CLINICAL STUDY

Adrenal function during coronary artery bypass grafting

Christoph Henzen, Richard Kobza, Birgit Schwaller-Protzmann, Peter Stulz1 and Verena A Briner
Department of Internal Medicine and 1 Department of Cardiothoracic Surgery, Kantonsspital, CH-6000 Luzern 16, Switzerland

(Correspondence should be addressed to C Henzen, Medizinische Klinik, Kantonsspital, CH-6000 Luzern 16, Switzerland; Email: Christoph.Henzen@ksl.ch)

Abstract

Objective: To assess adrenal function in patients undergoing coronary artery bypass grafting (CABG) by means of the low-dose (1 μg) ACTH test, and to correlate the adrenal function with clinical outcome.

Methods: During a 5-month period we prospectively included 45 patients undergoing elective CABG with cardiopulmonary bypass and without symptoms of endocrine disease. Low-dose (1 μg) ACTH tests were performed on the day before surgery (day −1), immediately after the operation (day 0), on the two subsequent days in the intensive care unit (day 1 and day 2), and on the day of discharge from the hospital. A number of clinical, hemodynamic and laboratory parameters were monitored throughout.

Results: On day −1, 75% of the study patients had normal stimulated plasma cortisol concentrations. Eleven patients (25%) had an impaired adrenal response to 1 μg ACTH. The stimulated plasma cortisol concentrations in patients who had an inadequate adrenal response on day −1 remained significantly reduced on day 1 (756 ±205 vs 949±259 nmol/l, P = 0.03) (mean±S.D.), day 2 (644 (580–793) vs 885 (713–1087), P = 0.03) (median (interquartile range)), and on the day of discharge (698 ±201 vs 854 ±186, P = 0.05). In patients with a normal adrenal response in the pre-operative setting peak cortisol concentrations were reached on day 1, in patients with a blunted adrenal response they were reached on day 2. There were significant correlations between the stimulated plasma cortisol concentrations and the blood loss (r =−0.50, P = 0.002) and volume balance (r =0.41, P = 0.015).

Conclusions: Occult (partial) adrenal insufficiency is common in patients undergoing CABG who are otherwise asymptomatic as regards endocrine disease. The adrenal function in these patients differs both in the magnitude of cortisol response to ACTH and in the time course, with significantly delayed peak cortisol concentrations. Adequate regulation of volume balance and the amount of blood loss seem to correlate with adequacy of adrenal function.

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Introduction

Cortisol has vital circulatory effects in stress response, and even a mild adrenal insufficiency can be hazardous in critical illness or major surgery (1). However, a random plasma cortisol measurement does not reliably identify the patients who may develop symptoms and signs of acute addisonian crisis (i.e. dehydration, fever, confusion, nausea, abdominal pain, hypoglycemia, hypotension, and shock) in a subsequent stressful event (2, 3). Therefore, stimulation tests are used in the assessment of the hypothalamic–pituitary–adrenal (HPA) axis. The widely used standard short Synacthen (250 μg tetracosactrin) test induces supraphysiological adrenocorticotropic (ACTH) concentrations, providing false-normal cortisol responses and low sensitivity in identifying acute-onset adrenal insufficiency. The insulin-induced hypoglycemia test is generally agreed to be the reference standard for testing the HPA adequacy in response to stress (4). However, this test is labor intensive and contraindicated in some patients. The low-dose (1 μg) ACTH test has recently been introduced and proved to be sensitive in revealing partial adrenal insufficiency by providing physiological adrenocortical stimulation (5, 6). The results of the low-dose (1 μg) ACTH test correlate closely with those of the reference test for the function of the HPA axis (7), and are superior to the standard (250 μg) ACTH test (8). However, the literature remains controversial about the cut-off point representing a normal adrenal.
response to 1 μg ACTH, and about the sensitivity of the low-dose (1 μg) ACTH test in the diagnosis of secondary hypoadrenalism (9).

During surgical procedures plasma ACTH and cortisol concentrations rise rapidly to maintain the homeostasis of, among others, blood oxygen, blood pH, and body temperature. The quantitative rise in postoperative cortisol levels correlates with the extent of surgery and the illness severity scores (10). A relative deficiency of the cortisol stress response can cause hemodynamic abnormalities that mimic hypovolemic or septic shock and may contribute to a fatal outcome (1).

The purpose of our study was to assess the adrenal response to the low-dose (1 μg) ACTH test in patients with no history of adrenal disease undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) which constitutes a defined and comparable stress situation. We also aimed to find out whether the adrenal function correlated with clinical outcome.

Subjects and methods

Participants

Between November 1999 and March 2000, we undertook a prospective cohort study in a large urban hospital, including patients undergoing elective CABG with CPB. We excluded patients with a history of exogenous glucocorticoid treatment (i.e. for oral, intravenous, intramuscular, and intra-articular forms of glucocorticoid treatment – topical and inhaled glucocorticoids during the last 6 months), endocrine diseases (i.e. Addison’s disease, Cushing’s disease, and adrenal metastases or hemorrhages), acute myocardial infarction, sepsis, and multiorgan failure. Etomidate was not allowed in the anesthetic regime and was considered an exclusion criterion. The low-dose (1 μg) ACTH test was performed in 45 patients (16 women and 29 men; mean age (±S.D.) 61 ± 13 years). Baseline characteristics are shown in Table 1.

The study was approved by the local institutional ethics committee, and informed consent was obtained from all participants.

Materials and methods

The following anesthetic induction regime was used: midazolam (7.5 mg), thiopentone (2 mg/kg), fentanyl (3 μg/kg), and rocuronium bromide (1 mg/kg). Continuous propofol and fentanyl infusions were used for maintenance of anesthesia. Monitoring included electrocardiography, pulse oximetry, end-tidal CO₂, arterial catheter, and central venous pressure. Antibiotic prophylaxis consisted of cefuroxime (1.5 g, t.i.d.) for 48 h. After heparin injection (300 IU/kg), moderate hypothermic CPB was achieved using a hollow fiber oxygenator. Myocardial preservation was performed with intermittent infusion of crystalloid cardioplegic solution and topical ice application.

For the low-dose (1 μg) ACTH test, a bolus i.v. injection of 1 μg (1–24)-corticotropin (tetracosactrin, Synacthen, Novartis Pharma, Berne, Switzerland) was given. One vial of 250 μg tetracosactrin was diluted in sterile saline solution to a concentration of 1 μg/ml, filtered in plastic syringes, and stored at 4°C as described elsewhere (5). The tests were carried out on the day before the operation (day 0), immediately after the operation on the intensive care unit (ICU) (day 1), on the next 2 days in the ICU

Table 1 Baseline characteristics of participating patients. Results are means±S.D. or median (interquartile range).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Normal adrenal response (n = 34)</th>
<th>Deficient adrenal response (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>23/11</td>
<td>6/5</td>
<td></td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>27.1</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Medication (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betablockers</td>
<td>18</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)*</td>
<td>130±21</td>
<td>134±14</td>
<td>0.65</td>
</tr>
<tr>
<td>Diastolic blood pressure†</td>
<td>72 (65–80)</td>
<td>80 (76–83)</td>
<td>0.23</td>
</tr>
<tr>
<td>Potassium (mmol/l)*</td>
<td>3.9±0.4</td>
<td>3.8±0.6</td>
<td>0.54</td>
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<tr>
<td>Glucose (mmol/l)*</td>
<td>6.2±1.2</td>
<td>5.7±1.8</td>
<td>0.33</td>
</tr>
<tr>
<td>White-cell count (G/l)*</td>
<td>5.7±2.1</td>
<td>5.3±2.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Eosinophils count (G/l)*</td>
<td>0.19±0.11 (3.3±1.9%)</td>
<td>0.23±0.20 (4.3±3.7%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Basal cortisol concentration (nmol)†</td>
<td>387 (247–526)</td>
<td>178 (117–213)</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal ACTH (pmol/l)*</td>
<td>9.2±4.4</td>
<td>6.5±5.3</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Mean±S.D.; difference tested by Student’s t-Test; †median (interquartile range); difference tested by Mann-Whitney test.

G/l, the absolute number of eosinophils (×10⁹/l), corresponding to the relative number (percentage) of 3.3±1.9% and 4.3±3.7%, respectively.

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(day 1 and day 2), and before discharge from the hospital. Blood samples were taken for the measurement of basal plasma cortisol concentration, glucose, electrolytes, and white-cell count; 1 μg ACTH was administered intravenously via a cannula (Vasofix Braunüle, B Braun, Melsungen, Germany) on day −1 and before discharge, and via a central venous line on days 0, 1, and 2, and another blood sample was taken after 30 min for measurement of stimulated plasma cortisol concentrations. The tests were carried out in the afternoon on day −1 and day 0, and at 0800 h on day 1, day 2, and on the day of discharge. The following clinical and hemodynamic parameters were monitored: duration of ischemia and time on CPB, time to weaning, left ventricular ejection fraction before and after the operation, glucose, electrolytes, pulse rate, blood loss, bleeding volume, volume replacement, and need for vasopressor drugs.

Plasma cortisol was measured by fluorometric enzyme-immunoassay (Dade Stratus, AHS, Merz+Dade, Munich, Germany). A normal response to i.v. ACTH was defined as a stimulated plasma cortisol concentration above 550 nmol/l (20 μg/dl). A deficient response to ACTH was defined as a plasma cortisol concentration below 550 nmol/l 30 min after the injection of 1 μg ACTH. The intra- and interassay coefficients of variation were 5.1% and 4.1% respectively. The sensitivity of the assay was 7.2 nmol/l (0.3 μg/dl). The assay was highly specific for cortisol with low crossreactivity to other glucocorticoids. (To convert values for plasma cortisol concentrations on day 1, whereas the maximum plasma cortisol concentrations in patients with an insufficient

**Results**

On day −1, 34 of the 45 (75%) study patients had stimulated plasma cortisol concentrations above 550 nmol/l and, therefore, were classified as having a normal adrenal response (mean (±S.D.) stimulated plasma cortisol concentrations 726±134 nmol/l). Eleven patients (25%) had stimulated plasma cortisol concentrations below this cut-off and were defined as having (partial) adrenal insufficiency (384±152 nmol/l). The mean basal plasma cortisol concentrations were also significantly lower in patients with deficient adrenal response (178 (IQR: 117–213) nmol/l) vs 387 (247–526) nmol/l, P=0.001). On day 0, basal and stimulated plasma cortisol concentrations were lower in the patients who had a deficient adrenal response on day −1, but the difference was no longer statistically significant (basal cortisol concentrations 408±216 vs 487±272 nmol/l, P = 0.41; stimulated cortisol concentrations 642±252 vs 735±239 nmol/l, P = 0.29). However, on day 1, day 2, and on the day of discharge, the stimulated plasma cortisol concentrations were again significantly reduced in the patients who started with an inadequate adrenal response on the day before the operation: 756±205 vs 949±259 nmol/l on day 1, P = 0.03; 779±404 vs 933±265 nmol/l on day 2, P = 0.03; 698±201 vs 854±186 nmol/l on the day of discharge. P = 0.05 (Fig. 1). There was a close correlation between the stimulated plasma cortisol levels and the increment of the cortisol levels after intravenous ACTH (Fig. 2). Patients with a normal adrenal response in the preoperative setting had peak cortisol concentrations on day 1, whereas the maximum plasma cortisol concentrations in patients with an insufficient
adrenal response were measured on day 2. Table 2 illustrates the clinical and hemodynamic differences between patients with normal and deficient adrenal response to 1 μg ACTH.

There were significant correlations between stimulated plasma cortisol concentrations and bleeding volume ($r = -0.50$, $P = 0.002$) (Fig. 3), and volume balance ($r = 0.41$, $P = 0.015$) (Fig. 4). There were no correlations between plasma cortisol concentrations and age, time to weaning ($r = 0.16$, $P = 0.35$), duration of ICU and hospital stay ($r = 0.21$, $P = 0.25$), use of vasopressor drugs ($r = 0.007$, $P = 0.96$), time of ischemia ($r = 0.10$, $P = 0.55$) and time on CPB ($r = 0.07$, $P = 0.68$), blood pressure ($r = 0.01$, $P = 0.93$), pulse rate ($r = 0.002$, $P = 0.93$), left ventricular ejection fraction ($r = 0.13$, $P = 0.70$), and electrolytes ($r = 0.11$, $P = 0.54$).

**Discussion**

The responsiveness of the hypothalamic-pituitary-adrenal axis to stress is essential for survival. The adrenal cortisol secretion is regulated by continuous tropic ACTH stimulation and varies little in the absence of stress. In case of severe illness, trauma and major surgery, however, the activation of the HPA axis results in an almost 10-fold increase in cortisol secretion in order to adapt to stress and to maintain homeostasis (1). This rise is essential for maintaining vascular tone, endothelial integrity and the distribution of body water. Cortisol, furthermore, enhances sensitivity to the pressor effects of the catecholamines and mobilizes energy via gluconeogenesis, proteolysis, and lipolysis. Although the incidence of complete adrenal insufficiency after routine surgery and in severely ill Table 2 Clinical and hemodynamic outcome in patients with normal and deficient adrenal response to 1 μg ACTH. Results are means±S.D. or median (interquartile range).

<table>
<thead>
<tr>
<th>Normal adrenal response ($n = 34$)</th>
<th>Deficient adrenal response ($n = 11$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of ischemia (min)$†$</td>
<td>62 (51–73)</td>
<td>60 (59–66)</td>
</tr>
<tr>
<td>Time on CPB (min)$*$</td>
<td>94±29</td>
<td>99±28</td>
</tr>
<tr>
<td>Use of vasopressor drugs (h)$†$</td>
<td>24 (8–57)</td>
<td>26 (6–72)</td>
</tr>
<tr>
<td>Time to weaning (h)$†$</td>
<td>13 (9.5–16.8)</td>
<td>12 (7.2–19.8)</td>
</tr>
<tr>
<td>Volume of blood loss (ml)$*$</td>
<td>1770±867</td>
<td>2082±1603</td>
</tr>
<tr>
<td>Volume balance (ml)$*$</td>
<td>–182±1266</td>
<td>–722±1904</td>
</tr>
<tr>
<td>Length of hospital stay (days)$†$</td>
<td>12 (11–13.5)</td>
<td>12 (12–14)</td>
</tr>
</tbody>
</table>

$*$Mean±S.D.; difference tested by Student’s $t$-test; $†$median (interquartile range): difference tested by Mann-Whitney test.
patients is low (10, 11), occurring in 2 to 3% of the patients, the adrenocortical production of cortisol may be impaired and represent an occult or relative adrenal insufficiency (12–14). Evidence of the fatal role of an occult relative adrenal insufficiency has been provided by recent reports of hydrocortisone administration in critically ill patients (15), but also by the massive rise of mortality with the use of etomidate in the ICU of the University Hospital of Glasgow. Etomidate, a short acting hypnotic drug, inhibits adrenal 11β-hydroxylase, which converts deoxycortisol to cortisol, and thus induces adrenal insufficiency (16, 17). Among the various factors leading to relative adrenal insufficiency, treatment with exogenous glucocorticoids is the most common (18). It is well recognised that adrenal function shows little correlation with the dose and duration of glucocorticoid treatment (i.e. a median duration of less than 12 days) the adrenal response was suppressed in 45% of the patients (20).

In the evaluation of the HPA axis, results of the low dose (1 μg) ACTH test correlate well with those of the insulin-induced hypoglycemia test. A single (stimulated) plasma cortisol concentration measured 30 min after the administration of 1 μg ACTH reliably reflects adrenal function without false normal results and, therefore, eliminates the shortcomings of the standard short (250 μg) ACTH test.

In the present study, the low dose (1 μg) ACTH test revealed a (partially) deficient adrenal response in 25% of 45 patients undergoing elective coronary artery bypass grafting. In these patients not only the magnitude of cortisol secretion but also the kinetics of the adrenal response were significantly altered, i.e. their maximum plasma cortisol concentrations were reached 24 h later than patients with normal adrenal function. The reason for the surprisingly high proportion of asymptomatic patients with partial adrenal insufficiency is unknown. Patients with possible causes for suppression of adrenal function such as neoplasia, bleeding disorders, infectious and polyglandular disease have been excluded. There were no significant differences in the baseline characteristics of the patients. However, the significant time delay compared with normal patients in these with a deficient adrenal response points to a potential relevance of these findings given the prognostic value of the cortisol response to ACTH (21). Among various clinical outcome parameters a correlation was clearly demonstrated between adrenal function and blood loss and volume balance respectively. The increased blood loss in patients with an inadequate adrenal response may be related to the plasma concentrations of factor VIII and von Willebrand factor, which are known to be increased in hypercortisolism (22). The diminished mineralocorticoid potency of deficient adrenal glands may explain the negative volume balance. However, it is possible that more subtle clinical effects of partial adrenal insufficiency, such as the reduced or absent need for vasopressor drugs following hydrocortisone replacement in patients with impaired adrenal function will be detected in larger study populations.

Symptoms and signs of acute adrenal crisis (i.e. dehydration, fever, confusion, nausea, abdominal pain, hypoglycemia, hypotension, and shock) may occur in the patients with partial adrenal insufficiency exposed to stress. The diagnosis is easily missed or delayed because the clinical findings in acute adrenal insufficiency may be interpreted as complications of surgery. Parenteral administration of 100 to 300 mg hydrocortisone should be given as soon as the diagnosis of acute adrenal insufficiency is suspected.

A deficient adrenal response to 1 μg ACTH is frequent in patients undergoing elective coronary artery bypass grafting who are asymptomatic as far as endocrine disease is concerned. The adrenal function in these patients differs both in the magnitude of the cortisol secretion and in the time course, with significantly blunted and delayed peak cortisol concentrations. Regulation of volume balance and the amount of blood loss correlated with the adequacy of the adrenal response.

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References


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