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Original article

Floppy mitral valve/mitral valve prolapse syndrome: Beta-adrenergic receptor polymorphism may contribute to the pathogenesis of symptoms

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ABSTRACT

Background: Certain patients with floppy mitral valve (FMV)/mitral valve prolapse (MVP) may have symptoms that cannot be explained on the severity of mitral valvular regurgitation (MVR) alone; hypersensitivity to adrenergic stimulation has been suggested in this group defined as the FMV/MVP syndrome.

Methods: Ninety-eight patients (75 men, 23 women) with mitral valve surgery for FMV/MVP were studied. Of those 41 (42%) had symptoms consistent with FMV/MVP syndrome [29 men (39%), 12 women (52%)]; median age of symptom onset was 30 years (range 10–63 years) and median duration of symptoms prior to valve surgery was 16 years (range 3–50 years). Ninety-nine individuals (70 men, 29 women) without clinical evidence of any disease were used as controls. Genotyping of β_1 and β_2 adrenergic receptors was performed.

Results: β-Adrenergic receptor genotypes (β_1 and β_2) were similar between control and overall FMV/MVP patients. Subgroup analysis of patients, however, demonstrated that the genotype *C/C* at position 1165 resulting in *389 Arg/Arg* of the β_1 receptor was more frequent in women compared to those without FMV/MVP syndrome and to normal control women ($p < 0.025$). This polymorphism may be related to hypersensitivity to adrenergic stimulation as reported previously in these patients.

Conclusion: This study shows a large proportion of patients with FMV/MVP, predominantly women, had symptoms consistent with the FMV/MVP syndrome for many years prior to the development of significant MVR, and thus symptoms cannot be attributed to the severity of MVR alone. Further, women with FMV/MVP syndrome, symptoms at least partially may be related to β_1-adrenergic receptor polymorphism, which has been shown previously to be associated with a hyperresponse to adrenergic stimulation.

Introduction

Certain patients with floppy mitral valve (FMV) associated with mitral valve prolapse (MVP) may have symptoms that cannot be explained on the severity of mitral valvular regurgitation (MVR) alone. Neuroendocrine-cardiovascular or autonomic nervous system functional abnormalities have been postulated as an explanation for the symptoms in this group of patients, which is classified as the FMV/MVP syndrome [1–14]. Many clinical observations during the past 140 years suggested that individuals with irritable heart, soldier's heart, and neurocirculatory asthenia, most likely related to FMV/MVP syndrome, had a disorder of the sympathetic nervous system as a basis for their symptoms [15–17]. Previous studies from our laboratory demonstrated that patients with the FMV/MVP syndrome, mostly females, had a high

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adrenergic tone at rest and a hyperresponse to adrenergic stimulation [9,10]. It is also known that certain polymorphisms of β_1-adrenergic receptors may result in an increased response to adrenergic stimulation [18–22]. It was hypothesized that hypersensitivity to adrenergic stimulation in certain patients with the FMV/MVP syndrome is at least partially related to β-adrenergic receptor polymorphism that results in hypersensitivity to β_1-adrenergic receptors. The present study was undertaken to test this hypothesis.

Materials and methods

Study population

Demographic data are shown in Table 1. Ninety-eight patients (75 men and 23 women) with a mean age of 57 ± 13 years who had mitral valve repair for severe MVR at St Lukas Hospital, Thessaloniki, Greece, due to FMV/MVP from November 2008 to January 2011 were studied. The mean systolic blood pressure was 135 ± 10 mmHg and the mean diastolic blood pressure was 80 ± 5 mm Hg; the resting heart rate was 76 ± 14 beats per minute. The FMV/MVP and the severity of MVR were established prior to surgery with two and three-dimensional transthoracic and transesophageal echocardiogram; FMV also was confirmed in the operating room [23–31]. Mitral leaflet prolapse was posterior in 53, anterior in 4, and bi-leaflet in 41 patients. Diffused thickening of the mitral valve was present in 40 and regional thickening in 58 patients (Table 2). All patients had an apical holosystolic murmur prior to surgery consistent with significant MVR. A detailed history, related to type, onset, and duration of symptoms, especially of those symptoms consistent with the FMV/MVP syndrome, was obtained [1–6,13]. Ninety-nine individuals (70 men and 29 women) with a median age of 63 years (range 31–80 years) without evidence of any disease were used as controls [26]. The study was approved by the Institutional Review Board of St. Lukas Hospital and written informed consent was obtained from all participants.

Table 1
Demographic data of the study population.

	Control ($n=99$)	FMV/MVP ($n=98$)
Male	70	75
Female	29	23
Age	64 ± 13	57 ± 13
Systolic blood pressure	27 ± 9	135 ± 10
Diastolic blood pressure	82 ± 6	85 ± 5

FMV, floppy mitral valve; MVP, mitral valve prolapse.

Table 2
Clinical and echocardiographic data in patients with FMV/MVP ($n=98$).

Male (n)	75
FMV/MVPS (n; %)	29 (38.6)
Female (n)	23
FMV/MVPS (n; %)	12 (52.2)
Leaflet prolapse (n)	
Posterior	53
Anterior	4
Bi-leaflet	41
Chordae tendinae rupture (n)	46
Flail leaflet (n)	32
Diffuse thickening of MV (n)	40
Regional thickening of MV (n)	58
LVEDD (mm)	55 ± 5
LA (mm)	46 ± 6
LVEF (%)	61 ± 9
RVSP (mmHg)	38 ± 13
4+ severity of MVR (n; %)	98 (100)

FMV/MVPS, floppy mitral valve/mitral valve prolapse syndrome; LA, left atrium; LVDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MV, mitral valve; MVR, mitral valve regurgitation; RVSP, right ventricular systolic pressure. The incidence of symptoms related to FMV/MVP syndrome were more common in women compared to men, $p < 0.05$.

Determination of β-adrenergic receptor polymorphisms

Genomic DNA was isolated from lymphocytes in whole blood using a commercially available kit (Qiagen DNA Blood Isolation Kit, Qiagen, Valencia, CA, USA). DNA samples were genotyped for two β_1-adrenergic receptors (*ADRB1*) including: *49 Ser/Gly* [amino acid substitution of serine for glycine at position 49 resulting in the nucleotide substitution of adenine for guanine at position 145 (*145 A/G*), rs1801252]; and *389 Arg/Gly* [amino acid substitution of arginine for glycine at position 389 resulting in the nucleotide substitution of cytosine for guanine at position 1165 (*1165C/G*), rs1801253]. In addition, DNA samples were genotyped for two β_2-adrenergic receptors (*ADRB2*) including: *16 Gly/Arg* [amino acid substitution of glycine for arginine at position 16 resulting in the nucleotide substitution of guanine for adenine at position 46 (*46 G/A*), rs1042713]; and *27 Gln/Glu* [amino acid substitution of glutamine for glutamic acid at position 27 resulting in the nucleotide substitution of cytosine for guanine at position 79 (*79C/G*), rs1042714]. Single-nucleotide polymorphisms (SNPs) were determined by polymerase chain reaction (PCR) followed by pyrosequencing using a PSQ HS96A SNP reagent kit according to the manufacturer protocol (Biotage AB, Uppsala, Sweden) and TaqMan allelic discrimination (Applied Biosystems, Foster City, CA, USA). The PCR primers and probes for *ADRB1 49 Ser/Gly* and *389 Arg/Gly* (IDs C___8898508_10 and C___8898494_10), and *ADRB2 16 Gly/Arg* and *27 Gln/Glu* (IDs C___2084764_20 and C___2084765_20) used in assays were purchased from Applied Biosystems (Applied Biosystems); 5 mL reactions in a 384-well plate were prepared and the assays were performed and analyzed according to the manufacturer's recommendations. The PCR and pyrosequencing primers for above-mentioned SNPs have been previously reported. Genotype accuracy was verified by genotyping 5–10% randomly selected duplicate samples for each SNP on the alternate platform [19,32].

Statistical analysis

Genotypes of β_1 and β_2-adrenergic receptors between the control group and the FMV/MVP patients were compared using a Chi-square or a Fisher exact test. Further, patients who had symptoms consistent with the FMV/MVP syndrome were compared with the control group and to those patients with FMV/MVP who did not have symptoms. A p-value of <0.05 was considered to be statistically significant.

Results

Forty-one patients (42%) had symptoms consistent with the FMV/MVP syndrome. Twenty-nine out of 75 men (39%) and 12 out of 23 women (52%) had symptoms consistent with the FMV/MVP syndrome (Table 2). The incidence of FMV/MVP syndrome was higher in women compared to men ($p < 0.05$). Twenty-one out of 40 patients (52%) with diffuse thickening of the mitral valve and 19 out of 58 patients (33%) with regional thickening of the mitral valve had symptoms consistent with the FMV/MVP syndrome. The median age of symptom onset was at 30 years (range 10–63 years) and the median duration of symptoms was 16 years (range 3–50 years). Symptoms with age of onset and duration are shown in Table 3. Twenty-five of the patients had a history of palpitations with a median age of onset at 20 years (range 10–55 years) and

Table 3
Floppy mitral valve/mitral valve prolapse syndrome.

Symptoms	Age of onset (median and range)	Duration in years (median and range)
Palpitations, $n=25$	20 (10–55)	16 (3–50)
Fatigue, $n=5$	25 (12–30)	16 (10–34)
Orthostatic phenomena, $n=5$ (syncope/presyncope)	35 (16–63)	7 (3–36)

median duration of 16 years (range 3–50 years); no patients had palpitations due to atrial fibrillation. Fatigue and exercise intolerance were present in 5 patients with a median age of onset at 25 years (range 12–30 years) and median duration of 16 years (range 10–34 years). Orthostatic phenomena associated with syncope or presyncope were seen in 5 patients with a median age of onset at 35 years (range 16–63 years) and median duration of 7 years (range 3–36 years). Three patients had dyspnea with age onset at 42, 44, and 47 years, and duration of 3, 4, and 10 years. Chest pain was present in 2 patients in which 1 patient's chest pain started at the age of 40 years and underwent mitral valve surgery at the age of 70 years; the other patient's chest pain started at the age of 50 years and underwent mitral valve surgery at the age of 71 years. One patient had frequent episodes of headaches that started at the age of 40 years and underwent mitral valve surgery at the age of 58 years. The duration of symptoms consistent with FMV/MVP syndrome in all patients was long and occurred many years prior to surgery, and thus symptoms cannot be attributed to the severity of MVR alone. Indications for surgery were based solely on the severity and symptoms related to mitral valve regurgitation. There was no relationship between symptoms or duration of symptoms due to FMV/MVP syndrome and surgery. After surgery none of the patients reported dyspnea, orthostatic phenomena, or fatigue; most of the patients (20 from 25) continued to have palpitations. The follow-up interval, however, was relatively short (1–4 years).

Frequencies of the β-adrenergic receptor genotypes (β_1-receptor and β_2-receptor) in the Greek population with and with FMV/MVP are shown in Table 4.

β-Adrenergic receptor genotypes were similar between control and overall FMV/MVP patients. β_1-Adrenergic receptor homozygous genotype *C/C* at position 1165 resulting in *389 Arg/Arg* in control and FMV/MVP patients is shown in Fig. 1.

Sub-group analysis of females demonstrated that from the 23 females with FMV/MVP, 12 had symptoms consistent with FMV/MVP syndrome in which 10 of these females (83%) had the genotype *C/C* at position 1165. In the 11 of the 23 females with FMV/MVP that did not have symptoms related to FMV/MVP syndrome, only 5 of these females (46%) had the genotype *C/C* at position 1165. In normal control females, 14 out of 29 (48%) had the genotype *C/C* at position 1165 ($p = 0.025$ among group; Fig. 2, Table 5); this difference was not apparent in males.

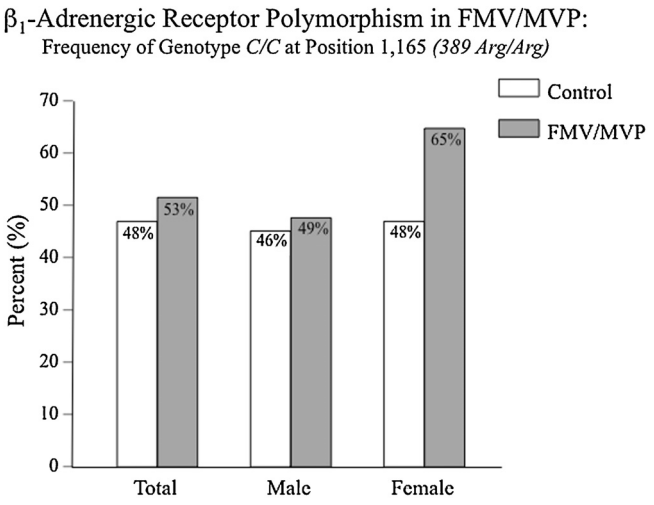

Fig. 1. Frequency of genotype *C/C* at position 1165 (*389 Arg/Arg*) in patients with FMV/MVP and in normal control subjects. FMV/MVP, floppy mitral valve/mitral valve prolapse.

There were no other differences found in the remaining β_1-receptor and β_2-receptor genotypes between patients with symptoms consistent with FMV/MVP syndrome and patients with FMV/MVP without symptoms related to the FMV/MVP syndrome.

Discussion

Preliminary data for the type and natural history of FMV/MVP syndrome symptoms were reported previously from our laboratory [33].

The present study has shown that in certain patients with the FMV/MVP syndrome, especially females, β-adrenergic receptor polymorphisms may play a role in the pathogenesis of symptoms. It also has shown that a large proportion of patients with FMV/MVP have symptoms for years prior to the development of significant MVR and thus, cannot be explained on the basis of MVR alone.

MVP results from the systolic movement of portion(s) or segments of the mitral valve leaflets into the left atrium during left ventricular systole [13,34]. It is well-recognized today that FMV is the central issue in the MVP/MVR story. The term FMV comes from surgical and pathologic studies and refers to the expansion of the area of the mitral valve leaflets with elongated chordae tendinae,

Table 4
β-Adrenergic receptor genotypes in the Greek population.

Gene	Receptor	Nucleotide	Amino acid	Control ($n=99$) Frequency (%)	FMV/MVP ($n=98$) Frequency (%)
ADRB1	β_1-AR	1165 (C/C)	389 (Arg/Arg)	48	51
		1165 (C/G)	389 (Arg/Gly)	41	42
		1165 (G/G)	389 (Gly/Gly)	10	5
ADRB1	β_1-AR	145 (A/A)	49 (Ser/Ser)	80	81
		145 (A/G)	49 (Ser/Gly)	16	17
		145 (G/G)	49 (Gly/Gly)	3	0
ADRB2	β_2-AR	46 (G/G)	16 (Gly/Gly)	39	28
		46 (G/A)	16 (Gly/Arg)	48	54
		46 (A/A)	16 (Arg/Arg)	12	16
ADRB2	β_2-AR	79 (C/C)	27 (Gln/Gln)	44	50
		79 (C/G)	27 (Gln/Glu)	47	36
		79 (G/G)	27 (Glu/Glu)	8	12

ADRB1, adrenergic receptor β_1; β_1-AR, β_1 adrenergic receptor; *ADRB2*, adrenergic receptor β_2; β_2-AR, β_2 adrenergic receptor; A, adenine; C, cytosine; G, guanine; T, thymine; Arg, arginine; Glu, glutamic acid; Gln, glutamine; Gly, glycine; Ser, serine; FMV/MVP, floppy mitral valve/mitral valve prolapse.

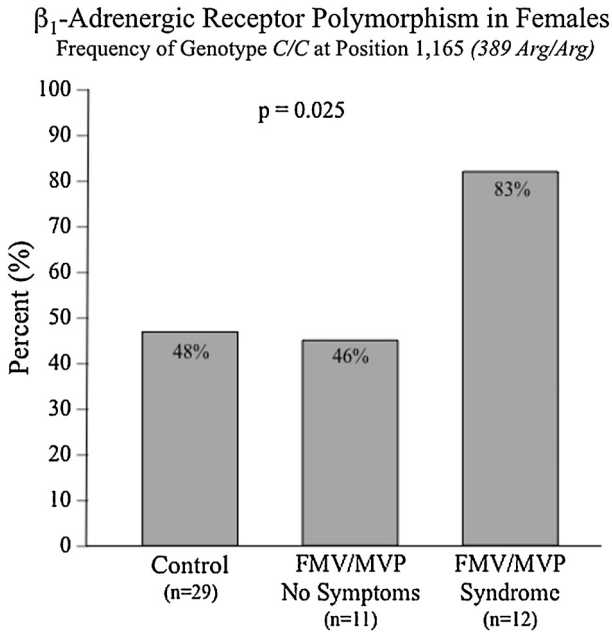

Fig. 2. Frequency of genotype *C/C* at position 1165 (*389 Arg/Arg*) in female patients with FMV/MVP with and without symptoms consistent with FMV/MVP syndrome. Frequency of the same genotype in the normal control females is also shown. FMV/MVP, floppy mitral valve/mitral valve prolapse.

chordae tendinae rupture, and often mitral annular dilatation. The prevalence of FMV/MVP in the general population is 2–3% [1,11,13,29,35]. FMV consists of a heritable heterogeneous group with at least two forms of inheritance. One form is transmitted by an autosomal dominant inheritance with a variable degree of penetration; this is the most common type. At present three gene loci have been reported. There is another less common form that is transmitted through chromosome X [36].

If one accepts the hypothesis that some of the patients with the FMV/MVP syndrome were previously considered to have an irritable heart, soldier's heart, or neurocirculatory asthenia, then physicians have attempted to provide an explanation for these symptoms for more than a century [15–17]. In all these earlier observations, metabolic abnormalities, autonomic dysfunction, and hyperresponse to adrenergic stimulation were considered as a possible explanation for the symptoms of the FMV/MVP syndrome. Fraser and Wilson [17], working in the Heart Section at a military hospital in England during World War I, demonstrated that very small doses of intravenous adrenaline produced a greater heart rate and blood pressure response in soldiers with an "irritable heart" compared to control subjects; they concluded that the sympathetic nervous system was unstable in the irritable heart soldiers. Peabody and his colleagues [16] at the United States Army Hospital, New Jersey, studied the effect of intramuscular injections of epinephrine in soldiers with irritable heart and compared the results to a control group; they also demonstrated a hyperresponse to epinephrine and concluded that "it is distinctly interesting therefore that so large a proportion should be hypersensitive to epinephrine, and one should at least consider carefully whether an unusually excitable sympathetic nervous system may play a part in determining their condition." Boudoulas et al. [10] demonstrated that symptomatic patients with the FMV/MVP syndrome, mostly females, with high adrenergic tone at rest had hypersensitivity to isoproterenol administration as manifested by dose-related reproduction of symptoms and greater heart rate response compared to control subjects. Increased 24-h urinary epinephrine and norepinephrine excretion, and high plasma catecholamines in symptomatic patients with MVP syndrome have been reported from our group and others [4,5,9,12]. The present study extends previous observations and provides insight into the pathophysiologic mechanisms related to hypersensitivity to adrenergic stimulation in patients with the FMV/MVP syndrome. Indeed the frequency of the homozygous genotype *C/C* at position 1165 resulting in *389 Arg/Arg* was more frequent in women who had symptoms consistent with the FMV/MVP syndrome [18–22,37]. This polymorphism may be related to a hyperresponse to adrenergic stimulation as reported previously [10]. High adrenergic activity in FMV/MVP further increases when significant MVR occurs and may have significant implications in myocardial function [38,39].

In addition to high adrenergic activity, there are several other mechanisms that may be related to the pathogenesis of symptoms in patients with the FMV/MVP syndrome including the development of the third chamber, papillary muscle traction, and mitral valve nerve ending stimulation. The third chamber is developed during left ventricular systole within the border of the mitral valve annulus and the prolapsing mitral valve leaflets. Thus, during left ventricular systole the heart consists of three chambers (left ventricle, left atrium, and the third chamber) [6,13]. The third chamber acts like a left ventricular aneurysm since blood within the space of the third chamber does not contribute to the effective stroke volume. The degree of prolapse increases in the upright position, which may further decrease the effective stroke volume and forward cardiac output contributing to the orthostatic phenomena [7,40]. Prolapsing mitral valve results in traction of the papillary muscles that may produce chest pain and activation of stretch receptors leading to membrane depolarization and cardiac arrhythmias [41–45]. Mechanical stimuli due to abnormal coaptation of the FMV/MVP may cause an abnormal autonomic nerve feedback between the central nervous system and the mitral valve [1,13].

This study shows that patients with FMV/MVP who developed significant MVR requiring surgery had symptoms for several years prior to surgery that were not directly related to the severity of MVR. Symptoms in patients with MVP without significant MVR (i.e. MVP syndrome) have been reported previously from numerous investigators [4,5,9,10,12,33]. However, in most of these previous studies symptoms were reported at one particular time

Table 5
Frequency (%) of β-adrenergic receptor genotypes in the patients with FMV/MVP syndrome ($n = 98$) and in the control group.

Gene	Receptor	Nucleotide	Amino acid	M-C	M-Sx	M-No Sx	F-C	F-Sx	F-No Sx
ADRB1	β_1-AR	1165 (C/C)	389 (Arg/Arg)	49	52	50	48	83	46
		1165 (C/G)	389 (Arg/Gly)	44	48	41	35	17	45
		1165 (G/G)	389 (Gly/Gly)	7	0	9	17	0	9
ADRB1	β_1-AR	145 (A/A)	49 (Ser/Ser)	80	76	85	86	83	82
		145 (A/G)	49 (Ser/Gly)	17	24	15	10	8.5	18
		145 (G/G)	49 (Gly/Gly)	3	0	0	4	8.5	0

ADRB1, adrenergic receptor β_1; β_1-AR, β_1 adrenergic receptor; A, adenine; C, cytosine; G, guanine; Arg, arginine; Gly, glycine; Ser, serine; FMV/MVP, floppy mitral valve/mitral valve prolapse; M-C, male control; M-Sx, male with symptoms consistent with FMV/MVP syndrome; M-No Sx, male with no symptoms related to FMV/MVP syndrome; F-C, female control; F-Sx, female with symptoms consistent with FMV/MVP syndrome; F-No Sx, female with no symptoms related to FMV/MVP syndrome. The 389 (Arg/Arg) genotype was more common in women with symptoms consistent with FMV/MVP syndrome compared to other groups, $p = 0.025$.

during the natural course of the disease, thus the duration of symptoms was not defined. In this study, symptoms were analyzed from their onset until surgery. In this group of patients, the incidence of the FMV/MVP syndrome was high and the duration of symptoms was exceptionally long. Further, in most previous studies the diagnosis of MVP was mostly based on echocardiographic criteria (M-mode or 2-dimensional) of mitral valve prolapse without defining if the mitral valve was floppy. It should be emphasized that MVP may be a non-specific finding since it also depends on left ventricular contractility, left ventricular volume, and other ventricular hemodynamics. In this study the diagnosis of FMV was established with transesophageal two- and three-dimensional echocardiography and also was confirmed in the operating room in all patients.

In conclusion, the results of this study have shown that a large proportion of patients with FMV/MVP have symptoms consistent with FMV/MVP syndrome for many years prior to the development of significant MVR and thus, cannot be attributed to MVR alone. These symptoms were more prominent in women compared to men. The diagnosis of FMV/MVP was established in all patients with transesophageal two- and three-dimensional echocardiography and it was confirmed in all patients in the operating room. It has also been shown that women with symptoms consistent with the FMV/MVP syndrome may be partially related to β-adrenergic receptor polymorphism that provides an explanation to the hyperresponse to adrenergic stimulation.

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Conflict of interest

None.

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