Assessment of Left Ventricular Systolic Function in Patients with Idiopathic Mitral Valve Prolapse Using Dobutamine Stress Echocardiography

HAKAN TIKİZ, M.D., YÜCEL BALBAY, M.D., TEVFIK KURAL, M.D., SİBER GÖKSEL, M.D.

Department of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara, Turkey

Summary

Background: Some previous studies performed with radionuclide ventriculography and thallium scintigraphy reported that patients with idiopathic mitral valve prolapse (MVP) had some degree of left ventricular (LV) systolic dysfunction and that this dysfunction was more commonly found in symptomatic patients.

Hypothesis: The aim of the present prospective study was to investigate LV systolic function and its relationship with symptoms in patients with MVP with dobutamine stress test without associated certain mitral regurgitation and coronary artery disease.

Methods: Thirty-three patients with echocardiographically diagnosed idiopathic MVP were enrolled into the study and were divided into two groups as symptomatic (MVP-s) and asymptomatic (MVP-a). Patients underwent dobutamine stress echocardiography (DSE) to determine wall motion abnormalities and ejection fraction (EF) changes during rest state and increased heart rates. Results were compared with the DSE findings of 25 healthy individuals.

Results: Symptomatic patients (MVP-s) had lower EFs during the pretest period than the control group ($59.0 \pm 4.8\%$ and $68.3 \pm 5.7\%$, respectively, $p < 0.05$). Basal wall motion abnormalities were found in one patient in the MVP-a group (6%) and in two patients in the MVP-s group (12%). During DSE, new wall motion abnormalities (inferoapical dyskinesia) occurred in two patients in the MVP-s group at submaximal heart rates. For EF values calculated when patients reached submaximal heart rate, the MVP-s group showed only a $2.7 \pm 3.1\%$ increase from baseline values. This increase was $5.1 \pm$

3.8% in the MVP-a group and $9.3 \pm 4.3\%$ in the control group ($p < 0.05$ between MVP-s and control groups).

Conclusion: There is a close relationship between symptoms and ventricular function in patients with idiopathic MVP, and although many asymptomatic patients had nearly normal LV function, a subgroup of symptomatic patients showed diminished LV function and wall motion abnormalities.

Key words: idiopathic mitral valve prolapse, left ventricle, systolic function, dobutamine stress test

Introduction

Idiopathic mitral valve prolapse (MVP) is characterized by myxomatous degeneration of the mitral valve and mid-systolic click or late systolic murmur. Symptoms such as typical or atypical chest pain, decrease in effort capacity, and presyncope or syncope, are frequent, suggesting that MVP could have a myocardial component^{1–4} and may even progress to a cardiomyopathic condition.^{5,6} Various studies done on patients with MVP have shown that since some have autonomous nervous system disorders, MVP may be a syndrome instead of an isolated valve disease.^{7–10} The typical or atypical chest pain, ventricular arrhythmias, and electrocardiogram (ECG) changes seen in this disorder may also simulate coronary artery disease (CAD).¹¹

Some studies performed with radionuclide ventriculography suggest that ejection fraction (EF) does not show a sufficient increase during exercise in patients with MVP.^{12–14} Moreover, it has been claimed that the EF values are low in symptomatic compared with asymptomatic patients.¹⁵ Even though the relationship between symptoms and left ventricular (LV) systolic dysfunction is not certain, it has been suggested that myocardial fibrosis and mitochondrial degeneration seen around papillary muscle and the ischemia caused by abnormal chordal stretching or reflex coronary vasospasm are the causes of wall motion abnormalities and symptoms.^{16,17}

In this study, dobutamine stress echocardiography (DSE) was performed to evaluate LV systolic function in patients with idiopathic MVP without CAD. Despite extensive literature searches of Medline and Index Medicus for DSE evaluation of systolic function and wall motion abnormalities in MVP, we identified no previous relevant study.

Address for reprints:

Dr. Hakan Tikiz
Taskent sokak, Ersan Apt 27/6
06600 Kurtulus,
Ankara, Turkey

Received: August 19, 1999

Accepted with revision: October 28, 1999

Methods

This prospective study enrolled 33 echocardiographically diagnosed consecutive patients with idiopathic MVP. The major and minor diagnostic criteria described by Perloff *et al.*, were used in the diagnosis of idiopathic MVP.¹⁸

Patients with MVP were further divided into two subgroups: symptomatic (MVP-s) (n = 17) and asymptomatic (MVP-a) (n = 16), according to symptoms such as typical or atypical chest pain, palpitations, near-syncope, or syncope. Patients with a history of rheumatic valve disease, hypertension, CAD, congenital heart disease, diabetes mellitus, cardiomyopathy, collagen tissue disease, hyperthyroidism, as well as patients with mitral regurgitation (MR) > 1° were excluded from the study. Beta blockers and Ca²⁺ channel blockers were stopped 72 h before the study began. The control group comprised 25 patients with angiographically normal coronary arteries and normal echocardiographic findings. The control and MVP groups were compatible with regard to age and body surface area.

Echocardiographic Technique

Basal echocardiographic examinations were performed in the 30° lateral position with a 3.75 MHz transducer connected to a Toshiba SSA-270A ultrasound system (Toshiba America Medical Systems, Inc., Tustin, Calif., USA). Left ventricular end-systolic and end-diastolic diameters were measured from the M-mode parasternal long axis; basal wall motion abnormalities and regurgitation were detected with two-dimensional and color Doppler echocardiography, respectively, in parasternal and apical three- and four-chamber views.

Dobutamine Stress Test

Dobutamine stress test was performed using a Freeland computer system (Freeland Systems, Inc., Boulder, Col., USA) with a 3.75 MHz transducer connected to a Toshiba SSA-270A ultrasound system. The recordings were taken in the 30° lateral position. Dobutamine stress echocardiograms were performed using a well-known protocol described by Markovitz *et al.*¹⁹ According to this protocol, dobutamine was administered as a continuous intravenous infusion in 5-min stages at doses of 5, 10, 20, 30 µg/kg/min. Heart rate was continuously monitored and blood pressure was measured every 5 min. Echocardiographic images were digitized at baseline, during 10 µg/kg/min infusion, at peak dobutamine infusion, and at 10 min of recovery, and recorded on a Freeland computer system. With this system it was possible to divide one cardiac cycle into eight intervals of 50 ms each, and it was possible to analyze each interval for wall motion abnormalities and to measure EF values with the modified Simpson formula. The test was prematurely interrupted if severe hypertension (systolic blood pressure > 220 mmHg or diastolic blood pressure > 120 mmHg) or major ventricular arrhythmias developed, or when the heart rate reached 85% of age-predicted maximum heart rate (submaximal heart rate). When submaximal heart rate could not be reached, 1 mg of atropine was administered intravenously.

All echocardiographic recordings were reviewed by an observer blinded to the patients' clinical data and who was an expert in DSE. For the purpose of analysis, the left ventricle was divided into 16 segments and wall motion was assessed in a qualitative manner and graded as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic, as described by the American Society of Echocardiography.²⁰ End-diastolic and end-systolic volumes and EF were calculated from the selected views of a cardiac cycle by using the modified Simpson method.

Coronary Angiography

Patients aged > 35 years underwent selective coronary angiography and left ventriculography. Patients with CAD were excluded from the study. Patients aged < 35 years only underwent an ECG treadmill test and were enrolled into the study only if the tests were negative.

Statistical Analysis

For statistical analysis of data, the Student's *t*-test and the chi-square test were used for comparison of unpaired data, and the analysis of variance (ANOVA) test was used to compare more than two groups. A value of *p* < 0.05 was considered statistically significant. All values are expressed as mean ± standard deviation.

Results

Clinical and echocardiographic results of 33 patients and the control group enrolled into the study are summarized in Table I. There was no significant difference among the three groups except for mild MR. Dobutamine stress echocardiography was well tolerated among the patients. There was no complication during DSE other than atypical chest pain, dyspnea, flushing, and atrial or ventricular premature contractions. There was no significant difference among the three groups in heart rate or systolic blood pressure during basal and peak doses. Atypical

TABLE I Clinical and basal echocardiographical data of both groups

	Control group (n = 25)	MVP-a (n=16)	MVP-s (n=17)	p Value
Age (years)	37.3 ± 9.5	33.20 ± 7.0	35.2 ± 8.1	NS
Surface area (m ²)	1.82 ± 0.35	1.70 ± 0.22	1.68 ± 0.31	NS
Heart rate (beats/min)	77 ± 6	74 ± 5	72 ± 6	NS
LV end-diastolic diameter (cm)	4.6 ± 0.4	4.7 ± 0.5	4.9 ± 0.5	NS
LV end-systolic diameter (cm)	3.1 ± 0.3	3.0 ± 0.4	3.2 ± 0.4	NS
LA diameter (cm)	2.9 ± 0.6	3.2 ± 0.4	3.4 ± 0.5	NS
Mitral regurgitation ^b	—	4	5	0.01 ^a

^a Statistical difference between the control group and the others.

^b Maximal 1° mitral regurgitation.

Abbreviations: MVP = mitral valve proapse, MVP-a = asymptomatic MVP group, MVP-s = symptomatic MVP group, LV = left ventricular, LA = left atrial.

chest pain was reported by 1 patient in the control group, 3 patients in the MVP-a group, and 12 patients in the MVP-s group without an ST-T segment change during DSE. Intravenous atropine was infused in two patients because they could not reach the target heart rate during DSE. Wall motion abnormality was detected in one patient in the MVP-a group and in two patients in the MVP-s group during basal recordings.

New wall motion abnormality was not detected during the peak stage of DSE among the control and MVP-a group, but was detected in two patients in the MVP-s group (dyskinesia in the inferoapical region); in addition, bigeminy ventricular premature contractions were detected in these two patients. No patient suffered sustained arrhythmias, and none required interruption of the test (Table II).

Before starting DSE, basal EFs were calculated as $68.3 \pm 5.7\%$ in the control group, $63.1 \pm 5.2\%$ in the asymptomatic group, and $59.0 \pm 3.8\%$ in the symptomatic group. There was a significant difference between the control and MVP-s group in EF values ($p < 0.05$) (Table III). At the peak stage of DSE, EF values were calculated as $76.1 \pm 6.3\%$ in the control, $68.3 \pm 5.9\%$ in the MVP-a, and $62.4 \pm 4.6\%$ in the MVP-s groups. A statistically significant difference was found between the control and MVP-s groups ($p < 0.05$) (Table IV). Between the basal and peak stage of DSE, there was an increase in EF of $2.7 \pm 3.1\%$ in the symptomatic group, of $5.3 \pm 3.4\%$ in the asymptomatic group, and of $9.3 \pm 5.3\%$ in the control group. There was a significant difference between the control and MVP-s groups ($p < 0.05$) (Table V, Fig. 1).

Discussion

Mitral valve prolapse has become a commonly recognized finding, occurring in 2.5 to 5% of the general population.¹¹ Although the cause(s) and accompanying anatomic features of primary mitral valve prolapse are unsettled, histopathologic studies have shown that widespread abnormalities are present in various connective tissue components of the leaflets and chordae tendineae, a condition that is called "myxomatous degeneration."^{21, 22}

Besides localized valve abnormality, the frequent occurrence of typical or atypical chest pain, ventricular arrhythmias or ECG abnormalities decrease in effort capacity, presyncope

TABLE II Dobutamine stress test data of both groups

	Control group (n = 25)	MVP-a (n = 16)	MVP-s (n = 17)	p Value
Basal systolic TA (mmHg)	118 ± 11	111 ± 15	105 ± 18	NS
Systolic TA in peak DST (mmHg)	142 ± 28	145 ± 22	131 ± 20	NS
IV atropine	1	1	—	NS
Chest pain	1	3	12	0.01 ^a
APS	—	1	3	NS
VPS				
Rare	2	4	5	NS
Bigeminy	—	—	2	NS
ST-segment depression	—	—	—	NS
Wall motion abnormality				
Basal	—	1	2	NS
At peak DSE	—	—	2	NS

^a Statistical difference between MVP-s and control, and MVP-a group.

Abbreviations: TA = arterial pressure, DST = dobutamine stress test, IV = intravenous, APS = atrial extrasystole, VPS = ventricular extrasystole, NS = statistically not significant. Other abbreviations as in Table I.

or syncope, and sudden death in patients with MVP has suggested a myocardial component.^{6, 23} Pathologic studies done with endomyocardial biopsies have shown myocardial fibrosis and mitochondrial degeneration, and these findings support the possibility of myocardial involvement.^{16, 27, 24}

Various scintigraphic studies have shown that myocardial ischemia and perfusion defects may be present in patients with MVP who have no coronary heart disease.^{5, 12, 25} Ischemia occurring especially during exercise in these patients is thought to be caused by increased prolapse of the mitral valve and precarious blood supply in the myocardium around the papillary muscle.^{23, 26} It has also been proposed that coronary artery spasm occurs as a reflex response to the prolapse of the posterior mitral leaflet and thromboembolism to coronary arteries, arising from the left atrium and leaflet.²⁷

Various studies to assess systolic left ventricular function in patients with MVP have been performed with radionuclide ventriculography, myocardial perfusion scintigraphy, and

TABLE III Resting end-diastolic, end-systolic, and ejection volumes and ejection fraction values of both groups calculated with modified Simpson method before dobutamine stress test (resting EF) (mean ± standard deviation)

	Control group (n = 25)	MVP-a (n = 16)	MVP-s (n = 17)	p 1–2	p 2–3	p 1–3
EDV (ml)	114.5 ± 15.1	106.6 ± 12.5	98.2 ± 11.4	NS	NS	NS
ESV (ml)	37.2 ± 5.3	38.2 ± 6.7	38.7 ± 6.3	NS	NS	NS
EV (ml)	77.3 ± 7.4	68.4 ± 8.1	59.5 ± 6.9	NS	NS	0.04
EF (%)	67.1 ± 5.7	63.2 ± 5.2	59.48 ± 6.9	NS	NS	0.03

p 1–2: statistical difference between control group and MVP-a group, p 2–3: statistical difference between MVP-a group and MVP-s group, p 1–3: statistical difference between control group and MVP-s group.

Abbreviations: EDV = end-diastolic volume, ESV = end-systolic volume, EV = ejection volume, EF = ejection fraction, NS = not significant.

TABLE IV End-diastolic, end-systolic, and ejection volumes and ejection fraction values of both groups calculated with modified Simpson method at the peak stage of the dobutamine stress test (mean $\pm$ standard deviation)

	Control group (n = 25)	MVP-a (n = 16)	MVP-s (n = 17)	p 1-2	p 2-3	p 1-3
Heart rate (beats/min)	148 $\pm$ 18	143 $\pm$ 22	141 $\pm$ 21	NS	NS	NS
EDV (ml)	88.3 $\pm$ 10.4	83.4 $\pm$ 9.8	81.4 $\pm$ 8.2	NS	NS	NS
ESV (ml)	21.1 $\pm$ 5.1	26.1 $\pm$ 5.1	30.4 $\pm$ 4.8	NS	NS	NS
EV (ml)	67.2 $\pm$ 7.2	57.3 $\pm$ 6.4	51.0 $\pm$ 6.1	NS	NS	0.05
EF (%)	76.1 $\pm$ 6.3	68.3 $\pm$ 5.9	62.4 $\pm$ 4.6	NS	NS	0.03

Abbreviations as in Table III.

TABLE V The difference between ejection fraction values during the resting period and at the peak stage of the dobutamine stress test

	Control group	MVP-a	MVP-s	p 1-2	p 2-3	p 1-3
EF-differences (%) ^a	8.3 $\pm$ 4.3	5.1 $\pm$ 3.8	2.7 $\pm$ 3.1	NS	NS	0.05

^a(EF% during peak DST) - (basal EF).

Abbreviations as in Table III.

transthoracic echocardiography. In most of these studies, changes in EF, left ventricular wall motion abnormalities, and myocardial perfusion defects were assessed and some conflicting results were established.^{5-8, 12-15, 23, 28, 29}

Dobutamine stress echocardiography has recently played an increasing role in the diagnosis of CAD. Several advantages make this method attractive: it is noninvasive, cost effective, equipment is widely available, and its sensitivity and specificity are as high as those with scintigraphic methods.¹⁹ The new wall motion abnormality seen during DSE is one of the most important diagnostic criteria for CAD.²⁰ Besides wall motion abnormalities, it is also possible to calculate EF during any phase of the test. A study performed in our clinic showed that results of EF calculation performed with DSE were very similar to those achieved with radionuclide ventriculog-

raphy.³⁰ Therefore, in this study we preferred to use DSE for evaluating wall motion abnormalities and EF changes in increasing heart rates.

A study by Dorn *et al.* showed that symptomatic patients with MVP demonstrate a decreased resting left ventricular EF and abnormal response to stress compared with asymptomatic patients with MVP and normal, but symptomatic control subjects.¹⁵ Our findings support the results of these investigators. Our study also showed that, although there is no significant EF difference between the asymptomatic MVP and control groups, the basal EF was low in the symptomatic MVP group and the EF response to increased heart rate induced with dobutamine was not satisfactory in this group.

Greenspan *et al.* have shown abnormal response to exercise myocardial scintigraphy in 2 (6.7%) of 30 patients with primary MVP without CAD.⁵ The persistency of perfusion defect after exercise myocardial scintigraphy was also shown in two patients, and nine (9%) scintigraphically normal patients had wall motion abnormalities. In our study, one patient (6%) in the asymptomatic group and in two patients (12%) in symptomatic group had wall motion abnormalities. During DSE, new wall motion abnormality was observed in two patients in the symptomatic group at the inferoapical region. This was thought to be due to chordal stretching after increased contractility and possibly to affect EF negatively.

Gottdiener *et al.* conducted a study to determine left ventricular function in 47 patients with MVP by using technetium-99m gated equilibrium radionuclide cineangiography.²³ They found out that in patients without MR the EF was normal at rest and exceeded the lower limits of normal in all but one patient. However, the EF values during maximal exercise were lower for the group of patients with MVP without MR than for normal subjects. In the patients with MVP and MR, the average EF was normal at rest but was diminished with exercise in comparison with both normal subjects and patients with MVP without MR.

FIG. 1 Resting ejection fraction (EF) calculated with modified Simpson formula was found lowest in the MVP-s group, and there was a statistical difference in resting EF values between the MVP-s and control groups ($p < 0.05$). Moreover, there was no sufficient increase in EF during the peak stage of DSE in the MVP-s group ($2.7 \pm 3.1\%$). The increase in EF was $> 5\%$ in the MVP-a and control groups. MVP-a = asymptomatic mitral valve prolapse group, MVP-s = symptomatic mitral valve prolapse group, DSE = dobutamine stress echocardiography. ■ = Control group, ■ = MVP-a group, □ = MVP-s group.

It is accepted that presence of MR in MVP patients is the most important factor that negatively affects left ventricular function during exercise.²⁸ It has been concluded in various studies that, although many patients with MVP have normal left ventricular function, there is a subgroup without MR in whom diminished left ventricular functional reserve may be suggestive of a cardiomyopathic component.^{5, 12, 15} Therefore, in our study, the patients with significant MR were excluded from the study and patients with only minimal and 1° MR were included.

Vidalon *et al.* studied left ventricular function in symptomatic patients with MVP without significant MR during the phenylephrine test, before and after digitalization.²⁹ In this study, the percentage of systolic shortening, EF, and mean velocity of circumferential fibers shortening were measured by M-mode echocardiography. Of 31 patients with MVP, 27 showed a decrease in the percentage of systolic shortening, EF, and mean velocity of circumferential fibers shortening. After digitalization there was no change during phenylephrine infusion.

Conclusion

We conclude that there is a close relation between symptoms and left ventricular function in patients with MVP. Although many asymptomatic patients with MVP have normal left ventricular function, symptomatic patients (especially those with typical or atypical chest pain) may show significantly decreased EF levels compared with controls and asymptomatic patients with MVP at rest and at submaximal heart rate levels. Wall motion abnormality seen in symptomatic patients at rest and increased heart rate levels were the most important markers of left ventricular dysfunction. This finding indicates the necessity for a closer echocardiographic follow-up of these patients.

References

- Devereux RB, Kramer-Fox R, Shear M, Kligfield P, Pini R, Savage DD: Diagnosis and classification of severity of mitral valve prolapse: Methodologic, biologic, and prognostic consideration. *Am Heart J* 1987;113:1265–1280
- Perloff JK, Child JS: Clinical and epidemiologic issues in mitral valve prolapse: Overview and perspective. *Am Heart J* 1987;113:1324–1332
- Wooley CF: Where are the diseases of yesteryear? Da Costa's syndrome, neurocirculatory asthenia, and mitral valve prolapse syndrome. *Circulation* 1976;53:749–751
- Boudoulas H, Wooley CF: Mitral valve prolapse and mitral valve prolapse syndrome. *Progr Cardiol* 1986;14:275–309
- Greenspan M, Iskandrian AS, Mintz GS, Croll MN, Segal BL, Kimbiris Dbernis CE: Exercise myocardial scintigraphy with thallium-201: Use in patients with mitral valve prolapse without associated coronary artery disease. *Chest* 1980;77:47–52
- Gulotta SJ, Gulko L, Padmanabhan V, Miller S: The syndrome of systolic click, murmur, and mitral valve prolapse—a cardiomyopathy? *Circulation* 1974;19:717–727
- Boudoulas H, Reynolds JC, Mazzaferri E, Wooley CF: Metabolic studies in mitral valve prolapse syndrome. *Circulation* 1980;61:1200–1205
- Rogers JM, Boudoulas H, Molarkey WB, Wooley CF: Mitral valve prolapse; disordered catecholamine regulation with intravascular volume maneuver. *Circulation* 1984;70:336–342
- Boudoulas H, Reynolds JC, Mazzaferri E, Wooley CF: Mitral valve prolapse syndrome: The effect of adrenergic stimulation. *J Am Coll Cardiol* 1983;52:638–644
- Bashore TM, Grines CL, Utlak D, Boudoulas H, Wooley CF: Postural exercise abnormalities in symptomatic patients with mitral valve prolapse. *J Am Coll Cardiol* 1988;11:499–507
- Levy D, Savage D: Prevalence and clinical features of mitral valve prolapse. *Am Heart J* 1987;113:1281–1290
- Ahmad M, Haibach H: Left ventricular function in patients with mitral valve prolapse. A radionuclide evaluation. *Clin Nucl Med* 1982;7(12):562–567
- Scampardonis G, Yang SS, Maranhao V, Goldberg H, Gooch AS: Left ventricular abnormalities in prolapsed mitral leaflet syndrome. *Circulation* 1973;48:287–297
- Colle JP, Legoff G, Bonnet J, Aouizerate E, Ohayon J, Besse P, Bricaud H: Left ventricular global and segmental function in pure mitral valve prolapse with poor tolerance for exertion. *Arch Mal Coeur Vaiss* 1984;77:616–624
- Dorn GW, Gertler AS, Gordon L, Usher BW, Hendrix GHI: Left ventricular dysfunction in symptomatic mitral valve prolapse. *Chest* 1989;95(2):370–373
- Malcolm AD, Darracott SC, Chayen J, Jenkins BJ, Webb-Peploe MM: Biopsy evidence of left ventricular myocardial abnormality in patients with mitral-leaflet prolapse and chest pain. *Lancet* 1979;1:1050–1055
- Mason JW, Koch FH, Billingham ME, Winkle RA: Cardiac biopsy evidence for a cardiomyopathy associated with symptomatic mitral valve prolapse. *Am J Cardiol* 1978;42:557–562
- Perloff JK, Child JS, Edwards JE: New guidelines for the clinical diagnosis of mitral valve prolapse. *Am J Cardiol* 1986;57:1124–1129
- Markovitz PA, Armstrong WF: Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. *Am J Cardiol* 1992;69:1269–1273
- Bourdillon PDV, Broderick TM, Sawada SG, Armstrong WF, Ryan T, Dillon JC, Fineberg NS, Feigenbaum H: Regional wall motion index for infarct and noninfarct regions after reperfusion in acute myocardial infarction: Comparison with global wall motion index. *J Am Soc Echocardiogr* 1989;2:398–412
- King BD, Clark MA, Baba N, Kilman JW, Wooley CF: "Myxomatous" mitral valves: Collagen dissolution as the primary defect. *Circulation* 1982;66:288–296
- Olsen EGJ, Rufaie HK: The floppy mitral valve: Study of pathogenesis. *Br Heart J* 1980;44:674–683
- Gottliener JS, Borer JS, Bacharach SL, Green MV, Epstein SE: Left ventricular function in mitral valve prolapse: Assessment with radionuclide cineangiography. *Am J Cardiol* 1981;47:7–13
- Tamura K, Fukuda Y, Ishizaki M, Masuda Y, Yamanaka N, Ferrans VJ: Abnormalities in elastic fibers and other connective-tissue components of floppy mitral valve. *Am Heart J* 1995;129:1149–1158
- Tress DD, Soin JS, Siegel R: Mitral valve prolapse: Evidence for a perfusion abnormality (abstr). *Am J Cardiol* 1978;41:441
- Boudoulas H, Kolibash AJ, Baker B, King BD, Wooley CF: Mitral valve prolapse and the mitral valve prolapse syndrome: A diagnostic classification and pathogenesis of symptoms. *Am Heart J* 1989;118:796–818
- Braunwald E: Valvular heart disease. In *Heart Disease. A Textbook of Cardiovascular Medicine*, 5th ed. (Ed. Braunwald E), p. 1031. Philadelphia: WB. Saunders Co., 1997
- Tischler MD, Battle RB, Ashigaka T, Niggel J, Rowen M, LeWinter MM: Effects of exercise on left ventricular performance determined by echocardiography in chronic, severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 1996;77:397–402
- Vidalon M, Tosta C, Oliveira JA, Pimenta J: Symptomatic mitral valve prolapse. Left ventricular dysfunction and beneficial effects of digitalis. *Arq Bras Cardiol* 1993;60:19–24
- Özdemir K, Kisacik HL, Oğuzhan A, Kural T, Göksel S: Comparison of exercise stress testing with dobutamine stress echocardiography and radionuclide ventriculography for diagnosis of coronary artery disease. *Türk Kardiyoloji Dergisi* 1997;1:28–35