Does the Association Between Mitral Valve Prolapse and Panic Disorder Really Exist?

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Objective: Although the possible relationship between panic disorder and mitral valve prolapse (MVP) attracted considerable research interest in the 1980s and 1990s, the reported prevalence of MVP in these patients has been inconsistent and widely variable. Clinical and epidemiologic studies have produced controversial data on possible association or definite causal relationship between these 2 entities. The primary objective of the present review was to summarize the current state of knowledge on the association between panic disorder and MVP, including the influence of diagnostic criteria for MVP on the controversial results.

Data Sources: We searched MEDLINE, LILACS, and EMBASE databases using the keywords *panic* and *mitral*. Inclusion criteria were articles concerning the reciprocal association of MVP and panic disorder, published from the earliest dates available through December 2006.

Study Selection: All relevant articles published in English, Spanish, or Portuguese and reporting original data related to the association of MVP and panic disorder were included. Forty articles fulfilling the criteria for inclusion in this review were identified.

Data Synthesis: Even though the reported prevalence of MVP in panic disorder varied from 0% to 57%, a significant association between the 2 disorders was documented in 17 of the 40 studies. Such inconsistent results were due to sampling biases in case or control groups, widely different diagnostic criteria for MVP, and lack of reliability of MVP diagnosis. None of the reviewed studies used the current state-of-the-art diagnostic criteria for MVP to evaluate the volunteers. Apparently, the more elaborate the study methodology, the lower the chance to observe a significant relationship between these 2 conditions.

Conclusions: Published results are insufficient to definitely establish or to exclude an association between MVP and panic disorder. If any relationship does actually exist, it could be said to be infrequent and mainly occur in subjects with minor variants of MVP. To clarify this intriguing issue, future studies should mainly focus on the observed methodological biases and particularly should use the current criteria for MVP as the standard for evaluation.

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The symptoms of panic disorder have long been considered to be part of a psychiatric condition, although they started to acquire greater relevance with the introduction of panic disorder and of agoraphobia with panic attacks as diagnostic categories in the DSM-III in 1980.

In the 1960s, Barlow and Bosman,[1] using left ventricular cineangiography, first identified the origin of late mitral systolic murmur, and later, Criley et al.[2] named this condition *mitral valve prolapse* (MVP). Starting in the 1980s with the dissemination of the use of echocardiography, an epidemic of MVP diagnoses occurred, especially among young women,[3,4] and the understanding of the normal and anomalous anatomy of the mitral valve greatly evolved thereafter.[3,5]

Cardiovascular complaints are among the most frequent in panic disorder, accompanied by marked anguish,[6,7] and panic attacks are often accompanied by tachycardia.[7,8] Patients with MVP and panic disorder complain of palpitations, chest pain, dyspnea, fatigue, dizziness, and a fainting sensation.[9,10] This similarity of many symptoms led to the speculation that in many cases panic disorder could be caused by MVP or, conversely, that panic disorder might lead to MVP.[11–14] The results of research on the possible connection between MVP and panic disorder, however, have been inconsistent regarding the strength of this association.[15] As will be demonstrated in the present review, this inconsistency may be caused by 3 major problems: widely differing diagnostic criteria for MVP, lack of reliability of the diagnoses, and sample biases in the case and control groups.

The objectives of the present review were to survey the studies on the prevalence of MVP in panic disorder and of panic disorder in MVP and to discuss the criteria for the diagnosis of MVP used in the various studies.

METHOD

The present study consisted of a literature survey focusing on reports concerning the reciprocal association of MVP and panic disorder. The survey was based on consultation of the electronic indexing services MEDLINE, LILACS, and EMBASE using the keywords *panic* and *mitral*.

Inclusion criteria were articles written in English, Spanish, and Portuguese published from the earliest dates available through December 2006. The number of articles meeting these criteria was 139. The reference lists of other papers and of reviews on the topic were also used as a source to identify 3 additional articles.

Fifty-five review articles, editorials, letters, and case reports were excluded, as were 43 articles that did not evaluate directly or indirectly the association between the 2 conditions and 4 that presented preliminary data later included in a full article.

A Better Understanding of Mitral Valve Prolapse

The mitral valve separates the left atrium from the left ventricle. It consists of anterior and posterior leaflets, which normally close completely when blood is ejected into the aorta during ventricular systole, thus preventing blood reflux into the left atrium. The prolapse of this valve is the displacement of one or both of its leaflets into the left atrium during systole,[16] usually accompanied by abnormal leaflet thickening. When the bulging of the leaflets can disrupt their normal positions, there may be blood regurgitation into the left atrium.[17]

MVP has been associated with serious complications such as bacterial endocarditis, severe mitral regurgitation, and sudden death.[18] Unfortunately, our current knowledge about the prevalence, rates of complication, and clinical disorders associated with MVP is quite limited, especially due to the use of different diagnostic techniques and criteria. However, we do know that MVP is the main cause of isolated mitral regurgitation that requires valve replacement or repair in the United States.[19–21]

MVP may be diagnosed during physical examination or accidentally discovered during an echocardiographic examination performed due to other reasons, or may also be detected when important complications of the prolapse occur.[3]

Since the early 1970s, echocardiography has been suggested as the ideal noninvasive method for assessing and diagnosing MVP.[16] However, continuous changes in the echocardiographic techniques used as well as in the diagnostic criteria for MVP have produced a widely variable prevalence of MVP in different populations.[22]

Physical Signs and Symptoms of Mitral Valve Prolapse

Auscultation of patients with MVP may reveal the presence of a mesosystolic click and of a delayed systolic murmur, which have been considered to be the diagnostic hallmark of this condition.[23,24] However, like all other diagnostic aspects of MVP, these changes revealed by auscultation vary widely among the different studies. In addition, more recent articles have reported a low association between these signs and the presence of MVP,[25,26] so that they cannot be considered to represent a specific or reliable method.

Palpitations, dyspnea, dizziness, chest pain, syncope, and anxiety were the symptoms associated with MVP most frequently described in several noncontrolled studies. However, no differences in the prevalence of symptoms have been detected between patients with and without MVP in community studies.[18,25,27–29]

M-Mode Echocardiography

In the 1970s after the publication of a few studies, M-mode echocardiography became the standard technique for diagnosis of MVP.[30,31] Although the late systolic posterior leaflet displacement has been described as a specific diagnostic criterion, it has been shown that it actually was insensitive and could be produced in 40% to 55% of normal subjects depending on the transducer position on the chest.[32,33]

Some investigators who studied the reliability of this method obtained discouraging results. Dager et al.[34] detected low indices of interrater ($\kappa = 0.11$) and test-retest ($\kappa = 0.41$) reliability. Gorman et al.[35] investigated a series of 15 patients with panic disorder who were independently evaluated by 2 experienced cardiologists and observed that, while the first detected 9 cases of MVP, the second did not diagnose it in any subject.

Thus, all studies using M-mode echocardiography seem to present a potential acquisition bias, a fact that has raised the hypothesis that this method is unreliable and of questionable validity.

Two-Dimensional Echocardiography

Although introduction of 2-dimensional echocardiography provided better imaging of the mitral valve and its spatial relationship with adjacent structures, diagnostic criteria initially established using this technique produced overdiagnosis of MVP. This occurred due to the equivocal assumption that the mitral annulus is planar. On the basis of these criteria, dislocation of the mitral valve displacement above the plane of the annulus in the long axis parasternal view or in the apical 4-chamber view was considered to be diagnostic of MVP.[3] Using these criteria, Warth et al.[4] documented a 35% prevalence of MVP

in adolescents who had been previously selected as "normals."

In the late 1980s, Levine et al.[36–38] elegantly redefined the anatomy of the normal mitral valve. Using 3-dimensional echo imaging reconstruction, they showed that the mitral ring was actually shaped like a saddle, so that a false-positive diagnosis of MVP could be made only on the basis of apical 4-chamber view images showing displacement of valve leaflets above the mitral annulus, when actually the anatomy of the valve was completely normal.[36] In addition, patients diagnosed as presenting MVP based only on images obtained in the apical 4-chamber view, but not in the long-axis view, did not present a higher risk of having MVP complications such as mitral regurgitation, left atrium dilatation, or thickening of the mitral leaflets as compared with patients who did not appear to have MVP.[37] In summary, current criteria define prolapse as single or bileaflet displacement by more than 2 mm above the highest points of the mitral annular plane, as documented by apical long axis views.[37,38] Furthermore, a prolapse associated with valvar leaflet thickening of more than 5 mm is classified as classic, whereas a prolapse with a thickening of less than 5 mm is considered to be nonclassic.[26]

Epidemiology of Mitral Valve Prolapse

The described prevalence of MVP is widely variable depending on the characteristics of the population studied, the diagnostic methods, and the criteria used. In older community studies using M-mode, the prevalence ranged from 4% to 7% of the general population,[16,39] while in the Framingham study conducted in the 1980s, one of the largest cohort studies of cardiovascular diseases, the overall prevalence of MVP was 5%.[29]

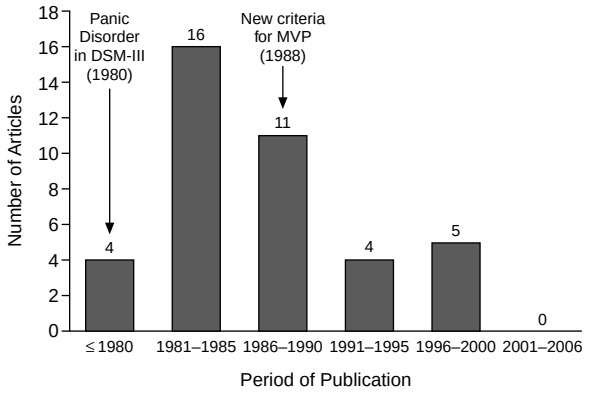
More recent echocardiographic criteria detected a 2.4% prevalence of MVP for the general population in a more recent evaluation of the Framingham cohort.[25] This difference is related to the more specific and strict criteria currently used, although it did not result in loss of sensitivity for the detection of complications.[26,40] Therefore, more recent data show a prevalence of MVP in the general population ranging from 2% to 3%,[3,17] with no gender differences and an equal distribution from 30 to 80 years of age.[25]

RESULTS

According to the inclusion and exclusion criteria described above, 40 articles that evaluated the possible connection between the 2 conditions were selected.

On the basis of the overlap of clinical manifestations, Pariser et al.[11] published the first case report that raised the hypothesis of an association between MVP and panic disorder. Two years later, panic disorder was included in the DSM-III as a distinct diagnostic entity and great interest in the topic arose thereafter, with the production of many studies despite widely varying methodologies and results. In the late 1980s after the redefinition of the diagnostic criteria for MVP, there was a gradual decline in the number of publications about this possible association, with no article being published after 2000. The distribution of articles on the subject according to the period of publication is illustrated in Figure 1.

Figure 1. Articles Published on Mitral Valve Prolapse (MVP) and Panic Disorder According to Period of Time[a]



[a]Articles identified through MEDLINE, LILACS, and EMBASE searches using the keywords *panic* and *mitral*.

To facilitate the demonstration of the results, the articles in this review were divided into 2 major groups: (1) studies evaluating the prevalence of MVP in patients with panic disorder or panic attacks and (2) studies evaluating the prevalence of panic disorder or panic attacks in patients with MVP.

Prevalence of Mitral Valve Prolapse in Patients With Panic Disorder/Panic Attacks

Twenty-nine studies on MVP in patients with panic disorder or agoraphobia were detected. The studies without and with a control group are presented in Tables 1 and 2, respectively. The distribution of the results occurred in a bimodal manner, with a group reporting low frequencies of 0% to 10% and another reporting high frequencies of 25% to 57%.

A total of 14 studies detected a significant association between the 2 conditions,[9,12–14,41–50] whereas the remaining 15 studies did not.[34,51–64]

This wide variability can be explained by different factors. As an example, not all studies used homogeneous samples; this was the case for the study by Kathol et al.,[51] who included patients with other anxiety disorders, and for the studies by Pariser et al.[12] and Carney et al.,[45] who included patients with major depression and panic attacks. Furthermore, in 18 studies there was no control group (Table 1), with the results being interpreted by

Table 1. Prevalence of MVP in Patients With Panic Disorder: Studies Without a Control Group

Study	Sample	N (Female/Male)	Age, y	Criteria for MVP	Results (% With MVP)
Pariser et al,[12] 1979	Patients with panic attacks	17 (9/8)	Range, 21–53	Ausc/M-mode echo	35
Kathol et al,[51] 1980	Patients with anxiety disorders	26 (12/14)	Range (mean), 17–57 (36)	Ausc/M-mode echo	4
Leor and Markiewicz,[52] 1981	Soldiers with anxiety neurosis	42 (0/42)	Mean = 24	Ausc/M-mode echo	9.5
Gorman et al,[14] 1981	Patients with panic disorder/agoraphobia	20 (15/5)	Range (mean), 27–58 (40)	Ausc/M-mode echo	50
Grunhaus et al,[41] 1982	Patients with panic disorder or agoraphobia/panic disorder	23 (15/8)	Range (mean), 22–54 (35.43)	Ausc/M-mode echo	30
Bass and Wade,[53] 1984	Patients with chest pain and anxiety/depressive neurosis	40 (not reported)	Range, 31–65	Ausc/M-mode and 2D echo	0
Hickey et al,[54] 1983	Patients with agoraphobia	50 (42/8)	Range (mean), 21–67 (36)	Ausc/M-mode echo	0
Mavissakalian et al,[55] 1983	Patients with agoraphobia and panic attacks	54 (46/7)	Mean = 36.7	Ausc/M-mode echo	5.5 defined, 7.5 probable
Chan et al,[56] 1984	Patients with anxiety disorders	19 (not reported)	Mean = 34	Ausc/2D echo	0
Harbauer-Raum and Strian,[57] 1985	Patients with panic disorder	27 (not reported)	Mean = 38	Ausc/M-mode echo	7.4
Liberthson et al,[9] 1986	Patients with panic disorder/agoraphobia	131 (84/47)	Range (mean), 20–63 (38)	Ausc/2D-echo	34 defined, 5 probable
Caetano,[42] 1986	Patients with panic disorder	50 (36/14)	Mean = 35	M-mode and 2D echo	36
Matuzas et al,[43] 1987	Patients with panic attacks	65 (49/16)	Mean = 36.9	M-mode and 2D echo	57
Min and Lee,[58] 1987	Patients with panic disorder/agoraphobia	86 (49/37)	Range (mean), 17–58 (39.3)	M-mode echo	0
Matuzas et al,[44] 1989	Patients with panic disorder	82 (48/34)	Range (mean), 21–65 (31.6)	M-mode and 2D echo	47.5
Dager et al,[34] 1989	Patients with panic attacks	50 (not reported)	Not reported	M-mode echo	10
Cordás et al,[46] 1991	Patients with panic disorder	65 (37/28)	Range (mean), 19–67 (39.8)	Ausc/M-mode and 2D echo	36.9
Yang et al,[48] 1997	Patients with panic disorder onset < 1 y	24 (14/10)	Mean ± SD = 37.7 ± 10.6	2D echo	25
	Patients with panic disorder onset > 10 y	21 (10/11)	Mean ± SD = 58.6 ± 11.3		29

Abbreviations: 2D echo = 2-dimensional echocardiography, Ausc = auscultation, MVP = mitral valve prolapse.

comparison with the estimated population prevalence of MVP. However, as previously mentioned, there was a wide variability in the diagnosis and in the prevalence of MVP in the general population.

All studies used echocardiography as the diagnostic technique, but none used current criteria for MVP. In 14 studies, only M-mode echocardiography was performed,* which, as mentioned earlier, is a method associated with an important acquisition limitation, so that it is no longer considered for the diagnosis of the disease. Similarly, in the studies that used 2-dimensional echocardiography for the diagnosis of MVP, the criteria varied widely, and today many of these criteria are also known to be of questionable validity. In 16 studies, auscultation was also used as a form of evaluation, although this diagnostic method does not contribute significantly to the definition of MVP, except for the more severe cases of the disease.[25,26]

In addition, in most studies the cardiologic diagnosis was made by evaluators who were not blind to the psychiatric diagnosis of the patients. Thus, for the diagnosis of MVP this was an important bias in view of the low reliability of the diagnostic methods used at that time.[4,32,33]

It should also be mentioned that the service of patient referral may have contributed to a higher true prevalence of MVP in some studies. It is known that patients with multiple diagnoses, whether psychiatric or clinical, have a greater probability of being referred to tertiary institutions, which could be the source of the volunteers included in most of the studies. Furthermore, it was argued that a proportion of referrals to psychiatry services may be made by cardiologists, which could result in a high prevalence of MVP.[7]

A control group of "normal" subjects was included in 11 studies (Table 2), with an important division occurring in these studies. In 7 of them, the control group consisted of hospital employees[13,47,50,64] or volunteers from the community,[49,59,61] a fact that can be considered another important selection bias. In 4 of these studies, a higher prevalence of MVP was detected in the case group.[13,47,49,50]

The other group of articles consisted of 4 studies in which the control group was formed by outpatients who were being followed due to complaints other than panic disorder/panic

*References 12–14, 34, 41, 47, 49, 51, 52, 54, 55, 57–59

Table 2. Prevalence of MVP in Patients With Panic Disorder: Studies With a Control Group

Study	Sample	N (Female/Male)	Age, y	Criteria for MVP	Results (% With MVP)
Venkatesh et al,[47] 1980	Patients with panic disorder	21 (15/6)	Range (mean), 21–62 (37)	Ausc/M-mode echo	38.1
	Hospital employees	20 (14/6)	Range (mean), 23–62 (37)		10
Kantor et al,[13] 1980	Patients with panic disorder/agoraphobia with a history of palpitations	25 (25/0)	Mean ± SD = 41.9 ± 9.4	Ausc/M-mode echo	32
	Hospital employees	23 (23/0)	Mean = 42		8.7
Shear et al,[59] 1984	Patients with panic disorder/agoraphobia	25 (14/11)	Mean = 35.8	M-mode echo	8
	Spouses of patients with MVP	25 (14/11)	Mean = 37		4
Nesse et al,[49] 1985	Patients with panic disorder/agoraphobia	20 (16/4)	Mean ± SD = 32.0 ± 11	Ausc/M-mode echo	35
	Volunteers from a newspaper ad with no panic disorder	3 (not reported)	Mean ± SD = 26.0 ± 5.2		0
Dager et al,[60] 1986	Patients with anxiety disorder and panic attacks	44 (30/14)	Mean = 35.4	M-mode and 2D echo	34 defined, 9 probable, 16 possible
	Patients with GAD and no panic attacks	20 (10/10)	Mean = 36.6		15 defined, 15 probable
Gorman et al,[50] 1988	Patients with panic disorder/agoraphobia	36 (18/18)	Range (mean ± SD), 22–53 (35.4 ± 7.3)	M-mode and 2D echo	39
	Hospital employees	22 (12/10)	Range (mean ± SD), 20–53 (29.3 ± 8.5)		18
Carney et al,[45] 1990	Patients with normal coronary arteries, with MDD/panic disorder	20 (11/9)	Mean ± SD = 52 ± 11	Left ventricular cineangiography	40
	Patients with normal coronary arteries, without MDD/panic disorder	28 (15/13)	Mean ± SD = 56 ± 9		7
Hamada et al,[61] 1998	Patients with panic disorder	121 (55/66)	Range (mean ± SD), 14–79 (38.3 ± 1.2)	M-mode and 2D echo	32.2
	University students and employees	37 (15/22)	Range (mean ± SD), 21–48 (31.6 ± 1.3)		16.7
Martín-Santos et al,[62] 1998	Patients with panic disorder and/or agoraphobia	84 (not reported)	Mean ± SD = 38.1 ± 12.6	M-mode and 2D echo	9.5
	Psychiatric patients without anxiety disorder	74 (not reported)	Mean ± SD = 38.5 ± 13.1		5.4
	Patients of other clinics without anxiety disorder	34 (not reported)	Mean ± SD = 38.9 ± 14.1		17.7
Toren et al,[63] 1999	Children with anxiety disorder	52 (26/26)	Range (mean ± SD), 6–18 (11.5 ± 3.0)	Ausc/M-mode and 2D echo	0
	Children without anxiety disorder	51 (22/29)	Range (mean ± SD), 6–18 (12.9 ± 3.2)		2
Tamam et al,[64] 2000	Patients with panic disorder	50 (34/16)	Range (mean ± SD), 116–55 (33 ± 8)	M-mode and 2D echo	12
	Hospital employees (with no psychiatric or cardiac history)	53 (30/23)	Range (mean ± SD), 17–63 (31 ± 9)		5.7

Abbreviations: 2D echo = 2-dimensional echocardiography, Ausc = auscultation, GAD = generalized anxiety disorder, MDD = major depressive disorder, MVP = mitral valve prolapse.

attacks,[45,60,62,63] with the origin of the volunteer groups thus becoming more equivalent. All but one of these studies showed no difference in MVP prevalence between groups,[45] supporting the hypothesis that the selection bias of most studies might have influenced the results obtained.

The sex and age variables did not seem to be associated with a possible increase in MVP prevalence in patients with panic disorder or with the disparity of the results, since, in the studies with a control group, the subjects were matched for these 2 variables and there were no differences in mean age or sex between studies with a high or a low frequency of MVP.[15]

Prevalence of Panic Disorder/Panic Attacks in Patients With Mitral Valve Prolapse

Thirteen articles dealing with the prevalence of panic disorder/panic attacks in patients with MVP were detected (Table 3). Two evaluated the association between the 2 conditions in both directions, and therefore, they were included in Table 1[54] and Table 2.[64]

Panic disorder prevalence varied widely from 0% to 30% among the studies, and the association between the 2 conditions was considered to be significant in 3 studies.[64–66]

Only 2 of the studies dealing with the evaluation of panic disorder/panic attacks in patients with MVP did not include a control group,[65,66] with a high prevalence of panic attacks in both of them. In 2 other studies, hospital employees without MVP were used as controls.[64,67] Tamam et al.[64] detected a higher prevalence of panic disorder in patients with MVP (16%) than in controls (2%), whereas Mazza et al.[67] did not detect panic disorder/panic attacks in any of the groups studied.

Again, we should emphasize the importance of study group selection bias, especially considering that patients evaluated in hospital settings are usually quite symptomatic. Two strategies have been used to overcome this limitation. In 7 studies, the control group consisted of subjects without MVP followed at outpatient clinics due to cardiac symptoms, with none of the studies finding differences between groups regarding the presence of panic disorder/panic attacks.[54,68–73] Thus, in general, there seems to be no higher prevalence of panic disorder/panic attacks in patients with MVP compared with subjects presenting other cardiac complaints. The other strategy was used by Hartman et al.[74] and Devereux et al.,[75] who first evaluated outpatients with MVP, detecting a high prevalence of panic disorder (15.6% and 30.7%, respectively), and then their relatives, who were assumed to represent a community sample. In this case, there was no difference in the prevalence of panic disorder/panic attacks between relatives with and without MVP. Thus, the authors raised the hypothesis that the prevalence of panic disorder/panic attacks in subjects with MVP who did not seek professional care would be low and similar to the prevalence among subjects without MVP.

It is important to point out that, as discussed earlier, in community investigations such as the Framingham studies using older or current criteria for MVP, no cardiovascular symptoms significantly associated with this cardiac alteration were detected.[18,25,27–29] This finding supports the hypothesis that studies of uncontrolled panic attacks/panic disorder and MVP in hospital settings may contribute to a type I error regarding the relationship between the 2 disorders.[73]

Some limitations repeatedly occurred in these studies. In all of them, the MVP criteria used involved auscultation and/or M-mode echocardiography, methods that are currently considered to be of low reliability for the diagnosis of MVP. Regarding the psychiatric diagnosis, most studies used structured interviews, and it is interesting to note that in the 3 studies in which high prevalences of panic disorder/panic attacks were detected, the evaluators were not blind to the cardiologic diagnosis of the patients.[64–66]

DISCUSSION

The possible relationship between panic disorder and MVP attracted considerable interest in the 1980s and 1990s, even though the results were quite variable. The data obtained thus far are not sufficient to establish or to exclude a greater association between the 2 conditions. However, if there is concomitance between panic disorder and MVP, it is possibly a weak association and mainly occurs in subjects with less severe variants of MVP. Moreover, this association appears to be nonspecific for panic disorder, as previous studies have reported comorbidity between MVP and other anxiety disorders such as generalized anxiety disorder,[60] social phobia,[76] and eating disorders.[77–80] Nevertheless, these studies have methodological limitations similar to those of the panic disorder studies, like sampling biases, older MVP diagnostic criteria, and the inclusion of patients with comorbidities.

Regarding the prevalence of panic disorder/panic attacks in patients with MVP, the studies show in a slightly more consistent manner the absence of significant differences between patients with MVP and patients with other cardiac complaints, and also in relation to normal controls when the studies were conducted outside hospital settings.

The validity of the results, however, is compromised by the differences in the diagnostic criteria and by the low inter-evaluator and test-retest reliability. Moreover, none of the studies examining the association of MVP with panic used what is considered the current state-of-the-art criteria, and the older modes of assessing MVP are expected to overestimate its reported prevalence. Other methodological problems include the lack of "blind"

Table 3. Prevalence of Panic Disorder in Patients With MVP

Study	Sample	N (Female/Male)	Age, y	Criteria for MVP	Results
Kane et al,[68] 1981	Patients with MVP	65 (45/20)	Mean = 43	Ausc/M-mode echo	8% Panic disorder, 25% panic attacks, 9% agoraphobia
	Cardiologic controls (without MVP)	33 (22/11)	Mean = 40.9		6% Panic disorder, 15% panic attacks, 12% agoraphobia
	Hospital employees	22 (17/5)	Mean = 40.3		5% Panic disorder, 5% panic attacks, 5% agoraphobia
Uretsky,[69] 1982	Patients with MVP	45 (not reported)	Mean = 49.9	Ausc	8.8% Chronic anxiety
	Patients with other medical conditions	707 (not reported)	Mean = 46.7		1.7% Chronic anxiety
	Patients "worried well"	184 (not reported)	Not reported		10.3% Chronic anxiety
Crowe et al,[66] 1982	Patients with MVP No control group	50 (not reported)	Not reported	Ausc/M-mode echo	24% Panic attacks
Hartman et al,[74] 1982	A: Patients with MVP	141 (103/38)	Range, 16–76	Ausc/M-mode echo	15.6% Panic disorder, 11.3% panic attacks
	B: Relatives of group A subjects, with MVP	33 (22/11)			3% Panic disorder, 6% panic attacks
	C: Relatives of group A subjects, without MVP	70 (27/43)			2.8% Panic disorder, 8.6% panic attacks
Hickey et al,[54] 1983	Patients referred for echocardiography	103 (55/48)	Range (mean), 23–78 (53)	Ausc/M-mode echo	3% Panic attacks, 1% agoraphobia
	Cardiologic controls (without MVP)	67 (34/33)	Range (mean), 18–77 (48)		0% Panic attacks or agoraphobia
Bowen et al,[70] 1985	Patients with MVP	16 (15/1)	Mean = 27.1	Ausc/M-mode echo	0% Panic disorder/agoraphobia, 6% GAD
	Patients with nonorganic chest pain	15 (11/4)	Mean = 33.4		7% Panic disorder/agoraphobia, 13% GAD
	Patients with a functional murmur	14 (11/3)	Mean = 26.7		0% Panic disorder/agoraphobia or GAD
Grinberg et al,[65] 1985	Patients with MVP No control group	20 (15/5)	Range (mean), 17–63 (37)	Ausc/M-mode echo	30% Agoraphobia + panic attacks, 5% agoraphobia, 10% panic attacks
Mazza et al,[67] 1986	Patients with MVP	48 (36/12)	Range (mean), 21–69 (42.9)	Ausc/M-mode echo	0% Panic disorder, 2% GAD
	Hospital employees and community volunteers (without MVP)	49 (36/13)	Range (mean), 18–71 (42.4)		0% Panic disorder or GAD
Devereux et al,[75] 1986	A: Patients with MVP	88 (62/26)	Range (mean ± SD), 16–65 (40 ± 12)	Ausc/M-mode and 2D echo	30.7% Panic disorder, 2.3% panic attacks
	B: First-degree relatives of group A subjects, with MVP	81 (56/25)	Range (mean ± SD), 16–71 (38 ± 14)		9.9% Panic disorder, 7.4% panic attacks
	C: First-degree relatives of group A subjects, without MVP	172 (80/92)	Range (mean ± SD), 16–84 (42 ± 16)		2.9% Panic disorder, 6.4% panic attacks
	D: Spouses, without MVP, of subjects of the other groups	60 (18/42)	Range, 25–66		5% Panic disorder, 10% panic attacks
Bowen et al,[71] 1991	Patients with MVP	19 (18/1)	Mean ± SD = 33.6 ± 8.6	Ausc/M-mode echo	5.3% Panic disorder/agoraphobia
	Patients with chest pain and no evidence of heart disease	26 (17/9)	Mean ± SD = 40.0 ± 6.5		11.5% Panic disorder/agoraphobia
Alpert et al,[72] 1992	Patients with MVP	44 (34/10)	Mean ± SD = 33 ± 8	M-mode and 2D echo	20% Panic disorder, 23% panic attacks
	Patients with chest pain/palpitations (without MVP)	55 (41/14)	Mean ± SD = 30 ± 10		22% Panic disorder, 25% panic attacks
Sivaramakrishnan et al,[73] 1994	Patients with MVP	33 (3/30)	Mean ± SD = 27 ± 6	M-mode echo	12.1% Panic disorder
	Controls with mild congenital heart changes	27 (5/22)	Mean ± SD = 29 ± 7		3.7% Panic disorder
Tamam et al,[64] 2000	Patients with MVP	50 (32/18)	Range (mean ± SD), 15–51 (31 ± 9)	M-mode and 2D echo	16% Panic disorder
	Hospital employees (without MVP)	50 (28/22)	Range (mean ± SD), 17–63 (31 ± 9)		2% Panic disorder

Abbreviations: 2D echo = 2-dimensional echocardiography, Ausc = auscultation, GAD = generalized anxiety disorder, MVP = mitral valve prolapse.

evaluators for panic disorder and MVP in some of the studies and sample biases regarding both patients and controls. These problems and the consequent wide variation in the results published prevent any definite conclusion or generalization of the data.

Although no causal hypothesis between the 2 conditions has been convincingly supported thus far, several possible causes exist for the hypothetical connection between the 2 conditions. Initially, symptoms common to both MVP and panic disorder such as palpitations, chest pain, dyspnea, fatigue, dizziness, and syncope led to the suspicion of an association.[12,13] Furthermore, cardiovascular complaints are among the most frequent and most anguish-producing symptoms of panic attacks. Thus, it was proposed that panic disorder may be caused by MVP or vice versa.[11–14] Some cases of MVP may result from physiologic changes associated with the emotional activity experienced by patients with panic disorder or may be secondary to the hemodynamic changes provoked by the panic attacks. Another possibility is that spontaneous panic attacks are provoked by cardiac arrhythmias, which have been reported in patients with MVP.[58]

An alternative to a direct causal relation could be that MVP contributes other factors to the triggering of panic crises in individuals with greater biological vulnerability. A cognitive model suggests that patients with panic disorder tend to interpret different stimuli or bodily sensations in a catastrophic manner.[81] These stimuli may include, for example, a cardiologic diagnosis communicated to the patient in an abrupt manner or the perception of a tachycardia with no major clinical significance, situations that can be encountered among patients with MVP. These stimuli may be interpreted as a risk to life and may lead to more anxiety, with autonomic symptoms triggering panic crises in predisposed persons.[46]

Furthermore, there may also be a third variable, such as joint hypermobility syndrome (JHS), acting as a confounding variable between MVP and panic disorder, or it may be possible that MVP, JHS, and panic disorder are in fact manifestations of parts of a more complex syndrome involving changes in connective tissue and anxiety disorders. Several studies have suggested that MVP and JHS, which is a benign change of connective tissue, may share similar physiopathologic mechanisms,[82–87] and other studies have demonstrated an association between anxiety disorders, mainly panic disorder, and JHS.[62,88–90] However, this variable was controlled in only one study on panic disorder and MVP,[62] so that no conclusions can be reached about this topic.

It would be easier to establish a causal connection if there were differences in other biological measurements between patients with panic disorder with and without MVP. However, no differences were detected in symptom profile,[62] response to lactate infusion,[14,91] or family risk for the disorder.[92]

Due to the overlap of clinical manifestations, it can be presumed that panic manifestations will occur at higher frequency in patients with MVP than in normal controls. On the other hand, it is not surprising that control groups of normal patients had lower prevalences but that no differences were detected when they were matched with subjects with other cardiac changes. Apparently, persons with MVP who seek medical care may have a higher frequency of panic attacks, but this does not reflect a causal relationship between the 2 conditions. Thus, it is also possible that comorbidity of these 2 disorders is seen more frequently because persons with both disorders are more likely to seek medical care and consequently to be selected for study.

It should also be mentioned that longitudinal studies have implicated thickening of the leaflets, which represents the myxomatous degeneration of the valve, as the major predictor of a worse prognosis, with a higher risk of sudden death, endocarditis, and mitral regurgitation in patients with classic prolapse.[26,93] These findings raise the possibility that nonclassic prolapse may be a variant of normality, or at least a benign abnormality of the mitral anatomy. Similarly, prolapse of the leaflets of less than 2 mm, which represented a large portion of the results obtained in the various articles reviewed, is not correlated with MVP complications.[37]

In order to reach a definitive conclusion about the association between panic disorder and MVP, future studies on this topic should be especially concerned about the methodological biases. It would be desirable to use more up-to-date and reliable diagnostic criteria for both panic disorder and MVP, with evaluators blind to the diagnosis of the participants, with paired samples regarding joint hypermobility syndrome, with no comorbidities, and with case and control groups from similar settings.

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