Original Research

Inverse Relation of C-Reactive Protein Levels to Heart Rate Variability in Patients After Acute Myocardial Infarction

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Introduction: Inflammation has a major role in atherosclerosis and the acute phase C-reactive protein (CRP) is elevated after acute myocardial infarction. Inflammation is also implicated in autonomic nervous system control. Heart rate variability (HRV) has been used as a marker of abnormal autonomic activity after myocardial infarction. Our purpose was to investigate the relation between CRP levels and autonomic tone in patients after acute ST-segment elevation myocardial infarction.

Methods: We studied prospectively 98 patients. CRP and the cardiac enzymes CK, CK-MB, and troponin-I were measured for a total of 72 hours and 24-hour Holter ECG recordings for HRV analysis were acquired before hospital discharge.

Results: The natural logarithm of CRP levels was inversely correlated with the following logarithmic transformed indices of HRV in the time and in the frequency domain: SDNN, standard deviation of all normal R-R intervals, ($r=-0.40$, $p<0.001$); SDANN index, standard deviation of the average normal R-R intervals for 5-minute segments, ($r=-0.46$, $p<0.001$); SDNN index, mean of the standard deviation of all normal R-R intervals for 5-minute segments ($r=-0.41$, $p<0.001$); total power (TP) ($r=-0.38$, $p<0.001$); high frequency power (HF) ($r=-0.31$, $p<0.01$); low frequency power (LF) ($r=-0.45$, $p<0.001$). The strong inverse relation between CRP and SDNN, SDANN, SDNN index, LF and TP persisted after adjustment for left ventricular function.

Conclusions: Increased levels of circulating CRP after acute myocardial infarction are associated with attenuated HRV indices, suggesting a possible relationship between inflammation and cardiac autonomic balance.

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Several clinical and laboratory studies have demonstrated profound abnormalities of autonomic tone after myocardial infarction, characterised by sympathetic predominance and parasympathetic withdrawal.[1-3] The autonomic nervous system has been implicated in triggering sudden death irrespective of the patient's substrate. Heart rate variability (HRV), a marker of autonomic tone, has been extensively studied after myocardial infarction and has been established as an independent factor influencing an adverse outcome.[4-6]

Recent research has focused on the major role of inflammation in atherothrombosis and plaque vulnerability.[7] Measurement of inflammatory markers, such as the acute phase C-reactive protein (CRP), provides a novel method for detecting individuals at high risk of plaque rupture, but is also an independent predictor of clinical outcome and prognosis after acute myocardial infarction.[8-11] CRP is synthesised by the liver after it has been stimulated by cytokines released from various sources and from the jeopardised tissue.[10,12] The cy-

tokines that stimulate CRP synthesis are also in a constant interaction with the nervous system.[13,14] Moreover, it has been suggested that part of the detrimental effect of sympathetic overactivity in various clinical settings may be the result of an enhanced inflammatory reaction.[15] In particular, HRV indices were associated with interleukin-6 levels in women with stable coronary artery disease and with CRP in patients with unstable angina.[16,17] After acute myocardial infarction levels of CRP rise substantially; however, whether this marker is related to autonomic indices remains to be elucidated.

The aim of the present study was to investigate possible relations between autonomic tone, assessed by HRV, and CRP in patients with acute ST-segment elevation myocardial infarction.

Methods

Patients

A total of 120 patients admitted for an acute ST-segment elevation myocardial infarction were recruited. All patients gave written consent, and the protocol was approved by the Hospital's Ethics Committee. Myocardial infarction was diagnosed according to the following criteria: 1) typical chest pain lasting >30 minutes; 2) ST-segment elevation of at least 1 mm in two contiguous limb leads or 2 mm in two contiguous chest leads, on the standard electrocardiogram; 3) serum creatine kinase-MB (CK-MB) concentration of more than twice the upper normal limit 6 to 12 h after admission. Thrombolytic treatment was administered according to the protocol of the clinic (rTPA 100 mg, reteplase 20 IU). Patients with no ST-segment elevation, a known history of autoimmune disorders or collagen disease, any febrile illness, cardiogenic shock, or atrial fibrillation, were excluded. Data were recorded concerning the patients' age, sex, history of previous coronary artery disease or previous myocardial infarction, treatment before hospital admission and coronary risk factors (smoking, dyslipidaemia, diabetes, hypertension).

Blood sampling and assays

Blood samples were drawn on admission and 8, 16, 24, 48 and 72 h after the onset of infarction for CK, CK-MB and troponin-I assessment. CK-MB curve area was calculated using the log normal function curve as previously described.[18] Plasma CRP levels were measured 24 and 72 h post infarction by an immunoassay technique (Dade Behring Laboratories, Newark, Delaware, USA) and an assay range of 0.2-12 mg/dl. Troponin-I levels were measured using a highly sensitive colorimetric immunoassay, (Dade Behring Laboratories, Newark, Delaware, USA). The assay range is 0.04-50.0 ng/ml. For values above the assay range there was appropriate predilution of the samples.

Holter monitoring and heart rate variability analysis

A 24-hour Holter recording was acquired for each patient 5 to 7 days after myocardial infarction using a 3-channel digital recorder and was analysed using a commercially available system (Galix Biomedical Instrumentation Inc., Florida, USA). The beat classification was in all cases verified and manually corrected by an experienced cardiologist. HRV analysis was performed on both time and frequency domain indexes as follows:

Time domain indexes. Mean RR and SDNN, mean and standard deviation of all normal R-R intervals; SDANN index, standard deviation of the average normal R-R intervals for 5-minute segments; SDNN index, mean of the standard deviation of all normal R-R intervals for 5-minute segments; rMSSD, root mean square successive difference; pNN50, percentage of differences between adjacent normal R-R intervals >50 ms.

Frequency domain indexes. Spectral measurements were accomplished using a fast-Fourier transform algorithm in the following bands: total power (TP) spectrum (0.0-0.5 Hz); high frequency (HF) power (0.15-0.4 Hz); low frequency (LF) power (0.04-0.15 Hz).

Statistical analysis

All analyses were performed using the "Statistica" software program (version 6.0, StatSoft Inc., Tulsa, Oklahoma, USA). Data are expressed as mean ± SD. Comparisons between continuous variables were performed using unpaired t-tests and for categorical variables using the chi-square test. HRV parameters and CRP values were logarithmically transformed for all analyses, since they showed skewed distribution. (However, in table 2 we present the mean and standard deviation of these values, to allow for realistic presentation and comparison with other studies.) The Pearson product-moment correlation analysis was used to test for significant associations between individual log transformed HRV data and log CRP or cardiac enzyme levels. Univariate and multivariate linear regression analyses were conducted to evaluate the association of car-

diac enzymes and log CRP values with log transformed HRV indices. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

Twenty-two of the 120 patients recruited initially in this prospective study were excluded for various reasons: atrial fibrillation (n=7), inadequate number of blood samples for biochemical markers (n=5), technical failure in Holter monitoring (n=5), or any of the previously described exclusion criteria (n=5). The clinical characteristics of the remaining 98 patients are presented in Table 1. The extent of myocardial damage, estimated by cardiac enzymes and peak CRP level, and the indices of HRV are presented in Table 2. We found a statistically significant correlation between the levels of circulating CRP and extent of necrosis, estimated by peak cardiac enzyme CK-MB, only in the patients who received thrombolysis, (r=0.42, p<0.01). This correlation was not significant in those not receiving thrombolysis.

Table 1. Baseline patient characteristics.

Age (years)	60 ± 12
Sex (M/F)	80/18
AMI location:	
Anterior	41
Inferior	51
Lateral	6
Thrombolysis (Y/N)	77/21
Current smoking (Y/N)	65/33
Hypertension (Y/N)	50/48
Diabetes (Y/N)	32/66
Cholesterol (mg/dl)	217.7 ± 55.7
Family history of CAD (Y/N)	30/68
Known history of CAD (Y/N)	25/73
Old MI (Y/N)	7/91
Drugs before AMI (Y/N)	37/61
Ejection fraction post AMI (%)	42.7 ± 8.6

AMI – acute myocardial infarction. CAD – coronary artery disease;

Relation between HRV, biochemical and clinical variables

Pearson analysis revealed significant negative correlations between log CRP values and the following log transformed time domain indices: SDNN (r=-0.40, p<0.001), SDANN index (r=-0.46, p<0.001), and SDNN index (r=-0.41, p<0.001). An inverse relation between log CRP and mean RR was also found (r=-0.47, p<0.05). CRP levels were also negatively correlated with the spectral indices: TP (r=-0.38, p<0.001), LF (r=-0.45, p<0.001), HF (r=-0.31, p<0.01). No correlations were found between CRP and the parasympathetic indices of rMSSD and pNN50. The results are summarised in Figure 1.

Table 2. Biochemical and heart rate variability data of the study population.

	Mean ± SD	95% CI
Maximum CK (mg/dl)	2254 ± 1544	1943-2565
Maximum CK-MB (mg/dl)	149 ± 115	126-172
CK-MB curve area (mg . min/dl)	3494 ± 2396	2954-4034
Maximum troponin-I (ng/ml)	74 ± 64	61-87
Maximum CRP (mg/dl)	72 ± 70	58-87
Time domain HRV indices:		
Mean RR (ms)	910 ± 130	885-936
SDNN (ms)	86 ± 29	79-93
SDANN index (ms)	73 ± 25.5	68-80
SDNN index (ms)	41 ± 15	37-44
pNN50 (%)	8 ± 9	6-10
rMSSD (ms)	28 ± 18	25-33
Frequency domain HRV indices:		
TP ($ms^{2)}$	1742 ± 1267	1442-2042
LF (ms^2)	329 ± 278	263-394
HF (ms^2)	150 ± 145	116-185
LF/HF	6.3 ± 2.1	5.8-6.8

Mean RR and SDNN – mean and standard deviation of all normal R-R intervals; SDANN index – standard deviation of the average normal R-R intervals for 5-minute segments; SDNN index – mean of the standard deviations of all normal R-R intervals for 5-minute segments; pNN50 – percentage of differences between adjacent normal R-R intervals >50 ms; rMSSD – root mean square successive difference; TP – total power spectrum (0.0-0.5 Hz); LF – low frequency power (0.04-0.15 Hz); HF – high frequency power (0.15-0.4 Hz);

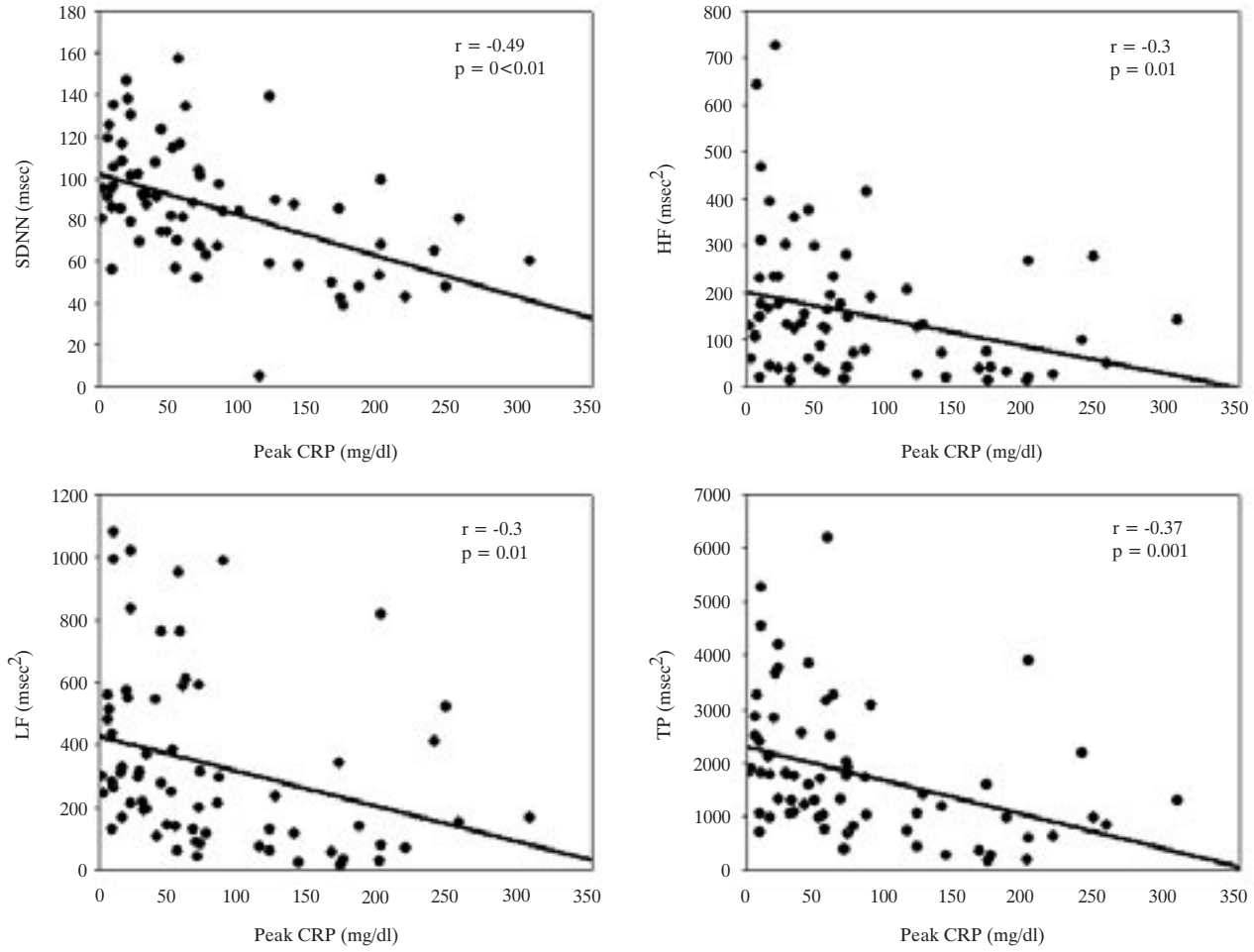

Figure 1. Scatterplot of the relations between log C-reactive protein (CRP) levels and log transformed heart rate variability (HRV) parameters. CRP levels are plotted against the time domain index of the standard deviation of all normal R-R intervals (SDNN) and the frequency domain indices of total power (TP), high frequency power (HF) and low frequency power (LF).

In a similar manner analyses were performed for CK-MB curve area. Univariate analysis revealed significant negative relations between CK-MB curve area values and the following log transformed time domain HRV indexes: mean RR ($r=-0.3$, $p<0.05$), SDANN index ($r=-0.38$, $p=0.003$), SDNN index ($r=-0.38$, $p=0.002$), and rMSSD ($r=-0.29$, $p=0.022$). CK-MB curve area values also correlated negatively with the log transformed spectral indices: TP ($r=-0.40$, $p=0.002$), LF ($r=-0.43$, $p=0.001$), HF ($r=-0.47$, $p<0.001$). No correlations were found between CK-MB curve area values and pNN50. The results are summarised in Figure 2.

Left ventricular function is a variable likely to be significantly associated with HRV after an acute myocardial infarction. To exclude the possible effect of this parameter on the association between the indices of HRV and CRP we performed a ridge regression analysis in which echocardiographic ejection fraction was included. After adjustment for ejection fraction the negative relation between log CRP and the log transformed indices of SDNN, SDANN, SDNN index LF and TP remained statistically significant (Table 3).

Discussion

The main finding of this study is the inverse relation between the inflammatory marker CRP, heart rate and HRV indices that express mainly sympathetic tone, after an acute myocardial infarction. Myocardial ischaemia and infarction are known to alter the autonomic balance towards sympathetic predominance.[1-3] Depressed HRV is a powerful predictor of mortality and arrhythmogenicity after acute myocardial infarction, independently of other risk factors such as left ventricular

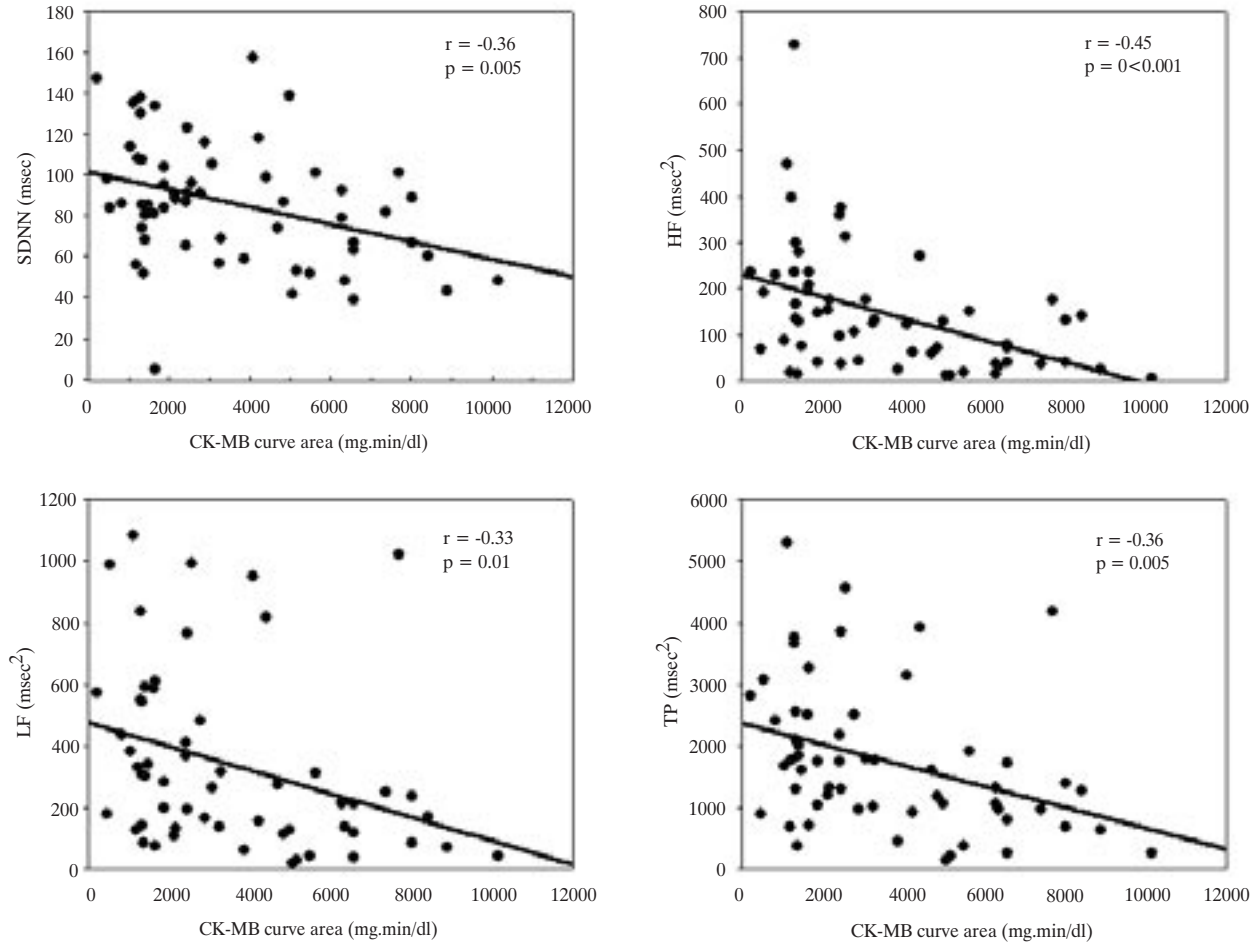

Figure 2. Scatterplot of the relations between CK-MB curve area levels and the log transformed heart rate variability (HRV) parameters. CK-MB curve area levels are plotted against the time domain index of the standard deviation of all normal R-R intervals (SDNN) and the frequency domain indices of total power (TP), high frequency power (HF) and low frequency power (LF).

Table 3. Relation between C-reactive protein levels and heart rate variability indices.

	Unadjusted		Adjusted for ejection fraction	
	Beta coefficient (SE)	p	Beta coefficient (SE)	p
log SDNN	-0.44 (0.09)	<0.001	-0.37 (0.10)	<0.01
log SDANN index	-0.53 (0.09)	<0.001	-0.36 (0.12)	<0.01
log SDNN index	-0.41 (0.09)	<0.001	-0.25 (0.12)	<0.05
log pNN50	0.04 (0.11)	NS	0.19 (0.13)	NS
log rMSSD	-0.12 (0.10)	NS	0.03 (0.13)	NS
log TP	-0.37 (0.11)	<0.001	-0.32 (0.12)	<0.05
log LF	-0.42 (0.09)	<0.001	-0.34 (0.12)	<0.01
log HF	-0.30 (0.10)	<0.01	-0.11 (0.13)	NS

log – natural logarithm. Other abbreviations as in table 2.

ejection fraction and the presence of increased ventricular ectopy.[4-6] The mechanisms that lead to depressed HRV after myocardial infarction are complex and are related to functional alterations in the autonomic innervation of the heart. According to our findings, HRV alterations might also be partly due to the inflammatory status of the patient after an acute myocardial infarction.

CRP in acute myocardial infarction

CRP is a marker of inflammation that also amplifies the immune response, leading to further tissue damage.[10-12] Although the role of CRP screening in primary prevention and in patients with unstable angina has been extensively studied in many clinical trials,[19-21] the value of CRP as a prognostic factor after acute myocardial infarction has not been fully elucidated. We chose to interpret data from CRP measurements at 24 and 72 hours in our patients because we aimed to investigate the post-infarction inflammatory reaction and the time lag of hepatic synthesis of acute phase proteins is at least 6 hours.[22] The significant correlation of CRP with the extent of myocardial damage in thrombolysed patients suggests a role for reperfusion injury in the inflammatory response in this group.

HRV indices and CRP levels

The inverse association between CRP levels and HRV indices that mainly express sympathetic tone provides evidence for a role of inflammation in the autonomic balance post myocardial infarction. It is possible that the inflammatory response after acute myocardial infarction may be associated with an increase in neurohumoral mediators that contribute to changes in autonomic tone as expressed by HRV. Cytokines, substances prodromal to CRP, are known to act on the nervous system.[13,14] In fact, certain cytokines activate both the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis, while *vice versa*, the sympathetic nervous system may exert pro- and anti-inflammatory effects.[23] A constant crosstalk exists between the nervous and the immune systems.[23-27] Inflammation increases oxidative stress, which may lead to inactivation of endothelial nitric oxide, a substance known to modulate autonomic control in the sinus and atrioventricular node and to enhance vagal tone in humans.[28,29] In diseases associated with the inflammatory process, such as ankylosing spondylitis, markers of inflammation have been found to be related to abnormal autonomic tone.[30] Interleukin-6 levels are also associated with attenuated HRV in patients with decompensated heart failure.[31] We have shown that in patients with renal failure the enhanced inflammatory status is related to HRV.[32] Sympathetic predominance is also associated with subclinical inflammation, estimated by increased CRP levels, in subjects with no apparent heart disease,[33] and inflammatory reaction has emerged lately as an explanation of a worse outcome in clinical conditions with enhanced sympathetic activity.[15] The presence of an inverse relationship between CRP and HRV indices has been demonstrated in patients with unstable angina pectoris,[17] suggesting a possible link between autonomic activity and inflammation. In a group of women with stable coronary artery disease the inflammatory marker interleukin-6 has also been correlated with HRV.[16] Thus, autonomic imbalance, especially with sympathetic predominance, could influence inflammatory reaction, or in turn, inflammation could influence autonomic tone.

Among the time domain indices of heart rate variability, SDNN, SDNN index and SDANN reflect both sympathetic and parasympathetic modulation, and reduced SDNN and SDANN are indicative of relative sympathetic predominance.[6] We did not find any relation between CRP and the vagally mediated indices of rMSSD and pNN50. This may indicate that our observation of an inverse relation between CRP and SDNN, SDNN index and SDANN is mainly due to enhanced sympathetic activity. However, LF and TP, which have been used as indexes of sympathetic tone, also have a large vagal component; therefore, we cannot exclude the possibility that both autonomic limbs may be affected. The cross-sectional design of this study does not allow us to deduce a cause-effect relationship between inflammation and HRV, as disturbances of both of them could be epiphenomena of atherosclerosis and acute myocardial infarction. Nevertheless, CRP could be not only a marker of inflammatory response, but also a marker of autonomic balance in post-infarction patients. It remains to be established which particular mediators of inflammation influence cardiac autonomic tone.

Study limitations

Our study has the following potential limitations: Age and diabetes are determinants of HRV.[34,35] In our sample these variables were not correlated with CRP: therefore, they were not entered into the multivariate regression analysis. The same was true of sex and infarct location. Pharmacological treatment with b-blockers and angiotensin converting enzyme inhibitors may also affect HRV indices.[36] The fact that all our patients were under similar medications for acute myocardial infarction minimised any treatment effect.

Conclusions

The results of this study suggest that abnormal auto-

nomic cardiac control after acute myocardial infarction is associated with increased levels of the acute phase protein CRP. The possibility of HRV indices being related to inflammation may further enhance their prognostic usefulness in risk stratification and late prognosis of patients who have suffered an acute myocardial infarction.

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