Severe mitral regurgitation requiring surgery is the most common life-threatening complication of mitral valve prolapse (MVP) and is due to progressive myxomatous change in the valve. We identified all residents of New South Wales, Australia, who had mitral valve surgery for myxomatous valve disease during 1982 and, using these data and the adult population statistics from 1982, estimated the cumulative risk of valve surgery in patients with MVP. In 1982, 50 of the 5.36 million New South Wales residents required surgery for this complication of MVP. Of the 50, 36 were men and 14 were women, which was significantly different from the population sex distribution ($p<0.02$) for mean age ± SD of 60 ± 11 years (range, 26–78 years). Using our previously determined 4% prevalence of adult MVP in New South Wales, we estimated the number of male and female patients with MVP at risk for each 5-year age interval and calculated age-specific event rates. The results show that the cumulative risk is minimal below the age of 50 years but then rises steeply, particularly in men. The risks in men aged 50, 60, and 70 years (with 95% confidence intervals) were 1:202 (130–448), 1:53 (37–82), and 1:28 (22–41), respectively. In women, the risk was less than half that in men ($p<0.001$). We conclude that the risk of developing severe mitral regurgitation is age and sex related, is minimal before the age of 50, and rises sharply after the age of 50, particularly in men, and that the current minimum number of patients requiring myxomatous mitral valve surgery in Australia is between 150 and 200 per year, a caseload that will increase with the advancing age of the population. The findings are consistent with the predictions of a response-to-injury hypothesis that explains the pathogenesis of progressive changes in the prolapsing mitral valve. (Circulation 1988;78:10-14)

Primary mitral valve prolapse, as opposed to that secondary to a systemic disorder of connective tissue or to a reduction in left ventricular cavity size, occurs with a prevalence of 2.5–5% in the adult population, according to recent surveys using careful clinical and echocardiographic diagnostic criteria. It is relatively uncommon before the growth spurt of adolescence, but thereafter, the prevalence in men remains relatively constant. Most studies have found a greater prevalence in women than in men, and among women, there are data suggesting a greater prevalence in adolescence and young adulthood. (However, some of the findings of early studies may have been influenced by the use of less strict diagnostic criteria.) Mitral valve prolapse is largely benign, and serious complications are uncommon, the most frequent being severe mitral regurgitation requiring valve surgery. This complication, which occurs in a small subset of patients with mitral valve prolapse, is due to progressive myxomatous changes in the valve, which eventually lead to marked regurgitation. In about 75% of these patients, there is sudden deterioration because of chordal rupture.

Increased awareness of the prevalence of mitral valve prolapse and improved diagnostic methods have led to its frequent identification in young adults. Because the occurrence of severe mitral regurgitation increases with age, it is important to establish at the time of diagnosis the future risk of this complication. In the state of New South Wales, Australia, all mitral valve surgery for myxomatous valve disease during 1982 was undertaken in Sydney in university teaching hospitals. With the
cooperation of each university hospital cardiothoracic unit, we have determined the number of New South Wales residents who had myxomatous mitral valve disease surgery during 1982. Using these data, as well as the state adult population statistics for 1982, we have estimated the risk of severe mitral regurgitation occurring among cohorts of male and female patients expected to have mitral valve prolapse, assuming an adult population prevalence of 4%, the prevalence we had found for both men and women in the same adult population. If the true prevalence is different from this, then our risk estimates would be altered as discussed below.

Patients and Methods

Study Population

We first established that each of the five Sydney cardiothoracic units followed the same indications for mitral valve surgery, namely, New York Heart Association Grade 3 or 4 symptoms or severe mitral regurgitation with evidence of deteriorating left ventricular function as assessed by either serial echocardiograms or gated blood-pool radionuclide scans or by ventriculography. We then identified from the hospital records of these university-based cardiothoracic units all residents of New South Wales who had surgery for myxomatous mitral valve disease during 1982. The study included patients with either acute or chronic severe mitral regurgitation requiring surgery. These index patients were characterized as having myxomatous valve disease from the operative findings when there were clear descriptions of the macroscopic features of a floppy mitral valve with or without chordal rupture, that is, a redundant thickened valve without restriction of motion as defined previously. The histology was examined with previously described diagnostic criteria in 76% of the patients, including all 12 patients from this institution, with confirmation of myxomatous valve disease in all.

Calculations and Statistics

Using the New South Wales resident population statistics for 1982, we determined the relations of the age and sex of the patients with mitral valve prolapse operated on during 1982 to the age and sex of residents expected to have had mitral valve prolapse in 1982; the latter were calculated from the population statistics with a mitral valve prolapse prevalence figure of 4% in each male and female age group. From these data, we calculated age-specific event rates for valve surgery for patients with mitral valve prolapse in New South Wales and constructed life tables.

Definition of Mitral Valve Prolapse

In our population and clinical studies, mitral valve prolapse was diagnosed when, at M-mode echocardiography, there was abrupt middle-systolic to late-systolic posterior displacement of part of the mitral systolic closure line to at least 2 mm below the line joining the point of valve closure in systole (C) to the point of valve opening in diastole (D) with superior leaflet displacement confirmed at cross-sectional echocardiography (see below). It was also diagnosed if there was pansystolic prolapse with posterior displacement of at least 3 mm below a line joining C and D with the nadir occurring in middle-systole when cross-sectional echocardiography also showed bulging of the mitral leaflet above the plane of the mitral annulus during systole on both apical four- and two-chamber views. In 70% of those identified echocardiographically in our population studies as having mitral valve prolapse, these echocardiographic features were accompanied by auscultatory features of mitral valve prolapse, namely, a nonejection click with or without a late-systolic murmur or a mitral systolic murmur alone. (These were documented phonocardiographically.) The remaining 30% detected echocardiographically in the absence of auscultatory features were classified as having “silent” mitral valve prolapse. All of these patients met our M-mode criteria for a diagnosis of mitral valve prolapse, so the problem of a false-positive diagnosis by two-dimensional echocardiography alone due to a nonplanar annulus or normal superior systolic motion did not arise. (Doppler facilities were not available at the time of our population studies.)

Results

During 1982, there were 50 New South Wales residents who had surgery for severe mitral regurgitation due to myxomatous valve disease. In two of the 50, there was, in addition, infective endocarditis. Of the 50, 36 were men and 14 were women, and this male predominance was significantly different from the predicted sex distribution ($p<0.02$, $\chi^2$ test). However, ages at the time of surgery were not different. For men, the mean age ± SD was 60 ± 10 years (range, 26–75 years), and for women, the mean age ± SD was 59 ± 13 years (range, 32–78 years).

In 1982, the New South Wales resident population was 5.36 million. The number of residents expected to have mitral valve prolapse in each age group over the range of 26–78 years, assuming a 4% prevalence, was related to the age and sex of the actual numbers of patients who were operated on. The resulting age-specific event rates are shown in Figure 1. The cumulative risk of severe mitral regurgitation requiring valve surgery is minimal below the age of 50 years but then rises steeply in men, approaching 4% by the age of 70 years. The risk increases much more slowly in women and is less than half the risk for men. This difference is highly significant ($\chi^2$ test = 11.7; $p<0.001$) when assessed with a generalized regression analysis of the age-specific rates.

The estimated cumulative risks for men and women by the ages of 50, 60, and 70 years together
with the 95% confidence intervals are shown in Table 1. Over the age of 60 years, the 95% confidence limits are narrow, and the results indicate that the risk in men with mitral valve prolapse is approximately 2.5 times that in women.

**Discussion**

Although primary mitral valve prolapse is thought of as an essentially benign condition, or possibly a variant of normal, the present analysis shows that there is a significant age- and sex-related risk of severe mitral regurgitation, requiring surgery, developing in mitral valve prolapse patients. Under the age of 50 years, this risk is negligible, but after the age of 50 years, it increases sharply—particularly in men. While the risks calculated from this analysis represent reasonable approximations, the sources of possible error require definition.

Because during 1982 all operations in the state of New South Wales were performed in university teaching hospitals in one city and all units followed the same indications for surgery and had obligatory peer review procedures, we are confident that all patients coming to surgery did have severe mitral regurgitation. However, among a population of 5.36 million, it is likely that some patients with severe mitral regurgitation due to myxomatous valve disease who required surgery did not receive it. This may have been more likely in patients in rural areas who had acute severe mitral regurgitation due to chordal rupture, the complication most commonly leading to surgery in myxomatous regurgitation patients. Another group in which surgery might not be undertaken despite a need for it would be among the elderly, a potentially important consideration in view of the age-related increase in prevalence of severe mitral regurgitation as a complication of mitral valve prolapse. Thus, the rate of 50 patients per year for New South Wales almost certainly defines a lower limit. Therefore, if the figure of a 4% prevalence of mitral valve prolapse is correct for the whole age group, the risk is likely to be somewhat greater than that calculated here.

The assumption of a 4% mitral valve prolapse prevalence across all adult age groups is another potential source of error. It seems clear from our own data and from that of Devereux et al that mitral valve prolapse is relatively uncommon before adolescence and only becomes evident after the growth spurt. Thereafter, recent studies in adults have been consistent in showing a prevalence of between 2.5% and 5%. In the one survey covering all ages in a free-living population, the Framingham study, the male prevalence among the 497 subjects between the ages of 20 and 40 years was 4%; it declined only slightly thereafter and was 2.7% at the age of 80 years and older. This agrees well with our finding of 4% among healthy Australian men of mean age ± SD of 39 ± 13 years (range, 18–79 years). These data provide support for the figure of 4% prevalence in men and for the risks we have estimated for men. However, as Levy and Savage point out, had more rigid diagnostic criteria been adopted in the Framingham study, the prevalence in men would have been in the range of 1–2%. If that figure is applicable to our population, the risk in men would be approximately double that which we have calculated.

With regard to women, the prevalence data are less clear. The Framingham study found a 13.7% prevalence among 591 women between the ages of 20 and 40 years with a striking decline thereafter to 1.4% at the age of 80 and over. Our own figure among 100 Australian women of mean age ± SD of 38 ± 10 years (range, 18–57 years) was 4%. This is similar to the 5.6% recently found by Devereux et al among healthy American women. It is noteworthy that the Framingham series contained a high proportion of silent mitral valve prolapse (about 80%) and that the criteria for the diagnosis of pansystolic prolapse, the usual reason for a false-positive diagnosis, were less rigid than our own. Moreover, when diagnostic criteria similar to our own are applied to the Framingham data in women, Levy and Savage estimate an actual prevalence in the range of 3–4%. While we felt that a 4% prevalence figure for women was the most appropriate one to use for our calculations, if the true preva-

### Table 1. Probability, With 95% Confidence Intervals, of Mitral Valve Prolapse Patients Requiring Valve Surgery by Age and Sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Probability</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>50</td>
<td>1:202</td>
<td>1:130 – 1:448</td>
</tr>
<tr>
<td>Women</td>
<td>50</td>
<td>1:285</td>
<td>1:172 – 1:837</td>
</tr>
<tr>
<td>Men</td>
<td>60</td>
<td>1:53</td>
<td>1:37 – 1:82</td>
</tr>
<tr>
<td>Women</td>
<td>60</td>
<td>1:142</td>
<td>1:86 – 1:415</td>
</tr>
<tr>
<td>Men</td>
<td>70</td>
<td>1:28</td>
<td>1:22 – 1:41</td>
</tr>
<tr>
<td>Women</td>
<td>70</td>
<td>1:83</td>
<td>1:56 – 1:165</td>
</tr>
</tbody>
</table>
lence is higher, then the already low risk of surgery for women will be even smaller than we have estimated.

It is possible that those patients with silent mitral valve prolapse [i.e., the echocardiographic features described above (see "Materials and Methods") in the absence of nonejection clicks or mitral murmurs (usually young patients, in our experience) would not be at risk of progressive changes. The proportion of patients with silent mitral valve prolapse among those identified in our population surveys was 31%—nine of the 29 patients with mitral valve prolapse so identified. None of these 29 was aware of any clinical abnormality. If the risk analysis is confined to only those with echocardiographic and auscultatory features for the diagnosis, as set out recently by Perloff and Child, and if the proportion with silent prolapse is excluded (assumed from our data to represent 30% of the total), the results would be altered. We would then find a prevalence rate of nonsilent mitral valve prolapse of approximately 3% in the general population, and for these patients, the risk of ever requiring surgery would be about 25% greater than that calculated here. Nevertheless, some patients with silent mitral valve prolapse are at risk. One such patient, a 58-year-old man, who presented initially with intermittent atrial fibrillation, had obvious leaflet billowing at echocardiography documented in the absence of any auscultatory signs on several occasions at routine assessments. Two years later, he again presented with sudden onset of dyspnea and clinically obvious gross mitral regurgitation. Chordal rupture was identified at echocardiography, and this was confirmed at surgery when a histologically proven myxomatous valve was partially resected and repaired.

A further assumption in our analysis is that the risk of death among unoperated patients is not different from that of the general population. While sudden death is a well-described complication of mitral valve prolapse, it is rare, and the evidence has been reviewed recently. Nevertheless, were the overall risk of death appreciably greater in nonoperated patients, this would also indicate a greater risk of surgery than we have calculated. For all of these reasons, we believe that our calculations are a conservative estimate of the true risk.

We chose to analyze data for 1982 because it was the middle year of our own 3-year study of patients coming to primary mitral valve replacement. When the number of histologically proven excised myxomatous mitral valves during 1981 and 1983 at the Prince Henry Hospital alone is added to the statewide figure for 1982 (50), there was a total of 80 patients. Of these, 57 were men and 23 women, with the mean age being 59 years for each sex. This predominance of male patients is highly significant (p<0.005). Since we can see no reason why women in New South Wales with mitral valve prolapse and severe mitral regurgitation would be less likely than men to come to surgery, the much greater risk of severe regurgitation in men appears well-founded. Other recent studies are also in accordance with this conclusion.

The reasons for this pronounced sex difference must remain speculative. The increased risk in men could be due to the higher systolic and diastolic blood pressures in Australian men and perhaps also due to a higher level of physical activity. Both factors would impose greater forces on the valve and, as a consequence, a greater propensity for repeated minor cyclical injury. We have proposed that the underlying pathophysiological mechanism for progressive changes is a process of repeated minor injury and repair occurring during the cardiac cycle in a mitral valve with minor congenital anatomic variations in the valve apparatus. Hut- chins et al. have recently shown that regional disjunction of the mitral annulus fibrosus is such an abnormality. Progressive prolapse due to intraventricular pressure effects on a congenitally weakened mitral valve is also possible. But biochemical studies of excised valves favor ongoing injury and repair in the valve leaflets as the final common pathway for the lesions. The age-related changes agree with a response-to-injury hypothesis that predicts that prolapsing valves that are normal or near normal at the age of 20 years may develop myxomatous and macroscopic appearance of floppy valves at the age of 60 years by this mechanism. Analysis of the clinical profile in relation to age is strongly suggestive of this pattern of progression, and the data of Kolibash et al provide clear evidence for progressive changes.

Finally, the knowledge of the occurrence of severe mitral valve regurgitation complicating mitral valve prolapse produced from the present study is relevant to health services planning. For example, the New South Wales data for 1982 indicate that in Australia, with a 1985 population of 16.0 million, at least 150 patients per year currently require surgery for myxomatous mitral valve disease and related medical investigation and treatment. This is an expensive commitment. Furthermore, we can confidently predict a significant increase in caseload for this age-related condition over the next 12 years; figures provided by the Australian Bureau of Statistics predict a 20% increase in the Australian population to 19.3 million by the year 2000, which includes a 27% increase in the age group of 65–79 years and a 77% increase in residents 80 years old or older. In 1985, 10.5% of the total population was 65 years or older. The projected figure for the year 2000 is 11.8%.

In summary, the present study defines the order of magnitude of the lifetime risk that patients with primary mitral valve prolapse have of developing severe mitral regurgitation, and it identifies the current minimum Australian caseload for surgical treatment. The risk is age and sex related and is minimal before the age of 50 years. It rises sharply thereafter, particularly in men, whose risk after the
age of 50 years is at least two to three times that in women. The results agree with the predictions of a response-to-injury hypothesis to explain the pathogenesis of progressive changes in the prolapsing mitral valve. Because these changes are age related, it seems certain that the surgical caseload will increase in parallel with the increase in the age of the population.

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**References**


**Key Words** • mitral valve surgery • myxomatous valve disease • chordal rupture • mitral valve prolapse
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D E Wilcken and A J Hickey

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