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EDITORIAL COMMENT

Sex Differences in Mitral Regurgitation Before and After Mitral Valve Surgery*

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Chronic severe mitral regurgitation (MR) due to primary abnormality of the mitral leaflets or chordae leads to left ventricle (LV) volume overload. Afterload is initially normal such that LVEF is typically high (>70%). Once the LVEF begins to fall toward 60% or there is evidence of LV dilation, it is likely that myocardial dysfunction is present, and therefore, surgery is recommended, even in asymptomatic patients (1,2). The traditional definition of LV dilation has long rested on a simple echocardiographic LV end-systolic diameter ≥40 mm, which remains in the current guidelines as one of the "triggers" for surgical referral (1,2). The others are LVEF declining toward 60% or less, pulmonary hypertension (PA systole approaching 50 mm Hg or greater) and new-onset atrial fibrillation (1,2).

SEE PAGE 388

In this issue of *iJACC*, Mantovani et al. (3) provide evidence that there are important differences between men and women referred for surgery for primary MR in an experienced mitral valve center of excellence. The authors report a retrospective analysis of 217 women and 447 men who underwent surgery at Mayo Clinic between 1990 and 2000 with comprehensive echocardiographic imaging, including MR quantitation performed pre-operatively (27 ± 35 days) and post-operatively (6 ± 10 months). Age and other demographic characteristics were very similar between the sexes, but women had smaller body surface area (BSA) and were more likely to have heart failure (HF) symptoms (41% vs. 19%, respectively; $p < 0.0001$) and be prescribed HF therapy. LV diastolic and systolic diameters, left atrial (LA) diameter, LV mass, regurgitant volume (RVol), and effective regurgitant orifice area (EROA) were all significantly smaller in women, and fewer women were classified with severe MR, presumably due to lower RVol and EROA. After they were indexed for BSA, women had slightly higher LV and LA diameters than men, with no differences in RVol, suggesting that the LV volume overload was similar between men and women when BSA was taken into account. This hypothesis is further supported by strikingly similar reductions in men and women in LV and LA diameters post-operatively. Reduction in PA systolic pressure post-operatively was slightly greater in women, despite starting with higher PA pressures.

Long-term follow-up after surgery showed no survival differences between men and women. Recurrence of moderate or greater MR was low (<1%) and not different between men and women. However, women had more post-operative HF than men. Differences in post-operative HF between the sexes were strongly associated with pre-operative HF but not age, comorbidity, LVEF, concomitant coronary artery bypass graft, or recurrent MR in multivariate modeling. It is somewhat of a mystery that there would be significantly more HF in women despite successful mitral valve repair with associated MR reduction, favorable LV remodeling, LA remodeling, and reduction in PA pressures slightly better than those achieved in men. The event curves for HF (see Figure 3 in Mantovani et al. [3]) appear to separate after approximately 2 years and continue to diverge with worsening HF in women than in men. This recurrent HF is difficult to attribute to either MR (which was corrected) or waiting too late to perform surgery (indexed LV and LA diameters improved and PA pressures declined significantly). The reason for HF cannot be determined from this study, but

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several possibilities must be considered. The post-operative mean mitral gradient was higher in women (3.9 ± 2.0 mm Hg vs. 3.4 ± 1.6 mm Hg, respectively; p = 0.006). Although this resting gradient was not statistically related to post-operative HF, it is possible that increases in gradient with exercise could be greater in women than in men due to smaller BSA and could be related to late post-operative HF symptoms. It is interesting that Chan et al. (4) report worsened exercise tolerance in patients with resting gradient >3 mm Hg after mitral valve repair and that exercise may significantly increase transmitral gradient after Mitraclip therapy (5). Another culprit could be diastolic dysfunction. The authors correctly note that it is difficult to assess LV diastolic dysfunction from traditional echocardiographic markers of mitral inflow velocities because the latter are altered by mitral valve disease. Diastolic strain measurements can overcome this limitation but were not available when these patients underwent echocardiography. Future studies are needed to assess whether sex differences in HF post-operatively have any relation to diastolic dysfunction or exercise-induced increase in mitral valve gradients.

Another possible explanation is that this is a spurious finding due to the difficulty of assessing HF retrospectively, even prospectively. According to HF guidelines (6), "there is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination." The authors used Framingham criteria for HF, which rely on symptoms and signs that could be caused by other conditions. They did not report New York Heart Association functional class, which, although notoriously subjective, has been shown to be prognostically important in MR (7). Standardized questionnaires, 6-min walk, or biomarkers are standard for assessing HF in clinical trials but were not available for this study. HF hospitalization is perhaps a more objective measure of HF but was not evaluated. In any case, there is a signal in this study that HF, as a binary variable, is more common in women than in men after successful mitral valve repair, and this needs to be reproduced prospectively using more objective HF criteria.

The study is intriguing but has significant limitations. It is a retrospective study of patients who underwent surgery 15 to 25 years previously. Since that time, surgical techniques have evolved with minimally invasive approaches, less leaflet resection, and more chord replacement. There has also been a trend toward earlier referral; current guideline-based "triggers" have evolved since the time of this report. Echocardiography has also improved since 1990, and it is now recommended that LV volumes provide better information than diameters and can be obtained accurately with 3-dimensional imaging (8). Both LV and LA volumes have been shown to regress after MR reduction by either surgery or Mitraclip method (9). LA volumes have been shown to be important predictors of outcomes in primary MR (10–12) but were not analyzed in this study. Finally, the study would be "cleaner" had a homogeneous patient population with only degenerative MR been studied.

It seems likely that LV dimension triggers for surgical repair of degenerative MR in women may need to be set lower than in men. Further studies are warranted to define the optimal threshold, hopefully using LV volumes instead of simple linear dimensions. The finding that HF symptoms recur after successful MR more often in women in men also deserves clarification and further study.

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