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Depression in patients with acute myocardial infarction: influence on autonomic nervous system and prognostic role. Results of a five-year follow-up study.

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ABSTRACT:

Background ó Although previous studies demonstrated an association between depressive symptoms and cardiac mortality after acute myocardial infarction (AMI) little is know about the possible mechanisms of this association. The aim of this study was to determine whether depressed patients present a cardiac autonomic dysfunction and whether this could represent the mediator of the influence of depression on their prognosis.

Methods ó One hundred consecutive patients with AMI were recruited between January and December 1998. Major Depressive Disorder (MDD) was diagnosed by structured clinical interview and the presence of symptoms of depression was evaluated with self-administered Beck Depression Inventory (BDI). The influence of depression on autonomic nervous system was investigated measuring heart rate variability (HRV) and heart rate (HR) during 24-hour electrocardiographic monitoring. The endpoints of the study were all-cause mortality, recurrent-AMI, revascularization and a composite end-point of all the previous. Potential cofounders for depression status and events were entered into a multivariate regression model.

Results ó Fifteen patients met the criteria for MDD and 35 patients showed mild-to-moderate symptoms of depression; women had a higher prevalence of depression than men (35% vs 9%; $p<0.01$). Depression was not related to the severity of ischaemic disease or to other clinical and demographic variables. Patients with MDD showed lower HRV (76 ± 25SD vs 99 ± 33SD msec; $p<0.01$) and higher HR (77 ± 12SD vs 68 ± 9SD bpm; $p<0.01$) than patients without MDD; moreover mild to moderate symptoms of depression (BDI score≥10) were associated with lower HRV (84 ± 25SD vs 102 ± 35SD msec; $p=0.01$) but not with significantly higher HR.

After a mean follow-up of 60 months MDD was associated with an increase of all-cause mortality (OR 12; 95% CI 2.6-56; $p<0.01$) and of composite end-point (OR 2; 95% CI 1.2-3.6; $p=0.01$) but not with re-AMI and revascularization. In a simple regression HRV values were predictor of mortality ($p<0.01$). However when added in the multiple regression model HRV did not have an independent correlation with the endpoints considered and did not modified the correlation between depression and mortality.

Conclusions ó Patients with post-AMI depression have a cardiac autonomic dysfunction as reflected by decreased HRV and increased HR. This autonomic dysfunction seems not to be an independent mediator of the increased mortality observed in depressed patients during 5-year follow-up.

Key words: acute myocardial infarction; depression; heart rate variability; mortality.

Abbreviations: Acute Myocardial Infarction (AMI); Major Depressive Disorder (MDD); Heart Rate Variability (HRV); Heart Rate (HR); Beck Depression Inventory (BDI); Odds Ratio (OD); Confidence Interval (CI); Standard Deviation Normal to Normal (SDNN); Creatinephophokinase (CPK). Creatinephophokinase Muscolar-Brain (CPK-MB).

INTRODUCTION

Depression after acute myocardial infarction (AMI) is associated with higher patient morbidity and mortality [1-5]. Little is known about the possible pathophysiologic mechanism of this association but factors such as lack of compliance on risk reducing recommendations and prescribed therapies [6] and high dropout from rehabilitation programs are common in depressed patients [7]. In addition to this alterations of behaviour, depression may be responsible of biological effects such as increased platelet activation [8] and cardiac autonomic dysfunction involving arrhythmias and cardiac deaths [9-11]. Heart rate variability (HRV) and mean heart rate (HR) are methods widely used to evaluate cardiac autonomic function and have been reported as relevant predictors of post-AMI mortality.

The aim of this study was to determine whether post-AMI depression is associated with decreased HRV and/or increased HR and whether these foundings represent the mediators of depression on patients prognosis.

METHODS

One hundred consecutive patients admitted in our coronary care unit for AMI were enrolled between January and December 1999. The protocol of the study was approved by the institutional review board and participants provided informed written consent. The diagnosis of AMI was based on the Joint ESC/ACC definition [12]. In-hospital mortality, the presence of other severe psychiatric diseases, alcoholism or antidepressant therapy were considered as exclusion criteria. All patients underwent examinations and therapies considered the most appropriate by the attending cardiologist.

The presence of Major Depression Disorder (MDD) was evaluated with council interview structured on the basis of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM IV) [13] by two psychiatrists between the 7th and the 14th day from admission. Diagnosis of MDD was defined as depressed humour or lost of interest together with at least other four of the

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following symptoms: changes in the weight or in the hunger, lost or excessive sleep, tiring or lost of energies, slowness or restlessness, difficulty to concentrate or fall asleep, guilty feelings, decrease in self-esteem, thoughts of death or suicide. The listed disturbs had to be present since the hospitalisation and causing a functional damage representing a change towards the past.

Patients were also asked to answer the self-administered Beck Depression Inventory (BDI) to measure the severity of humour disease investigated by 21 items on behaviours and symptoms commonly observed in depressed patients [14]. Patients with BDI ≥10 were considered affected by mild-to-moderate symptoms of depression.

Heart rate variability was measured with a 24-hour Holter monitoring after patient mobilisation performed with a DELMar Digicoder. It was obtain before rather than after discharge in order to minimised the potential confound between depression and physical activity. Standard deviation of R-waves intervals of consecutive QRS complexes (Standard Deviation Normal to Normal =SDNN) was used to measure HRV. It reflects all the time-domain HR variability and it is an independent predictor of mortality after AMI [15].

All patients underwent echocardiography and 67 patients coronary angiography.

The interviewing cardiologist was blind to the results of the psychiatric evaluations.

Follow-up: a first medical examination was performed after 3-6 month and a phone interview or an ambulatory examination every year. The follow-up was ended after 5 years. For fatal events the death certificates diagnosis was used.

Endpoints: the adverse events we considered were: all-cause mortality, recurrent AMI, need to further revascularization after discharge (percutaneous or surgical), and a composite end-point of all the previous.

Statistical analysis: continuous variables including age, creatinephosfokinase (CPK), Creatinephosfokinase Muscolar-Brain (CPK-MB) are expressed as medians ± standard deviation and categorical parameters as percentages of the respective strata. The Student t test was used to compare homogeneous continuous variables and the Mann-Whitney unpaired U rank sum test for

non homogeneous distribution (CPK, CPK-MB). The Maximum-Likelihood Chi square test was performed for the categorical variables. All the tests were two-tailed. The multiple regression analyses were run as best subset models applying odds ratio (OR) likelihood scores using as potential confounders in the model the age and gender.

For the composite end-point a multiple regression model was also performed considering as potential confounders all the following variables: age, gender, diabetes mellitus, dyslipidaemia, previous AMI, anterior AMI, non preserved left ventricle ejection fraction, acute treatment with thrombolysis or primary coronary angioplasty and HRV value.

The Kaplan Meier survival and event free actuarial method was used to compare events incidence by different subgroups of patients. The Cox's test was used to test statistical significance of the observed differences.

RESULTS

One hundred patients were enrolled, 77 males and 23 females, with a mean age of 62 ±13SD years. According to the DSM IV criteria 15 patients were affected by MDD; the incidence of MDD was higher among women than in men (35% vs 9%; p<0.01). According to BDI 35 patients showed mild-to-moderate symptoms of depression (BDI ≥10), 30% of men vs 52% of women (p=0.09). The mean BDI value of the entire study population was 8.5 ±8.4SD; patients with MDD showed higher mean values of BDI compared to their counterparts without MDD (22 ±10SD vs 6 ±5SD, p<0.01).

No statistical difference was found for all the variables taken in account, except for gender, when comparing demographic and clinical characteristics of patients with and without depression (Table 1).

Ecg-Holter evaluation: patients with MDD showed significantly lower HRV (SDNN 76 ±25SD vs 99 ±33SD msec; p=0.01) and higher HR (77 ±12SD vs 68 ±9SD bpm; p<0.01) compared to

patients without MDD. HRV was significantly decreased also in patients with BDI ≥10 (84 ±25SD vs 102 ±35SD msec; p=0.01) and the HR was higher (71 ±11SD vs 67 ±9SD bpm) but without statistical significance (p=0.07).

Follow-up: 98 of 100 patients ended the study with a mean follow-up of 60 months (range 54-69). Thirty major adverse events occurred and 6 patients died during the follow-up. In the multiple regression analysis MDD emerged as a significant risk factors for mortality [odds ratio (OR) 12; 95% confidence interval (CI) 2.6 to 56; p<0.01)] and for composite end-point both when correcting for age and gender (OR 1.9; 95% CI 1.01 to 3.4; p=0.04) than when inserting in the model other clinical possible covariates (diabetes mellitus, dyslipidaemia, previous AMI, anterior AMI, non preserved left ventricle ejection fraction, acute treatment with thrombolysis or primary coronary angioplasty and HRV value)(OR 2; 95% CI 1.2 to3.6; p=0.01). Similar to MDD also BDI ≥10 was significantly related in multivariate analysis corrected for age and gender to long-term mortality (OR 9; 95% CI 2 to 43; p<0.01) and to the composite end-point (OR 1.03; 95% CI 1 to 1.1; p=0.02). Both MDD and BDI did not have an independent effect on the revascularization and re-infarction rates (Table 2).

A significant inverse correlation in simple regression was observed between values of HRV and the adverse events occurred (p<0.01). When added in the multiple regression model HRV did not have an independent correlation (p=0.39) with the endpoints considered and did not modified the correlation between depression and mortality (p=0.01), suggesting that HRV was not the mediator of the influence of depression on patients prognosis.

The Kaplan Meier event-free curves for all-cause mortality showed a significant trend between patients with and without MDD (event-free: 79% vs 96%; p=0.008) (Figure1a). Furthermore for the composite end-point a significant difference in event-free survival was observed (50% vs 73%; p=0.02) starting to diverge from the 12th month of follow-up (Figure 1b). For the others tested end-points non statistical significance emerged in event-free curves.

DISCUSSION

Depression is a common co morbidity in patients with AMI, similarly to previous researches in our sample 35% of patients showed mild-to-moderate symptoms of depression (BDI ≥10) and 15% were affected by MDD[1-4,19]. The higher incidence of depression observed in women is well known in general population, although in patients with AMI this finding was not uniformly referred from previous studies [1-4,19].

Several authors observed that depressive symptoms increase mortality risk after AMI, raising the question if depression is a causative factor contributing to a worse prognosis, a consequence, or both [1-5]. In the present study, apart from gender, the presence of depression was not correlated with any other clinical and demographic variables or with severity of ischaemic disease, suggesting that depression was not a consequence of a worse disease.

We observed that both MDD and mild-to-moderate symptoms of depression were associated with increased mortality, even more patients with MDD showed higher risk of mortality than patients with mild-to-moderate symptoms suggesting a direct correlation between severity of depression and influence on the prognosis.

This finding were not univocally referred in literature. Frasure-Smith et al. considering 225 patients with AMI, founded that MDD and BDI ≥10 were both significantly associated with patients cardiac mortality at 6 months follow-up. Although among those patients that survived more than 6 months MDD no longer had an impact on mortality, while BDI ≥10 showed an impact even stroger [4]. Similarly Bush et al. observed that even minimal symptoms of depression (BDI 4 to 9) increased mortality risk after AMI, while the presence of a major psychiatric disorders (MDD, dysthymia, bipolar psychiatric disorder) had no influence on patients prognosis [1]. This finding are not completely clear since patients with MDD should have a higher BDI score and of consequence a stronger association with mortality, fact surprisingly not proven in the previously listed researches.

The association between post-AMI depression and mortality has been indirectly put in question by the ENRICHD clinical trial. This study compared psychological and pharmacological anti-depressive therapy to usual care in 2481 post-AMI depressed patients. After an average follow-up of 29 months anti-depressive therapy failed to reduce the risk of mortality [17] suggesting that the worse prognosis observed in depressed was not a consequence of the presence of depression.

In the present study we observed that event-free curves for the composite end-point start to diverge after 12 months, the reason is probably not unique but the more frequent follow-up visits and the closer time from the event probably represents a stimulus on the unstable treatment compliance of the MDD patients that decreases with the passing of the months.

The correlation of depression with other endpoints than mortality has been previously tested in literature. Similarly to other authors [5-20,21] we observed that depression was associated with increased mortality but not with revascularization and re-AMI; this observation could support the hypothesis of the presence of an autonomic unbalance causing arrhythmia and sudden death rather than other pathophysiologic mechanisms such as platelet activation. However a recent meta-analyses of 22 studies (6367 patients) with an average follow-up of 13.7 months observed that depression was associated with higher risk for mortality and also for new cardiovascular events [18].

The present study shows that MDD and BDI ≥10 are both associated with a relevant cardiac autonomic dysfunction as reflected by increased HR and decreased HRV. Those are two well known indices of cardiac autonomic activity and of risk stratification after AMI. Copie et al. [15] observed that HRV and 24-hour mean HR were strong predictors of mortality in patients with AMI and found that their values could compete with left ventricular ejection fraction for positive predictive accuracy, sensitivity and specificity. Moreover the Cardiac Arrhythmia Suppression Trial (CAST) reported that HRV is a predictor of post-AMI mortality largely independent from clinical and demographic factors [16]. The results of the present study are generally consistent with those of Carney et al revealing the presence of a great autonomic dysfunction in depressed

patients, however Carney did not evaluate the influence of this association on the prognosis with a clinical follow-up [11]. In the present study, during 5-year follow-up we could observed a significant inverse correlation between values of HRV and the composite end-point (p<0.01), confirming the prognostic value of HRV also in this sample. Although when inserted in the multiple regression model the HRV value did not have an independent correlation with any of the endpoints considered. Even more the correlation between depression and mortality remained statistically significant also inserting HRV as covariate in the multiple regression suggesting that this was not the mediator of the influence of depression on patients prognosis.

Limits: the main limit of this study is represented by the small number of the sample and by the low number of deaths (six) that limits the statistical power. Furthermore even if sudden death and not all-causes death is the end-point most related with cardiac autonomic dysfunction and arrhythmias, unfortunately, routine death certificates did not allow a scientifically valid decision about whether deaths were to be considered as sudden or not.

Conclusion – Patients with MDD and mild-to-moderate depressive symptoms after AMI had higher mortality and relevant dysfunction of cardiac autonomic tone, however there is no evidence that this unpaired autonomic function represents the mediator of this increased mortality observed during a long term follow-up.

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Table 1: Clinical characteristics of patients with and without Major Depressive Disorder (MDD), and of patients with symptoms (BDI<10) and without symptoms (BDI ≥10) of depression. (Data shown as number and percentage of the respective strata when not stated)

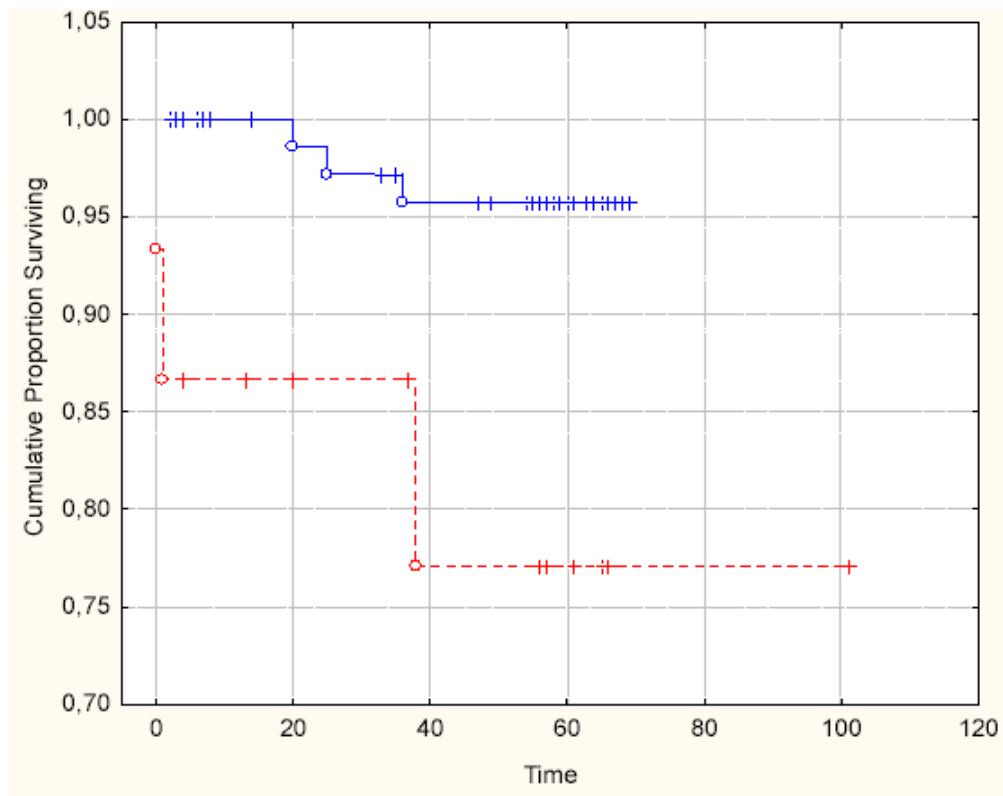|	All patients	Without MDD	With MDD	p	BDI<10	BDI≥10	p
Number of patients	100	85	15		65	35	
Male	77	70 (91%)	7 (9%)		54 (70%)	23 (30%)	
Female	23	15 (65%)	8 (35%)	<0.01	11 (48%)	12 (52%)	0.09
Age (mean and SD in years)	62 ± 13	62 ± 12	63 ± 10	0.71	61 ± 13	63 ± 11	0.42
Diabetes Mellitus	14	11(13%)	3 (20%)	0.42	9 (14%)	5 (14%)	0.98
Smoke	58	51(60%)	7 (47%)	0.58	37 (57%)	21 (60%)	0.97
Hypertension	51	41(48%)	10 (67%)	0.57	35 (54%)	16 (46%)	0.71
CHD family history	31	27 (32%)	4 (27%)	0.81	20 (31%)	11 (31%)	0.96
Dislipidemia	50	43 (51%)	7 (47%)	0.98	33 (51%)	17 (49%)	0.98
CPK (mean and SD in ng/ml)	1984±1913	1947±1897	2198±2130	0.72	2034±1945	1885±1875	0.73
CPK-MB (mean and SD in ng/ml)	189	178±142	249±278	0.41	183±142	200±218	0.81
EF<40%	16	14 (15%)	2 (18%)	0.67	8 (12%)	8 (23%)	0.21
ß-blockers	75	66 (78%)	9 (60%)	0.22	53 (82%)	22 (63%)	0.83
No coronary disease	2	2 (3%)	0	/	1 (5%)	1 (2%)	0.92
Single vessel disease	24	20 (35%)	4 (40%)	0.61	10 (47%)	14 (30%)	0.77
Two vessels	17	14 (24%)	3 (30%)	0.73	3 (14%)	14 (30%)	0.21
Three vassels or TC disease	25	22 (38%)	3 (30%)	0.67	7 (34%)	18 (38%)	0.97

(MDD: Major Depressive Disorder. BDI: Beck Depression Inventory score. CHD: Coronary Heart Disease. CPK: Creatinphosfokinase. CPK-MB Creatinphosfokinase Muscolar-Brain. EF: Ejection Fraction. TC: Truncus Communis)

Table 2: Adverse events occurred during 5-year follow-up in patients with and without Major Depressive Disorder (MDD), and in patients with (BDI<10) and without (BDI ≥10) symptoms of depression. (data presented as odds ratio with confidence interval 95%, OR>1 if the event is more common in MDD or BDI≥10 patients)

	Without MDD (84)	With MDD (14)	Odds Ratio (95% CI)	p	BDI<10 (65)	BDI≥10 (33)	Odd Ratio (95% CI)	p
Revascularization	16 (19%)	3 (21%)	1 (0.4-2.2)	0.96	12 (19%)	7 (21%)	1 (0.9-1.2)	0.61
Recurrent AMI	4 (5%)	1 (7%)	1.2 (0.7-8.3)	0.12	1 (2%)	4 (12%)	1.1 (0.9-1.1)	0.09
Mortality	3 (4%)	3 (21%)	12 (2.6-56)	<0.01	3 (5%)	3 (9%)	9.2 (2 - 43)	<0.01
Total adverse events	23 (27%)	7 (50%)	1.9 (1.1- 3.4)	0.01	16 (25%)	14 (42%)	1.1 (1-1.1)	0.01

Figure 1: Event free curves (Kaplan Meier) for all-cause mortality (1a) and composite end-point (1b, all-cause mortality, recurrent infarction, revascularization) in the group of patients with MDD (dashed line) vs without MDD (continuos line).

a)

b)