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Short communication

Depression 12-months after coronary artery bypass graft is predicted by cortisol slope over the day

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ABSTRACT

Alterations in the diurnal profile of cortisol have been associated with depressed mood in patients with coronary heart disease. The relationship between cortisol output and depressed mood has not been investigated prospectively in coronary artery bypass graft (CABG) patients before. We aimed to study the relationship between cortisol measured pre- and post-operatively and depression symptoms measured 12 months after CABG surgery. We analysed data from 171 patients awaiting first-time, elective CABG surgery from the pre-assessment clinic at St. George’s Hospital, London. The Beck Depression Inventory (BDI) was used to assess depression symptoms and saliva samples were collected to measure diurnal cortisol. Baseline assessments of depression and cortisol were obtained an average 29 days before surgery, short-term follow-up of cortisol occurred 60 days after surgery and long-term follow-up of depression was assessed 378 days after surgery. Baseline cortisol slope was not associated with depression at 12-month follow-up. However, a steeper cortisol slope measured 60 days after surgery predicted reduced odds of depression (BDI ≥ 10) 12 months after surgery (odds ratio 0.661, 95% confidence interval 0.437–0.998, p = 0.049) after controlling for covariates. These findings suggest interventions aimed at improving adaptation in the early recovery period may have long-term benefits in this patient group.

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1. Introduction

Cortisol is implicated in the pathophysiology of depression (Zunszain et al., 2011). Hypothalamic-Pituitary-Adrenal (HPA) axis abnormalities have been observed in patients with major depression, including increased secretion and reactivity of cortisol (Cowan, 2010), elevated corticotropin releasing hormone (Nemeroff et al., 1984), and increased size and activity of the pituitary and adrenal glands (Nemeroff et al., 1992). Elevated cortisol has also been linked to cardiac risk factors (Brown et al., 2004) and we recently reported that dysregulated diurnal cortisol profiles prior to coronary artery bypass graft (CABG) surgery predicted increased risk of death or adverse cardiac events in subsequent years (Ronaldson et al., 2015).

Alterations in the diurnal profile of cortisol have been associated with depressed mood in patients with coronary heart disease (Bhattacharyya et al., 2008), and with history of depression in acute coronary syndrome patients (Messerli-Bürgy et al., 2012). HPA axis dysregulation has also been associated with greater cardiac-related mortality in depressed patients (Jokinen and Nordström, 2009). There are limited studies investigating cortisol in CABG patients, although there is some evidence of heightened cortisol output in the post-operative period (Gibbison et al., 2015; Roth-Isgiekt and Schmucker, 1997). The relationship between cortisol output and depressed mood has not been investigated in CABG patients before. We aimed to study the prospective relationship between cortisol rhythm across the day measured pre- and post-operatively and depression symptoms measured 12-months after CABG surgery.

2. Method

2.1. Sampling and procedure

Full details of the methods and participants used in the ARCS (Adjustment and Recovery after Cardiac Surgery) study can be found elsewhere (Poole et al., 2014; Ronaldson et al., 2015). Briefly, we conducted complete case analysis on data from 171 patients awaiting first-time, elective CABG surgery, who were recruited
Table 1
Demographic, clinical and biological characteristics of the sample (N = 171).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD or N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.29 ± 8.87</td>
</tr>
<tr>
<td>Female</td>
<td>26 (15.2)</td>
</tr>
<tr>
<td>Ethnicity – White British/White Other</td>
<td>154 (90.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.16 ± 3.85</td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>36 (21.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>134 (78.4)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Extracardiac arteriopathy</td>
<td>12 (7.0)</td>
</tr>
<tr>
<td>Clinical factors</td>
<td></td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>4.73 ± 3.21</td>
</tr>
<tr>
<td>CABG in isolation</td>
<td>45 (26.3)</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>2.85 ± 1.13</td>
</tr>
<tr>
<td>On-pump</td>
<td>138 (80.7)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Baseline BDI (≥10)</td>
<td>55 (32.2)</td>
</tr>
<tr>
<td>Long-term follow-up BDI (≥10)</td>
<td>39 (22.8)</td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
</tr>
<tr>
<td>Baseline slope (nmol/L/hour)</td>
<td>1.82 ± 1.12</td>
</tr>
<tr>
<td>Short-term follow-up slope (nmol/L/hour)</td>
<td>1.71 ± 1.11</td>
</tr>
</tbody>
</table>

* N = 169.

from the pre-assessment clinic at St. George’s Hospital, London. Inclusion criteria permitted only patients who were undergoing elective CABG surgery or CAGB plus valve replacement to participate. CABG surgery was defined to include both on-pump (i.e. cardiopulmonary bypass) and off-pump surgical procedures. In addition, participants had to be able to complete the questionnaires in English, and be 18 years or older. The ARCS study was powered to assess the importance of a broad range of psychological, behavioural, and social factors. On average, baseline assessments occurred 29 days before surgery, short-term follow-up occurred 60 days after surgery and long-term follow-up was 378 days after surgery. All procedures were carried out with the written consent of the participants. We obtained ethical approval from the South West London research ethics committee.

2.2. Measures

2.2.1. Predictor variable: cortisol slope

Full details of the saliva collection protocol has been described elsewhere (Ronaldson et al., 2015). In brief, the saliva samples were collected using Salivettes (Sarstedt, Leicester, UK) at set time points across the day: on awakening, 30 min after awakening, 10 am, midday, 4 pm, and bedtime. Saliva samples were obtained at baseline and short-term follow-up; they were returned via post and stored at −20 °Celsius for analysis at a later date. Cortisol levels were assessed using a time resolved immunoassay with fluorescence detection, at the University of Dresden. The intra- and inter- assay coefficients of variation were less than 4%. The slope of cortisol decline over the day was calculated as the reduction in cortisol per hour (nmol/L/hour), using regression methods. The slope excluded the 30-min post-awakening sample (Messerli-Bürgy et al., 2012). Slope values closer to zero reflect flatter diurnal rhythms. Two participants had missing baseline slope values (n = 169).

2.2.2. Outcome variable: depression

The Beck Depression Inventory (BDI) (Beck et al., 1988) was used to measure depression symptoms at baseline and 12 months after surgery. It is a 21-item questionnaire which asks the respondent to reflect on how they have been feeling over the past two weeks. Ratings were summed and we used a standard cut-off of <10 to indicate no depression and mild to severe depression respectively.

2.2.3. Covariates

Clinical risk was assessed using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (Roques et al., 2003). EuroSCORE is a composite measure of procedural mortality risk. Items were scored in accordance with the ‘logistic EuroSCORE’ method to generate a percentage mortality risk estimate (http://www.euroscore.org/logisticEuroSCORE.htm). Smoking was measured as a binary variable (current smoker/non-smoker). Body mass index (BMI) was assessed at the pre-operative clinic appointment and calculated using the standard formula (kg/m²).

2.3. Statistical analysis

Associations between variables were assessed using Pearson’s correlations and dependent and independent t-tests as appropriate. Cortisol slope data were normally distributed, so the raw data are reported here. Outliers greater than 3 standard deviations from the mean were excluded from the analysis. We used logistic regression analyses to assess the association between cortisol slope and depression status. We controlled for several potential confounders of the associations, namely BMI, smoking status, baseline depression status and EuroSCORE. Age and sex are included in EuroSCORE so were not entered separately to avoid double adjustment. Inclusion of on pump surgery as a covariate did not change the results so is not included in the models presented here. Results are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Secondary analyses were performed using continuous BDI scores. All analyses were conducted using SPSS version 21.

3. Results

The demographic and clinical characteristics of the sample are described in Table 1. The majority of ARCS participants were White (90.1%), overweight (BMI > 25 = 79.5%) and male (84.8%). The mean age of the sample was 69.29, with a range of 44–90 years. The mean BDI value at baseline was 8.15 (SD: 6.00) and at 12-month follow-up was 6.33 (SD: 5.69) reflecting an overall decline in depression over time (t = 4.296, p < 0.001). Cortisol slope was slightly higher/steeper at baseline (mean: 1.82 nmol/L/hour, SD: 1.12) than at short-term follow-up (i.e. two months post-CABG) (mean: 1.71 nmol/L/hour, SD: 1.11), but this change was non-significant (t = 0.934, p = 0.352). Univariate analyses revealed no difference in 12-month depression status by baseline cortisol slope values (t = 1.459, p = 0.146), so fully adjusted models were not performed. Logistic regression analyses, controlling for covariates revealed short-term follow-up cortisol slope was a significant predictor of depression status 12 months after CABG (OR: 0.661, 95% CI 0.437–0.998, p = 0.049). This finding suggests that a one unit increase in slope (i.e. a steeper slope) is associated with a 34% reduction in the odds of depression 12 months after surgery. Baseline depression was also a significant predictor in this model (OR: 8.050, 95% CI 3.525–18.383, p < 0.001). This pattern of results was confirmed in multiple linear regression models with short-term follow-up cortisol slope (β = −0.126, p = 0.049) and baseline BDI (β = 0.537, p < 0.001) predicting continuous BDI scores 12 months after surgery. The relationship between short-term follow-up cortisol output across the day and depression 12 months after surgery is illustrated in Fig. 1.

4. Discussion

We found that cortisol slope measured two months after CABG surgery was predictive of depression status 12 months later. These
results remained true even after controlling for potential con-
founders of this relationship, namely BMI, smoking and disease
severity. These are the first findings to our knowledge that has
implicated cortisol in the manifestation of depression symp-
toms following CABG surgery.

Previous studies have reported that there is heightened cortisol
output in the days following CABG surgery (Gibbison et al., 2015).
There are likely multiple factors implicated in the dysregulation
of cortisol after surgery, including both physiological mechanisms
linked to marked increases in inflammation during the procedure
(Biglioni et al., 2003) and recovery periods (Poole et al., 2013), as well
as psychological factors such as the experience of stress associated
with undergoing a major operation and the related pain, discomfort
and reduced mobility. We did not see a significant change in cortisol
slope over time, though our results did indicate a reduction in slope
(i.e. a flatter slope) at short-term follow-up compared to baseline. It
is possible that this small difference in cortisol slope partly explains
why we did not observe an association with baseline slope and later
depression. Future replication in larger studies is needed to confirm
this hypothesis.

In a previous study our group recruited patients with suspected
coronary artery disease from hospital outpatient’s clinics prior
to diagnostic angiography. Findings showed that a flatter corti-
sol slope was associated with depression in patients who went
on to receive a positive diagnosis for coronary artery disease, but
not related to depression in those patients who did not receive
a coronary artery disease diagnosis (Bhattacharyya et al., 2008).
Otte and colleagues (Otte et al., 2004) also found an association
between cortisol and depression in the Heart and Soul study,
however the 24-h urinary cortisol samples did not allow diurnal
patterns to be explored. Combined, these findings suggest that
cortisol dysregulation and depression may be related to the underly-
ing disease processes in cardiac patients; the exact mechanisms for
these effects are not yet clear though as alluded to, one possibility
draws on the inflammatory model of depression in coronary heart
disease (Poole et al., 2011). For example, there is evidence to sug-
gest that pre-operative C-reactive protein levels predict depression
experienced 6 months after CABG surgery (Yang et al., 2012) and
interferon-gamma measured in the days following surgery predicts
depression 12-months after surgery (Steptoe et al., 2015). Inflam-
matory data was not collected in ARCS at the same post-operative
time point as cortisol, preventing this hypothesis from being tested.
However, our study is one of the few studies to examine the com-
plex interaction between cardiac disease, cortisol and depression
using a CABG population. The findings are clinically significant in
that interventions to enhance recovery and reduce stress in the
immediate post-operative period may have long-term benefit.

Our study has a number of strengths. The prospective nature
of our analyses allows the direction of the effect to be explored, with
multiple assessments of cortisol and depression. The ARCS study
examined patients undergoing CABG at a single hospital and there-
fore removes the influence of inter-hospital variation in patient care
policy. However, there are also some limitations to our study. First is
the reliance on questionnaire measures of depression, since these
cannot be used to define clinical depression. Secondly, since our
sample was predominately of White ethnicity and male, our find-
ings may not readily generalise to other populations. Next, since
we only had a small number of depression cases, this limited the
number of covariates we could include in our models. Finally, cor-
tisol was measured over a single day; although this is also the case
in the majority of studies of cortisol and health outcomes, values
on a single day may be affected by situational factors, increasing
variability in findings.

5. Conclusions

A steeper cortisol slope measured two months following CABG
surgery was associated with reduced odds of depression 12 months
later. These findings suggest therapeutic benefit may be attained by
intervening in the weeks following cardiac surgery.

Conflict of interest

None.

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in the decision to submit the article for publication.

Contributors

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