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A preliminary investigation into adrenal responsiveness and outcomes in patients with cardiogenic shock after acute myocardial infarction

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ABSTRACT

Purpose: This study investigated the significance of baseline cortisol levels and adrenal response to corticotropin in shocked patients after acute myocardial infarction (AMI).
Methods: A short corticotropin stimulation test was performed in 35 patients with cardiogenic shock after AMI by intravenously injecting of 250 μg of tetracosactrin (Synacthen). Blood samples were obtained at baseline (T0) before and at 30 (T30) and 60 (T60) minutes after the test to determine plasma total cortisol (TC) and free cortisol concentrations. The main outcome measure was in-hospital mortality and its association with T0 TC and maximum response to corticotropin (maximum difference [Δ max] in cortisol levels between T0 and the highest value between T30 and T60).
Results: The in-hospital mortality was 37%, and the median time to death was 4 days (interquartile range, 3-9 days). There was some evidence of an increased mortality in patients with T0 TC concentrations greater than 34 μg/dL ($P = .07$). Maximum difference by itself was not an independent predictor of death. Patients with a T0 TC 34 μg/dL or less and Δ max greater than 9 μg/dL appeared to have the most favorable survival (91%) when compared with the other 2 groups: T0 34 μg/dL or less and Δ max 9 μg/dL or less or T0 34 μg/dL or higher and Δ max greater than 9 μg/dL (75%; $P = .8$) and T0 greater than 34 μg/dL and Δ max 9 μg/dL or less (60%; $P = .02$). Corticosteroid therapy was associated with an increased mortality ($P = .03$). There was a strong correlation between plasma TC and free cortisol ($r = 0.85$).
Conclusions: A high baseline plasma TC was associated with a trend toward increased mortality in patients with cardiogenic shock post-AMI. Patients with lower baseline TC, but with an inducible adrenal response, appeared to have a survival benefit. A prognostic system based on basal TC and Δ max similar to that described in septic shock appears feasible in this cohort. Corticosteroid therapy was associated with adverse outcomes. These findings require further validation in larger studies.

1. Introduction

The activation of the hypothalamic-pituitary-adrenal axis during critical illness results in an enhanced adrenal cortical secretory activity [1]. Cortisol levels are increased in critically ill patients [2], with higher values being reported in patients with the greater severity of illness [3]. Despite demonstrable high circulating cortisol levels (normal defined as >20 μg/dL [4]), patients with critical illness have been reported to have a relative adrenal insufficiency (RAI) [2,5], which is defined as a less than 9 μg/dL absolute increment in cortisol concentrations after a short corticotropin stimulation test [6]. A high baseline cortisol and a suboptimal adrenal response to corticotropin stimulation are associated with increased mortality and have been proposed as prognostic markers for patients with septic shock [7-9].

Although absolute adrenal insufficiency is rare in critically ill patients, debate continues as to the prevalence of RAI [10,11]. Some investigators have suggested rates as high as 50% in patients with septic shock [12,13]. As a result, low-dose steroids have also been attempted in patients with septic shock with variable benefit [14]. Despite the physiological rationale, the potential benefits of corticosteroid therapy in this setting remain controversial [15].

Despite a plethora of work on RAI and steroid therapy in septic shock [16], data pertaining to possible RAI in patients with cardiogenic shock after acute myocardial infarction (AMI) are limited to sporadic case reports [17-19]. The most common etiology of cardiogenic shock is an AMI and occurs in approximately 6% of patients [20]. Despite an increase in timely reperfusion strategies and overall medical management practices, hospital mortality rates for these patients remain

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high, ranging from 48% to 74% [21,22]. This has resulted in a paradigm shift in the approach to cardiogenic shock. There has been an interest in other complicating factors such as systemic inflammatory response, cytokine release, compliment activation, and increased inducible nitric oxide synthase expression, which may lead to inappropriate vasodilatation and affect survival [21]. Similar pathways are activated in septic shock, and RAI in these patients has been shown to reduce vasopressor responsiveness to noradrenaline [23] and may adversely affect survival [8]. In this context, the role of RAI and potential for corticosteroid therapy in patients with cardiogenic shock merit further investigation.

The primary aim of this pilot study was to investigate the association, if any, between baseline (T0) total cortisol (TC), maximum difference (Δ max) in TC levels between T0 and the highest value between the levels at 30 (T30) or 60 minutes (T60), and hospital mortality in patients with cardiogenic shock after revascularization for AMI. Total cortisol cut-off values similar to those used for prognostication of patients with septic shock [7] (T0 >34 or ≤34 μg/dL and Δ max >9 or ≤9 μg/dL) were tested. In addition, the utility of free cortisol (FC) measurements in predicting mortality was also explored.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Ethics approval was obtained from the local ethics committee (EC2847). After informed consent from patients or their appropriate surrogate decision makers, 35 consecutive patients admitted to intensive care unit (ICU) with cardiogenic shock between September 2008 and December 2010 were enrolled for this study.

Adult patients older than 18 years presenting with cardiogenic shock after AMI were included. *Cardiogenic shock* was defined as [24] persistent hypotension (systolic blood pressure <90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline for at least 30 minutes), low cardiac index (<1.8 L/min per square meter without support or <2.0-2.2 L/min per square meter with support, estimated by echocardiography) manifesting as clinical signs of hypoperfusion including decreased urine output, altered mental status, and peripheral vasoconstriction. Echocardiography was used in all patients as a primary tool for assessment of biventricular function, stroke volume, and left ventricular ejection fraction (LVEF) and for confirmation of elevation of left ventricular filling pressures [24]. Patients were excluded if they were pregnant or had congenital heart disease, septal defects, hypertrophic cardiomyopathy, myocarditis, suspected sepsis, or receiving exogenous steroids before corticotropin testing. Corticosteroid treatment at any time point after the measurement of test parameters was at the discretion of treating clinicians, and they had no access to results.

2.2. Cortisol assays

After baseline (T0) blood sampling (2 mL) for adrenocorticotropic hormone, plasma TC, and FC estimation on ICU admission, a short corticotropin stimulation test was performed by injecting 250 μg of tetracosactrin (Synacthen) intravenously. Blood samples (2 mL) were also obtained at 30 (T30) and 60 minutes (T60) of injection to evaluate the maximal adrenal response to exogenous stimulation. All samples were collected in a lithium-heparin tube and were sent to the laboratory for analysis.

Plasma TC concentrations were measured by a paramagnetic particle, chemiluminescent immunoassay using Access Immunoassay systems (DxI 800 immunoanalyser; Beckman Coulter, Brea, CA). Plasma FC was measured by a sensitive liquid chromatography–tandem mass spectrometry assay coupled with ultrafiltration. Liquid chromatography–tandem mass spectrometry assay avoids the cross-reactivity problem between cortisol and other steroids when using an immunoassay. It also provides better selectivity and sensitivity than high-performance liquid chromatography–ultraviolet absorbance detection for measuring a low level of cortisol in biological matrices. The plasma was ultrafiltrated under strict temperature control conditions. The ultrafiltrate was then extracted using solid phase extraction columns and the purified extract run on ultra performance liquid chromatography–tandem mass spectrometry assay [25].

2.3. Data collection

Data pertaining to patient demographics and physiology including hemodynamic parameters, inotropes and vasopressor use, fluid balance in first 24 hours, severity of illness scores, and laboratory data were collected prospectively.

2.4. Statistical analysis

Demographics and clinical differences between study groups were assessed using a χ^2 test, Fisher exact test, the Student *t* test, or Kruskal-Wallis rank sum test, as appropriate. $P < .05$ was considered to be statistically significant. We used a paired *t* test examining differences in cortisol levels within patients over time, and an unpaired *t* test when examining differences in cortisol levels between patients who lived and died. Fisher exact test was used for the association between the threshold cortisol levels and whether the patient lived or died. For variables found to be statistically significant

Table 1
Baseline characteristics, severity of illness scores, and physiologic and cortisol data in survivors and nonsurvivors

	Survivors (n = 22)	Nonsurvivors (n = 8)	*P*
	Median (IQR)	Median (IQR)	
Age (y)	66 (54.5-73)	67 (64-70)	.85
Sex (male)	12 (55%)	8 (62%)	.68[a]
Body mass index	27.7 (23.2-30.7)	27 (23.7-33.1)	.60
LVEF (%)	30 (27.8-44.5)	31.5 (25.0-41.3)	.15
Troponin I (peak, ng/mL)	13 (0.2-98)	95 (7.1-98)	.60
Heart rate (beats per minute)	90 (86.3-109)	90 (80-112)	.96
APACHE III	74 (63.3-92.3)	95 (83-105)	.04[b]
SOFA day 1	8.5 (7-11)	9 (7-11)	.08
SOFA day 2	7.5 (7-10.5)	10 (8-12)	.78
Mean arterial blood pressure (mm Hg)	65 (60-70)	65 (60-70)	.77
Pao_2/Fio_2 ratio	274 (154.8-306.5)	161 (89.5-334)	.91
White cell count ($\times 10^9$/L)	14.9 (11.9-19.8)	16.9 (11.6-21.8)	.92
Platelets ($\times 10^9$/L)	206 (152-240)	240 (188-337)	.13
Serum creatinine (μmol/L)	120.0 (99.5-163.5)	134 (108-208)	.06
Arterial pH	7.3 (7.3-7.4)	7.2 (7.2-7.3)	.08
Arterial lactate (mmol/L)	3.8 (2.5-5.1)	7 (4-9.3)	.14
Albumin (g/L)	34.5 (32-36)	31 (28-32)	.21
Dopamine dose (μg/kg/min)	5 (2.5-7.5)	5 (5-10)	.47
Adrenaline dose (μg/kg/min)	0 (0-0.1)	0.1 (0-0.2)	.12
Dobutamine dose (μg/kg/min)	0 (0-3.8)	0 (0-5)	.75
Noradrenaline dose (μg/kg/min)	0 (0-0.1)	0.1 (0.1-0.2)	.08
Fluid balance first 24 h (mL)	541 (−571-1666)	1888 (1213-2182)	.01[b]
Steroid replacement, n (%)	1 (5%)	5 (62%)	.01[a,b]
Adrenal response			
ACTH baseline (ng/L)	24 (14-79)	63 (18-100)	.82
TC baseline (μg/dL)	31.1 (25.0-38.5)	55.1 (46.7-72)	.01[b]
TC 30-min post-SST (μg/dL)	42.8 (31.3-47.8)	67.3 (59.4-75.6)	.02[b]
TC 60-min post-SST (μg/dL)	45.1 (33.2-52.7)	69.8 (60.1-73.8)	.07
Δ max (TC)	11.9 (6.5-15.7)	9.6 (3.6-19.1)	.77
FC baseline (μg/dL)	3.5 (2.5-5.3)	8.4 (5.8-10.3)	.01[b]
FC 30-min post-SST (μg/dL)	5.2 (2.9-7.2)	8.3 (7.1-11.2)	.07
FC 60-min post-SST (μg/dL)	5.8 (3.5-9.5)	9 (7.3-10.4)	.05

Fio_2 indicates fractional inspired oxygen concentration; SOFA, Sequential Organ Failure Assessment; ACTH, adrenocorticotropic hormone; SST, short Synacthen test.
[a] Fisher exact test used.
[b] Statistically significant differences.