Depression as an independent determinant of decreased heart rate variability in patients post myocardial infarction

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Objective. Depression is associated with an increased risk of cardiac morbidity and mortality in patients following myocardial infarction (MI). Our objective was to investigate the potential role of the autonomic nervous system in mediating this detrimental effect.

Methods. The study group consisted of 95 consecutive post-MI patients without depression and 53 post-MI patients with depression. Depressive symptoms were assessed by the Beck Depression Inventory (BDI). Activity of the autonomic nervous system was assessed by analysing heart rate variability (HRV) using 24-hour ambulatory electrocardiographic recordings as obtained three months post MI.

Results. Higher age, female gender and left ventricular ejection fraction <0.40 were associated with lower HRV (SDANN, and very-low-frequency and low-frequency power, but not RMSSD and high-frequency power), as was depression. In the multivariate analysis, age and left ventricular ejection fraction but not gender emerged to be independently associated with HRV. After adjustment for these two covariates, depression remained significantly associated with low HRV.

Conclusions. Patients with depression in the present post-MI study are characterised by decreased longer-range HRV compared with the patients without depression, independent of other clinical variables. This observation supports the concept that one of the mechanisms underlying the detrimental effect of depression on post-MI prognosis may be that depression adds to the autonomic derangement post MI. (*Neth Heart J* 2005;13:165-9.)

Key words: depression, heart rate, post myocardial infarction

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Depression is associated with an increased risk of subsequent cardiac morbidity and mortality in patients following myocardial infarction (MI). In a recent meta-analysis, the excess risk was found to be on average 2 to 2.5 fold for both mortality and morbidity.[1] As to the mechanism behind how depression portends a poor prognosis in post-MI patients, several possibilities have been reported. These include abnormal platelet function, hypercortisolaemia, endothelial dysfunction as well as poor patient compliance.[2] In addition, the autonomic nervous system might be implicated. Depression per se is associated with sympathetic activation (and vagal deactivation) as indicated by elevated catecholamines, reduced baroreflex sensitivity and reduced heart rate variability (HRV).[3-5] Since sympathetic activation is in turn an established risk factor for poor outcome in post-MI patients,[6] depression may thus play its detrimental role. This possibility is supported by a study by Carney et al. who reported that HRV was decreased in a group of post-MI patients with depression as opposed to post-MI patients without depression, independent of other clinical variables known to affect HRV.[7] The purpose of the present study was to extend this important finding by studying a group of patients which is probably more representative of clinical practice and by analysing both frequency and time domain HRV parameters.

Methods

Design

The present study was a predefined substudy of the 'Depression and Myocardial Infarction study' (DepreMI), which will be reported separately. DepreMI was a prospective observational cohort study in consecutive patients admitted for acute MI. The objective of DepreMI was to study the impact of post-MI depression on cardiac prognosis in the Dutch setting, controlling for cardiac risk factors. DepreMI was performed in one university hospital, one large hospital and two smaller hospitals in rural areas in the northern part of the Netherlands. Patients admitted for MI between September 1997 and October 2001 were evaluated for eligibility for DepreMI. MI was documented by the presence of chest pain and cardiac enzymes (plasma creatinine phosphokinase ≥2 times the upper limit of normal or plasma creatinine phospokinase MB >10%) and characteristic evolutionary ST-T changes or new Q waves on the electrocardiogram in at least two contiguous leads. Exclusion criteria were serious noncardiac conditions limiting one-year survival, cognitive dysfunction and inability to speak or read Dutch. During hospitalisation, the following clinical variables were systematically collected: presence of diabetes, evidence of previous MI, Killip class on admission (<2 or ≥2), site of MI (anterior or non-anterior), thrombolysis, peak plasma creatinine phospokinase and left ventricular ejection fraction (LVEF, < or ≥0.40), as assessed by echocardiography, radionuclide scanning or angiography. After discharge from hospital, patients were followed for one year and new cardiac events were noted. Depression was assessed three months post MI in all patients. In addition, in a random sample of patients with depression and in a random sample of patients without depression, 24-hour ambulatory electrocardiographic (Holter) monitoring was performed at three months post MI. Of note, in order to ensure clinical stability, patients readmitted to hospital because of recurrent ischaemia, arrhythmias or heart failure between discharge from hospital and three months were excluded from Holter monitoring. Also, given the impact of diabetes on HRV (even without overt neuropathy),[8] no Holter monitoring was performed in patients with diabetes. DepreMI was approved by the institutional review boards of the four participating hospitals and written informed consent was obtained from all patients. Of note, since DepreMI was an observational study, the patients received medical care as usual and no information was provided to them or their treating physicians on depression status.

Depression assessment

Depressive symptoms were assessed by the Beck Depression Inventory (BDI).[9] The BDI is a widely used, 21-item measure of self-reported presence and severity of symptoms of depression. Respondents are instructed to rate every symptom on a 0 to 3 scale, with '0' representing 'absent' and '1', '2' and '3' representing increasing severity of the symptom. A total score of 10 or higher indicates at least a moderate level of depression.[9]

Heart rate variability analysis

Methods have been detailed previously and followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[10,11] In brief, Holter monitoring was performed using a Marquette Holter recorder (GE Medical system Holter recorder, series 8500, Milwaukee, WI, US). Three electrocardiographic leads were used: modified leads V_1, V_5, and aVF. The recordings were analysed in a core laboratory (Groningen University Hospital) on a GE Medical system Mars 8000 analyser and reviewed by an experienced analyst. Recordings with >5% noise or ectopic beats, including atrial fibrillation, were excluded from analysis. The following time domain parameters were analysed: mean normal-to-normal (NN) RR interval (mean NN), standard deviation of the means of NN intervals in all five-minute segments (SDANN) and square root of the mean of the squares of differences between adjacent NN intervals (RMSSD). Discrete Fourier transformation was used for the analysis of the frequency (spectral) domain parameters. The following parameters were calculated: very-low-frequency power (VLF, 0.0033-0.04 Hz), low-frequency power (LF, 0.04-0.15 Hz), high-frequency power (HF, 0.15-0.40 Hz) and the ratio of low-frequency power and high-frequency power (LF/HF).

Data analysis

Normally distributed variables are given as mean ± standard deviation (SD). In case of a skewed distribution, the HRV parameter was log transformed to produce a normal distribution. Univariate analysis was then performed comparing patients with and without depression, both regarding potentially relevant clinical variables and HRV parameters. Thereafter, for every HRV parameter univariately related to depression, univariate analysis was performed to establish the relation with the clinical variables. Parametric tests and nonparametric tests for continuous and discrete variables were used as appropriate. Pearson's test was used to analyse correlations. Finally, stepwise multivariate analysis with backward elimination was performed to establish the independent determinants of the HRV parameters, entering all variables univariately related to HRV into the analysis. For all analyses, commercially available computer software (Statistical Analysis System version 6.12, SAS Institute, Cary, NC) was used. A p value <0.05 was considered to indicate statistical significance.

Results

Altogether, 528 patients were enrolled in DepreMI, and 158 of them underwent Holter monitoring at three

Table 1. Clinical characteristics.

	Total (n=148)	No depression (n=95)	Depression (n=53)	p
Age (years)	59.4±(11.4)	59.5±(10.9)	59.2±(12.1)	0.85
Gender, female (%)	22.3	13.7	37.7	0.002
Previous MI (%)	8.1	8.4	7.5	1.00
Killip class ≥2 (%)	12.9	8.5	20.7	0.042
Anterior MI (%)	29.1	29.4	28.3	1.00
Thrombolysis (%)	43.5	45.7	39.6	0.49
Peak CK (U/l)	829±(120)	916±(126)	700±(108)	0.11
LVEF <0.40 (%)	17.6	16.8	18.9	0.82
CABG (%)*	3.4	2.1	5.7	0.35
Hypertension (%)*	34.5	31.1	40.0	0.38
Smoking (%)*	36.3	29.3	50.0	0.039
Beta-blocker (%)*	81.0	80.5	82.0	1.00

*Data obtained at three months post MI, including CABG performed between discharge and three months.
Hypertension was defined as blood pressure >140/90 mmHg.
CABG=coronary bypass grafting, CK=creatinine phosphokinase, LVEF=left ventricular ejection fraction, MI=myocardial infarction.

months. In ten of these 158 patients the Holter recording was inadequate, due to technical failures, noise or ectopy, including atrial fibrillation, precluding further analysis. The remaining 148 patients constitute the present study group; their clinical characteristics are listed in table 1. According to the BDI score, 95 patients had no depression (BDI score <10), whereas 53 patients were considered to have depression (BDI score ≥10). Mean scores (SD) in the two groups were 2.8 (2.3) and 16.2 (7.6), respectively (p<0.001). In the group of patients with depression there were more females, more patients in Killip class ≥2 and more smokers than in the group of patients without depression. Otherwise the two groups were comparable. Univariate data on HRV according to depression status are given in table 2. VLF, LF and SDANN were lower in patients with depression. Regarding the clinical variables, univariate analysis revealed that higher age, female gender and LVEF <0.40 were significantly associated with lower HRV (data not shown), which was true for all these three HRV parameters. In addition, SDANN was also lower in patients who underwent CABG and in patients without a β-blocker. In the multivariate analysis, age and LVEF emerged to be

Table 2. Unadjusted heart rate variability according to depression status.

	No depression (n=95)	Depression (n=53)	p
Mean NN (ms)	942±(115)	904±(124)	0.10
lnSDANN (ms)	4.90±(0.24)	4.76±(0.32)	0.003
lnRMSSD (ms)	3.53±(0.49)	3.47±(0.48)	0.87
lnVLF (ms^2)	7.41±(0.56)	7.16±(0.79)	0.027
lnLF (ms^2)	6.35±(0.75)	6.06±(1.03)	0.050
lnHF (ms^2)	5.52±(0.91)	5.28±(1.03)	0.15
LF/HF	1.75±(0.44)	1.72±(0.44)	0.63

Table 3. Adjusted heart rate variability according to depression status.

	No depression (n=95)	Depression (n=53)	p
lnVLF (ms^2)	7.28±(0.73)	7.03±(0.67)	0.018
lnLF (ms^2)	6.17±(0.94)	5.88±(0.86)	0.030
lnSDANN (ms)	4.76±(0.24)	4.62±(0.35)	0.002

independently associated with HRV. However, after adjustment for these two covariates, depression remained significantly associated with all three HRV parameters (table 3).

Discussion

Main findings

Patients with depression in the present post-MI study were characterised by decreased HRV compared with patients without depression. Furthermore, the relation between depression and HRV remained significant after adjusting for clinical covariates, including age and LVEF, indicating that depression was an independent determinant of HRV. Of note, the relation between depression and HRV was confined to 'longer-range' HRV (VLF, LF and SDANN), suggesting that particularly the sympathetic limb of the autonomic nervous system was implicated.

Comparison with previous studies

The relation between stable coronary disease (i.e. angina pectoris), depression and decreased HRV is firmly established.[2] In contrast, only limited data are available on depression and HRV in the post-MI setting, which is surprising since MI has a major impact on HRV (particularly in case of concomitant heart failure) and depression is very common after MI. Pitzalis et al. investigated a group of 103 post-MI patients of whom 32 were depressed.[12] Among the patients not taking a β-blocker, HRV, as measured by the standard deviation of RR intervals, was found to be lower in the depressed patients. However, no multivariate analysis was performed to establish the independent role of depression. Carney et al. were the first to investigate whether depression is related to decreased HRV, independent of clinical covariates.[7] In a substudy of ENRICHD, they found that HRV was indeed decreased in the group of patients with depression compared with the group of patients without depression, independent of other clinical variables known to potentially affect HRV in the post-MI setting. However, the study by Carney et al. was limited in several ways. First, the patients in that study may not be entirely representative of clinical practice since they were recruited in four university hospitals and they were participating in a clinical trial. Moreover, the control group consisted of patients with low levels of social inhibition, which might have introduced a bias. Finally, analysis of HRV was confined to frequency domain parameters of HRV. In our study, these limitations were circumvented. Our patients were also recruited in four hospitals, but three of these hospitals were nonuniversity hospitals, including two small hospitals in rural areas. Further, the control patients were randomly selected. Finally, in accordance with the recommendations,[11] we analysed both frequency and time-domain parameters of HRV. As it turned out, our study confirms the general observation by Carney et al. that HRV is independently related with depression in the post-MI setting, patients with depression being characterised by decreased HRV.

Possible underlying mechanism

In their final model, Carney et al. reported a relation between longer-range HRV (ULF, VLF and LF) and depression, but the relation between short-range HRV (HF) and depression was no longer significant.[7] Of interest, we made essentially the same observation, both in terms of the frequency and time-domain HRV parameters; HF and RMSSD (short-range HRV) were not related to depression, whereas LF, VLF and SDANN (longer-range HRV) were related to depression. Taken together, these findings argue against a chance finding and suggest a real phenomenon. Since long-range HRV is generally accepted to reflect particularly activity of the sympathetic limb of the autonomic nervous system,[11] the data are consistent with the concept that depression is associated with sympathetic activation, vagal deactivation not playing a major role.

Study limitations

This study was limited since coronary angiography was not routinely performed. Also, in the time period that the study was performed, primary coronary angioplasty was not yet part of a routine therapeutic strategy. Therefore, the study lacks systemic data on the extent of coronary disease, which is known to affect HRV.[13] However, we accounted for the clinical factors known to influence HRV in the post-MI setting.[14] In addition to the factors accounted for by Carney et al. in their study, we also included Killip class, site of MI, thrombolysis and peak CK in the analysis. Finally, the study was not designed and sample size was too small to analyse the independent prognostic value of decreased HRV versus depression on cardiac outcome.

Conclusions

Decreased HRV is associated with poor outcome after MI.[15] Depression was found to be associated with decreased longer-range HRV independent of clinical factors affecting HRV. This observation supports the concept that one of the mechanisms underlying the detrimental effect of depression on post-MI prognosis may be that depression adds to the autonomic derangement post MI. The relative contribution of this mechanism compared with the other possible mechanisms (e.g. abnormal platelet function, hypercortisolaemia, endothelial dysfunction, poor patient compliance) remains to be established. ■

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