Evaluation of heart rate recovery index in heavy smokers

Mehmet Erat, Mehmet Doğan, Hamza Sunman, Lale Dinç Asarcıklı, Tolga Han Efe, Murat Bilgin, Tolga Çimen, Ahmet Akyel, Ekrem Yeter

Department of Cardiology, Ministry of Health Dışkapı Yıldırım Beyazıt Research and Educational Hospital; Ankara-*Turkey*

Abstract

Objective: Cigarette smoking increases the risk of cardiovascular events. The heart rate recovery index (HRRI) is an indicator of autonomous nervous system function and is an independent prognostic risk factor for cardiovascular diseases. In this study, we aimed to evaluate HRRI in heavy smokers.

Methods: A total of 179 apparently healthy subjects (67 non-smokers as the control group and 112 heavy smokers) were enrolled into this prospective cross-sectional study. The presence of hypertension, diabetes mellitus, and known cardiac or non-cardiac diseases was specified as the exclusion criteria. Heavy cigarette smoking was defined as the consumption of more than one packet of cigarette per day. All subjects underwent the maximal Bruce treadmill test. HRRIs of the heavy cigarette smoker group at 1, 2, 3, and 5 min after maximal exercise were calculated and compared to those of the control group. Student t-test, chi-square test, and analysis of covariance were used for statistical analysis.

Results: The baseline characteristics of the two groups were similar, except for body mass index and high-density lipoprotein level. HRRIs at 1, 2, 3, and 5 min after maximal exercise were found to be significantly lower in the heavy smoker group (HRRI1: 26.78±8.81 vs. 32.82±10.34, p<0.001; HRRI2: 44.37±12.11 vs. 51.72±12.87, p<0.001; HRRI3: 52.73±11.54 vs. 57.22±13.51, p=0.018; and HRRI5: 58.31±10.90 vs. 62.33±13.02, p=0.029).

Conclusions: In the present study, we found that HRRI was impaired in heavy smokers. Our results suggest that beside previously known untoward effects on vascular biology, heavy smoking also has deleterious effects on the neuro–cardiovascular system. *(Anatol J Cardiol 2016; 16: 667-72)*

Keywords: exercise stress test, heart rate recovery index, smoking

Introduction

Smoking is a major risk factor for atherosclerosis and cardiovascular diseases, and there is a dose-dependent relationship between the daily number of cigarettes smoked and cardiovascular morbidity and mortality. Underlying triggering mechanisms include endothelial dysfunction, enhanced thrombocyte aggregation, and coronary vasoconstriction. Smoking is an important but preventable cardiovascular risk factor with both short- and long-term harmful effects. One of the harmful effects of smoking occurs on the autonomous nervous system. It is believed that nicotine accounts for majority of smoking-related effects on the neuro–cardiovascular system (1, 2).

The heart rate recovery index (HRRI) is calculated by extracting the maximum heart rate during treadmill stress testing from the heart rate in the 1st, 2nd, 3rd, 4th, and 5th minutes during the post-exercise resting period. Sympathetic activity increases during exercise but decreases in the resting period, whereas parasympathetic activity is suppressed during exercise but activated in the resting period, leading to a decrease in the heart rate (3, 4). In various studies, an abnormal HRRI has been defined as a decrease by less than 12 bpm in the 1st-minute heart rate in the resting period, and this is an independent predictor for both cardiovascular and all-cause mortality (5, 6). The present study aimed to demonstrate whether HRRI is influenced in heavy smokers.

Methods

Characteristics of the patient group

This prospective cross-sectional study comprised heavy smokers and non-smoker healthy subjects. Heavy cigarette smoking was defined as the consumption of more than one packet of cigarette per day. The subjects admitted to our cardiology clinic were evaluated for the study. Detailed anamnesis was obtained from the patients; physical examination was performed, and demographic information such as age, gender, height, and body weight were recorded. The smoking status of the patients,

Address for correspondence: Dr. Hamza Sunman, Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü, 06110 Ankara-*Türkiye*
Phone: +90 312 596 29 41 Mobile: +90 555 705 30 54 E-mail: hamzasunman@gmail.com

Accepted Date: 04.08.2015 **Available Online Date:** 18.11.2015

DOI:10.5152/AnatolJCardiol.2015.6500

as well as the duration and amount of cigarette smoking, was recorded. Blood glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and hemoglobin levels and kidney, liver, and thyroid function tests of the patients were performed . Blood samples were collected from the patients after 12-h fasting. All patients enrolled in the study underwent 12-lead ECG recording. For standard assessment, ECG recorded at the speed of 25 mm/s and amplitude of 10 mm/mV was examined. The presence of coronary artery disease, serious cardiac valve diseases, hypertension, thyroid dysfunction, atrial fibrillation, chronic obstructive lung disease, diabetes mellitus, and abnormal laboratory results (i.e., abnormality of hemoglobin, alanine aminotransferase, thyroid-stimulating hormone, creatinine, or blood glucose levels) was specified as the exclusion criteria. To detect an effect size of 0.10 at an alpha error of 0.05 and statistical power of 0.80, a minimum of 168 participants was required for our study. The patients were informed about the aim and protocol of the study in detail, and they were included after their informed voluntary consent forms were obtained. The approval of the Local Ethics Committee was also obtained.

Laboratory

Stress ECG testing

All heavy smokers and non-smokers underwent "treadmill" stress ECG testing according to the Bruce protocol. Drugs that are likely to influence the reliability of the test were discontinued 48 h earlier. To obtain a qualified recording without artifacts, the regions where the electrodes would be attached were shaved, cleaned with alcohol, and the electrodes were then placed in a way such that the 12-lead recording could be obtained. Stress testing was performed using the Schiller CS-200 Schiller AG, Baar, Switzerland) device, which was already present in our hospital. After obtaining resting ECG and blood pressure recordings, the test was started. Blood pressure and 12-lead ECG recordings were obtained every 3 min over the course of stress testing and in the 1st, 2nd, 3rd, and 5th minutes of recovery. The criteria to finalize the test were based on the definition of the American Heart Association, and patients' achieving maximum heart rate was considered to be adequate (7). Of the patients who underwent stress testing, resting heart rate, resting systolic blood pressure (SBP) and resting diastolic blood pressure (DBP), duration of exercise, effort capacity, maximum heart rate, maximum SBP and DBP, and 1st, 2nd, 3rd, and 5th minute HRRIs were recorded. HRRI was calculated by extracting the heart rate during the 1st, 2nd, 3rd, and 5th minutes after the test was finalized from the patient's maximum heart rate during exercise.

Echocardiographic evaluation

Echocardiographic examination (Philips IE 33 S5-1 probe) (Philips IE 33 S5-1 probe, Philips, Bothell, Washington, United States) was performed through appropriate echocardiographic windows using M-mode, two-dimension, color Doppler, and pulse-wave Doppler echocardiography while the patient was in the supine or left lateral decubitus position. Images were obtained in accordance with the recommendations of the American Society of Echocardiography (8).

Statistical analyses

Statistical analyses were done using Statistical Package for the Social Sciences (SPSS) 15.0 software (Chicago, IL, USA). Visual (histogram and probability graphics) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) were used to assess whether the variables are suitable for normal distribution. Normally distributed continuous variables were analyzed using Student's t-test and were expressed as mean±standard deviation (SD). Abnormally distributed continuous variables were analyzed using Mann–Whitney U test and were expressed as median (min–max). Categorical variables were presented as percentages (%) and analyzed using chi-square test. As it was determined that HRRI was normally distributed among smokers and non-smokers, these parameters were compared by Student's t-test. Analysis of covariance (ANCOVA) was also performed to identify the independent contributions of smoking to HRRI, after adjusting for prespecified variables thought to be associated with HRR.

Results

The study was conducted in a total of 179 healthy subjects aged between 18 and 67 years, of whom 66 (36.87%) were females and 113 (63.12%) were males. The subjects were divided into two groups as "smoker" and "non-smoker." The smoker group consisted of a total of 112 subjects of whom 72 (64.28%) were males and 40 (35.71%) were females, whereas the non-smoker group consisted of a total of 67 subjects, of whom 41 (61.19%) were males and 26 (38.80%) were females. The subjects in the smoker group had been consuming at least one package of cigarette daily, and the number of cigarette package/year was ranging from 2 to 50 with a mean of 20.65±10.63 package. The mean ages of the smoker and non-smoker groups were 39.52±9.33 years and 41.90±9.61

Table 1. Baseline characteristics of smoker and non-smoker groups

	Smoker n=112	Non-smoker n=67	*P**
Age, years	39.52±9.33	41.90±9.61	0.108
Gender-female; n (%)	40 (35.7)	26 (38.8)	0.678
BMI, kg/m^2	25.41±3.10	26.50±2.51	0.017
Resting HR, beat/min	85.7±12.7	87.5±12.8	0.366
Rest. SBP, mm Hg	116.5±16.3	120.3±14.7	0.119
Rest. DBP, mm Hg	71.9±7.7	73.3±7.3	0.225
Cigarette, mean package/day	1.08±0.24	–	
Duration of smoking, year	18.97±9.17	–	
Smoking, package/year	20.65±10.63	–	

*Student's t-test, chi-square test
BMI - body mass index; HR - heart rate; Rest. DBP - resting diastolic blood pressure; Rest. SBP - resting systolic blood pressure

years, respectively (p=0.108). Moreover, there was no significant difference between the groups in terms of resting heart rate, resting SBP, and resting DBP. The body mass index (BMI) was significantly higher in the non-smoker group than in the smoker group (26.50±2.51 and 25.41±3.10 kg/m^2, respectively; p=0.017) (Table 1).

No significant difference was observed between the two groups in terms of laboratory analyses comprising fasting blood glucose, creatinine, and hemoglobin levels. With regard to the lipid profile, while there was no significant difference between the groups in terms of total cholesterol (176.9±24.2 vs. 179.0±31.2 mg/dL; p=0.634), LDL (107.9±20.1 vs. 105.2±24.3 mg/dL; p=0.429), and triglyceride levels (140.4±63.1 vs. 130.7±52.4 mg/dL; p=0.291), the HDL level was significantly lower in the smoker group than in non-smoker group (42.91±8.22 and 47.34±9.32 mg/dL, respectively. p=0.002). Moreover, the left ventricular ejection fraction (65.4±2.2 vs. 65.3±2.7; p=0.849) and left atrial size (3.3±0.3 vs. 3.3±0.3 cm; p=0.571) were similar in both groups (Table 2).

Appropriate records of the stress test according to the Bruce protocol were successfully obtained for all subjects. No statistically significant difference was observed between the smoker and non-smoker groups in terms of exercise duration (9.96±1.69 and 9.50±1.79 min, respectively; p=0.087) and exercise capacity [metabolic equivalents (METs): 12.32±1.95 and 11.79±2.05, respectively; p=0.087). There was no significant difference between the two groups in terms of maximum heart rate, maximum SBP, and maximum DBP achieved during treadmill stress testing (164.0±12.3 vs. 164.8±12.0 beat/min, p=0.704; 162.6±22.2 vs. 164.7±20.0 mm Hg, p=0.519; 85.0±19.5 vs. 86.0±12.0 mm Hg, p=0.688; respectively). The 1st-minute HRRI was significantly lower in the smoker group than in the non-smoker group (26.78±8.81 and 32.82±10.34, respectively; p<0.001). Likewise, the 2nd-minute HRRI (44.37±12.11 and 51.72±12.87, respectively; p<0.001), 3rd-minute HRRI (52.73±11.54 and 57.22±13.51, respectively; p=0.018), and 5th-minute HRRI (58.31±10.90 and 62.33±13.02, respectively; p=0.029) were significantly lower in the smoker group (Fig. 1). HRRI of the smoker and non-smoker groups is demonstrated in Table 3. No abnormal stress test result in terms of significant coronary artery disease was encountered, and all tests had a low Bruce treadmill risk score.

BMI and HDL levels were significantly different between the groups. Due to an association between smoking and a low HDL level, two separate ANCOVA analyses were performed with or without HDL. After adjustment according to BMI and HDL levels, HRRIs at the 1st, 2nd, 3rd, and 5th minutes were significantly lower in the smoker group than in the non-smoker group (6.152, 95% CI: 3.128–9.175, p<0.001; 7.148, 95% CI: 3.160–11.135, p=0.001; 4.103, 95% CI: 0.156–8.051, p=0.042; and 3.832, 95% CI: 0.062–7.603, p=0.046; respectively). The ANCOVA analysis also demonstrated that HRRIs at the 1st, 2nd, 3rd, and 5th minutes were significantly lower in the smoker group than in the non-smoker group after adjusting for only BMI (6.234, 95% CI: 3.329–9.139, p<0.001; 6.952, 95% CI: 3.120–10.784, p<0.001; 4.141, 95% CI: 0.348–7.933, p=0.033; and 4.118, 95% CI: 0.492–7.744, p=0.026; respectively) (Table 4).

Table 2. Distribution of laboratory and echocardiographic data among groups

	Smoker n=112	Non-smoker n=67	*P**
Fasting glucose, mg/dL	83.9±10.0	86.4±8.2	0.093
Creatinine, mg/dL	0.82±0.2	0.81±0.2	0.560
Hemoglobin, g/dL	14.9±1.5	14.5±1.3	0.074
Total cholesterol, mg/dL	176.9±24.2	179.0±31.2	0.634
HDL, mg/dL	42.91±8.22	47.34±9.32	0.001
LDL, mg/dL	107.9±20.1	105.2±24.3	0.429
TG, mg/dL	140.4±63.1	130.7±52.4	0.291
LVEF, %	65.4±2.2	65.3±2.7	0.849
LA size, cm	3.3±0.3	3.3±0.3	0.571
sPAP, mm Hg	22.20±3.78	21.96±3.44	0.670

*Student t-test
HDL - high-density lipoprotein; LA - left atrium; LVEF - left ventricular ejection fraction; LDL - low-density lipoprotein; sPAP - systolic pulmonary artery pressure; TG - triglyceride

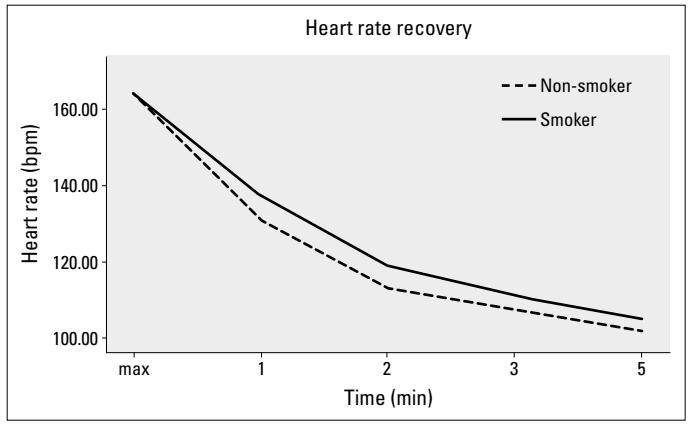

Figure 1. The mean 1st-, 2nd-, 3rd-, and 5th-minute heart rates in the smoker and non-smoker groups. The maximum heart rate was similar between the two groups (*P*=0.704). The 1st-, 2nd-, 3rd-, and 5th-minute HRRIs were lower in the smoker group that in the non-smoker group (*P*<0.001, *P*<0.001, *P*=0.018, *P*=0.029, respectively). Student's t-test was used for statistical analysis

Discussion

The present study determined that the 1st, 2nd, 3rd, and 5th minute HRRIs after maximum stress testing were statistically significantly lower in the heavy smoker group than in the non-smoker healthy control group.

Unfavorable effects of smoking on the autonomous nervous system have been studied in detail. Alyan et al. (9) investigated increased high-sensitive C-reactive protein levels and impaired autonomous activity in smokers, evaluated heart rate variability, and demonstrated impaired autonomous activity in smokers. Barutçu et al. (10) demonstrated the effect of smoking on heart rate variability in healthy subjects and impaired cardiac parasympathetic effect in heavy smokers. Impaired cardiac autonomic effect could be the reason for adverse cardiac events. Çağırcı et al. (11) in-

Table 3. Distribution of the results of exercise testing among groups

	Smoker n=112	Non-smoker n=67	*P**
Duration of exercise, min	10.0±1.7	9.5±1.8	0.087
METs	12.3±2.0	11.8±2.0	0.087
Max. HR, beat/min	164.0±12.3	164.8±12.0	0.704
Baseline SBP, mm Hg	117.4±12.8	120.3±14.7	0.166
Baseline DBP, mm Hg	71.9±7.7	73.3±7.3	0.225
Max. SBP, mm Hg	162.6±22.2	164.7±20.0	0.519
Max. DBP, mm Hg	85.0±19.5	86.0±12.0	0.688
SBP changes, mm Hg	41.5 (5–113)	42.0 (15–88)	0.850
DBP changes, mm Hg	8 (-19–68)	11 (-9–45)	0.459
HRRI1	26.78±8.81	32.82±10.34	0.001
HRRI2	44.37±12.11	51.72±12.87	0.001
HRRI3	52.73±11.54	57.22±13.51	0.018
HRRI5	58.31±10.90	62.33±13.02	0.029

*Student's t-test, Mann–Whitney U test
HRRI - heart rate recovery index; Max. DBP - maximum diastolic blood pressure; Max. HR - maximum heart rate; Max. SBP - maximum systolic blood pressure; MET - metabolic equivalent

vestigated the relationship of heavy smoking with heart rate variability and heart rate turbulence. They demonstrated that heavy smoking has a negative effect on the autonomous nervous system and suggested that an abnormal response in heart rate variability and heart rate turbulence may be the parameters that explain the increased risk of cardiovascular events in heavy smokers.

HRRI indicates the degree of post-exercise decrease in the heart rate (12). In normal asymptomatic subjects and athletes, a rapid decrease is observed within 30 s after exercise followed by a slower decrease (13). While the activation of the parasympathetic nervous system is significant in the decrease observed in the early period of resting, the withdrawal of the sympathetic system is effective on the decrease in the later period (14). Imai et al. (13) determined that the vagal effect is prominent in decreased heart rate in the short and intermediate period after resting. The fact that this rapid reduction can be prevented with atropine in the early period indicates that reduction occurs due to the vagal effect; a decrease in heart rate observed at 30th second and 2nd minute after resting was weakened with atropine and with dual blockade. However, weakening in the 2nd minute was higher with dual blockade than that achieved with atropine; i.e., the heart rate had been higher, indicating that late-phase sympathetic nervous system modulation plays a more important role on the improvement in heart rate (13). HRRI is an important predictor of all-cause mortality independent from the extensiveness of coronary atherosclerosis, left ventricle function, and exercise capacity (15). Morshedi-Meibodi et al. (16) investigated the relationship between HRRI and cardiovascular events in a study comprising 2967 patients. They determined that higher the reduction in the 1st minute was closely related to the lower risk of coronary heart disease and cardiovascular disease.

Table 4. Independent contributions of smoking to HRRI after adjustment for BMI and HDL

Parameters	B	95% confidence interval		*P**
		Lower bound	Upper bound	
HRRI1				
HDL	0.017	-0.148	0.181	0.841
BMI	-0.236	-0.723	0.251	0.340
Smoking	6.152	3.128	9.175	<0.001
HRRI2				
HDL	-0.040	-0.257	0.177	0.718
BMI	0.308	-0.334	0.950	0.345
Smoking	7.148	3.160	11.135	0.001
HRRI3				
HDL	0.008	-0.207	0.222	0.945
BMI	0.399	-0.237	1.035	0.217
Smoking	4.103	0.156	8.051	0.042
HRRI5				
HDL	0.053	-0.153	0.259	0.612
BMI	0.115	-0.494	0.724	0.710
Smoking	3.832	0.062	7.603	0.046
HRRI1				
BMI	-0.245	-0.723	0.234	0.314
Smoking	6.234	3.329	9.139	<0.001
HRRI2				
BMI	0.328	-0.303	0.959	0.306
Smoking	6.952	3.120	10.784	<0.001
HRRI3				
BMI	0.395	-0.229	1.020	0.214
Smoking	4.141	0.348	7.933	0.033
HRRI5				
BMI	0.088	-0.511	0.687	0.772
Smoking	4.118	0.492	7.744	0.026

*Analysis of covariance (ANCOVA)
BMI - body mass index; HDL - high-density lipoprotein; HRRI - heart rate recovery index

All parameters, including fasting blood glucose level, triglyceride/HDL ratio, diabetes, endothelial dysfunction, and having a history of recent MI , have been found to be associated with a low HRRI (17). As the present study was conducted in healthy subjects, the medical history of the patients did not comprise diabetes, hypertension, coronary artery disease, or hyperlipidemia. In addition, the results of the laboratory parameters such as hemoglobin, glucose, and creatinine levels were similar in both groups and were within normal ranges; accordingly, only the effect of heavy smoking on HRRI after maximum exercise testing has been investigated.

Jouven et al. (18) followed 5713 asymptomatic male subjects for 23 years and determined that the risk of sudden death due to myocardial infarction is 2-fold higher in subjects with 1st-minute HRRI of ≤25 beats than the subjects with 1st-minute HRRI of ≥25 beats. In the Lipid Research Clinics Prevalence Study, 2nd-minute HRRI was calculated after a submaximal exercise, and it was determined that the risk of all-cause mortality during the 12-year follow-up period was 2.58-fold higher in those with HRRI of <43 beats than in those with HRRI of ≥43 beats (19). Cheng et al. (20) followed 2333 diabetic patients for 15 years and divided the patients into four groups according to post-exercise 5th-minute HRRI: those with HRRI of <55 beats were allocated to the 1st group, those with HRRI of 55-66 beats were allocated to the 2nd group, those with HRRI of 67–75 beats were allocated to the 3rd group, and those with HRRI of >75 beats were allocated to the 4th group; the groups were compared among themselves after 15 years. Both cardiovascular and all-cause mortality rates were found to be 1.5–2-fold higher in those with low HRRI than in those with higher HRRI at the end of the 15 years (20). In the present study, the 1st-minute HRRI was 26.78±8.81 and the 2nd-minute HRRI was 44.37±12.11 in heavy smokers, and the fact that these values were very close to the above-mentioned values and attracted our attention. In addition, the present study found that the 5th-minute HRRI was 58.31±10.90, which was consistent with that in the 2nd group in the study conducted by Cheng et al. (20).

Papathanasiou et al. (21) previously investigated the effect of smoking on HRRI in healthy young adults. In that study, the mean duration of smoking was 4.7±1.7 years in females and 5.8±2.3 years in males. The study, which evaluated HRRI1 and HRRI2, demonstrated that HRRI1 and HRRI2 were lower in female smokers than in non-smokers. In the present study, the ages of the patients ranged between 18 and 67 years, which represent the whole population, and the effect of heavier smoking on HRRI has been demonstrated as the exposure to smoking was 20.65±10.63 package/year and 1.08±0.24 package/day. Moreover, the present study evaluated HRRI3 and HRRI5 in addition to HRRI1 and HRRI2.

Smoking has an indirect effect on lipoprotein metabolism by influencing lipoprotein lipase, which is an important factor in cholesterol and triglyceride metabolism (22). Smoking reduces the antiatherogenic effect of HDL by reducing the concentration of this lipoprotein (23). In the present study as well, a significantly lower HDL concentration in heavy smokers than in non-smokers (42.91±8.22 and 47.34±9.32, respectively; p=0.002) is consistent with currently available data. Although BMI was significantly higher in the non-smoker group than in the smoker group (26.50±2.51 and 25.41±3.10, respectively; p=0.017), patients with BMI of ≥30 kg/m^2 were not included in the present study. Moreover, the 1st-, 2nd-, 3rd-, and 5th-minute HRRIs after adjusting according to BMI and HDL levels were also significantly lower at each time point in the smoker group than in the non-smoker group.

Study limitations

There are some limitations. Firstly, our results should be verified in larger studies including a higher number of heavy smokers. Secondly, all individuals included in the study group were selected among those who applied to our cardiology clinic. This may partially make the definition of "healthy subject" debatable. Thirdly, coronary artery disease was defined as an exclusion criterion. Because the study subjects did not undergo coronary angiography, the actual incidence of coronary artery disease was unknown. Fourthly, gas change analysis devices have not been used during stress testing. Finally, parameters such as heart rate variability and baroreceptor sensitivity were not used as the indicators of autonomic response during exercise testing.

Conclusion

HRRI was found to be lower in the 1st, 2nd, 3rd, and 5th minutes in heavy smokers. Our results suggest that beside previously known untoward effects on vascular biology, heavy smoking also has deleterious effects on the neuro–cardiavascular system. Notwithstanding, the exact mechanisms of the differences observed between smokers and non-smokers regarding HRRI is not well known and requires more research.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept- M.E., M.D.; Design- T.H.E., M.D.; Supervision-A.A., E.Y.; Funding-E.Y.; Materials- M.E., M.B., L.D.A.; Data collection &/or processing –M.E., M.B., L.D.A.; Analysis and/or interpretation– H.S., M.B., L.D.A.; Literature search- T.Ç., L.D.A.; Writing – M.E., H.S.; Critical review- A.A., H.S.

References

1. Moliterno DJ, Willard JE, Lange RA, Negus BH, Boehrer JD, Glamann DB, et al. Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. N Engl J Med 1994; 330: 454-9.
2. Karakulak UN, Maharjan N, Tutkun E, Yılmaz ÖH. Additional diagnostic parameter for coronary artery disease during exercise test: heart rate recovery. Anatol J Cardiol 2015; 15: 163. Crossref
3. Pierpont GL, Voth EJ. Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. Am J Cardiol 2004; 94: 64-8. Crossref
4. Kaya EB, Yorgun H, Akdoğan A, Ateş AH, Canpolat U, Sunman H, et al. Heart-rate recovery index is impaired in Behçet's disease. Tex Heart Inst J 2009; 36: 282-6.
5. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. JAMA 2003; 290: 1600-7.
6. Dufay-Bougon C, Belin A, Dahdouh ZS, Barthelemy S, Mabire JP, Sabatier R, et al. The prognostic value of the cardiopulmonary exercise test in patients with heart failure who have been treated

with beta-blockers. Turk Kardiyol Dern Ars 2013; 41: 105-12.
7. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002; 40: 1531-40. Crossref
8. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-63. Crossref
9. Alyan O, Kaçmaz F, Özdemir O, Karahan Z, Taşkesen T, İyem H, et al. High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers. Turk Kardiyol Dern Ars 2008; 36: 368-75.
10. Barutçu I, Esen AM, Kaya D, Türkmen M, Karakaya O, Melek M, et al. Cigarette smoking and heart rate variability: dynamic influence of parasympathetic and sympathetic maneuvers. Ann Noninvasive Electrocardiol 2005; 10: 324-9.
11. Çağırcı G, Çay S, Karakurt O, Eryaşar N, Kaya V, Çanga A, et al. Influence of heavy cigarette smoking on heart rate variability and heart rate turbulence parameters. Ann Noninvasive Electrocardiol 2009; 14: 327-32. Crossref
12. Lauer M, Froelicher ES, Williams M, Kligfield P; American Heart Association Council on Clinical Cardiology SoECR, Prevention. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2005; 112: 771-6. Crossref
13. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994; 24: 1529-35. Crossref
14. Sears CE, Choate JK, Paterson DJ. Inhibition of nitric oxide synthase slows heart rate recovery from cholinergic activation. J Appl Physiol (1985) 1998; 84: 1596-603.
15. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003; 42: 831-8. Crossref
16. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). Am J Cardiol 2002; 90: 848-52. Crossref
17. Panzer C, Lauer MS, Brieke A, Blackstone E, Hoogwerf B. Association of fasting plasma glucose with heart rate recovery in healthy adults: a population-based study. Diabetes 2002; 51: 803-7. Crossref
18. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951-8. Crossref
19. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med 2000; 132: 552-5.
20. Cheng YJ, Lauer MS, Earnest CP, Church TS, Kampert JB, Gibbons LW, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. Diabetes Care 2003; 26: 2052-7. Crossref
21. Papathanasiou G, Georgakopoulos D, Papageorgiou E, Zerva E, Michalis L, Kalfakakou V, et al. Effects of smoking on heart rate at rest and during exercise, and on heart rate recovery, in young adults. Hellenic J Cardiol 2013; 54: 168-77.
22. Bizzi A, Tacconi MT, Medea A, Garattini S. Some aspects of the effect of nicotine on plasma FFA and tissue triglycerides. Pharmacology 1972; 7: 216-24. Crossref
23. Hegarty KM, Turgiss LE, Mulligan JJ, Cluette JE, Kew RR, Stack DJ, et al. Effect of cigarette smoking on high density lipoprotein phospholipids. Biochem Biophys Res Commun 1982; 104: 212-9. Crossref