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The relationships among heart rate variability, inflammatory markers and depression in coronary heart disease patients

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ABSTRACT

Studies show negative correlations between heart rate variability (HRV) and inflammatory markers. In cardiac patients, depression is related to both. We investigated links between short-term HRV and inflammatory markers in relation to depression in acute coronary syndrome (ACS) patients.

We measured C-reactive protein (CRP), interleukin-6 (IL-6), depression symptoms (Beck Depression Inventory, BDI-II), and SDNN, high frequency (HF) and low frequency (LF) power at rest in 682 (553 men) patients approximately two months post-ACS.

There were no differences in HRV measures between those with and without elevated depressions symptoms (BDI-II $\geqslant$ 14). However, all HRV measures were negatively and significantly associated with both inflammatory markers. Relationships were stronger in patients with BDI-II $\geqslant$ 14. Differences were significant for CRP and not explained by covariates (including age, sex, previous MI, left ventricular ejection fraction, coronary bypass surgery at index admission, diabetes, smoking, body mass index (BMI), fasting cholesterol, fasting glucose, angiotensin-converting-enzyme inhibitors, beta-blockers, statins, and antidepressants). HRV independently accounted for at least 4% of the variance in CRP in the depressed, more than any factor except BMI.

Relationships between measures of inflammation and autonomic function are stronger among depressed than non-depressed cardiac patients. Interventions targeting regulation of both autonomic control and inflammation may be of particular importance.

1. Introduction

Heart rate variability (HRV) provides a non-invasive index of autonomic nervous function. It is well-established that decreased HRV is associated with an increased risk of cardiovascular and arrhythmic death in patients with coronary heart disease (CHD) (Camm et al., 1996). Increased inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) are also associated with cardiovascular mortality (Ridker et al., 1998, 2000a,b; Sabatine et al., 2007). Similarly, depression is at least a marker for increased cardiac mortality risk (Rumsfeld and Ho, 2005; Frasure-Smith and Lesperance, 2006).

There have also been multiple reports demonstrating higher resting heart rates and lower HRV in depressed CHD patients (Carney et al., 2005). However, not all studies have shown significant results (Gehi et al., 2005). In fact, a recent meta-analysis (Rottenberg, 2007) reported that depression predicts only about 2% of the variance in HRV in both CHD and non-CHD samples. One potential reason for inconsistencies among studies is that depression-related differences in HRV may vary depending on participants' level of physical activity and psychological stress during the period of HRV evaluation (Roach et al., 2004). Thus, there can be advantages to assessment in more controlled conditions where physical and mental activity is better standardized.

There is also a growing body of literature demonstrating that depression is related to increases in inflammatory processes in those with and without CHD (Irwin and Miller, 2007). Studies have reported inflammatory increases associated with both major depressive disorder (MDD) and sub-threshold elevations of depres-

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sion symptoms (Rohleder and Miller, 2008). However, not all investigations have confirmed these relationships (Hemingway et al., 2003; Ladwig et al., 2005; Whooley et al., 2007), with lack of control for various potential confounding factors, as well as methodological differences among studies at least partially involved in the discrepancies (Bremmer et al., 2008).

There have been multiple reports of significant relationships between HRV and inflammatory markers, most commonly C-reactive protein (CRP), in CHD patients (Haensel et al., 2008), type-II diabetics (Aso et al., 2006; Lanza et al., 2007), and apparently normal adults (Sajadieh et al., 2004a,b, 2006; Kon et al., 2006; Araujo et al., 2006; Felber et al., 2006; Sloan et al., 2007; von Kanel et al., 2008; Lampert et al., 2008). Recently, Carney and colleagues (Carney et al., 2007) examined frequency-domain measures of HRV during sleep in a sample of 44 CHD patients with MDD assessed in a sleep lab. Inflammatory markers were obtained soon after awakening. None of the measures of HRV were related to CRP or TNF-α levels, but there were significant negative correlations between log-transformed low frequency, very low frequency and ultra-low frequency power and IL-6. However, only depressed individuals were involved in this study. In fact, to our knowledge, no studies have evaluated how depression influences the relationships between HRV and inflammation (Haensel et al., 2008).

In this context, we examined the cross-sectional relationships between resting short-term HRV and resting morning measures of IL-6 and CRP, as a function of the level of depression symptoms in stable CHD patients assessed approximately two months after hospital discharge for an acute coronary syndrome (ACS).

2. Methods

2.1. Design and participants

This paper is based on data collected for the Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions (ESCAPE). ESCAPE was designed to explore pathophysiological mechanisms that might link depression with cardiac prognosis, and the study's general methodology has been described previously (Lespérance et al., 2004; Frasure-Smith et al., 2007). Patients were recruited between August 31, 1999 and August 2, 2001 from the Montreal Heart Institute and Hopital du Sacré-Coeur de Montréal, with ethics approval from both institutions. All participants had a cardiac catheterization during admission for an acute MI or episode of unstable angina with elevated Troponin-T levels (based on each hospital's standards).

2.2. Procedures

Approximately 2 months after hospital discharge, consenting patients (55.3% of eligible men and 40.4% of eligible women) came to the Montreal Heart Institute Research Centre in the morning following an overnight fast. After completing informed-consents, patients rested in a supine position for 5 min, and then had their blood pressure taken. Antecubital blood was drawn to assess lipids, glucose, insulin, and inflammatory markers, and two-channel Holter monitors were installed using five leads and the standard technique. Participants then rested in a darkened room for approximately 30 min. After this, patients took their usual medications, had a light breakfast, and completed a brief neuropsychological test battery, self-report measures, including the Beck Depression Inventory (BDI-II) (Beck et al., 1996), and were interviewed by trained psychologists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) to assess major depressive disorder (MDD). Digital markers were placed on Holter recordings at the end of the rest period, and the Holters were removed following the cognitive tests. This allowed HRV indices to be calculated separately for the rest period.

2.3. HRV analyses

A Marquette Holter Analysis System was used to calculate RR intervals and label each QRS as normal or abnormal on the basis of morphology and timing. This automated analysis was screened and corrected by a technician. To be included in the study, resting recordings had to be at least 20 min long, (Camm et al., 1996) and, as in our previous work (Lespérance et al., 2003), had to contain $\geqslant$70% normal beats. Time-domain measures included the mean RR interval and the standard deviation of all RR intervals (SDNN). Only normal RR intervals were used in these calculations. For frequency-domain measures, the Fast Fourier Transform algorithm was used to calculate power within the low frequency (LF; 0.04–0.15 Hz) and high frequency bands (HF; >0.15 Hz) in 5-min segments.

2.4. Analyses of inflammatory markers

Blood was drawn for IL-6 using citrated tubes that were immediately centrifuged at 4 °C with the plasma aliquots frozen at −80 °C until analysis. Samples for CRP were collected in plain tubes, with the serum aliquots frozen at −80 °C. Blood was drawn between 8:15 and 10:40 AM, with 95% sampled before 10:00 AM. All analyses were carried out blind to patient characteristics.

As previously described (Lespérance et al., 2004; Frasure-Smith et al., 2007), inflammatory markers were assessed using commercially available ELISA kits. CRP was measured using the Dade Behring N *High Sensitivity* CRP assay (Dade Behring Diagnostics, Marburg, Germany) on the BN ProSpec. Levels of IL-6 were assessed in duplicate with commercially available ELISA (R&D Systems, Minneapolis MN, USA) with a mean coefficient of variation of 7.296.

2.5. Data analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) was used for data analysis. p-values $\leqslant$.05 were considered significant using 2-tailed tests. All variables were assessed for skewness. The BDI-II, the inflammatory markers, and low and high frequency power had standardized skew indices of >1, and were analyzed using natural log transformations.

Data set-specific and step-wise approaches to covariate selection have been criticized because of the instability of the models generated and their lack of replicability in other studies.(Steyerberg et al., 2000; Babyak, 2004) Therefore, we adjusted results for the following pre-selected covariates based on literature showing their relationships with HRV, inflammatory markers or both: age (Waddington et al., 1979; Umetani et al., 1998; Wong et al., 2001; Parati and Di Rienzo, 2003; Nabi et al., 2008), sex (Umetani et al., 1998; Wong et al., 2001; De Meersman and Stein, 2007; Nabi et al., 2008), previous myocardial infarction (MI) (Bigger et al., 1991, 1995), left ventricular ejection fraction (Malave et al., 2003), coronary artery bypass surgery at index admission (Stein et al., 2004; Laitio et al., 2006), diabetes (Liao et al., 1995; Wong et al., 2001; Stein et al., 2004; Nabi et al., 2008), smoking (Minami et al., 1999; Wong et al., 2001; Nabi et al., 2008), body mass index (BMI) (Karason et al., 1999; Emdin et al., 2001; Wong et al., 2001; Miller et al., 2002; Ladwig et al., 2003; Nabi et al., 2008), cholesterol (Lanza et al., 2006; Nabi et al., 2008), glucose (Singh et al., 2000), systolic blood pressure (Bautista et al., 2001; Wong et al., 2001), angiotensin-converting-enzyme (ACE) inhibitor prescription (Bonaduce et al., 1994; Montecucco et al., 2009), beta-blocker prescription (Sandrone et al., 1994; Cogliati et al., 2004), and statin prescription (Lanza et al., 2006). While there is preliminary evidence that antidepressant treatment may reduce inflammation (O'Brien et al., 2006), and inconsistent evidence of its impact on HRV (Glassman et al., 2007), because of the low prevalence of antidepressant use in this sample, and its high association with depres-

sion, including antidepressant use as an additional covariate could have produced misleading findings. Therefore, for sensitivity purposes, all analyses were repeated omitting those patients taking antidepressant medication.

Background characteristics, inflammatory markers, and HRV measures were compared in those with and without elevated BDI-II scores ($\geqslant$14 (Beck et al., 1996)). Dichotomous dependent variables were compared using logistic regression analysis, and analysis of variance was used for continuous dependent measures.

Pearson's product moment correlations were calculated between the Holter measures and the inflammatory markers, and between each baseline variable and both Holter and inflammatory measures. Statistical adjustment for the pre-selected covariates was carried out using multivariate regression analyses and by calculating partial correlation coefficients taking covariates into account. The potential differences in correlations between those with and without elevated depression symptoms were assessed using individual multiple regression analyses assessing the additive value of each interaction term involving elevated depression symptoms and each HRV measure in predicting IL-6 and CRP to the model including elevated depression symptoms and the HRV measure of interest. Separate correlations were calculated between the HRV measures and inflammatory markers for those with and without elevated symptoms. The Fisher r-to-z transformation was used to assess the *p*-values for differences between correlations.

3. Results

3.1. Participant characteristics

A total of 741 of the 811 patients in the ESCAPE study were not taking antibiotics, not currently abusing or dependent on alcohol, and had analyzable blood samples for inflammatory markers. Eleven patients had pacemakers or ECG evidence of atrial fibrillation, and did not have Holter data. Of the remaining 730 participants, the 682 with resting recordings of at least 20 min with < 30 percent abnormal beats were included in the current analyses. The included participants did not differ from the 129 who were excluded in terms of age ($p = 0.16$), sex ($p = 0.74$), or mean BDI-II score ($p = 0.67$). They did, however, have a slightly lower education level (mean = 11.3 years, SD = 4.3) than those excluded (mean = 12.5 years, SD = 4.3; $p = 0.057$). Women made up 18.9% ($n = 129$) of the final sample. While 28.0% ($n = 191$) of the included patients had BDI-II scores $\geqslant$14, indicating at least mild to moderate depression symptoms, 6.9% ($n = 47$) met DSM-IV criteria for MDD, and 8.4% ($n = 57$; 14 with MDD, 43 without) were taking antidepressants.

3.2. Background characteristics in relation to depression symptom levels

Comparisons between those with and without elevated BDI-II scores for background characteristics, and inflammatory markers appear in Table 1. Patients with elevated depression symptoms were younger, more likely to be female, less likely to be married or living with a partner, more likely to smoke, and more likely to have had a previous MI than those with lower BDI-II scores. They also had higher fasting cholesterol and glucose levels, but did not differ in the percent prescribed any individual medications (except for antidepressants) from those with lower BDI-II scores.

3.3. Depression and HRV

The HRV measures were strongly and significantly inter-related, with the SDNN correlating .85 with LF power and .75 with HF power. The correlation between LF and HF power was .80. All three measures also correlated significantly and negatively with heart rate (correlations from −.34 to −.45). While participants with elevated depression symptoms had significantly higher resting heart rates (lower mean RR intervals) than those without elevated symptoms, adjustment for covariates reduced the strength of the relationship to non-significance. There were no differences associated with elevated depression symptoms in any HRV measure either before or after control for covariates (see Table 2). Similarly, there were no HRV differences between those meeting DSM-IV criteria for MDD and those not meeting criteria, but the number with MDD was small ($n = 47$; data not shown). When analyses were repeated excluding the 57 patients taking antidepressants, there remained no evidence of links between elevated depression symptoms and HRV.

Table 1
Inflammatory markers and background characteristics in relation to depression symptom levels assessed two months after acute coronary syndrome.

Characteristics	Not depressed (BDI-II < 14; $n = 491$)	At least mild to moderate depression symptoms (BDI-II $\geqslant$ 14; $n = 191$)	*p*
Inflammatory markers (median, 25th, 75th percentile)			
IL-6 (ln)	0.78 ± 0.70	0.88 ± 0.68	0.096
pg/ml, Median (25th, 75th percentile)	2.03 (1.41, 3.12)	2.31 (1.50, 3.57)	
CRP (ln)	0.67 ± 1.06	0.88 ± 1.11	0.021
mg/L, Median (25th, 75th percentile)	1.73 (0.98, 4.01)	2.45(1.04, 5.76)	
Demographic variables			
Age (y)	60.1 ± 10.6	58.3 ± 10.5	0.053
Female, %	16.5	25.1	0.010
Education (y)	11.5 ± 4.3	10.9 ± 4.3	0.17
Married/living with partner, %	77.2	69.6	0.041
Risk factors and cardiac history			
Current daily smokers, %	14.1	24.6	0.001
Previous MI,%	19.3	29.3	0.005
Left ventricular ejection fraction <45%, %	20.5	21.3	0.81
Coronary bypass surgery at index, %	20.8	16.8	0.24
Body mass index (kg/m^2)	28.2 ± 4.3	28.6 ± 4.5	0.29
Fasting cholesterol level (mmol/L)	4.51 ± 1.03	4.75 ± 1.07	0.006
Fasting glucose level (mmol/L)	6.13 ± 1.61	6.61 ± 2.46	0.003
Systolic blood pressure (mm Hg)	135.0 ± 23.4	135.1 ± 23.2	0.97
Medications, %			
Aspirin	90.2	90.1	0.95
Beta-blockers	77.8	74.9	0.41
Angiotensin-converting enzyme inhibitors	51.7	50.3	0.73
Hypoglycemics	18.7	20.9	0.51
Calcium-channel blockers	20.2	22.5	0.50
Statins	71.3	70.7	0.88
Antidepressants	4.9	17.3	<0.001

Unless otherwise noted data are means ± standard deviation for continuous variables.
BDI-II, Beck Depression Inventory-II; IL-6, interleukin-6; ln, natural log transformation; CRP, C-reactive protein.

3.4. Depression and inflammatory markers

IL-6 and CRP were significantly correlated ($r = .58$, $p < 0.001$). As reported previously for the ESCAPE study (Frasure-Smith et al., 2007), patients with elevated depression symptoms had significantly higher CRP levels than those without elevated symptoms ($p = 0.021$, see Table 1). CRP levels were also significantly correlated with BDI-II scores ($r = .11$, $p = 0.004$). Other baseline variables

Table 2
Depression symptom levels and heart rate variability[a].

	Not depressed (BDI-II < 14; $n = 491$)	At least mild to moderate depression symptoms (BDI-II ⩾ 14; $n = 191$)	p	p adjusted for covariates[b]
RR interval[c]	1030 ± 152	997 ± 164	0.013	0.20
SD of RR intervals (SDNN)[d]	56.9 ± 25.1	56.2 ± 27.7	0.77	0.99
Low frequency power (ln)[d]	2.92 ± 0.51	2.92 ± 0.54	0.98	0.76
ms^2, median (25th, 75th percentile)	176.3 (125.0, 2524)	169.7 (119.6, 266.5)		
High frequency power (ln)[e]	2.60 ± 0.50	2.62 ± 0.54	0.68	0.66
ms^2, median (25th, 75th percentile)	123.0 (84.6, 185.3)	122.7 (83.3, 197.9)		

[a] The mean length of the Holter recordings was 32.2 ± 3.8 min in the not depressed, 31.9 ± 4.1 min in the depressed; $p = 0.48$.
[b] Adjusted for pre-selected covariates: age, sex, current smoking, previous MI, left ventricular ejection fraction, coronary bypass surgery at index admission, body mass index, cholesterol, glucose, systolic blood pressure, hypoglycemics, angiotensin-converting-enzyme-inhibitors, beta-blockers, and statins.
[c] Covariates significantly ($p \leqslant 0.05$) associated with lower RR Interval (higher heart rate) were younger age, current smoking, low left ventricular ejection fraction, coronary bypass surgery at index admission, higher body mass index, higher cholesterol, higher glucose, hypoglycemics, and absence of beta-blockers.
[d] Covariates significantly ($p \leqslant .0.05$) associated with lower SDNN and low frequency power were older age, previous MI, low left ventricular ejection fraction, coronary bypass surgery at index admission, higher glucose, higher systolic blood pressure, hypoglycemics, and absence of beta-blockers.
[e] Covariates significantly ($p \leqslant 0.05$) associated with lower high frequency power were older age, previous MI, low left ventricular ejection fraction, coronary bypass surgery at index admission, higher body mass index, higher glucose, higher systolic blood pressure, hypoglycemics, and absence of beta-blockers.

significantly correlated with higher CRP were female sex, previous MI, coronary bypass surgery at index admission, higher BMI, higher fasting cholesterol level, higher fasting glucose level, absence of prescription of beta-blockers and absence of prescription of statins (data not shown). IL-6 levels were not significantly related to depression symptoms measured as either a dichotomous ($p = .096$, see Table 1) or a continuous variable ($r = .038$, $p = .32$). The baseline variables significantly related to higher IL-6 levels included older age, previous MI, bypass surgery at index admission, higher BMI, higher fasting glucose level, higher systolic blood pressure and absence of prescription of beta-blockers (data not shown). In sensitivity analyses restricted to those not taking antidepressants, the links between CRP and depression symptoms remained significant and there continued to be little evidence of a relationship between depression and IL-6.

3.5. HRV and inflammatory markers

As shown in Table 3, all HRV measures were negatively and significantly correlated with both IL-6 and CRP. HRV accounted for between 3.2% and 4.4% of the variance in IL-6, and between .8% and 4.4% of the variance in CRP. The magnitudes of the correlations between HRV indices and IL-6 were reduced by at least one-half by covariate adjustment, but remained significant. However, for CRP only the correlation with the SDNN retained its significance after covariates were taken into account. In summary, in the overall sample, most of the relationship between lower HRV and higher CRP was explained by background characteristics. While links between HRV and IL-6 levels were somewhat more robust, after covariate adjustment HRV accounted for at most 1.0% of the variance in IL-6. Results were similar when the 57 patients taking antidepressants were excluded.

3.6. HRV and inflammatory markers in relation to depression

The raw correlations between all HRV measures and CRP were significantly higher among those with elevated depression symptoms than in those with lower depression levels (see Table 4). These relationships are illustrated for the SDNN in Fig. 1. For IL-6, although there were numerically stronger correlations in those with elevated depression symptoms than in those without, none of the differences were significant. Similar patterns of results were observed when those taking antidepressant medication were excluded from the analyses.

Table 5 shows the covariate-adjusted correlations between HRV measures and CRP for individuals with and without elevated depression symptoms. In those with low depression symptoms all the relationships between HRV and CRP remained non-significant after covariate control (all p-values ⩾ .46). Among those with elevated depression symptoms, all relationships were attenuated by covariate control, but all p-values remained significant. When analyses were repeated restricting the sample to patients with elevated depression symptoms who were not taking antidepressants ($n = 158$), only the p-value associated with the link between CRP and high frequency power increased to above .05 ($p = .061$). The adjusted percentage of variance in CRP explained by the SDNN (4.4%), and LF power (3.2%) both retained statistical significance (data not shown).

The multivariate adjusted models for CRP as a function of HRV in those with and without elevated depression symptoms are illustrated in Table 6 using the SD of the RR intervals (SDNN). Although there was no difference in the variance in CRP between those with and without elevated depression symptoms (Levene's statistic for homogeneity = .58, $p = 0.45$), multivariate models were able to predict more than 50% more of the adjusted variance in CRP in the patients with elevated depression symptoms (17.6%) than in those without (10.9%). BMI was the most important predictor in both depression groups. In those without elevated depression symptoms, after inclusion of other covariates, HRV did not explain any additional variance in CRP. In contrast, among patients with elevated depression symptoms, after covariate adjustment HRV ex-

Table 3
Correlations (p-values) between measures of heart rate variability and inflammatory markers in the full sample ($n = 682$) before and after covariate adjustment.

	IL-6[a]		CRP[a]	
	Raw	Covariate adjusted[b]	Raw	Covariate adjusted[b]
RR interval	−.19 (<0.001)	−.14 (<0.001)	−.21 (<0.001)	−.12 (0.002)
SD of RR intervals (SDNN)	−.19 (<0.001)	−.095 (0.014)	−.14 (<0.001)	−.078 (0.044)
Low frequency power[a]	−.21 (<0.001)	−.10 0.010)	−.11 0.003)	−0.041 (0.29)
High frequency power[a]	−.18 (<0.001)	−.078 (0.045)	−.087 (0.023)	−0.025 (0.52)

IL-6, interleukin-6; CRP, C-reactive protein.
[a] Natural log-transformed data.
[b] Adjusted for pre-selected covariates: age, sex, previous MI, left ventricular ejection fraction, coronary bypass surgery at index admission, current smoking, body mass index, cholesterol, glucose, systolic blood pressure, hypoglycemics, angiotensin-converting-enzyme-inhibitors, beta-blockers, and statins.

Table 4
Correlations (*p*-values) between measures of heart rate variability and inflammatory markers in patients with and ithout elevated depression symptoms.

	IL-6[a]			CRP[a]		
	Not depressed (BDI-II < 14; *n* = 491)	At least mild to moderate depression Symptoms (BDI-II ⩾ 14; *n* = 191)	*p* for difference between depressed and not depressed	Not depressed (BDI-II < 14; *n* = 491)	At least mild to moderate depression symptoms (BDI-II ⩾ 14; *n* = 191)	*p* for difference between depressed and not depressed
RR intervals	−.16 (<0.001)	−.25 (<0.001)	0.25	−.19 (<0.001)	−.25 (<0.001)	0.42
SD of RR intervals (SDNN)	−.18 (<0.001)	−.21 (0.003)	0.74	−.066 (0.15)	−.31 (<0.001)	0.0036
Low frequency power[a]	−.20 (<0.001)	−.25 (<0.001)	0.49	−.033 (0.47)	−.30 (<0.001)	0.0012
High frequency power[a]	−.14 (0.002)	−.29 (<0.001)	0.080	−.009 (0.83)	−.27 (<0.001)	0.0019

IL-6, interleukin-6; ln, natural log transformation; CRP, C-reactive protein.
[a] Natural log-transformed data.

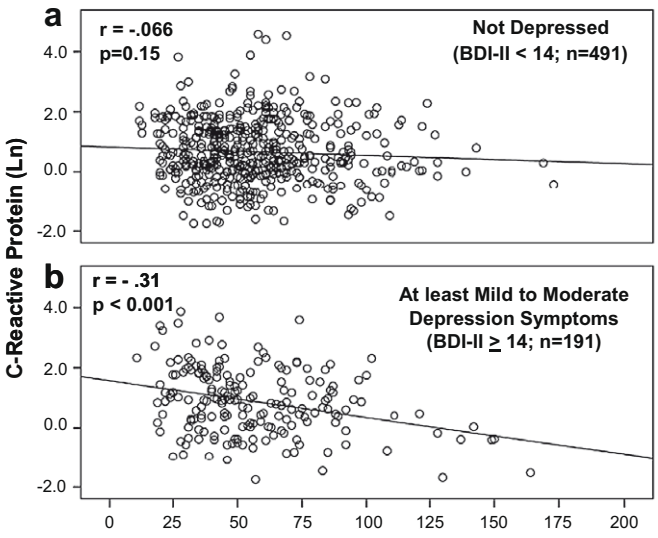

Fig. 1. SD of RR intervals (SDNN).

plained almost as much variance (4.1%) in CRP as was explained by body mass index.

4. Discussion

In this sample of stable CHD patients there was no evidence that depression assessed either as self-report symptoms or psychiatric interview was related to HRV either before or after adjustment for other factors known to influence HRV, or when those taking antidepressants were excluded from the analyses. This partially replicates results reported by Gehi and colleagues (Gehi et al., 2005) in a similar sample of stable CHD patients in which a different measure of depression was used and HRV measures were based on 24-h recordings. Further, in our sample, as in that of Gehi et al. (Gehi and Whooley, 2006), adjustment for age did not increase the degree of relationship between HRV and depression.

We also replicated the results of many teams showing that HRV and inflammatory markers are significantly and negatively interrelated (Carney et al., 2007; Haensel et al., 2008). What is new and intriguing about our results is that the links between HRV and inflammation were stronger in patients with elevated depression symptoms, particularly the links with CRP, and that these relationships held even after statistical adjustment for a variety of factors previously demonstrated to be related to HRV and inflammation or both. These factors included potentially confounding cardiac medications that are frequently prescribed for CHD patients (beta-blockers, statins and angiotensin-enzyme-converting inhibitors), and that have been previously documented to have links with both inflammation and HRV. However, in our sample only beta-blocking medication was significantly related to HRV measures (positively) as well as inflammatory markers (negatively). Further, the depression-related difference in the relationships between HRV and inflammation was similar in those prescribed and not-prescribed beta-blockers. Statistical adjustment for prescription of beta-blockers did not explain the results.

In summary, we observed that lower HRV measures were significantly related to higher IL-6 levels, but that after adjustment for covariates HRV explained no more than 1.0% of the variance in IL-6. We also found that relationships between HRV measures and CRP were markedly stronger in patients with elevated depression symptoms than in the non-depressed. In patients with BDI-II scores ⩾14, HRV accounted for 4–5% of the variance in CRP even after adjustment for covariates, with only some attenuation when

Table 5
Correlations (*p*-values) between measures of heart rate variability and CRP[a] in sub-groups based on level of depression symptoms (before and after covariate adjustment).

	Not depressed (BDI-II < 14; *n* = 491)		At least mild to moderate depression symptoms (BDI-II ⩾ 14; *n* = 191)	
	Raw	Covariate adjusted[b]	Raw	Covariate adjusted[b]
RR intervals	−.19 (<0.001)	−.12 (0.011)	−.25 (<0.001)	−.12 (0.13)
SD of RR intervals (SDNN)	−.066 (0.15)	−.003 (0.95)	−.31 (<0.001)	−.23 (0.003)
Low frequency power[a]	−.033 (0.47)	0.028 (0.54)	−.30 (<0.001)	−0.19 (0.014)
High frequency power[a]	−.009 (0.83)	.039 (0.39)	−.27 (<0.001)	−.16 (0.030)

CRP, C-reactive protein.
[a] Natural log-transformed data.
[b] Adjusted for pre-selected covariates: age, sex, previous MI, left ventricular ejection fraction, coronary bypass surgery at index admission, current smoking, body mass index, cholesterol, glucose, systolic blood pressure, hypoglycemics, angiotensin-converting-enzyme-inhibitors, beta-blockers, and statins.

Table 6
Multivariate models of relationship between SDNN and CRP in patients with and without elevated levels of depression symptoms.

	Not depressed (BDI-II < 14; $n = 491$)		At least mild to moderate depression symptoms (BDI-II ⩾ 14; $n = 191$)	
	Percent change in variance explained in CRP (R^2) by adding measure to model including all other variables (%)	p	Percent change in variance explained in CRP (R^2) by adding measure to model including all other variables (%)	p
SDNN	<0.0	0.91	4.1	0.003
Age (per SD increase)	0.4	0.070	0.1	0.63
Female	0.8	0.035	1.0	0.14
Current daily smoker	0.3	0.20	0.4	0.33
Previous MI	0.2	0.27	0.2	0.53
Left ventricular ejection fraction < 45%	0.2	0.34	<0.0	0.81
Coronary bypass surgery at index	1.3	0.008	1.4	0.070
Body mass index (per SD increase)	5.4	<0.001	5.5	<0.001
Fasting cholesterol level (per SD increase)	0.9	0.028	0.6	0.25
Fasting glucose level (per SD increase)	0.4	0.12	0.0	0.83
Systolic blood pressure (per SD increase)	<0.0	0.89	0.4	0.37
Beta-blockers	1.3	0.009	1.1	0.12
Angiotensin-converting enzyme inhibitors	0.3	0.22	<0.0	0.98
Hypoglycemics	0.3	0.21	<0.0	0.86
Statins	<0.0	0.86	0.9	0.16
Total percent of variance explained in CRP (R^2)	13.6	<0.001	24.0	<0.001
Total adjusted percent of variance explained in CRP	10.9	<0.001	17.6	<0.001

CRP, C-reactive protein.

patients taking antidepressants were excluded from the analyses. Among the non-depressed there was no independent contribution of HRV to explaining variance in CRP.

There is much data showing that depression is associated with HPA (hypothalamic–pituitary-adrenal) activation and increased sympathetic drive, as well as reduced vagal (parasympathetic) activity (Dunn et al., 2005). One suggested explanation for the link between reduced HRV and cardiac mortality is that it reflects reduced vagal responsivity to varying environmental demands. The traditional interpretations of the HRV measures used in our study are that the SDNN and HF power estimate vagal tone (Haensel et al., 2008), while LF power reflects both vagal and sympathetic influences (Pagani et al., 1986; Sheffield et al., 1998; Mozaffarian et al., 2008). However, it has also been reported that when LF power is assessed in the supine position, administration of atropine (a potent inhibitor of parasympathetic muscarinic receptors) eliminates most of the LF region of the power spectrum (Pomeranz et al., 1985). This does not occur when LF power is assessed in the sitting position, and suggests that resting LF power may primarily reflect vagal influences (Sloan et al., 2007). In this context, our results showing significantly stronger links between CRP and resting SDNN, LF and HF measures in depressed CHD patients in contrast to the non-depressed, suggest that depression-related differences in vagal function may be particularly important.

Tracey (Tracey, 2002) coined the phrase "the cholinergic anti-inflammatory pathway" to describe the inter-relationship between autonomic nervous system regulation and the inflammatory response. According to this view, peripheral cytokine release in response to infection or injury signals the brain by several routes including the afferent vagal nerve leading to acetylcholine release from the efferent vagus. This acts to inhibit further cytokine release from macrophages, providing some protection from cytokine-related tissue damage. Acetylcholine release from the efferent vagal terminus in the sinoatrial node reduces heart rate and increases HRV, providing a link between inflammation and HRV. Although it might be hypothesized that in the chronic state of inflammation accompanying depression, the normal reflex action of the vagally-dependent anti-inflammatory pathway is not sufficient to modulate levels of inflammation and HRV, this study did not find that HRV-based measures of vagal tone were different in those with elevated depression symptoms. Hence, alternative explanations are needed to understand the more robust associations between vagal activity and CRP in depression. We speculate that the chronic stress-induced down-regulation of glucocorticoid receptors thought to be related to the HPA axis activation in depression (Raison and Miller, 2003) might play a role in explaining the higher association between vagal activity and inflammation among the depressed. Increased HPA activity is known to be related to decreased vagal function (Thayer and Sternberg, 2006) and lower HRV. The down-regulation of glucocorticoid receptors has also been found to induce chronic activation of inflammatory signaling (Cole et al., 2007; Miller et al., 2008). Thus, depression-related HPA activity influences on both HRV and inflammatory processes could lead to the more salient association between vagal activity and markers of inflammation that we observed. However, we have no additional data to support or contradict these hypotheses.

Our study has several other limitations. Inflammatory markers were measured only once. Because of short-term HRV recording we were unable to assess reliably very low or ultra-low frequency power measures for which strong links with depression have been reported (Carney et al., 2001; Lampert et al., 2008). Although we have used standard interpretations of various HRV measures as estimates of parasympathetic and sympathetic input, their precise meaning remains controversial, particularly for LF power (Berntson et al., 1997; Parati et al., 2006; Taylor and Studinger, 2006; Haensel et al., 2008). Because of the cross-sectional study design we do not know whether HRV changed inflammation or vice versa, and bi-directional associations are also plausible (Lampert et al., 2008). We carried out a large number of statistical tests and, although as others have documented (Camm et al., 1996), the HRV measures reported were highly inter-correlated, some of the results may represent falsely positive outcomes. Finally, the prevalence of major depression was too low in our sample to control for covariates using this variable, so we do not know the extent to which the greater inter-relationship between HRV and CRP in patients with elevated depression symptoms extends to and may be even stronger in those with major depression.

This is the first study to demonstrate a markedly stronger relationship between HRV and inflammatory markers in CHD patients with elevated depression symptoms than among the non-depressed. Even after control for age, sex, previous MI, left ventricular ejection fraction, recent coronary bypass surgery, diabetes, smoking, BMI, fasting cholesterol, fasting glucose, and systolic blood pressure, as well as major cardiac medications including use of angiotensin-converting-enzyme inhibitors, beta-blockers and stat-

ins, HRV still accounted for approximately 4% of the variance in CRP in those with elevated depression symptoms, more than any other clinical factor assessed except body mass index. These findings have potentially important clinical implications, and suggest that either pharmacological or behavioral treatments that target autonomic balance might have the additional benefit of constraining inflammation in depressed CHD patients.

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