CORONARY ARTERY DISEASE

Heart rate and microinflammation in men: a relevant atherothrombotic link

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Objective and background: To explore the possibility that increased resting heart rate (HR) is associated with a microinflammatory response. Such an association could explain, at least in part, the recently described worse cardiovascular prognosis in individuals with increased HR.
Methods: Concentrations of fibrinogen and high-sensitivity C-reactive protein, as well as the absolute number of polymorphonuclear leucocytes, were analysed in a cohort of 4553 apparently healthy men and in those with atherothrombotic risk factors.
Results: Following adjustment for age and body mass index, lipid profile and cardiovascular risk factors, a significant ($p<0.001$) difference was noted between individuals in the first quintile of HR ($\leqslant 58$ beats/min) and those in the fifth quintile ($\geqslant 79$ beats/min) regarding all the above-mentioned inflammatory biomarkers, the respective mean values being 7.38 and 8.11 μmol/l, 1.12 and 1.61 mg/l, and 4.23 and 4.74×10^9/l.
Conclusions: Resting HR is associated with a microinflammatory response in apparently healthy men and in those with atherothrombotic risk factors. Sympathetic activation might be a common factor explaining such an association. If confirmed in additional studies, this association might be a relevant target for therapeutic manipulations.

Increased heart rate (HR) is an emerging new cardiovascular risk factor.[1] In fact, it has been shown that high HR is prospectively related to the development of cardiovascular morbidity and mortality.[2–6] The finding that even a single resting HR measurement has a predictive value[5 7] has created a situation where every nurse or primary care physician can obtain a costless prognostic marker that is related to future cardiovascular morbidity and mortality. Moreover, this simple measurement can be a target for therapeutic interventions including drugs or lifestyle modification. Explaining the potential mechanisms that relate this measurement to future cardiovascular events might therefore be of relevance.

We herewith examined the inter-relationships between a single resting HR measurement and the presence of a microinflammatory response in a group of apparently healthy individuals and in those with atherothrombotic risk factors. The significant correlation that we found might shed more light on the potential mechanisms that link HR with future cardiovascular events.

METHODS

Study population

The present study was restricted to men, solely due to the microinflammatory changes that are observed during the menstrual cycle in women.[8–10] We analysed the data that are currently available in the Tel Aviv Medical Center Inflammation Survey (TAMCIS), a registered data bank, Data Banks Registry, Ministry of Justice, State of Israel.[11–15] This is a relatively large survey, in which we recruited apparently healthy individuals and those with atherothrombotic risk factors who were examined during their routine annual general health check-up. All the individuals included in the present survey gave their written consent according to the instructions of the institutional ethics committee.

Protocol

Patients attending the Tel Aviv Sourasky Medical Center (Tel Aviv, Israel) for a routine health examination between September 2002 and July 2006 were asked to participate in the TAMCIS. A total of 9289 subjects (5821 males, 3468 females) agreed to participate. Systematic examination of the reasons for participation yielded no effect of sociodemographic or biomedical variables. We excluded all female subjects from this analysis, owing to the effect of hormonal therapy (hormonal replacement therapy or oral contraceptives) and the effect of day of period on the inflammatory variables. From the 5821 men, an additional 947 subjects were later excluded from the analysis because of known inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc), steroidal or non-steroidal treatment (except for aspirin at a dose of $\leqslant 325$ mg/dl), acute infection or invasive procedures (surgery, catheterisation, etc) during the last 6 months. An additional 181 subjects were excluded due to missing high-sensitivity C-reactive protein (hs-CRP) concentrations, as well as the 1.5% of the highest hs-CRP concentrations, and 140 subjects were excluded due to missing resting HR measurement. First, we analysed this cohort of 4553 individuals, and then excluded any individual with a history of proven vascular disease, including ischaemic heart disease, cerebrovascular accident or peripheral artery occlusive disease, as well as any individuals taking medications with a potential influence on HR, including nitrates, α blockers, β blockers, calcium channel blockers, antiarrhythmic drugs and digoxin, as well as any medications with a potential influence on inflammatory variables, including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), HMG-CoA reductase inhibitors and fibrates. We further excluded any individual with anaemia, defined as haemoglobin concentration below the lower normal limit according to our laboratory (which is 135 g/l), and any smoking individual, leaving 2878 individuals for the concise analysis. Finally, in order to test our hypothesis without any

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; HDL, high density lipoprotein; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; TAMCIS, Tel Aviv Medical Center Inflammation Survey; WBCC, white blood cell count

influence of proinflammatory conditions, we limited our cohort further to apparently healthy individuals, by excluding any individual with diabetes mellitus, hypertension or hyperlipidaemia, leaving 1879 individuals. Baseline resting HR was obtained manually at enrolment, with one radial pulse measurement during 60 s with the patient in a sitting position.

Definition of risk factors

Diabetes mellitus was defined as a blood glucose level of ⩾7 mmol/l fasting or the use of insulin or oral hypoglycaemic medications. Hypertension was defined as a blood pressure of ⩾140/90 mm Hg or the use of any antihypertensive medications, whereas hyperlipidaemia was defined as low-density lipoprotein (LDL) cholesterol concentration or non-high-density lipoprotein (HDL) cholesterol concentrations, for individuals with triglyceride concentrations of ⩾2.26 mmol/l, above the recommended goal according to the risk profile defined by the updated ATP III recommendations[16] or the use of lipid-lowering medications. Smokers were defined as those who smoke at least five cigarettes daily, whereas past smokers were defined as those who quit smoking for at least 30 days before examination.

Analytical methods

The white blood cell count (WBCC) and differential were determined by using the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic cell analyser, quantitative fibrinogen level by the method of Clauss[17] and a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) autoanalyzer, whereas the hs-CRP level was determined by using a Behring BN II Nephelometer (DADE Behring, Marburg, Germany).[18] The inter-assay and intra-assay variabilities did not exceed 3% for the hs-CRP and 5% for the WBCC or fibrinogen assay.

Statistical analysis

All data were summarised and displayed as mean (standard deviation (SD)) for the continuous variables (age, body mass index(BMI), all the inflammation markers, etc), and as number of patients plus the percentage in each group for categorical variables (cardiovascular risk factors, etc). The crosstabs and descriptive procedures were used to produce frequencies of categorical variables and mean (SD) of continuous variables. The hs-CRP and the triglyceride concentrations have non-normal distribution; hence, we used a logarithmic transformation that converts it to a normal distribution for all statistical procedures such as corrections, analysis of variance (ANOVA) and analysis of covariance, and all the results for hs-CRP or triglyceride concentrations were expressed as a back-transformed geometrical mean (SD). The one-way Kolmogorov–Smirnov test and the Q–Q plot were used to assess the distributions.

Pearson's partial correlations for confounding variables were performed to evaluate the association between resting HR and the different inflammatory variables. All correlations were carried out once bivariate, and then adjusted for age and BMI. To assess the gradual influence of resting HR, we divided our population into quintiles based on HR. For all continuous variables, the comparison between the different quintiles of HR was carried out using one-way ANOVA, whereas for all categorical variables, it was carried out using The χ^2 phi and Cramer's V statistics.

Estimated marginal means of inflammatory variables for the quintiles of resting HR were adjusted for age, waist, BMI, complete lipid profile, including LDL, HDL and triglycerides, diastolic and systolic blood pressure measurements, haemoglobin concentration, glucose concentration, alcohol consumption, sport intensity, medications, including nitrates, α blockers, β blockers, calcium channel blockers, ACE inhibitors, ARB, statins, fibrates, digoxin and antiarrhythmic drugs, and cardiovascular risk factors, including current and past smoking status, diabetes mellitus and family history of coronary heart disease, history of proven vascular disease including myocardial infarction, cerebrovascular accident or peripheral vascular disease, using analysis of covariance, under a general linear model. We further assessed the p value for trend, and the pairwise statistical significance between the quintiles of HR using the Bonferroni correction.

The level of significance used for all of the above analyses was two tailed, $p<0.05$. The SPSS statistical package, v 14.0, was used to perform all statistical evaluation.

RESULTS

We analysed a total of 4553 men at a mean (SD) age of 44.8 (11.2) years. Their characteristic age, BMI, blood pressure as well as alcohol consumption and sport intensity according to quintiles of resting HR and the percentages of individuals with different cardiovascular risk factors are presented in table 1, whereas the respective percentages of individuals with different relevant medications are presented in table 2. As expected, patients with lower HR exercise more, are leaner and overall healthier or use β blockers. A significant age- and BMI-adjusted Pearson's partial correlation was noted between resting HR and the concentration of fibrinogen ($r = 0.190$, $p<0.001$), absolute polymorphonuclear count ($r = 0.177$, $p<0.001$) and hs-CRP ($r = 0.171$, $p<0.001$).

The estimated marginal mean (SE) of the different inflammatory biomarkers according to quintiles of resting HR after adjusting for age, BMI, waist, various medications, lipid profile and cardiovascular risk factors are reported in table 3. It can be seen that the inflammatory biomarkers increase pari pasu with the resting HR increment. To minimise the effects of the different medications and conditions like anaemia and smoking on HR, we further excluded all individuals taking any medication with potential influence on HR or on inflammatory biomarkers, as well as any smoking patients and patients with anaemia, and performed the analysis again. This analysis demonstrates the same trend, as was in the entire cohort. Further exclusion of individuals with hypertension, diabetes mellitus or hyperlipidaemia, leaving just apparently healthy individuals, did not change the results significantly.

DISCUSSION

There are multiple lines of evidence to suggest a role for low-grade, subclinical and smoldering internal inflammation (the so-called microinflammation) in the pathogenesis of the atherothrombotic disease.[19–25] Several recent studies have reported a relationship between this low-grade inflammation and HR—an eventual predictor of future cardiovascular events.[26 27] It is assumed that the sympathetic activation is the explanation, at least in part, for the association between increased HR and a heightened microinflammatory response.[28]

We have presently included three biomarkers that have an established association with cardiovascular morbidity and mortality, including the WBCC,[29] quantitative fibrinogen[30] as well as hs-CRP.[31] A main limitation of the leucocyte count in the present context is the possibility that both leucocyte count and HR can be the results of a transient surge of a sympathetic activity due to the stress of the examination itself. However, although leucocyte demargination during epinephrine release can increase within a couple of minutes, the time course for increment of hs-CRP and especially fibrinogen are completely different.[32] Therefore, the correlation with markers that are probably not influenced by a transient stressogenic stimulus is of special significance.

Table 1 Mean (SD) of the different variables according to the quintiles of resting heart rate (HR), the one-way ANOVA between the quintiles and the linear trend (upper part) and the number and percentage of the relevant cardiovascular risk factors according to the quintiles of resting HR, and the χ^2 overall statistical significance between the quintiles (lower part)

	1st quintile n = 876 HR ⩽ 58	2nd quintile n = 964 59 ⩽ HR ⩽ 65	3rd quintile n = 830 66 ⩽ HR ⩽ 71	4th quintile n = 953 72 ⩽ HR ⩽ 78	5th quintile n = 930 HR ⩾ 79	ANOVA	p for linear trend
Age (years)	45 (12)	46 (12)	45 (11)	44 (11)	44 (11)	0.028	0.006
BMI (kg/m^2)	26.2 (3.2)	26.7 (3.4)	27.1 (4.0)	27.1 (3.8)	27.6 (4.1)	<0.001	<0.001
Waist circumference (cm)	93 (9)	95 (10)	96 (10)	96 (11)	98 (11)	<0.001	<0.001
Diastolic blood pressure (mm Hg)	76 (8)	78 (8)	78 (8)	78 (8)	80 (8)	<0.001	<0.001
Systolic blood pressure (mm Hg)	123 (14)	125 (15)	125 (14)	125 (14)	129 (16)	<0.001	<0.001
Alcohol consumption (glasses/week)	1.6 (2.4)	1.5 (2.6)	1.2 (1.9)	1.2 (2.6)	1.1 (2.0)	<0.001	<0.001
Sport intensity (h/week)	3.4 (3.4)	2.7 (3.4)	2.4 (2.9)	2.3 (3.0)	1.7 (2.3)	<0.001	<0.001
	n (%)	n (%)	n (%)	n (%)	n (%)	χ^2	
Current smokers	142 (16.2)	155 (16.1)	129 (15.5)	156 (16.4)	167 (18.0)	0.704	
Past smokers	267 (30.5)	266 (27.6)	234 (28.2)	246 (25.8)	227 (24.4)	0.044	
History of vascular event	54 (6.2)	51 (5.3)	34 (4.1)	27 (2.8)	36 (3.9)	0.006	
Diabetes mellitus	33 (3.8)	41 (4.3)	39 (4.7)	46 (4.8)	76 (8.2)	<0.001	
Hypertension	207 (23.6)	230 (23.9)	215 (25.9)	201 (21.1)	301 (32.4)	<0.001	
Family history of CHD	149 (17.0)	138 (14.3)	136 (16.4)	143 (15.0)	149 (16.0)	0.518	
Hyperlipidaemia	272 (31.1)	339 (35.2)	292 (35.2)	367 (38.5)	384 (41.3)	<0.001	

ANOVA, analysis of variance; BMI, body mass index; CHD, coronary heart disease; HR, heart rate.

Although women were evaluated in the past,[33] we did not include them in the present study. This was done because of potential confounders like oestrogen concentrations during the menstrual cycle[34 35] or the influence of this cycle on the synthesis of inflammatory biomarkers.[8–10] Therefore, relatively large cohorts of pre-menopausal and post-menopausal women are needed for a similar analysis in women.

The growing number of studies that relate a single resting HR measurement to future cardiovascular disease is of special interest due to the fact that this is almost a cost-less marker. If confirmed in additional studies, the findings of the present study might be significant in that they shed some light on the possible associations between HR and the cardiovascular events. In fact, it is now conceivable that the inflammatory biomarkers are not necessarily innocent bystanders and might actually participate in the progression of the disease. This is true for both the white blood cells[36] and the C-reactive protein,[37] as well as clottable fibrinogen.[38] Therefore, the association of HR with these biomarkers might be relevant for the potential usefulness of HR as a predictor of cardiovascular diseases. In addition, therapeutic implications in terms of reducing both HR and inflammatory biomarkers by using β blockers might be of interest.[39 40]

Finally, it should be pointed that there is growing evidence to suggest an association between the autonomous nervous system and the inflammatory response. In fact, it has been shown that vagus nerve stimulation attenuates the LPS-induced increases in plasma and splenic concentrations of proinflammatory cytokines, including TNF-α and IL-6.[41] Electrical stimulation of the efferent vagus nerve reduced the release of TNF-α in rats,[42 43] an effect that appeared to be mediated by an effect of acetylcholine on α7 cholinergic receptors or macrophages.[44] Electrical vagus nerve stimulation also inhibited the acute inflammatory response to acute hypovolaemic shock,[45] splanchnic artery occlusion shock[46] and intestinal inflammation during experimentally induced ileus.[47] In addition, stimulation of the α7 cholinergic receptors attenuated systemic inflammation in mice with abdominal sepsis,[48] reduced cytokine release in peritonitis,[49] diminished the severity of experimental pancreatitis[50] and suppressed endothelial cell activation during the localised Shwartzman reaction.[51] Thus, one could suggest that individuals with increased vagal tone might present a less intense baseline inflammatory profile. It is tempting to assume that these vagotonic individuals also present a reduced heart rate, thus providing at least a partial explanation to our present observation.

CONCLUSIONS

Resting HR is associated with a microinflammatory response in apparently healthy men and in those with atherothrombotic risk factors. Sympathetic or vagal activation might be a common denominator that explains such an association.[41–52] If confirmed in additional studies, this association might be a relevant target for therapeutic manipulations.

Table 2 Number and percentage of the relevant medications according to the quintiles of resting heart rate with the χ^2 overall statistical significance between the quintiles

	1st quintile n = 876 HR ⩽ 58		2nd quintile n = 964 59 ⩽ HR ⩽ 65		3rd quintile n = 830 66 ⩽ HR ⩽ 71		4th quintile n = 953 72 ⩽ HR ⩽ 78		5th quintile n = 930 HR ⩾ 79		χ^2
Aspirin	88	10.0	85	8.8	71	8.6	70	7.3	70	7.5	0.231
α Blockers	23	2.6	20	2.1	10	1.2	8	0.8	21	2.3	0.021
β Blockers	82	9.4	58	6.0	43	5.2	17	1.8	16	1.7	<0.001
Calcium channel blockers	22	2.5	25	2.6	24	2.9	23	2.4	36	3.9	0.314
ACE inhibitors	42	4.8	29	3.0	30	3.6	26	2.7	55	5.9	0.002
ARB	10	1.1	7	0.7	4	0.5	7	0.7	10	1.1	0.533
Statins	91	10.4	110	11.4	83	10.0	80	8.4	84	9.0	0.204
Fibrates	9	1.0	5	0.5	10	1.2	12	1.3	15	1.6	0.242
Oral hypoglycaemics	14	1.6	15	1.6	15	1.8	19	2.0	27	2.9	0.217

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; HR, heart rate.

Table 3 Estimated marginal mean (SE) of the different inflammatory variables according to the quintiles of resting heart rate, with the one-way ANOVA between the quintiles in the cohort

	1st quintile n = 876 HR ⩽ 58	2nd quintile n = 964 59 ⩽ HR ⩽ 65	3rd quintile n = 830 66 ⩽ HR ⩽ 71	4th quintile n = 953 72 ⩽ HR ⩽ 78	5th quintile n = 930 HR ⩾ 79	ANOVA	Pairwise comparison using Bonferroni correction	p Value	p for linear trend
Fibrinogen (μmol/l)	7.38 (0.62)	7.53 (0.62)	7.64 (0.62)	7.85 (0.62)	8.11 (0.62)	<0.001	1–3	0.001	<0.001
							1, 2–4, 5	<0.001	
							3–4	0.043	
							3–5	<0.001	
							4–5	0.009	
Polymorphonuclear count ($\times 10^{9/l}$)	4.23 (0.48)	4.39 (0.48)	4.38 (0.48)	4.47 (0.48)	4.74 (0.48)	<0.001	1–2	0.041	<0.001
							1–4	<0.001	
							1, 2, 3, 4–5	<0.001	
hs-CRP (mg/l)	1.12 (1.42)	1.26 (1.43)	1.31 (1.43)	1.46 (1.43)	1.61 (1.43)	<0.001	1–2	0.050	<0.001
							1–3	0.004	
							1–4, 5	<0.001	
							2–4	0.003	
							2, 3–5	<0.001	

ANOVA, analysis of variance; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*All results are adjusted for age, waist, body mass index, complete lipid profile including LDL, HDL and triglycerides, diastolic and systolic blood pressure measurements, haemoglobin concentration, glucose concentration, alcohol consumption, sport intensity, medications including nitrates, α blockers, β blockers, calcium channel blockers, angiotensin converting enzymes inhibitors, angiotensin II receptor blockers, statins, fibrates, digoxin, antiarrhythmic drugs, and cardiovascular risk factors, including current and past smoking status, diabetes mellitus, family history of coronary heart disease and history of proven vascular disease, including myocardial infarction, cerebrovascular accident or peripheral vascular disease.

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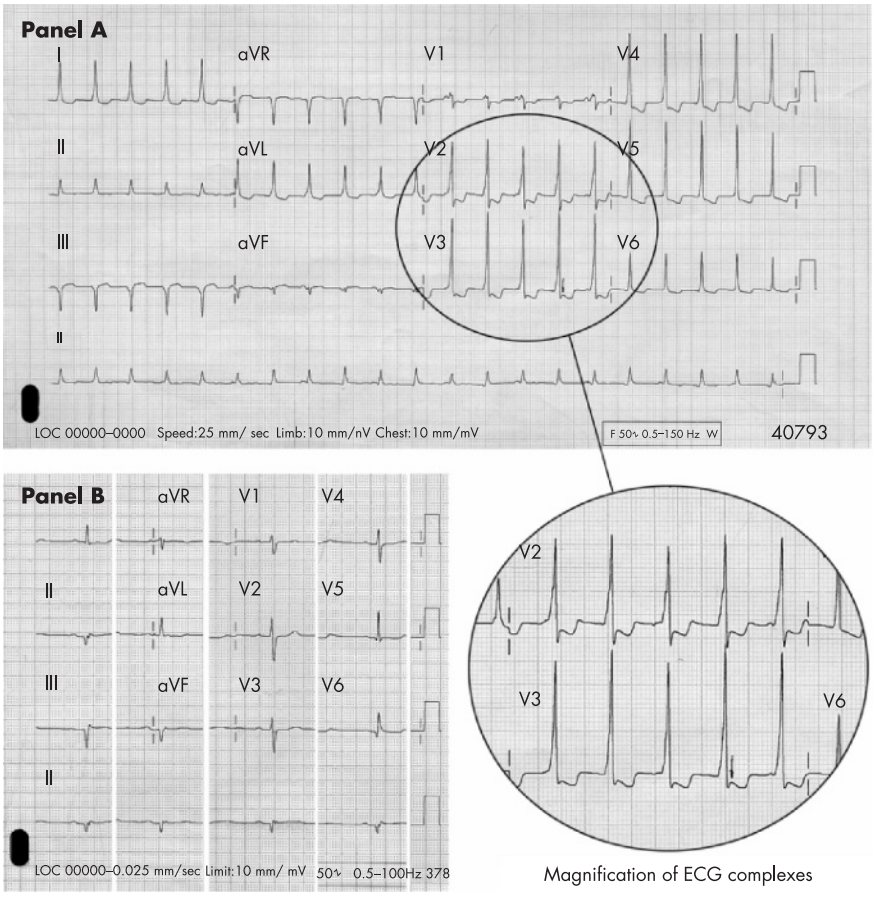
Pseudo-pre-excitation terminated by overdrive pacing

A 67-year-old Caucasian man presented with gradual onset exertional dyspnoea over the past few months. On one occasion he experienced some chest pain at work and he had to stop work. He was an ex-smoker and his cholesterol was raised at 5.4 mmol/l. An echocardiogram showed a dilated left ventricle with moderately impaired systolic function. An ECG (panel A) showed tachycardia and suggested ventricular pre-excitation compatible with Wolff–Parkinson–White (WPW) syndrome. However, the nature of the rhythm was not clear, as P waves were not present before each QRS complex. At this stage, differential diagnoses were WPW syndrome, atrial flutter, chaotic atrial rhythm and atrial parasystole. Coronary angiography and electrophysiological studies (EPS) were carried out to identify the origin of the arrhythmia and convert his heart to sinus rhythm. Coronary arteriography showed an occluded right coronary artery with minor disease in the left circumflex artery. During EPS it was clear that there was independent atrial activity. The EPS confirmed that the rhythm was ventricular in origin, suggesting it was HIS bundle or of fascicular origin. The arrhythmia was terminated by overdrive pacing. An ECG after EPS showed a normal sinus rhythm (panel B). He was treated and maintained with amiodarone. At 6 months' follow-up, he remains well without recurrence of ventricular tachycardia.



Magnification of ECG complexes

This is an interesting case of ventricular tachycardia mimicking pre-excitation and reinforces the important message that atrioventricular dissociation should be looked for in all cases of tachyarrhythmia.

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