Assessment of autonomic dysfunction and anxiety levels in patients with mitral valve prolapse

Mitral kapak prolapsı olan hastalarda otonomik disfonksiyon ve anksiyete değerlendirmesi

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Objectives: This study aimed to assess autonomic dysfunction parameters and anxiety levels in patients with mitral valve prolapse (MVP).

Study design: We evaluated 33 patients (mean age 25±5 years) with MVP and 14 healthy subjects (mean age 25±4 years). The patients were divided into two groups according to the presence (anatomical MVP, n=11) or absence (MVP syndrome, n=22) of abnormal leaflet thickening (>5 mm). Spielberger's Situational Anxiety Scale (SSAS) and Continuous Anxiety Scale (SCAS) were administered to all the subjects, and heart rates (HR) and arterial blood pressures (BP) were measured in the supine and standing positions.

Results: Mid-systolic click and late systolic murmur were significantly more frequent in patients with anatomical MVP, while nonspecific symptoms such as dyspnea, vertigo, and atypical chest pain were more frequent in patients with MVP syndrome ($p<0.05$). Mitral insufficiency (mild) was significantly more frequent in patients with anatomical MVP (72.7% vs. 22.7%; $p<0.009$). Patients with MVP syndrome had significantly higher SSAS and SCAS scores (41.0±15.6 and 38.5±15.5) compared to patients with anatomical MVP (15.8±7.5 and 17.0±9.1) and controls (14.9±7.4 and 16.9±8.7, respectively; for both $p<0.001$). Orthostatic differences in BP and HR were significantly greater in patients with MVP syndrome than those having anatomical MVP ($p<0.001$ and $p=0.032$, respectively). Orthostatic HR differences showed a significant correlation with SSAS in both MVP groups ($r=0.536$, $p=0.001$) and a significant correlation with SCAS in patients with MVP syndrome ($r=0.523$, $p=0.002$). There was an inverse correlation between orthostatic BP differences and anxiety parameters in all MVP patients ($r=-0.391$, $p=0.025$ for SSAS, and $r=-0.320$, $p=0.048$ for SCAS).

Conclusion: Our data suggest that patients with MVP syndrome have increased autonomic dysfunction and anxiety scores compared to patients with anatomical MVP.

Key words: Anxiety; autonomic nervous system; blood pressure; heart rate; hypotension, orthostatic; mitral valve prolapse.

Amaç: Bu çalışmada mitral kapak prolapsı (MKP) olan hastalarda otonomik fonksiyon bozuklukları ve anksiyete düzeyleri değerlendirildi.

Çalışma planı: Çalışmaya MKP tanısı konan 33 hasta (ort. yaş 25±5) ve 14 sağlıklı kişi (ort. yaş 25±4) alındı. Hastalar kapakçık kalınlığında anormal artış (>5 mm) olup (anatomik MKP, n=11) olmamasına (MKP sendromu, n=22) göre iki gruba ayrıldı. Hasta ve kontrol gruplarına Spielberger Durumluluk Anksiyete Ölçeği (SDAÖ) ve Spielberger Süreklilik Anksiyete Ölçeği (SSAÖ) uygulandı ve kalp hızı (KH) ve arteryel kan basınçları (KB) sırtüstü yatış ve ayakta pozisyonlarında ölçüldü.

Bulgular: Anatomik MKP'li hastalarda fizik muayenede orta sistolik klik ve geç sistolik üfürüm daha sık görülürken, MKP sendromlu hastalarda nefes darlığı, vertigo, atipik göğüs ağrısı gibi spesifik olmayan semptomlar daha yüksek oranlarda görüldü ($p<0.05$). Mitral yetersizliği (orta derecede) anatomik MKP grubunda anlamlı derecede daha yüksek oranda görüldü (%72.7 ve %22.7; $p<0.009$). Ortalama SDAÖ ve SSAÖ skorları MKP sendromlu hastalarda (41.0±15.6 ve 38.5±15.5) anatomik MKP grubundakilere (15.8±7.5 ve 17.0±9.1) ve kontrollere (14.9±7.4 ve 16.9±8.7) göre anlamlı derecede yüksekti ($p<0.001$). Ortostatik KB ve KH farklılıkları MKP sendromlu grupta anatomik hastalığı olanlara göre anlamlı derecede fazlaydı (sırasıyla, $p<0.001$ ve $p=0.032$). Ortostatik KH farklılıkları her iki MKP grubunda SDAÖ ile anlamlı ilişki gösterirken ($r=0.536$, $p=0.001$), SSAÖ ile sadece MKP sendromlu grupta anlamlı ilişkiliydi ($r=0.523$, $p=0.002$). Ortostatik KB farklılıkları her iki hasta grubunda da aksiyete parametreleri ile negatif ilişkili bulundu (SDAÖ için, $r=-0.391$, $p=0.025$; SSAÖ için $r=-0.320$, $p=0.048$).

Sonuç: Bulgularımız, otonomik fonksiyon bozukluğu ve anksiyete göstergelerinin MKP sendromlu hastalarda anatomik MKP'li olgulara göre daha yüksek olduğunu göstermektedir.

Anahtar sözcükler: Anksiyete; otonomik sinir sistemi; kan basıncı; kalp hızı; hipotansiyon, ortostatik; mitral kapak prolapsı.

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Mitral valve prolapse (MVP) is the most common valvular abnormality affecting 2-6% of the general population.[1,2] It has been classified into two groups: classical MVP (anatomical MVP) which is characterized by leaflet thickening due to increased mucopolysaccharide structure and myxomatous proliferation, and nonclassical MVP (MVP syndrome) which is characterized by dynamic systolic expansion of the mitral annulus due to variable relation of the mitral annulus with left ventricular diameters.[3,4]

Studies investigating anxiety symptoms in MVP have reported inconclusive data.[3-7] The causes of controversies may be related to patient selection, diagnostic criteria, and insufficient anxiety evaluations. Moreover, symptoms of chest pain, palpitation, dyspnea, syncope, and vertigo might be a result of autonomic dysfunction in MVP patients. Only the mechanical phenomenon, the exaggerated movement of the leaflets, cannot explain all these symptoms.[4] These symptoms might be related to an excessive response to adrenergic stimulation and/or abnormalities of the parasympathetic system.[4-8] Additionally, these symptoms may have potential to trigger anxiety.

The present study aimed to assess autonomic dysfunction and anxiety scores in patients with anatomical MVP and MVP syndrome.

PATIENTS AND METHODS

Study patients. Thirty-three consecutive symptomatic patients (mean age 25±5 years) diagnosed as having primary MVP upon referral to our echocardiography laboratory were included in the study. Patients were divided into two groups according to the presence (anatomical MVP, n=11) or absence (MVP syndrome, n=22) of >5 mm leaflet thickening. Fourteen healthy subjects (mean age 25±4 years) with normal left ventricular functions comprised the control group.

Exclusion criteria were use of active drugs for MVP, secondary MVP, primary MVP associated with other congenital abnormalities, history of previous myocardial infarction (MI) or heart failure, presence of a chronic disease (e.g. diabetes mellitus, chronic pulmonary disease, chronic renal insufficiency), anemia, and thyroid dysfunction. Patients with a history of smoking, alcohol intake or substance use, history of traumatic accident within the past year, body mass index ≥30 kg/m^2, hemodynamically significant (moderate-severe) mitral insufficiency or left atrial enlargement (in parasternal long-axis image, anteroposterior diameter >40 mm) on echocardiographic examination were also excluded.

The study was conducted in compliance with the Declaration of Helsinki, and Ethics Committee of our institution approved the study protocol. Informed consent was obtained from all subjects included.

Spielberger's Situational Anxiety Scale (SSAS) and Continuous Anxiety Scale (SCAS) were administered to all the subjects, and tests for autonomic dysfunction were performed.

Echocardiography. Standard echocardiographic examination (GE Vivid 7, Norway) was performed with a 3-MHz sector transducer. For the diagnosis of MVP and exclusion of moderate–severe mitral insufficiency, left atrial diameters were measured from 2-dimensional targeted M-mode echocardiographic tracings in the parasternal long axis. Left ventricular ejection fraction at rest was computed from 2- and 4-chamber views, using a modified Simpson's biplane method. Each representative value was obtained from the average of three consecutive measurements. All measurements were made according to the American Society of Echocardiography guidelines.[9] The images were analyzed by an echocardiographer who was blind to the study design.

Diagnostic interviews. To evaluate axis I disorders, a structured psychiatric interview designed according to the DSM-III criteria was made with all the patients and controls.[10]

The patients were asked to complete a data form containing questions about their psychiatric history and demographic characteristics. A detailed history was taken and especially symptoms of palpitation, dyspnea, chest pain, and vertigo were questioned.

Spielberger's Situational and Continuous Anxiety Scales. To determine the anxiety levels of the patients and controls, SSAS and SCAS, each of which is comprised of 25 items, were used.[11]

Tests for Autonomic Dysfunction. After a relaxing period in a cool room, heart rates and arterial blood pressures of all subjects were measured in the supine position (Braun BP 3510 Easy Click, Germany). Each subject was asked to stand up slowly, and the measurements were repeated one minute after standing. Systolic blood pressure difference was expressed as ΔSBP (supine BP-standing BP) and heart rate difference was expressed as ΔHR (supine HR-standing HR).

Table 1. Social-demographic characteristics of the patient and control groups

	Anatomical MVP (n=11)			MVP syndrome (n=22)			Control group (n=14)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Age (years)			26.2±5.7			24.4±4.5			24.6±3.6
Sex									
Males	5	45.5		10	45.5		6	42.9	
Female	6	54.6		12	54.6		8	57.1	
Body mass index (kg/m^2)			22.3±2.2			21.4±2.0			23.1±4.6
Marital status									
Married	4	36.4		12	54.6		5	35.7	
Single	7	63.6		8	36.4		9	64.3	
Divorced	–			2	9.1		–		
Education									
Elementary school	1	9.1		3	13.6		1	7.1	
Secondary school	3	27.3		5	22.7		2	14.3	
High school	6	54.6		10	45.5		5	35.7	
University	1	9.1		4	18.2		6	42.9	
Occupation									
Housewife	3	27.3		8	36.4		–		
Officer	1	9.1		4	18.2		9	64.3	
Worker	2	18.2		3	13.6		4	28.6	
Student	4	36.4		5	22.7		1	7.1	
Tradesman-merchant	1	9.1		1	4.6		–		
Professional	–			1	4.6		–		

MVP: Mitral valve prolapse.

Psychiatric interviews and anxiety scale tests were performed by a psychiatrist who was blind to the cardiac diagnosis.

Statistical analysis. Values were presented as mean±standard deviation (SD). Qualitative parameters and anxiety score categories for each group were evaluated with the chi-square test or Fisher's exact test. Friedman test was used for the alterations of heart rate and systolic blood pressure and Kruskall-Wallis test was used for heart rate and blood pressure differences. Spearman's rank correlation test was used as a measure of relationship between autonomic dysfunctional parameters and anxiety scores. Calculations were made with SPSS 10 statistical software packet and differences were considered statistically significant when p value was less than 0.05.

RESULTS

Social-demographic characteristics. Social-demographic characteristics of the patient and control groups are summarized in Table 1. The three groups were similar with respect to age, gender, and marital status (p>0.05). There was a statistically significant difference with respect to occupation, mainly because the individuals in the control group were chosen among the hospital staff, making the number of offi-

Table 2. Comparison of physical examination findings and symptoms of patients with anatomical MVP and MVP syndrome

	Anatomical MVP (n=11)		MVP syndrome (n=22)		
	n	%	n	%	*p*
Mid-systolic click	6	54.6	3	13.6	**0.033**
Late-systolic murmur	8	72.7	5	22.7	**0.009**
Palpitation	6	54.6	14	63.6	0.091
Dyspnea	2	18.2	13	59.1	**0.034**
Atypical chest pain	3	27.3	16	72.7	**0.024**
Vertigo	2	18.2	13	59.1	**0.034**
Repolarization abnormalities on the electrocardiogram	2	18.2	11	50.0	0.125

MVP: Mitral valve prolapse.

Table 3. Supine and standing systolic blood pressures and heart rates

	Anatomical MVP (1)	MVP syndrome (2)	Control group (3)	*p (1-2)*	*p (1-3)*	*p* (2-3)
Systolic blood pressure (mmHg)						
Supine	110.9±17.2	105.9±9.2	105.9±10.2			
Standing	108.6±17.6	95.2±10.2	105.4±8.2			
ΔSBP	-2.3±3.4	-10.7±6.0	-0.4±7.7	**<0.001**	0.053	**<0.001**
Heart rate (beat/min)						
Supine	78.1±11.3	78.7±7.8	74.4±10.9			
Standing	88.4±11.2	92.5±9.3	76.1±11.6			
ΔHR	10.3±3.2	13.8±4.5	1.6±4.6	**0.032**	**<0.001**	**<0.001**

cers and workers significantly high. Therefore, after excluding the control group, it was found that occupational distribution was similar in the two patient groups.

Clinical characteristics. On physical examination, mid-systolic click and late systolic murmur were significantly more frequent in patients with anatomical MVP, while nonspecific symptoms such as dyspnea, vertigo, and atypical chest pain were more frequent in patients with MVP syndrome (Table 2). Palpitation and repolarization abnormalities on the electrocardiogram were also more frequent in this group, but these did not reach significance.

Echocardiography. Mitral insufficiency (mild) was significantly more frequent in patients with anatomical MVP (72.7% *vs*. 22.7%; p<0.009). Left atrial diameters were 32.7±4.5 mm and 29.9±3.8 mm, respectively (p>0.05). Left ventricular ejection fraction did not differ significantly in the patient and control groups (66.7± 4.4% for anatomical MVP, 67.2±3.6% for MVP syndrome, and 65.6±4.8% for control group; p>0.05).

Spielberger's Situational and Continuous Anxiety Scale Scores. The Mean SSAS score was 15.8±7.5 in patients with anatomical MVP, 41.0±15.6 in patients with MVP syndrome, and 14.9±7.4 in the control group. Patients with MVP syndrome had significantly higher SSAS scores compared to the control group and anatomical MVP group (p<0.001).

Similarly, patients with MVP syndrome exhibited significantly higher SCAS scores (38.5±15.5) than the control group (16.9±8.7; p<0.001) and anatomical MVP group (17.0±9.1; p<0.001).

When anxiety was defined as SSAS and SCAS scores of above 50 (clear anxiety), six patients with MVP syndrome had an SSAS score of greater than 50 compared to none in the control group and anatomical MVP group. This difference was significant (p=0.02). Similarly, there were no patients exceeding SCAS >50 in the anatomical MVP group and control group, compared to five patients in the MVP syndrome group (p=0.042).

Results of tests for autonomic dysfunction. Baseline systolic blood pressures measured in the supine position did not differ significantly in the three

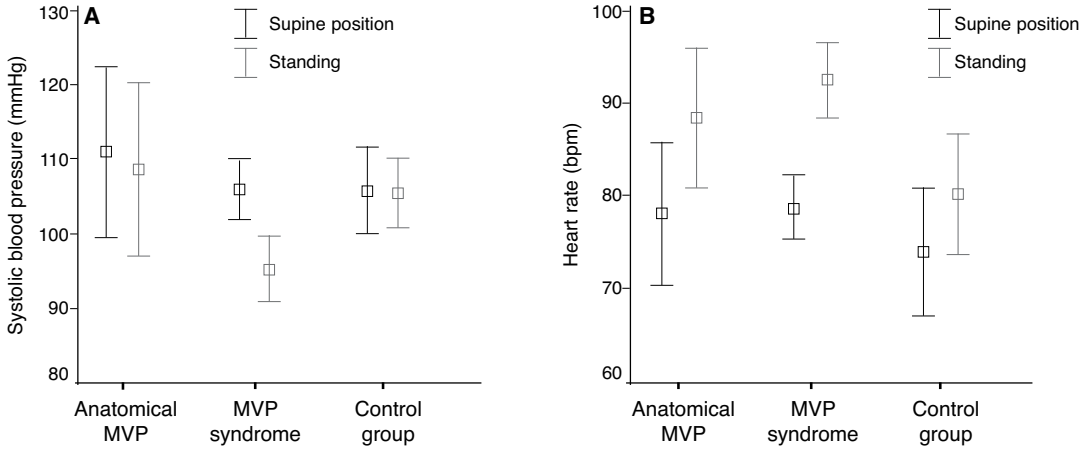

Figure 1. Comparison of **(A)** systolic blood pressures and **(B)** heart rates in the supine and standing positions in the study groups. MVP: Mitral valve prolapse.

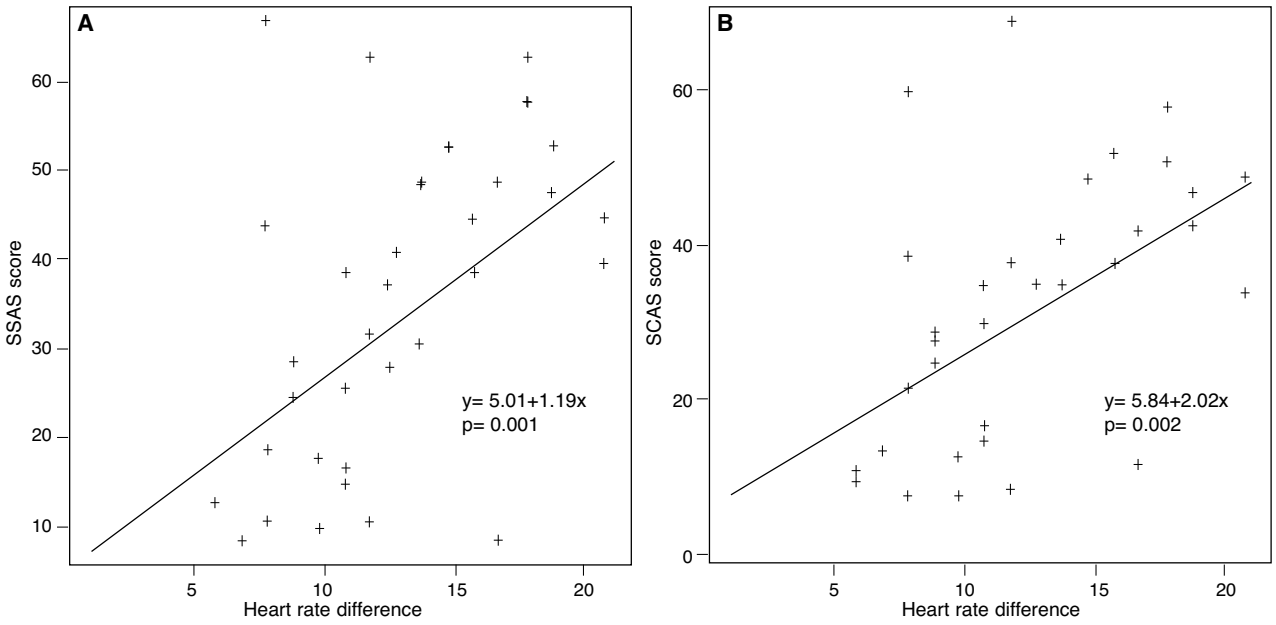

Figure 2. Correlations of **(A)** situational and **(B)** continuous anxiety scores with heart rate changes in patients with mitral valve prolapse. SSAS: Spielberger's Situational Anxiety Scale; SCAS: Spielberger's Continuous Anxiety Scale.

groups (p=0.869; Table 3). The analysis of orthostatic ΔSBP showed that ΔSBP was significantly greater in patients with MVP syndrome than those having anatomical MVP and the control group (p<0.001; Table 3). Patients with anatomical MVP also had a higher blood pressure variability compared to the control group, but this difference did not reach a significant level (p=0.053; Fig. 1a).

Baseline heart rates measured in the supine position were similar in the three groups (p=0.272; Table 3). Within-group comparisons showed statistically significant changes between supine and standing HRs in patients with anatomical MVP and MVP syndrome (p<0.001), but no significant change was seen in the control group (p=0.838; Fig. 1b). Concerning orthostatic ΔHR values, all the patients with MVP showed significant ΔHR values, being more dramatic in patients with MVP syndrome (Table 3).

The relation of autonomic dysfunctional parameters with Spielberger's Situational and Continuous Anxiety Scale scores. A significant correlation between SSAS and ΔHR was found in patients with anatomical MVP and MVP syndrome (r=0.536, p=0.001; Fig. 2a), but no relation was found in the control group. Likewise, a positive correlation between SCAS score and ΔHR was determined in patients with MVP syndrome (r=0.523, p=0.002; Fig. 2b).

There was a significant negative correlation between ΔSBP and anxiety parameters in all MVP patients (r=-0.391, p=0.025 for SSAS, and r=-0.320, p=0.048 for SCAS), whereas no correlation was found in the control group. There was also a strong positive correlation between SCAS and SSAS scores (r=0.941, p<0.001) in all study patients.

DISCUSSION

Mitral valve prolapse is an important clinical condition because of its unique characteristics. It is the most frequently diagnosed cardiac valvular abnormality, affecting 2-6% of the general population, and is the most frequent cause of significant mitral valve regurgitation and the most common substrate for mitral valve endocarditis in Western countries.[1,2]

Mitral valve prolapse has caused confusion and concern for both patients and physicians for several years. Recent studies focusing on epidemiology, pathophysiology, diagnosis, and treatment of this condition have provided a rational approach to the management of patients with MVP. It is important to differentiate between the normal variant forms and the primary form of MVP and MVP subgroups.

Primary MVP occurs mostly as an isolated valve dysfunction, but can also be associated with connective tissue diseases such as Marfan's syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and muscular dystrophy. In addition, MVP also seems to be associated with congenital cardiac abnormalities

such as Ebstein malformation of the tricuspid valve and secundum type atrial septal defect.[3]

Some patients with MVP become symptomatic without significant mitral valve dysfunction. Atypical chest pain, dyspnea, palpitations, vertigo, anxiety, and neuropsychiatric symptoms, which are not correlated with mitral valve function, are described as the MVP syndrome.[3-6] The cause of these symptoms is unknown, but an association between dysfunction of the autonomous nervous system and MVP has been suggested.

The present study aimed to assess autonomic dysfunction and anxiety scores in MVP subgroups and a strong correlation was found between autonomic dysfunction and anxiety scores in patients with MVP.

Despite several cardiologic and psychiatric studies, several issues related to MVP and anxiety remain under debate.[3-7] The most typical MVP is characterized by important mitral valve regurgitation, significant enlargement of the mitral valve leaflets and annulus, elongation of the chordal apparatus, and loss of leaflet apposition. At the other end of the spectrum are patients who have dominant anxiety with mild bowing and normal-appearing leaflets. In the latter group, the management of MVP should be centered on patient education, symptom recognition, and risk management. If symptoms persist, administration of beta-blocker treatment and cooperation with the psychiatry clinics will be useful both for the life quality of patient and for the efficacy of cardiology clinics. Evaluation of the anxiety states more objectively and additional consultation with psychiatry clinics may decrease visits to cardiology clinics.

The role of postural change on mitral valve and left ventricular dynamics is an important feature in patients with MVP. It has been suggested that decrease in cardiac output and cardiac index may be associated with postural change or peripheral blood pooling.[12] Upright posture leads to rapid pooling of 300-600 ml blood in the lower extremities and shifts plasma fluid into surrounding tissues that results in decrease in venous return. Thus, standing up may result in a decrease in cardiac filling pressures and in arterial blood pressure.[12] This results in the stimulation of compensatory reflexes, all of which are under the control of the autonomic nervous system.[13] In case of autonomic dysfunction, reflex mechanisms may not be sufficient enough to maintain arterial blood pressure and a significant decrease in arterial blood pressure is observed. This condition might be so severe as to limit the individual's daily activities. Orthostatic hypotension can be defined as decreases of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure after sudden standing up from the supine position.[14] Although orthostatic changes may not always reach abnormal levels, they can cause some symptoms causing limitations in daily activities. Nausea, chest pain, and vertigo may accompany orthostatic blood pressure changes.[15] Although ΔSBP was significantly higher in patients with MVP syndrome than the anatomical MVP and control groups, we observed a strong negative correlation between ΔSBP and anxiety parameters in all MVP patients (Fig. 2 and Table 3). Increase in sympathetic activity and inappropriate parasympathetic response in these patients may trigger anxiety via autonomic dysfunctional signs.[6-8]

Among the predicted arrythmia mechanisms frequently seen in MVP are stimulation of atrial pacemakers by the effects of prolapsed leaflets or mitral leak jets and stimulation of electrically active beta-adrenoreceptors placed on the mitral leaflets.[16] It has been suggested that these arrhythmias may have a role on anxiety and other symptoms.

In our study, we observed a strong correlation between heart rate changes and anxiety scores in patients with MVP (Fig. 2). Determination of high anxiety scores with the high frequency of atypical complaints particularly in patients with MVP syndrome suggests that the relative enlargement of the mitral annulus due to increased sympathetic activity may trigger the symptoms. These autonomic abnormalities may be a result of defective sensing, inadequate central processing, or altered end-organ responsiveness, with or without underlying structural abnormalities of the nervous system.[8]

It has been suggested that autonomic dysfunction may be the main mechanism in patients with MVP syndrome. A vicious cycle involving anxiety and cardiac symptoms may be the cause. Under these circumstances, approach to the evaluation of these patients and their treatment will be different from that to patients with anatomical MVP.

It is known that only a small percentage of patients with documented MVP develop complications. The risk for developing complications such as infective endocarditis, stroke, and severe mitral insufficiency increases with age, male sex, elevated blood pressure, increased body weight, and annular dilatation, mak-

ing the prognosis worse.[1,17,18] During the follow-up of MVP patients with leaflet thickening, redundancy, and/or mitral insufficiency in cardiology departments, informing them about the probable MVP-related complications and hypertension control, which is a risk factor for the progression of valvular insufficiency, should not be ignored.[19] Beta-blockers may be useful in the control of hypertension and possible arrhythmias in these patients.[16]

Although only a small percentage of patients with documented MVP develop complications, evaluating not only the anatomical structures, but also the symptoms, effects of symptoms on life quality, autonomic dysfunction indicators, and anxiety levels will increase productivity.

Limitations. In a small-sample and cross-sectional design, this study identified relationships between anxiety and MVP more clearly in a homogenous group. Although palpitation was evaluated as a symptom, no objective arrhythmia analysis with ECG-Holter recording was performed. On greater scales, controlled and multicenter studies will be useful in clarifying this relationship.

In conclusion, patients with MVP syndrome exhibit increased anxiety scores and orthostatic changes in heart rate and systolic blood pressure compared to patients with anatomical MVP and healthy controls. The classification of MVP on the basis of mitral leaflet thickness and evaluation of autonomic dysfunction and anxiety levels in MVP subgroups may lead to further investigations. More focus on this topic will enhance the cooperative work of diverse medical departments, increase patients' benefits, and decrease unnecessary diagnostic tests and observations, resulting in a more rational use of the sources.

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