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The effect of asthma controlling on heart rate recovery in patients with asthma

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Abstract

Aim: The heart rate recovery index (HRRI) impairment was found in patients with pulmonary disease such as obstructive sleep apnea syndrome. Asthma is one of the most prevalent respiratory diseases in worldwide. In this study, we aimed to investigate the presence of HRRI impairment with asthma control test in patients with asthma.
Material and Methods: A total of 45 people with asthma and 47 healthy participants were consequently enrolled to study from December 2019 through March 2020. The Asthma Control Test™(ACT) survey was used to evaluate the status of asthma. All participants were to undergo cardiopulmonary exercise testing. Heart rate recovery was calculated according to heart rate decreasing in recovery period.
Results: Two groups had similar results in terms of laboratory parameters and demographic features. There was a statistically difference in exercise capacity, peak exercise heart rate, (METs) and duration of exercise. Also, all HRRI parameters were reached statistically significant when compared with control group. However, there was no statistically significance in HRRI when ACT groups were compared with each other.
Conclusions: The differences of HRRI in ACT groups did not reach to statistically significance. This result could be a consequence of having only two ACT groups and not having any patients belonging to the well-controlled group.

Introduction

Heart rate (HR) which is described as heart beat per minute is mainly regulated by autonomic nervous system (ANS) which has close relationship with physical activity. ANS has balancing effect on HR by stimulating sympathetic and/or parasympathetic activation. This balancing can be shown by calculating HR recovery index (HRRI) in exercise test. This parameter can be calculated by subtracting the 1st, 2nd, 3rd, and 5th minute recovery period heart rates from the maximal heart rate after an exercise stress test in individuals who achieved at least 85% of age-adjusted maximum heart rate (1).

Cardioacceleration are the main components of cardiac regulation of HR during exercise while cardiodeceleration are the main mechanism for HR recovery statement (2-4). This effect leads to decreasing HR in the early phase of recovery period, while subsequent phase is affected by sympathetic system (5). Also, vagal reactivation is related with a reduction in the risk of death (6-7). And, delayed decrease in HR in the first minute after exercise has been found to be an independent and strong predictor of all-cause mortality (5, 6, 8). Asthma is one of the most common chronic inflammatory airways disease that is prevalent worldwide.

Asthma generally has an inflammatory nature which has similarity with processing of coronary heart disease (CHD). The association between CHD and asthma might be the reason of the inflammatory cytokine alterations (10). A few studies have found a relation between cardiovascular (CVD) disease and asthma (8, 10-12) while other studies have failed to verify this relationship (13-15). In a meta-analysis of 11 studies, Wang et al. found that the risk of CHD was higher with about 32% in patients with asthma than without asthma (16). In our best knowledge, there is no study which investigated the relationship between HRRI and asthma control test. The aim of the present study was to ascertain the association between HR decrease after exercise and asthma control test parameters.

Material and Methods

The study was conducted as prospective, non-randomized and single-blinded. A total of 92 subjects, including asthma patients and healthy volunteers, were enrolled in this study. All

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data were prospectively collected from consecutive adult patients who applied to our hospital due to chest pain and/or dyspnea between December 1, 2019, and March 30, 2020. The determination of asthma was made according to Global Initiative for Asthma criteria (17). Forty-five asthma patients without attack consequently were enrolled to the study. All patients were questioned with the Asthma Control Test™(ACT) which was carried out to determine asthma control status. The ACT is a self-report questionnaire consisting of 5 items with 5 response options with values that range from 1 to 5. These five questions assess each of the following for over the last four weeks: (1) the effect of asthma on daily functioning, (2) the frequency of shortness of breath (3) awaking due to asthma symptoms, (4) use of rescue medications and (5) global self-appraising of asthma control. In scoring, the sum score reflects asthma control with values ranging from 5 (poor control of asthma) to 25 (complete control of asthma). Patients were classified as not controlled in group I (<19), poorly controlled in group II (20-24) and well controlled in group III (18, 19). 47 healthy volunteers, with similar characteristics to the patient group in terms of age, gender and education level were enrolled. None of the subjects were in any regular physical activity. The age range was determined as 18-65 years. The exclusion criteria were any cardiovascular disease, heart failure, moderate-advanced valvular heart disease, hypertension, pregnancy, liver or renal failure, any other chronic disease and active infection, diabetes mellitus and endocrine diseases and arrhythmias. Approval of the local ethics committee was obtained.

All participants were informed about the study and all gave informed consent to participate in the study. All participants underwent cardiac examination. Echocardiography was performed and cardiac parameters such as left and right heart chambers diameters, ejection fraction (%EF) and valvular pathologies which were obtained from apical and parasternal axis by using 2.5 MHZ transducer of Vivid 5 echocardiography (GE Medical Systems, Hortan, Norway) were recorded. The arterial blood pressure and HR of all participants, which was measured after 5 minutes rest at the outpatient clinic, was recorded. The blood sample tests including fasting blood glucose, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides and hemogram parameters were recorded. Electrocardiography (ECG) was obtained from all participants during the cardiac examination. After cardiac evaluation, the participants who had normal ECG and echocardiography have been oriented for exercise test for accessing their cardiac discomfort. Exercise stress test was performed according to Bruce protocol via Kardiosis TM Pro 2200 in our hospital. The ECG was recorded continuously during the treadmill test. The subjects who performed 85 percent of maximum HR were included in the study. The maximum HR was calculated according to the following formula: 220 - age. The recordings of heart rates were collected at the beginning of the rest and during the 5 minutes. Then, HRRIs were calculated by subtracting the heart rates at 1st (HRRI1), 2nd (HRRI2), 3rd (HRRI3), and 5th (HRRI5) minutes from the peak heart rate of exercise test. Also, peak exercise HR, exercise duration, exercise capacity were recorded. The protocol of the current study was approved by the local ethics committee (08/11/2019.K-2044). The study was conducted in full accordance with the principles highlighted in Good Clinical Practice and Helsinki Declaration.

Table 1. Demographic Parameters and Blood Sample Tests Results

	Group 1 (n = 45)	Group 2 (n = 47)	P
Gender (female/male)	39/6	37/10	0.320
Mean age (year)	35.8±11.8	32.0±8.3	0.820
Hypertension	7	5	0.489
Diabetes Mellitus	3	1	0.965
Total cholestrol (mg/dL)	207.7±42.4	180.6±31.0	0.058
LDL (mg/dL)	122.3±31.7	110.9±30	0.254
HDL (mg/dL)	60.8±10.8	53.7±11.9	0.070
Triglycerides(mg/dL)	122.0±44.5	106.5±49.4	0.331
Glucose (mg/dL)	105.9±23.4	98.8±7.9	0.390
Hemoglobin (g/dL)	12.9±1.4	13.2±1.3	0.381
MPV (fL)	9.8±1.1	9.8±1.3	0.985
MCV (fL)	85.1±7.8	85.9±5.0	0.682

cm: centimeter; dL: decilitre; fL: femtolitre; HDL: High density lipoprotein; L: litre; LDL: Low density lipoprotein; MCH: Mean cell hemoglobin; MCHC: Mean cell hemoglobin concentration; MCV: Mean cell volume; mg: miligram; mmHg: milimetres of mercury; MPV: Mean platelet volume; N/L: Neutrophil/lymphocyte ratio; pg: picogram; * : Non significant

Statistical analysis

Statistical Package for Social Sciences (SPSS) 20.0 (for Windows, USA, Armonk New York) program was used for statistical analysis in our study. Sample size calculator point out needs at least 42 participants to realize a group difference. The descriptive statistical methods (mean, standard deviation) were used to calculate the data. The Kolmogorov-Smirnov test was used to determine whether the variables were in normal distribution. Non-normal distributed variables, such as ACT groups and exercise capacity were assessed with Mann-Whitney U test, and normal distributed variable was assessed with The Student's t-test. The categorical variable was analyzed with Chi-Square test. When $p<0.05$ was reached, result was accepted meaningful.

Results

The average age of asthma patients (group 1) was 35.8±11.8 years, while the average age of control group (group 2) was 32.04±8.3 years and there was no statistical difference ($p = 0.082$). There was no statistically difference in demographic features and laboratory parameters (Table 1).

There was no discrepancy in terms of systolic, diastolic arterial pressure and beginning HR between the groups. All individual record of exercise stress tests was assessed for HR recovery index (HRRI) and other parameters. The results of exercise stress test are shown in table 2. According to statistical analysis a meaningful difference was found in terms of peak exercise HR, exercise capacity (METs), duration of exercise (respectively $p = 0.0001; < 0.0001; < 0.0001$).

Also, the HRRI1, HRRI2, HRRI3, HRRI5 were statistically significant when groups were compared. There were 33 patients in group I, 12 patients in group II and there were no patients in group III of ACT. When these groups were compared by means of HRRI, there was no statistical difference (Table 3).

Table 2. Heart Rate Recovery Indices of the Groups

	Group 1 (n = 45)	Group 2 (n = 47)	P
Peak exercise heart rate (beat/min)	160.7±17.5	173.0±13.5	0.0001
Exercise capacity (METs)	9.1±2.0	11.8±1.0	<0.0001
Duration of exercise, sec	430.9±92.2	641.6±107.9	<0.0001
HRRI 1st min, beats/min	20.3±10.3	31.0±11.0	<0.0001
HRRI 2nd min, beats/min	44.6±13.1	50.0±12.9	0.048
HRRI 3rd min, beats/min	53.7±12.4	59.3±10.7	0.021
HRRI 5th min, beats/min	56.4±13.0	63.5±12.1	0.008

HRRI: Heart rate recovery index; METs: Metabolic equivalent units p, Independent sample t test , When it is <0.05, it was associated meaningful

Table 3. Comparing the Relationship Between Asthma Control Test and HRRI with Mann Whitney U Test

Groups	N	Mean rank	p
HRRI1			
Group II	12	21.38	.616
Group I	33	23.59	
Total number	45		
HRRI2			
Group II	12	21.13	.563
Group I	33	23.68	
Total number	45		
HRRI3			
Group II	12	22.46	.867
Group I	33	23.20	
Total number	45		
HRRI5			
Group II	12	24.83	.572
Group I	33	22.33	
Total number	45		

HRRI: Heart rate recovery index

Furthermore, there was no statistical significance in terms of smoking status. Also, all echocardiographic measurements of left and right heart chambers dimensions were not statistically significant.

Discussion

The key finding of this study is that HRRI (1, 2, 3, 5) following maximal exercise is slower in asthma patients when compared to healthy individuals. This verifies that autonomic function is impaired in asthma patients as shown in previous studies (12, 20, 21). However, a difference in this impairment could not be found between the two asthma groups (group I and group II) that were rated as per the ACT scores. This result may not be meaningful due to sample size and absence of group III (well controlled) patients.

The association between asthma and the higher risk of CVD and all-cause mortality has been found in a meta-analysis including several studies. It has been found that asthma was related with an increased risk of CVD and all-cause mortality (22). A recent meta-analysis of prospective cohort studies has concluded that attenuated HRR is related with increased risk of cardiovascular events and all-cause mortality. And it is recommended that HRRI can be used for risk assessment in routine clinical practice (23).

There was no difference in terms of all-cause mortality in both genders although risk of CVD was higher in women (22). It has been concluded by several studies that chronic inflammatory disease is thought to be the main pathway which could explain this association between asthma and CVD (24, 25). However, Altuntas et al. have found that chronic urticaria was not related with HHRI (26). Also, it has been shown that allergic asthma could accelerate atherosclerosis by changing immune response (25). So, it may be reasonable to checking the outpatient clinic patients with asthma for potential risk of CVD complications. So, it has been intended to determine whether ACT had additional information for checking these risks of CVD in this study. Interestingly, we found that HRRI was not significantly different when ACT groups were compared, meaning that ACT scores were not meaningful in terms of HRRI in asthma patients while asthma had significant association with HRRI. However, we need to consider that there were no patients belonging to group III, and all patients were in group I and II of ACT classification. Viewed in this context, the study result could be a consequence of having only two ACT groups, and not having any patient from group III. In our opinion, this is the main reason for not establishing significance between groups. Failure of HR to fall rapidly during recovery might indicate dysregulation of the parasympathetic branch of the autonomic nervous system due to early phase recovery mostly assumes to exist with parasympathetic inhibition. This hypothesis has been verified in a study that cardiac HR deceleration in early phase of recovery was prevented by using atropine for blocking parasympathetic activation (6). And this impairment of HRRI has been described as an independent predictor of all-cause mortality, and related with worsening coronary artery disease, carotid atherosclerosis, and cardiovascular disease (4, 9, 27, 28). Also, it has been found that impaired HRRI is independently related with perioperative myocardial injury and all-cause and cardiovascular morbidity of surgery was more common in these patients (29). Recently, it has been figure out that chronic exposure of coal dust which may lead to respiratory disease is associated with impaired HRRI in coal miners (30). Similar with these findings, HRRI following maximal exercise is slower in asthma patients when compared to healthy individuals in our study.

Limitations

There are some limitations concerning this study. Firstly, our sample size was relatively small. We have not determined the type of asthma and its duration. Additionally, the study population did not contain any patients from group III (well controlled group) of ACT. So, we cannot generalize our results to general population.

Conclusion

In conclusion, our study demonstrates that HRRI is significantly slower in asthma patients although no difference between groups could be found when asthma patients were divided into groups depending on ACT scores. This result could be a consequence of having only two ACT groups and not having any pa-

tients belonging to the well-controlled group. Moreover, future studies are recommended to evaluate HRRI changing depending on ACT groups especially including the well-controlled group.

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