

Mitral Valve Prolapse and Borderline Hypertension

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SUMMARY Systemic hemodynamics, plasma volume and circulating catecholamine levels were measured under baseline conditions in 21 patients with idiopathic mitral valve prolapse (IMVP), 13 with and eight without borderline hypertension, and compared with two control populations comprised of 34 normotensive and 15 borderline hypertensive subjects without mitral valve prolapse. The IMVP population had a faster heart rate (73 ± 2 vs 67 ± 2 beats/minute; $p < 0.05$) and a greater cardiac index (3.5 ± 0.1 vs 3.0 ± 0.1 liters/min/m²; $p < 0.025$) than the normotensive controls. However, heart rate and cardiac index were similar in IMVP and borderline hypertensive patients. The IMVP patients showed an increased responsiveness of heart rate and systolic arterial pressure during beta-adrenergic receptor stimulation (isoproterenol infusion) when compared to the second control group of patients with borderline hypertension who had similar hyperdynamic circulation. Responses to upright tilt, Valsalva maneuver, and handgrip, however, did not differ between the IMVP and the two control groups. Circulating catecholamine levels were slightly higher in IMVP patients. It is concluded that some IMVP patients (with or without hypertension) demonstrate increased beta-adrenergic receptor responsiveness associated with a hyperkinetic circulation. Therefore, a hyperbeta-adrenergic state could possibly account for the observed abnormal left ventricular contraction pattern and clinical symptoms in the mitral valve prolapse syndrome. (Hypertension 1: 518-522, 1979)

KEY WORDS • beta-adrenergic receptor • essential hypertension • hyperkinetic circulation
• adrenergic nervous system • cardiac output • isoproterenol • labile hypertension
• catecholamines

IN recent years idiopathic mitral valve prolapse (IMVP) has become an increasingly common finding occurring in 5 to 20% of apparently healthy people.^{1, 2} The prolapse may be idiopathic³ or associated with a wide variety of underlying conditions.³⁻¹² Some authors have observed abnormal patterns of left ventricular contraction and suggested the involvement of a myocardial component in this syndrome.^{13, 14}

Systemic hemodynamic findings in patients with mitral valve prolapse have been reported to be normal unless a significant degree of mitral regurgitation is present.¹²⁻¹⁷ Most of these studies included patients with varied manifestations associated with mitral valve prolapse, and little is known about the hemodynamic characteristics of the idiopathic form when compared to a normal population.

As part of a long-standing interest in the pathophysiology and hemodynamic alterations in borderline (labile) hypertension (and especially patients with a hyperdynamic circulation), we have studied some patients with idiopathic mitral valve prolapse syndrome who bear a remarkable resemblance to those with hyperdynamic beta-adrenergic circulatory state.¹⁸⁻²⁰ Furthermore, a similar clinical overlap between IMVP and the so-called Da Costa or Lewis syndrome has been suggested.²¹

The present study was designed to investigate the hemodynamic characteristics of IMVP and to explore the possibility that at least some of these patients demonstrate an increased beta-adrenergic receptor responsiveness.

Methods

Study Population

The subjects of this study included 21 patients (11 women and 10 men) with IMVP (13 with and eight without borderline hypertension), as defined clinically and by echocardiography;^{22, 23} none had evidence of mitral regurgitation or of arrhythmia. These patients were compared with 34 normal subjects (five women

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and 29 men); and a second control population consisting of 15 borderline essential hypertensive patients (four women, 11 men) as previously defined.²⁴ All patients with IMVP had an early systolic click and/or a murmur and the echocardiographic findings were interpreted by two cardiologists independently. Both concurred that the motion of the mitral valve was diagnostic of prolapse. No clinical or echocardiographic evidence of IMVP was present in the two control populations. All patients were younger than 45 years and had normal electrocardiograms. In our patients' history, physical examination, resting electrocardiogram and exercise testing did not suggest coronary disease. Sophisticated radionuclide studies and invasive techniques were not performed. Most patients had never been treated for cardiovascular disease previously. In the few who had been, treatment was discontinued at least 4 weeks before hemodynamic evaluation. Clinical and laboratory evaluations were performed in all 70 subjects, and all who were suspected of having definable causes of increased beta-adrenergic activity had studies to exclude pheochromocytoma, hyperparathyroidism, or other "high cardiac states" of known etiology. All patients provided informed consent for these studies.

Referral Characteristics

No extrapolations should be made from our patient populations concerning the epidemiological or prevalence-rate characteristics of IMVP or borderline hypertension. The patients represent a selected group of individuals who were referred primarily because of our investigative and academic interest in borderline hypertension and in symptomatic clinical conditions associated with a hyperdynamic circulation. Not infrequently, these patients were referred because of symptoms of cardiac awareness (including palpitations, chest discomfort or pain, and rapid heart action) associated with varying degrees of physical limitation. This, indeed, is a common observation in patients with IMVP syndrome. Because of our interest in borderline hypertension associated with similar symptoms, several of our cardiovascular associates referred patients with IMVP who were either normotensive or had hypertension. Moreover, ever since we have included echocardiography by M-Mode as part of our hemodynamic assessment²⁵ we have been able to evaluate the mitral valve in all patients who had a meaningful study.

Hemodynamic Studies

Hemodynamic studies were performed in the morning after an overnight fast as described previously,^{22, 26} including measurement of blood volume (plasma volume and red cell mass) and of plasma catecholamines.^{27, 28} These measurements were obtained after resting for at least 60 minutes in the supine position. Cardiac output was determined in triplicate from indocyanine green dye-dilution curves in the supine position, and subsequently during

forearm isometric exercise (three minutes of 1/3 maximum sustained handgrip) and during the fifth minute of 50° upright tilt. After these interventions, Valsalva maneuver was performed after expiration with sustained intrathoracic pressure at 40 mm Hg for 30 seconds. This was monitored by a pressure gauge and an appropriate increase in central venous pressure.

Twenty to 30 minutes were allowed to elapse between hemodynamic measurements in order to achieve stability. Subsequently, the effects of steady-state isoproterenol infusion were determined in 17 IMVP patients (eight men and nine women) and in 15 borderline hypertensive subjects to compare those with IMVP to a group with documented hyperdynamic circulation (borderline hypertensives). The beta-adrenergic receptor agonist was infused at increasing doses in a sequential fashion (0.01, 0.02, and 0.03 µg/kg/min) with each dose level being maintained for at least 5 minutes before hemodynamic measurements were repeated. These intravenous infusions were monitored by a continuously recorded electrocardiogram and by direct arterial pressure recordings. Infusion was discontinued if excessive cardiac awareness, intolerable emotional response, excessive increase in heart rate, or any significant electrocardiographic abnormality occurred. Propranolol hydrochloride was kept available for administration should any of these responses occur. (Too few patients with IMVP completed the third infusion level because of symptoms, however, to permit inclusion of data at this infusion level.)

A statistical comparison of results was performed by a two-tailed Student's *t* test, and expressed as mean ± one standard error of the mean.

Results

Hemodynamic Studies

The patients with IMVP showed a significantly faster heart rate ($p < 0.05$) and higher cardiac index ($p < 0.025$) than the normotensive control subjects (table 1). Although stroke and left ventricular ejection rate were greater than normal, the differences were not significant. Patients with borderline hypertension differed from the normal group by age, arterial pressures, heart rate, cardiac index, stroke index, and left ventricular ejection rate index (table 1); and they differed from the IMVP group only by their higher arterial pressures ($p < 0.005$).

The hemodynamic responses of the patients with mitral valve prolapse during isometric exercise, head-up tilt, and Valsalva maneuver were similar to those of normal subjects and of the borderline hypertensive patients (table 2). However, the increase in diastolic pressure during head-up tilt was of lesser magnitude in borderline hypertensive patients with IMVP than in normal subjects (3% vs 7%; $p < 0.05$). Plasma catecholamine levels in this population revealed the following values: norepinephrine, 342 ± 23 pg/ml (normal: 206 ± 39 pg/ml); epinephrine, 98 ± 5 pg/ml (normal: 69 ± 15 pg/ml); and dopamine, 73 ± 18

TABLE 1. Study Populations and Hemodynamic Characteristics

Index	Normotensive control	Mitral prolapse	Borderline hypertensive control
Sex (female:male)	5 : 29	11 : 10	4 : 11
Age (yrs)	35 ± 2	32 ± 2	28 ± 2†
Body surface area (m ²)	1.9 ± 0.03	1.8 ± 0.05	2.0 ± 0.06
Systolic pressure (mm Hg)	123 ± 3	127 ± 5	140 ± 4‡
Diastolic pressure (mm Hg)	72 ± 2	77 ± 2	86 ± 3‡
Mean arterial pressure (mm Hg)	89 ± 2	94 ± 3	104 ± 3‡
Heart rate (beats/min)	67 ± 2	73 ± 2*	77 ± 4†
Cardiac index (ml/min/m ²)	2968 ± 83	3464 ± 181†	3697 ± 214‡
Stroke index (ml/beat/m ²)	44 ± 1	48 ± 2	48 ± 1*
Mean rate of left ventricular ejection (ml/sec/m ²)†	145 ± 4	158 ± 8	168 ± 7‡
Total peripheral resistance (units)	16.4 ± 0.5	15.4 ± 0.7	14.9 ± 0.9

**p* < 0.05.†*p* < 0.025.‡*p* < 0.005 vs normotensive control group.

pg/ml (normal: 42 ± 27 pg/ml). Although these differences did not reach statistical significance, they suggest higher circulating levels of all three catecholamines in patients with the IMVP syndrome.

The normotensive IMVP subjects differed from the hypertensive subgroup by demonstrating lower supine plasma volume (*p* < 0.025), lower arterial pressures (*p* < 0.005), and a faster heart rate during upright tilt (*p* < 0.005). The difference in plasma volume between these subgroups could be explained, at least to some extent, by the predominance of women in the normotensive group.

Isoproterenol Infusions

In response to isoproterenol infusion, all 21 patients with mitral valve prolapse had a greater increase of systolic pressure (during 0.01 µg/kg/min; *p* < 0.025) and of heart rate than the borderline hypertensive control population (table 3). In fact, this infusion had to be terminated at the level of 0.02 and 0.03 µg/kg/min in two and five patients, respectively, as a result of emotional outburst, excessive tachycardia (> 140 beats/min) or T-wave inversion (one patient).^{18, 19} These responses were promptly reversed with discon-

TABLE 2. Comparison of Clinical, Hemodynamic and Reflex Data in Normotensive Subjects and Patients with Idiopathic Mitral Valve Prolapse (IMVP): Normotensive and with Borderline Hypertension

Group	Age (yrs)	Plasma volume (ml/cm)	Valsalva maneuver overshoot (% diast.)	Arterial pressure (mm Hg)			Heart rate (beats/min)			Cardiac index (ml/min/m ²)		
				Supine	Grip	Tilt	Supine	Grip	Tilt	Supine	Grip	Tilt
Normal subjects (n = 34)												
Mean	35	18.0	37	123/72	150/90	122/78	67	85	86	3.0	3.27	2.58
± 1 SEM		0.4	4	3/2	3/3	2/2	2	4	3	0.1	0.3	0.2
Borderline patients without IMVP (n = 11)												
Mean	29	17.5	34.6	130/75	159/95	123/76	77	88	89	3.8	4.4	2.9
± 1 SEM	2	0.6	5	4/3	5/4	4/3	4	3	4	0.1	0.3	0.1
All patients with IMVP (n = 21)												
Mean	32	16.8	32	127/77	152/93	124/80	73	87	89	3.5	3.8	2.9
± 1 SEM	2	0.6	4	5/2	5/2	5/3	2	3	3	0.2	0.2	0.2
Normotensive patients with IMVP (n = 10)												
Mean	31	15	27	112/69	134/85	106/69	78	92	98	3.5	3.6	2.7
± 1 SEM	4	0.7	3	2/1	6/3	3/2	4	4	6	0.2	0.2	0.2
Hypertensive patients with IMVP (n = 17)												
Mean	33	18.0*	34.9	137/82†	163/99†	135/87†	71†	84	83	4	4	3
± 1 SEM	2	0.8	6	6/3	6/2	5/3	3	3	3	0.3	0.3	0.2

**p* < 0.025.†*p* < 0.005 vs normotensive IMVP.

TABLE 3. Hemodynamic Responsiveness to Isoproterenol Percentage Changes During Infusions (mean \pm 1 SEM)

	Isoproterenol (0.01 μ g/kg/min)		Isoproterenol (0.02 μ g/kg/min)	
	BH-controls	IMVP	BH-controls	IMVP
Systolic pressure (mm Hg)	3 \pm 2	10 \pm 2*	6 \pm 2	11 \pm 2
Diastolic pressure (mm Hg)	-5 \pm 1	-6 \pm 1	-9 \pm 2	-9 \pm 2
Heart rate (beats/min)	12 \pm 3	31 \pm 6*	22 \pm 4	53 \pm 8
Cardiac index (ml/min/m ²)	37 \pm 7	69 \pm 14	57 \pm 8	73 \pm 9
Stroke index (ml/beat/m ²)	20 \pm 7	26 \pm 8	23 \pm 8	16 \pm 6
Mean left ventricular ejection (ml/sec/m ²)	34 \pm 9	53 \pm 12	53 \pm 11	48 \pm 6

**p* < 0.025.

Abbreviations: BH-controls = borderline hypertension; IMVP = Idiopathic mitral valve prolapse.

tinuation of infusion or by treatment with propranolol (5 mg, I.V.). Only four patients complained of chest discomfort or actual pain, unrelated to palpitations or electrocardiographic changes, during infusion.

Discussion

The results of this study reveal that a subset of patients with IMVP syndrome demonstrate a hyperdynamic circulation characterized by a faster heart rate and higher cardiac output than a similar population without mitral valve prolapse. Further, hyperresponsiveness to beta-adrenergic receptor stimulation was demonstrated in these IMVP syndrome patients by an exaggerated increase in heart rate and systolic pressure when this population was compared to a second control group of borderline hypertensive patients who also demonstrated a similar hyperdynamic circulation, but who did not have mitral valve prolapse.

Symptoms of patients with IMVP are remarkably similar to those of other patients having hyperdynamic beta-adrenergic circulatory state that we have described previously.¹⁸⁻²⁰ These patients may be normotensive or hypertensive; and if they do have hypertension, it need not be borderline.¹⁹ Some patients with idiopathic mitral valve prolapse seem to have a hyperdynamic myocardial contraction as defined echocardiographically by increased mean velocity of circumferential fiber shortening.^{16, 29} By the data of this study, some of the findings in IMVP could be explained by an excessive beta-adrenergic responsiveness. However, other investigators have suggested that these observations may be explained on the basis of an imbalance of the autonomic nervous system.³⁰

These observations, therefore, have prompted us to evaluate the responsiveness to administration of a beta-adrenergic receptor agonist and reflex stimulation. Thus, in the present study, a group of patients with idiopathic mitral valve prolapse syndrome did, indeed, demonstrate evidence of a hyperdynamic circulation and increased responsiveness of heart rate and systolic pressure to beta-adrenergic receptor stimulation with isoproterenol. However, their hemodynamic responses to passive upright tilting, Valsalva maneuver, and isometric handgrip were normal.

Eight patients with IMVP syndrome were normotensive and 13 had borderline (essential) hypertension. It was for this reason we selected two different control groups for comparison with these patients: one, normotensive subjects; the other, patients with borderline hypertension who did not have mitral valve prolapse. We had previously reported that the hemodynamic responsiveness to isoproterenol may be normal in patients with borderline and mild essential hypertension.³¹ It is important to realize, however, that these borderline hypertensive patients had the same level of increased cardiac output under baseline conditions as the patients with IMVP syndrome, but they did not have an increased responsiveness to isoproterenol infusion.

The hyperkinetic circulatory findings in the IMVP syndrome patients that we have investigated contrast with those reports of a normal or reduced mean cardiac output in some of these patients.¹³⁻¹⁷ Nonetheless, the faster heart rate, increased cardiac output, and relatively greater myocardial contractility in the patients that we studied were consistent with their symptoms.

In conclusion, our findings suggest that a subset of patients with idiopathic mitral valve prolapse, whether hypertensive or not, have evidence of a hyperdynamic circulation and increased myocardial beta-adrenergic receptor site responsiveness. It is tempting to speculate that in these patients the clinical symptoms and the abnormal left ventricular contraction pattern may result from an imbalance of the autonomic nervous system.

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