

## LACK OF EVIDENCE OF AN ASSOCIATION BETWEEN MITRAL-VALVE PROLAPSE AND STROKE IN YOUNG PATIENTS

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### ABSTRACT

**Background** Previous studies have reported a high prevalence of mitral-valve prolapse among patients with embolic stroke (28 to 40 percent), especially among young patients (those  $\leq 45$  years old); this finding has practical implications for prophylaxis. However, diagnostic criteria for prolapse have changed and are now based on three-dimensional analysis of the shape of the valve; use of the current criteria reduces markedly the frequency of such a diagnosis and increases its specificity. Previously described complications must therefore be reconsidered.

**Methods** In a case-control study, we reviewed data on 213 consecutive patients 45 years of age or younger with documented ischemic stroke or transient ischemic attack between 1985 and 1995; they underwent complete neurologic and echocardiographic evaluations. The prevalence of prolapse in these patients was compared with that in 263 control subjects without known heart disease, who were referred to our institution for assessment of ventricular function before receiving chemotherapy.

**Results** Mitral-valve prolapse was present in 4 of the 213 young patients with stroke (1.9 percent), as compared with 7 of the 263 controls (2.7 percent); prolapse was present in 2 of 71 patients (2.8 percent) with otherwise unexplained stroke. The crude odds ratio for mitral-valve prolapse among the patients who had strokes, as compared with those who did not have strokes, was 0.70 (95 percent confidence interval, 0.15 to 2.80;  $P=0.80$ ); after adjustment for age and sex, the odds ratio was 0.59 (95 percent confidence interval, 0.12 to 2.50;  $P=0.62$ ).

**Conclusions** Mitral-valve prolapse is considerably less common than previously reported among young patients with stroke or transient ischemic attack, including unexplained stroke, and no more common than among controls. Using more specific and currently accepted echocardiographic criteria, therefore, we could not demonstrate an association between the presence of mitral-valve prolapse and acute ischemic neurologic events in young people. (*N Engl J Med* 1999;341:8-13.)

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PREVIOUS studies have reported an association between acute ischemic neurologic events and mitral-valve prolapse, especially in young patients (those  $\leq 45$  years old), who are less likely than older patients to have atherosclerosis or hypertension as the cause of stroke.<sup>1-8</sup> Such reports have aroused concern among patients, phy-

sicians, and insurers about the potential risk of stroke and transient ischemic attack and the need for prophylaxis.<sup>5,9</sup> Special attention was drawn to this association by Barnett et al.,<sup>1</sup> who examined 60 consecutive patients 45 years of age or younger who had acute ischemic neurologic events and found that 40 percent had mitral-valve prolapse according to single-dimensional (M-mode) echocardiographic criteria. Similarly, Scharf et al.<sup>2</sup> found prolapse in 28 percent of patients in this age group who had otherwise unexplained strokes, as have several others.<sup>3-7</sup> Although controversial,<sup>8-14</sup> and despite the questions subsequently raised by Boughner and Barnett regarding the echocardiographic technique they used and its specificity,<sup>13</sup> the validity of this association remains widely accepted.<sup>15,16</sup>

The diagnostic criteria for mitral-valve prolapse, however, have changed on the basis of findings on two-dimensional echocardiographic imaging and improved understanding resulting from three-dimensional analysis of the shape of the valve; the use of the newer criteria greatly decreases the frequency of the diagnosis and improves its specificity.<sup>17-20</sup> It is therefore necessary to reconsider the previously described associations that were based on nonspecific M-mode and two-dimensional echocardiographic criteria. In particular, using the new, more specific echocardiographic criteria, we assessed, first, whether the frequency of mitral-valve prolapse uncomplicated by endocarditis among young patients with stroke or transient ischemic attack is as high as that previously reported with the nonspecific criteria and, second, whether there is an association between prolapse and stroke or transient ischemic attack.

### METHODS

#### Case Patients

We studied the records of consecutive patients 45 years of age or younger who were admitted to Massachusetts General Hospital between 1985 and 1995 and who were given a diagnosis of acute ischemic stroke or transient ischemic attack. We included all 213 such patients (113 men and 100 women; mean [ $\pm$ SD] age,  $32.5 \pm 12.0$  years) who were listed in our stroke data base.

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### Neurologic Evaluation

The patients underwent complete neurologic evaluations, including history taking to identify risk factors, lipid and coagulation profiles, and imaging studies (vascular Doppler imaging, transcranial Doppler imaging, computed tomographic scanning, and magnetic resonance imaging or contrast angiography), as well as standardized two-dimensional and Doppler echocardiography. Acute ischemic stroke was defined as the occurrence of brain deficit due to vascular insufficiency less than one week before admission and leading to clinical signs that persisted for more than 24 hours. Transient ischemic attack was defined as a temporary brain or retinal deficit caused by vascular insufficiency that resolved completely within 24 hours. The diagnosis and the results of the neurologic evaluation were confirmed by chart review for each of the patients.

### Control Group

The control group consisted of 263 consecutive patients (135 men and 128 women; mean age,  $25.7 \pm 12.5$  years) identified through the hospital's cardiac ultrasonographic data base, who had undergone echocardiography during the same period as the patients with stroke for a reason considered to be independent of mitral-valve prolapse. These patients had no known heart disease and were referred for routine measurement of left ventricular systolic function before the initiation of chemotherapy with an anthracycline, most commonly doxorubicin, since such treatment may decrease contractility.

### Echocardiographic Diagnosis of Mitral-Valve Prolapse

Mitral-valve prolapse was defined as superior displacement of the leaflets during systole in a two-dimensional echocardiographic long-axis view of the left ventricle (Fig. 1). We used widely accepted criteria in which findings of nonspecific anterior-leaflet displacement in the apical four-chamber view were excluded and that were based on descriptions of the three-dimensional shape of the valve and clinical correlations.<sup>17-26</sup>

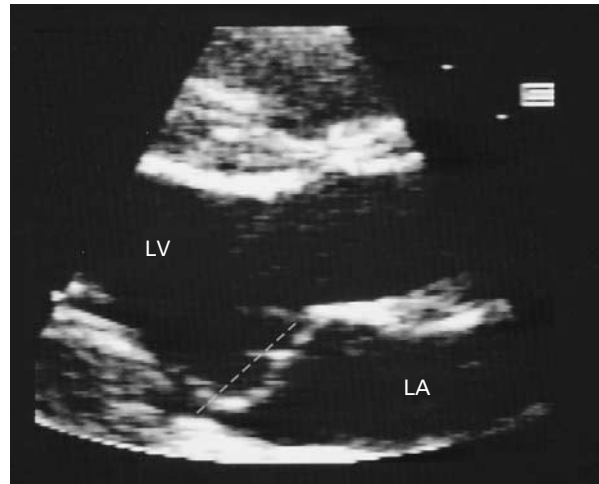
### M-Mode Echocardiography

In order to compare the frequency of mitral-valve prolapse with previously reported frequencies, we studied 87 patients randomly selected from each group (43 case patients and 44 controls) and derived M-mode tracings from their echocardiograms by recording leaflet motion over time along one line of sight, as previously described<sup>23,25</sup>; these patterns coincided with videotaped M-mode recordings made with the beam aimed in the same direction, which had been obtained in 68 percent of these patients as part of a standard series of imaging studies to determine the dimensions of the left ventricle.

Because M-mode patterns are highly dependent on the direction of the beam,<sup>24</sup> for each subject we used two beam directions that were based on the structures intersected by the beam at the onset of systole. The first beam intersected the point closest to the left atrium where the leaflets met, and the second beam was aimed approximately 0.5 cm more toward the apex and initially passed through the coapted tips of the leaflets more distally. The pattern of prolapse was defined as leaflet motion of at least 2 mm posterior to the point of closure of the leaflets, either throughout systole or in mid-to-late systole.

### Statistical Analysis

We determined the proportion of patients in each group who had mitral-valve prolapse and the exact binomial 95 percent confidence intervals for these proportions. We compared the odds of prolapse among the patients with ischemic neurologic events with the odds of prolapse among the controls without such events. We also compared the odds of prolapse among the groups in our study with the odds among corresponding groups in a previous study.<sup>1</sup> Because of the small number of patients with prolapse, we used exact stratified methods<sup>27</sup> to control for the possi-



**Figure 1.** Two-Dimensional Echocardiographic Parasternal Long-Axis View of the Left Ventricle (LV), Showing Prolapse of Both Mitral Leaflets into the Left Atrium (LA).

The dashed line connects the annular-hinge points.

bly confounding effects of age (per decade of age) and sex. Conditional maximum-likelihood estimates of the (common) odds ratio are given, as well as exact 95 percent confidence intervals and P values. All statistical analyses were performed with the statistical programs Stata (version 5.0, Stata, College Station, Tex.) and StatXact 3 (version 3.0, Cytel Software, Cambridge, Mass.).

To assess interobserver variability with respect to the diagnosis of mitral-valve prolapse, we reviewed the two-dimensional echocardiograms of all patients with prolapse in both groups and a random sample of 50 patients who did not have prolapse. An independent observer who was unaware of the patients' status with respect to prolapse or stroke also assessed these studies.

## RESULTS

### Case Patients

Of the 213 patients who had acute ischemic neurologic events, 142 had identifiable and recognized cardiac and vascular causes of stroke or transient ischemic attack and 71 had no definite cause (Table 1). Of the 142 patients with identifiable and recognized causes, 93 had established disease of the carotid or vertebral system, including stenosis or dissection, and 49 had a cardiac source of embolism, including vegetation, dilated cardiomyopathy, a prosthetic valve, congenital heart disease (including left ventricular diverticulum and atrial septal defect), atrial fibrillation, or a recent history of coronary-artery bypass grafting (immediately before the acute event). Of the 71 patients with no definite cause of stroke, 46 had strongly recognized risk factors for atherosclerotic disease, including hypertension, diabetes, a history of smoking, and hypercholesterolemia.

Four patients had clinical conditions associated with vascular events: systemic lupus erythematosus in two and deficiencies of protein S and protein C in one each. Three patients had patent foramen ovale (one with

**TABLE 1. CAUSES OF AND RISK FACTORS FOR STROKE OR TRANSIENT ISCHEMIC ATTACK IN 213 PATIENTS ≤45 YEARS OLD.**

CAUSE OR RISK FACTOR	No. OF PATIENTS
<b>Identifiable and recognized causes</b>	142
Carotid or vertebral disease	93
Cardiac source of embolism	49
Vegetation	13
Dilated cardiomyopathy	11
Prosthetic valve	13
Congenital heart disease (including left ventricular diverticulum and atrial septal defect)*	7
Atrial fibrillation	4
Coronary-artery bypass grafting immediately before stroke	1
<b>Risk factors for vascular events</b>	55
Strongly recognized risk factors for atherosclerotic disease	46
Systemic lupus erythematosus	2
Coagulation abnormality	2
Patent foramen ovale†	3
Alcoholism	2
<b>No identifiable cause or risk factor</b>	16

\*One patient with atrial septal defect had a history of migraine, smoking, and oral-contraceptives use, and one had an atrial septal defect and deep venous thrombosis.

†One patient had a history of migraine, and one had deep venous thrombosis.

**TABLE 2. PREVALENCE OF MITRAL-VALVE PROLAPSE AMONG THE CASE PATIENTS AND CONTROLS.\***

VARIABLE	ALL CASE PATIENTS (N=213)	CASE PATIENTS WITH NO DEFINITE CAUSE OF STROKE OR TIA (N=71)	CONTROLS (N=263)
Age — yr	32.5±12.0	34.6±11.0	25.7±12.5
Mitral-valve prolapse — no. (%)	4 (1.9)	2 (2.8)	7 (2.7)
Odds ratio (95% CI)†	0.70 (0.15–2.80)	1.06 (0.11–5.73)	
P value	0.80	1.0	

\*Plus-minus values are means ±SD. TIA denotes transient ischemic attack, and CI confidence interval.

†The crude odds ratios are for the odds of prolapse in the case patients as compared with the controls.

a history of migraine and another with deep venous thrombosis), and two had alcoholism. Therefore, 16 patients had neither an identifiable cause of nor risk factors for stroke or transient ischemic attack.

**Frequency of Mitral-Valve Prolapse**

The frequency of mitral-valve prolapse was 1.9 percent among the case patients (4 of 213 patients; 95 percent confidence interval of the frequency, 0.5 to

4.7 percent), and 2.7 percent among the controls (7 of 263 patients; 95 percent confidence interval, 1.1 to 5.4 percent; P=0.80) (Table 2). Three case patients had bileaflet prolapse (Fig. 1), and one had posterior-leaflet prolapse. None of the patients in either group had classic mitral-valve prolapse (maximal leaflet thickness of at least 5 mm during diastasis), more than trace mitral regurgitation, or left atrial dilatation.<sup>18,28,29</sup> The frequency of prolapse among the case patients was considerably lower than the frequency of 40 percent (24 of 60 patients) reported by Barnett et al.<sup>1</sup> (odds ratio for prolapse among patients with stroke in our study as compared with the prior study, 0.03; 95 percent confidence interval, 0.01 to 0.09; P<0.001).

Among the 71 patients without identifiable or recognized causes of stroke or transient ischemic attack, 2 (2.8 percent) had prolapse; this rate was also not significantly different from that among the control patients (P=1.0) and differed markedly from the previously reported frequency of 64 percent (18 of 28 patients; odds ratio, 0.02; 95 percent confidence interval, 0.01 to 0.09; P<0.001).<sup>1</sup> None of the 16 patients with neither identifiable causes of nor recognized risk factors for stroke or transient ischemic attack had prolapse in this study, as compared with 8 of 18 (44 percent) in the previous report.<sup>1</sup>

The crude odds ratio for prolapse among the patients with stroke or transient ischemic attack, as compared with those with no ischemic event, was 0.70 (95 percent confidence interval, 0.15 to 2.80; P=0.80), and after adjustment for age and sex, the odds ratio was 0.59 (95 percent confidence interval, 0.12 to 2.50; P=0.62) — considerably smaller than the odds ratio of 9.33 (95 percent confidence interval, 6.21 to 12.45) previously reported.<sup>1</sup> The distribution of patients with mitral-valve prolapse and neurologic events according to age is presented in Table 3. For the 71 case patients with no definite explanation for stroke or transient ischemic attack, the crude odds ratio was 1.06 (95 percent confidence interval, 0.11 to 5.73; P=1.0).

**M-Mode Echocardiography**

The frequency of the prolapse pattern seen on M-mode echocardiography in the randomly selected subgroup of case patients was not significantly different from that in the corresponding subgroup of control patients, but it varied with changes in the angulation of the beam. With the more apical beam direction, prolapse was identified in 2 of 43 case patients (5 percent) and 6 of 44 controls (14 percent, P=0.28). With the more basal beam direction, prolapse was identified in 22 of 43 case patients (51 percent) and 24 of 44 controls (55 percent, P=0.92). The M-mode patterns reflect the movement of different portions of the mitral apparatus through the fixed beam as the base of the heart moves toward the

**TABLE 3.** ASSOCIATION OF MITRAL-VALVE PROLAPSE AND CEREBROVASCULAR ACCIDENT IN 476 CASE PATIENTS AND CONTROLS ACCORDING TO AGE.\*

AGE	NO MITRAL-VALVE PROLAPSE OR CEREBRO-VASCULAR ACCIDENT	CEREBRO-VASCULAR ACCIDENT BUT NO MITRAL-VALVE PROLAPSE	MITRAL-VALVE PROLAPSE BUT NO CEREBRO-VASCULAR ACCIDENT	MITRAL-VALVE PROLAPSE AND CEREBRO-VASCULAR ACCIDENT
0–9 yr	21	10	0	0
10–19 yr	92	13	1	0
20–29 yr	36	39	3	2
30–39 yr	59	65	2	2
40–49 yr	48	82	1	0

\*Cerebrovascular accident was defined as stroke or transient ischemic attack.

apex in systole. A more apically angled beam intersects first the distal and then the basal ends of the coapted rough zones of the leaflets, which are equidistant from the transducer, producing a horizontal tracing without showing prolapse. A more basally angled beam often passes through the posterior leaflet as it slants downward from the coaptation point toward its posterior annular insertion, producing the appearance of prolapse without actual displacement of the leaflets toward or into the left atrium in relation to the annulus, as can be confirmed by two-dimensional echocardiography from the same window.<sup>23,25</sup>

There was complete concordance between our interpretations of the echocardiographic studies and those of the independent observer with respect to the presence or absence of mitral-valve prolapse.

### DISCUSSION

The proposal that mitral-valve prolapse may be a cause of stroke in young people has been the subject of ongoing controversy.<sup>2-14,30</sup> In contrast to the findings of Barnett et al.,<sup>1</sup> others have found a low frequency of stroke among populations with prolapse who have been followed over time<sup>10,12,28-32</sup> and have expressed concern that the use of nonspecific diagnostic criteria for mitral-valve prolapse in examining patients with stroke could falsely lead to an apparent association between the two abnormalities<sup>31</sup> (although such a faulty association could then also be found among patients in control groups<sup>1</sup>). In a subsequent editorial, Boughner and Barnett expressed concern regarding the specificity of the echocardiographic technique and the criteria they had used.<sup>13</sup> Despite such skepticism, the concept that there is evidence of such an association has remained unrefuted.

Since the 1980 study by Barnett et al.,<sup>1</sup> there have been major advances in our ability to evaluate non-

invasively the billowing of the leaflet referred to as prolapse. There has been growing recognition that the original one-dimensional, or M-mode, technique could produce variable results depending on the position of the transducer.<sup>23-25</sup> More fundamentally, prolapse, by definition and as recognized by surgeons and pathologists,<sup>33,34</sup> is bulging of the leaflet into the left atrium superiorly in an apex-to-base direction. This motion is perpendicular to the M-mode beam, which therefore cannot record it directly.<sup>23,25</sup> The M-mode technique displays only the posterior motion of the valve, frequently in the absence of actual superior motion into the left atrium in simultaneous two-dimensional views obtained with the same position and orientation of the transducer.<sup>23,25</sup>

Some of the original two-dimensional views used in neurologic studies also led physicians to diagnose prolapse frequently in normal subjects,<sup>19,21</sup> reflecting the overall saddle shape of the valve as opposed to any localized distortion or abnormality of the leaflets.<sup>17</sup> The revision of the diagnostic criteria to eliminate such diagnoses has improved the correspondence of findings both with concomitant hallmarks of myxomatous valve disease and with the development of clinical complications (e.g., severe mitral regurgitation requiring surgery and endocarditis), without decreasing sensitivity.<sup>18,22,26</sup>

We used a design similar to that of Barnett et al.<sup>1</sup> — that is, we evaluated a consecutive group of young patients with stroke or transient ischemic attack; the principal difference was that we used the current noninvasive diagnostic criteria instead of the former, less specific criteria. In our study, the frequency of prolapse among 213 consecutive young patients with ischemic neurologic events was low and not significantly different from that among the controls. The same conclusions pertained to the patients without identifiable or recognized causes of stroke or transient ischemic attack, as well as to those without either recognized causes of or risk factors for stroke or transient ischemic attack, none of whom had prolapse. It is worth noting that, in this and another study,<sup>32</sup> identifiable causes of or risk factors for stroke other than mitral-valve prolapse were often present, even in young patients.

The low prevalence of mitral-valve prolapse among both case patients and controls makes it extremely difficult to rule out the possibility of a small association. However, the case for the lack of an association appears to be stronger, because none of the young patients with stroke had the abnormally thickened leaflets characteristic of myxomatous degeneration and associated with valve-related complications.<sup>18,26,28,29,35,36</sup>

Although a small number of case reports<sup>37-39</sup> suggest a potential association between prolapse and stroke, such reports are generally inconclusive because of confounding factors, including the presence of atrial fibrillation and arrhythmias,<sup>37</sup> the concur-

rent use of oral contraceptives and tobacco,<sup>39</sup> uncertain evidence of prolapse on M-mode scanning or in the four-chamber view,<sup>38</sup> and uncertain evidence of valve-associated thrombi (for example, a mass in the left ventricular outflow tract that remains unchanged over a period of six months<sup>37</sup>) in the absence of pathological confirmation to rule out other valve-associated masses that could embolize.<sup>37,38</sup>

Despite the high resolution of transesophageal echocardiography and its widespread use, no studies in which this technique was used have documented in vivo the presence of thrombi on the atrial surface of prolapsing valves that had been postulated to cause stroke. In summary, although we cannot rule out a small association, our results provide no clear evidence of one.

Because of the uncertainties associated with the diagnosis of prolapse by M-mode scanning,<sup>23-25</sup> we no longer use this procedure for diagnosis. However, we were able to derive M-mode tracings from the recorded data by tracing leaflet motion along a single line of sight, as described in previous reports<sup>23,25</sup>; these tracings coincided with M-mode echocardiograms recorded with the same angulation of the beam that had been used for most patients as part of an assessment of left ventricular measurements. These tracings showed no significant differences in the frequency of prolapse between the case patients and the controls for any consistent beam angulation. However, the frequency of prolapse ranged from 5 percent to 55 percent, depending on the direction of the beam. This range includes the frequencies reported by Barnett et al. (40 percent in case patients and 7 percent in controls).<sup>1</sup> We speculate that although the interpretation of their M-mode scans was blinded with respect to stroke status, scanning itself was unintentionally not done in a blinded fashion (and in fact could not have been blinded as long as signs of stroke were evident during the procedure). Thus, the prevalence of mitral-valve prolapse may have been higher among their patients with stroke than among their controls because the diligence of the M-mode echocardiographic search increased the likelihood of finding an association.<sup>1</sup>

Our control group was made up of patients referred for measurement of ventricular systolic function before chemotherapy. Prolapse is not a contraindication to chemotherapy, nor is it associated with the cancers treated; therefore, the control group was likely to be fairly representative of the population from which the case patients were drawn with respect to the prevalence of prolapse. These controls did not substantially differ in this respect from those in previous studies. Although the controls were slightly younger than the case patients, adjustments for age did not markedly alter the measures of association, and Freed et al., using the same criteria, reported a similar prevalence of 2.4 percent among

members of the offspring cohort of the Framingham Heart Study with a mean age of 55 years.<sup>40</sup>

In conclusion, we found that the frequency of mitral-valve prolapse in young patients with stroke or transient ischemic attack, including unexplained stroke, was considerably lower than previously reported and was not significantly different from that among controls. Using current criteria, therefore, we could not demonstrate an association between mitral-valve prolapse and acute ischemic neurologic events in persons 45 years old or younger.

Supported in part by grants (HL38176 and HL53702) from the National Institutes of Health. Dr. Gilon's work was supported in part by a grant from the American Physicians Fellowship for Medicine in Israel.

*We are indebted to Dr. Jae-Kwan Song for his assistance with the review of the echocardiographic data and to Melissa Fox and Shirley Sims for their editorial assistance.*

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