Assessing adrenal status in patients before and immediately after coronary artery bypass graft surgery

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Short Title: Investigation of the HPA axis during CABG

Words: 4143
Abstract

Objective: Patients with cortisol deficiency tolerate poorly any Systemic Inflammatory Response Syndrome (SIRS), and may die if not treated with sufficient exogenous glucocorticoids. Controversy surrounds what constitutes a ‘normal’ adrenal response in critical illness. Our study uses conventional tests for adrenal insufficiency to investigate cortisol status in patients undergoing elective coronary artery bypass surgery (CABG), a condition frequently associated with SIRS.

Design: Prospective, observational study.

Methods: Thirty patients with impaired left ventricular function (ejection fraction >23% < 50%) underwent basal adrenocorticotropic hormone (ACTH) measurement, and a short Cosyntropin test (250mcg i.v.) one week preoperatively, and at +4 hours following induction of general anaesthesia. Preoperatively, a 30-minute cortisol level post-Cosyntropin >550nmol/l was taken as a normal response.

Results: Prior to surgery all patients had a normal response to Cosyntropin. Postoperatively, eight patients (26.7%) did not achieve stimulated-cortisol levels >550nmol/l and the mean peak cortisol postoperatively was lower (1048vs730nmol/l;p<0.001). There was a significant rise in ACTH after surgery (21vs 184ng/l;p=0.007) and reduction in Δ-cortisol post-Cosyntropin (579vs229nmol/l; p<0.001). There was no change in basal cortisol pre and postoperatively (447vs 501;p=0.4). All patients underwent routine, uneventful postoperative recovery.

Conclusion: Up to one quarter of patients with a normal cortisol status preoperatively demonstrate a raised ACTH and deficient cortisol response postoperatively. Despite these responses all patients had uneventful outcomes. These data reinforce the need for
caution when interpreting results of endocrine testing following major surgery or in the Intensive Care environment, and that prognostic value of these results may be of limited use.
Introduction

Cortisol is a critical player in the endocrine response to stress and is essential for survival in critical illness ¹. Activation of the hypothalamic-pituitary-adrenal (HPA) axis represents one of several important responses to physiological stresses, such as surgery and critical illness. Despite a large volume of published data on this topic, controversy remains as to the definition of a ‘normal’ adrenal response, and what is meant by the concept of relative adrenal insufficiency or critical illness-related corticosteroid insufficiency (CIRCI) ².

In the unstressed subject cortisol has a distinct circadian rhythm; high on waking and low on going to sleep ³. In contrast, surgery stimulates both the endocrine and immune systems to mount a systemic reaction to the associated injury as part of the healing process and cortisol levels may increase to 830 – 1400 nmol/l, with phase shifting of the physiological rhythm depending on the degree of surgical stress ⁴, ⁵. This principally occurs through cytokine regulation of the HPA axis primarily by direct or indirect stimulation of hypothalamic CRH, especially by IL-1, IL-6 and TNF-α, and also by directly affecting the pituitary and adrenal glands ⁶. To balance the inflammatory response IL-10 acts as an immunosuppressant neutralising pro-inflammatory effects ⁷. In a subpopulation of patients exposed to cardiopulmonary bypass, this systemic reaction can propagate a huge pro-inflammatory response, similar to that seen in sepsis. The systemic inflammatory response syndrome (SIRS) describes the clinical manifestation of
this response and progression to an advanced stage of SIRS is associated with prolonged cardiovascular support and a high mortality.

Studies generally show that during surgery the HPA is activated especially after extubation, whereby plasma ACTH levels are increased and are associated with elevated serum cortisol concentrations. Thereafter, plasma levels of ACTH decline rapidly to normal levels, whereas serum cortisol concentrations decrease slowly, reaching high normal values approximately 48–72 h after the procedure. This has been confirmed in coronary artery bypass graft operations, associated with SIRS consequent to sternotomy and cardio-pulmonary bypass, where basal and stimulated cortisol levels have been correlated with severity of stress, peaking shortly after extubation and being similar to levels during other major surgical procedures and critical illness.

It has been stated that adrenal insufficiency is rare in the setting of critical illness, but the methods commonly used to make the diagnosis of adrenal insufficiency are not necessarily applicable in the critically-ill patient, and the incidence may therefore have been underestimated. In contrast other authors have reported significantly higher rates of insufficient adrenal response in critical illness especially in those with a prolonged stay on ICU, and in those over 55 years of age. In view of such conflicting published data, we have performed a prospective study to investigate the immediate impact of major surgery on the tests used to diagnose adrenal insufficiency.
Subjects and Methods

Study Population

A prospective, observational study was performed at Sheffield Teaching Hospitals Cardio-Thoracic Surgical Unit and Cardiac Intensive Care Unit to analyse tests for adrenal insufficiency pre- and postoperatively. The study was also set up to examine the impact of low dose hydrocortisone therapy, and patients were randomised to treatment with a low dose hydrocortisone infusion or placebo after all tests, assessing each participant’s adrenal status, were complete. However, measurement of cortisol levels during the infusion showed no difference between groups and these data have not been included in the analysis of the 30 patients reported in this paper. Thirty consecutive patients, >17 years of age with impaired left ventricular function (ejection fraction >23% <50%) were recruited. Patients with severe ventricular electrical irritability, congenital or valvular heart disease, cardiac ejection fraction <23%, systemic corticosteroids within the previous 3 months, severe renal impairment (creatinine > 200 µmol/dl), asthma, insulin-treated diabetes, those needing emergency cardiac surgery, and those with an abnormal cortisol response (peak cortisol <550nmol/l) after a 250 mcg Cosyntropin test, were excluded. These criteria were used in an effort to ensure that as homogenous population as possible were recruited. The study was approved by the North Sheffield Research Ethics Committee and all patients gave written informed consent prior to participation in the trial.

Materials and Methods
One week prior to surgery the patients had basal adrenocorticotrophic (ACTH) and a short Cosyntropin test for adrenal function. Immediately prior to surgery a pulmonary artery flotation catheter (PAFC) (Baxter Healthcare Corp, Irvine, California, USA) was placed for cardiovascular monitoring. Use of etomidate, which causes reversible inhibition of the adrenal 11β-hydroxylase, was avoided for anaesthetic induction. Following induction of anaesthesia, and sternotomy patients were placed on cardiopulmonary bypass (CPB) during coronary artery grafting, and on completion were weaned off CPB. Inotrope support was commenced where necessary as decided by the anaesthetist and surgeon. Patients were then transferred to the CICU, received routine recovery care and had a postoperative Cosyntropin test around 4 hours from the time of induction. All operations were complete by this time. Parameters related to surgery were measured: cardiopulmonary bypass time, aortic cross clamping time and total theatre time (Table 1).

The following tests were analysed pre and postoperatively: basal cortisol, stimulated 30-minute cortisol post-Cosyntropin (peak cortisol), difference between stimulated and basal cortisol (Δ-cortisol) post-Cosyntropin (peak-basal), % change in cortisol (100%*peak-basal cortisol/basal cortisol), ACTH, cortisol/ACTH. A stimulated cortisol level <550nmol/ or a Δ-cortisol <250 nmol/l post-Cosyntropin were taken as abnormal responses, since a normal response is widely regarded as a 30-minute cortisol value >550nmol/L\(^{16-18}\), and a Δ-cortisol >250 nmol/l. The latter has been used previously as a criterion for a normal adrenal response in studies investigating the HPA axis during septic shock\(^{19-21}\). High ACTH levels in the presence of relatively low cortisol values, that
is a low cortisol/ACTH, may be indicative of primary adrenal insufficiency, whilst low to normal ACTH levels in the presence of low cortisol values, are principally indicative of secondary adrenal insufficiency\textsuperscript{22, 23}.

The following were deemed indicative of an adverse event: tachycardia (sustained (>5 mins) pulse rate >130% baseline), hypertension (sustained (>5 mins) mean arterial pressure >130% baseline), hypotension (sustained (>5 mins) mean arterial pressure <70% baseline), presence of myocardial ischaemia (new, sustained (> 5 mins) ST changes >1.0 mm ST depression/ elevation), new arrhythmias, and failure to wean from bypass.

**Assays**

Total serum cortisol was measured in a Siemens Advia Centaur Cortisol assay: analytical range 5.5 - 2069 nmol/l; inter-assay co-efficient of variation (CV), 6.2% at 134 nmol/l, 5.5% at 491 nmol/l and 6.0% at 837 nmol/l. Normal 0900h cortisol reference range was 198mmol/l to 720 mmol/l. Plasma ACTH was measured in a Siemens Immulite 2000 chemiluminescent assay: Analytical range 5 - 1250 ng/l; inter-assay CVs 6.4% at 32.1 ng/l, 6.5% at 478 ng/l. Normal 0900h ACTH reference range was < 46 ng/l.

**Statistical Analyses**

Database management and all statistical analyses were performed using SPSS Version 13.0 and Microsoft Excel Version 2007. Rates and percentages were calculated for categorical data, and means and 95% confidence intervals for continuous data. For continuous variables, differences within the same group were analysed by the paired
sample t-test. Correlation analyses were determined by calculating Pearson’s $r$ coefficient. A significant result was taken as $p < 0.05$.

Results

Thirty patients were recruited and all patients completed the study. Demographic data are shown in Table 1.

**Basal and 250mcg Cosyntropin-stimulated Cortisol levels**

Preoperatively, all patients achieved a 30-minute cortisol level $>550$ nmol/l after the Cosyntropin test, thereby excluding adrenal insufficiency. Mean (95% CI) preoperative basal cortisol and Cosyntropin-stimulated cortisol levels were 447.0 (385.4-508.6) nmol/l and 1048 (945 – 1151) nmol/l, respectively. There was no significant difference in the basal postoperative mean cortisol level 501 (393 – 609) nmol/l compared to preoperative levels ($p=0.4$), but there was a significant difference in the postoperative Cosyntropin-stimulated mean cortisol 730.2 (632.2 – 828.2) nmol/l ($p<0.001$) compared to the preoperative value. Eight patients (26.7%) had stimulated-cortisol levels $<550$ nmol/l postoperatively (Figure 1).

No correlation was found between basal or stimulated preoperative and postoperative cortisol values but there was a significant strong correlation between postoperative basal and stimulated cortisol levels ($r=0.841; p<0.001$) (Figure 2).
All patients had a Δ-cortisol, that is the difference between stimulated-cortisol (peak) and basal cortisol, >250nmol/l preoperatively whilst 17/30 (57%) had a Δ-cortisol <250nmol/l postoperatively. The mean (95%CI) Δ-cortisol preoperatively was 578.6 (503.7– 653.5) nmol/l, with a mean percentage change of 161% (112 – 210), whilst that postoperatively was 229.1 (170.4 - 287.8) nmol/l with a mean percentage change of 76.5% (45.5 – 107.5). A significant difference was shown when comparing pre and postoperative mean Δ-cortisol (p<0.001), and pre and postoperative percentage change in cortisol (p=0.002). (% change in cortisol = 100% * peak-basal cortisol/basal cortisol) (Figure1).

There was no correlation between pre and postoperative Δ-cortisol (r=0.09; p=0.6) or % change in cortisol levels (r=0.2; p=0.4). Analysis of postoperative tests showed a significantly, weak correlation between Δ-cortisol and peak stimulated cortisol levels (r=0.4; p=0.04) (Figure 2).

**ACTH and cortisol/ACTH ratios**

Mean (95%CI) basal ACTH levels preoperatively were 21.1 ng/l (16.4 - 25.8), all were within the normal reference range. Compared to preoperative levels, there was a significant increase in ACTH levels to 183.8 (71.9 – 295.7) ng/l (p=0.007) postoperatively. The mean basal cortisol/ACTH ratio preoperatively was 24.0 (21.24 – 26.76) and this was significantly different (p<0.001) to the postoperative mean level of 8.9 (6.08 – 11.7) (Figure 3).
Both preoperative ACTH and postoperative ACTH correlated significantly with preoperative (r=0.7; p<0.001) and postoperative (r=0.433; p=0.017) basal cortisol levels, respectively, but the correlation was weaker postoperatively (Figure 4).

**Patient outcomes**

Only one patient had an episode of sustained hypotension. His postoperative basal cortisol was 245 nmol/l, stimulated-cortisol 364nmol/l, Δ-cortisol 119nmol/l and cortisol/ACTH ratio 3.61. He remained intubated for 17 hours and was on inotropes for 21 hours. He was not given corticosteroids and was discharged from CICU after <24 hours. This patient had a temperature > 38.3°C and a raised WCC of 12.1 x 10^3. 11/22 patients with a response to Cosyntropin >550nmol/l and 5/8 patients with a response <550nmol/l required inotropes. One patient had sustained tachycardia, one other patient had sustained hypertension and two patients had ischaemic episodes. One patient had sustained tachycardia, hypertension and an ischaemic episode.

**Discussion**

We have shown that up to a quarter of patients with a normal HPA axis preoperatively have a reduced cortisol response to cosyntropin immediately following coronary arterial bypass grafting surgery. The advantage of our study is the demonstration of a normal HPA axis preoperatively. During stressful events the HPA axis is activated with a resultant increase in ACTH and cortisol levels. Cortisol at these levels then exerts its suppressive or anti-inflammatory effects which are crucial for re-establishing homeostasis. In patients undergoing CABG, cortisol levels around 1200 nmol/l have been
shown to suppress plasma IL-6 while significantly increasing plasma IL-10 potentiating the anti-inflammatory response. Our results differ from previous publications as although ACTH was elevated postoperatively the basal cortisol was not increased and thus the ratio of cortisol to ACTH was reduced. These results may suggest an element of insensitivity to ACTH. Our patients were studied immediately after surgery in contrast to previous studies which were undertaken at the time of extubation.

In studies investigating the adrenal response to critical illness, results have been conflicting and no defined criteria exist. Most publications have adopted the serum cortisol response to the standard Cosyntropin test (250 µg, iv) to characterize patients as ‘responders’ (those who had an increment of >250 nmol/l in serum cortisol) and ‘nonresponders’ (those who had an increment of <250 nmol/l in their serum cortisol levels), regardless of their baseline values. Other studies evaluated the prognostic value of measuring baseline and Cosyntropin-stimulated serum cortisol. Proposed lower thresholds for stress-elevated basal cortisol concentrations vary widely in the literature and it has been proposed that cortisol levels less than 414 nmol/l are in keeping with adrenal insufficiency whilst, stimulated or non-stimulated levels greater than 827 - 940 nmol/l, are unlikely to indicate any deficiency. In the Corticosteroid Therapy for Septic Shock (CORTICUS) study investigating the use of intravenous hydrocortisone in patients with septic shock it was shown that hydrocortisone did not significantly improve survival in patients who did not respond to Cosyntropin (Δ cortisol after Cosyntropin < 250nmol/l). Hence, the Cosyntropin test was deemed not to be useful in determining which patients should receive hydrocortisone therapy.
Our study showed that the adrenal status of patients undergoing major stress during a CABG showed significant changes, with many not achieving criteria for adrenal sufficiency. All tests were normal prior to surgery but four hours postoperatively there was a significant difference in ACTH, cortisol/ACTH ratios and response to Cosyntropin. Around 25% of patients failed to achieve a stimulated cortisol >550 nmol/l post-Cosyntropin and this was not predictable from preoperative tests. An equal number of individuals from those either failing or passing the Cosyntropin test required inotropes. Interestingly there was no significant difference in basal cortisol levels pre and postoperatively. Previously it has been shown that during CABG maximal cortisol levels are achieved post extubation with maximal stress. Adrenal status tests in our patients were performed four hours after induction whilst most patients were still intubated (mean time for extubation 7.2 hours) and therefore potentially a further rise in cortisol levels may have been expected if the tests were done later. Irrespective, at this point of the surgical procedure one would have expected mean cortisol levels higher than 501nmol/l, as measured in our patients. 57% of patients did not achieve ∆4-cortisol >250 nmol/l post-Cosyntropin. The clinical outcome for all these patients was not significantly different from those who did achieve a change in cortisol >250nmol/l and postoperative recovery was uneventful.

A reason for an apparent lower baseline cortisol or stimulated cortisol could be related to these being measured as total cortisol levels. Total cortisol, during major surgery or illness with associated hypoalbuminaemia and low cortisol-binding globulin (CBG), will
be low, although free cortisol levels, the fraction of cortisol exerting physiological function, may be normal or high \(^{29}\). This possibly explains why our patients had a good final outcome as in general glucocorticoid secretion would have been increased although this was not discernible in this case. Measuring albumin and CBG levels together with estimations of free cortisol in patients undergoing CABG would be useful to help clarify this hypothesis \(^{30}\). Dilution of proteins, such as CBG and albumin, due to the large amount of fluids given to patients during resuscitation results in a lower level of measured total cortisol. This has previously been reported in patients undergoing CABG \(^{31}\) in which there was a highly significant correlation between the degree of haemodilution and the percentage rise in the free cortisol fraction.

Potentially a low baseline cortisol and a low stimulated cortisol could also represent an element of relative adrenal insufficiency or CIRCI. This must have been short lived as all patients recovered from surgery. CIRCI is defined as inadequate corticosteroid activity for the severity of the illness of a patient secondary to either glucocorticoid resistance or HPA axis failure \(^2\). In glucocorticoid resistance, in the face of excessive cytokine production during critical illness, there is a decreased number and binding affinity of glucocorticoid receptors, with post receptor alterations resulting in high cortisol levels \(^{32}\). Alternatively, various factors have been suggested to influence the HPA axis and confound its evaluation. Both primary and secondary types of adrenal insufficiency have been reported to occur during critical illness \(^{33, 34}\). The results from our study show an impaired adrenal response to Cosyntropin with a low cortisol/ACTH ratio postoperatively in keeping with primary adrenal failure. A number of mechanisms may be responsible.
TNFα reduces adrenal cortisol synthesis by reducing the sensitivity of adrenal receptors to ACTH resulting in a blunted response to Cosyntropin and high ACTH levels with relatively low cortisol levels in the setting of acute illness. In addition, corticostatins or defensins produced by cells, such as macrophages and neutrophils, and which may proliferate in a systemic inflammatory response, inhibit the steroidogenic activity of ACTH. They have been shown to increase 20-fold in plasma and 10-fold in adrenal tissue during bacterial infection in rabbits. Corticostatins compete with ACTH on their binding sites and exert an inhibitory effect on the adrenal cells resulting in decreased cortisol production. Another possible mechanism for primary adrenal failure is the release of a number of factors by lipopolysaccharide-stimulated macrophages, similar as to what happens in endotoxic shock, that suppress the steroidogenic response of adrenocortical cells to ACTH; the amount of factors released regulated by lymphokines. Further, transforming growth factor-β, another cytokine derived from monocytes, is also known to inhibit both basal and ACTH-stimulated steroidogenesis. A strong correlation identified between postoperative basal and peak levels and a weaker correlation between ACTH and cortisol postoperatively compared to preoperative values could support this hypothesis. A number of drugs used during surgical procedures are known to affect the HPA axis and direct cortisol production in the adrenal gland. Etomidate, an anaesthetic agent which can reversibly inhibit 11-hydroxylase enzyme and result in decreased cortisol secretion from the adrenal gland, was not used in any of the procedures and so does not account for these findings.
Our data confirm that there are limitations in the tests used to assess for adrenal insufficiency in the critically ill patient. Studies have been controversial giving conflicting and unclear results. Baseline serum cortisol levels and stimulated cortisol, preferably measuring the free cortisol levels, are most probably the most practical tests although further studies to assess the impact of these tests on outcome and their importance in predicting the benefits of glucocorticoids in these scenarios are necessary.

Declaration of Interest: There are no conflicts of interest.

Funding: This research was funded in part from the Sheffield Teaching Hospitals Charitable Trust, generously donated by Dr Kath Sherry FRCA.

Acknowledgements: The assays were completed by Miss Emma Hall (recipient of Anaesthetic Research Society Vacation Studentship), and Ms Wendy Russell.

References

to provide circadian cortisol profiles. *J Clin Endocrinol Metab* 2009 94 1548-1554.


27. Sam S, Corbridge TC, Mokhlesi B, Comellas AP & Molitch ME. Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf)* 2004 **60** 29-35.


Figure Legends

**Figure 1:** Changes between mean (±95% CI) pre and postoperative measurements of i) basal cortisol (447 (385-509) vs 501 (393-609) nmol/l; p = 0.4), ii) stimulated 30 minute cortisol post-Cosyntropin (peakcortisol) (1048 (945-1151) vs 730.1 (632-828) nmol/l; p<0.001), iii) Δ cortisol post-Cosyntropin (peak-basal) 579 (504-654) vs 229 (170-288) nmol/l; p <0.001), iv) % change in cortisol (100%*peak-basal cortisol/basal cortisol) 161 (112-210) vs 77 (45-107); p=0.002) estimated by paired sample t-test. Bold lines (mean); light lines (individuals).

**Figure 2:** Pearson’s correlation between postoperative i) basal cortisol and stimulated (peak) cortisol post-Cosyntropin (r=0.84; p<0.001) and ii) Δ cortisol and stimulated (peak) cortisol post-Cosyntropin (r=0.4; p=0.04). These correlations potentially highlighting lack of adrenal sensitivity to endogenous ACTH and Cosyntropin in a number of individuals immediately post CABG.

**Figure 3:** Changes between mean (95% CI) pre and postoperative measurements of i) ACTH (21 (16-26) vs 184 (72-296) ng/l; p=0.007) and ii) cortisol/ACTH ratio (24 (21-27) vs 9 (6-12); p<0.001) estimated by paired sample t-test. Bold lines (mean); light lines (individuals).

**Figure 4:** Pearson’s correlation between i) pre-operative ACTH and basal cortisol (r=0.7; p<0.001) and ii) post-operative ACTH and basal cortisol (r=0.433; p=0.02). These correlations reveal the maintenance of, but slight worsening of the adrenal response to ACTH post-operatively when compared to preoperative values.

**Table 1:** Demographic data and peri-operative intensive care parameters in thirty CABG patients. CPB: cardiopulmonary bypass; AXC: aortic cross-clamping.
Figure 2
Figure 3

i) ACTH

Log ACTH

Preop ACTH  Postop ACTH

ii) Cortisol/ACTH ratio

Cortisol/ACTH preop  Cortisol/ACTH postop
Figure 4
Table 1. Demographic Data and Peri-Operative Intensive Care Parameters

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<tr>
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<td>BMI (95% CI)</td>
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<td>Total Theatre Time (range)</td>
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