Mitral Valve Prolapse and Panic Disorder: A Review of their Relationship

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There has been considerable speculation about a possible relationship between panic disorder and mitral valve prolapse syndrome (MVP), although empirical results have been highly inconsistent. Some studies report low frequencies of 0–8%, others high frequencies of 24–35% "definite" MVP in panic patients (average across 17 studies: 18% of panic patients, 1% of normal controls). Elevated prevalences of MVP were also reported for generalized anxiety disorder, bipolar affective disorder, and anorexia nervosa. Studies of MVP patients generally failed to find elevated prevalence of panic compared to other cardiac patients or normal controls (averages across seven studies: 14%, 10%, and 8%, respectively). Inconsistent results may be due to widely different diagnostic criteria for MVP, low reliability of this diagnosis, inadequate control groups, "non-blind" ratings of panic or MVP, and sampling bias in both patient and control populations. These problems as well as the great variations in the published results preclude any final judgment. If there is concomitance between MVP and panic, it is small and primarily involves subjects with milder or reversible variants of MVP. At present it seems most justified, however, to assume co-morbidity in highly symptomatic individuals rather than a functional relationship.

INTRODUCTION

Mitral valve prolapse (MVP) and panic disorder are two newly defined disorders—the first cardiological and the second psychiatric. In recent years the possible relationship between these disorders has received considerable attention in both clinical areas. Research findings have been inconsistent as to the strength of their association. As we will demonstrate in this review, this inconsistency may stem from three problems: widely different diagnostic criteria for MVP, a lack of reliability of this diagnosis, and sampling bias in both patient and control populations.

Although the auscultatory signs of MVP have been known for over 100 yr (1), it was not until the 1960s that mid-systolic clicks and late systolic murmurs were related to the mitral valve. Confirmation of the intracardiac origin of these sounds by Reid (2) and Barlow et al. (3, 4) marked the recognition of the prolapsed mitral valve as a cardiac syndrome. Since the publication of the influential review by Devereux et al. (5), this syndrome has been commonly designated by the term MVP. In the past decade MVP has become the most frequently diagnosed cardiac valvular abnormality.

The symptoms of panic disorder have been seen as part of some psychiatric entity since the time of Freud and before, but were given cardinal diagnostic relevance

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only with the introduction of panic disorder and agoraphobia with panic attacks as diagnostic categories in DSM-III in 1980. The changes in the classification of anxiety disorders reflect the influence of biological models of panic attacks (6). Today, panic disorder leads the list of psychiatric disorders for which people seek professional help (7).

A primary feature of both patients with panic disorder and many agoraphobics are panic attacks, periods of intense apprehension or fear during which the patient experiences a multitude of somatic symptoms. Cardiovascular complaints number among the most frequent and distressing of these symptoms (8, 9). In addition, panic attacks are sometimes accompanied by tachycardias (9–13). Cardiovascular manifestations of anxiety have been known to medicine and psychology for a long time (for a review, see Skerritt, 14).

Clinical descriptions of patients with various diagnoses on the borderline of psychiatry and cardiology such as "Da Costa's syndrome," "soldier's heart," "effort syndrome," "neurocirculatory asthenia," or "cardiac neurosis" bear many similarities to current diagnostic criteria for panic disorder. The same applies to today's MVP syndrome, the heir of these cardiological "diseases of yesteryear" (1). Both MVP and panic disorder patients complain of palpitations, chest pain, dyspnea, fatigue, lightheadedness, dizziness, and actual or near syncope (15–17). While the apparent association between MVP and chest pain and dyspnea may be an artifact of patient selection (18–22), the general similarity of subjective complaints has lead to speculation that panic disorder may in some cases be "caused" by mitral valve prolapse, or conversely that panic disorder may lead to mitral valve prolapse (1, 23–26). Studies of the possible concomitance of MVP and panic disorder, however, have yielded surprisingly inconsistent results (27). It is the purpose of this article to review the results of these studies and to critically evaluate possible explanations for these inconsistencies.

RELIABILITY OF DIAGNOSING MVP AND PANIC DISORDER

The mitral valve separates the left atrium from the left ventricle. It consists of an anterior and a posterior leaflet, which are attached to the papillary muscles of the left ventricular wall by the chordae tendineae. Normally, the mitral valve closes completely when blood is ejected into the aorta during ventricular systole, thus preventing back-flow into the left atrium. In the case of MVP, however, the mitral valve bows back into the left atrium during systole. Typically, this involves the posterior leaflet or both leaflets, but rarely the anterior leaflet alone (5). Rarely, the bulging of the leaflets is sufficient to disrupt their normal apposition, which permits regurgitation of blood into the left atrium. Evidence of at least mild mitral regurgitation is detected by auscultation or Doppler echocardiography in at least one-third of MVP patients (21, 28).

MVP was originally diagnosed by auscultation. The abrupt tensing during systole of the leaflets and the chordae tendineae generally produces a characteristic clicking sound. This occurs most often during mid-systole. In addition, if blood leaks back into the left atrium, a typical late systolic murmur can often be heard. Today the diagnosis of MVP is usually based on echocardiography, which allows noninvasive visualization and measure-

ment of the mobility of the mitral valve (29). A recent review by Devereux et al. compares the performance of the different methods of diagnosing MVP (30). While echocardiography is generally more sensitive than auscultation, there is also great variability in the criteria used to detect MVP by this method. Although there are published guidelines (e.g., 29, 31–33), their application is still fairly subjective. This may in part explain the the widely discrepant findings obtained from different studies.

Even within the same study, the prevalence of MVP may vary from 13% to 0.5% (34) or from 59% to 34% (35) depending on the stringency of the criteria. An estimate of the retest and interrater reliability of raters from the same laboratory using the same criteria was attempted by Wann et al. (36), who demonstrated a disconcerting lack of diagnostic precision: The percent agreement between the three independent raters ranged from 52% to 80% for one- and two-dimensional echocardiography, the mean being a low 64%. Intraindividual agreement (a measure of retest reliability) ranged from 80% to 98% (mean: 88%). Reliability seemed to be highest when the most stringent and conservative criteria were used. It can be expected that agreement between raters from different institutions may be even less satisfactory. This is in fact indicated by the recent study of Gorman et al., who investigated a series of 15 patients with panic disorders (37). One experienced echocardiogram reader diagnosed MVP in nine patients, while a second did not make the diagnosis in any patient. A third study compared ratings of M-mode recordings of two cardiologists who had received specialty training in echocardiography in the same university center (38). The results confirmed unacceptably low levels of inter-rater reliability (kappa: .11) and retest-reliability (after 10 months: .41–.45). Although better reliability has been reported in studies that explicitly paid attention to tracing quality (39–41), the lack of diagnostic precision documented above must be taken into consideration when evaluating the following sections on the epidemiology of MVP and its possible relationship to panic disorder.

Panic disorder, on the other hand, can be diagnosed quite reliably. For a long time, research in psychiatry was hampered by a low reliability of psychiatric diagnoses, especially those of neurotic disorders (42). However, in recent years significant progress has been made in improving diagnostic reliability. DSM-III has contributed to this development by specifying symptoms and criteria for each diagnostic category. Another important contribution was the development of structured diagnostic interviews. With these interviews, interrater and test-retest reliabilities for panic disorder now reach kappas of 0.6 to 0.8 (43, 44).

EPIDEMIOLOGY OF MVP AND PANIC ATTACKS

The estimated prevalence of MVP has ranged widely from 4% to 21% (5, 32) depending on the population studied and the diagnostic method employed. Since samples of physician-referred or self-referred patients, or arbitrarily chosen nonclinical subjects, are unlikely to be representative of MVP prevalence in the general population, community surveys like the Framingham Heart Study (45) are more valid sources of that information. In the Framingham sample of 4,967 subjects, the

overall rate of MVP was 5%. This relatively low percentage is likely still to be an overestimate because relatively nonspecific echocardiographic criteria were used: More recent studies suggest a true prevalence of 3–4% or even less (46–50). The Framingham Study revealed a striking effect of age and sex: While prevalence in men ranged from 2% to 4% at all ages, the rates in women decreased strongly with increasing age. The rate for women between 20–29 yr was 17%, but for women over 70 years, less than 2%. The strongest drop in frequency of MVP appeared between middle age (40s and 50s) and older age (60s and 70s). Since other studies suggest that MVP does not shorten the average life span (see below for details), this age dependency in the female population could not be an artifact of cross-sectional sampling. In addition, other studies have confirmed these age and sex differences (30, 48, 51).

Recent large-scale epidemiological studies of psychiatric morbidity have established a high prevalence for disorders associated with panic attacks (52, 53). Lifetime prevalence rates for panic disorder without agoraphobia range from 1.4% or 1.5% in the United States to 2.4% in Germany. Even higher rates are found for agoraphobia with panic attacks. Panic attacks also occur in patients with other psychiatric disorders and in substantial proportions of nonclinical populations (54–56).

Given this background, what is the relationship of MVP and panic disorder? The question has been approached from two perspectives. Most researchers studied the prevalence of MVP in patients that were diagnosed as having panic attacks. A smaller number of studies investigated the opposite question, namely the prevalence of panic attacks in samples of MVP patients. The two strategies have yielded different results, as we will present in the following sections.

PREVALENCE OF MVP IN PANIC ATTACK PATIENTS

After Pariser et al. first described a case of combined MVP and panic disorder (23), several studies reported high prevalences of MVP in panic attack patients. These studies led to the claim that MVP may be one frequent cause of panic attacks (24, 25). However, among more recent studies are several that report no elevated frequency of MVP. A summary of the 17 studies of MVP in patients with panic disorder or agoraphobia is given in Table 1. Not all studies used homogeneous patient samples. Pariser et al. included 10 patients with major depression (MD) (24), Kathol et al. included three with generalized anxiety disorder (GAD) or simple phobias (57), and out of the 31 chest pain patients with normal coronary arteries studied by Bass et al., only 12 met criteria for anxiety or phobic neurosis (58). All of the studies have been published as papers or abstracts with the exception of study 17 (Taylor et al., Department of Psychiatry and Behavioral Sciences, Stanford University, in preparation).

Only five studies included "normal" control subjects (N from 3 to 25), most of whom were "professionals" (e.g., hospital employees). This limits the interpretability of the findings, considering the great variability in diagnosis and published prevalence of MVP in the general population. In addition, in a number of the studies cardiological diagnoses were performed unblindly by raters with knowledge of the psychiatric status of the patients. That blind ratings are important is

emphasized by the study of Gorman and coworkers (60) in which one blind rater found 35% MVP, while the nonblind rater found 50% MVP among their panic attack patients.

Most of the studies used two sets of criteria for the diagnosis of MVP, usually termed definite and probable criteria. Eighteen percent (N = 106) of the 589 patients in the 17 studies that had panic disorder or agoraphobia met criteria for definite MVP, and 27% (N = 157) met criteria for probable or definite MVP. (These numbers do not include the small samples of depressive, GAD, or undiagnosed patients that several studies contained.) In one study (35), a clinical control group of patients with generalized anxiety disorder was tested. Their rates of definite or probable/definite MVP were 15% and 30%, respectively. In the 81 normal controls, the average rate of definite MVP was 1% (N = 1). Probable and/or definite MVP was diagnosed in 12% (N = 10). This rate of definite MVP is lower than that reported for the general population, which may be related to the lack of representativeness of health professionals as control subjects. In this context it is interesting to note that the two studies using community volunteers rather than health professionals as control subjects found no difference in the prevalence of MVP (studies 11, 17). The pooled differences between panic disorder, GAD, and normals are significant for both the definite ($chi^2 = 15.15$, df = 2, $p < 0.0005$) and probable criteria for MVP ($chi^2 = 10.71$, df = 2, $p < 0.0047$). However, all of these pooled results are tentative, since they are based on studies that used very different and probably unreliable criteria for MVP.

Eleven studies allow an estimate of the percentage of subjects that met both auscultatory and echocardiographic criteria for MVP. Ten percent (N = 45) of the 464 panic attack patients in these reports (studies 2–4, 7–10, 12, 14, 16, 17) and 2% of the control subjects met both criteria (1 of 57, studies 2, 3, 17). Again this difference is statistically significant (Fisher's exact probability test, $p < 0.0001$).

The methodological problems discussed above (studies of clinical series of highly symptomatic referred patients, lack of adequate control groups, nonblind ratings, unreliable diagnosis of MVP) and the great variations in published results preclude final judgment of the concomitance of MVP and panic disorder. These variations have a bimodal distribution: One group of studies reports low frequencies of 0% to 8%, the other high frequencies of 24% to 35% for "definite" MVP. This suggests systematic differences in diagnostic criteria or the operation of other factors as yet undetected. Until these factors have been controlled, the computation of averages across the two groups of studies above is suspect. This must be kept in mind when we interpret the average findings as indicating a possible elevated prevalence of MVP in panic attack patients studied in clinical settings. In addition, different referral patterns might contribute to a true high prevalence of MVP in some but not other panic disorder populations. Patients with multiple diagnoses may be more likely to receive care in tertiary care institutions. If a substantial proportion of referrals to a specific psychiatric or psychological service came from internists or cardiologists, a higher prevalence of MVP could result.

Could the increased prevalence of MVP in panic patients be due to the sex and age characteristics of the samples studied? The average age of the patients across all stud-

TABLE 1. Prevalence of MVP in Panic Attack Patients

Study	Panic patient sample	Control sample	"Blind" ratings?	Criteria for MVP	Number of subjects with MVP
1. Pariser et al. (1979) (24)	5 PD, 10 MD, 2 undiagnosed; 9F/8M, 21–53 yrs.	None	?	Ausc./echo.	PD: 1 (20%), MDE: 3 (30%) undiagnosed: 2 (100%)
2. Venkatesh et al. 1980 (59)	21 anxiety neurosis (Feighner); 15F/6M, 37 yrs.	20 hospital employees; 9F/8M, 37 yrs.	Yes	Ausc./echo. (Markiewicz)	Patients: 5 only met ausc. (24%), 3 only echo. (14%) 5 ausc. + echo. criteria (24%); controls: 5 (25%), 1 (5%), 1 (5%), respectively.
3. Kantor et al. 1980 (25)	25 PD/AG, history of palpitations; all F, 42 yrs.	23 hospital employees; all F, same age.	Yes	Ausc./echo.	Patients: 2 only met ausc. (8%), 3 (12%) ausc. and echo. criteria; controls: 2 (9%) met only echo. criteria.
4. Kathol et al. 1980 (57)	18 PD, 5 AG, 3 GAD or simple phobia; 12F/14M, 36 yrs.	None	?	Ausc./echo. (Markiewicz)	PD: 1 (4% of PD/AG)
5. Gorman et al. 1981 (60)	20 PD/AG; 15F/5M, 40 yrs.	None	1 of 2 raters blind	Ausc./echo. (Markiewicz)	Non-blind rater: 10 (50%), blind rater: 7 (35%).
6. Grunhaus et al. 1982 (61)	23 PD/AG; 15F/8M, 35 yrs.	None	?	Ausc./echo. (Weiss)	2 only usc. (9%), 7 (30%) ausc. and echo. criteria.
7. Bass et al. 1983 (58)	31 chest pain with normal coronary arteries, includes 12 anxiety neurosis; 17F/14M, 44.5 yrs.	None	Yes	Ausc./echo. (Wann)	None
8. Hickey et al. 1983 (62)	50 AG; 42F/8M, 36 yrs.	None	?	Ausc./echo. (Markiewicz)	None

9. Mavissakalian et al. 1983 (63)	54 AG; 46F/7M, 37.6 yrs.	None	?	Ausc./echo. (Markiewicz)	3 definite (6%), 4 probable (7%)
10. Chan et al. 1984 (64)	10 PD, 4 AG, 4 GAD, 1 social phobia	None	?	Ausc./echo. (Wann)	None
11. Shear et al. 1984 (65)	25 PD/AG; 14F/11M, 35.8 yrs.	25 spouses of MVP patients from earlier study, 14F/11M, 37 yrs.	Yes	Echo.	Patients: 2 definite (8%), 2 probable (8%); controls: 2 probable 8%).
12. Harbauer-Raum & Strian 1985 (66)	27 PD	None	?	Ausc./echo.	2 definite (7%)
13. Nesse et al. 1985 (67)	20-PD/AG; 16F/4M, 32 yrs.	3 volunteers	Yes	Ausc./echo. (Markiewicz)	Patients: 7 (35%); controls: 0.
14. Ballenger et al. 1986 (68)	78 PD/AG	None	?	Ausc./echo.	9 ausc. and echo. (12%), 19 echo only (24%)
15. Dager et al. 1986 (35)	24 PD, 11 AG, 9 GAD with panic attacks; 30F/14M, 35.4 yrs.	20 GAD; 10F/10M, 36.6 yrs.	Yes	Echo.	Panic patients: 15 definite (34%); 4 probable (9%), 7 possible (16%); GAD: 3 definite (15%), 3 probable (15%).
16. Liberthson et al. 1986 (15)	131 PD/AG; 84F/47M, 38 yrs.	None	?	Ausc./echo.	44 definite (34%) (includes 22 = 17% ausc. and echo.), 7 probable (5%).
17. Taylor et al. (in prep.)	12 PD/AG; all F, 39.8 yrs.	12 volunteers, all F, 35.5 yrs.	Yes	Ausc./echo.	None

Note: "Blind" ratings refers to whether the cardiologist was aware of the subjects' psychiatric status. The study of Hickey et al. (1983) is the same as that listed in Table 2, where only the results for the MVP and cardiac control samples are reported. The descriptions of the samples list the number and type of patients or controls, the ratio of female and male subjects, and mean ages (if available).

Abbreviations: ausc., auscultation; echo., echocardiogram; yrs., years, F, female; M, male; PD, panic disorder; PA, panic attacks; AG, agoraphobia with panic attacks; GAD, generalized anxiety disorder; MDE, major depressive episode; MVP, mitral valve prolapse.

ies was 37.6 yr, and 68% were women. As discussed above, the prevalence of MVP is indeed highest in women under age 50. If we calculate from the Framingham Heart Study, we can expect to see a prevalence of 13.1% (with stringent echocardiographic criteria) for this group of subjects. Two reasons, however, argue against this tempting explanation for an elevated prevalence of MVP in panic attack patients. First, the control groups were matched for age and sex. Second, the proportion of female subjects and their average ages are not different in studies with a low frequency of MVP (38 yr and 67% women) from those in studies with a high frequency (37.3 yr and 69% women).

Is the possible higher prevalence of MVP specific to panic disorder or does it exist in other psychiatric populations as well? Dager et al. (35) found a higher prevalence in panic disorder than in generalized anxiety disorder. However, their rate of 30% definite or probable MVP in GAD is higher than in any reported control population. Meyers et al. (74) found 32% of 28 anorexia nervosa patients had MVP as compared to 7% of a control group. MVP was a result of the anorectic state since it remitted in all patients who subsequently approached normal weight. Bipolar affective disorder patients have also been reported to have a high prevalence (44%) of MVP, though there was no control group (75). These authors used the simultaneous presence of positive echocardiographic and auscultatory findings as the criterion for MVP.

A definite answer to the question of concomitance of MVP and panic disorder will only be possible after unselected panic disorder patients from community surveys will have been screened with reliable criteria for MVP and compared with controls from the same population. Until then we can only say that at least 80% of the panic attack patients studied so far do not show "definite" MVP, and about 90% do not meet both echocardiographic and auscultatory criteria.

PREVALENCE OF PANIC ATTACKS IN MVP PATIENTS

The results from the eight studies of this topic are summarized in Table 2. Overall there seems to be no elevated prevalence of *panic attacks* in MVP patients compared to subjects with other cardiac complaints. The figures in MVP patients range from 0% to 24% with an average of 14% (76 of 543 patients, based on studies 2–8). For cardiac control subjects the average prevalence of panic attacks is 10% (6 of 62, studies 2, 6). This difference is not significant ($chi^2 = .89$, $df = 1$, $p > 0.05$). The figure for normal controls, many of which were hospital employees, is 7% (27 of 373, based on studies 2, 4, 7, 8). The difference between MVP patients and controls is significant ($chi^2 = 10.12$, $df = 1$, $p < .01$). The mean prevalence of *panic disorder* was 8% among MVP patients (41 of 493, based on studies 2, 4–8), 5% among cardiac control subjects (3 of 62, studies 2, 6), and 2% among normal controls (8 of 373, studies 2, 4, 7, 8). Again, the difference between MVP patients and cardiac controls is not significant ($chi^2 = .91$, $df = 1$, $p > 0.05$), while the difference between MVP patients and normal controls is significant ($chi^2 = 15.15$, $df = 1$, $p < 0.001$). Finally, there were no significant differences between MVP and cardiac control patients in the prevalence of "chronic anxiety" (study 1), "phobic disorder," and agoraphobia (studies 2, 5–7), generalized anx-

iety disorder (study 6), or depression (study 6). In addition to the studies summarized in Table 2, Chesler et al. (76) reported no difference between MVP patients and normal controls with respect to "anxiety neurosis" or trait anxiety. However, this study did not specifically address the issue of panic attacks and thus is not included in the table. Similarly, Devereux et al. (21) found no differences in high trait anxiety between first-degree relatives of MVP patients with and without MVP.

Patients with MVP generally scored higher than normal controls but similarly to cardiac control subjects on questionnaire measures of hypochondriasis (Whitely Index), avoidance behavior (Maudsley-Oxford Fear Questionnaire), cardiac and neuropsychiatric symptoms, chronic anxiety, general neurotic symptoms (General Health Questionnaire), neuroticism (Eysenck Personality Inventory), the Zung Anxiety Scale, and all the SCL-90 scales except paranoid ideation (studies 1, 2, 4, 7). The scores on anxiety scales, while being higher than those of the normal controls, were considerably lower than the norms reported for patients with anxiety disorders (studies 2, 6). In one study (72, study 6), a group of patients with nonorganic chest complaints without any signs of panic attacks scored significantly higher on the somatization and anxiety scales of the SCL-90 than the MVP patients.

None of these studies were based on community surveys, and referral populations in hospital settings may represent a selection of highly symptomatic individuals. This has been termed "ascertainment bias" by Motulsky (77). In this context, the control groups employed by Uretsky (18, 19), Hartman et al. (71), Bowen et al. (72), and Devereux et al. (21) are especially interesting. These authors looked for strategies to circumvent or control the problem of biased selection. Uretsky (18, 19) separated his medical control group into those that had evidence of medical disease and those that had sought professional help but did not show any identifiable disease (the "worried well"). The second group scored just as high as the patients with MVP on his measures of neuropsychiatric symptoms, cardiac symptoms, and chronic anxiety. Bowen et al. (72) compared patients with nonorganic chest complaints with MVP patients. The only patient with panic disorder they found was from the cardiac control group (i.e., the chest complaint group), whose members also scored higher on two SCL-90 scores, anxiety and somatization. Using a different approach, Hartman et al. (71) studied the family members of their MVP patients who had not sought professional help and thus presumably represented a group with less selection bias. Family members with MVP were not different from those without MVP. Both groups had fewer panic attacks than the original sample of MVP patients who had been referred to the clinic. Using the same method, Devereux et al. (21) got the same results in larger samples of relatives and spouses of MVP patients.

These findings are consistent with the lack of significant cardiovascular symptoms (including many typical panic attack symptoms) found in the Framingham Heart Study discussed above (20, 45, 78). These studies clearly illustrate the relevance of ascertainment bias for our topic. If this bias is eliminated or controlled, the prevalence of panic attacks or psychiatric symptoms is not higher than among all patients in cardiologic practice. It is possible, however, that all of these groups have a higher prevalence of panic attacks than normal control subjects who are not seeking

TABLE 2. Prevalence of Panic Attacks in MVP Patients

Study	MVP Patient sample	Control sample	"Blind" ratings?	Criteria for MVP/panic	Number of subjects with panic and other results
1. Uretsky 1980, 1982 (18,19)	45 medical outpatients (includes 29 without any other disease); 49.9 yrs.	972 medical outpatients, (includes 184 without any disease = the "worried well" 46.7 yrs.	No	Auscultatory; symptom reports	Chronic anxiety: MVP = "worried well" (10.3% vs. 7.1%); both groups more symptoms than med. outpatients in general (4.2%).
2. Kane et al. 1981 (69)	65 referrals for echocardiography; 45F/20M, 43 yrs.	A: 33 cardiac controls ("CC", no MVP); 22F/11M, 40.9 yrs. B: 22 hospital employees; 17F/5M, 40.3 yrs.	Yes	Echo.; DSM-III, questionnaires	MVP: 5 PD (8%), 16 PA (25%), 6 AG (9%); A ("CC"): 2 PD (6%), 5 PA (15%), 4 AG (12%); B (hosp. empl.): 1 PD (5%), PA (5%), 1 AG (5%). MVP = A ("CC") on questionnaires, both higher than hospital employees.
3. Crowe et al. 1982 (70)	50 outpatients	None	?	Ausc./echo.; DSM-III	MVP: 12 PA (24%)
4. Hartman et al. 1982 (71)	A: 141 referrals for echo.; 103F/38M, 16–76 yrs. B: 33 family members of subjects from A; 22F/11M.	70 family members MVP; 27F/43M.	?	Ausc./echo. (Markiewicz); DSM-III	MVP-A: 22 PD (16%), 29 PA (21%); MVP-B: 1PD (3%), 3 PA (9%); non-MVP family members: 2 PD (3%), 8 PA (10%).
5. Hickey et al. 1983 (62)	103 referrals for echo.; 55F/48M, 53 yrs.	67 cardiac controls ("CC", no MVP); 34F/33M, 48 yrs.	?	Ausc./echo. (Markiewicz, 10 patients echo. only); DSM-III, questionnaires	MVP: 3 PA (3%), 1 AG (1%); CC: no PA, no AG; MVP = CC on neuroticism and neurotic symptoms.

6. Bowen et al. 1985 (72)	16 cardiological outpatients; 15F/1M, 27.1 yrs.	A: 15 non-organic chest complaints; 11F/4M, 33.4 yrs. B: 14 "functional murmurs"; 11F/3M, 26.7 yrs.	Yes	Aus./echo. (Markiewicz); SADS-L and RDC, questionnaires	MVP: no PD/AG, 1 GAD, 3 major depression; A (chest complaints): 1 PD, 2 GAD, 7 major depression, 2 mania/hypomania; B (functional murmurs): no PD/AG, no GAD; A score higher on SCL-90 somatization and anxiety than MVP or B.
7. Mazza et al. 1986 (73)	48 referrals for echo.; 36F/12M, 42.9 yrs.	49 hospital employees and volunteers (no MVP); 36F/13M, 42.4 yrs.	Yes	Ausc./echo.; DSM-III, questionnaires	MVP and controls: no PD/AG. MVP more anxious than controls (Zung Scale), but lower than norms for anxiety disorder patients
8. Devereux et al. 1986 (21)	A: 88 outpatients with consenting family members; 62F/26M, 40 yrs. B: 81 first-degree relatives of subjects from A; 56F/25M, 38 yrs.	A: 172 first-degree relatives without MVP of subjects from A; 80F/92M, 42 yrs. B: 60 spouses without MVP of subjects from A; 18F/42M, 25–66 yrs.	?	Ausc./echo. (Markiewicz); DSM-III and Feighner, STAI	MVP-A: 12 PD (14%), 14 PA (16%); MVP-B: 4 PD (5%), 7 PA (9%); non-MVP relatives: 4 PD (2%), 14 PA (8%); spouses: 1 PD (2%), 2 PA (3%). Differences between family members with and without MVP not significant. Similar results for scores >50 on STAI 12, 6, 6, 7% for the 2 MVP and the 2 non-MVP groups).

Note: "Blind" ratings refers to whether the psychiatric diagnostician was aware of the subject's cardiological status. The study of Hickey et al. (1983) is the same as that listed in Table 1, where only the results for the agoraphobic sample are reported. The descriptions of the samples list the number and type of patients and controls, the ratio of female and male subjects, and mean ages (if available). The numbers given for the diagnoses panic disorder, agoraphobia, and panic attacks are overlapping.

Abbreviations: ausc., auscultation; echo., echocardiogram; yrs., years, F, female; M, male; PD, panic disorder; PA, panic attacks; AG, agoraphobia with panic attacks; GAD, generalized anxiety disorder; MVP, mitral valve prolapse; CC, cardiac control subjects; STAI, State-Trait Anxiety Inventory (trait form).

professional help, although the family studies of Hartman et al. (71) and Devereux et al. (21) do not support this notion.

PHYSICAL MORBIDITY IN MVP

Would an association between MVP and panic disorder have any implications for the physical health of panic patients? Whether physical morbidity or excess mortality is associated with MVP is controversial (79, 80). Inconsistencies between the results of different studies may result from the lack of diagnostic reliability discussed above or to discrepancies between patient samples in clinical series and community surveys. In addition, MVP may represent a heterogeneous entity that is benign in some forms but not in others.

Until recently, most studies of associated pathology in MVP were based on patients referred with cardiac complaints or other diseases. While the majority of patients in these studies did not show significant cardiac pathology, certain patients had anatomical abnormalities such as thickening of the leaflets or elongated, thin, and attenuated chordae tendineae (5). Such abnormalities could be the basis of rare complications reported for MVP: infective endocarditis, spontaneous rupture of the chordae tendineae, and progressive mitral regurgitation (for reviews, see 5, 81). There have been a small number of documented cases of sudden death in MVP patients, although the relationship between MVP and the cause of death was not always clear (82). A small minority of MVP patients have coexisting cardiac conditions such as the Marfan and Ehlers-Danlos syndromes (5). MVP patients from clinical series have an increased prevalence of dysrhythmias (83, 84). Other reported findings from such samples include higher plasma levels and urinary excretion of catecholamines (85–90; but not in 76), although, surprisingly, this was not the case in patients with both anxiety disorders and MVP (67, 91).

Clinical series like those reported above, however, may not be representative of patients with MVP, since people seeking professional help may have more pathology than asymptomatic subjects. This bias can only be overcome by largescale community surveys such as the Framingham Heart Study, the results of which support the notion that MVP in general is a harmless condition. In this study, subjects with and without MVP (determined by m-mode echocardiograms) were not significantly different with respect to the prevalence of the Marfan or Ehlers-Danlos syndromes, significant cardiac disease (including inherited connective tissue syndromes and coronary artery disease), left ventricular function, cardiovascular symptoms (including chest pain, dyspnea, and syncope), abnormal standard 12-lead EKG findings (including ST-T and QT_c changes), response to treadmill exercise testing, or dysrhythmias during 24-hour ambulatory EKG monitoring or treadmill exercise (20, 78). Thus, although MVP may be more common in specific cardiovascular conditions, these are a small fraction of MVP cases.

Data from long-term follow-up studies of clinical series of MVP patients suggest that the outcome of MVP is generally benign, consistent with the implications of the cross-sectional Framingham Heart Study. These long-term studies do not find a higher death rate in people with MVP (92–98).

Perhaps MVP is not a homogeneous entity, but has several forms of different prognostic significance. In a recent editorial in the New England Journal of Medi-

cine, Wynne (81) suggests that the advent of the more sensitive echocardiographic methods have led to the inclusion of normal variants into the MVP syndrome. He points out that the diagnosis is based on the mobility of the mitral valve, which is a continuous, not a dichotomous variable. Therefore, the findings of the Framingham study can be interpreted as meaning that the diagnosis of MVP is applied to two groups of individuals. The first contains subjects that are no more symptomatic and have no more arrhythmias than their peers without MVP. They are at low risk for complications. In general, their diagnosis is based on echocardiography, and the typical auscultatory signs are missing. The second group contains subjects who, in addition to the echocardiographic findings, also show evidence of mitral regurgitation (often with auscultatory signs). These subjects have more symptoms and appear to be at greater risk for complications. Additional evidence for this is presented by Nishimura et al. (98), who found that in almost every case, complications occurred in subjects with anatomical abnormalities. Thus, it is possible that the majority of the cases diagnosed by echocardiography alone are variants of normal functioning, perhaps even dependent on the state of the individual at the time of testing. Only a minority of cases may represent anatomical abnormalities of perhaps greater pathological significance. This minority might be more likely to have mitral regurgitation and infective endocarditis, an association occurring primarily in older patients and men (49, 99, 100). These same populations are far less likely to have coexisting panic disorder than young women, in whom MVP generally is free of cardiologic complications.

If MVP of a type associated with higher mortality rates were more common in panic disorder, panic disorder patients should show higher mortality rates. Existing studies of the long-term outcome of panic disorder are all retrospective, and none has looked at a possible relationship to MVP. In two independent follow-up studies of 113 and 155 patients, Coryell and colleagues (101, 102) found an increased mortality for male panic disorder patients, the increase being accounted for by cardiovascular death and suicide. However, these results are based on very small numbers of expected and observed deaths: in the first study six men were expected to die of cardiovascular disease or its complications whereas 12 men actually so died, and in the second study 1.8 total male deaths were expected whereas four men actually died, three of them from cardiovascular causes. In no case was there evidence for death being a complication of MVP. There was no increased death due to natural causes (including cardiovascular disease) in follow-ups of 62 anxiety neurotics (103) or of 384 neurotics with anxiety, somatization, or obsessive compulsive disorders (104). Winokur and Black (105) also found no such relationship. In summary, any link between panic disorder and cardiovascular mortality has to be considered tentative at most.

DISCUSSION

At present the available information neither supports nor excludes a higher prevalence of MVP in panic disorder patients. If there is a concomitance between panic disorder and MVP, it is small, affecting less than 8% of MVP and less than 20% of clinical (and thus presumably highly selected) samples of panic disorder patients. Such a concomitance must consist primarily of subjects with milder variants

of MVP that represent functional and perhaps reversible rather than anatomical and permanent abnormalities (29), since those subjects are more numerous and only a low proportion of panic attack patients have both echocardiographic and auscultatory evidence for MVP. The reversibility of MVP in panic disorder is supported by the recently presented data of Gorman (106) showing that evidence of MVP often disappears after remission of panic attacks has been achieved for at least 6 months. Unfortunately, we have no information about the retest reliability of the diagnostic methods used to determine MVP in this study. The anorectics of Meyers et al. (74) also evidenced reversible MVP.

Several causal links between MVP and panic disorder are possible. For example, certain forms of MVP may result from the physiological changes associated with the acute or chronic emotional arousal experienced by panic disorder patients. This would be consistent with the reversibility of MVP in panic patients. Experiments show that mild MVP can be induced in the context of high heart rate and low ventricular volume or by direct programmed ventricular stimulation (68, 107). Combs et al. (108) showed that psychological stress (increasingly difficult guessing tests) exerts a significant effect on the rhythm and click in some patients with MVP. Ballenger (68, 109) recently suggested that high levels of circulating catecholamines in the presence of a rapid heart rate can result in MVP. While a number of studies discussed above have reported increased levels of plasma and urinary catecholamines (85–90), this does not seem to be the case in anxiety disorder patients. Nesse et al. (67) found elevated urinary catecholamine excretion only in panic patients without MVP. Panic patients with MVP showed significantly lower levels of norepinephrine and epinephrine and were not different from normal controls. Similarly, Weissman et al. (17) recently reported lower catecholamine excretion in subjects with MVP than in control subjects with similar symptoms but without MVP. In the same vein, Dager et al. (91) found no differences in MHPG/creatinine excretion, platelet and plasma MAO-B activity, heart rate, and blood pressure between panic and generalized anxiety disorder patients with and without MVP. Furthermore, panic patients do not seem to have continuously elevated heart rates compared to normal controls (110).

Another possible causal link is that patients perceive the symptoms of MVP and react to them with panic. In an experimental study, we were able to show that panic patients respond with larger increases in anxiety and physiological arousal (111) or even a full-blown panic attack (112) to falsely elevated feedback of their heart rates. A similar finding was obtained by Strian (84) and Harbauer-Raum (113) in a 24-hr ambulatory EKG monitoring study comparing panic attack patients diagnosed using DSM-III criteria, MVP patients, and normal controls. Only panic attack patients responded with anxiety to perceived arrhythmias (monotope ventricular extrasystoles). The average anxiety score on a scale from 0 to 100 after an arrhythmia was 45 for panickers, 1 for MVP patients, and 0 for normals. In addition, panickers were more accurate in their perception of arrhythmias. Less consistent with a general causal role of MVP in the development of panic attacks, however, is the fact that the study failed to show any differences in the accuracy of perception or the appraisal of arrhythmias between MVP patients and normals. Furthermore, as shown above, MVP patients do not have a higher incidence of panic attacks.

Establishing causal links would be easier if there were differences between panic disorder patients with and without MVP, but generally the two groups are similar: There are no differences between them in symptoms (63, 69), their responses to lactate infusions are similar (114, 115), and they have similar familiar morbidity risks (116). The only difference reported so far is that panic patients with MVP are more likely to respond favorably to placebo than those without MVP (115).

Neither of the explanations discussed above have been supported in a convincing way. This leaves us with two other possibilities: First, both phenomena could be produced by a third factor such as an as yet unknown autonomic abnormality. If this explanation is accepted, one would still have to explain the possibly elevated prevalence of MVP in other psychiatric disorders such as bipolar disorder or anorexia nervosa. This observation is more easily explained by the second possibility, namely that we are dealing with a problem of co-morbidity. People with two disorders are more likely to seek treatment or to be detected in community surveys than people with one disorder alone. That the two disorders are distinct autonomically has been given recent support by Weissman et al. (17), who found different patterns of autonomic responses to postural and positive intrathoracic pressure stresses between patients with MVP and patients with panic disorder. The co-morbidity explanation is a kind of null hypothesis. At the present state of our knowledge we suggest that this hypothesis cannot be refuted.

Although the relationship between MVP and panic disorder is an important theoretical issue, the diagnosis of MVP in an individual panic-attack patient rarely has any implications for clinical management of that patient. Unless significant cardiovascular complications are present, MVP does not require specific treatment in addition to antianxiety therapy (27, 80). Shear et al. (65) suggest that "routine screening of patients with panic disorder for MVP may not be warranted, and psychiatric treatment of panic disorder should not be different for a patient with MVP" (p. 303). Several studies have shown that MVP does not have effects on the outcome of treatments for panic attacks (61, 63, 114). There are now effective behavioral as well as pharmacologic treatments available for panic disorder (117–126) that lead to clinically significant improvement or even complete remission in the great majority of cases.

SUMMARY

The possible relationship between panic disorder and mitral valve prolapse syndrome (MVP) has attracted considerable interest in recent years. Epidemiological research has demonstrated that both disorders have relatively high prevalences and most frequently affect young women.

Reports of the prevalence of MVP in panic disorder patients have been highly inconsistent. Some investigations find frequencies of 0–8%, and others, 24–35% for "definite" MVP. The average across 17 studies reviewed was 18% for panic patients and 1% for normal controls (averages for "probable" MVP: 27% versus 12%). Elevated prevalences of MVP also have been reported in patients with GAD, bipolar affective disorder, and anorexia nervosa. Studies of the prevalence of panic attacks in MVP patients, on the other hand, have consistently failed to demonstrate significant differences between MVP patients, patients with other cardiac complaints or disorders, and normal controls (averages

across seven studies: 14%, 10%, and 7%, respectively). In addition, the groups have not differed with respect to the prevalence of other psychiatric diagnoses.

The validity of these results is compromised by widely different diagnostic criteria and unacceptably low interrater and retest reliabilities for MVP. Other methodological problems include inadequate control groups, a lack of "blind" ratings for panic or MVP, and sampling bias in both patient and control populations. These problems, as well as the great variations in the published results, preclude any final judgment. If there is a concomitance between MVP and panic, it affects less than 8% of MVP and less than 20% of panic disorder patients in clinical settings, and primarily involves subjects with milder and perhaps reversible variants of MVP. No hypothesis of a causal relationship between the disorders has been convincingly supported. Rather than any functional relationship, the evidence suggests co-morbidity in more symptomatic individuals. Finally, studies of physical morbidity in MVP have generally found benign outcomes, with only a small subgroup of more severe cases developing complications. The presence of MVP seems to have no consequences for the treatment of panic disorder, for which effective methods are now available.

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