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Analysis of resting heart rate and clinical characteristics in outpatients with stable coronary artery disease in Turkey: PULSE study*

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Abstract

Background: *An association between resting heart rate (RHR) and cardiovascular morbidity and mortality has been shown in patients with coronary artery disease (CAD). We aimed to evaluate the RHR and its relationship with clinical variables in outpatients with stable CAD at secondary and tertiary care centers in Turkey.*

Methods: *Adults with stable CAD in sinus rhythm were included in this non-interventional, national, cross-sectional, multicenter study. Data were collected at a single study visit from 83 centers.*

Results: *The mean ± standard deviation age of all patients (n = 2,919) was 61 ± 10 years and 73% were males. The mean (SD) RHR was 73 ± 12 bpm, and 62% of patients had RHR of ≥ 70 bpm. Females more frequently had RHR ≥ 70 bpm compared with males (67% vs. 60%; p = 0.002). RHR was significantly higher in patients with angina than in those without (76 ± 13 vs. 73 ± 11 bpm, p < 0.001). Left ventricular ejection fraction and heart rate lowering drug use were significantly lower in patients with a RHR ≥ 70 bpm (p < 0.05).*

Conclusions: *The RHR of outpatients with stable CAD was not within the level recommended by the guidelines.* (Cardiol J 2014; 21, 4: 378–383)

Key words: stable coronary artery disease, resting heart rate, outpatient

Introduction

Epidemiological studies have demonstrated the importance of resting heart rate (RHR) in healthy subjects [1]. Also, an association between RHR and cardiovascular (CV) morbidity and mortality has been shown in patients with CV disease [2–6]. A recent study showed that lowering RHR decreased the CV mortality in coronary artery disease (CAD) patients [7, 8]. RHR has also been integrated into the risk assessment in acute coronary syndrome (ACS) [9]. Although a great number of studies have shown that RHR is a predictor of total and CV mortality independent of other risk factors, there is no data regarding the RHR in outpatients with stable CAD in Turkey.

This study aimed at evaluating RHR, clinical variables influencing RHR, the use of heart rate (HR)-lowering drugs in outpatients with stable CAD in Turkey.

Methods

The PULSE Study was a non-interventional, national, cross-sectional, multicenter study conducted by 86 cardiologists at 83 secondary and

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tertiary healthcare centers in Turkey, between February and July 2011. The study population comprised 2,919 adult outpatients with stable CAD in sinus rhythm, as verified with standard 12-lead electrocardiography (ECG).

Patients with a history of ACS, or who underwent coronary revascularization more than 3 months prior, or angiographic evidence of coronary stenosis of at least 50% of one of the major arteries, were included in the study.

Patients hospitalized for CV disease within the preceding 3 months, and patients with advanced heart failure, a permanent pacemaker, sick sinus syndrome, sinoatrial block, total atrioventricular block, atrial fibrillation (AF), severe kidney or liver disease, secondary angina, and pregnant or breast-feeding women were excluded from the study. Written informed consent was obtained from all the participants.

Data on patient demographics, medical history of CAD, angina, concomitant diseases, physical examination, anthropometric measurements, laboratory tests, RHR, and HR-lowering medications were collected at a single study visit. In the morning hours, RHR was determined by ECG performed after resting for 10 min. Laboratory tests and echocardiographic examination were performed within 3 months before the inclusion visit.

Data were collected using a standardized case report form, and were sent electronically to the data management center where checks for completeness, internal consistency, and accuracy were run.

Statistical analyses

Statistical analyses were performed using computer software (SPSS version 17.0, SPSS Inc. Chicago, IL, USA). Fisher's exact and χ^2 tests were used for the comparison of categorical data, while the student's t test and Mann-Whitney U-test were used for the analysis of parametric variables. A p value < 0.05 was considered statistically significant.

Results

A total of 2,919 patients from 83 centers were included in the present study. The mean ± standard deviation (SD) age was 61 ± 10 (min–max: 23–90) years. The majority of the study population was male (73%, $p < 0.001$); 37% (n = 1,065) of the patients had a history of ACS, 72% (n = 2,102) had a history of percutaneous/surgical coronary revascularization, and 34% (n = 999) had angiographic evidence of at least 50% stenosis in more than one of the major coronary arteries. The patients were divided into two groups according to their RHR. Lower RHR group (n = 1,107; 38%) had a RHR of < 70 bpm and higher RHR group (n = 1,812; 62%) had RHR of ≥ 70 bpm. If we regard 60 bpm as a threshold for the RHR analysis, 90% of our study population would have RHR > 60 bpm.

Characteristics of both groups are shown in Table 1. The RHR was 73 ± 12 bpm. A significantly higher percentage of females had RHR ≥ ≥ 70 bpm compared with males (67% vs. 60%, $p = 0.002$). The mean ± SD ages of each gender did not differ between RHR groups ($p = 0.523$). In the higher RHR group, females were older than males (62.4 ± 10.8 vs. 60.9 ± 10.1 years, $p = 0.001$). The RHR was significantly higher in patients with angina than in those without (76 ± 13 vs. 73 ± 11 bpm, $p < 0.001$).

In the higher RHR group, systolic and diastolic blood pressure, left atrial (LA) diameter, body mass index (BMI), body weight, and fasting blood glucose, total cholesterol (TC), and low density lipoprotein cholesterol (LDL-C) were significantly higher, while left ventricular ejection fraction (LVEF) and use of HR-lowering drugs were significantly lower ($p < 0.05$) (Table 1). With respect to HR-lowering medications, 70% of the population were treated with beta-blockers, 4% received verapamil or diltiazem, 1.6% ivabradine, and 0.3% digoxin (Table 1). Metoprolol (48.5%), carvedilol (11.6%), nebivolol (4.86%), bisoprolol (3.97%) were the most commonly used beta-blockers. In overall population use of survival-improving medications (antiplatelet drug, beta-blocker, angiotensin converting enzyme inhibitor [ACEI], statin) was 1,646 (56.4%) patients received antiplatelet agent(s) (acetylsalicylic acid: 1,520 [52.1%], other antiplatelet drugs: 274 [9.4%]), 2,042 (70%) beta-blockers, 691 (23.7%) ACEI, and 939 (32.2%) statins.

A history of ACS and coronary revascularization more than 3 months prior, the presence of angina, any co-morbid disease particularly chronic obstructive pulmonary disease (COPD) and/or asthma, diabetes mellitus, and a low LVEF (< 40%) were significantly more prevalent in the higher RHR group ($p < 0.05$) (Tables 1, 2). Active smokers comprised 7.5% of the study population (Table 1). Hypertension was the most prevalent comorbidity (71%) (Table 2).

Discussion

According to current guidelines lowering RHR is an important part of CAD and heart failure treat-

Table 1. Characteristics of the study population relative to resting heart rate.

	Total population (n = 2919)	Lower RHR group (< 70 bpm) (n = 1107)	Higher RHR group (≥ 70 bpm) (n = 1812)	P
Age [years]*	61 ± 10	61 ± 10	61 ± 10	0.523
Males	73%	76%	71%	**0.002**
Females	27%	24%	29%	
Weight [kg]*	80 ± 12	79 ± 12	80 ± 12	**0.049**
Body mass index [kg/m^2]*	28 ± 4	28 ± 4	29 ± 4	**0.024**
Waist circumference [cm]*	95 ± 12	95 ± 12	95 ± 13	0.790
Resting heart rate [bpm]*	73 ± 12	61 ± 5	80 ± 9	**< 0.001**
Systolic BP [mm Hg]*	132 ± 19	130 ± 18	134 ± 20	**< 0.001**
Diastolic BP [mm Hg]*	79 ± 11	78 ± 119	80 ± 11	**< 0.001**
LVEF [%]*	53 ± 10	54 ± 10	52 ± 11	**< 0.001**
LVEF < 40%	12%	10%	14%	**0.003**
LVEF ≥ 40%	88%	90%	86%	
LA diameter [cm]*	3.8 ± 0.6	3.8 ± 0.6	3.9 ± 0.5	**0.007**
Fasting blood glucose [mg]*	123 ± 54	113 ± 39	129 ± 60	**< 0.001**
Total cholesterol [mg/dL]*	187 ± 47	185 ± 51	188 ± 45	**0.018**
Triglycerides [mg/dL]*	155 ± 87	163 ± 86	167 ± 87	0.163
LDL cholesterol [mg/dL]*	118 ± 43	116 ± 44	119 ± 42	**0.010**
HDL cholesterol [mg/dL]*	43 ± 12	43 ± 13	43 ± 12	0.466
Smoking status:				
Current smoker	7.5%	7.9%	7.2%	0.524
Occasional smoker	1.6%	1.8%	1.5%	
Former smoker	60%	60%	59%	
Never smoker	31%	30%	32%	
Cigarette consumption (package-year)*	13 ± 24	13 ± 22	13 ± 24	0.082
Heart rate lowering drug use:	75%	79%	72%	**< 0.001**
Beta-blockers	70%	75.5%	66.6%	**< 0.001**
Verapamil or diltiazem	4.0%	3.5%	4.2%	0.38
Ivabradine	1.6%	0.6%	2.2%	**0.001**
Digoxin	0.3%	0.1%	0.4%	0.166
Presence of angina	50%	45%	53%	**< 0.001**
History of ACS	37%	32%	39%	**<0.001**
History of CR	72%	81%	66%	**< 0.001**
Angiographic CAD	34%	33%	35%	0.265

*These variables are expressed in mean (standard deviation); ACS — acute coronary syndrome; BP — blood pressure; CAD — coronary artery disease; CR — coronary revascularization (percutaneous and surgery); HDL — high density lipoprotein; LA — left atrial; LDL — low density lipoprotein; LVEF — left ventricular ejection fraction

Table 2. Associated co-morbidities of the study population.

	Total population (n = 2,919)	Lower RHR group (< 70 bpm) (n = 1,107)	Higher RHR group (≥ 70 bpm) (n = 1,812)	P
All comorbidities	71%	66%	75%	**< 0.001**
COPD and/or asthma	15%	11%	17%	**< 0.001**
Diabetes mellitus	42%	37%	44%	**0.002**
Hypertension	72%	72%	72%	0.924
Heart failure	13%	12%	14%	0.185
Peripheral artery disease	2%	2.8%	1.6%	**0.079**
Others	28%	31%	26%	**0.011**

COPD — chronic obstructive pulmonary disease; RHR — resting heart rate

ment [10, 11], and an elevated HR still remains a neglected CV risk factor to a large extent. Data on RHR obtained in routine practice show that it is poorly controlled [2, 3, 12–15].

According to studies that have evaluated healthy subjects and CAD patients, lowering HR improves CAD outcome in patients with RHR ≥ 70 bpm [1–7]. These results led to the suggestion that RHR ≥ 70 bpm could be used as a relevant threshold to stratify the risk of CV events in patients with CAD. In our study, 70 bpm was used as a threshold for the RHR analysis due to its prognostic value established in numerous epidemiologic and clinical studies. The mean RHR was 73 bpm in our study population, and more than half of the patients (62%) had RHR ≥ 70 bpm. This was consistent with the observations of European Heart Survey on stable angina [3], in which the mean RHR was 73 bpm and 52% had RHR > 70 bpm. The proportion of males in our study was larger than females in both RHR groups, with women having a significantly higher RHR, as shown in other studies [2, 14–16]. If we had regarded 60 bpm as the treatment goal for RHR in stable CAD patients, as recommended in the ACC/AHA guideline [10], it would not have been achieved in 90% of the entire study population. This rate was 72.1% in one study [17] and 94.5% in another study [3].

Angina was detected more frequently in patients with RHR ≥ 70 bpm. Ischemia may be a consequence of high RHR where myocardial oxygen demand will increase and coronary perfusion will decrease. Surprisingly, in patients with RHR ≥ 70 bpm, HR-lowering drugs were underused. Similar results were demonstrated in other studies [12, 14, 17].

Sympathetic activity is increased in left ventricular (LV) systolic dysfunction. Over time this over-activity causes decreased myocardial contractility and progressive mechanical dyssynchrony [18]. The importance of RHR in LV systolic dysfunction is highlighted in a study which demonstrated that for every RHR beat increase the risk of a primary composite endpoint increased by 3% ($p < 0.0001$) [6]. The average LVEF in both groups was over 50%, whereas LVEF was lower in patients with RHR ≥ 70 bpm. The frequency of patients with a LVEF < 40% was higher in patients with RHR ≥ 70 bpm. This was consistent with previous studies [2, 7].

Similar rates of prior ACS in different RHR groups have been reported in previous studies [12, 13]. Similar to the results of Seabra-Gomes et al. [14] we found a higher prevalence of prior ACS in patients with a higher RHR.

Patients with any co-morbid disease, particularly COPD and/or asthma, had a significantly higher RHR. Our finding on co-morbid disease is consistent with other studies [3, 14].

The autonomic nervous system has a natural balance between sympathetic and parasympathetic activities and high RHR is an indicator of sympathetic over-activity [18]. Both epidemiological and prospective cohort studies suggest that chronic sympathetic over-activity, reflected as fast HR and high blood pressure, affects glucose tolerance and subsequently increases the risk of developing diabetes mellitus [19–22]. Myocardial energy production in diabetic patients is mostly dependent on non-esterified fatty acids. When compared to glucose oxidation, this pathway results in higher myocardial oxygen consumption, and in turn, this leads to higher RHR [19]. Our study revealed that high systolic and diastolic blood pressures, high fasting blood glucose, and evidence of diabetes mellitus, were more frequent in patients with high RHR.

BMI is a marker of general adiposity. However, waist circumference is an anthropometric indicator of central obesity and is related to visceral adiposity [23]. In our study, patients in higher RHR group had higher BMI but similar finding was not statistically confirmed for waist circumference. A previous study showed that waist circumference or BMI was significantly associated with increased RHR in men but not in women [24]. In another study, which included a high-risk population, both BMI and waist circumference were significantly higher in patients with higher RHR [20].

As our study population comprised high-risk patients, LDL-C and TC were higher in patients with RHR ≥ 70 bpm. Similar results were found for both LDL-C and TC in the study by Ó Hartaigh et al. [20]. While Vitale et al. [15] did not show any relationship between the RHR and TC, Okin et al. [21] found that higher RHR was related to high TC, but not to HDL-C. Steg et al. [17] reported no data on blood lipid levels but observed more anti-hyperlipidemic drug use in patients with high RHR.

Abnormal LA function during adrenergic stress has been studied [25, 26]. LA size is largely determined by the factors influencing diastolic LV filling pressures [27, 28]. During tachycardia, LV filling and LA emptying are more compromised in patients with ischemia, heart failure, and hypertension than healthy subjects. This leads to an LA enlargement. LA dilatation, in the absence of organic mitral valve disease or AF, has been shown to reflect the burden of CV disease [29, 30]. In the present study, the LA

was larger in patients with higher RHR, however mean LA diameters were within normal limits in both groups. There are currently no reports on the association of LA size with RHR in patients with stable CAD in sinus rhythm.

Limitations of the study

While the PULSE study is the first large-scale, real-life data of RHR in stable CAD in Turkey, it is subject to limitations. The RHR inherently varies during the day. The RHR recorded at any particular time of the day may be a limitation. However, there are noteworthy studies which examined HR with a single measurement to determine stable CAD prognosis [1, 2, 4, 7, 13]. Inclusion of patients with AF could have led to error in interpretation of HR findings. Therefore, patients with AF were excluded from the study. Thus, our findings cannot be generalized to all stable CAD patients.

Conclusions

Reasons of inadequate control of HR in stable CAD patients were already well documented, and it has been reinforced in the Turkish population with this study.

Contributors

B. Gunsoy, E. Okuyan, N. Ozer, E. Ozdemir, S. Akyuz, M. Kalyoncuoglu, H.A. Gumrukcuoglu, I. Goksen, M. Fazlioglu, A. Boyaci, B. Ozturk, M. Ethemoglu, M. Yetim, F.F. Tipi, H. Aluzum, F. Oguz, T. Tavli, V. Davutoglu, M. Tekin, E. Dogan, E. Akkaya, B. Kilicarslan, I. Gunaydin, A. Ozyol, M. Balin, A.S. Balcioglu, F. Albayrak, P. Pinar, A. Emek, G.L. Topkara, E. Saglam, P.A. Ulken, Z. Aktas, M. Gonencer, M.G. Kutucularoglu, A. Tastan, O.Y. Akbal, O.U. Ozcan, F. Gulen, E. Oztekin, O. Kuru, H. Tolunay, M. Yilmaz, Y. Yalcinkaya, D.S. Kuru, A. Pinar, C. Basel, E. Demirci, H. Bozdemir, M. Erden, O.E. Aydin, M. Kurt, F. Besnili, M. Bozkurt, M.B. Tascanov, E.E. Gunturk, M. Ziyrek, A. Mutlu, I.H. Tanboga, B. Tosun, Y. Turan, H. Demir, O. Karaaslan, F. Gundogdu, A. Kale, M. Ekinci, B. Turel, M. Gurdogan, O. Hascan, S. Gunduz, S.B. Akyildiz, Y. Amasyali, A. Birsin, M. Kuçuk, C. Gul, S. Ozyildirim, I. Bolat, M. Akkaya, C. Kilit, E. Sagatli, B. Yavuz, J.K. Erenler, O. Kose.

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Conflict of interest: Oktay Ergene — Servier, Boehringer, Sanofi Aventis, AstraZeneca, Pfizer, Daichi Sankio, Menarini Honorarium, Consultancy Fee; Akyildiz Zehra Ilke Akyildiz — No relationship with the industry.

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