Mitral Valve Prolapse in Patients with Anorexia Nervosa

Two-Dimensional Echocardiographic Study

Yukiko OKA, M.D., Takashi ITO, M.D., Shinsaku MATSUMOTO, M.D., Hiroyuki SUEMATSU, M.D.,* *and* Etsuro OGATA, M.D.

SUMMARY

To examine the prevalence of mitral valve prolapse (MVP) and to define the mechanisms of its development in patients with anorexia nervosa, we studied the cardiac function of 23 patients with anorexia nervosa by two-dimensional (2-D) echocardiography. MVP was present in 19 of 23 patients (82.6%), 10 having double MVP in both the anterior and posterior mitral leaflets and 9 having a single MVP in the anterior leaflet. There was no difference in echocardiographic parameters between the MVP(+) and MVP(−) groups. The heart rate was lower in the double MVP group (46.3±8.1; mean±SD) than in the non MVP group (64.0±6.3; $p<0.01$) and the single MVP group (55.9±10.9; $p<0.05$). The presence of bradycardia in these patients suggests an increase in vagal tone. The present study suggests that the incidence of MVP in anorexia nervosa is among the highest compared with its incidence in association with any other disorders, and an increase in vagal tone may be responsible for the development of MVP in patients with anorexia nervosa.

Additional Indexing Words:

Mitral valve prolapse Bradycardia Autonomic dysfunction Vagal tone Anorexia nervosa

ALTHOUGH a mid-systolic click or a late systolic murmur may occasionally be encountered in patients with anorexia nervosa, the presence of mitral valve prolapse (MVP) in this disorder has not been well documented, except for our preliminary report.[1] Since MVP is a possible cause of sudden death[2),3] and since the mortality rate of patients with anorexia nervosa is the highest of any psychiatric disease,[4),5] and may be due to cardiovascular abnormalities,[5)–8] the possibility exists that MVP might be a cause of cardiac death in patients with anorexia nervosa. Therefore, in the present study we

From the Fourth Department of Internal Medicine, Faculty of Medicine, and Faculty of Psychosomatic Medicine,* University of Tokyo, Tokyo, Japan.

Address for reprint: Yukiko Oka, M.D., Fourth Department of Internal Medicine, Faculty of Medicine, University of Tokyo, 3–28–6 Mejirodai, Bunkyo-ku, Tokyo 112, Japan.

Received for publication April 25, 1986.

Manuscript revised May 6, 1987.

have assessed the cardiac function and the prevalence of MVP, using 2-D echocardiography, in patients with anorexia nervosa.

Methods

Profiles of the 23 patients studied are summarized in Table I. The diagnostic criteria for anorexia nervosa were those defined by the Special Study Group on Anorexia Nervosa sponsored by the Japanese Ministry of Welfare,[9] a slight modification of Feigner's criteria.[10] They include that the patient actively refused to eat, had body weight loss of more than 20% of ideal body weight (IBW) [(height in cm$-100)\times 0.9$], and had amenorrhea for at least 3 months, but without evidence of organic psychiatric or thyroid disease. None of our patients had any cardiovascular symptoms, or identifiable cardiovascular diseases except for MVP, or thoracic skeletal deformities such as funnel chest and pigeon chest. Informed consent was obtained from each patient before the study.

Echocardiograms were obtained in the 3rd or the 4th intercostal space along the left parasternum with a 2.4 MHz transducer connected to a Toshiba SSH-11A type ultrasound unit. Echocardiographic images were recorded and analyzed by a SONY video-TV model VO 5800. All patients were studied at rest in both the supine and left oblique positions. The diagnosis of MVP by 2-D echocardiography was based on the diagnostic criteria of Weyman,[11] the principal point being the mitral leaflet movement into the left atrial cavity beyond the functional mitral annulus, i.e., the line crossing the immobile portion of the anterior mitral leaflet and the base of the posterior mitral leaflet on the long-axis view of the left ventricle.

Left ventricular size and function were analyzed by M-mode echocardiogram, electrocardiogram, electrophonocardiogram, and the carotid arterial pulse wave recorded simultaneously. Left ventricular end-systolic volume (ESV) and end-diastolic volume (EDV) were calculated as $(7/2.4+D)\times D$ in ml (Teichholz), where D is the left ventricular diameter at end-systole (Ds) or end-diastole (Dd).

Stroke volume (SV) was calculated as EDV$-$ESV in ml, and ejection fraction (EF) was calculated as EDV$-$ESV/EDV. Mean velocity of circumferential fiber shortening (mVcf) was calculated as $(Dd-Ds)/Dd\times 1/ET$, where ET is the left venticular ejection time obtained from the onset of the upstroke to the incisural notch on the carotid arterial tracing. Systolic time interval was calculated by Weissler's method, i.e. PEP/ET$=[(Q\text{-}S2)-ET]/ET$, where PEP is the left ventricular pre-ejection period calculated as (Q-S2)$-$ET. The Q-S2 interval represents electromechanical systole (beginning of QRS complex to

the first high frequency vibration of the second heart sound).

Eleven of the 23 patients were studied again 2 to 24 months later (mean 12 months).

Statistical analysis: Statistical analysis was made using Student's unpaired t-test for comparison of the data of the initial study. In 5 of the 11 patients, body weight returned to the normal range. The data obtained both before and after body weight gain[12] were compared and analyzed using Student's paired t-test.

Results

Results of the initial study are summarized in Table II. Figure 1 shows the prolapse of the anterior mitral leaflet in case No. 12. Nineteen of 23 patients had MVP (82.6%) and the remaining 4 patients had no evidence of MVP (17.4%). Ten of 19 patients with MVP had combined or double MVP of the anterior and posterior mitral leaflets, and the remaining 9 patients had a single MVP of the anterior leaflet. There was no correlation between existence or severity of MVP and body weight reduction (Tables I and II).

Left ventricular size and function were compared in patients in the double MVP group, the single MVP group, and those without MVP, as summarized in Table II. Parameters were significantly smaller in anorexia nervosa than the normal values from Machii.[13] Left ventricular function parameters were mostly within normal limits except for PEP/ET, and there were no differences in any parameter among the 3 groups (Table II). Bradycardia was seen in all groups. However, the heart rate was significantly lower in patients with combined or double MVP than in those without MVP ($p<0.01$), and it was intermediate in those with a single MVP ($p<0.05$)

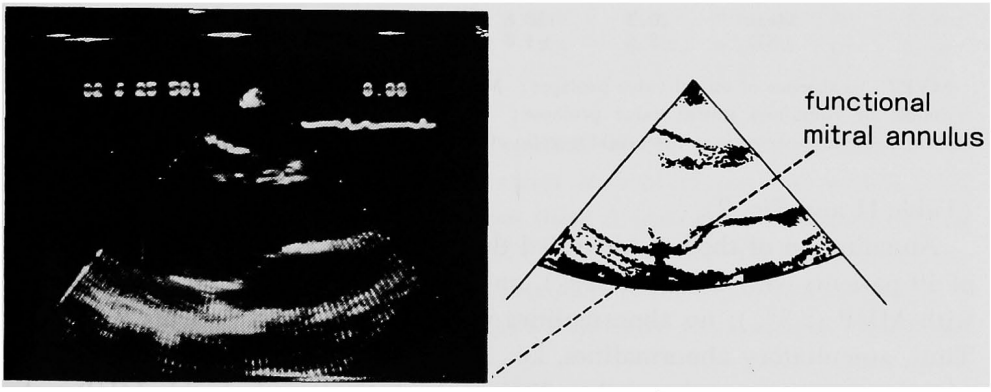

Fig. 1. A typical long-axis view of the 2-D echocardiogram of mitral valve prolapse of the anterior leaflet (case No. 12).

Table I. Patient Profile

	Case No	Age (years)	Height (cm)	Weight (kg)	BW reduction from IBW (%)	Auscultatory abnormality	CTR (%)
MVP (−)	1	14	156	38	28	no	43
	2	20	151	34	33	no	42
	3	17	152	30	41	no	41
	4	23	158	32	40	no	37
	Mean ±SD	18.5 ±3.8	154.3 ±3.3	33.5 ±3.4	35.5 ±6.1		40.8 ±2.6
MVP (S)	5	21	155	35	33	no	43
	6	27	156	35.8	32	no	45
	7	21	158.5	34	36	no	35
	8	13	160	33	39	no	36
	9	25	159	31	42	msc	38
	10	20	152	30	41	no	44
	11	16	157	30	43	msc	34
	12	17	164	43	25	no	38
	13	14	156.7	37	29	msc	43
	Mean ±SD	19.3 ±3.8	157.6 ±3.4	34.3 ±4.1	35.6 ±6.3		39.1 ±3.8
MVP (D)	14	18	165	33.5	43	no	42
	15	23	158	29	45	msc	35
	16	17	155	30.6	41	no	43
	17	18	161	30	45	no	34
	18	19	159	39.5	26	no	40
	19	18	160	40	26	no	40
	20	20	151	35	31	no	44
	21	17	163.6	37.5	34	lsm	44
	22	26	152	37	27	msc	41
	23	26	163	37	35	no	39
	Mean ±SD	20.2 ±3.5	158.8 ±4.8	34.9 ±4.0	35.3 ±7.8		40.2 ±3.5

MVP (−)=absence of mitral valve prolapse; MVP (S)=single mitral valve prolapse; MVP (D)=double or combined mitral valve prolapse; BW=body weight; IBW=ideal body weight; CTR=cardiothoracic ratio; msc=mid-systolic click; lsm=late systolic murmur.

(Table II and Fig. 2).

Auscultation of the heart revealed the presence of a mid-systolic click in 5 of 19 patients with MVP (26.3%), and a late systolic murmur in 1 patient with MVP (5.3%); no abnormalities were detected in 13 patients (68.4%). Thus, auscultatory abnormalities, i.e., non-ejection click and/or late or mid-systolic murmur were detected in 30% of the patients with double MVP and in 33.3% of those with single MVP.

Table II. Echocardiographic Data of Left Ventricular Size and Function at the Initial Study

	Case No	HR/min	LAD (mm)	LV diameter (mm)		CI (L/min/M²)	SI (ml/beat/M²)	EF	mVcf (circ/sec)	PEP/ET
				Dd	Ds					
MVP (−)	1	72	29	46	31	2.4	43.7	0.61	0.96	0.32
	2	66	27	47	33	1.8	35.2	0.57	0.92	0.49
	3	60	22	42	27	3.9	48.1	0.66	1.26	0.34
	4	58	20	43	26	2.1	46.0	0.70	1.07	0.29
	Mean ±SD	64.0 ±6.3	24.5 ±4.2	44.5 ±2.4	29.3 ±3.3	2.6 ±1.0	43.3 ±5.7	0.64 ±0.06	1.05 ±0.15	0.36 ±0.09
MVP (S)	5	52	27	48	27	3.3	62.0	0.75		
	6	50	18	43	26	2.3	46.8	0.69	1.13	0.29
	7	79	23	39	23	3.0	38.2	0.73	1.32	0.26
	8	65	23	40	22	3.0	35.0	0.61	1.50	0.36
	9	60	12	44	32	2.1	42.7	0.53	0.94	0.34
	10	54	23	46	25	5.7	65.2	0.77	1.61	0.37
	11	48	17	35	21	1.1	28.8	0.79	1.05	0.35
	12	53	19	40	20	1.9	39.0	0.81	1.50	0.44
	13	42	24	45	29	2.0	46.2	0.66	0.90	0.39
	Mean ±SD	55.9 ±10.9	20.7 ±4.6	42.2 ±4.1	25.0 ±3.9	2.7 ±1.4	44.9 ±12.0	0.70 ±0.09	1.26 ±0.29	0.35 ±0.06
MVP (D)	14	36	18	41	26	2.3	39.4	0.70	1.27	0.41
	15	53	18	31	20	1.1	20.7	0.66	1.17	0.39
	16	60	23	38	22	3.3	39.0	0.74	1.41	0.24
	17	37	20	43	32	1.3	33.9	0.50	0.62	0.38
	18	36	28	55	38	2.2	62.3	0.58	0.88	0.31
	19	43	20	42	29	1.7	34.5	0.61	0.88	0.31
	20	49	20	42	28	2.0	39.5	0.62	0.96	0.29
	21	48	23	45	30	1.7	42.2	0.62	1.02	0.36
	22	49	34	39	23	1.9	38.9	0.73	1.12	0.33
	23	52	25	41	27	1.8	35.3	0.64	0.99	0.34
	Mean ±SD	46.3 ±8.1	22.9 ±5.0	41.7 ±6.0	27.5 ±5.3	1.9 ±0.6	38.6 ±10.3	0.64 ±0.07	1.03 ±0.22	0.34 ±0.05

Eleven of the 23 patients were studied again 2 to 24 months later. Body weight increased to the normal range in 5 of 11 patients within 2–24 months. Results of follow-up studies in these 5 patients are summarized in Table III. Cardiothoracic ratio (CTR), cardiac index (CI) and stroke index (SI) increased significantly. However, MVP remained unchanged in 4 patients and in 1 patient who had no MVP initially a new double MVP developed.

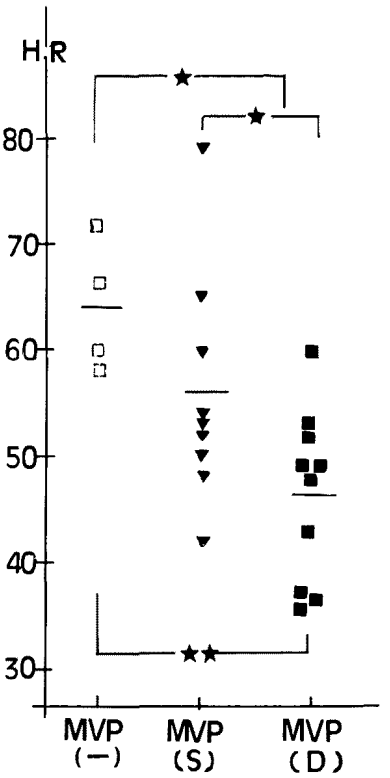

Fig. 2. Relationship between MVP and heart rate (HR) in patients with anorexia nervosa. MVP=combined or double MVP; MVP=single (D) (S) MVP; MVP=absence of MVP. * $p<0.05$, ** $p<0.01$. (−)

Discussion

The incidence of MVP assessed by M-mode echocardiography has been reported to be 5–10% in the general population,[14)–17)] 21% in young healthy women[18)] and 38.5% in patients with hyperthyroidism.[19)] Some investigators reported an incidence of MVP of about 40% in patients with neurosis or panic disorders,[20)–25)] while others denied its high prevalence in patients with panic disorder.[26),27)] Therefore, the incidence (82.6%) of MVP detected by 2-D echocardiogram in anorexia nervosa patients in our present series is disproportionately high. This high incidence agrees with the value of 74% we reported earlier.[1)] The diagnosis of MVP by 2-D echocardiography was based on the diagnostic criterion of the presence of mitral leaflet movement into the left atrial cavity beyond the functional mitral annulus on

the long-axis view of the left ventricle. This criterion using the functional mitral annulus is a suitable method for the diagnosis of MVP.

Although the causes and mechanisms of development of MVP have not been well defined, autonomic disorders,[28),29)] particularly an increase in α-sympathetic tone and a decrease in vagal tone, and thoracic skeletal abnormalities[30),31)] have been implicated. It has been suggested that anorexia nervosa is associated with autonomic dysfunction with an increase in vagal tone.[18),32)-35)] It is also associated with hormonal alterations.[6),35)] The reason for the high incidence of MVP in anorexia nervosa is not clear. There was no apparent correlation between the presence of MVP and cardiac size or reduction in body weight. In addition, MVP remained unchanged in 4 patients and newly developed in 1 patient after body weight gain and/or an increase in cardiac size (Table III). These results suggest that a reduction in body weight or cardiac size is not responsible for the development of MVP in patients with anorexia nervosa. It seems unlikely that alterations in left ventricular function may be responsible for the development of MVP in anorexia nervosa, since there was no apparent correlation between left ventricular function parameters and the presence of MVP (Tables II and III).

The increased vagal tone represented by bradycardia was present in all patients in the present study, and the severity of bradycardia was correlated with that of MVP (Fig. 2). Imataka et al[36)] produced MVP-like lesions in mitral valves and subvalvular apparatus by electrical or mechanical stimulation of the cervical vagus nerve in rabbits, observations supporting the role of increased vagal tone for the development of MVP. These experimental and clinical observations support the hypothesis that an increase in vagal tone may be responsible for the development of MVP in anorexia nervosa.

However, it is not clear whether the MVP in anorexia nervosa is the same as that seen in other disorders. Furthermore, it is not known whether MVP is responsible for the cases of sudden death often seen in patients with anorexia nervosa; we had no cases of death in our present series.

Acknowledgments

The authors are grateful to Imao Sekine, M.D., Toshikatsu Sada, M.D., Fujiko Okabe, M.D., and Akira Naito, M.D. for their help with the cardiological studies, and to Tomifusa Kuboki, M.D. and Shinobu Nomura, M.D. for the care of patients, to Kiyoshi Kurokawa, M.D. for his revision of the English manuscript.

Note added in proof:

Since our paper was submitted, Meyers et al and Johnson et al reported[37),38)] that mitral valve prolapse occurs frequently in patients with anorexia nervosa.

Table III.

Case		BW reduction from IBW (%)	CTR (%)	HR/min	LAD (mm)	LV diameter (mm)	
						Dd	Ds
Case 12	B	25	38	53	22	40	20
	A	13	43	56	26	45	28
Case 15	B	45	35	53	18	31	20
	A	20	44	52	20	42	23
Case 17	B	45	37	37	20	43	20
	A	−4	44	68	34	47	30
Case 18	B	26	40	36	28	55	38
	A	11	47	58	35	55	33
Case 2	B	33	42	66	27	47	33
	A	−18	42	85	29	54	36
Mean ±SD	B	34.8 ±9.8 **	38.4 ±2.7 **	49.0 ±12.6	23.0 ±4.5	43.2 ±8.8	26.2 ±8.7
	A	4.4 ±6.2	44.0 ±1.9	64.0 ±13.0	28.8 ±6.1	48.6 ±5.7	28.1 ±7.0

* $p<0.05$, ** $p<0.01$. B=before weight gain; A=after weight gain.

References

1. Oka Y, Ito T, Sekine I, Sada T, Okabe F, Naito A, Matsumoto S, Suematsu H, Kuboki T, Nomura S: Mitral valve prolapse in patients with anorexia nervosa. J Cardiogr **14**: 483, 1984 (in Japanese with English abstr)
2. Pocock WA, Bosman CK, Chesler E, Barlow JB, Edwards JE: Sudden death in primary mitral valve prolapse. Am Heart J **107**: 378, 1984
3. Jeresaty RM: Mitral Valve Prolapse, Raven Press, New York, p 86, 209, 1979
4. Task force on nomenclature and statistics of the American Psychiatric Association: Progress report on the preparation of DSM-111. University of Missouri Press, St. Louis, 1976
5. Isner JM, Roberts WC, Heimsfield SB, Yager J: Anorexia nervosa and sudden death. Ann Int Med **102**: 49, 1985
6. Warren MP, Van de Wiele RL: Clinical and metabolic features of anorexia nervosa. Am J Obst Gynecol **117**: 435, 1973
7. Thurston J, Marks P: Electrocardiographic abnormalities in patients with anorexia nervosa. Br Heart J **36**: 719, 1974
8. Palossy B, Oo M: ECG alterations in anorexia nervosa. Adv Cardiol **19**: 280, 1977
9. Suematsu H, Ishikawa H, Kuboki T, Ito T: Statistical studies on anorexia nervosa in Japan: Detailed clinical data on 1,011 patients. Psychother Psychosom **43**: 96, 1985
10. Feigner JP, Robine E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R: Diagnostic criteria for use in psychiatric research. Arch Gen Psychiat **26**: 57, 1972
11. Weyman AE: Cross-sectional Echocardiography, Lea & Febiger, Philadelphia, p 169, 1982
12. Snedacor GW, Cochran WG: Statistical Methods, Iowa State Univ Press, Iowa, p 91, 1967
13. Machii K: Two-Dimensional Echocardiography, Chugai Igaku Co., Tokyo, p 524, 1981
14. Procacci PM, Savran SV, Schreiter SL, Bryson AL: Prevalence of mitral valve prolapse in 1169 young women. New Engl J Med **294**: 1086, 1976
15. Scharbaro JA, Mehlman D, Wu L, Brooks HL: A prospective study of mitral valve prolapse in young men. Chest **75**: 555, 1979
16. Valdez RS, Motta JA, London E, Martin RP, Haskell WL, Farquhar JW, Popp RL, Horlick

Follow-up Study

CI (L/min/M²)	SI (ml/beat/M²)	mVcf	EF	PEP/ET	MVP type	Follow-up period (month)
1.92	36.2	1.50	0.81	0.44	D	6
2.20	39.3	1.17	0.67	0.35	D	
1.10	20.6	1.17	0.66	0.39	D	12
2.37	45.6	1.40	0.77	0.34	D	
1.29	34.9	0.62	0.50	0.38	D	10
2.79	41.0	1.08	0.66	0.35	D	
2.25	56.3	0.88	0.58	0.31	D	9
4.10	70.7	1.19	0.71	0.31	D	
1.76	26.7	0.92	0.57	0.49	non	24
4.63	54.5	1.10	0.61	0.32	D	
1.66 ±0.47 **	34.9 ±13.5 *	1.02 ±0.33	0.62 ±0.12	0.40 ±0.07		
3.22 ±1.09	50.2 ±12.9	1.19 ±0.13	0.68 ±0.06	0.33 ±0.02		

Dd=left ventricular diameter at end-diastole; Ds=left ventricular diameter at end-systole.

L: Evaluation of the echocardiogram as an epidemiologic tool in an asymptomatic population. Circulation **60**: 921, 1979

17. Bryhn M, Persson S: The prevalence of mitral valve prolapse in healthy men and women in Sweden: An echocardiographic study. Acta Med Scand **215**: 157, 1984
18. Markiewicz W, Stoner J, London E, Hunt SA, Popp RL: Mitral valve prolapse in one hundred presumably healthy young females. Circulation **53**: 464, 1976
19. Yamaguchi T: Phonocardiographic and echocardiographic study of mitral valve disorders in patients with hyperthyroidism. Tokyo J Med Sci (in press)
20. Pariser SF, Jones BA, Pinta ER, Young EA, Fontana ME: Panic attacks: diagnostic evaluations of 17 patients. Am J Psychiatry **136**: 105, 1979
21. Kantor JS, Zitrin CM, Zeldis SM: Mitral valve prolapse syndrome in agoraphobic patients. Am J Psychiatry **137**: 467, 1980
22. Vankatesh A, Pauls DL, Crowe R, Noyes R Jr, Valkenburg CV, Martins JB, Kerber RE: Mitral valve prolapse in anxiety neurosis (panic disorder). Am Heart J **100**: 302, 1980
23. Grunhaus L, Gloger S, Rein A: Mitral valve prolapse and panic disorders. Isr J Med Sci **18**: 221, 1982
24. Boudoulas H: MVP: a marker for anxiety or overlapping phenomenon? Psychopathology **17** (suppl I): 98, 1984
25. Kathol RG, Noyes R, Slyman D: Propranolol in chronic anxiety disorders. Arch Gen Psychiatry **37**: 1361, 1980
26. Hickey AJ, Andrews G, Wilcken DE: Independence of mitral valve prolapse and neurosis. Br Heart J **50**: 333, 1983
27. Shear MK, Devereux RB, Kramer-Fox R, Mann JJ, Frances A: Low prevalence of mitral valve prolapse in patients with panic disorder. Am J Psychiatry **141**: 302, 1984
28. Gabbney FA, Karlsson ES, Campbell W, Schutte JE, Nixon JV, Willerson JT: Autonomic dysfunction in women with mitral valve prolapse syndrome. Circulation **59**: 894, 1979
29. Boudoulas H, Reynolds JC, Mazzaferri E, Wooley CF: Metabolic studies in mitral valve prolapse syndrome. Circulation **61**: 1200, 1980
30. Tempo CPB, Ronan JA, Leon AC, Twigg HL: Radiographic appearance of the thorax in

systolic click-late systolic murmur syndrome. Am J Cardiol **36**: 27, 1975
31. Salmon J, Shan PM, Heinle RA: Thoracic skeletal abnormalities in idiopathic mitral valve prolapse. Am J Cardiol **36**: 32, 1975
32. Gould L, Reddy CVR, Singh BK, Zen B: Evaluation of cardiac conduction in anorexia nervosa. Pace **3**: 660, 1980
33. Matsunuma K, Matsushita S, Wakasa Y, Ikeda T, Hayakawa H, Inasaka A, Hattori S, Dohi K, Shigeta K: A case of anorexia nervosa with marked bradycardia studied by electrophysiological and autonomical examinations. Heart **13**: 465, 1981 (in Japanese)
34. Gross HA, Lake CR, Ebert MH, Ziegler MG, Kopin IJ: Catecholamine metabolism in primary anorexia nervosa. J Clin Endocrinol Metab **49**: 805, 1981
35. Brown M, Garfinkel PE, Jeuniewic N, Moldofsky H, Stancer HC: Endocrine profiles in anorexia nervosa. *in* Anorexia Nervosa, ed by Vigersky RA, Raven Press, New York, p 123, 1977
36. Imataka K, Takahashi N, Seki A, Fujii J: Experimental production of papillary muscle and mitral valve lesions by vagal manipulations in rabbits. Jpn Circ J **46**: 362, 1982
37. Meyers DG, Starke H, Pearson PH, Wilken MK: Mitral valve prolapse in anorexia nervosa. Ann Int Med **105**: 384, 1986
38. Johnson GL, Humphries LL, Shirley PB, Mazzoleni A, Noonan JA: Mitral valve prolapse in patients with anorexia nervosa and bulimia. Arch Intern Med **146**: 1525, 1986