Heart rate and blood pressure in mitral valve prolapse patients: divergent effects of long-term propranolol therapy and correlations with catecholamines

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ABSTRACT

Objective: There is a well known association between mitral valve prolapse (MVP) and low blood pressure (BP), although patients often have high levels of catecholamines and high heart rate (HR). The main objective of our study was to evaluate the effects of long-term adrenergic beta-blockade on these parameters.

Methods: The study population consisted of 46 patients with MVP and the control group consisted of 20 normal individuals. The study had two phases: in the first phase, patients were free of medications. In the second phase, patients were under treatment with propranolol for 10 to 12 months. The tests were performed in normal individuals and patients in the first phase. Only patients underwent the same tests in the second phase. Measurement of urinary epinephrine and norepinephrine levels, by high performance liquid chromatography, was done. Rest HR was determined by electrocardiogram (ECG), and ambulatory blood pressure and HR were evaluated by 24 hours ambulatory blood pressure monitoring (ABPM) using the auscultatory method.

Results: The levels of epinephrine and norepinephrine were significantly higher in patients than in normal controls and decreased under propranolol. Rest and ambulatory HR were higher in patients and decreased under propranolol. The 24 hours systolic and diastolic BPs were lower in patients, and their values increased under propranolol. Heart rate decreasing and epinephrine levels reduction were positively correlated. No correlation was found between BP increase and catecholamine levels.

Conclusion: The study results show divergent effects of propranolol on blood pressure, which increased, and on heart rate, that decreased, in patients with MVP. Heart rate decrease was an expected result and depends, namely, on β_1 receptors blockade. Increase in BP is an unusual response to adrenergic beta-blockade in normal conditions, and this finding supports the preponderance of β_2 receptors on the BP control in patients with MVP. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 107-9)*

Key words: mitral valve prolapse, blood pressure, heart rate, beta-blockade

Introduction

Low blood pressure is a common feature in patients with mitral valve prolapse (MVP), and association between the two entities was found in population-based studies (1, 2). In symptomatic patients, high heart rate and high levels of catecholamines have been demonstrated by several authors (3-7).

Heart rate, cardiac inotropism and, hence, blood pressure (BP) increase with stimulation of β_1 adrenergic receptors and decrease with their blockade. The β_2 postsynaptic receptors stimulation causes arteriolar vasodilatation and can decrease BP.

The exaggerated response of β_2 receptors has been described in MVP patients, when exposed to the agonist isoproterenol (5, 6, 8, 9), which was attributed to receptor supercoupling (8).

We hypothesized that β_2 postsynaptic receptors supercoupling plays an important role in the genesis of low BP in patients with mitral valve prolapse, and that their blockade may increase blood pressure levels.

Methods

Population

The study population consisted of 46 consecutive symptomatic patients with MVP recruited from an out-patient clinic of cardiology, 15 male (mean age 49.3±15.5 years) and 31 female (mean age 42.0±12.8 years). The diagnosis of mitral valve prolapse was based upon current echocardiographic criteria on 2D parasternal and apical long axis views. Mitral leaflets were redundant in 28 patients and non-redundant in 18. Associated mitral regurgitation was mild in 34 patients, moderate in one and was absent in 11 patients. The dimensions of the cardiac chambers and the systolic function of the left ventricle were normal in all the cases.

The control group consisted of 20 normal individuals, 8 male (mean age 49.9±12.9 years) and 12 female (mean age 41.8±11.8 years).

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Methods

The study had 2 phases: in phase 1 the patients were free of medications; the tests were performed in patients and in normal individuals. In the phase 2, the patients underwent the same tests while taking propranolol 10 mg tid for 10 to 12 months (median 10.8 months).

The urine of 24 hours was collected for measurement of epinephrine and norepinephrine by high performance liquid chromatography (HPLC) and creatinine by the Jaffé method.

Rest heart rate was evaluated on conventional 12-lead electrocardiogram (ECG).

Blood pressure and ambulatory heart rate were analysed by 24 hours ambulatory blood pressure monitoring (ABPM) with equipment using the auscultatory method. The test began at 8 am. Time intervals between measurements were 15 minutes from 8 am to 11 pm, and 30 minutes from 11 pm to 8 am.

Statistical analysis

Results are expressed as mean±SD. The t-student test was used to compare the data between the groups. A value of $p<0.05$ was considered significant. Spearman coefficient was used for correlation analysis.

Results

Phase 1

Epinephrine and norepinephrine values were significantly higher in MVP patients than in the control group: 11.0±6.8 ng/mg creatinine vs 5.7±3.0 ng/mg creatinine for epinephrine and 41.5±17.5 ng/mg creatinine vs 25.2±7.2 ng/mg creatinine for norepinephrine (Table 1).

Rest heart rate was 67±6 beats/min in the normal individuals and 76±5 beats/min in MVP patients (Basal). The values were higher in patients ($p<0.01$).

Ambulatory blood pressure and heart rate

The number of measurements considered for analysis was at least 60 per recording. The curves of the mean values of systolic BP and diastolic BP of normal individuals and MVP patients are expressed in Figure 1. The morphology of the curves was quite similar, with nocturnal dip. The values were significantly lower in patients in 98% of measurements for systolic BP, and in 92% for diastolic BP.

Ambulatory heart rate was significantly higher in 71% of the measurements, but not significantly higher in the remaining.

Table 1. Catecholamine levels in patients with MVP and control subjects and in MVP patients before and after beta-blockade

Catecholamines	Normals	MVP (Basal)	p
Epinephrine, ng/mg creatinine	5.7±3.0	11.0±6.8	<0.01
Norepinephrine, ng/mg creatinine	25.2±7.2	41.5±17.5	<0.001
Catecholamines	**MVP (Basal)**	**MVP (beta-blockade)**	
Epinephrine, ng/mg creatinine	11.0±6.8	9.3±4.9	<0.02
Norepinephrine, ng/mg creatinine	41.5±17.5	30.2±11.8	<0.001

MVP- mitral valve prolapse

Phase 2

Epinephrine and norepinephrine values were significantly lower in patients under beta-blocker therapy related to patients free of medication: 9.3±4.9 ng/mg creatinine vs 11.0±6.8 ng/mg creatinine for epinephrine and 30.2±11.8 ng/mg creatinine vs 41.5±17.5 ng/mg creatinine for norepinephrine (Table 1).

Rest heart rate was 66±5 beats/min in MVP patients under propranolol. The values decreased significantly related to patients free of medication.

Ambulatory blood pressure and heart rate

The curves of mean values of systolic BP and diastolic BP are displayed in Figure 2. Both systolic and diastolic BPs were higher in patients medicated with propranolol versus patients free of medications. The difference was significant in 78% of the measurements for systolic BP and 73% for diastolic BP. Ambulatory heart rate was significantly lower under propranolol in 92% of the evaluations (Fig. 3).

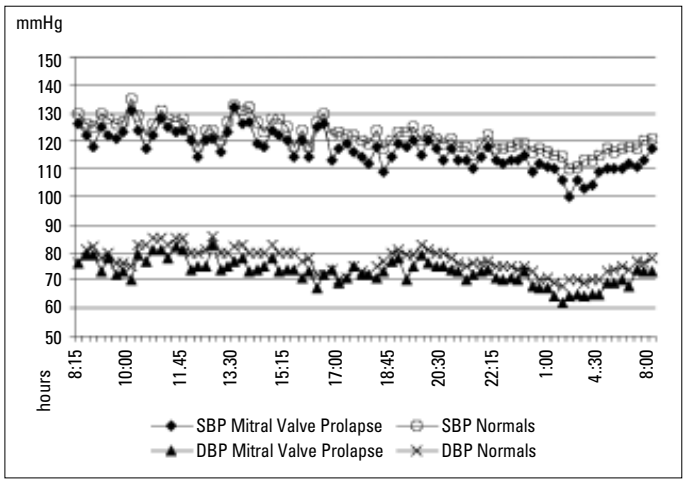

Figure 1. 24 hours ambulatory blood pressure in MVP patients and normal individuals. The values were significantly lower in patients in 98% of measurements for SBP and 92%-for DBP.

DBP- diastolic blood pressure, MVP- mitral valve prolapse, SBP- systolic blood pressure

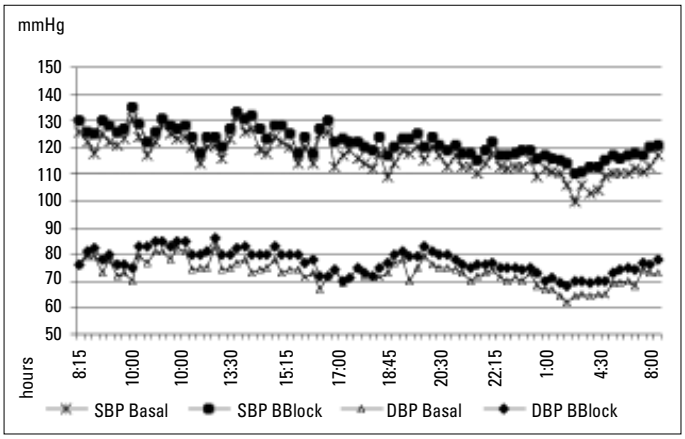

Figure 2. 24 hours ambulatory blood pressure in MVP patients free of medications and MVP patients under long-term adrenergic beta-blockade. The values were significantly higher in medicated patients, in 78% of measurements for SBP and 73%-for DBP.

BBlock- under beta-blockade, DBP- diastolic blood pressure, MVP- mitral valve prolapse, SBP- systolic blood pressure

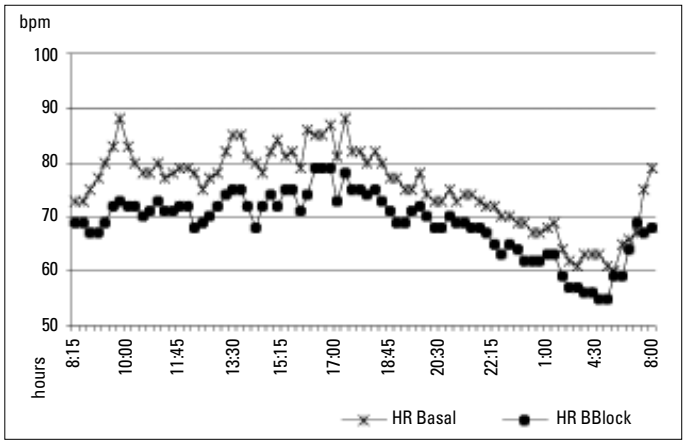

Figure 3. 24 hours ambulatory heart rate in MVP patients free of medications (Basal) and MVP patients on long-term adrenergic beta-blockade. Heart rate was significantly lower in medicated patients in 92% of the measurements.

B Block- under beta-blockade, bpm- beats per minute, HR- heart rate, MVP- mitral valve prolapse

There was a positive correlation between epinephrine levels decrease and heart rate decrease (Spearman correlation coefficient=0.78). No correlation was found between the increasing in blood pressure and the decreasing of either epinephrine or norepinephrine levels.

Discussion

As it has been found in previous studies (1, 2), our MVP patients, when free of medications, had low blood pressure and high heart rate. Like in other studies, the levels of epinephrine and norepinephrine were high (3-7).

Low BP in presence of high levels of catecholamines, raises the probability of β_2 receptor supercoupling being present in our patients as it was in other cases (8, 9). At pre-synaptic level, it carries greater release of norepinephrine to the synaptic cleft and the blood stream. At postsynaptic level, it implies greater arteriolar dilatation and eventual descent of BP.

One can admit that supercoupling exists also at central β_2 receptors. This would explain a greater sympathetic traffic and greater stimulation of the adrenal glands, with greater secretion of epinephrine as a final result.

Both pre- and postsynaptic receptors are preferentially stimulated by epinephrine, which high levels in our patients imply a greater stimulation.

Although enhanced response of $\beta 2$ receptors to stimulation with agonist has been demonstrated in patients with MVP (8, 9), to our knowledge, there are no published studies focusing on the effects of beta-blockade therapy in this situation.

The present study results show divergent effects of propranolol on BP, which increased, and on heart rate, that decreased, in patients with MVP.

Propranolol is a non-selective beta-blocker. Heart rate decrease was an expected result and depends, namely, on β_1 receptors blockade. Increase in blood pressure is an unusual response to adrenergic beta-blockade in normal conditions and supports the preponderance of β_2 receptors on the blood pressure control in patients with mitral valve prolapse.

References

1. Devereux RB, Kramer-Fox R, Brown WT, Shear MK, Hartman N, Kligfield P, et al. Relation between clinical features of the mitral prolapse syndrome and echocardiographically documented mitral valve prolapse. J Am Coll Cardiol 1986; 8: 763-72.
2. Devereux RB, Lutas EM, Brown WT, Kramer-Fox R, Laragh J. Association of mitral valve prolapse with low body weight and low blood pressure. Lancet 1982; 2: 792-5.
3. Boudoulas H, Reynolds JC, Mazzaferry E, Wooley CF. Metabolic studies in mitral valve prolapse syndrome: a neuroendocrine-cardiovascular process. Circulation 1980; 61: 1200-5.
4. Pasternac A, Tubau JF, Puddu PE, Król RB, Champlain J. Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. Am J Med 1982; 73: 783-90.
5. Boudoulas H, Reynolds JC, Mazzaferry E, Wooley CF. Mitral valve prolapse syndrome: the effect of adrenergic stimulation. J Am Coll Cardiol 1983; 2: 638-44.
6. Taylor AA, Davies AO, Mares A, Rascho J. Spectrum ot dysautonomia in mitral valvular prolapse. Am J Med 1989; 86: 267-74.
7. Micieli G, Cavallini A, Melzi d'Eril GV, Tassorelli C, Barzizza F, Verri AP, et al. Haemodynamic and neurohormonal responsiveness to different stress tests in mitral valve prolapse. Clin Autonomic Res 1991; 1: 323-7.
8. Davies AO, Mares A, Pool JL, Taylor AA. Mitral valve prolapse with symptoms of beta-adrenergic hypersensitivity. Beta 2–adrenergic receptor supercoupling with desensitization on isoproterenol exposure. Am J Med 1987; 82: 193-201.
9. Anwar A, Kohn SR, Dunn JF, Hymer TK, Kennedy GT, Crawford MH, et al. Altered β adrenergic receptor function in subjects with symptomatic mitral valve prolapse. Am J Med Sci 1991; 302: 89-97.