ORIGINAL ARTICLE

Evaluation of increase in intraventricular gradient and dynamic obstruction during exercise stress test in competitive runners

Profesyonel koşucularda egzersiz sırasında intraventriküler gradient artışı ve dinamik obstrüksiyonun değerlendirilmesi

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ABSTRACT

Objective: Sudden cardiac death in athletes is one of the most tragic health events seen both in our country and all over the world. In some of those athletes, there is no obvious structural abnormality. Dynamic changes in intracardiac hemodynamics during exercise may be a cause for sudden death in these athletes, the impact of exercise on intracardiac gradient and cardiac hemodynamic parameters in athletes was compared with healthy controls.

Methods: A total of 21 professional male athletes and 21 healthy male controls were included in the study. Transthoracic echocardiography was performed in all participants both at rest and maximal exercise level to assess the intraventricular gradient (IVG) and cardiac systolic and diastolic functions. Abnormal IVG was defined as gradient of >30 mm Hg at peak exercise level.

Results: Both groups reached the level of predicted maximum exercise. There was no exercise limiting symptom among participants during exercise test. The athletes revealed a higher maximum peak systolic IVG at baseline and after exercise in comparison with the control group. None of the participants showed an abnormal IVG level.

Conclusion: Our results showed that there was no dynamic intraventricular obstruction with aerobic exercise in subjects with a structurally normal heart.

ÖZET

Amaç: Atletlerde ani kardiyak ölüm hem ülkemizde hem de dünyada en üzücü olaylardan biridir. Ani ölümle kaybedilen bu atletlerin bir kısmında açık bir yapısal kalp anormalliği bulunmamaktadır. Dolayısıyla bu çalışmada egzersizin ventrikül içi basınç farkı ve kardiyak hemodinamik parametreler üzerine etkisi atletlerde ve sağlıklı kontrol grubunda karşılaştırılmıştır.

Yöntemler: Çalışmamıza 21 profesyonel erkek koşucu ve 21 sağlıklı erkek kontrol grubu olarak alındı. Tüm katılımcılara hem istirahatte hem de maksimal egzersiz düzeyinde iken transtorasik ekokardiyografi yapılarak ventrikül içi basınç farkı ve kardiyak sistolik ve diyastolik fonksiyonlar değerlendirildi. Zirve egzersiz düzeyinde ventrikül içi basınç farkının >30 mm Hg saptanması anormal artmış basınç farkı olarak kabul edildi.

Bulgular: Her iki gruptaki katılımcıların tamamı öngörülen maksimum egzersiz düzeyine ulaştı. Katılımcıların hiçbirinde maksimum egzersiz düzeyine ulaşmayı engelleyen bir semptom gelişmedi. Atletlerde hem bazal ölçümlerde hem de maksimum egzersiz sonrasındaki ölçümlerde zirve sistolik ventrikül içi basınç farkı kontrol grubundan daha yüksek bulundu. Hiçbir bireyde anormal artmış zirve sistolik ventrikül basınç farkı saptanmadı.

Sonuç: Bulgularımız aerobik egzersizin yapısal olarak normal kalbe sahip bireylerde ventrikül içi dinamik obstrüksiyona yol açmadığını ortaya koydu.

Sudden death of the young is one of the most tragic health events seen in our country and around the world. Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden cardiac death (SCD) among the young, and the second most common cause is coronary artery disease.[1–3] The risk of SCD is 2.8-fold higher in athletes than in non-athletes.[4,5] Increased risk has been found to be associated with male gender.[6] Approximately 20% to 25% of the deaths occur during participation in sports.[7] SCD frequently occurs in the early recovery period after peak exercise or during the exertion period of physical activity. In-

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creased risk has been found in athletes without any structural heart disease.[6] Myocardial hypercontraction during exertion causes intraventricular pressure overload, thus left ventricle outflow tract (LVOT) dynamic obstruction can occur. Both insufficient perfusion of the heart via the coronary arteries due to LVOT dynamic obstruction and an increase in myocardial oxygen demand during exercise can lead to myocardial ischemia. Hence, myocardial ischemia may facilitate the provocation of lethal ventricular arrhythmia.

Abbreviations:

HCM	*Hypertrophic cardiomyopathy*
IVG	*Intraventricular gradient*
LV	*Left ventricle*
LVOT	*Left ventricle outflow tract*
MET	*Metabolic equivalent of task*
SCD	*Sudden cardiac death*

Furthermore, the majority of cardiac conditions that cause SCD in athletes may be asymptomatic. SCD is rare, though there is a paucity of data to quantify the athletes at risk. Evaluation of intraventricular gradient (IVG), which is increased by exercise, can be useful to determine the risk of SCD in competitive athletes without warning symptoms.

The aim of the present study was to use echocardiographic methods to evaluate the effect of exercise on the increase in IVG and on cardiac hemodynamic functions in professional male athletes without structural heart disease.

METHODS

In the present study, 21 male professional marathon runners aged 18 to 68 and 21 gender- matched healthy controls were enrolled. All of the runners had been training intensively for at least 5 years. Prior to data collection, the study was approved by the Eskisehir Osmangazi University institutional ethics review committee, and written, informed consent was obtained from each participant.

A detailed cardiovascular and systemic examination of all of the participants was performed at the beginning of the study, including demographic data and anthropometric measures of weight, height, and body mass index (weight/height^2; kg/m^2). Biochemical and hematological measurements were also obtained from all of the study participants.

Echocardiography was performed with GE Vingmed Vivid 5 system (General Electric Vingmed Ultrasound AS, Horten, Norway) ultrasound machine and a 3S-RS (3.5 MHz) probe. A single-lead ECG was recorded continuously during the echocardiographic examination. Two-dimensional and M-mode images were acquired from the parasternal long and short axis and apical 4-chamber views. All measurements were averaged from 3 cardiac cycles. Two-dimensional echocardiographic measurements were performed according to the standards outlined by the American Society of Echocardiography.[8]

Mitral inflow velocity was evaluated using pulsed-wave Doppler echocardiography with the sample volume placed at the tip of the mitral leaflets in the apical 4-chamber view. Diastolic peak early (E) and peak late (A) transmittal flow velocity, peak E to peak A velocity (E/A), deceleration time of peak E velocity, and isovolumetric relaxation time were measured. Tissue Doppler imaging was performed in the apical 4-chamber view using a 5-mm pulsed Doppler sample volume with the minimum optimal gain possible to obtain the best signal-to-noise ratio. In apical 4-chamber view, the pulsed Doppler sample volume was subsequently placed at the level of the left ventricle (LV) lateral mitral annulus. The myocardial peak systolic (Sm), and early diastolic (E') velocity, and late diastolic (A') velocity were obtained from the lateral wall of the LV.[9]

Echocardiography was performed in the left lateral decubitus position at rest. IVG was measured in the lateral decubitus and upright positions at rest using continuous-wave Doppler. Each participant performed the treadmill exercise test with the Bruce protocol[10] until their heart rate reached 85% of target heart rate (220-age) and was closely monitored for the development of any cardiovascular symptoms. The exercise workload was defined as the total metabolic equivalent (MET) achieved during exercise. In addition, IVG was measured within 30 to 60 seconds after peak treadmill exercise in the lateral decubitus and upright positions. Furthermore, hemodynamic functions of IVG and systolic and diastolic functions were evaluated with echocardiography at rest and peak treadmill exercise. LVOT obstruction in HCM was defined as a resting LVOT gradient of ≥30 mm Hg, and severe obstruction was defined as ≥50 mm Hg.[11,12] As previously published, an estimated instantaneous outflow gradient of at least 30 mm Hg according to the continuous-wave Doppler echocardiography was accepted as increased intraventricular gradient in the present study. The groups were compared using the development of cardiac symptoms, and systolic and diastolic functions within each group,

and between groups with respect to the presence or absence of an increase in IVG. Ultimately, the development of symptoms, the frequency in the increase of IVG, systolic and diastolic functions were compared between the athletes and controls. In addition, the potential relationship between the frequency in the increase of IVG and increased IVG, cardiovascular symptoms, and LV functions in professional athletes and healthy adults during exercise were examined.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY USA). The variables were expressed as mean±SD. The variables were tested for normal distribution using the Shapiro-Wilk test. The independent samples t-test was used to analyze normally distributed variables and the Mann-Whitney U-test was used for the analysis of non-normally distributed variables. Correlation was performed using Spearman's correlation coefficient (r). Categorical data were presented as frequencies and percentages, and were analyzed using Pearson's chi-square test, the continuity correction chi-square test, and Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

RESULTS

In this study, 21 male professional runners and 21 gender-matched healthy controls were evaluated (mean age: 32.2±11.7 years). The marathon runner group was older than the control group (37.75±14.8 years *vs*. 26.95±2.8 years; p=0.004) and the mean heart rate was significantly lower in the professional athletes (68.1±12.7 bpm *vs*. 87.9±13.9 bpm, p<0.001). Height, weight, and systolic and diastolic blood pressure were similar between groups. Hematological and biochemical parameters were also similar, with the exception of triglyceride level. The athletes' triglyceride level was significantly lower than that of the controls (146±106 mg/dL *vs*. 150±113 mg/dL; p=0.004). Demographic, clinical, and laboratory findings of the groups are presented in Table 1.

When compared with the control group, the ath-

Table 1. Demographic, clinical, and laboratory findings of the groups

	Athletes (n=21)	Control (n=21)	*p*
	Mean±SD	Mean±SD	
Height (cm)	176.2±7	176.3±6.2	0.93
Weight (kg)	70.8±13.3	74.7±9.9	0.3
Body mass index (kg/m^2)	22.7±3.2	24±2.7	0.18
Systolic blood pressure (mm Hg)	114.2±10.4	112.5±11.6	0.61
Diastolic blood pressure (mm Hg)	72.2±6.6	73.2±8.6	0.68
Heart rate (bpm)	68.1±12.7	87.9±13.9	<0.001
Hemoglobin (g/dL)	15.2±1.1	15.6±0.88	0.28
White blood cells (/mm^3)	6933±1088	10338±1501	0.35
Platelet (10^3/mm^3)	222.44±37.4	222.94±45.4	0.97
Glucose (mg/dL)	83.58±15.48	85.41±8.51	0.67
Blood urea nitrogen (mg/dL)	14.51±3.23	13.07±3.75	0.23
Creatinine (mg/dL)	0.96±0.18	1.01±0.20	0.44
Alanine aminotransferase (U/L)	33.11±16.51	29.44±20.20	0.56
Aspartate aminotransferase (U/L)	42.82±15.01	31.16±16.01	0.34
Total cholesterol (mg/dL)	199±33	173±47	0.71
Trigliseride (mg/dL)	146±106	150±113	0.004
High density lipoprotein (mg/dL)	60.73±13.05	46.84±9.91	0.14
Low density lipoprotein (mg/dL)	129.60±31.44	108.62±39.83	0.91

SD: Standard deviation.

letes had a larger right atrial diameter (39.21±3.93 mm *vs*. 34.60±2.58 mm; p<0.001) as seen on echocardiography. In the athletes, the left ventricle, right ventricle, left atrial, and aortic root diameters were also larger than in the controls, but the difference was not statistically significant (p>0.05). Moreover, the interventricular septum and posterior free wall thickness were also larger in the athletes, but without significance (p>0.05). Diastolic functions were similar between groups according to Doppler and tissue Doppler parameters (E, A, E', A', Sm). The systolic and diastolic time intervals and the systolic ejection time were significantly longer in the athletes than in control group participants (292.39±26.86 milliseconds *vs*. 255.70±36.05 milliseconds; p<0.001). Echocardiographic findings are provided in Table 2.

The treadmill exercise test results revealed that the total exercise time was longer in the athlete group than in the control group (15.4±3.2 minutes *vs*. 13±1.05 minutes; p=0.002). As expected, the MET level of professional athletes was greater than that of the control group (16.02±2.25 *vs*. 13.71±1.07; p<0.001). Heart rate at rest was similar between groups, while the peak heart rate was lower in the athletes (174.55±9.59 bpm *vs*. 188.81±18.38 bpm; p=0.004). There were no cardiac or non-cardiac symptoms to prevent the achievement of the maximum level of exercise. Higher IVG measurements in the professional runners were seen in the supine position at rest when compared with the controls (7.86±2.63 mm Hg *vs*. 5.88±1.39 mm Hg; p=0.006). Similarly, IVG measurements during peak exercise in the supine position were higher in the athletes than in the controls (22.6±4.6 mm Hg *vs*. 17.4±3.8 mm Hg; p<0.001). No participant's basal or peak exercise IVG was greater than 30 mm Hg. The IVG data of all of the participants can be seen in Table 3 (Fig. 1).

Table 2. Echocardiographic findings of the study population

	Athletes (n=21)	Control (n=21)	*p*
	Mean±SD	Mean±SD	
Left ventricle end diastolic diameter (mm)	50.3±2.99	46.1±4.58	0.02
Left ventricle end systolic diameter (mm)	31.55±2.54	30.42±3.37	0.23
Posterior wall thickness (mm)	9.25±1.16	9.14±1.35	0.78
Interventricular septum thickness (mm)	9.2±1.79	8.61±1.07	0.21
Ejection fraction (%)	67±3.4	65.1±3.1	0.07
Aortic diameter (mm)	26.36±2.75	25.80±3.79	0.59
Left atrial diameter (mm)	32.70±2.88	31.61±3.07	0.25
Right ventricle end diastolic diameter (mm)	36.05±4.02	34.60±3.18	0.22
Right atrium (mm)	39.21±3.93	34.60±2.58	<0.001
Mitral E (cm/s)	0.97±0.6	0.81±0.15	0.248
Mitral A (cm/s)	057±0.19	0.57±0.08	0.993
E Dec (ms)	181.80±45.17	157.90±37.09	0.071
A Dec (ms)	95.25±25.50	100.29±21.92	0.501
Isovolumetric relaxation time (ms)	97.30±30.94	76.80±14.43	0.009
Isovolumetric contraction time (ms)	70.95±17.93	73.57±18.81	0.651
Ejection time (ms)	292.39±26.86	255.70±36.05	<0.001
E time (ms)	226.65±38.09	192.71±40.39	0.009
A time (ms)	25.60±5.72	29.18±6.36	0.78
Lateral S (cm/s)	0.089±0.02	0.025±0.005	0.85
Lateral E' (cm/s)	0.150±0.033	0.042±0.009	0.35
Lateral A'	0.36±0.008	0.37±0.008	0.51

SD: Standard deviation; Mitral E: The peak early filling of mitral inflow; Mitral A: The peak late diastolic filling of mitral inflow; A dec: Mitral A decelaration time; E dec: Mitral E decelaration time.

Table 3. Findings of exercise stress test in study popuation

	Athletes (n=21)	Control (n=21)	*p*
	Mean±SD	Mean±SD	
Exercise time (min)	15.4±3.2	13±1.05	0.002
Estimated metabolic equivalents of task	16.02±2.25	13.71±1.07	<0.001
Peak systolic blood pressure (mm Hg)	148.33±22.59	141.05±16.37	0.307
Peak diastolic blood pressure (mm Hg)	71.66±9.12	76.05±13.07	0.319
Peak heart rate (bpm)	174.55±9.59	188.81±18.38	0.004
Rest intraventricular gradient (supine) (mm Hg)	7.86±2.63	5.88±1.39	0.006
Rest intraventricular gradient (upright) (mm Hg)	5.53±1.83	4.6±1.2	0.06
Peak intraventricular gradient (supine) (mm Hg)	22.6±4.6	17.4±3.8	<0.001
Peak intraventricular gradient (upright) (mm Hg)	14.3±4.8	13.6±3.2	0.5

SD: Standard deviation.

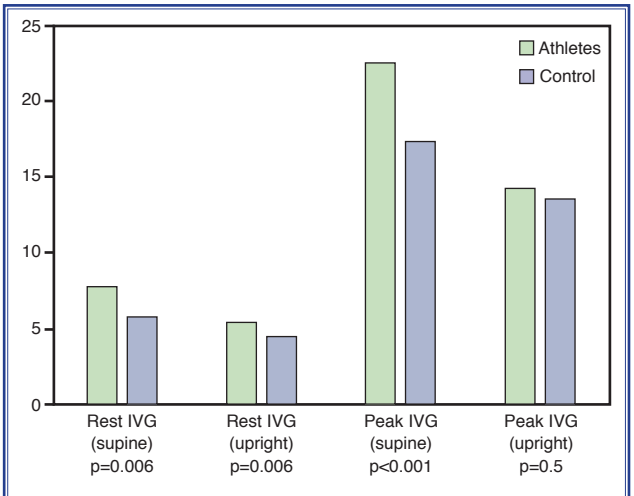

Figure 1. Comparison of IVG (intraventricular gradient) among groups.

DISCUSSION

Myocardial hypercontraction during exertion can cause intraventricular pressure overload, and thus LVOT dynamic obstruction, which could lead to myocardial ischemia. Beta-blocker therapy has been demonstrated to provide symptomatic relief for athletes who have LVOT obstruction induced by exercise.[3,13] Maron et al.[11] reported that patients with IVG (defined as a gradient of at least 30 mm Hg) had an increased risk of death from HCM or progression to severe congestive symptoms of more than 4 times that of patients without obstruction. The threshold value for the outflow tract gradient that proved to be clinically relevant was relatively low, namely, 30 mm Hg. Our study population contained marathon runners who primarily perform dynamic exercise. Dynamic exercise causes a volume load on the LV, whereas static exercise causes a pressure load. A relatively lower incidence of LV wall thickness was encountered in athletes performing dynamic exercise.[14] IVG >30 mm Hg was not observed in the athletes participating in the present study as a result of the absence of LV hypertrophy. Our study results support the association between IVG during exercise and symptoms that has previously been reported.[15,16] Cotrim et al.[16] demonstrated that 52 (37.4%) of 139 athletes with normal echocardiographic findings and positive screening test results developed IVG, suggesting that the development of IVG during exercise was possibly involved in the genesis of the symptoms. Nonsignificant IVG (<30 mm Hg) in our study was postulated to indicate that the participants had no symptoms.

Our results demonstrated that the competitive athletes (runners) had a higher IVG than the control group, both at rest and peak exercise. Studies related to SCD in the young population have been based on athletes. The most common cause of SCD in athletes is as a consequence of an underlying cardiac abnormality. In athletes younger than 35 years of age, the vast majority of instances of SCD are due to HCM, while in athletes over the age of 35 years, the main cause of SCD is coronary artery disease, as in the general population.[17–31] SCD in athletes occurs most commonly in participants of team sports, such as basketball and football, and the male gender has a 9-fold higher risk of death.[3] Previously, it has been reported that the incidence of SCD in athletes was between 1/50,000 and 1/300,000.[18–21]

Furthermore, a positive correlation between exercise intensity and sudden death has been demonstrated.[31] According to data from the Minneapolis Heart Institute Foundation Registry, the distribution of cardiovascular causes of sudden death in 1435 young competitive athletes indicated that HCM was the cause in 36% and coronary artery anomalies were the cause in 17% of the population.[17] In a recent study, 21% of all SCD victims had no evidence of structural abnormalities even after a detailed gross and histological examination of the heart.[32] Among 6.3 million military recruits age 18 to 35 years, cardiac causes were attributed to half (51%) of sudden deaths. One-third of SCD victims had an anomalous coronary artery. More than one-third of the deaths had no explanation.[22] SCD in this population can be hypothesized to be due to a long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, or abuse of anabolic steroids.[23–26] We compared marathon runners without structural abnormalities and control subjects with respect to IVG during exercise as a potential cause of SCD. We could not demonstrate IVG in our study population.

The study data indicated that the cardiac chambers and aortic diameters were greater in the athletes than in the controls. The chronic adaptation of the cardiovascular system to repeated bouts of dynamic exercise results in an increase in maximal oxygen uptake. Athletes who train in sports with a high dynamic component have a large chamber.[1,33] Dynamic exercise performed with a large muscle mass causes a marked increase in oxygen consumption. There is a substantial increase in cardiac output, heart rate, stroke volume, and systolic blood pressure, a moderate increase in mean arterial pressure, and a decrease in diastolic blood pressure.[21] Athletes who train in sports with a high dynamic component have "eccentric" hypertrophy, whereas athletes who participate in sports with a high static component have "concentric" hypertrophy. These changes that occur as a result of rigorous training are referred to as "athlete's heart".[26,27] The degree of hypertrophy associated with athletic physiological adaptations can overlap with HCM, leading to difficulty in distinguishing between the 2 entities. Previous studies in this field have indicated that it takes approximately 2 years of intensive training of at least 5 hours per week to induce these adaptive changes, which are considered to be normal and are reversible with cessation of training.[33,34] The impact of hypertrophy on mortality in professional athletes is uncertain.[28,29] Adaptive cardiac changes should reverse after approximately 3 months of complete halt to vigorous sporting activity, which suggests that they are physiological. In our study, the cardiac chambers of athletes were larger than those of the controls, and the left atrial diameter of the athletes was also significantly enlarged. Our results are compatible with previous, well-established studies.

SCD is a very real public health issue and a personal issue for not only the athletes, but also for nonathletes. Observation of the appropriate measures of prevention and treatment is critical. However, based on the best available evidence, it is evident that conclusively effective measures to reduce athletic SCD remain unknown.[4,35] Occasionally, echocardiography may also be required to assess cardiac structure and function in athletes. It is clear that vigorous exertion transiently increases the risk of SCD in individuals with cardiovascular disease.[36] The general population often has a higher risk of SCD in comparison with an athletic population. In young people (<35 years of age), the incidence of SCD is 0.3 to 3.6 per 100,000 persons per year.[37,38] Among European countries, Turkey has the largest population of young people at 16.6%. SCD is rare, but devastating, especially in a young individual. SCD urgently requires primary prevention, because the first clinical event is often fatal. SCD is a public health issue that has a special effect on the young population and causes social and economic problems.

Aerobic exercise can make a substantial contribution to the well being of people in developing countries. Sports and physical activity are a strong means of prevention of disease, and represent a cost-effective method of improving public health across national populations. However, the media attention given to athletes who experience SCD during a competition can cause skepticism of the benefits of exercise. Previous data indicated that the prevalence of sudden death was 0.75/100,000/year among young nonathletes and 1.6/100,000/year among young athletes.[39] However, a decreased risk of overall mortality, cardiac mortality, and the development of coronary artery disease with regular exercise have been clearly demonstrated in nearly all epidemiological studies.[4] Cardiovascular screening is an obtainable objective and should be mandatory for all athletes. The European Society of Cardiology (ESC) recommends that a history, a physical examination, and a 12-lead ECG be performed before participation in competitive sports.[13,40,41] Al-

though echocardiography is the main diagnostic tool for the recognition of HCM, it is expensive and impractical for screening large populations. A 12-lead ECG has been proposed as an alternative, cost-effective method for population-based screening. Echocardiography is necessary if any pathological finding exists in the preliminary ECG. The prevalence of echocardiographic evidence of LV hypertrophy consistent with HCM is approximately 1/500, or 0.2%, among American adolescents,[42] but the incidence of exercise-related SCD is much lower.[43] We aimed to evaluate the increase in IVG during exercise, which can be a cause of SCD in professional male athletes. But LVOT dynamic obstruction was not demonstrated during strenuous exercise in our participants.

Study limitations

The most important limitation of the current study is the number of study participants. Further controlled studies with more participants are needed. Moreover, there were some technical difficulties with some participants in the evaluation of peak IVG, especially during upright exercise. In these participants there was a 2 to 3-second delay after peak exercise when measuring optimal IVG. In addition, we did not follow up with the participants. A final weakness of this study is the lack of reporting on the aerobic fitness level of the participants, such as maximum rate of oxygen consumption.

Conclusion

LV intraventricular dynamic obstruction did not develop during peak exercise testing in marathon runners with a structurally normal heart and without any symptoms. Our results indicated that in patients with a structurally normal heart, aerobic exercise did not lead to dynamic obstruction.

Conflict-of-interest: None declared.

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