

Original Articles

Depression is associated with flatter cortisol rhythms in patients with coronary artery disease

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Abstract

Objective: Depression is associated with coronary heart disease, but the underlying mechanisms are not fully understood. Cortisol is involved in the development of coronary artery disease (CAD), but evidence directly linking depression with cortisol in patients with CAD is limited. This study evaluated cortisol output over the day in patients with suspected CAD in relation to depressive symptoms. **Methods:** Eighty-eight patients who were being investigated for suspected CAD (defined by clinical symptoms plus positive exercise tests or myocardial perfusion scans) took eight saliva samples over the day and evening. Depressed mood was assessed with the Beck Depression Inventory. Actigraphy was used to define time of waking objectively. **Results:** The cortisol awakening response and cortisol rhythm over the remainder of the day and evening were analyzed

separately. Fifty-two (61.9%) patients were later found to have definite CAD on angiography, while the remainder did not. The cortisol slope over the day was flatter in more depressed patients with CAD ($P<.001$) but was not related to depression in patients without CAD ($P=.68$). This effect was due to the combination of lower cortisol early in the day and higher cortisol in the evening in more depressed CAD patients, independent of age, gender, medication, and times of waking and sleeping ($P=.003$). Additionally, cortisol measured on waking and 15 and 30 min after waking was greater in CAD than in non-CAD patients ($P=.04$), but was not related to depression. **Conclusions:** The flatter cortisol rhythms of more depressed CAD patients may contribute to the progression of coronary atherosclerosis.

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Introduction

Major depressive disorders and subclinical depression are associated with future coronary heart disease (CHD) in initially healthy populations, and with adverse cardiac prognosis following acute coronary syndrome (ACS) [1,2]. One of the mechanisms that may link depression with CHD is disturbed cortisol regulation. Cortisol is involved in the pathophysiological processes contributing to atherogenesis including disturbed metabolism, abdominal adiposity and insulin resistance, prothrombotic responses and vascular

inflammation [3]. Heightened cortisol output is partly responsible for vascular endothelial dysfunction in depressed individuals [4]. Coronary artery calcification is associated with flattened cortisol profiles over the day in middle-aged adults [5]. A prospective association between cortisol and future CHD has been documented in middle-aged men [6], while acute cortisol elevation following ACS predicts adverse cardiac outcomes [7,8]. Raised cortisol concentrations also predict mortality in patients with chronic heart failure [9].

The literature relating cortisol with depression is complex, but impaired suppression of cortisol secretion by dexamethasone is characteristic of a subset of clinically depressed individuals, and elevated basal levels may also be present [10–13]. Elevated cortisol in the morning is a predictor of future depression in high-risk individuals

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[14,15] and has been associated with a history of depression [16]. An association between cortisol levels over the day and depressed mood assessed with the Beck Depression Inventory (BDI) has also been described [17].

There is, however, limited evidence directly linking depression with cortisol in coronary artery disease (CAD). Otte et al. [18] found that elevated 24-h urinary cortisol was associated with clinical depression in patients with established CAD, but studies of patients following ACS have been inconsistent [19,20]. An additional problem is that awareness of disease may contribute to disturbed mood and cortisol profiles. A diagnosis of coronary disease is stressful, and patients may respond with neuroendocrine activation and depressed mood. In the present study, we therefore investigated patients with chest pain who had been referred to hospital for specialist diagnosis before definitive coronary angiography had been carried out. The majority of patients were diagnosed with CAD, but some were found not to have occluded arteries. Neither investigators nor patients were aware of actual clinical disease state at the time of cortisol measurement. This allowed us to assess the relationship between depressed mood and cortisol in patients with and without definite CAD who had endured similar clinical experiences in terms of diagnostic testing. We also evaluated the possible role of sleep, since disturbed sleep in depression may influence diurnal cortisol profiles [21].

Methods

Patients

Participants were 88 patients recruited from Rapid Access Chest Pain clinics in three London hospitals. They had been referred to the clinics by general practitioners or hospital physicians because of chest pain and were regarded as probable CAD cases on the basis of symptomatology plus positive exercise tests or positive myocardial perfusion scans. They participated in the study prior to coronary angiography. All patients had experienced new onset chest pain, had been referred to the specialist clinic, and had positive results on risk-stratifying tests. Patients who were and were not subsequently diagnosed as having definite current CAD thus underwent identical clinical procedures and were all likely to have anticipated a cardiac diagnosis. Patients were excluded if they were prescribed antidepressant or steroid medication, had a current psychiatric illness, could not speak English, or suffered from significant noncardiac (cancer, renal, pulmonary, or neurological) disease, or other cardiac disorders (heart failure, valvular disease, major arrhythmia).

A total of 144 patients were eligible to take part, of whom 56 refused. The main reasons given were travel problems (patients had to come to the laboratory on two consecutive days), or because patients were too busy with work or other commitments. Patients who declined were significantly older

(mean 64.9, S.D. 10.2 years) than those who took part (mean 61.1, S.D. 9.8 years, $t=2.16$, $P=.032$), but did not differ in gender distribution. The study was approved by the medical research ethics committees of the participating hospitals, and all patients provided signed consent.

Procedure

Patients were recruited in the outpatient clinics, where the study was explained. Subsequently, they attended the research laboratory at University College London individually on the morning of Day 1 of the study. Anthropometric measures were taken and participants were equipped with a 24-h Holter monitor (data described elsewhere) and a wrist actigraph. The cortisol sampling procedure was explained and practiced. Patients returned to the laboratory at the same time on the next day (Day 2), at which time an interview about the study period was completed. A questionnaire including the BDI was also administered.

Measures

Depression was assessed with the BDI [22]. Scores could range from 0 to 63, with higher values indicating more depressive symptoms. The BDI is widely used in studies of cardiac patients and is one of the questionnaires recommended in the National Heart Lung and Blood Institute Working Group Report on depression in cardiovascular disease [23]. The sample was divided into patients with elevated BDI scores (≥ 10) and low BDI scores for analysis. Information about age, marital status, ethnicity, whether or not the patient lived alone, education, employment, household income, medication, smoking status, and psychiatric history was obtained by interview. Weight and height were measured, from which body mass index (BMI) was calculated. Prior history of CHD (previous myocardial infarction, percutaneous coronary intervention, etc.) was obtained from clinical notes. After the patients had completed the study, we collected findings from their subsequent angiography, recording the presence or absence of current CAD, and the number of significantly diseased coronary arteries.

Cortisol was collected from saliva samples using Salivettes (Sarstedt, Leicester, UK). Measures were taken soon after arriving in the laboratory (between 9:00 and 10:00 a.m.), and patients were instructed to take further samples at 11:00 a.m., 4:00 p.m., 7:00 p.m., and just before bed. On Day 2, they were asked to take samples immediately on waking and at 15 and 30 min after waking. Samples were returned to the laboratory later in the morning, and salivas were stored in a freezer at -20°C until analysis which was carried out using a high-sensitivity chemiluminescence assay at Technical University Dresden (Dresden, Germany). Inter- and intra-assay coefficients of variance were $<8\%$.

Physical activity was measured with a wrist actigraph (Actiwatch, Cambridge Neurotechnology, Cambridge, UK).

This device (distributed in the USA by Mini Mitter) is a piezoelectric motion sensor. Data were analyzed using proprietary software to define the following parameters: wake time in the morning, sleep latency (interval between going to bed and falling asleep), and sleep efficiency (proportion of the time in bed spent sleeping). The Actiwatch has been validated against polysomnography in both healthy populations and insomnia samples [24], and is used extensively in population and clinical studies (e.g. Ref. [25]). Patients were also asked whether or not they had slept well on the night before morning cortisol assessments.

Statistical analysis

Two patients failed to complete the BDI, and two patients had missing cortisol data over the day, so analyses were carried out on 84 individuals. Fifty-two (61.9%) were diagnosed as having CAD on the basis of having one or more vessels with $\geq 50\%$ stenosis on angiography, while 32 (38.1%) did not have significant CAD. The CAD group had an average 1.95 ± 0.82 significantly stenosed vessels. The CAD and non-CAD groups were compared on socio-demographic, clinical, and sleep characteristics using χ^2 for categorical and *t*-tests for continuous variables. Separate analyses were carried out of cortisol over the day (measured on Day 1) and the cortisol awakening response (CAR) measured on Day 2. Cortisol over the day was analyzed using repeated measures analysis of variance with clinical group (CAD/non-CAD) and depression group (BDI ≥ 10 / <10) as between-subject factors, and the five samples over

the day and evening as within-subject factors. The Greenhouse Geisser correction of degrees of freedom was computed when appropriate. Subsequently, analyses of covariance were performed with age, gender, and medication with β -blockers as covariates. The slope of cortisol decline was calculated as the reduction in cortisol per hour between the laboratory (10:00 a.m.) and bed time sample.

The CAR is the change in cortisol that occurs over the first 20–30 min following waking [26] and was assessed by repeated measures analysis of the waking, 15-, and 30-min saliva samples. The CAR is critically dependent on the waking cortisol sample being obtained without substantial delay, since postponement can reduce the magnitude of the awakening response [27]. Time of waking on Day 1 was based on self-report, while time of waking on Day 2 (when the CAR was assessed) was defined objectively on the basis of characteristic increases in physical activity assessed using the Actiwatch. We have recently shown that delaying the ‘waking’ sample by up to 15 min following objectively defined waking does not substantially influence the CAR [28]. Only individuals with delays >15 min were therefore excluded from CAR analyses, leaving 72 patients in the analyses.

Results

Patients with CAD were significantly older and more likely to be male than those without CAD (Table 1). There were no differences in education, marital status, smoking, or

Table 1
Characteristics of patients with and without CAD

	Coronary artery disease (<i>n</i> =52)	No coronary artery disease (<i>n</i> =32)	<i>P</i> difference
Gender			
Men	41 (78.8%)	17 (53.1%)	.017
Women	11 (21.2%)	15 (46.9%)	
Age (years)	63.9 \pm 8.8	58.3 \pm 9.7	.008
Ethnicity (white)	37 (71.2%)	24 (75.0%)	.80
Educational attainment (high school and above)	30 (57.7%)	16 (50.0%)	.51
Marital status (married)	29 (55.8%)	22 (68.8%)	.26
Smoking status			
Current smoker	13 (25.0%)	7 (21.9%)	.45
Former smoker	23 (44.2%)	12 (37.5%)	
Never smoker	16 (30.8%)	13 (40.6%)	
Body mass index (kg/m ²)	26.0 \pm 3.5	27.7 \pm 4.4	.078
Medication			
β -Blockers	38 (73.1%)	18 (56.3%)	.15
Statins	44 (84.6%)	25 (78.1%)	.56
Aspirin	47 (92.2%)	27 (84.4%)	.30
ACE Inhibitors	24 (52.2%)	3 (10.0%)	.001
Previous CHD	14 (26.9%)	2 (6.3%)	.022
History of depression	8 (15.4%)	9 (28.1%)	.17
BDI (mean)	10.12 \pm 6.7	10.25 \pm 8.0	.94
BDI ≥ 10	23 (44.2%)	13 (40.6%)	.82
Sleep latency (min)	12 \pm 14	20 \pm 26	.073
Sleep efficiency (%)	78.9 \pm 16.9	79.1 \pm 17.0	.96
Wake up time (h \pm min)	6:14 \pm 64	6:03 \pm 63	.43
Sleep quality (good)	31 (59.6%)	23 (74.2%)	.24

Table 2
Summary of statistical associations

		Waking cortisol level	Cortisol awakening response	Cortisol over the day	Cortisol slope over the day
CAD vs. non-CAD	Complete sample	$F=0.48, P=.49$	$F=4.36, P=.04$	$F=0.45, P=.72$	$F=0.01, P=.93$
CAD group	High vs. low BDI	$F=2.96, P=.09$	$F=2.39, P=.13$	$F=9.32, P<.001$	$F=16.7, P<.001$
Non-CAD group	High vs. low BDI	$F=0.80, P=.38$	$F=2.34, P=.14$	$F=0.54, P=.58$	$F=0.01, P=.97$

F values from analysis of variance and associated *P* values.

history of clinical depression. The majority of the participants were prescribed β -blockers, aspirin, and statins, with no differences between groups. However, CAD patients were more likely to be prescribed ACE inhibitors. CAD patients were more likely to have a history of CHD (previous ACS, etc.), though rates were low. A total of 19.0% of the sample had a previous history of CHD, and as would be expected significantly more (26.9%) of the CAD-positive group had a previous history compared to the non-CAD group (6.3%) ($P=.02$). Scores on the BDI averaged 10.17, with 42.9% scoring ≥ 10 , while 14% had BDI scores ≥ 18 . There were no differences between CAD and non-CAD patients in depression scores. The two groups did not differ in sleep characteristics.

Depression and cortisol over the day

The reported times of cortisol samples over Day 1 were 09:48 h \pm 30.7 min, 11:34 h \pm 43.0 min, 16:14 h \pm 26.1 min, 19:18 h \pm 37.4 min, and 23:24 h \pm 68.5 min, indicating good adherence to the protocol. Cortisol averaged 6.25 \pm 2.5 nmol/l over the day, and the cortisol slope averaged 0.74 \pm 0.48 nmol/l per hour. Cortisol over the day was not associated with age, smoking status, BMI, medication with statins, aspirin or ACE inhibitors, or with time of waking in the morning. But women had lower cortisol over the day than men (means 5.04 \pm 1.79 vs. 6.79 \pm 2.53 nmol/l, $P=.002$) and flatter cortisol slopes (means 0.46 \pm 0.30 vs. 0.87 \pm 0.49 nmol/l per hour, $P<.001$). Additionally, patients taking β -blockers had higher average cortisol over the day and evening (means 6.67 \pm 2.55 vs. 5.39 \pm 2.06 nmol/l, $P=.024$).

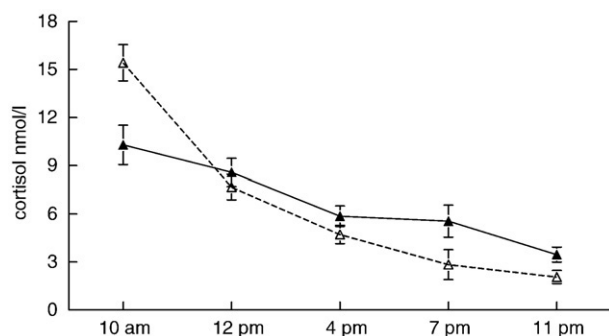


Fig. 1. Mean salivary cortisol across the five sample points of the day and evening in CAD patients with BDI scores ≥ 10 (solid lines) and < 10 (dashed lines), adjusted for age, gender, β -blockade, and reported time of waking and going to bed. Error bars are standard errors of the mean (S.E.M.).

Table 2 summarizes the statistical analyses of cortisol. There was a significant interaction between CAD status, depression, and time in the repeated measures analysis of variance ($P=.009$). Depression was related to cortisol output in CAD patients ($P<.001$), but not in the non-CAD group ($P=.68$). The results for CAD patients are summarized in Fig. 1. Cortisol early in the day was lower in the depressed than in the nondepressed CAD patients after adjustment for age, gender, β -blockade, and time of waking in the morning ($P=.003$). But the reverse pattern emerged later in the day, with cortisol being higher among depressed CAD patients at bed time ($P=.038$), with a near significant effect at 7 p.m. ($P=.060$). The cortisol slope over the day was therefore substantially lower in depressed than in nondepressed CAD patients (means 0.51 \pm 0.49 vs. 0.99 \pm 0.46 nmol/l per hour, adjusted for age, gender, β -blockade, and time of going to bed, $P<.001$). The same pattern of results emerged when the BDI was entered as a continuous variable into a regression on the cortisol slope over the day, and when a more stringent criterion for depression (BDI ≥ 15) was applied. Cortisol over the day and evening was unrelated to sleep latency, sleep efficiency, or subjective sleep quality.

Depression and cortisol awakening responses

Participants woke at 06:19 h \pm 65 min on average. Cortisol increased markedly between waking and 30 min in the complete sample ($P<.001$). Sleep efficiency and sleep latency were unrelated to CAD status or to cortisol over the early morning period. More depressed patients woke

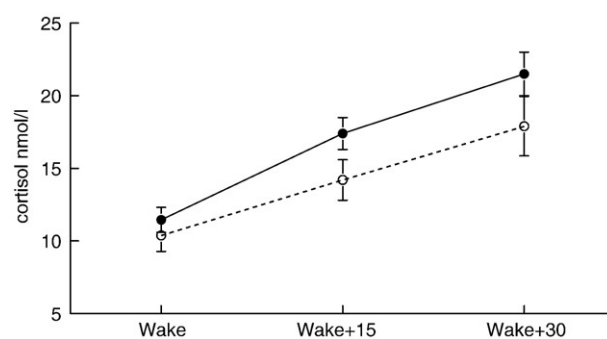


Fig. 2. Mean salivary cortisol on waking (wake), 15 min (wake+15) and 30 min (wake+30) after waking in CAD patients (solid line) and non-CAD patients (dashed lines), adjusted for age, gender, β -blockade, and objective time of waking. Error bars are S.E.M.

earlier in the morning, and early waking was in turn associated with a lower cortisol on waking ($r=0.26, P=.029$). The CAR was not related to depression, but cortisol levels were greater in CAD than in non-CAD groups ($P=.04$). As shown in Fig. 2, cortisol was higher in the CAD than in non-CAD groups throughout the waking period after adjustment for gender, β -blockade, and waking time. The increase in cortisol between waking and 30 min did not differ in CAD and non-CAD groups.

Discussion

This study evaluated cortisol output over the day in patients with suspected CAD in relation to depressive symptoms measured with the BDI. The results indicate that the cortisol slope over the day was flatter in depressed patients with CAD, but was not related to depression in patients without CAD. This effect was due to the combination of lower cortisol early in the day and higher cortisol in the evening in more depressed CAD patients and was independent of age, gender, medication, and times of waking and sleeping. Additionally, cortisol early in the day, measured on waking and 15 and 30 minutes after waking, was greater in CAD than in non-CAD patients, but did not relate to depression.

Depression was assessed as a subclinical mood variable rather than a clinical category in this investigation. The reason is that subclinical depressive symptoms are associated with the development of CAD and with prognosis following acute cardiac events [1,2]. Moderately elevated BDI scores (≥ 10 , the same criterion as used in this study) have been shown to predict cardiac mortality and nonfatal recurrence in patients following ACS [29–31]. The association with the flatter cortisol rhythm over the day in CAD patient is therefore potentially significant clinically.

Previous studies of cortisol and depression in patients with documented CAD have been mixed. Otte et al. [18] showed a positive relationship between depression assessed by both diagnostic interview and questionnaire and 24-h urinary cortisol in the Heart and Soul Study. This was independent of age, gender, BMI, smoking, comorbid illness, medication, and cardiac function. Twenty-four-hour measures do not allow the profile of cortisol output over the day to be analyzed. Whitehead et al. [20] measured salivary cortisol over the day and evening in patients hospitalized for ACS and found no association with depression, although type D (distressed) patients had an elevated CAR. By contrast, a positive correlation between morning cortisol and depression was recorded in a study of 285 patients assessed 3–6 months after ACS [19]. The absence of an association in patients without CAD is consistent with the findings of Taylor et al. [32] in depressed individuals with elevated cardiovascular risk factors but without coronary disease.

Flatter cortisol rhythms over the day can only be defined using repeated sampling and are difficult to assess using blood sample in everyday life settings. Flatter cortisol slopes have previously been associated with greater tension and anger over the day [33], posttraumatic stress disorder [34], and poor marital relationship quality in both younger and older adults [35,36]. Women with metastatic breast cancer have flatter cortisol slopes than healthy comparison groups [37], and those with the flattest rhythms appear to have greater mortality risk [38]. Matthews et al. [5] recently demonstrated that flatter cortisol profiles were associated with coronary artery calcification (an indicator of subclinical CAD) in apparently healthy middle-aged adults. One feature of flatter rhythms is that cortisol levels are elevated in the evening, even though values are low compared with earlier in the day. This pattern was apparent in the present study, with higher cortisol among depressed than among nondepressed CAD patients. An elevation of cortisol in the evening has been demonstrated in a number of studies of clinically depressed patients [39].

Cortisol early in the day and the CAR were analyzed separately from cortisol over the remainder of the day and evening. The CAR is a distinctive component of the diurnal cortisol profile [26]; correlations between the CAR and other indicators of cortisol over the day are low [40,41], and heritability patterns differ [42]. In the present study, we found no differences in the magnitude of the CAR (the rise from waking to 30 min) in relation to depression, or between CAD and non-CAD patients. However, the overall level of cortisol output was elevated in CAD patients (Fig. 2). This indicates that raised cortisol levels in the early morning period are associated with definite coronary disease in patients with cardiac symptoms. This study was cross sectional, so the causal significance of this pattern cannot be determined. Nevertheless, the findings are consistent with the study of 238 women following ACS, in which early morning cortisol was elevated in only those with significant ($\geq 50\%$) coronary stenosis [43]. Davey Smith et al [6] showed that cortisol/testosterone ratios predicted the incidence of CHD over a 16.5-year follow-up of middle-aged men in Wales, but that effects were mediated by insulin resistance. In a large case-control study, patients prescribed oral glucocorticoids were found to be at an increased risk of CHD and heart failure [44]. A recent prospective study of patients with chronic heart failure showed that cortisol sampled early in the day was an independent predictor of mortality [9].

A strength of this study is that patients were investigated prior to a definitive diagnosis of current CAD. Thus the CAD and non-CAD groups were both in the same clinical situation and knowledge of illness could not influence either depression ratings or cortisol. The study therefore included a comparison group of patients without CAD, unlike most studies of depression and cortisol in relation to cardiovascular disease [18–20]. The delineation between the two groups was based on whether they had current CAD of a sufficient severity to cause chest pain. Some patients may have had a previous history of CHD but a normal coronary angiogram and would

not then be placed in the CAD-positive group. It should also be noted that the non-CAD group not only had chest pain, but also positive exercise and/or myocardial perfusion scans. These participants were therefore distinct from the group of patients who present with chest pain of noncardiac origin but no other positive objective test results, among whom psychiatric problems are relatively common [45]. We do not know whether mild atheroma or other factors such as gastro-oesophageal disease or chest wall syndromes accounted for the positive objective test results [46], since it was not feasible to follow the non-CAD group further to establish a definitive diagnosis of the causes of their chest pain. It is probable, however, that these factors would serve to reduce the differences between CAD and non-CAD groups, so the presence of distinctive cortisol patterns is even more striking. It should also be noted that the levels of depressed mood were comparable with those found in other investigations of patients with CAD [18,47].

The study also has a number of limitations. The sample size was relatively small, and patients could not be assessed in the absence of medication. Cortisol was recorded over a single day, and repeated measures are likely to generate more robust findings [48]. Compliance with the sampling times was assessed by self-report and it was not possible to assess the reliability of these reports objectively. Nonetheless, the results add to the evidence linking cortisol, depression, and cardiovascular disease, in showing that depressed patients with definite CAD have flatter cortisol profiles over the day than nondepressed patients, while an elevated cortisol level in the first 30 min after waking is characteristic of patients with CAD. Future studies will determine whether these patterns predict prognosis, and whether modifying depression will lead to an altered profile of cortisol secretion in cardiac patients and thereby influence the progression of CAD.

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