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# Depression and anxiety as predictors of heart rate variability after myocardial infarction

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**Background.** Reduced heart rate variability (HRV) is a prognostic factor for cardiac mortality. Both depression and anxiety have been associated with increased risk for mortality in cardiac patients. Low HRV may act as an intermediary in this association. The present study examined to what extent depression and anxiety differently predict 24-h HRV indices recorded post-myocardial infarction (MI).

**Method.** Ninety-three patients were recruited during hospitalization for MI and assessed on self-reported symptoms of depression and anxiety. Two months post-MI, patients were assessed on clinical diagnoses of lifetime depressive and anxiety disorder. Adequate 24-h ambulatory electrocardiography data were obtained from 82 patients on average 78 days post-MI.

**Results.** In unadjusted analyses, lifetime diagnoses of major depressive disorder was predictive of lower SDNN [standard deviation of all normal-to-normal (NN) intervals;  $\beta = -0.26, p = 0.022$ ] and SDANN (standard deviation of all 5-min mean NN intervals;  $\beta = 0.25, p = 0.023$ ), and lifetime anxiety disorder of lower RMSSD (root mean square of successive differences;  $\beta = -0.23, p = 0.039$ ). Depression and anxiety symptoms did not significantly predict HRV. After adjustment for age, sex, cardiac history and multi-vessel disease, lifetime depressive disorder was no longer predictive of HRV. Lifetime anxiety disorder predicted reduced high-frequency spectral power ( $\beta = -0.22, p = 0.039$ ) and RMSSD ( $\beta = -0.25, p = 0.019$ ), even after additional adjustment of anxiety symptoms.

**Conclusions.** Clinical anxiety, but not depression, negatively influenced parasympathetic modulation of heart rate in post-MI patients. These findings elucidate the physiological mechanisms underlying anxiety as a risk factor for adverse outcomes, but also raise questions about the potential role of HRV as an intermediary between depression and post-MI prognosis.

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**Key words:** Anxiety, depression, heart rate variability, myocardial infarction.

## Introduction

Heart rate variability (HRV) analysis is a widely used method for studying cardiac autonomic modulation (Malik *et al.* 1996). Impaired autonomic nervous system control of heart rate is a strong independent predictor of long-term mortality in post-myocardial infarction (MI) patients (Bigger *et al.* 1993; Zuanetti *et al.* 1996; Dekker *et al.* 2000; Huikuri *et al.* 2003; Stein *et al.* 2005). In turn, depression has been associated with a twofold increased risk of mortality, and increased morbidity and rehospitalization post-MI (Ladwig *et al.* 1994; Frasure-Smith *et al.* 1995a; Barefoot *et al.* 1996; Lespérance *et al.* 2002). Some studies have also reported symptoms of anxiety to be predictive of subsequent cardiac events and mortality post-MI,

independent of established biomedical risk factors (Frasure-Smith *et al.* 1995b; Moser & Dracup, 1996; Strik *et al.* 2003), while others found no association (Mayou *et al.* 2000; Lane *et al.* 2001).

Alterations in cardiac autonomic tone, reflected by increased sympathetic or decreased parasympathetic nervous system activity, predisposes cardiac patients to ventricular fibrillation and tachycardia, and sudden cardiac death (Podrid *et al.* 1990; Pruvot *et al.* 2000), and can be a mechanism linking depression and anxiety to increased mortality in cardiac patients (Sloan & Bigger, 1991; Watkins *et al.* 1999). Several studies have demonstrated an association between depression and low 24-h HRV in post-MI patients (Carney *et al.* 2001; Pitzalis *et al.* 2001; Vigo *et al.* 2004). A review on laboratory and ambulatory HRV in depressive and anxiety disorders indicated that patients with anxiety disorders exhibit chronically reduced HRV (Gorman & Sloan, 2000), with panic disorder patients having

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reduced parasympathetic innervation to the heart compared with normal adults (Yeregani *et al.* 1993; Klein *et al.* 1995). Consequently, low HRV may act as an intermediary between depression and anxiety and adverse outcomes in cardiac patients. However, negative findings have also been reported. In one study, depression but not anxiety was found to negatively influence autonomic control of heart rate in post-MI patients (Pitzalis *et al.* 2001), whereas another study found that anxiety but not depression was independently associated with reduced HRV post-MI (Watkins *et al.* 2002). A cross-sectional study on 873 out-patients with stable coronary artery disease (CAD) found no association between depression and HRV, raising questions about the potential intermediate role of HRV (Gehi *et al.* 2005).

Given the relative lack of knowledge about the potentially deleterious effects of depression and, in particular, anxiety on HRV, the present study aimed to examine to what extent acute depressive and anxiety symptoms during hospitalization and a more chronic predisposition for depression and anxiety, indicated by lifetime diagnosis, differently predict 24-h time and frequency domain HRV indices post-MI.

## Method

### *Study design and patient population*

Ninety-three patients hospitalized for acute MI were recruited from the St Elisabeth Hospital, Tilburg, The Netherlands, between September 2003 and November 2005. MI was defined according to the following criteria: troponin I levels >1.0, with typical ischaemic symptoms (e.g. chest pain) lasting for more than 10 min or electrocardiogram (ECG) evidence of ST segment elevation or new pathological Q-waves. For patients without typical angina, the day of MI onset was identified as the day during hospitalization with peak levels of troponin I levels >1.0 and ECG evidence of ST segment elevation or new pathological Q-waves. Inclusion criteria were age >30 years and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia), severe co-morbidities (e.g. cancer), and insufficient command of the Dutch language.

Symptoms of depression and anxiety were assessed at the time of MI, using two self-report measures, and demographic and medical characteristics were obtained. Two months post-MI ( $56 \pm 17$  days), patients were evaluated carefully in the cardiology department by a trained psychologist using the Composite International Diagnostic Interview (CIDI; WHO, 1990) for diagnoses of depression and anxiety. At this visit, patients were asked to participate in an additional

study, concerning digital 24-h ECG recordings (Holter). This Holter recording took place on average 78 days (s.d. = 42) post-MI for logistic reasons. The research protocol was approved by the medical ethics committee of the participating hospital, and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from every patient before entering the study.

## Measures

### *Demographic and clinical characteristics*

Age, sex and smoking status were determined by questionnaire. Medical variables obtained from the medical records included co-morbidity (defined as arthritis, renal insufficiency or chronic obstructive pulmonary disease), cardiac history [defined as MI, angina or percutaneous coronary intervention (PCI) prior to the MI], left ventricular ejection fraction, multi-vessel disease, anterior MI location, blood pressure, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels, LDL/HDL ratio, cardiac rehabilitation, medications [beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, vasodilators, aspirin, and psychotropics], diabetes mellitus and obesity [body mass index (BMI)  $\geq 30$ ].

### *Clinical diagnoses of depression and anxiety disorder*

The World Health Organization (WHO)-authorized Dutch version of the CIDI (WHO, 1990; Smeets & Dingemans, 1993) was used to assess lifetime diagnoses of major depressive disorder and anxiety disorder (consisting of panic disorder, social phobia and/or generalized anxiety disorder) based on the diagnostic criteria of the DSM-IV (APA, 1994). The CIDI had acceptable inter-rater and test-retest reliability for most non-psychotic diagnoses, including major depressive disorder (Wittchen *et al.* 1991; Wittchen, 1994).

### *Self-reported symptoms of depression and anxiety*

Symptoms of depression and anxiety were assessed using two self-report questionnaires: the Beck Depression Inventory (BDI) and the State Trait Anxiety Inventory (STAI). The BDI is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms (Beck *et al.* 1988; Beck & Steer, 1993); it is a reliable and well-validated measure of depressive symptomatology and is widely used as a self-report measure of depression. BDI scores  $\geq 10$  are indicative of at least mild to moderate symptoms of depression and have been associated with poor prognosis in MI patients (Frasure-Smith *et al.*

1995b, 1999; Lespérance *et al.* 2002). The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety (Spielberger *et al.* 1983). In the current study, we included the state scale of the STAI. Elevated scores on the STAI have been associated with poor prognosis in MI patients (Frasure-Smith *et al.* 1995b). The STAI has been demonstrated to have adequate validity and reliability (Knight *et al.* 1983). Both the BDI and STAI have been used in previous studies on HRV in post-MI patients (Carney *et al.* 2001; Watkins *et al.* 2002).

#### Heart rate variability (HRV)

All patients received a digital, 24-h ECG Holter recording from a three-lead configuration. ECG data were digitized at a sampling rate of 125 Hz. Computer software (Mars<sup>®</sup> 6.5; General Electrics Medical Systems Information Technologies, Freiburg, Germany) was used to scan for rhythm disturbances (of both ventricular and atrial origin) and detect and label each QRS complex. A qualified Holter analyst, who was not otherwise involved in the study, processed all ECG recordings. If premature ventricular contractions (PVCs) reached >100/h, the recording was excluded from the analysis ( $n=8$ ). Rhythm disturbances were discarded automatically by the computer program. On average, 99.4% of the recordings contained normal sinus rhythm that was used to calculate the HRV measures.

The following time domain measures of HRV were assessed: the standard deviation of all normal-to-normal (NN) intervals (SDNN) as a measure of total variance in heart rate; the standard deviation of all 5-min mean NN intervals (SDANN), reflecting long-term or irregular modulation of HRV; and the root mean square of successive differences (RMSSD), reflecting parasympathetic modulation of heart rate. Frequency domain measures were also extracted from the ECG data using standardized fast Fourier transformation, and included the very low frequency spectral power (VLF; 0.003–0.04 Hz) reflecting long-term trends in HRV, the low frequency spectral power (LF; 0.04–0.15 Hz) as a measure of sympathetic modulation of heart rate, and the high frequency spectral power (HF; 0.15–40 Hz) reflecting parasympathetic modulation of heart rate. The LF/HF ratio was computed as a measure of autonomic balance (Malik *et al.* 1996).

#### Statistical analysis

The HRV distributions were tested for outliers. HRV values more than 3 standard deviations (s.d.) from the mean were excluded from the analysis. After

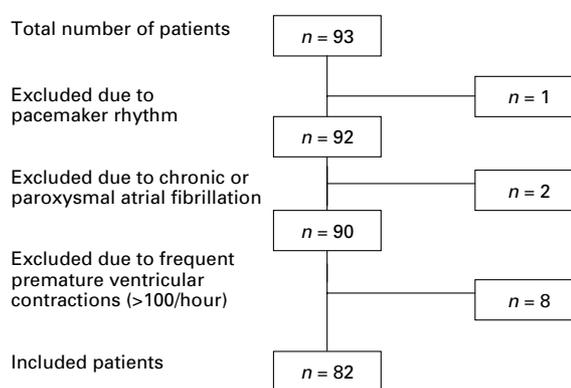


Fig. 1. Flowchart of patient selection.

correction for outliers, HRV distributions were near normal (skewness <1.4). Therefore, it was not necessary to normalize the data. Pearson correlations were used to determine whether the demographic and medical variables that have been associated with HRV in previous studies (Stein *et al.* 2000b) were significantly associated with HRV in this study. Variables that emerged from these analyses as potential confounders were then entered into separate multiple regression analyses to remove redundant covariates (if any). All retained variables were then used as covariates in the adjusted models. The bivariate relationship between depression/anxiety and HRV was examined using regression analysis. Separate multiple linear regression analyses were used to examine the independent impact of depression/anxiety on HRV indices. In a subsequent step, we adjusted for depressive and anxiety symptoms respectively to examine the impact of depression/anxiety above and beyond the impact of symptoms on HRV. A  $p$  value of <0.05 was considered significant in all tests.  $p$  values <0.10 are reported in the results tables. All statistical analyses were performed using SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Of the 93 post-MI patients, 82 patients were included in the final analyses (Fig. 1). Nineteen (23%) patients had lifetime diagnoses of major depressive disorder and seven (9%) of anxiety disorder prior to the MI. Only three (4%) patients had diagnoses of both depressive disorder and anxiety disorder. Table 1 shows demographic and clinical characteristics of the 82 study participants. The valid ambulatory recording time was on average 2347 h (s.d. = 0.51 min). Table 2 presents the means and standard deviations for all HRV indices, stratified by diagnoses.

**Table 1.** Characteristics of 82 patients with acute MI

Age, mean (s.d.)	56 (10)
Female sex, <i>n</i> (%)	15 (18)
Current smoker, <i>n</i> (%)	36 (44)
Body mass index, kg/m <sup>2</sup> , mean (s.d.)	27 (3.6)
Co-morbidity, <i>n</i> (%)	
Arthritis	7 (9)
Chronic obstructive pulmonary disease	2 (3)
Renal insufficiency	8 (10)
Diabetes mellitus	11 (13)
Hypertension	30 (40)
Hypercholesterolaemia	30 (38)
Cardiac history, <i>n</i> (%) <sup>a</sup>	16 (20)
Laboratory test results, mean (s.d.)	
HDL cholesterol level, mmol/l	1.2 (0.3)
LDL cholesterol level, mmol/l	3.2 (0.9)
LDL/HDL ratio, mmol/l	4.6 (1.1)
Cardiovascular function, mean (s.d.)	
Systolic blood pressure, mmHg	138 (27)
Diastolic blood pressure, mmHg	81 (19)
Disease severity, <i>n</i> (%)	
LVEF ≤ 40% <sup>b</sup>	13 (16)
Multi-vessel disease	26 (35)
PCI <sup>c</sup>	52 (63)
Anterior MI location	28 (36)
Cardiac rehabilitation	55 (75)
Medication use, <i>n</i> (%)	
Beta-blockers	74 (90)
ACE-inhibitors	22 (27)
Anti-coagulants	69 (84)
Statins	74 (90)
Diuretics	16 (20)
Vasodilators	40 (49)
Aspirin	67 (82)
Psychotropics <sup>d</sup>	8 (10)
Depressive disorder, <i>n</i> (%) <sup>e</sup>	19 (23)
Anxiety disorder, <i>n</i> (%) <sup>e</sup>	7 (9)
Depression score (BDI), mean (s.d.)	6.7 (6.6)
Anxiety score (STAI), mean (s.d.)	40 (11.7)

MI, Myocardial infarction; s.d., standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

<sup>a</sup>MI, angina or PCI prior to the MI.

<sup>b</sup>Information on LVEF was available for only 64 patients (78%), in whom an echocardiogram (ECG) was performed.

<sup>c</sup>Reference group: conservatively treated.

<sup>d</sup>Selective serotonin reuptake inhibitors, benzodiazepines.

<sup>e</sup>According to the Composite International Diagnostic Interview (CIDI).

### Unadjusted analyses

In unadjusted analyses, depressive disorder was a significant predictor of both lower SDANN and SDNN

post-MI. Anxiety disorder was found to be predictive of lower RMSSD and a trend was observed for reduced HF power. Depressive and anxiety symptoms were not significantly predictive of HRV indices, although trends were observed for depressive symptoms and reduced VLF power, LF power and SDNN, and for anxiety symptoms and reduced LF/HF ratio (Table 3).

### Adjusted analyses

Consistent with findings from previous studies, age, sex, beta-blockers, aspirin, cardiac history, anterior MI location and multi-vessel disease were related to one or more HRV indices in univariate analyses. Age, sex, cardiac history and multi-vessel disease were retained in the multiple regression analyses and were therefore entered as covariates into the adjusted models (Table 2). After adjustment for these covariates, depressive disorder was no longer predictive of HRV indices. Anxiety disorder was found to significantly predict reduced HF power and RMSSD, and trends were observed for lower VLF power, LF power, SDANN and SDNN. Depressive and anxiety symptoms were not predictive of HRV indices and no trends were observed (Table 3).

After additional adjustment for depressive symptoms, depressive disorder remained non-predictive of all HRV indices. However, when adjusting for anxiety symptoms, anxiety disorder remained predictive of reduced HF power and RMSSD, and strong trends were observed for reduced SDANN and SDNN with *p* values of 0.050 and 0.051 respectively (Table 4).

### Discussion

The present study estimated the predictive power of lifetime depressive disorder, anxiety disorder and self-reported symptoms of depression and anxiety on 24-h HRV, assessed in both the time and frequency domain, post-MI. After adjustment for significant demographic and clinical confounders, depressive disorder was no longer predictive of HRV indices, while anxiety disorder predicted reduced HF power and RMSSD. Further analyses revealed that after additional adjustment for current anxiety symptoms, lifetime anxiety disorder remained predictive of reduced HF power and RMSSD, suggesting a chronically reduced activity of the parasympathetic nervous system (Malik *et al.* 1996). In addition, strong trends were observed for reduced SDANN and SDNN, indicating a potentially altered function of more long-term influences on HRV, which might reflect a smaller range of physical activity engaged in by these patients (Thayer *et al.* 2006).

**Table 2.** Twenty-four-hour averages of heart rate variability (HRV) measures and the influence of age, sex, cardiac history and multi-vessel disease

HRV index	Twenty-four-hour averages of HRV measures <sup>a</sup>										Covariates					
	Total sample (n = 82)	Patients without depressive or anxiety disorder (n = 59)	Depressive disorder (n = 19)	Anxiety disorder (n = 7)	Age		Female sex		Cardiac history		Multi-vessel disease					
					β	p	β	p	β	p	β	p				
VLF (ms <sup>2</sup> )	28.3 (9.2)	29.1 (9.3)	25.4 (8.9)	24.2 (8.2)	-0.35	0.010	0.04	0.779	-0.30	0.027	0.19	0.150				
LF (ms <sup>2</sup> )	18.2 (7.1)	18.5 (7.4)	17.4 (6.4)	15.5 (6.3)	-0.38	0.003	-0.07	0.582	-0.36	0.005	0.25	0.047				
HF (ms <sup>2</sup> )	10.2 (4.3)	10.4 (4.8)	9.8 (3.0)	7.4 (2.4)	-0.47	<0.0001	0.26	0.039	-0.16	0.209	0.24	0.056				
LF/HF (ms <sup>2</sup> )	1.9 (0.5)	1.9 (0.5)	1.8 (0.5)	2.1 (0.4)	-0.15	0.242	-0.48	<0.0001	-0.18	0.175	-0.04	0.767				
SDANN (ms)	105.8 (29.3)	111.7 (30.2)	92.6 (26.0)	89.0 (24.1)	-0.02	0.871	0.08	0.569	-0.29	0.052	0.11	0.449				
SDNN (ms)	122.4 (32.3)	128.6 (33.5)	107.6 (27.0)	103.7 (27.2)	-0.07	0.622	0.10	0.478	-0.32	0.029	0.13	0.352				
RMSSD (ms)	25.6 (9.2)	25.9 (10.1)	24.9 (7.4)	18.7 (5.2)	-0.38	0.004	0.29	0.021	-0.21	0.107	0.32	0.013				

VLF, Very low frequency spectral power; LF, low frequency; HF, high frequency; SDANN, standard deviation of all 5-min mean normal-to-normal (NN) intervals; SDNN, standard deviation of all NN intervals; RMSSD, root mean square of successive differences.

Three patients had co-morbid depression and anxiety and were included in both the depression and anxiety columns. Bold indicates significant values.

<sup>a</sup> Values are expressed as mean (standard deviation).

To date, only a few studies have examined the predictive value of anxiety on HRV measures in patients with CAD, and these have shown mixed results. In the present study, we found no relationship between self-reported current depressive and anxiety symptoms and HRV. Watkins and colleagues reported that levels of anxiety symptoms, but not depression, were associated with reduced vagal control in patients with recent MI (Watkins *et al.* 2002) and in non-cardiac patients with depressive disorder (Watkins *et al.* 1999). However, other studies have shown that depressive but not anxiety symptoms negatively influence autonomic control of heart rate in hospitalized MI patients (Pitzalis *et al.* 2001) and CABG patients (Hallas *et al.* 2003).

Regarding the clinical diagnosis of anxiety, our study provides evidence that anxiety disorder is an independent predictor of reduced vagal control of the heart in post-MI patients. This is consistent with the conclusion of a recent review incorporating over 20 studies indicating that anxiety disorder is associated with autonomic nervous system dysregulation, and that patients with heart disease and anxiety are at increased risk for morbidity and mortality (Cohen & Benjamin, 2006). One exception is a study in CAD patients with panic disorder that showed unchanged parasympathetic activity, while sympathetic modulation of HRV was reduced compared to CAD patients without panic disorder (Lavoie *et al.* 2004).

In adjusted analyses we found no association between depressive disorder or depressive symptoms and indices of HRV. Some studies have reported reduced HRV in relation to depressive disorder and depressive symptoms in CAD patients (Carney *et al.* 2001; Pitzalis *et al.* 2001; Vigo *et al.* 2004), but others have found only a small or no relationship (Carney *et al.* 1995, 2003; Gehi *et al.* 2005). In line with our results, the Heart and Soul Study (Gehi *et al.* 2005) reported no association between depressive disorder and both time and frequency domain indices of HRV in 873 CAD patients. In contrast to this study, Birkhofer *et al.* (2006) recently proposed that the age difference between depressed and non-depressed patients could be an alternative explanation for the absence of differences in HRV. In their reply, Gehi & Whooley (2006) showed that this was not the case, as in our study. In two studies of CAD patients by Carney and colleagues, depressive disorder was only associated with SDANN and not with SDNN index, RMSSD and pNN50 (Carney *et al.* 1995), and no relationship was found between depressive disorder and an HRV measure equivalent to SDNN (Carney *et al.* 2003). Conversely, these authors also reported in some other studies that depressive disorder was associated with reduced HRV in both the frequency and

**Table 3.** Unadjusted and adjusted HRV in post-MI patients with depression and anxiety

	Depressive disorder		Anxiety disorder		Depressive symptoms		Anxiety symptoms	
	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>	$\beta$	<i>p</i>
Unadjusted HRV								
VLF	-0.17	N.S.	-0.14	N.S.	-0.20	0.082	-0.12	N.S.
LF	-0.06	N.S.	-0.12	N.S.	-0.19	0.086	-0.16	N.S.
HF	-0.06	N.S.	-0.20	0.072	-0.04	N.S.	0.01	N.S.
LF/HF	-0.04	N.S.	0.12	N.S.	-0.17	N.S.	-0.19	0.090
SDANN	-0.25	<b>0.023</b>	-0.18	N.S.	-0.18	N.S.	-0.06	N.S.
SDNN	-0.26	<b>0.022</b>	-0.18	N.S.	-0.20	0.078	-0.09	N.S.
RMSSD	-0.04	N.S.	-0.23	<b>0.039</b>	-0.05	N.S.	-0.02	N.S.
Adjusted HRV <sup>a</sup>								
VLF	-0.15	N.S.	-0.19	0.085	-0.14	N.S.	-0.09	N.S.
LF	-0.06	N.S.	-0.17	0.090	-0.10	N.S.	-0.08	N.S.
HF	-0.11	N.S.	-0.22	<b>0.039</b>	-0.01	N.S.	-0.02	N.S.
LF/HF	0.04	N.S.	0.08	N.S.	-0.09	N.S.	-0.06	N.S.
SDANN	-0.18	N.S.	-0.21	0.075	-0.14	N.S.	0.09	N.S.
SDNN	-0.20	N.S.	-0.22	0.063	-0.16	N.S.	0.05	N.S.
RMSSD	-0.09	N.S.	-0.25	<b>0.019</b>	-0.01	N.S.	-0.03	N.S.

HRV, Heart rate variability; MI, myocardial infarction; VLF, very low frequency spectral power; LF, low frequency; HF, high frequency; SDANN, standard deviation of all 5-min mean normal-to-normal (NN) intervals; SDNN, standard deviation of all NN intervals; RMSSD, root mean square of successive differences; N.S., not significant.

Bold indicates significant values.

<sup>a</sup> Age, sex, cardiac history, and multi-vessel disease were entered into the adjusted models.

**Table 4.** Major depressive disorder and anxiety disorder as multivariate predictors of HRV<sup>a</sup>

	Depressive disorder <sup>b</sup>		Anxiety disorder <sup>c</sup>	
	$\beta$	<i>p</i>	$\beta$	<i>p</i>
VLF	-0.15	N.S.	-0.18	N.S.
LF	-0.06	N.S.	-0.17	N.S.
HF	-0.12	N.S.	-0.22	<b>0.043</b>
LF/HF	0.04	N.S.	0.10	N.S.
SDANN	-0.16	N.S.	-0.23	0.050
SDNN	-0.18	N.S.	-0.23	0.051
RMSSD	-0.13	N.S.	-0.25	<b>0.022</b>

HRV, Heart rate variability; VLF, very low frequency spectral power; LF, low frequency; HF, high frequency; SDANN, standard deviation of all 5-min mean normal-to-normal (NN) intervals; SDNN, standard deviation of all NN intervals; RMSSD, root mean square of successive differences; N.S., not significant; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

Bold indicates significant values.

<sup>a</sup> Age, sex, cardiac history, and multi-vessel disease were entered into both multivariate models.

<sup>b</sup> Depression score (BDI) was entered into the multivariable model.

<sup>c</sup> Anxiety score (STAI) was entered into the multivariate model.

time domain (Stein *et al.* 2000a; Carney *et al.* 2001, 2005), and with decreased survival (Carney *et al.* 2005). The effect of depression on survival in this latter study was only partially mediated by low HRV. Another recent study indicated that patients with post-MI depressive disorder showed lower SDNN but that this autonomic dysfunction was not a mediator of increased mortality observed in these patients during a 5-year follow-up (Drago *et al.* 2007). Hence, it is still unclear whether autonomic nervous system dysfunction is a plausible mechanism linking depression to adverse outcomes in post-MI patients.

There are several possible explanations for the inconsistent findings and differences between our results and those of prior studies. Variation in assessment of the physiological and psychological measures, patient population, time of assessment, and study design may account for the inconsistent findings. In addition, the use of self-report measures or of clinical diagnosis of depression and anxiety yields different results regarding HRV. Studies are very heterogeneous in nature, which makes it difficult to compare our results with the literature. The only fairly consistent finding in the literature that is in line with our results is that anxiety disorder is associated with impaired HRV (Gorman & Sloan, 2000). However, it should be noted that these studies were conducted in

non-cardiac patients. In unadjusted analyses, our results regarding depression are similar to the adjusted results of Carney *et al.* (2001). The fact that depression was not predictive of HRV in our adjusted analyses may be explained by the relatively small sample size. To obtain a comprehensible and inclusive picture of the relationship between depression and anxiety and HRV, it is important for future studies to assess both diagnosis and symptoms of depression and anxiety, and to assess a variety of HRV indices in both the time and frequency domain in post-MI patients. In addition, it might be interesting to take a look at specific symptoms of depression or anxiety and their association with HRV.

The results of this study have implications for research and clinical practice. Screening for symptoms of depression and anxiety may not be sufficient because our results indicate that we need a clinical diagnosis to detect post-MI patients who are at risk of reduced HRV. The predictive value of anxiety disorder with reference to low values of the parameters reflecting parasympathetic cardiac modulation of heart rate may help to identify patients at high risk of cardiac events. A recent study in post-MI patients indicated that anxious patients were at increased risk of 8-year cardiac mortality and that reduced HF power increased this risk (Carpeggiani *et al.* 2005). However, to date only a few studies have been performed on the mechanisms underlying the link between anxiety and prognosis, and therefore the findings of the current study need to be replicated, preferably in a larger sample, with anxiety disorder, HRV and mortality assessed prospectively. This is in line with a recent call for further studies including patients with co-existing anxiety disorders and heart disease, incorporating assessment of indices of HRV (Cohen & Benjamin, 2006).

A limitation of this study may be the fact that we used lifetime diagnosis instead of current diagnosis of depressive and anxiety disorder, as a result of the limited number of current diagnoses in this sample. However, the use of lifetime diagnosis would in fact lead to a conservative estimation of the effect on HRV. Moreover, the inclusion of a lifetime diagnosis may indicate more long-term influences on HRV. Several studies have shown depression and CAD to have genetic communalities (Scherrer *et al.* 2003). Similarly, as lifetime diagnosis seems to have a chronic influence on HRV, this might be caused by a shared, underlying genetic predisposition (Scherrer *et al.* 2003; McCaffery *et al.* 2006). Shared genes may underlie both depressive and anxiety disorder (Middeldorp *et al.* 2005) and HRV in cardiac patients. In addition, the delay between the psychiatric interview and HRV assessment prevents this study from determining the direct effects

of depression or anxiety on HRV. However, because we assessed lifetime instead of current diagnoses of depression and anxiety, this time gap is of less importance. Furthermore, the sample size is limited, especially for evaluating the independent impact of anxiety disorder on HRV, and those findings should be interpreted with caution. We also had no data on physical activity levels during the day, which can be an important confounding variable. Despite these limitations, the present study has several strengths. We included both the clinical diagnosis and symptoms of depression and anxiety, all assessed by standardized, validated measures. The design of our study was also prospective in nature, resulting in the opportunity to draw conclusions beyond the correlational level.

In conclusion, the results of this preliminary study indicate that anxiety disorder, but not depressive disorder, was an independent predictor of reduced parasympathetic cardiac modulation in post-MI patients. These findings indicate the potentially important role of anxiety in determining individual differences in HRV and cardiac risk in post-MI patients. Whether these anxiety-related alterations in HRV do indeed explain increased morbidity and mortality in post-MI patients is a subject for further study.

#### Declaration of Interest

None.

#### References

- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.
- Barefoot JC, Helms MJ, Mark DB (1996). Depression and long-term mortality risk in patients with coronary artery disease. *American Journal of Cardiology* **78**, 613–617.
- Beck AT, Steer RA (1993). *Manual for the Revised Beck Depression Inventory*. Psychological Corporation: San Antonio, TX.
- Beck AT, Steer RA, Garbin MC (1988). Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clinical Psychology Review* **8**, 77–100.
- Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC (1993). The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation* **88**, 927–934.
- Birkhofer A, Schmidt G, Förstl H (2006). Heart rate variability and depression. *Archives of General Psychiatry* **63**, 1052.
- Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS (2005). Low heart rate variability and the effect of depression on post-myocardial

- infarction mortality. *Archives of Internal Medicine* **165**, 1486–1491.
- Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE** (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation* **104**, 2024–2028.
- Carney RM, Freedland KE, Stein PK, Watkins LL, Catellier D, Jaffe AS, Yeragani VK** (2003). Effects of depression on QT interval variability after myocardial infarction. *Psychosomatic Medicine* **65**, 177–180.
- Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS** (1995). Association of depression with reduced heart rate variability in coronary artery disease. *American Journal of Cardiology* **76**, 562–564.
- Carpeggiani C, Emdin M, Bonaguidi F, Landi P, Michelassi C, Trivella MG, Macerata A, L'Abbate A** (2005). Personality traits and heart rate variability predict long-term cardiac mortality after myocardial infarction. *European Heart Journal* **26**, 1612–1617.
- Cohen H, Benjamin J** (2006). Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Autonomic Neuroscience* **128**, 1–8.
- Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG** (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities. *Circulation* **102**, 1239–1244.
- Drago S, Bergerone S, Anselmino M, Varalda PG, Cascio B, Palumbo L, Angelini G, Trevi PG** (2007). Depression in patients with acute myocardial infarction: influence on autonomic nervous system and prognostic role. Results of a five-year follow-up study. *International Journal of Cardiology* **31**, 46–51.
- Frasure-Smith N, Lespérance F, Juneau M, Talajic M, Bourassa MG** (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosomatic Medicine* **61**, 26–37.
- Frasure-Smith N, Lespérance F, Talajic M** (1995a). Depression following myocardial prognosis after myocardial infarction. *Circulation* **91**, 999–1005.
- Frasure-Smith N, Lespérance F, Talajic M** (1995b). The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychology* **14**, 388–398.
- Gehi A, Mangano D, Pipkin S, Browner WS, Whooley MA** (2005). Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Archives of General Psychiatry* **62**, 661–666.
- Gehi A, Whooley M** (2006). Heart rate variability and depression – reply. *Archives of General Psychiatry* **63**, 1052.
- Gorman JM, Sloan RP** (2000). Heart rate variability in depressive and anxiety disorders. *American Heart Journal* **140**, 77–83.
- Hallas CN, Thornton EW, Fabri BM, Fox MA, Jackson M** (2003). Predicting blood pressure reactivity and heart rate variability from mood state following coronary artery bypass surgery. *International Journal of Psychophysiology* **47**, 43–55.
- Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Juhani Airaksinen KE, Myerburg RJ** (2003). Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. *Journal of the American College of Cardiology* **42**, 652–658.
- Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA** (1995). Altered heart rate variability in panic disorder patients. *Biological Psychiatry* **37**, 18–24.
- Knight RG, Waal-Manning HJ, Spears GF** (1983). Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression Scale. *British Journal of Clinical Psychology* **22**, 245–249.
- Ladwig KH, Roll G, Breithardt G** (1994). Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* **343**, 20–23.
- Lane D, Carroll D, Ring C, Beevers DG, Lip GY** (2001). Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosomatic Medicine* **63**, 221–230.
- Lavoie KL, Fleet RP, Laurin C, Arsenault A, Miller SB, Bacon SL** (2004). Heart rate variability in coronary artery disease patients with and without panic disorder. *Psychiatry Research* **128**, 289–299.
- Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG** (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* **105**, 1049–1053.
- Malik J, Bigger JT, Camm J, Kleiger RE, Malliani A, Moss AJ, Schwartz PJ; Task Force Writing Committee** (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* **93**, 1043–1065.
- Mayou RA, Gill D, Thompson DR, Day A, Hicks N, Volmink J, Neil A** (2000). Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosomatic Medicine* **62**, 212–219.
- McCaffery JM, Frasure-Smith N, Dube MP, Theroux P, Rouleau GA, Duan Q, Lesperance F** (2006). Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. *Psychosomatic Medicine* **68**, 187–200.
- Middeldorp CM, Cath DC, Van Dyck R, Boomsma DI** (2005). The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. *Psychological Medicine* **35**, 611–624.
- Moser DK, Dracup K** (1996). Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosomatic Medicine* **58**, 395–401.
- Pitzalis MV, Iacoviello M, Todarello O, Fioretti A, Guida P, Massari F, Mastropasqua F, Russo GD, Rizzon P** (2001). Depression but not anxiety influences the autonomic control of heart rate after myocardial infarction. *American Heart Journal* **141**, 765–771.
- Podrid PJ, Fuchs T, Candinas R** (1990). Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. *Circulation* **82**, 103–113.

- Pruvot E, Thonet G, Vesin JM, van-Melle G, Seidl K, Schmidinger H, Brachmann J, Jung W, Hoffmann E, Tavernier R, Block M, Podczeczek A, Fromer M (2000). Heart rate dynamics at the onset of ventricular tachyarrhythmias as retrieved from implantable cardioverter-defibrillators in patients with coronary artery disease. *Circulation* **101**, 2398–2404.
- Scherrer JF, Xian H, Buchholz KK, Eisen SA, Lyons MJ, Goldberg J, Tsuang M, True WR (2003). A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosomatic Medicine* **65**, 548–557.
- Sloan RP, Bigger Jr. JT (1991). Biobehavioral factors in Cardiac Arrhythmia Pilot Study (CAPS). Review and examination. *Circulation* **83**, II52–II57.
- Smeets R, Dingemans P (1993). *Composite International Diagnostic Interview (CIDI), Version 1.1*. University of Amsterdam: Amsterdam, The Netherlands.
- Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983). *Manual for the State-Trait Anxiety Inventory (Form Y)*. Consulting Psychologists Press: Palo Alto, CA.
- Stein PK, Carney RM, Freedland KE, Skala JA, Jaffe AS, Kleiger RE, Rottman JN (2000a). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research* **48**, 493–500.
- Stein PK, Domitrovich PP, Huikuri HV, Kleiger RE (2005). Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction. *Journal of Cardiovascular Electrophysiology* **16**, 13–20.
- Stein PK, Domitrovich PP, Kleiger RE, Schechtman KB, Rottman JM (2000b). Clinical and demographic determinants of heart rate variability in patients post myocardial infarction: insights from the Cardiac Arrhythmia Suppression Trial (CAST). *Clinical Cardiology* **23**, 187–194.
- Strik JJ, Denollet J, Lousberg R, Honig A (2003). Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *Journal of the American College of Cardiology* **42**, 1801–1807.
- Thayer JF, Wang X, Snieder H (2006). Ethnic differences in heart rate variability: does ultra-low frequency heart rate variability really measure autonomic tone? *American Heart Journal* **152**, e27.
- Vigo DE, Nicola Siri L, Ladron De Guevara MS, Martinez-Martinez JA, Fahrner RD, Cardinali DP, Masoli O, Guinjoan SM (2004). Relation of depression to heart rate nonlinear dynamics in patients  $\geq 60$  years of age with recent unstable angina pectoris or acute myocardial infarction. *American Journal of Cardiology* **93**, 756–760.
- Watkins LL, Blumenthal JA, Carney RM (2002). Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *American Heart Journal* **143**, 460–466.
- Watkins LL, Grossman P, Krishnan R, Blumenthal JA (1999). Anxiety reduces baroreflex cardiac control in older adults with major depression. *Psychosomatic Medicine* **61**, 334–340.
- WHO (1990). *Composite International Diagnostic Interview (CIDI)*. World Health Organization: Geneva, Switzerland.
- Wittchen HU (1994). Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI). *Journal of Psychiatric Research* **28**, 57–84.
- Wittchen HU, Robins LN, Cotter LB, Sartorius N, Burke JD, Regier D (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI): the Multicentre WHO/ADAMHA Field Trials. *British Journal of Psychiatry* **159**, 645–653.
- Yeragani VK, Pohl R, Berger R, Balon R, Ramesh C, Glitz D, Srinivasan K, Weinberg P (1993). Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. *Psychiatry Research* **46**, 89–103.
- Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ (1996). Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. *Circulation* **94**, 432–436.