseline	60 Min	Delta
Adrenal insufficiency	8 (14%)	16.0 ± 3.9	34.4 ± 10.2	17.3 ± 10.7
Functional hypoadrenalism	3 (5%)	24.8 ± 4.2	27.6 ± 1.5	2.80 ± 3.4
Preserved adrenal function	46 (81%)	68.8 ± 63.4	76.7 ± 55.5	9.4 ± 18.3

TABLE 2. Baseline Adrenocorticotropic Hormone (ACTH) Concentrations (pg/mL) ± SD

Adrenal Functional Status*	*n*	ACTH (pg/mL)†
AI	4	13 ± 10
FH	1	205
PAF	38	99 ± 120

*AI = adrenal insufficiency; FH = functional hypoadrenalism; PAF = preserved adrenal function.
†Normal range for ACTH in nonstressed healthy subjects is 10–130 pg/mL.

ing functional hypoadrenalism (FH). The remaining 46 patients had a baseline cortisol of >20 μg/dL and a post-ACTH level of >9 μg/dL, thus demonstrating preserved adrenal function (PAF) in response to critical illness. These results are listed in Table 1. ACTH concentrations were determined for 43 of 57 patients and the results are listed in Table 2. In the AI and PAF patients, the mean ACTH levels were 13.5 and 99.5 pg/mL, respectively. In the patient with FH, plasma ACTH was 205 pg/mL (Table 2).

There was no difference in gender distribution between AI and PAF, while all three patients with FH were male. In addition, the group with PAF was slightly but significantly older than the AI group ($p < 0.004$; Table 3). There was no significant difference between groups in vital signs (Table 4) or in baseline laboratory test values (Table 5). Survival data showed a high mortality overall (51%, Table 6). There was no significant difference in mortality between the AI and PAF patients ($p = 0.052$).

DISCUSSION

Adrenal insufficiency occurs with a high incidence in the critically ill patient population. In both medical and surgical critical care units, the respective incidences of AI are markedly increased, ranging from <0.01% to 20%[5,26] and <2% to 27%,[19] respectively; whereas the incidence in the general population is approximately 0.005%.[13]

Laboratory tests allow further categorization of AD in the setting of critical illness. First, the classically described AI marked by persistent subnormal cortisol production from the adrenal gland; and second, the entity of FH, which manifests during stressful conditions with inadequate cortisol production (although within the normal or at the upper limit for the unstressed state). Thus, patients with FH are characterized by inability to respond with cortisol increases that would be appropriate for the clinical setting. In general, critically ill patients do respond with appropriate elevation in response to ACTH stimulation despite increased basal cortisol levels.[5,6,11] Furthermore, patients with serum cortisol levels much higher than normal may still respond to steroid replacement therapy with improved survival.[6,15] Therefore, patients with severe illnesses who are unable to attain supranormal cortisol levels are thought to be at higher risk for the development of complications.[25] In fact, it has been suggested that relative AI may be a contributing factor in poor outcomes in the setting of severe illness.[5,12,15,24,25]

The clinical presentation of the "high-risk" AI is one who has been adequately fluid resuscitated with persistent hypotension often necessitating vasopressors for hemodynamic support.[27] Besides hypotension and decreased cardiac output, some patients with AI may present with a septic appearance (high-output circulatory failure, fever, and mental status changes), although they are abacteremic.[3,7,15,18] Adding further complexity is the absence of laboratory abnormalities and physical findings that are characteristic of adrenal failure (i.e., hyponatremia, hyperkalemia, and cutaneous hyperpigmentation) in the early course of these critically ill patients.[3,5,7,15,28] There is therefore a need for early recognition of hypotensive patients who may be experiencing AI, as it is relatively easy to diagnose and treat while a potential cause of mortality.[12]

A large proportion of patients experiencing extreme hypotension or acute shock syndrome, present initially to the ED. Cortisol is needed for effective endogenous catecholamine pressor action; we hypothesized that a subset of patients who are in shock and require vasopressor support may have occult adrenal failure not previously identified. That was indeed the case in 14% of our patients.

Our study also found a small group of patients with FH, who had adequate initial cortisol levels, subnormal response to ACTH, and a mortality rate of 66% (2 of 3). Rothwell et al.,[25] who evaluated a group of 32 patients in septic shock and adequate

TABLE 3. Demographics

Adrenal Functional Status	*n*	Gender		Age (Years) ± SD
		Female	Male	
Adrenal insufficiency	8	3 (38%)	5 (62%)	55 ± 4
Functional hypoadrenalism	3	0 (0%)	3 (100%)	68 ± 15
Preserved adrenal function	46	25 (54%)	21 (46%)	72 ± 12

TABLE 4. Vital Signs: Mean ± SD

Adrenal Functional Status	Temperature (°C)	Heart Rate (Beats/Min)	Blood Pressure (mm Hg)		
			Systolic	Diastolic	MAP*
Adrenal insufficiency	36.5 ± 2.1	107 ± 25	76 ± 11	43 ± 19	54 ± 16
Functional hypoadrenalism	35.8 ± 2.0	83 ± 38	70 ± 17	30 ± 26	43 ± 22
Preserved adrenal function	35.6 ± 2.9	101 ± 27	78 ± 21	37 ± 20	51 ± 19
p-value	—	0.404	0.811	0.608	0.701

*MAP = mean arterial pressure.

TABLE 5. Baseline Laboratory Tests: Mean ± SD

Laboratory Test	Adrenal Functional Status*			p-value
	AI	FH	PAF	
Sodium (mEq/L)	135 ± 6	141 ± 12	142 ± 10	0.254
Potassium (mEq/L)	4.6 ± 1.2	3.3 ± 0.7	4.6 ± 1.4	0.27
Bicarbonate (mmol/L)	15 ± 6	16 ± 11	18 ± 8	0.69
Glucose (mg/dL)	194 ± 224	127 ± 69	206 ± 272	0.384
Calcium (mg/dL)	8.1 ± 1.5	7.8 ± 1.3	8.5 ± 1.0	0.533
Magnesium (mg/dL)	1.6 ± 0.3	1.3 ± 0.3	2.1 ± 0.8	0.047
BUN (mg/dL)	47 ± 38	50 ± 47	52 ± 40	0.949
Creatinine (mg/dL)	2.8 ± 2	3.8 ± 2.4	2.5 ± 1.5	0.408
Hemoglobin (g/dL)	10.7 ± 3.1	11.2 ± 5.8	11.8 ± 3.3	0.681
WBC count (thousand/mm^3)	8.2 ± 2.9	4.9 ± 0.3	13.3 ± 5.9	—
Eosinophils (no./mm^3)	0.60 ± 1.34	0	0.38 ± 1.39	—
Lactate (mM/L)	2.4 ± 2.3	7.5 ± 5.4	5.6 ± 4.6	0.14
pH (units)	7.25 ± 0.19	7.16 ± 0.42	7.3 ± 0.22	0.563

*AI = adrenal insufficiency; FH = functional hypoadrenalism; PAF = preserved adrenal function.

basal cortisol concentrations, found that 13 had a defective response to ACTH stimulation and fatal outcome (100%). By comparison, of the 19 remaining patients with normal ACTH responses, only six (32%) died. Moran et al.[24] also noted a positive correlation between decreased response to the ACTH stimulation and increased mortality; moreover, patients had a low probability of responsiveness to ACTH within the 24 hours preceding their deaths. Nevertheless, several studies have reported a high mortality associated with high cortisol levels thought to be a function of the underlying severe illness.[5,6,10,11,20,24] In this study, mortality rate was also extremely high among the patients with PAF. In a recent study of cortisol kinetics during and after cardiopulmonary arrest in the ED, it was noted that failure to attain a cortisol level of at least 30 μg/dL was associated with 100% mortality at 24 hours.[28]

The pathogenesis of AD in this setting continues to evolve. Plasma ACTH levels, which were at the low end of normal in the AI group, may reflect hypothalamic–pituitary axis suppression. The elevated levels in the patient with FH may, however, represent true adrenal failure. The pathogenesis of AD in the setting of shock may include decreased adrenal blood flow leading to primary adrenal failure. Inflammatory mediators may also cause primary adrenal failure through impairing cortisol receptors in the adrenal gland. These mediators have also been shown to decrease corticotropin-releasing hormone secretion leading to hypothalamic–pituitary axis suppression or secondary adrenal dysfunction.[24,29,30] AD associated with septic shock has been described as transient,[30] with recovery occurring after resolution of the inflammatory insult.[31]

LIMITATION AND FUTURE QUESTIONS

A limitation in this study is the inability to precisely define and control for the duration of hypotension before presentation to the ED, although our sample size is comparable to other investigations of adrenal function in the critically ill. We also did not control for those patients who subse-

TABLE 6. Outcome

Adrenal Functional Status*	*n*	No. Surviving to Discharge (%)
AI	8	7 (86%)
FH	3	1 (33%)
PAF	46	21 (46%)
TOTAL	57	29 (51%)

*AI = adrenal insufficiency; FH = functional hypoadrenalism; PAF = preserved adrenal function.

quently received replacement glucocorticoids in the intensive care unit. Outcome-based evidence for treatment recommendations cannot be made because of the study design, however, hemodynamic improvement and decreased vasopressor requirements have been reported with physiologic replacement doses of glucocorticoids.[30,32,33]

CONCLUSION

Nineteen percent of the hemodynamically unstable patients who still require vasopressor therapy after adequate volume resuscitation have adrenal insufficiency (adrenal dysfunction). This result is consistent with the findings in similar populations of high-risk intensive care unit patients. The effect of diagnostic and therapeutic interventions on outcome remains to be determined.

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