Original Article

Heart Rate and Cardiovascular Events: A Nested Case-Control in Isfahan Cohort Study

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Abstract

Introduction: Elevated heart rate (HR) is known to be a risk factor. The aim of the present study was to investigate the association of HR with the incidence of cardiovascular disease (CVD) in Iranian adults.

Methods: The Isfahan cohort study (ICS) was a longitudinal study started in 2001 on 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 occurring 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 the crude model (P = 0.208), it was detrimentally associated with them when age was included (OR = 1.01, 95% CI: 1.00 – 1.02, P = 0.024). A dose response effect of quintiles of HR was seen in which significant association with CVD events started at third quintile [OR = 1.98 (1.15 – 3.41)] and increased toward fifth quintile [OR = 2.53 (1.47 – 4.36)] in the adjusted model for age, sex and HR-lowering drugs (P for trend = 0.001). This association remained statistically significant when other traditional risk factors were included in the model.

Conclusions: An elevated heart rate was associated with the occurrence of cardiovascular events. It can be considered as a predictor of cardiovascular disease independently of other risk factors in Iranian adults.

Keywords: Cardiovascular disease, heart rate, stroke

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1] It is a major cause of morbidity and mortality in the Iranian population.[2] Heart rate (HR), as a marker of the autonomic nervous system tone, mainly indicates the sino-atrial node actions.[3] The hemodynamic disturbances related to increased heart rate may affect the arterial wall and promote the development of atherosclerosis and CVD.[4,5] In addition, elevated 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. reported that lowering the heart rate has beneficial effects in preventing coronary heart disease.[8] To our knowledge, there has not been any report regarding the influence of heart rate on incidence of 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 the Isfahan Cohort Study.

Methods

This was a nested case-control study in the Isfahan Cohort Study (ICS). The ICS is a population-based, ongoing longitudinal study of adults aged 35 years or more, living in urban and rural areas of three counties in central Iran, who 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 living in urban and rural areas of Isfahan, Najaf-Abad and Arak. According to the national population census in 1999, the total population was 1,777,185 in Isfahan, 261,215 in Najaf-Abad and 401,680 in Arak. Participants were selected through multistage random sampling and were recruited to reflect the age, sex and urban/rural distribution of the community. Details of the sampling method are described in a previous publication.[9,10] Ethical approval was obtained from the Ethics Committee of Isfa-

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After obtaining informed written consent, medical interview and physical examination were conducted. Blood pressure, anthropometric parameters and fasting blood were measured following standard protocols and using calibrated instruments as described previously.[10] Among antihypertension drugs that were taken by some subjects, verapamil, diltiazem, metoral, digoxin, amiodarone, propranolol, atenolol and timolol were defined as heart rate-lowering drugs. 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 the events of interest. All participants were followed by telephone interviews using standard questionnaires. In the case of any report of relevant events or hospital admissions by the 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 acute myocardial infarction (AMI), sudden cardiac death (SCD) and unstable angina (USA) or stroke.

All participants with incident acute coronary syndrome (AMI and USA), SCD and stroke as well as unknown death during follow-up were placed in the case group. The diagnosis of acute AMI was based on the presence of at least two of the following criteria: 1) typical chest pain lasting more than 30 min, 2) ST elevation 40.1mV in at least two adjacent electrocardiograph leads and 3) an increase in serum level of cardiac biomarkers. The definition of USA required typical chest discomfort lasting more than 20 min within the 24 h preceding hospitalization and representing a change in the usual pattern of angina or pain: occurring with a crescendo pattern, being severe and described as a frank pain. The diagnosis of USA might be new or based on dynamic ST-segment or T-wave changes in at least two adjacent electrocardiogram leads. Sudden cardiac death was defined as death within 1 h of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by 41 h of symptoms. The World Health Organization stroke definition was used, that is a rapid-onset focal neurological disorder persisting at least 24 h of probable vascular origin. The diagnosis of incident stroke was made based on the clinical criteria.[10]

The controls were selected among those without the aforementioned events but were matched with the case group on follow-up time (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. In other words, the resulting case-control sample was matched with respect to the time scale used for survival analysis.

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 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 were assessed by another cardiologist independently based on small squares. Using the same calculation method, HRs were identified and compared with the primary measurements to evaluate agreement between the two observers.

Statistical 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. A series of regression analysis was conducted each of which included four dependent variables, heart rate, age, sex and one CVD risk factor. The models were carried out twice, first including HR as a continuous variable then using HR quintiles. P-values for trend were tested by including HR quintiles as continuous variables in the conditional logistic regression models. All statistical analyses were performed with Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, TX, USA). P-values less than 0.05 were considered as statistically significant.

Results

The original longitudinal study had a sample size of 6504 subjects from which 6323 did not have 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%) USA. In combination with 40 deceased participants with unknown diagnosis, these subjects made up the 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 the 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 the rhythm was non-sinus in 8 participant, all of whom were excluded from the analysis. Finally, 432 participants in the case group and 401 non-duplicate participants in the control group were included in the bivariate analysis (n = 833, sample size). Table 1 shows the basic characteristics of the two groups. Case subjects had an overall worse CVD risk factor profile than the control group and the observed differences were statistically significant except for sex, HDL-C and HR.

ICC was calculated as 0.932 between two cardiologists, showing a very good strength of agreement. The distribution of measurements was nearly symmetrical on Bland-Altman plot. Only 2 (5%) subjects were located outside the limits of agreement. The 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 the average 6.0 bpm (95% CI for mean difference 3.5 – 8.4, $P < 0.001$) higher than the rest of

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
Heart rate (bpm)	73.4 ± 13.0	74.5 ± 12.8	0.223
Heart rate-lowering drugs (n %)	22 (5.5%)	86 (19.9%)	< 0.001

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/m^2 ≤ Body mass index < 30 Kg/m^2; Obesity: Body mass index ≥ 30 Kg/m^2; 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					P for trend
			Q1	Q2	Q3	Q4	Q5	
	Range*(bpm)		34.4-62.5	63.3 – 70.3	71.4 – 75.0	76.2 – 83.3	84.9 – 150.0	
	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)	0.124
	P-value	0.208	- - -	0.129	0.897	0.658	0.303	
Model 1	OR (95% CI)	1.01 (1.00 – 1.02)	Ref.	0.82 (0.51 – 1.31)	1.32 (0.82 – 2.13)	1.35 (0.83 – 2.21)	1.65 (1.03 – 2.63)	0.013
	P-value	0.013	- - -	0.421	0.244	0.223	0.036	
Model 2	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)	0.017
	P-value	**0.024**	- - -	0.328	0.217	0.171	**0.045**	
Model 3	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)	0.010
	P-value	**0.013**	- - -	0.375	0.134	0.093	**0.023**	
Model 4	OR (95% CI)	1.02 (1.01 – 1.03)	Ref.	0.96 (0.57 – 1.61)	1.98 (1.15 – 3.41)	2.06 (1.17 – 3.63)	2.53 (1.47 – 4.36)	0.001
	P-value	**< 0.001**	- - -	0.887	**0.013**	**0.012**	**< 0.001**	
Model 5	OR (95% CI)	1.02 (1.00 – 1.03)	Ref.	0.96 (0.57 – 1.64)	1.88 (1.07 – 3.29)	1.88 (1.05 – 3.38)	2.12 (1.21 – 3.73)	0.005
	P-value	**0.005**	- - -	0.908	**0.027**	**0.032**	**0.009**	
Model 6	OR (95% CI)	1.02 (1.00 – 1.03)	Ref.	0.95 (0.57 – 1.61)	1.91 (1.10 – 3.30)	1.85 (1.03 – 3.29)	2.31 (1.33 – 4.03)	0.003
	P-value	**0.002**	- - -	0.876	**0.020**	**0.036**	**0.003**	
Model 7	OR (95% CI)	1.02 (1.01 – 1.03)	Ref.	0.97 (0.58 – 1.62)	1.93 (1.12 – 3.33)	1.99 (1.12 – 3.51)	2.49 (1.44 – 4.30)	0.001
	P-value	**< 0.001**	- - -	0.914	**0.017**	**0.017**	**0.001**	
Model 8	OR (95% CI)	1.02 (1.01 – 1.04)	Ref.	0.97 (0.57 – 1.63)	1.91 (1.10 – 3.30)	2.08 (1.17 – 3.70)	2.56 (1.48 – 4.43)	< 0.001
	P-value	**< 0.001**	- - -	0.922	**0.021**	**0.012**	**0.001**	
Model 9	OR (95% CI)	1.02 (1.01 – 1.03)	Ref.	0.93 (0.55 – 1.56)	1.92 (1.11 – 3.32)	2.01 (1.14 – 3.54)	2.45 (1.42 – 4.24)	0.001
	P-value	**< 0.001**	- - -	0.380	**0.019**	**0.015**	**0.001**	

Model 1: Adjusted for heart rate-lowering drugs; Model 2: Age adjusted; Model 3: Adjusted for age and sex; Model 4: Adjusted for age, sex and heart rate-lowering drugs; Models 5 – 9: Adjusted for age, sex, heart rate-lowering drugs and hypertension[5], diabetes[6] high LDL-C[7] central obesity[8] and smoking[9]; bpm: beats per minute; OR: Odds ratio; CI: Confidence interval; *Quintile boundaries (minimum-maximum) of heart rate; §Average of heart rate in each quintile; †Numerical values of heart rate as continuous variable.

participants. The same pattern, but weaker than that of 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) or low HDL-C (P = 0.121). Unlike 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 the crude model, it was detrimentally associated with them when age or anti-hypertensive drugs were included in the model (Table 2). The association remained significant when sex and other traditional CVD risk factors were included in the model. Presence of heart rate-lowering drugs augmented the relationship between HR and CVD events. A statistically significant dose-response effect of quintiles of heart rate was seen in which significant detrimental association with CVD events started at third quintile and increased toward fifth quintile compared to the first quintile. This pattern did not change when the association was adjusted for traditional CVD risk factors. Accordingly, those with heart rate above 71 bpm had increased risk of CVD events from 88% to 2.5 -fold. Two-way interaction was analyzed between HR quartiles and age, sex, heart rate-lowering drugs 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-fold (95% CI: 1.4 – 27.2, P = 0.016) higher risk for CVD events.

Discussion

The present study showed that elevated HR at rest 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, smoking and 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.

A Chinese study on 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 with participants with lowest quintile (HR < 62), independently of cardiovascular risk factors. In this study, however, there was not any association between HR and CHD incidence.[16] In another study, the risk of CVD mortality increased 24% in men and 32% in women for each 15 bpm increase in resting HR.[14]

Elevated HR was related to 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 persisted when most 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 impairment of autonomic control of cardiovascular system.[19]

The mechanism linking elevated HR to higher risk of CVD has been proposed to be the effect 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 causes imbalance between oxygen consumption and myocardial demand that can lead to CVD. Elevated HR may result in autonomic dysfunction in the 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, as well.[8,21,22]

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 occur. On the other hand, when anti-hypertensive drugs with HR-lowering effects were included in the model, the strength of the association doubled and the detrimental effect started at the third rather than the fifth quintile in the model only adjusted for age. This makes the associated risk start at substantially lower HR than known boundaries for normal HR.

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 lower than the 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 and HR-lowering drugs needs to be investigated in future studies.

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Author contribution

The idea of the 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 the ICS. RI helped with the main ICS project. MT and FE wrote the first draft. All authors read and approved the manuscript.

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