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Heart rate and cardiovascular event: A nested case-control in Isfahan Cohort Study

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Heart rate and cardiovascular events: A nested case-control in Isfahan Cohort Study

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Abstract

Introduction: The aim of the present study was to investigate the association of elevated heart rate (HR) with the occurrence of cardiovascular disease (CVD) events in Iranian adults.

Methods: Isfahan cohort study (ICS) was a longitudinal study started in 2001 among 6504 adults aged ≥35 years in urban and rural areas of central Iran. In a nested case control study, a control was randomly selected for each CVD event occurred during 7 years of follow up using density sampling method. HR at baseline was assessed by electrocardiogram. CVD was defined as incident coronary heart disease (myocardial infarction, unstable angina and sudden cardiac death) and stroke. The odds ratios (OR) were estimated by conditional logistic regression.

Results: 432 participants with CVD events in the case group and 401 participants free of CVD in the control group were included in the analysis. While HR did not show any significant relationship with CVD events in crude model (P = 0.208), it was detrimentally associated with CVD when age was included (OR = 1.01, 95% CI 1.00-1.02, P = 0.024). Last quintile (> 84.9 bpm) of HR showed 65% age adjusted increased risk of CVD events (OR = 1.65, 95% CI 1.01-2.70, P = 0.045). Except for diabetes (OR = 1.63, 95% CI 0.97-2.73, P = 0.061), this association remained significant when other risk factors were included in the model.

Conclusions: An elevated heart rate may be considered as a predictor of cardiovascular disease independently of other risk factors in Iranian adults.

Keywords: Heart rate, cardiovascular disease, stroke

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (1). It is a major reason of morbidity and mortality among Iranian population (2). Heart rate as a marker of autonomic nervous system tone mainly indicates the sinoatrial node actions (3). The hemodynamic disturbances related to increased heart rate may have impact on the arterial wall and promote the development of atherosclerosis and CVD (4;5). In addition, high heart rate can be a marker of the presence of other cardiovascular risk factors (4;6).

Several epidemiological studies reported that increased heart rate predicts cardiovascular events independently of other risk factors such as age, gender, hypertension, diabetes and obesity; and it has been associated with increased cardiovascular mortality (3;6;7). Giannoglou et al. revealed that heart rate lowering has beneficial effect in preventing coronary heart disease (8).To our knowledge, there has not been any report regarding the influence of heart rate on incidence cardiovascular events in Iranian adults. The purpose of this study was to explore the association of elevated heart rate with the incidence of CVD events in adults who participated in Isfahan Cohort Study.

Methods

The Isfahan Cohort Study (ICS) is a population-based, ongoing longitudinal study of adults aged 35 years old or more, living in urban and rural areas of three counties in central Iran; who had participated in the baseline survey of a community trial for CVD prevention and control, entitled the Isfahan Healthy Heart Program (IHHP) (9). The participants were recruited from January 2 to September 28, 2001.

The baseline survey was conducted in a representative population of adults who were living in urban and rural areas of Isfahan, Najafabad and Arak. Participants were selected by multistage random sampling and were recruited to reflect the age, sex and urban/rural distribution of the community. Details of the sampling method were described in a former publication (9;10). Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Centre (ICRC), a WHO collaborating center.

After obtaining informed written consent, a medical interview and physical examination was conducted. Measurement of blood pressure, anthropometric parameters as well as fasting blood measurements was carried out following standard protocols and using calibrated instruments as has been described previously (10). Follow-up surveys were carried out almost every two years and this paper is based on the seventh year of follow-up. Multiple sources were used to find events of interest. All participants were followed by telephone call interview using standard questionnaires. In the case of any report of relevant events or hospital admissions by participants or their close relatives, a group of trained nurses tried to find reliable documents describing the events such as registry or medical records and death certificates and carry out secondary interviews or verbal autopsies. Two separate outcome adjudication panels of specialists consisting of four cardiologists and a neurologist reviewed all relevant patient documents and decided on the outcomes based on defined criteria (10). CVD was defined as either coronary heart disease (CHD) including fatal and non-fatal (AMI), sudden cardiac death (SCD) and unstable angina (USA) or stroke.

HR was measured using baseline electrocardiograms (ECG). RR-intervals were identified as small squares counts between identical points on two consecutive R waves. Small squares were counted by a cardiologist in three leads (D2, V3 and V5) and their mean value of them was calculated for each subject. HR was calculated as 1500 divided by mean RR-intervals.

A random sample of ECGs (n = 40) was selected and RR-intervals was independently assessed by another cardiologist based on small squares. Using the same calculation method, HRs were identified and were compared with the primary measurements to evaluate agreement between the two observers.

Statistical analysis

All participants who suffered from AMI, SCD, stroke and USA as well as unknown death were determined as case group. Controls were selected among those without aforementioned events but were matched with the case group on follow-up times (density sampling) to make time at risk similar between each pair. Incidence density sampling was used so that the likelihood of being selected as a control was proportional to the person time at risk. For each case, the controls were chosen randomly from those members of the cohort who were at risk at the failure time (event date) of the case. That is, the resulting case-control sample was matched with respect to the time scale used for survival analysis.

Inter-rater agreement was measured by intraclass correlation coefficient (ICC) and Bland-Altman graph was plotted. Numerical values were presented as mean ± standard deviation. Categorical factors were reported as number (percentage). Chi-square test and Student's t-test were used to compare case and control groups for quantitative and qualitative factors, respectively. The logistic regression was used to estimate odds ratios, which are unbiased estimates of incidence rate ratios in incidence density sampling (11) independent of any assumption (12). Conditional logistic regression was employed using incident CVD events as dependent variables and HR as independent variable, adjusted for age, sex and traditional CVD risk factors. In order to maintain stable models, a series of regression analysis was conducted that each one included four dependent variables, heart rate, age, sex and one CVD risk factor. The models were repeated using HR quintiles. All statistical analyses were performed with Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, TX, USA). P-value less than 0.05 was considered as statistically significant.

Results

The original longitudinal study had a sample size of 6504 subjects from which, 6323 were free of a history of CVD. After a median follow-up of 6.8 years, 427 CVD events occurred (229 in men). It consisted of 89 (20.8%) AMI, 91 (21.3%) stroke, 54 (12.6%) SCD and 193 (45.1%) subjects with USA. In combination with 40 deceased participants with unknown diagnosis, these subjects made case group (n = 467). Density sampling randomly selected the same number of subjects as control group including 46 subjects selected twice or more. Two participants in case group were selected as control at the time prior to event. ECG records of 45 (20 in control and 25 in case group) participants were lost and they inevitably excluded from the analysis. The rhythm was non-sinus in 8 participant, they were also excluded from the analysis. Finally, 432 participants in the case group and 401 non-duplicate participants in the control group were included in bivariate analysis (n = 833). Table 1 shows the basic characteristics of the two groups.

ICC was calculated as 0.932 between two cardiologists, showing a very good strength of agreement. The distribution of measurements was nearly symmetrical in Bland-Altman plot. Only 2(5%) subjects were located outside the limits of agreement. Mean difference for the two observations was -0.07 (95% limits of agreement: -2.41, 2.26). HR was categorized based on its quintiles at the following boundaries (minimum-maximum): 34.4-62.5 beats per minute (bpm) (Q1), 63.3-70.3 bpm (Q2), 71.4-75.0 bpm (Q3), 76.2-83.3 bpm (Q4) and 84.9-150.0 bpm (Q5).

HR in subjects with diabetes was on average 6.0 bpm (95% CI for mean difference 3.5-8.4, $P < 0.001$) higher than the rest of participants. The same pattern, but weaker than diabetes, was seen for other risk factors with 2.0 bpm (0.1-3.9, $P = 0.038$) higher HR for hypertension, 5.2 bpm (3.3-7.1, $P < 0.001$) for central obesity, 1.9 bpm (0.1-3.7, $P = 0.038$) for overweight and 2.4 bpm (0.7-4.2, $P = 0.006$) for high LDL-C. No statistically significant association was found between HR and hypertriglyceridemia ($P = 0.068$) and low HDL-C ($P = 0.121$). Despite other risk factors, current smoking significantly decreased HR with a mean difference of 5.3 bmp (3.0-7.6, $P < 0.001$).

While HR did not show any significant relationship with CVD events in crude model, it was detrimentally associated with them when age was included in the model (Table 2). The association remained significant when sex and other CVD risk factors were included, except for diabetes that yielded marginal

significance. However, only the last quintile of heart rate was significantly associated with CVD events in all models except the model that included diabetes. Accordingly, those with heart rate more than 85 bpm had increased risk of CVD events from 63% to 80%. Tow way interaction was analyzed between HR quartiles and age, sex and other adjusting risk factors. No significant interaction was found except for smoking. The forth quintile of HR in combination with current smoking had 6.2 (95% CI 1.4-27.2, P = 0.016) times more risk for CVD events.

Discussion

The present study showed that elevated HR (the last quintile) was a predictor of CVD risk in Iranian adults, independent of other known risk factors such as age, sex, blood pressure, LDL-C, central obesity and smoking, but not diabetes. The association between HR and risk of CVD was investigated in some previous studies. Kristal-Boneh et al. reported that higher HR was independently associated with cardiovascular mortality (7). Other studies demonstrated an independent relationship between resting HR and incident CVD and atherosclerosis (4;13;14). Our findings were in line with these studies; however, after adjusting for diabetes, this association was of borderline significance. None of these studies adjusted the association between HR and CVD events for diabetes.

A Chinese study of 6837 men and women reported that HR ≥ 90 bpm increased the risk of CHD and stroke after multivariate adjustment (15). Another study showed that subjects from the highest quintile (HR > 79) had 85% increased risk of cardiovascular mortality compared to participants with lowest quintile (HR < 62), independently of cardiovascular risk factors. However, in this study there was not any association between HR and CHD incidence (16). The risk of CVD mortality increased 24% in men and 32% in women in another study for each 15 bpm increase in resting HR (14).

Elevated HR was related with other risk factors. High HR was associated with high blood pressure, and blood pressure was introduced as a pathway that links the elevated HR with CVD (17;18). In contrast, we found that the risk of high HR was persisted when most of risk factors were included in the adjustment models. This indicates that elevated HR may have an independent adverse effect rather than merely a pathway. Elevated HR was associated with diabetes that may be due to the cardiac parasympathetic damage. Type 2 diabetes is known as a risk factor for the impairment of autonomic control of cardiovascular system (19).

The mechanism linking elevated HR to the higher risk of CVD has been proposed to be the effects of blood flow on the arterial wall which may cause injury to the endothelium. The velocity and turbulence in blood flow result in morphological changes in the vascular endothelium cells, increase arterial stiffness and thickening, and intensify the atherosclerosis process as well as pulsatile motion (20;21). In addition, elevated HR makes imbalance between oxygen consumption and myocardial demand that can lead to CVD. Elevated HR may result in autonomic dysfunction in heart that can reflect vagal impairment and sympathetic over activity. Increased sympathetic tone with high catecholamine levels may have

effects on vascular muscle cells and promote the progression of atherosclerosis too (8;21;22). On the other hand, HR was only associated with CVD events if the model was adjusted for age. Aging, as a dominant CVD risk factor, decreases HR. These show that the detrimental effect of elevated HR may only have emerged when the expected decrease with aging did not take place.

Of importance is the cutoff point for elevated HR in which CVD risk starts. Most previous studies used arbitrary cutoffs like <60, 60-74, 75-89 and ≥90 bpm (15) or calculated the risk for each 10 bmp increase in HR (7) or used quintiles (23) and deciles (24). Special attention was given to HR >90 bpm, which is less than well-known clinical definition of tachycardia (>100 bpm). Future studies should try to provide evidence for the definition of abnormal HR with regard to CVD risk. Furthermore, the risk of elevated HR for incident CHD and stroke should be compared and the confounding role of diabetes needs to be investigated in future studies.

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Author contribution: The idea of project was developed by MS and NS. MT designed the study and performed statistical analysis. IZ carried out heart rate measurements using electrocardiograms. MS and SO were key members of adjudication panel in ICS. RI helped with main ICS project. MT and FE wrote the first draft. All authors read the manuscript and approved it.

Table 1. Characteristics of participants

	Control n = 401	Case n = 432	P-value
Age at baseline (year)	50.03 ± 11.39	58.29 ± 11.58	< 0.001
Female sex	198 (49.4%)	210 (48.6)	0.825
Systolic blood pressure (mmHg)	120.02 ±20.00	135.37 ± 25.11	< 0.001
Diastolic blood pressure (mmHg)	78.02 ±10.81	84.04 ± 13.78	< 0.001
Hypertension n(%)	83 (20.7%)	230 (53.2%)	< 0.001
Fasting plasma glucose (mg/dl)	88.85 ± 32.89	98.57 ±45.59	< 0.001
Diabetes n(%)	40 (10.0%)	83 (19.2%)	< 0.001
LDL-Cholesterol (mg/dl)	125.95 ± 41.32	140.85 ± 45.95	< 0.001
High LDL-C n(%)	174 (43.4%)	246 (56.9%)	< 0.001
HDL-Cholesterol (mg/dl)	47.26 ± 10.87	46.45 ± 10.29	0.270
Low HDL-C n(%)	173 (43.1%)	214 (49.5%)	0.064
Triglyceride (mg/dl)	186.47 ± 100.97	220.83 ± 116.73	< 0.001
Hypertriglyceridemia n(%)	230 (57.4%)	308 (71.3%)	< 0.001
Body mass index	26.21 ± 4.10	27.36 ± 4.84	< 0.001
Normal Weight n(%)	166 (41.4%)	142 (32.9%)	0.011
Overweight n(%)	163 (40.6%)	182 (42.1)	
Obesity n(%)	72 (18.0)	108 (25.0%)	
Waist circumference (cm)	93.60 ± 12.73	97.36 ± 12.79	< 0.001
High Waist Circumference n(%)	266 (66.3%)	328 (75.9%)	0.002
Hear rate (bpm)	73.4 ± 13.0	74.5 ± 12.8	0.223

Numerical values are presented as mean ± standard deviation, categorical factors are number (percentages).

Diabetes mellitus: Fasting plasma glucose ≥126 mg/dl or 2-hour postprandial glucose ≥200 mg/dl receiving anti-diabetic agents
Hypertension: Systolic blood pressure ≥140 mmHg, Diastolic blood pressure ≥90 mmHg, or current treatment for hypertension
Central obesity: Waist circumference ≥94 cm in men and ≥80 cm in women
Overweight: 25 kg/m2 ≤ Body mass index <30 kg/m2; Obesity: Body mass index ≥30 kg/m2
Hypertriglyceridemia: Triglyceride ≥150 mg/dl; Hypercholesterolemia: Total cholesterol ≥200mg/dl
High LDL-C: LDL-C ≥160 mg/dl, Low HDL-C: HDL-C <40 mg/dl in men and <50 mg/dl in women
bpm: beats per minute

Table 2. The association of heart rate with cardiovascular events

		Heart rate (bpm)	Heart rate quintiles				
			Q1	Q2	Q3	Q4	Q5
	mean±SD*		57.3±4.6	67.1±2.0	73.4±1.5	80.4±2.3	93.5±7.6
	n		177	190	171	171	169
Crude	OR (95% CI)	1.00(0.99-1.01)	Ref.	0.71(0.45-1.10)	1.02(0.66-1.60)	1.10(0.70-1.74)	1.25(0.81-1.94)
	P-value	0.208	-	0.129	0.897	0.658	0.303
Model 1	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.78(0.48-1.27)	1.36(0.83-2.23)	1.42(0.85-2.37)	1.65(1.01-2.70)
	P-value	**0.024**	-	0.328	0.217	0.171	**0.045**
Model 2	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.80(0.49-1.30)	1.47(0.88-2.43)	1.56(0.92-2.64)	1.79(1.08-2.97)
	P-value	**0.013**	-	0.375	0.134	0.093	**0.023**
Model 3	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.89(0.53-1.49)	1.64(0.95-2.83)	1.65(0.94-2.90)	1.76(1.03-3.03)
	P-value	**0.029**	-	0.673	0.073	0.080	**0.038**
Model 4	OR (95% CI)	1.01(0.99-1.02)	Ref.	0.80(0.49-1.30)	1.41(0.85-2.34)	1.40(0.82-2.39)	1.63(0.97-2.73)
	P-value	0.056	-	0.376	0.181	0.206	0.061
Model 5	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.81(0.50-1.33)	1.44(0.86-2.39)	1.52(0.90-2.58)	1.78(1.07-2.96)
	P-value	**0.015**	-	0.419	0.155	0.116	**0.025**
Model 6	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.77(0.47-1.25)	1.41(0.85-2.35)	1.51(0.89-2.56)	1.73(1.04-2.87)
	P-value	**0.019**	-	0.297	0.181	0.120	**0.033**
Model 7	OR (95% CI)	1.01(1.00-1.02)	Ref.	0.80(0.49-1.30)	1.40(0.84-2.33)	1.56(0.92-2.65)	1.80(1.08-2.99)
	P-value	**0.012**	-	0.380	0.189	0.096	**0.023**

Model 1: Age adjusted; Model 2: Adjusted for age and sex; Models 3-7: Adjusted for age, sex and hypertension (3), diabetes (4), high LDL-C (5), central obesity (6) and smoking (7).

bpm: beats per minute, OR: Odds ratio, CI: Confidence interval

* Average of heart rate in each quintile

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