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Comparison of endothelial vasodilator function, inflammatory markers, and N-terminal pro-brain natriuretic peptide in patients with or without chronotropic incompetence to exercise test

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Objective: To investigate the role of endothelial function, inflammatory markers, and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with impaired chronotropic response during exercise test.
Methods: 86 subjects were enrolled. Treadmill exercise test was conducted according to the modified Bruce protocols. Brachial ultrasound was used to measure endothelium dependent flow mediated vasodilatation (FMD). Chronotropic incompetence was defined as either failure to achieve 85% of the age predicted maximum heart rate or a low chronotropic index (< 0.8).
Results: Of the 86 patients, 20 (23%) exhibited chronotropic incompetence. The patients were divided into three groups according to chronotropic index: group 1, < 0.8 (n = 20); group 2, 0.8–1.0 (n = 26); and group 3, > 1.0 (n = 40). Patients with impaired chronotropic response had significantly lower FMD than those with higher chronotropic response (mean (SD) 2.8 (1.9)% *v* 5.0 (2.8)% *v* 5.3 (2.5)%, p = 0.002, for groups 1, 2, and 3, respectively). Serum concentrations of high-sensitivity C reactive protein (hsCRP), monocyte chemoattractant protein-1 (MCP-1), and NT-proBNP were significantly higher in group 1 than in groups 2 and 3 (hsCRP: 19 (12) *v* 9 (6) *v* 9 (6) mg/l, $p < 0.05$; MCP-1: 140 (51) *v* 133 (60) *v* 108 (46) pg/ml, p = 0.046; NT-proBNP: 4760 (1980) *v* 3710 (850) *v* 3910 (1060) mg/l, p = 0.019, respectively). In addition, chronotropic index was significantly related to FMD ($r = 0.380$, p = 0.001) and inversely related to hsCRP ($r = -0.267$, p = 0.013). By multivariate analysis, impaired chronotropic response was significantly related to endothelial dysfunction (p = 0.012).
Conclusion: Patients with impaired chronotropic response to graded exercise had endothelial dysfunction, enhanced systemic inflammation, and higher NT-proBNP concentrations. These findings may partly explain the mechanism of chronotropic incompetence as a predictor of cardiovascular risk and increased mortality.

An impaired heart rate (HR) response to exercise, also known as chronotropic incompetence, has been shown to predict cardiovascular risk and is strongly linked to cardiac mortality.[1 2] Lauer *et al*[2] showed that both failure to achieve 85% of the age predicted maximum HR and chronotropic incompetence were associated with adverse risk profiles and thallium perfusion defects. Wiens *et al*[3] and Bruce *et al*[4] also proved that peak HRs of patients with coronary artery disease were significantly lower than those of normal subjects at maximal exercise and that impaired chronotropic response was a relatively specific predictor for coronary artery disease.

Impaired HR response to exercise may be a protective effect against early cardiac ischaemia or be a reduced HR variability with adverse outcome.[3 5] However, the exact mechanisms by which chronotropic incompetence during exercise predicts coronary artery disease risk or increased mortality remain unclear. The present study was designed to test the hypothesis that impaired HR response to exercise is associated with endothelial dysfunction and increased systemic vascular inflammation.

METHODS

Study population

The study population was composed of 86 consecutive patients with symptoms of typical or atypical chest pain who were referred for exercise testing and agreed to receive brachial ultrasonography for endothelial function evaluation and blood sampling between July 2003 and June 2004. Patients were excluded if they had a history of cardiac surgery (including coronary artery bypass grafting and valve replacement surgery), myocardial infarction, hospitalisation due to heart failure, congenital heart disease, valvar heart disease (moderate to severe aortic or mitral regurgitation), malignant hypertension, or significant endocrine, hepatic (total bilirubin > 27 μmol/l), or renal disease (serum creatinine > 177 μmol/l). Patients taking β blockers or digoxin were also excluded from the study.

Before the study, each patient's chart was reviewed and an interview was conducted to gather data on symptoms, medications, coronary risk factors, previous cardiac events, smoking habit, exercise habits, family history, and other systemic diseases. Chronic smoking was defined as a history of smoking for ≥ 1 pack year. Exercise habits were defined as presence or absence of regular exercise (duration ≥ 30 minutes, frequency ≥ 3 times a week) in a patient's day to day life. Body mass index was calculated as weight (kg) divided by height (m^2). Cardiovascular medications were classified as non-dihydropyridine calcium channel blockers (for example, diltiazem, verapamil), dihydropyridine calcium

Abbreviations: FMD, flow mediated vasodilatation; GTN, glyceryl trinitrate; HR, heart rate; hsCRP, high-sensitivity C reactive protein; MCP-1, monocyte chemoattractant protein-1; METs, metabolic equivalents; NT-proBNP, N-terminal pro-brain natriuretic peptide

channel blockers (for example, nifedipine, felodipine), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, antiplatelet agents (aspirin, ticlopidine, clopidogrel), nitrates, and statins. Blood biochemistry was analysed for lipid profiles, fasting sugar, and creatinine after 12 hour overnight fasting. All patients gave written informed consent.

Exercise testing

Treadmill exercise testing was conducted according to the modified Bruce protocols used in our laboratory. Participants were encouraged to exercise until they attained at least 90% of their age predicted maximum HR or until fatigue or medical contraindication occurred. Data on symptoms, HR, and blood pressures were collected and an ECG was recorded before exercise, at the end of each exercise stage, at peak exercise, one minute after the cessation of exercise, and every minute thereafter during the recovery period. During the study, an ischaemic response was considered present if there was more than 1 mm of horizontal or downsloping ST segment depression 80 ms after the J point or more than 1 mm of additional ST segment elevation in leads without pathological Q waves.[2] All data were entered on to a computer database for final analysis.

Chronotropic incompetence

Chronotropic incompetence was defined as failure to achieve 85% of the age predicted HR. Because this method may be confounded by effects of age, physical fitness, and resting HR, chronotropic response was also assessed by calculating the ratio of the percentage of HR reserve used to the percentage of metabolic reserve used at peak exercise, as described elsewhere.[1 6] For any given stage of exercise, the percentage metabolic reserve used was determined as $[(METs_{stage} - METs_{rest})]/[(METs_{peak} - METs_{rest})] \times 100$, where METs refers to metabolic equivalents of oxygen consumption, stage refers to any given stage of exercise, and peak refers to peak exercise. The value of $METs_{peak}$ refers to actual oxygen consumption noted, not a theoretical peak value. In an analogous fashion, the percentage of HR reserve used is equal to $[(HR_{stage} - HR_{rest})]/[(HR_{peak} - HR_{rest})] \times 100$. As in previous studies, in a group of healthy adults, the ratio of the percentage of HR reserve used to the percentage of metabolic reserve used during exercise was approximately 1.0 (95% confidence interval 0.8 to 1.3).[6] Thus, a ratio $\leqslant 0.8$ can be defined as chronotropic incompetence, and the cut off point of 0.8 was used to define chronotropic incompetence as in previous studies.[2 7] The chronotropic index has also been shown not to be related to physical activity and functional capacity and not to be affected by exercise protocol or during which stage of exercise measurements are taken.[1 8]

Endothelium dependent flow mediated vasodilatation

Endothelium dependent flow mediated vasodilatation (FMD) was assessed with a 7.5 MHz linear array transducer (Hewlett Packard Sonos 5500, Andover, Massachusetts, USA) to scan the brachial artery in longitudinal section, as described previously.[9 10] All patients were asked to fast, refrain from smoking, and withhold all medications for 12 hours before the endothelial function test. To minimise mental stress, care was taken to make the patients as comfortable as possible, and the procedure was performed in a quiet air conditioned room (22–25℃). The left arm was stabilised with a cushion and a sphygmomanometric cuff was placed on the forearm. A baseline image was acquired and blood flow was estimated by time averaging the pulsed Doppler velocity signals obtained from a mid artery sample volume. Then the cuff was inflated to at least 50 mm Hg above systolic pressure to occlude arteries for five minutes and released abruptly. Post-occlusion diameters were obtained at 60, 80, 100, and 120 seconds after deflation. A mid artery pulsed Doppler signal was obtained immediately on cuff release and no later than 15 seconds after cuff deflation to assess hyperaemic velocity. FMD was calculated as the maximum post-occlusion diameter relative to the averaged pre-occlusion diameter.

Endothelium independent glyceryl trinitrate mediated vasodilatation

At least 10 minutes of rest was given after the reactive hyperaemia before another image was acquired to reflect the re-established baseline conditions. Diameter was measured at least three times at 3−4 minute intervals after 0.6 mg sublingual glyceryl trinitrate (GTN) administration. The maximum FMD and GTN mediated vasodilatation diameters were determined as the average of the three consecutive maximum diameter measurements after reactive hyperaemia and GTN use, respectively. FMD and GTN mediated vasodilatation were then calculated as the percentage change in diameter compared with baseline. An experienced operator who was blinded to all clinical data took all measurements of endothelial function.

Measurement of high-sensitivity C reactive protein, monocyte chemoattractant protein-1, and N-terminal pro-brain natriuretic peptide

All participants underwent blood sampling before endothelial function measurement and exercise testing. After 12 hour overnight fasting, all patients had a venous blood sample taken for measurement of high-sensitivity C reactive protein (hsCRP), monocyte chemoattractant protein-1 (MCP-1), and N-terminal pro-brain natriuretic peptide (NT-proBNP). The blood samples were centrifuged at 3000 rpm for 10 minutes immediately after collection and then the serum samples were kept frozen at −70℃ until analysis. hsCRP concentration was determined with the use of a latex enhanced immunophelometric assay (Dade Behring, Marburg, Germany). MCP-1 in serum was quantified by a sandwich enzyme immunoassay technique (human MCP-1, Quantikine; R&D Systems, Wiesbaden, Germany) according to the manufacturer's protocol. The serum NT-proBNP was determined by a sandwich immunoassay (enzyme immunometric assay) with two antibodies (Cortez Diagnostics, Calabasas, California, USA).[11] All the procedures were carried out according to the manufacturers' instructions. Each standard and each serum sample were analysed two times, and the mean value was used for all subsequent analysis.

Statistical analysis

The primary end point of this study was endothelium dependent FMD. All data were expressed as mean (SD). A value of $p < 0.05$ was considered to indicate significance. Differences in baseline characteristics of underlying diseases, smoking habit, exercise habits, and medications were compared by the χ^2 test. The three groups were compared by analysis of variance for continuous variables and Kruskal-Wallis test for normally distributed variables. The degree of association between the independent variables age, sex, body mass index, current smoking, hypertension, diabetes mellitus, serum lipid profiles, fasting glucose, systolic blood pressure, diastolic blood pressure, pulse pressure, resting HR, total exercise time, HR after exercise, chronotropic index, hsCRP, MCP-1, and NT-proBNP was measured by means of simple linear regression and multiple regression analyses. The SPSS 9.0 (SPSS, Chicago, Illinois, USA) software package was used for statistical analysis.

Table 1 Baseline characteristics and medication use of 86 studied patients in three groups

	Group 1 (n = 20)	Group 2 (n = 26)	Group 3 (n = 40)	p Value
Age (years)	57 (18)	57 (14)	60 (12)	0.637
Men	17 (85%)	22 (85%)	30 (75%)	0.642
Body mass index (kg/m^2)	25 (3)	26 (3)	25 (2)	0.465
Current smoking	6 (30%)	7 (27%)	9 (23%)	0.821
Exercise habits	3 (15%)	4 (15%)	6 (15%)	1.000
Systemic hypertension	10 (50%)	9 (35%)	16 (40%)	0.608
Diabetes mellitus	2 (10%)	1 (4%)	2 (5%)	0.707
Hypercholesterolaemia*	7 (35%)	15 (58%)	18 (45%)	0.300
Lipid profile (mmol/l)				
Total cholesterol	5.10 (0.9)	5.67 (1.2)	5.23 (0.9)	0.132
Triglycerides	1.87 (1.1)	2.65 (4.8)	1.65 (5.5)	0.613
High density lipoprotein	1.24 (0.4)	1.24 (0.3)	1.14 (0.3)	0.364
Fasting glucose (mmol/l)	6.10 (2.2)	5.72 (1.7)	5.38 (0.6)	0.180
Medication use				
Non-dihydropyridine CCB	2 (10%)	5 (19%)	3 (8%)	0.387
Dihydropyridine CCB	2 (17%)	3 (12%)	7 (18%)	0.781
ACE or ARB	5 (25%)	3 (12%)	9 (23%)	0.475
Antiplatelet agent	6 (30%)	5 (19%)	3 (8%)	0.076
Nitrate	5 (25%)	5 (19%)	4 (10%)	0.271
Statin	3 (15%)	4 (15%)	3 (8%)	0.511

Values are mean (SD) or number (%).
*Total cholesterol ⩾5.18 mmol/l.
ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

RESULTS

Patients' baseline and exercise characteristics

A total of 86 patients (31–78 years, mean (SD) age 59 (14) years; 80% men) were enrolled in the study. The 86 patients were then divided into three groups according to chronotropic index: group 1, < 0.8 (n = 20); group 2, 0.8–1.0 (n = 26); group 3, > 1.0 (n = 40). Twenty patients (23%; group 1) had a low chronotropic incompetence response (chronotropic index < 0.8) during the exercise test, including 16 patients (19%) who failed to reach 85% of their age predicted maximum HR in this study. Table 1 shows the baseline characteristics of the 86 participants.

No significant differences were found between the three groups in terms of age, sex, body mass index, smoking status, exercise habits, underlying diseases (hypertension, diabetes), or medications. Table 2 lists the results of the exercise test in the three groups of patients. No significant differences were found in resting blood pressure and pulse pressure between the three groups of patients. However, patients with impaired chronotropic response were shown to have lower resting HR, lower peak HR, shorter exercise duration, and attenuated HR recovery at the third minute after peak exercise ($p < 0.05$). Moreover, more patients in group 1 than in group 2 and group 3 (30% *v* 19% *v* 8%, p = 0.076) tended to terminate the exercise test due to effort chest pain or ECG changes.

FMD, GTN mediated vasodilatation, hsCRP, MCP-1, and NT-proBNP

Table 3 lists the mean percentage changes of brachial artery diameters at baseline, during reactive hyperaemia, and after GTN administration, as well as the serum concentrations of hsCRP, MCP-1, and NT-proBNP in the three groups. Baseline diameter did not differ significantly in the three groups. Patients in group 1 had significantly lower FMD responses than those in group 2 and group 3 (2.8 (1.9)% *v* 5.0 (2.8)% *v* 5.3 (2.5)%, p = 0.002) but not significantly lower GTN mediated vasodilatation (9.6 (4.7)% *v* 13.2 (6.5)% *v* 13.1 (6.6)%, p = 0.082). Patients with a lower chronotropic index

Table 2 Exercise test results of 86 studied patients in three groups

	Group 1 (n = 20)	Group 2 (n = 26)	Group 3 (n = 40)	p Value
Blood pressure at rest (mm Hg)				
Systolic	129 (21)	134 (20)	132 (18)	0.534
Diastolic	75 (9)	77 (8)	81 (10)	0.068
Pulse	53 (18)	57 (17)	52 (15)	0.379
Resting HR (beats/min)	69 (14)	77 (13)	82 (16)	0.009
HR after exercise (1st min) (beats/min)	96 (18)	107 (12)	114 (13)	0.001*
Increased HR at 1st min (beats/min)	26 (9)	31 (10)	32 (8)	0.114
HR after exercise (3rd min) (beats/min)	110 (18)	119 (15)	131 (18)	0.001
Increased HR at 3rd min (beats/min)	41 (10)	42 (13)	49 (16)	0.056
Peak HR (beats/min)	130 (27)	157 (14)	169 (11)	0.001*
Peak metabolic equivalents	8.0 (2.3)	9.7 (2.0)	9.2 (2.2)	0.027
HR recovery at 1st min (beats/min)	20 (9)	24 (15)	27 (13)	0.150
HR recovery at 3rd min (beats/min)	42 (14)	54 (17)	56 (17)	0.010
Total exercise duration (s)	410 (134)	515 (118)	492 (119)	0.014
Chronotropic index	0.6 (0.2)	0.9 (0.1)	1.2 (0.1	0.001
Terminated exercise due to chest pain or ECG change	6 (30%)	5 (19%)	3 (8%)	0.076

Values are mean (SD).
*p<0.05 between groups by Kruskal-Wallis test.
HR, heart rate.

Table 3 Comparison of baseline brachial artery diameter, mean percentage change of diameter in response to FMD and GTN mediated dilatation, and hsCRP and NT-proBNP in the three groups of patients

	Group 1 (n = 20)	Group 2 (n = 26)	Group 3 (n = 40)	p Value
Baseline diameter (mm)	3.9 (0.6)	3.7 (0.6)	3.7 (0.7)	0.658
Maximum diameter (mm)	4.0 (0.5)	3.9 (0.6)	3.9 (0.7)	0.915
FMD (%)	2.8 (1.9)	5.0 (2.8)	5.3 (2.5)	0.002
Flow change during hyperaemic phase (%)	353 (188)	345 (181)	360 (173)	0.948
Baseline diameter before GTN mediated vasodilatation (mm)	3.9 (0.6)	3.7 (0.6)	3.7 (0.7)	0.465
GTN mediated vasodilation (%)	9.6 (4.7)	13.2 (6.5)	13.1 (6.6)	0.082
hsCRP (mg/l)	19 (12)	9 (6)	9 (6)	<0.05*
MCP-1 (pg/ml)	140 (51)	133 (60)	108 (46)	0.046
NT-proBNP (mg/l)	4760 (1980)	3710 (850)	3910 (1060)	0.019

Values are mean (SD).
*p<0.05 between groups by Kruskal-Wallis test.
FMD, flow mediated vasodilatation; GTN, glyceryl trinitrate; hsCRP, high sensitivity C reactive protein; MCP-1, monocyte chemoattractant protein 1; NT-proBNP, N-terminal pro-brain natriuretic peptide.

(group 1) had significantly higher serum concentrations of hsCRP and MCP-1 than those with a higher chronotropic index (group 2 and group 3) (19 (12) *v* 9 (6) *v* 9 (6) mg/l, $p < 0.05$; 140 (51) *v* 133 (60) *v* 108 (46) pg/ml, $p = 0.046$, respectively). In addition, patients in group 1 were observed to have higher NT-proBNP concentrations than those in group 2 and group 3 (4760 (1980) *v* 3710 (850) *v* 3910 (1060) mg/l, $p = 0.019$). Figures 1 and 2 compare the percentage changes of FMD and hsCRP between the three groups of patients.

Correlation between chronotropic index and FMD

As table 4 shows, simple linear regression analysis of data from all participants showed that the chronotropic index and HR recovery after exercise (first minute) were positively correlated with FMD ($r = 0.380$, $p = 0.001$ and $r = 0.213$, $p = 0.049$, respectively). When all univariate baseline parameters were entered into a multiple regression analysis, the results showed that endothelium dependent FMD was significantly related to chronotropic index ($p = 0.012$) and serum triglyceride concentration ($p = 0.011$) (table 5).

DISCUSSION

To the best of our knowledge, this is the first study to show that impaired chronotropic response to exercise is significantly related to endothelial vasodilator dysfunction in patients with suspected coronary artery disease referred for a treadmill exercise test. In addition, patients with chronotropic incompetence during exercise were found to have higher serum concentrations of hsCRP, MCP-1, and NT-proBNP than those with a normal chronotropic response to exercise.

Several large scale studies have proved that chronotropic incompetence is independently predictive of all cause mortality, even after the angiographic severity of coronary

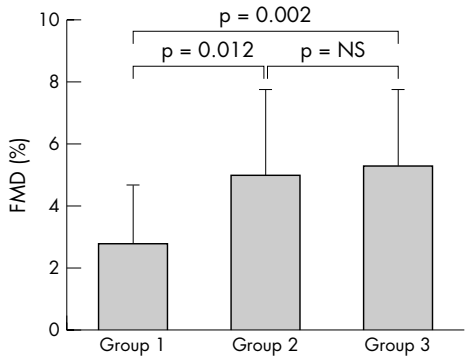

Figure 1 Comparison of percentage changes of endothelium dependent flow mediated dilatation (FMD) between the groups of patients by post hoc test. Group 1 *v* group 2, $p = 0.012$; group 2 *v* group 3, not significant (NS); group 1 *v* group 3, $p = 0.002$; all three groups by analysis of variance, $p = 0.002$.

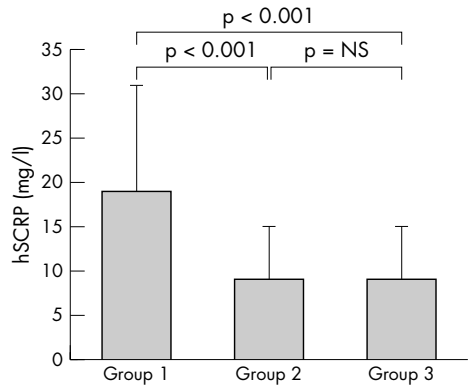

Figure 2 Comparison of mean serum concentrations of high sensitivity C reactive protein (hsCRP) between the groups of patients by post hoc test. Group 1 *v* group 2, $p < 0.001$; group 2 *v* group 3, NS; group 1 *v* group 3, $p < 0.001$; all three groups by Kruskal-Wallis test, $p < 0.05$.

Table 4 Simple linear regression analysis for determinants of FMD

Variable	*r*	p Value
Age	−0.131	0.228
Chronotropic index	0.380	0.001
hsCRP	−0.267	0.013
MCP-1	−0.200	0.065
NT-proBNP	−0.174	0.108
Total cholesterol	0.073	0.502
Triglycerides	0.203	0.060
High density lipoprotein	0.094	0.389
Fasting glucose	−0.090	0.411
Systolic blood pressure	0.064	0.559
Diastolic blood pressure	0.119	0.274
Pulse pressure	0.007	0.950
Resting HR	0.069	0.527
Total exercise time	0.195	0.072
Increased HR at 1st min	0.119	0.275
HR recovery after exercise (1st min)	0.213	0.049

Table 5 Multiple regression analysis for determinants of FMD

Variable	Coefficient	95% confidence interval	Standardised coefficient	p Value
Chronotropic index	3.056	0.691 to 5.421	0.287	0.012
Triglycerides	0.003	0.001 to 0.005	0.271	0.011
MCP-1	−0.004	−0.015 to 0.007	−0.084	0.440
hsCRP	−0.324	−1.004 to 0.355	−0.108	0.355
NT-proBNP	−0.001	−0.005 to 0.004	−0.011	0.919
HR recovery after exercise (1st min)	0.029	−0.012 to 0.071	0.287	0.160

artery disease or thallium perfusion defects are accounted for.[2 12] In the Framingham heart study, Lauer *et al*[1] showed that an attenuated HR response to exercise was associated with higher total mortality and with an increased risk of coronary heart disease presenting as myocardial infarction, angina pectoris, and sudden cardiac death.

It is well known that most myocardial perfusion occurs during the diastolic phase and that, as the HR increases, the diastolic phase is reduced from about 70% of the cardiac cycle at rest to about 20% at maximum HR.[13] During exercise, patients with coronary artery disease face an increased oxygen demand and decreased coronary perfusion due to a reduced diastolic phase. Therefore, we may propose that inhibition of HR increase during exercise may be a protective physiological response to avoid excessive myocardial ischaemia. In this study, chronotropic incompetence was shown to be significantly related to endothelial dysfunction and systemic vascular inflammation. Recently, Aronson *et al*[14] also showed that patients with the metabolic syndrome who maintain a high fitness level have much lower CRP concentrations than do those with a low fitness level. Furthermore, the effect of physical fitness on patients with the metabolic syndrome is more pronounced than that in those without the metabolic syndrome. This finding may explain why patients with an impaired HR response to exercise have increased coronary heart disease events and implies that vascular atherosclerosis develops in stages.

It is interesting to find, however, that patients with chronotropic incompetence to exercise test had a lower resting HR than those with a normal HR response during exercise, which was previously thought to be a protective factor against cardiovascular events.[7] This finding was also observed in previous clinical studies.[2 8] Elhendy *et al*[8] showed that resting HR was significantly lower in patients with chronotropic incompetence than in those without chronotropic incompetence. The reason underlying this phenomenon is unclear, but a decreased response of the heart to β stimulation due to frequent sympathetic hyperactivation may be responsible in these patients.

NT-proBNP, a circulating hormone released from the cardiac ventricles in response to increased cardiac wall stress, had been proved to be a strong predictor of cardiovascular events and congestive heart failure.[15 16] The measurement of NT-proBNP has also been shown to be useful in detecting left ventricular dysfunction.[17] In our study, patients with chronotropic incompetence were found to have higher serum concentrations of NT-proBNP, and this finding suggests that patients with impaired HR responses during exercise have greater ventricular wall stress or may have more intermittent and transient ventricular ischaemia. This consequence may result in sympathetic hyperactivity and ultimately lead to decreased sensitivity of the heart to β adrenergic receptor stimulation.

More and more evidence has shown that the autonomic system has a critical role in regulating cardiovascular function in both healthy and diseased populations.[5 18 19] In the present study, patients with impaired chronotropic response to exercise had attenuated HR recovery, which had been proved to be an independent predictor of all cause mortality in several large scale studies.[20] Chronotropic incompetence may reflect a modulation of autonomic tone that implies more severe cardiovascular perturbations. Fei *et al*[21] showed that HR variability is significantly decreased in patients with congestive heart failure who have chronotropic incompetence. The low frequency component of spectral HR variability gives a predominant measure of sympathetic activity, and the high frequency is almost exclusively mediated by vagal activity. The low, but not the high, frequency components was significantly lower in patients with chronotropic incompetence.[21] The finding that only the low frequency component was significantly reduced suggests that impaired sympathetic activity may be an important factor contributing to chronotropic incompetence. Previous studies have also shown that increased sympathetic tone may lead to endothelial dysfunction.[22 23] These data clearly showed the close relation between the autonomic system regulated chronotropic response during exercise and endothelial function. Therefore, patients with impaired chronotropic responses during exercise, reflecting a higher systemic inflammatory status, greater ventricular wall stress, and endothelial dysfunction, are warranted to receive more aggressive antiatherosclerosis treatment and lifestyle modification in preventing further cardiovascular events. However, further studies are needed to support this finding and may focus on whether improving endothelial function can improve chronotropic HR response to exercise.

Study limitations

In this study, some of the relations between chronotropic index and markers of inflammation may have been mediated by other covariates or confounders. Except for the analysis of FMD, the analyses presented are univariate analyses and may not be adequately adjusted.

Conclusion

We found a significant relation between chronotropic incompetence to exercise and endothelial dysfunction. Enhanced vascular inflammation was also noted in this high risk group, and the early stage of vascular injury may account for the impaired chronotropic response to exercise being predictive of increased coronary heart disease risk and long term survival. More aggressive risk factor modification and antiatherosclerosis treatment may be needed in such group of patients.

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Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome

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Background: Cardiovascular mortality is increased in rheumatoid arthritis. Possible reasons include an increased incidence of ischaemic heart disease or worse outcome after acute coronary syndrome (ACS).

Objectives: To assess the outcome of ACS in rheumatoid arthritis compared with case matched controls in the context of underlying cardiac risk factors, clinical presentation, and subsequent management.

Methods: 40 patients with rheumatoid arthritis and ACS identified from coronary care admission registers between 1990 and 2000 were case matched as closely as possible for age, sex, classical cardiovascular risk factors, type and severity of ACS, and admission date ($\pm$3 months) with 40 controls. A standardised proforma was used for detailed case note review.

Results: Age, sex, other cardiovascular risk factors, and type and severity of presenting ACS were not significantly different between cases and controls. Recurrent cardiac events were commoner in rheumatoid arthritis (23/40, 57.5%) than controls (12/40, 30%) ($p = 0.013$); there were 16/40 deaths in rheumatoid arthritis (40%) *v* 6/40 (15%) in controls ($p = 0.012$). Recurrent events occurred earlier in rheumatoid arthritis (log rank survival, $p = 0.05$). Presentation with chest pain occurred in all controls compared with 33/40 rheumatoid patients (82%) ($p = 0.006$); collapse occurred in one control (2.5%) *v* 7/40 rheumatoid patients (17.5%) ($p = 0.025$). Treatment during the ACS was not significantly different in the two groups.

Conclusions: Recurrent ischaemic events and death occur more often after ACS in rheumatoid arthritis. Atypical presentation is commoner in rheumatoid arthritis. There is an urgent need to develop identification and intervention strategies for ACS specific to this high risk group.

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