Adrenal insufficiency in acute coronary syndrome

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ABSTRACT

Introduction: Acute coronary syndrome (ACS) is an acute stressful condition which stimulates the hypothalamus-pituitary-adrenal axis that regulates neurovascular and hormonal responses. Functional hypoadrenalism has been shown to be associated with significant morbidity and mortality in the critically-ill patient, but there is to date, no known study done to determine its prevalence in patients with ACS.

Methods: 37 patients who fulfilled the diagnostic criteria of ACS were subjected to the low-dose (1 µg) ACTH stimulation test (LDT), followed by a standard-dose (250 µg) ACTH stimulation test (SDT) two hours later.

Results: 14 (37.8 percent) patients had ST acute myocardial infarction, eight (21.6 percent) patients had non-ST elevation myocardial infarction, and 15 (40.5 percent) patients had unstable angina. Based on an increment of less than 250 nmol/L post-SDT, no patient had adrenal insufficiency. However, using a similar criteria with the LDT, eight (21.6 percent) patients had adrenal insufficiency. Four patients died during the study and they had very high cortisol levels. The diagnosis of adrenal insufficiency is not associated with any significant morbidity and mortality in our group of patients.

Conclusion: Utilising the LDT, adrenal insufficiency is present in 21.6 percent of patients admitted with ACS. However, this is not associated with any significant morbidity and mortality.

Keywords: ACTH stimulation test, acute coronary syndrome, adrenal insufficiency, cortisol

INTRODUCTION

The hypothalamus-pituitary-adrenal (HPA) axis response is a self-defensive mechanism to maintain cardiovascular and cellular homoeostasis or adapt to illness and stress.

Even a minor degree of adrenal insufficiency has been shown to be associated with mortality in critically ill patients. Circulating levels of glucocorticoids in patients who are critically-ill are often more than three times higher than those of healthy individuals.[1] This is not only due to an increased cortisol production by the activation of the HPA axis, but also due to a reduced hepatic degradation and feedback mechanism, corticosteroid-binding globulin activity and a loss of the normal diurnal pattern of secretion.[2-5] Another cause of cortisol elevation may be a shift in adrenal steroid synthesis, from androgens and mineralocorticoids to cortisol.[6,7] High levels of glucocorticoids during stress have negative effects on many organ systems and may impair the immune system, and affect protein, carbohydrate and fat metabolism, as well as myocardial functions.[8] Patients with critical illnesses would have an elevated serum cortisol concentration, which is positively correlated with the severity of the illness and negatively correlated with survival. The incidence of reported adrenal insufficiency in critical illness varies from 1% to 9%.[9]

Functional adrenal insufficiency or relative adrenal insufficiency is used to describe the subnormal production of corticosteroid during critical illness, in the absence of structural defects in the HPA axis. This is due to high levels of inflammatory cytokines, resulting in the direct inhibition of adrenal cortisol synthesis and mediating tissue-specific corticosteroid resistance.[10] Previous studies have shown that either a basal cortisol level of < 550, 690, 825 nmol/L or an incremental response of < 250 nmol/L after cosyntropin stimulation predicted a poor outcome, and identified patients who responded favourably to glucocorticoid administration.[11-13] Only one previous study reported on the prevalence of functional hypoadrenalism in acute myocardial infarction (AMI),[14] but none had occurred in the spectrum of acute coronary syndrome (ACS). Hence, this study was done to evaluate the prevalence of adrenal insufficiency in ACS patients and to correlate its results with the inhospital mortality.

METHODS

This study was performed in the coronary care unit of our institution which is a tertiary centre, and it was approved by the institutional Ethics Committee and Research. All

the patients gave written informed consent prior to the onset of the study. 37 patients (25 male [67.6%] and 12 female [32.4%]) who fulfilled the criteria of ACS were recruited. Patients were excluded if they were on herbal medication or steroid treatment up to six months prior to the admission; had a history of hypothalamus-pituitary, adrenal or liver diseases (ALT ≥ twice normal upper limit), systemic inflammatory response syndrome (SIRS; temperature ≥ 38°C or ≤ 36°C, heart rate > 90 beats/min, respiratory rate ≥ 20 breaths/min, $PaCO_2$ ≤ 32 mmHg, white blood cell count ≥ 12,000/μL or ≤ 4,000/μL or > 10% immature forms) and cardiogenic shock (Killip IV); and were in an unconscious state or required inotropic support. AMI (ST elevation MI [STEMI]) was diagnosed according to the World Health Organization criteria.[15] Unstable angina (UA) was diagnosed based on the Braunwald classification and non-STEMI (NSTEMI) if they did not meet the AMI and UA criteria.[16]

On admission, a random serum cortisol level was obtained. All the subjects had a low-dose (1 μg) ACTH stimulation test (LDT) done, followed by a one-hour interval before having a standard dose (250 μg) ACTH stimulation test (SDT) done. A 23G branula was inserted and a baseline serum cortisol was obtained within 48 hours of admission. The baseline serum cortisol was drawn at zero min (0_{LD}), 1 μg ACTH was given intravenously and further serum cortisol levels were drawn at 30 min (30_{LD}) and 60 min (60_{LD}). Two hours after 0_{LD}, the SDT was started with the second baseline serum cortisol level drawn at 120 min (0_{SD}), followed by the administration of 250 μg ACTH intravenously. Three further serum cortisol levels were drawn at 150 min (30_{SD}), 180 min (60_{SD}) and 210 min (90_{SD}).

A 120-minute interval between the two doses of ACTH allowed cortisol levels to return to baseline levels before the second dose and permitted the two tests to be performed under as similar clinical circumstances as possible. The order of the tests was maintained throughout the study as the SDTs caused a more sustained rise in cortisol, which would have necessitated increasing the time interval between the two tests. For the LDT, a vial of 250 μg ACTH (Alliance Pharmaceuticals Ltd, Chippenham, UK) was diluted in normal saline solution to a concentration of 0.5 μg/mL and was used immediately.

The serum cortisol was immediately separated and stored at −20°C until it was assayed. The cortisol was measured using commercially-available chemiluminescent enzyme immunoassays (Immulite, Diagnostic Product Corp, Los Angeles, CA, USA). The quality control samples were 91–141 nmol/L for low level, 254–386 nmol/L for moderate level and 750–1,126 nmol/L for

Table I. Baseline demographical data.

| Demographics	No. (%) of patients
Mean age and standard deviation (year)	53.32 ± 10.90
Gender	
Female	12 (32.4)
Male	25 (67.6)
Acute coronary syndrome	
Acute myocardial infarction	14 (37.8)
Non-ST elevation myocardial infarction	8 (21.6)
Unstable angina	15 (40.5)

Table II. The prevalence of adrenal insufficiency by using various criteria.

| Criteria	No. (%) of patients
Baseline cortisol < 550 nmol/L	19 (51.4)
Low-dose ACTH stimulation test	
Peak cortisol (< 700 nmol/L)	7 (18.9)
Increment (< 250 nmol/L)	8 (21.6)
Standard-dose ACTH stimulation test	
Peak cortisol (< 938 nmol/L)	4 (10.8)
Increment (< 250 nmol/L)	0

high level. All of the eight cortisol samples from a single patient were analysed together in the same analysis. The cortisol samples from all 37 patients were assayed during a single-batch analysis to avoid inter-assay variation. The diagnosis of adrenal insufficiency was made using the following criteria: baseline cortisol levels of < 550 nmol/L; cortisol response following LDT, increment of cortisol < 250 nmol/L and peak cortisol < 700 nmol/L;[17] and following SDT, increment of cortisol < 250 nmol/L[18] and peak cortisol < 938 nmol/L.[12] Statistical analysis was performed using the Wilcoxon rank test for repeated measurements. The Mann-Whitney test was used to determine the significance between two groups (survival and non-survival) and for numerical variables. A p-value of < 0.05 was deemed to be of statistical significance.

RESULTS

The baseline demographical data of all the subjects are presented in Table I. 25 (67.6%) patients were male and 12 (32.4%) were female. The age range was 34–70 (mean and standard deviation 53.32 ± 10.90) years. 17 (45.9%) patients were Malay, 13 (35.1%) were Chinese, and the remaining seven patients (18.9%) were Indian. 14 (37.8%) had AMI, eight (21.6%) had NSTEMI, and 15 (40.5%) had UA. In this study, all of our AMI patients received thrombolysis as a mode of emergent reperfusion strategy. The prevalence of adrenal insufficiency was 51.4% (19 patients), if the baseline cortisol of < 550 nmol/L was taken. When the peak cortisol response to LD and SD
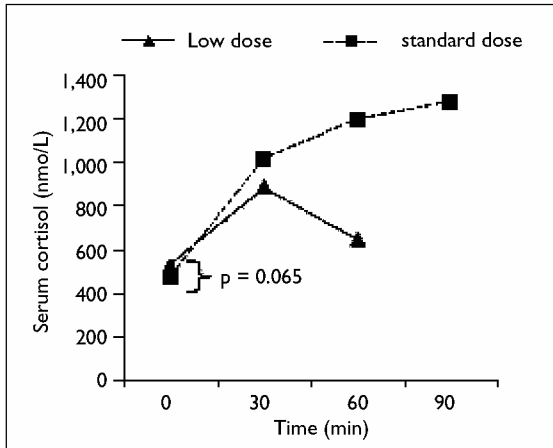
Fig. 1 Graph shows the comparison of low-dose and standard-dose ACTH stimulation tests in the study population.
There was no significant difference between the median serum cortisol level at 0LD and 0SD (p = 0.065), indicating that both tests were independent of each other. In contrast, the increments to ACTH were significant in both tests (p = 0.005).
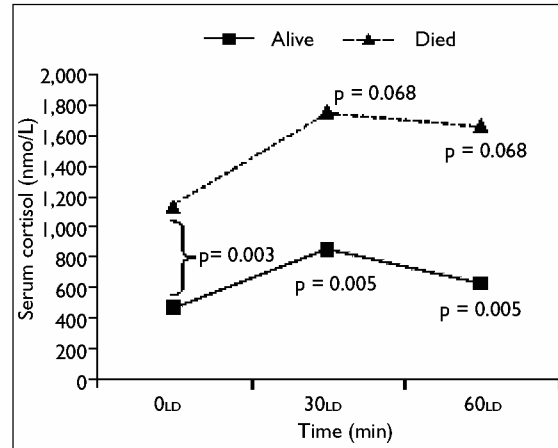
Fig. 2 Graph shows the comparison of cortisol response with the low-dose ACTH stimulation test in survivors and non-survivors. Non-survivors had a higher baseline serum cortisol which was increased further after 30 min post-ACTH stimulation, but the increment was not significant (p = 0.068). Survivors had lower baseline cortisol levels compared to non-survivors (p = 0.003).
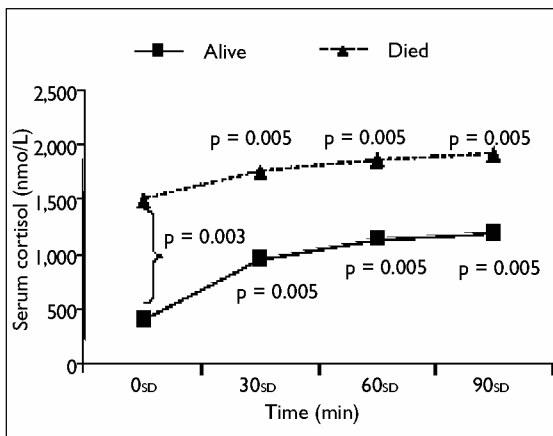
Fig. 3 Graph shows the comparison of cortisol response with the standard-dose ACTH stimulation test in survivors and non-survivors.
Survivors had lower baseline cortisol levels compared to non-survivors (p = 0.003).

were taken, 18.9% (seven patients) and 10.8% (four patients) prevalence were respectively noted. Upon taking an increment of cortisol of < 250 nmol/L, 21.6% (eight patients) and no patients were found to have adrenal insufficiency with LD and SD, respectively (Table II). There was no significant difference between the median serum cortisol levels of the 37 patients at 0LD and 0SD (p = 0.065), indicating that the serum cortisol had returned to the baseline levels before the SDT started (Fig. 1). There was significant correlation between serum cortisol at baseline and brain natriuretic peptide (BNP) (p = 0.046).

There were four mortalities within seven days of their coronary events. Three of them had NSTEMI and one had extensive MI. Two of these patients had underlying diabetes mellitus. There was no significant increment of serum cortisol at 30 min (p = 0.068) and 60 min (p

= 0.068) from the baseline in non-survivors using LDT (Fig. 2). Non-survivors were found to have significantly higher baseline cortisol (median cortisol 1,217.60 nmol/L, interquartile range [IQR] 853.0–1,631.73), compared to the survivor group (median cortisol 474.00 nmol/L, IQR 361.50–592.50) (p = 0.003) (Figs. 2 & 3). The BNP level was significantly higher in the non-survivor group (median BNP 4.12 vs. 0.24 pg/ml; p = 0.045). There were no significant correlations between mortality and the left ventricular fraction, creatine kinase (CK), CK-myocardial band (MB) fraction, troponin T or T peak levels in the MI group. There was also no significant difference between the Killip classification and mortality (p = 0.63).

DISCUSSION

The objective of this study was to determine the prevalence of adrenal insufficiency by using LDT and SDT in patients with ACS. The higher prevalence of males with ACS has been reported in numerous other studies. There were various criteria used to diagnose adrenal insufficiency in previous studies. However, those studies were conducted in severely-ill patients, and none has been done on ACS patients so far. In this respect, the cut-off cortisol level which indicates adrenal insufficiency in severely-ill patients is still debatable. The proposed random levels ranged from 276 nmol/L to 938 nmol/L, but several studies have suggested that a threshold of 414 nmol/L best identifies persons with clinical features of corticosteroid insufficiency or who would benefit from corticosteroid replacement.[12]

Barquist and Kirton considered a baseline cortisol level of < 414 nmol/L in critically-ill patients to indicate adrenal insufficiency, regardless of the stimulated cortisol

levels. In this study, patients with a baseline cortisol level of between 414 nmol/L and 550 nmol/L and a response of < 690 nmol/L after 30 min of ACTH stimulation were considered as having adrenal insufficiency.[19] However, Oelkers[20] and Grinspoon and Biller[21] recommended that a basal level of 500 nmol/L or a post-corticotropin stimulation plasma cortisol level of ≥ 500 nmol/L was adequate to rule out adrenal insufficiency. Bourne et al used a peak cortisol of < 700 nmol/L and an increment of < 250 nmol/L, using a LDT as the cut-off points, to diagnose adrenal insufficiency,[17] while Annane et al recommended that a lack of increment of 250 nmol/L suggested an inadequate response for the SDT.[18] To date, no similar study had been done to determine the cortisol level in ACS patients. As a result, we used the cortisol level in critically-ill patients to make a diagnosis of adrenal insufficiency. In comparing the various criteria used in our study, 51.4% of our patients had adrenal insufficiency (baseline cortisol level < 550 nmol/L). This figure was higher compared to Rivers et al's study, which found that 14% of critically-ill patients had functional adrenal insufficiency, using the same criteria.[22]

However, using the peak cortisol response (< 700 nmol/L with a low-dose and < 938 nmol/L with a standard-dose), we found that seven (18.9%) and four (10.8%) patients had adrenal insufficiency, respectively. Based on this result, we would have missed adrenal insufficiency in four patients with the SDT as compared to the LDT. These results were lower compared to a previous study by Bourne et al which reported a 39.4% prevalence of functional adrenal insufficiency.[17] Using the criteria of cortisol increment < 250 nmol/L post-corticotropin stimulation, eight (21.6%) of our patients had adrenal insufficiency with the LDT, but none with the SDT. All of these patients had a baseline cortisol level < 680 nmol/L. These results were much lower compared to that reported by Bourne et al, where the prevalence was 70.4%.[17] Their study involved 71 septic shock patients, and the LDT was used. In contrast, Rothwell et al found that 19% of their septic shock patients had functional adrenal insufficiency, using the SDT.[23] The reason for this discrepancy may be related to the differences in the study population, the background of medical problems and the small sample sizes. In this study, low-dose ACTH was used to diagnose adrenal insufficiency instead of the standard-dose ACTH, because the latter would have resulted in a false-negative result.

All the patients had the LDT, followed by the SDT with a two-hour interval between the two tests. The time interval between the tests was to allow the cortisol levels to return to the baseline prior to starting the second test

using a standard dose. There was no significant difference between the serum cortisol levels at 0 min with a low-dose and at 0 min of the standard dose (p = 0.10), which suggests that the two tests were performed independent of each other. Crowley et al observed that the maximum cortisol level response in a LDT was at 15 minutes in the majority of their normal subjects.[24] For the LDT in this study, blood levels were taken at 0, 30 and 60 min. All our patients attained the maximum response at 30 min. The study by Beale et al showed there was no significant difference between the serum cortisol at 0 and 60 min of a LDT.[25] However, in our patients, the serum cortisol were significantly higher at 30 and 60 min with the LDT (p = 0.005), indicating that the patients had responded to the ACTH given and that their values did not return to baseline even at 60 min. With the SDT, the increment of cortisol persisted even after 90 min, indicating a more prolonged response. This validated our approach of not beginning the test with the standard dose, as the prolonged response will definitely interfere with the results of the second test.

In this study, four (10.8%) patients with a high baseline cortisol level (> 1,217.6 nmol/L) and a small increment post-corticotropin stimulation, died within five days of their acute coronary event. These deaths were unexpected in three of them at the time of the cortisol sampling and ACTH stimulation tests. Two of them had recurrent NSTEMI, while the third succumbed to initial NSTEMI and extensive MI. Whether these findings can be used to further stratify ACS or AMI is still premature, as more numbers are needed to arrive at a firm conclusion. Currently, patients who had thrombolysis treatment are stratified according to the Thrombolysis In Myocardial Infarction trial (TIMI) guidelines. This will influence the need for a more aggressive intervention in the form of percutaneous coronary intervention or coronary artery bypass grafting. It is interesting to speculate whether the addition of random cortisol or cortisol response to the LDT could complement the treatment guidelines of TIMI. The patients who demonstrated adrenal insufficiency based on the LDT and SDT did not suffer any excess in morbidity and mortality despite the well-known associations in other critical illness studies. In conclusion, a high cortisol level above 1,217 nmol/L in patients with ACS on admission tends to be associated with an inhospital mortality. The prevalence of adrenal insufficiency in our cohort of ACS varied, depending on the criteria used – using a baseline cortisol level below 550 nmol/L gave the highest prevalence of 51.4%, while an increment of 250 nmol/L on a LDT gave a value of 21.6%. Peak cortisol during the LDT and SDT gave a prevalence of 18.9% and 10.8%, respectively.

ACKNOWLEDGEMENTS

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