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Mitral annular calcification is associated with postexercise heart rate recovery

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Abstract
Mitral annular calcification (MAC) is a chronic, degenerative disease characterized by accumulation of calcium and lipid in the fibrous ring of the mitral valve. Heart rate recovery index (HRR) calculated after treadmill exercise test is a predictor of autonomic dysfunction and cardiovascular mortality. The aim of this study was to investigate the relationship between MAC and HRR parameters. 64 patients with MAC (mean age 54.9±5.8, 40 males) and 44 healthy controls (mean age 55.1±6.5, 28 males) were included in the study. All subjects in the MAC group and control group underwent basal 12-lead electrocardiography, echocardiography, and treadmill exercise test at a target rate determined by age. HRR indices were calculated from the maximal heart rate by subtracting the heart rate at the 1st, 2nd and 3rd minutes of the recovery period. Baseline demographic and laboratory data were similar in both groups. Compared with healthy controls, individuals with MAC had decreased HRR at 1 (HRR1), 2 (HRR2), and 3 (HRR3) minutes [16.9 ± 4.5 vs. 19.2 ± 3.9, p = 0.009; 33.9 ± 4.6. 36.2 ± 5.1, p = 0.019; 49.6 ± 7.1. 52.4 ± 6.1, p = 0.035; respectively]. These results show that heart rate recovery after exercise is impaired in individuals with MAC. Given the independent prognostic value of HRR, these findings can be evaluated in terms of symptomology of autonomic dysfunction in people with MAC. Because HRR is a simple and inexpensive method, it may be useful in identifying high-risk patients, especially in individuals with MAC.

Keywords: Heart rate recovery, Mitral annular calcification, Treadmill exercise test

Introduction

Mitral annular calcification (MAC) is a chronic degenerative change of the mitral valve which is more common in women and increases with age. It does not require treatment unless valve dysfunction and/or embolic complications develop. MAC is a noninflammatory pathology of the mitral valve diagnosed by echocardiography [1]. The incidence increases with age and end-stage renal disease [2]. MAC is a benign character and is a common finding in surgical operations and autopsy series as well as incidental detection in cardiovascular imaging (echocardiography) studies. MAC develops as a result of calcification in the basal section of the mitral valve leaflets and annulus. The posterior mitral annulus is affected more frequently than the anterior annulus. Calcifications usually accumulate irregularly and cluster. Sometimes it is seen as nodular calcification involving the valves and subvalvular structures. As the annular calcification progresses, sinus node disease, atrioventricular block and branch blocks may be observed due to the neighboring conduction system between the interventricular septum and anulus [3]. Many studies have shown that MAC is associated with atherosclerotic diseases such as carotid artery disease and coronary artery disease [4]. MAC is associated with an increase in total and cardiovascular mortality [1,5].

An exercise treadmill test is a widely used and important test in the diagnosis and follow-up of cardiovascular diseases. Several parameters are routinely derived from this test and are used to assess cardiovascular events and mortality risk [6]. Exercise treadmill test, exercise capacity, chronotropic response determination, heart rate recovery (HRR) and ventricular ectopic beat level can be determined. It is an important advantage that these parameters are reliable, reproducible and easily measured. HRR is an important indicator of autonomic activity that reveals a decrease in heart rate after a gradual exercise [7]. HRR; It is defined as the difference between the maximum heart rate during exercise and the heart rate during the recovery phase. HRR is an important and complex indicator of cardiac autonomic function that reflects the balance of sympathetic-parasympathetic effects and the interaction of each other with regulating heart rate [8]. It has an important prognostic value in normal population as well as those with cardiac disease. It also provides prognostic information for all-cause death, cardiac-related death and sudden death risk [7,9,10]. A better understanding

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of the pathophysiological mechanism of the relationship between decreased HRR and increased mortality will contribute to the development of strategies to improve HRR and improve survival. Studies have shown that both MAC and impaired HRR are associated with increased cardiovascular (CV) risk factors.

The aim of this study was to investigate the differences between HRR parameters and Treadmill exercise testing in patients with MAC detected by transthoracic echocardiography.

Material and Methods

Study population

The study was conducted at the Department of Cardiology, Faculty of Medicine, Bozok University. Between June 2017 and November 2019, 64 consecutive patients with a sinus rhythm in the 40-65 age range with a mitral valve area greater than 2.5 cm^2 and a transmitral mean gradient of less than 2 mmHg were included in the study. The control group consisted of healthy subjects in the same age and sex group without mitral annular calcification on echocardiography. All control subjects had normal physical examination and echocardiographic findings. Coronary artery disease, moderate-severe valvular heart disease, history of acute rheumatic fever, prosthetic valve, left ventricular systolic dysfunction (ejection fraction <50%), advanced lung disease, pulmonary hypertension, chronic or acute infective disease, patients with dysrhythmia, those with electrolyte imbalance and those with disability to perform stress testing were excluded from the study. Exercise test abnormalities and those who did not complete the test were also excluded. Baseline demographic characteristics and clinical data were recorded. Body mass index (BMI) was calculated as (kg/m^2). Standard 12-lead surface electrocardiography (ECG) was performed to all subjects at rest using the device (Nihon Kohden, Tokyo, Japan. Blood samples were taken after twelve hours of fasting. Written informed consent was obtained. Ethical approval was obtained by the local ethics committee (Approval no:2017-KKAEK-189-2017.08.24).

Echocardiographic assessment

Echocardiographic examinations of the participants were performed with Philips Affiniti 50 echocardiography device (Philips Healthcare, Netherlands). Patients were placed in left lateral decubitus position during echocardiographic examination. Measurements were performed from parasternal short-and long-axis views and apical two/four chambers conventionally. MAC is defined as an echocardiographic structure in M-mode or 2-dimensional (parasternal-apical) images, seen as an echogenic band that is thicker than 1 mm thick at the base of the mitral leaflets and does not change along the systole and diastole [11].

Exercise Stress Test Protocol

In the study, maximum exercise test was done by treadmill in Bruce protocol. The highest heart rate during the test (220 - age), the target was to reach at least 85% of the heart rate calculated by age [6]. After reaching maximal heart rate, an active recovery period was started at 1.5 MPH and 2.5 slopes. Continuous electrocardiogram monitoring was performed during the test and recovery period and data on symptoms, heart rate and blood pressure were recorded. HRR1, HRR2 and HRR3 values were calculated by subtracting the heart rate values at the first, second and third minutes after exercise from the maximum heart rate reached during the exercise. The metabolic equivalent 1 MET is expressed as (equivalent to 3.5 mL of oxygen uptake per kilogram per minute).

Statistical analysis

Shapiro wilk test was used to evaluate the distribution of normality of continuous variables. Statistical analysis of the clinical data between the two groups was evaluated by Student's t test for normally distributed parameters and Mann Whitney U test for those without normal distribution. Chi-square test was used for categorical variables. SPSS 20 (SPSS/IBM, Chicago, IL, USA) software was used for the analysis and p value of less than 0.05 was considered statistically significant.

Results

The study was carried out with 108 subjects between the ages of 40-65 years. The subjects were divided into two groups as MAC and control. The MAC group consisted of 64 subjects (40 males and 24 females), and the control group consisted of 44 males (28 males and 16 females). Demographic, clinical and biochemical characteristics of individuals with MAC and control group are summarized in Table 1. The resting heart rate and arterial blood pressures of the two groups were within normal range and there was no significant difference between the two groups. Appropriate records of the stress test according to the Bruce protocol were successfully obtained for all subjects. Resting heart rate, maximum heart rate, exercise duration, and maximal METs values were similar between the groups (Table 2). The HRR1 was significantly lower in the MAC group than in the control group (16.9±4.5 and 19.2±3.9, respectively; p=0.009). Likewise, the HRR2 (33.9±4.6 and 36.2±5.1, respectively; p=0.019), HRR3 (49.6±7.1 and 52.4±6.1, respectively; p=0.035), were significantly lower in the MAC group (Figure1).

Table 1. Baseline clinical and laboratory parameters

Variables	MAC (n=64)	Control (n=44)	P value
Age, years	54.9 ± 5.8	55.1 ± 6.5	0.800
Gender (Female/Male)	24/40	16/28	0.645
Body Mass Index (kg/m²)	24.3 ± 2.4	24.5 ± 2.3	0.612
SBP (mmHg)	131.1 ± 19.5	128.3 ± 16.8	0.454
DBP (mmHg)	80.9 ± 14.6	79.3 ± 8.2	0.495
Hypertension, n (%)	38 (59)	23 (54)	0.638
Diabetes mellitus, n (%)	26 (41)	17 (40)	0.988
Smoking, n (%)	24 (41)	23 (54)	0.121
Serum Glucose (mg/dL)	118.6 ± 39.8	117.6 ± 37.7	0.888
Hemoglobin, (g/dL)	14.5 ± 1.4	14.3 ± 1.5	0.346
Serum Creatinine (mg/dL)	0.93 ± 0.29	0.89 ± 0.18	0.432
AST(U/L)	21.9 ± 8.3	25.8 ± 17.7	0.293
ALT(U/L)	24.3 ± 11.6	25.6 ± 19.1	0.673
Total Cholesterol (mg/dL)	185.1 ± 38.7	189.9 ± 45.1	0.405
Triglycerides (mg/dL)	158.7 ± 78.4	173.3 ± 90	0.379
High-density lipoprotein (mg/dL)	43.4 ± 15.6	40.6 ± 10.3	0.318
Low-density lipoprotein (mg/dl)	114.5 ± 37.1	117.5 ± 36.1	0.678

Expressed as Mean ± Standard Deviation or as Percentage (%), p values were compared by Student' T-test or chi-square test as appropriate, p<0.05 significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low density lipoprotein

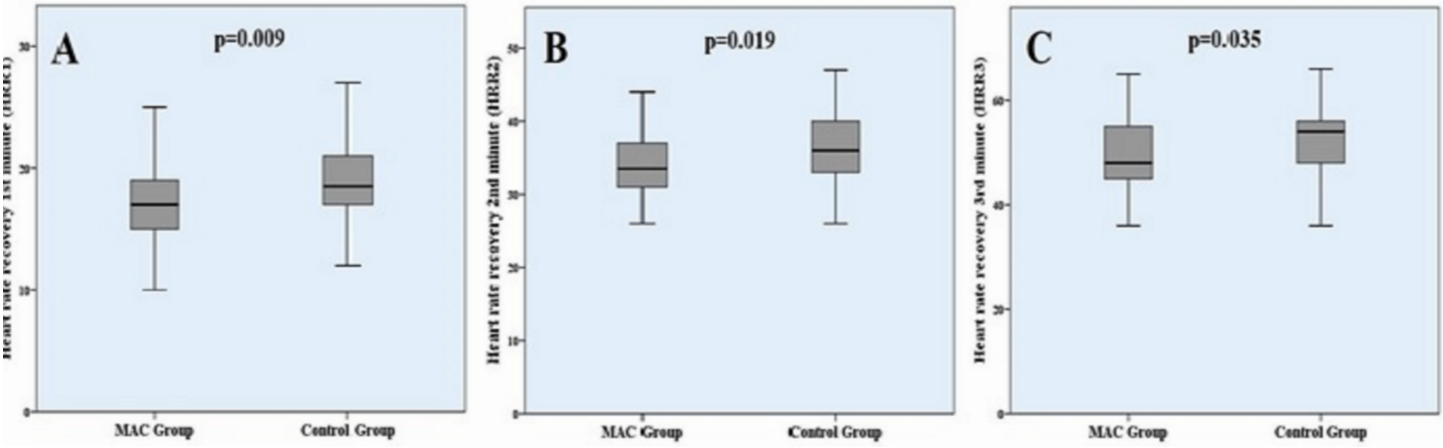

Figure 1. Comparison of HRR indices between the MAC and control groups

Table 2. Comparison of treadmill exercise test parameters

Variables	MAC (n=64)	Control (n=44)	P value
Maximal METs	10.7 ± 1.9	10.9 ± 1.8	0.376
Resting heart rate (beat/min)	69.2 ± 9.9	68.8 ± 10.1	0.826
Exercise duration (minutes)	9.4 ± 2.3	9.3 ± 1.9	0.770
Maximum heart rate (beat/min)	159.6 ± 15.9	163 ± 12.7	0.246
HRR1(beat/min)	16.9 ± 4.5	19.2 ± 3.9	0.009
HRR2 (beat/min)	33.9 ± 4.6	36.2 ± 5.1	0.019
HRR3(beat/min)	49.6 ± 7.1	52.4 ± 6.1	0.035

Expressed as Mean ± Standard Deviation or as Percentage (%), p<0.05 significant. METs: Metabolic equivalent, HRR1: First minute heart rate recovery, HRR2: Second minute heart rate recovery, HRR3: Third minute heart rate recovery

Discussion

The main objective of this study was to show how HRR changes in individuals with MAC compared to normal healthy subjects. In patients with MAC, HRR parameters were significantly impaired (decreased) compared to controls. This is the first study in the literature to evaluate the relationship between the presence of MAC and HRR in individuals of similar age and similar risk factors for cardiovascular disease.

In previous studies, risk factors such as age, DM, HT and obesity, which are risk factors for atherosclerotic heart disease, have been shown to be risk factors for MAC [2,5]. Mitral annular calcification is closely associated with cardiovascular diseases such as coronary artery disease, carotid and aortic atherosclerosis, heart failure and stroke [4]. The imbalance in calcium and phosphorus metabolism, which leads to an increased risk of atherosclerosis, plays an important role in MAC formation, along with an unknown pathophysiology [2]. The relationship between experimentally induced systemic artery atherosclerosis and accumulation of fatty plaques on the ventricular side of posterior mitral leaflets has been demonstrated [3]. In the light of this information, MAC is thought to be a form or symptom of atherosclerosis because it has pathological findings similar to that of atherosclerotic lesions and its close association with risk factors for atherosclerosis. In a study of Boon et al. The incidence of hypertension, hyperlipidemia and DM was found to be significantly higher in MAC patients than in the control group [12]. Similarly, in the Framingham Heart Study; The incidence of DM, HT and obesity was found to be significantly higher in MAC patients than in the control group [5].

There is a complex relationship between various intrinsic, neural and humoral factors that control the slowing of heart rate after exercise [13,14]. However, autonomic nervous system mediated responses, particularly parasympathetic reactivation, are major determinants for HRR. Delayed HRR after exercise is an indicator of decreased parasympathetic activity [15] and is associated with increased long-term mortality [5,10]. Since our study was performed cross-sectionally, it is not appropriate to make this judgment in individuals with MAC in terms of long-term mortality and prognosis. However, long-term studies with people with MAC will inform us about this.

In our study; Although the incidence of cardiovascular risk factors were similar and relatively high in both groups, the reason for the lack of a statistically significant difference between them may be due to the small sample size and the inclusion of people older than 65 years. Arrhythmia and conduction disorders can be seen in patients with MAC. Both the severity and prevalence of ventricular arrhythmias have been shown to increase in patients with MAC. However, in the literature, there is not enough data about the procedures to identify patients with MAC at high risk for arrhythmic events. Increased sympathetic and decreased parasympathetic activity is associated with an increased risk of sudden death and ventricular arrhythmia [16]. Therefore, it is important to evaluate autonomic functions in identifying high-risk patients for sudden death.

Analysis of HRR parameters is one of the inexpensive and noninvasive methods that can be used to evaluate cardiac autonomic functions [7,8]. The combination of sympathetic withdrawal and parasympathetic reactivation after exercise regulates HRR. In one study, abnormal HRR response was an important indicator of impaired autonomic function, and increased mortality in patients with decreased HRR was more likely to be due to cardiac autonomic dysfunction than underlying coronary artery disease [6,17]. In our study, it was shown that there was

a significant decrease in HRR1, HRR2 and HRR3 in individuals with MAC. These findings suggest that the decrease in HRR is may be one of the predictors of increased cardiac death in people with MAC.

Limitations

Our study presents some limitations. Our study is a single center and the number of subjects is relatively low. Adults consisted of both MAC and control groups. Therefore, further studies are needed to investigate whether the results of our study can be applied to young and old population.

Conclusion

Looking at the relationship between HRR and MAC; HRR can be used as an indicator to identify patients at higher risk for atherosclerotic burden and arrhythmia in individuals with MAC. Closer follow-up of arrhythmia and risk of sudden cardiac death can be arranged in individuals with MAC and decreased HRR. However, multicenter, large-scale, randomized and prospective studies are required to clarify this hypothesis.

Competing interests
The authors declare that they have no competing interest.

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Ethical approval
The study was approved by Presidency of T.C. Bozok University Ethics Committee.

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