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Morning and afternoon serum cortisol level in patients with post-myocardial infarction depression

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Abstract

Background: *Post-myocardial depression is a highly prevalent condition which worsens the course and prognosis of coronary artery disease. One possible pathogenetic factor is dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in cortisol profile disturbances.*

Methods: *Thirty seven patients hospitalized due to a first myocardial infarction (MI) were enrolled in this study. The Beck Depression Inventory (BDI) was used to rate the severity of their depressive symptoms. Morning and afternoon serum cortisol samples were taken on the fifth day of the MI.*

Results: *Depression, defined as BDI ≥ 10, was present in 34.4% of the patients. A statistically significant difference was observed between the mean morning and the evening plasma concentrations in patients with depression compared to the no-depression group: $F(1.29) = 5.0405$, $p = 0.0328$.*

Conclusions: *Patients with depressive symptoms directly after MI have a flattened diurnal serum cortisol profile. This is particularly expressed in patients with longer lasting symptoms.* (Cardiol J 2019; 26, 5: 550–554)

Key words: depression, myocardial infarction, cortisol, hypothalamic pituitary adrenal axis

Introduction

Approximately 1 in 5 patients after myocardial infarction (MI) develop depression during their initial hospitalization [1]. Depending on the diagnostic method and criteria used, the prevalence of post-MI depression varies from 7.2% to 47%.

The pathogenesis of post-MI depression is complex. Apart from psychological and psychosocial factors, biological elements play a significant role. They include immune, endocrine, autonomous and nutritional aspects [2–5]. Post MI depression can be defined as an "acute sickness response" triggered by MI [6]. This response includes the activation of proinflammatory cytokines, the autonomous nervous system and hypothalamic-pituitary-adrenal (HPA) axis, which in some cases may prolong dysregulation in these systems. One of the effects of this dysregulation is probably the selective dysfunction of the prefrontal cortex and anterior cingulate gyrus, precipitating depressive symptoms [7]. Studies involving the immune and endocrine (mainly HPA axis) profiles in patients with post-MI depression may elucidate the pathophysiology of post-MI depression and its effect on the course and prognosis of the condition in patients after MI [7]. Unfortunately there remain very few studies in this area.

The aim of this study was to evaluate morning and afternoon serum cortisol concentrations as parameters of the HPA axis function in patients with depression after MI. The comparison group was composed of patients after MI without depression.

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Methods

Thirty-seven patients (8 women; 22%) admitted to the First Cardiology Department at the Medical University of Gdansk were enrolled, 32 patients completed the study. They were hospitalized due to a first myocardial infarction with ST elevation (STEMI). The left ventricular ejection fraction (LVEF) was ≥ 40%, and mean body mass index 26.9 kg/m^2. All patients had a cardiovascular intervention and received standard pharmacological treatment. Exclusion criteria were endocrine diseases such as diabetes, hypo- or hyperthyroidism, severe renal or hepatic failure, hormone therapy, active addiction to psychoactive substances and the presence of psychiatric disorders other than depression.

The study was approved by the Independent Ethics Committee of the Medical University of Gdansk (approval number NKEBN/205/2006). For each participant written consent was obtained.

All patients were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders [8] and rated with the Beck Depression Inventory (BDI) [9]. The evaluation took place 3 times over a 6 month period: on the fifth day (during the first 5 days) and on the third and sixth month after MI. Medical history of 9 patients revealed depression in the past — none of them suffered from the disorder directly before MI. All patients included in the depression group met the criteria of post-MI depression.

Blood samples for cortisol analysis were collected on the fifth day of the MI twice. First between 8 and 10 am and later between 3 and 5 pm. Both times, two samples were taken at least 20 min apart: two samples in the morning and two samples in the afternoon. The blood was centrifuged immediately and the serum was frozen at –80°C for batch analysis.

The cortisol concentration was measured with a chemiluminescent microparticle immunoassay (CIMA) for the quantitative determination of cortisol in the human serum, on the Architect system (Architect®, Abbott, DE) kit. The intra-assay coefficient of variation (CV) ranged from 2.1% to 5.5% and total CV values ranged from 2.5% to 7.7%. The sensitivity was 22.07 nmol/l (0.8 μg/dL). The cortisol concentration units were nmol/L and the result was an average of two measurements. All protocol requirements (6-month observation, complete blood sampling) being fulfilled, 32 patients (including 7 women — 22%) qualified for further analysis. These patients were divided into two groups depending on their BDI score on the fifth day after MI: < 10 (non-depressed) and ≥ 10 (depressed).

Statistical analysis

Statistical analysis was performed with the use of Statistica v.12.5.1920 and StatsDirect v.3.0.183. Depending on the distribution (Wilk-Shapiro test), comparison was done with the help of the Student t-test or Mann-Whitey U test. ANOVA with repeated measures was used when the changes between the morning and afternoon cortisol levels were compared between the two groups. All tests were two-tailed with an alpha = 0.05.

Results

Demographic, clinical and hormonal characteristics of the two groups are presented in Table 1.

There were no differences in the morning and afternoon cortisol concentrations between depressed and non-depressed groups (Table 1).

The changes of cortisol levels between the morning and afternoon in the two groups are shown in Figure 1. A statistically significant difference was found between the groups (ANOVA with repeated measurement).

Post-hoc analysis (Bonferroni test) showed a significant difference between the morning and afternoon cortisol levels only in the non-depressed group ($p = 0.0004$). The presence of depressive episodes in the past did not change these results ($F = 5.04$, $p = 0.0328$ ANOVA with repeated measures).

No differences in cortisol concentrations were observed between women (n = 6) and men (n = 7) in the depressed group ($F(1.9) = 0.067$, $p = 0.8019$).

No significant differences between morning and afternoon levels of cortisol were found in both subgroups based on the length of depression. The longer lasting depression group (≥ 3 months) differed significantly from the no depression group in the morning and afternoon ratio (Table 2)

In the depression group (BDI ≥ 10), patients with the diagnosis of major depression (n = 4) did not differ in their cortisol concentrations from the rest of depression group patients (n = 7) (unpaired t-test).

Discussion

In this study the BDI was used to measure depression. The cut-off score of 10 was used to differentiate between depressed and non-depressed

Table 1. Demographic and clinical variables.

	All patients	Beck Depression Inventory (BDI)	
		≥ 10	< 10
N	32	11 (34.4%)	21 (65.6%)
Women	7 (22%)	6 (55%)	1 (5%)
Age [years]#	54.7 (51.9, 57.5)	53.4 (47.0, 59.7)	55.4 (52.3, 58.5)
Weight [kg]#	81.2 (75.4, 87.0)	80.0 (68.2, 91.8)	81.8 (74.7, 88.9)
Body mass index [kg/m^2]#	26.9 (25.5, 28.3)	25.5 (23.1, 27.9)	27.6 (25.8, 29.4)
Tail circumference [cm]#	96.2 (92.1, 100.2)	94.2 (85.7, 102.7)	97.3 (92.5, 102.1)
Waist to hip ratio#	0.96 (0.93, 0.98)	0.95 (0.89, 1.00)	0.96 (0.93, 0.99)
Depression in the past	9	5	4
BDI score (3rd day)##	5 (1, 12)	14* (12, 21)	2 (1, 5)
BDI (3rd month)## Incidence	6	6	0
BDI (6th day)## Incidence	3	2	1
Major depressive disorder (DSM IV-TR)+	4	4	0
Morning plasma cortisol level [nmol/L]#	366.3** (327.7, 404.8)	368.8 (299.1, 438.4)	364.9*** (314.4, 415.5)
Afternoon plasma cortisol level [nmol/L]#	292.8 (245.3, 340.4)	351.6 (261.5, 441.6)	262.0 (206.1, 317.9)
Morning/afternoon cortisol ratio#	1.55 (1.32, 1.78)	1.21 (0.94, 1.49)	1.73**** (1.42, 2.03)

+DSM IV-TR — Diagnostic and Statistica Manual of Mental Disorders Fourth Edition Text Revision
#mean (95% confidence interval [CI])
##median (interquartile range)
*vs. group (< 10): p < 0.0001; Mann-Whitney U test, difference between medians = 12 (9, 17)
**vs. afternoon cortisol: p = 0.0006; paired t-test, difference between means (95% CI) = 73.4 (34.5, 112.3)
***vs. afternoon cortisol: p = 0.0001 paired t-test, difference between means (95% CI) = 102.9 (57.9, 148.0)
****vs. group (≥ 10): p = 0.0228; Student's t-test, mean of differences (95% CI) = 0.34 (0.06, 0.97)

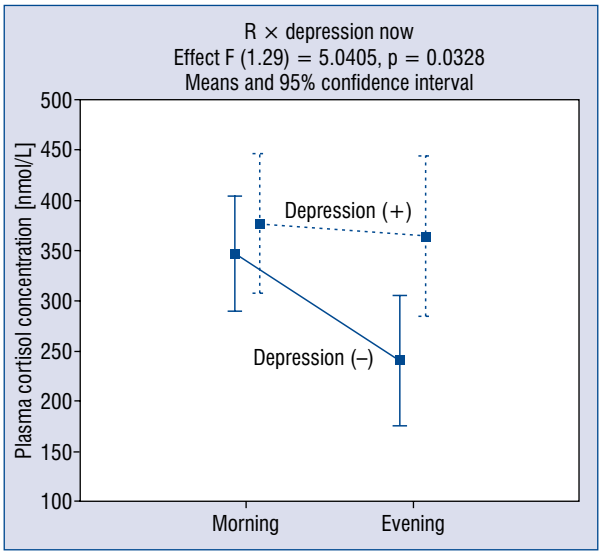

Figure 1. Diurnal change of plasma cortisol level and the presence of depression (Beck Depression Inventory ≥ 10): ANOVA with repeated measures.

patients. It is this criterion that is most commonly used in post-myocardial depression studies. Many studies have shown that depression as defined by a BDI ≥ 10 is related to increased cardiovascular risk, including death [10–14].

A BDI score ≥ 10 was observed in 11 (34.4%) patients. Four (12.5%) patients met criteria of having suffered a major depressive episode according to DSM-IV-TR. These data correspond with other studies [1, 10, 11].

An immediate increase in cortisol after MI has been previously reported [15, 16]. In the (aforementioned) studies cortisol concentration normalised during the first 72 h after MI. In the present study, serum cortisol was measured on the fifth day of MI. Morning as well as afternoon concentrations did not exceed physiological values. The depressed and non-depressed groups did not differ from each other in either morning or afternoon cortisol concentration, which is in line with the results published by Whitehead et al. [17]. However, a significant difference was found in the diurnal profile (morning–afternoon) of the cortisol level between these two groups. The non-depressed group showed a normal cortisol secretion rhythm; the morning cortisol level was significantly higher than the afternoon level. Such a significant difference was not recorded in the de-

Table 2. Clinical variables and length of depression (BDI ≥ 10)

	Presence of depression (BDI ≥ 10) after myocardial infarction		
	NO {1}	≥ 3 months {2}	< 3 months {3}
N	21 (65.6%)	6 (18.8%)	5 (15.6%)
BDI score (3rd day)##	2 (1, 5)	14* (12, 18)	15** (11, 21)
BDI score (3rd month)##	3 (1, 5)	12*** (12, 14)	4 (4, 6)
BDI score (6th day)##	2.5 (1, 5)	10§ (8, 12)	3.0 (3, 5)
Major depressive episode (DSM IV-TR)+	0	3	1
Morning plasma cortisol level [nmol/L]#	364.9§§ (314.4, 415.5)	353.0 (348.3, 457.7)	387.7 (242.9, 532.5)
Afternoon plasma cortisol level [nmol/L]#	262.0 (206.1, 317.9)	344.8 (239.2, 450.5)	359.7 (137.3, 582.2)
Morning/afternoon cortisol ratio#	1.73 (1.42, 2.03)	1.07§§§ (0.66, 1.48)	1.38 (0.89, 1.88)

+DSM IV-TR — Diagnostic and Statistica Manual of Mental Disorders Fourth Edition Text Revision
#mean (95% confidence interval [CI])
##median (interquartile range)
*vs. group {1}: p = 0.00001; Mann-Whitney U test 12 (9, 17)
**vs. group {1}: p = 0.00003; Mann-Whitney U test 12 (8, 20)
***vs. group {1}: p = 0.00004; Mann-Whitney U test (95% CI) = 10 (7, 14); {3}: p = 0.008; Mann-Whitney U test (95% CI) = 8 (4, 17)
§vs. group {1}: p = 0.002; Mann-Whitney U test (95% CI) = 7 (3, 10); {3}: p = 0.016; Mann-Whitney U test (95% CI) = 6 (2, 10)
§§vs. afternoon cortisol: p = 0.0001; paired t-test (95% CI) = 102.9 (57.9, 148.0)
§§§vs. group {1}: p = 0.0331; Student's t-test (95% CI) = –0.31 (–1.25, –0.06)

pressed group, which suggests that flattened daily rhythm of cortisol is more expressed in patients with a longer (≥ 3 months) duration of depression.

According to available research there have been no previous studies on diurnal cortisol profile in patients with depression shortly after MI.

These observations may have important clinical implications. A flattening of the diurnal rhythm of cortisol has been observed in young patients with major depressive disorder [18] and in adolescence patients after major depression [19]. This had a negative impact on health [20]. In a healthy population it is connected with a decline in cognitive functions [21] which could lead to a lowered ability in dealing with stress.

The absence of normal cortisol diurnal rhythm in the present post-infarct depression group could influence abilities in dealing with stress and, as a result, maintain depressive symptoms and increase the risk of somatic complications. In the presented study patients with longer depression (lasting at least 3 months) had a particularly low morning to afternoon cortisol concentration ratio. A flatter diurnal rhythm of cortisol secretion has been observed before in patients with coronary artery disease (CAD) who scored ≥ 10 points in BDI [22].

A flatter diurnal cortisol slope is related to a worse prognosis in patients after coronary artery bypass graft surgery [23], and it can be also responsible for the progression of atherosclerosis in patients with depression and CAD [24]. No somatic complications were observed in either the depressed or non-depressed group during the 6-month study. The interrelations however, between post-MI depression, the course of CAD and diurnal cortisol rhythm disturbance needs further study.

Limitations of the study

This study has a number of limitations. Firstly, the study group is quite small. Secondly, cortisol concentration was only tested on 1 day. Additional samples on subsequent visits after 3 and 6 months, could broaden interpretation of the results. Thirdly, to some extent, the lack of a control group is also a limitation, although the aim of this study was to determine the cortisol profile in patients with depression compared to patients without depression on the fifth day after MI. Another shortcoming is the small number of women in the study group (22%) and the imbalance between the number of women in the depressed (6) and the non-depressed group (1). Preliminary findings of this study need further confirmation in larger groups with comparisons to healthy controls.

Conclusions

The presence of depressive symptoms (BDI ≥ 10) directly after MI is related to a flattening of the diurnal serum cortisol profile. This seems to be expressed particularly in patients with longer lasting (≥ 3 months) depression.

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Conflict of interest: None declared

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