The relationship between resting heart rate and atherosclerosis risk factors

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Abstract

Background and aim: The imbalance between sympathetic and parasympathetic activity is one of the important factors in pathogenesis of cardiovascular diseases (CVD). There is a relationship between sympathetic activity and some CVD risk factors. Also heart rate (HR) is related to the autonomic nervous system. We analysed the relation of mean resting HR to hypertension, diabetes, obesity and to some risk factors [body mass index (BMI), hsCRP, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL cholesterol (LDL), triglycerides (TG) and glucose (G)].

Methods: 6977 men and 7792 women, aged 20-74, randomly selected from the Polish population, were screened in 2003-2005 within the framework of the National Multicentre Health Survey (WOBASZ). Resting HR and blood pressure were measured 3 times using an automatic device and for analyses only the mean value of the 2nd and 3rd measurement was used.

Results: Out of screened subjects, HR <60/min was found in 11% of men and 7% of women, and HR >90/min – in 6% and 5% respectively. Medication that influenced HR was taken by 16% of men and 17% of women. Resting HR was correlated ($p < 0.0001$) with BMI, SBP, DBP, hsCRP, LDL and G in men and with SBP, DBP, hsCRP and G in women. After adjustment for medication significantly higher HR was observed both in men and in women with obesity, diabetes, hypertension, high hsCRP and in smoking persons. The prevalence of obesity, diabetes, hypertension, high hsCRP and smoking habit rose with increasing HR and the highest one was found in persons with HR >90/min. In multivariate logistic regression models resting HR was positively associated with hypertension, obesity and diabetes. In men, with every increase in HR by 10 beats/min, OR for hypertension was 1.28 (95% CI: 1.22-1.35), for obesity 1.24 (95% CI 1.17-1.30) and for diabetes 1.36 (95% CI: 1.26-1.48) after adjustment for age, medication and other factors (in women: 1.42 for hypertension, 1.14 for obesity and 1.47 for diabetes).

Conclusions: Resting heart rate is correlated with cardiovascular risk factors (body mass index, blood pressure, glucose and cholesterol level) and with high hsCRP. Heart rate is positively associated with hypertension, obesity and diabetes which indirectly confirms the autonomic nervous system contribution to the pathogenesis of these diseases.

Keys words: resting heart rate, hypertension, diabetes, obesity

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Introduction

The resting heart rate (HR) is a basic and simple element of physical examination. Numerous prospective epidemiological studies have demonstrated a positive correlation between the resting HR and morbidity and mortality, both general and caused by cardiovascular diseases (CVD) (Framingham Study, NHANES I, BRH study, CASS, Pol-MONICA) [1-5]. Increased mortality was observed together with increased HR. In the Framingham study a correlation between the resting HR and general mortality as well as mortality due to ischaemic cardiac disease and due to CVD was observed for both genders and all age ranges [1]. The NHANES I study demonstrated that increased HR significantly enhanced the risk of death after adjustment for age, cigarette smoking, systolic blood pressure, total cholesterol

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concentration and diabetes [2]. In the CASS study the risk of death, as well as the risk of hospitalisation due to cardiovascular causes and heart failure, increased along with the increase of HR [4]. Epidemiological findings were confirmed by clinical studies which demonstrated in patients treated with beta blockers after MI decreased mortality, proportional to the reduction of HR [6]. Elevated resting HR can also be considered as a marker of the dominance of the sympathetic over the parasympathetic system, sympathetic hyperactivity, unfavourable neurohormonal changes (elements of the metabolic syndrome) as well as increased inflammatory reaction [7]. Heart rate is regulated by the autonomic system and disturbances of autonomic system balance are considered an element of the pathogenesis of CVD. There are data showing that HR correlates with the advancement of coronary vessel atherosclerosis [8]. It was shown that the average area of the artery damage in patients with low HR is by 2/3 smaller than in patients with high HR. This is probably associated with local haemodynamic disturbances. The formation of atherosclerotic plaque depends on disturbed blood flow; the higher the average HR the shorter the heart diastolic phase and the greater the changes in the vascular tension and probability of its damage. The vascular damage leads to numerous immunological reactions and occurrence of the inflammatory process. This was confirmed by studies which demonstrated that a high HR was associated with increased concentration of inflammatory markers (CRP) [9].

There are no studies in Polish literature evaluating the value of resting HR as a risk factor of atherosclerosis, based on a large randomised representative group of the total Polish population.

The aim of the study was to analyse the correlation between the mean HR and hypertension, diabetes, obesity, inflammatory reaction (measured by hsCRP values), and metabolic disturbances which are the cause of cardiovascular events.

Methods

Study group

The study group consisted of a representative randomised Polish population at the age of 20-74 years. 6392 male and 7153 female patients were examined during the period 2003-2005 in the National Multicenter Health Survey (WOBASZ study). The examination included questionnaires, physical examination, anthropometric measurements and laboratory tests. The aims and the methods of the study were described previously [10, 11].

Data concerning hospitalisations due to exacerbation of coronary disease, MI and/or coronary angioplasty or coronary artery bypass were obtained from the questionnaire of the WOBASZ study. The patients after MI were chosen on the basis of hospital data or to the diagnosis of MI established without previous hospitalisation.

Hypertension was diagnosed in those patients in whom the mean value of the 2nd or 3rd measurement was ≥140/90 mmHg and/or in patients treated with hypotensive medications. Patients with diabetes were selected on the basis of fasting glucose concentration ≥7.0 mmol/l and/or treatment with hypoglycaemic medications. The hsCRP concentration was measured with the high sensitivity method and the result is presented in mg/dl (reference values: 0.0-0.5 mg/dl).

Heart rate measurement

Mean HR was obtained as an average of the 2nd and 3rd measurement, which was made along with the blood pressure measurement using an electronic OMRON M5-I device, certified by AAMI (Association for the Advancement of Medical Instrumentation). The measurements were made after 5 minute rest, in the sitting position, with 2 minute intervals.

Statistical analysis

All analyses were conducted separately for male and female patients. In order to compare the mean HR values in groups of subjects with hypertension, diabetes, obesity and increased concentration of hsCRP, the General Linear Model (GLM) procedure was used. In order to evaluate the frequency of hypertension, diabetes, cigarette smoking or increased concentrations of hsCRP in the group of patients with resting HR, Chi^2 and Fisher's tests were performed. Multiple logistic regression was used in order to evaluate the correlation between HR and the above-listed conditions with adjustment for age, hypertension, diabetes, obesity and the use of medications directly or indirectly influencing HR (drugs: beta-blockers, calcium channel blockers, anti-arrhythmic drugs, hypotensive drugs with central mechanisms of action, digoxin).

Results

The resting HR differed significantly between male and female patients (males – 72.7.±11.0/min; females – 73.3±9.8/min) ($p < 0.0001$). Among the examined patients 11% of males and 7% of females presented with resting HR of <60/min. In 6% of males and 5% of females the resting HR was >90/min. The majority of patients, both male (35%) and female (38%), presented with resting HR of 70-79/min (Figure 1). Sixteen percent of males and 17% of females were treated with medications affecting HR.

Resting HR correlated significantly and positively with BMI, blood pressure (both systolic and diastolic), hsCRP, cholesterol and glucose concentration in males (Table I). In females HR correlated only with blood pressure, hsCRP and glucose concentration (Table I).

The conducted analysis of the prevalence of CVD risk factors in the three groups HR <60/min, 60-90/min and >90/min (excluding patients treated with medications

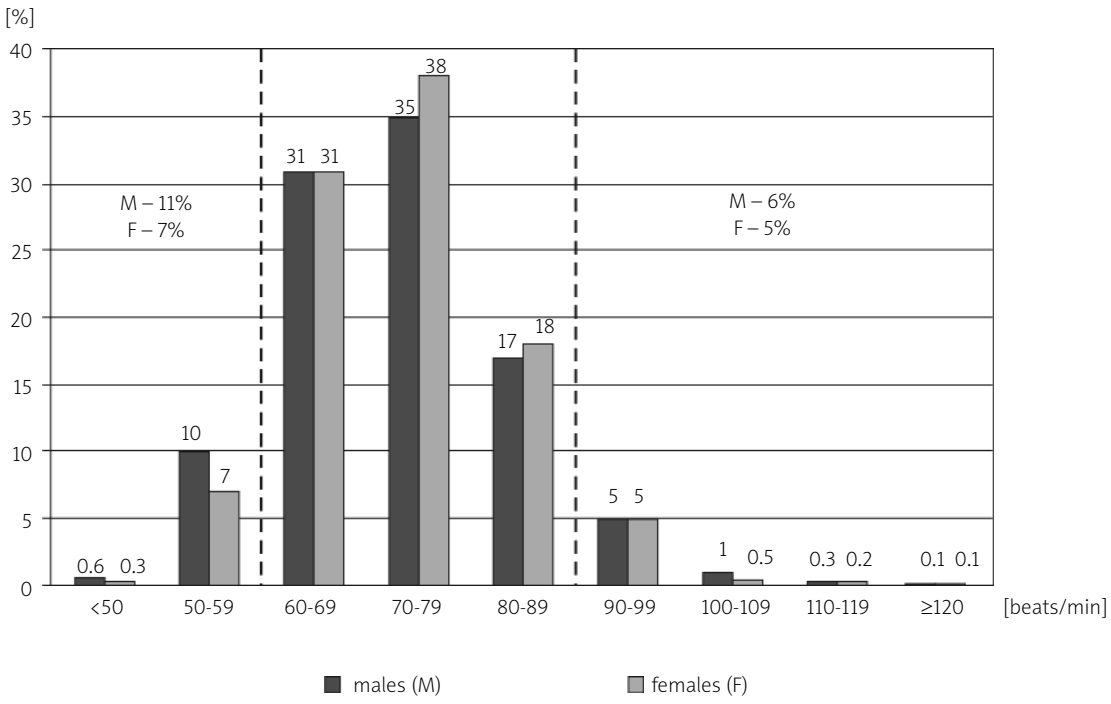

Figure 1. The distribution of the resting heart rate in the studied population

influencing HR) demonstrated that the higher HR the greater the frequency of all analysed parameters, both in males and in females (Table II).

The prevalence of MI and hospitalisations due to CVD (data obtained from the questionnaire) in all three HR groups were also analysed (Table II). The prevalence of MI was significantly higher both in males presenting with HR <60/min (10%) and males with HR >90/min (8%) compared with males with HR in the range 60-90/min (5%). A similar association was observed for the frequency of hospitalisation due to CVD, which was higher in males with both low (<60/min) as well as high HR values (>90/min) compared with subjects who presented with HR values of 60-90/min. Similar results were obtained for females.

The mean HR values in subjects with hypertension, diabetes, obesity, increased concentrations of hsCRP and patients those smoking cigarettes were also analysed and compared with the values in subjects who did not suffer from any of the diseases, presenting with normal concentrations of hsCRP and not smoking cigarettes. Patients treated with medications influencing HR were not excluded from the analyses; however, the results were adjusted according to the fact of medications intake. The mean value of HR in patients with hypertension, diabetes, obesity or high hsCRP concentration was significantly higher than in subjects without diabetes, obesity or high hsCRP concentration (Table III).

Moreover, the higher the concentration of hsCRP the greater the values of HR were found (Table III). The

Table I. The correlation between resting heart rate and the risk factors of atherosclerosis risk (Pearson's correlation index)

	Males					
	BMI	SBP	DBP	hsCRP	Chol	Glucose
Heart rate	0.09844	0.13108	0.23072	0.09630	0.13117	0.12941
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Females					
	BMI	SBP	DBP	hsCRP	Chol	Glucose
Heart rate	0.00753	0.05418	0.16625	0.07319	0.00051	0.09008
	NS	<0.0001	<0.0001	<0.0001	NS	<0.0001

Abbreviations: BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, hsCRP – high-sensitivity C-reactive protein, Chol – total cholesterol

Table II. Prevalence (%) of risk factors of cardio-vascular diseases, myocardial infarction and hospitalisations in reference to the heart rate*

Parameter	Males			Females		
	heart rate			heart rate		
	<60/min	60-90/min	>90/min	<60/min	60-90/min	>90/min
Hypertension	35	39	61	37	31	49
Diabetes	5	6	15	4	5	11
Obesity	15	20	31	21	22	26
Cigarette smoking	27	40	48	18	24	30
hsCRP (>N)	4	6	8	4	6	11
Myocardial infarction	10	6	8	6	3	4
Hospitalisation	13	7	9	9	5	7

** only subjects who did not take medications influencing the heart rate*

correlation between hsCRP and HR was found not only for increased concentration of hsCRP, but also for its normal concentrations (in males for the 3 hsCRP groups (0.0-0.15, 0.16-0.3, 0.31-0.5) HR 71.4/min, 73.3/min, 74.2/min, respectively; in females 72.2/min, 73.3/min, 73.4/min (data not shown in Tables).

A correlation between HR and hypertension, diabetes and obesity was demonstrated in the multivariate logistic regression (after excluding the influence of age, medications and 2 out of 3 conditions – excluding the analysed condition as a dependent variable) (Table IV). In the male population an increase of HR of 10/min enhanced the risk of hypertension by 28% (OR=1.28; 95% CI: 1.21--1,35), obesity by 24% (OR=1.24; 95% CI: 1.17-1.30), and diabetes by 36% (OR=1.36. 95% CI: 1.26-1.48). In females these values were respectively 42, 14 and 47%.

Discussion

The evaluation of resting HR is an easy measurement with multiple clinical impacts. Numerous studies have demonstrated the effect of HR on morbidity and general mortality as well as mortality due to CVD (including sudden cardiac death), independently of other risk factors: hypertension, cigarette smoking or diabetes [4, 5]. There is an inverse correlation between resting HR and life expectancy: the lower the HR the longer the life expectancy [12].

Numerous experimental studies conducted on animals, as well as clinical studies, showed that a decrease of HR is associated with an improvement in endothelial function, and can delay the progression of atherosclerosis [13, 14]. This was confirmed by the BCAPS study (Beta-Blocker Cholesterol Lowering Asymptomatic Plague Study), which demonstrated that beta-adrenergic drugs decrease the apposition of the intima/media membrane in the carotid artery [15].

The relationship between HR and some risk factors or diseases is well known; however, there has not been any epidemiological study performed in such a large population in Poland which would confirm the above correlations. The WOBASZ study conducted on a representative Polish population (over 14 thousand subjects) in the years 2003--2005 confirmed the known fact of the correlation between resting HR and selected risk factors of CVD; it also indirectly confirmed the relationship between these factors and the autonomic system. Attention should be paid to the very significant correlation between HR and inflammation, which was present also in the case of hsCRP values within the reference values. Rogowski et al. in their

Table III. Comparision of the mean resting heart rate* between patients with or without analysed condition

Parameter	Males			Females		
	heart rate [beats/min]			heart rate [beats/min]		
	yes	no	p	yes	no	p
Hypertension	74.7	71.2	0.0001	74.8	72.5	0.0001
Diabetes	76.5	74,1	NS	75.9	71.2	0.0033
Obesity	75.1	71.7	<0.0001	74.2	73.1	0.0003
Cigarette smoking	74.4	71.6	0.0001	74.7	72.8	0.0001
hsCRP (>N)	75.0	72.5	<0.0001	75.6	73.1	<0.0001

** adjusted to the fact of the intake of medications that influence the heart rhythm, N-norm*

Table IV. The correlation between resting HR and adjusted variables and selected clinical conditions (the results of multivariate logistic regression)

Analysed factors	Males			Females		
	hypertension	obesity	diabetes	hypertension	obesity	diabetes
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Heart rate [Δ10/min]	1.28 (1.21-1.35)	1.19 (1.17-1.30)	1.34 (1.24-1.45)	1.42 (1.08-1.09)	1.08 (1.02-1.15)	1.43 (1.30-1.57)
Age [years]	1.04 (1.04-1.05)	1.02 (1.01-1.02)	1.02 (1.04-1.06)	1.09 (1.08-1.09)	1.03 (1.03-1.04)	1.07 (1.06-1.08)
Drugs	5.05 (4.23-6.03)	1.58 (1.76-2.40)	1.60 (1.29-1.99)	7.87 (6.58-9.42)	1.62 (1.39-1.87)	1.69 (1.35-2.11)
Hypertension		2.42 (2.10-2.76)	2.10 (1.67-2.63)		2.67 (2.32-3.07)	1.93 (1.48-2.52)
Obesity [BMI ≥ 30kg/m^2]	2.36 (2.06-2.69)		2.72 (2.24-3.30)	2.63 (2.29-3.02)		2.96 (2.40-3.66)
Diabetes [glucose ≥7.0 mmol/l]	1.89 (1.51-2.39)	2.49 (2.06-3.03)		1.60 (1.21-2.12)	2.37 (2.12-3.25)	

study of 4553 males, both healthy and presenting with risk factors of CVD, demonstrated a correlation between resting HR and the inflammatory response measured with CRP, fibrinogen or the leucocyte count [16]. One of the theories proposes a genetic predisposition which causes the dominance of the sympathetic system, which leads to damage of the blood vessel walls and triggers the mechanisms of the inflammatory response through neurohormonal mechanisms and haemodynamic disturbances (due to increased vascular tension and disturbances of the blood flow) [7]. Activation of the sympathetic system induces an increase in concentration of inflammatory cytokines, including TNF-α and IL-6 [17].

In the WOBASZ study a positive correlation was observed between HR and BMI, systolic and diastolic blood pressure, total cholesterol and glucose concentration. The higher the HR the higher the concentrations of lipids, which might be related to the action of catecholamines, which influence both HR and lipid metabolism through α_1-receptors stimulation, increasing the activity of enzymes that catalyse cholesterol synthesis and decrease VLDL catabolism and HDL cholesterol synthesis, as well as negatively influence the activity of the LDL cholesterol receptors [18]. Moreover, the correlation between HR and lipid concentrations might be explained by the influence of the diet on the activity of the sympathetic system (starvation decreases whereas carbohydrates and lipids increase its activity) [19].

A positive correlation between HR and both systolic and diastolic blood pressure may be explained by the increased catecholamine concentrations in patients with elevated blood pressure. Moreover, patients with hypertension have hypersensitivity to catecholamines [20]. A significant correlation between resting HR and systolic and diastolic blood pressure was found also in the National Health Examination Survey (HES), which examined subjects from similar age groups (18-79 years) as in the WOBASZ study [21]. Increased catecholamine concentration as well as increased resting HR were also observed in cigarette smokers and the correlation was significantly positive. Obese subjects, especially with abdominal type of obesity [4], as well as patients with diabetes, presented with increased resting HR values. The latter correlation may result from damage of the parasympathetic and/or sympathetic system, and therefore from the disturbed autonomic balance [1]. The occurrence of the listed disturbances was confirmed by others, who compared the variations of the sinus rhythm in 32 patients with diabetes, 26 patients with diabetic neuropathy and in 72 control patients. They demonstrated that the patients with diabetes had greater activity of the sympathetic system and decreased parasympathetic activity, regardless of the presence or the absence of autonomic neuropathy, which promotes increased values of HR [20]. Moreover, pharmacological doses of insulin, contrary to physiological ones, increase the concentration of catecholamines [22].

In the WOBASZ study patients with increased HR presented with an unfavourable profile of CVD risk factors. Patients with HR >90/min presented with hypertension, diabetes, obesity and cigarette smoking significantly more often than those with HR<60/min. Similar results were presented by Diaz et al., who examined more than 24 000 patients from one of the centres performing coronary angiography [4]. The

frequency of hypertension, diabetes or cigarette smoking occurrence increased along with the increase of HR values: hypertension – 35.7% (HR ≤62/min) and 49.5% (HR ≥83/min), diabetes – 9.6% (HR ≤62/min), 12.5% (HR ≥83/min). It might be hypothesised that the occurrence of selected CVD risk factors is associated with hyperactivity of the sympathetic system [23-25].

Increased HR value is a prognostic factor of acute coronary events, and therefore of hospitalisations and re-hospitalisations due to CVD, both in the general population and in the population of patients with coronary artery disease. In most of the studies, contrary to the WOBASZ study, the frequency of re-hospitalisations, which increases along with the increase of HR values was analysed. In a study of 18 000 patients with the suspicion of or with the diagnosis of coronary artery disease, a correlation between re-hospitalisations for cardiovascular reasons and resting HR was observed. The lowest relative risk (RR) of re-hospitalisation was found in subjects with HR in the range 71-76/min (RR=0.97, CI 0.88-1.08), and the highest with HR ≥83/min (RR=1.14, CI 1.02-1.27), whereas the RR in subjects with HR ≤62/min was 1.0 [4].

Conclusions

The results of the WOBASZ study conducted on a representative group of the Polish population confirmed the results of numerous studies, both cross-sectional and follow-up studies, demonstrating an independent correlation between resting heart rate and cardiovascular diseases, atherosclerosis risk factors and metabolic diseases.

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Związek spoczynkowej częstotliwości rytmu serca z czynnikami ryzyka rozwoju miażdżycy

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Streszczenie

Wstęp: Spoczynkowa częstotliwość rytmu serca (RS) stanowi podstawowy i łatwy do przeprowadzenia element badania przedmiotowego. Rytm serca podlega regulacji układu autonomicznego, a zaburzona równowaga w postaci wzrostu napięcia układu współczulnego lub spadku napięcia układu przywspółczulnego jest jednym z ważnych czynników w patogenezie chorób układu krążenia (ChUK). Istnieje zależność pomiędzy aktywnością układu współczulnego a niektórymi czynnikami ryzyka ChUK.

Cel: Przeanalizowaliśmy związek średniej wartości częstotliwości RS z nadciśnieniem tętniczym, cukrzycą, otyłością oraz z niektórymi czynnikami ryzyka ChUK [skurczowe (RRS) i rozkurczowe ciśnienie tętnicze (RRR), cholesterol całkowity (chol), glukoza (G), wskaźnik masy ciała (BMI), białko C-reaktywne oznaczane metodą o dużej czułości (hsCRP)].

Metody: Reprezentatywna próba populacji polskiej – 14 769 osób (6977 mężczyzn i 7792 kobiety), w wieku 20–74 lat, została zbadana w latach 2003–2005 w ramach Wieloośrodkowego Ogólnopolskiego Badania Stanu Zdrowia Ludności (WOBASZ). Spoczynkowa częstotliwość RS została zmierzona 3-krotnie, podczas pomiaru ciśnienia tętniczego krwi przy użyciu automatycznego aparatu OMRON M5-I. Do analiz użyto średniej z 2. i 3. pomiaru.

Wyniki: Spośród zbadanych osób średnią częstotliwość RS <60/min zaobserwowano u 11% mężczyzn i 7% kobiet, a RS >90/min odpowiednio u 6% mężczyzn i 5% kobiet. Leki wpływające na częstotliwość RS przyjmowało 16% mężczyzn i 17% kobiet. Spoczynkowa częstotliwość RS korelowała (p <0,0001) z BMI, RRS, RRR, hsCRP, chol i G u mężczyzn i z RRS, RRR, hsCRP i G u kobiet. Po adjustacji na leki istotnie wyższą częstotliwość RS obserwowano, zarówno w grupie mężczyzn, jak i kobiet, u osób z otyłością, cukrzycą, nadciśnieniem tętniczym, wysokim hsCRP oraz palących papierosy. Częstość występowania otyłości, cukrzycy, nadciśnienia tętniczego, wysokiego poziomu hsCRP oraz nałogu palenia papierosów rosła wraz ze wzrostem częstotliwości RS i była najwyższa u osób z RS >90/min. W wielozmiennej analizie regresji logistycznej spoczynkowa częstotliwość RS była istotnie i dodatnio związana z nadciśnieniem, otyłością i cukrzycą. W grupie mężczyzn przy wzroście częstotliwości RS o 10 uderzeń/min szansa stwierdzenia nadciśnienia tętniczego rosła o 28% (OR 1,28; 95% CI 1,22–1,35), otyłości – o 24% (OR 1,24; 95% CI 1,17–1,30), a cukrzycy – o 36% (OR 1,36; 95% CI 1,26–1,48) po wyłączeniu wpływu wieku, leków oraz innych analizowanych czynników (w grupie kobiet odpowiednio: 42% dla nadciśnienia, 14% dla otyłości i 47% dla cukrzycy).

Wnioski: Spoczynkowa częstotliwość RS była skorelowana z czynnikami ryzyka ChUK (ciśnieniem tętniczym krwi, poziomem glukozy, wskaźnikiem masy ciała oraz poziomem cholesterolu), a także z podwyższonym poziomem hsCRP. Częstotliwość RS była dodatnio związana z występowaniem nadciśnienia tętniczego, otyłości i cukrzycy, co może świadczyć o roli autonomicznego układu nerwowego w patogenezie tych chorób.

Słowa kluczowe: spoczynkowa częstotliwość rytmu serca, nadciśnienie tętnicze, cukrzyca, otyłość

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