It has long been understood that left ventricular ejection fraction (LVEF) is a poor measure of LV systolic function because of load dependence, measurement error, and observer variability. In addition, LVEF, which is calculated from end-diastolic and end-systolic chamber volumes, is really a measure of chamber function not myocardial function. These issues are particularly problematic in mitral regurgitation (MR), where favorable loading conditions can preserve LVEF even when cardiomyocytes demonstrate loss of contractile elements and abnormal mitochondria. More sophisticated measures of LV systolic function, such as end-systolic elastance and arterial-elastic coupling, are of value in MR but are complicated and time-consuming and have not been adopted into clinical practice. Despite its flaws, LVEF remains important in MR because it is widely available and easy to measure. Both the American and European guidelines indicate that asymptomatic patients should be considered for mitral valve surgery before LVEF falls <60%, particularly when the anatomy is suitable for mitral valve repair. In addition, guidelines suggest that once LVEF falls <30%, the risks of mitral valve surgery might outweigh its benefits. These guidelines are based on expert opinion (Level of Evidence C) because there are limited data to support specific LVEF cutoff values in MR.

In this issue of Circulation: Cardiovascular Imaging, Tribouilloy et al report the relation of LVEF to outcomes in a large series of 1875 patients with MR because of flail leaflet in the Mitral Regurgitation International Database (MIDA) registry. Flail leaflet is a common manifestation of degenerative MR, is a known predictor of outcome, and usually is associated with severe MR. Only patients in sinus rhythm at the time of index echocardiography were included because measurement of LVEF is confounded by atrial fibrillation. Mean age was 65 years; 72% were men. Despite having a flail mitral leaflet, only 25% had New York Heart Association (NYHA) Class III-IV symptoms and 45% were asymptomatic (NYHA Class I). Coronary artery disease (CAD) was present in 10%, and 8% had infective endocarditis. In 85.5% of patients, isolated posterior leaflet flail was present. Details are not provided regarding the prevalence of Barlow’s disease versus fibroelastic deficiency or extensive mitral annular calcification. The decision to refer to mitral valve surgery was left to the discretion of the physicians managing the patient; patients in MIDA are not systematically under the care of a multidisciplinary valve team. Of the 1875 patients, 432 (23%) were treated medically and 1443 (77%) underwent mitral valve surgery at varying time points after the index echocardiogram. Of those, 85% underwent mitral valve repair.

A substantial majority (74%) of patients with flail leaflet had LVEF≥60%; 23% had LVEF 45% to 60%, and only 3% had LVEF<45%. LVEF<30% was rare (0.3%). These findings are consistent with augmentation of LVEF by the favorable loading conditions of pure MR. Patients with LVEF<45% tended to be older and with a higher comorbidity index, more CAD, and larger LV dimensions. By cubic spine analysis adjusted for differences in sex, comorbidity index, symptoms, and CAD, mortality during medical management was stable when LVEF>60% but increased linearly and sharply as LVEF fell <60%. After adjustment, the elevated risk of mortality was statistically significant in those with LVEF<60% compared with LVEF>60%. In those with LVEF<45%, the risk of death adjusted for covariates was 2.5 times higher than in those with LVEF>60%.

In the patients treated surgically, operative mortality was 1.7% with LVEF<60% and 1.1% with LVEF>60%. The 8-year mortality after surgery was 20% in those with LVEF>60%, 28% with LVEF 45% to 60%, and 62% with LVEF<45% (P=0.0001). This difference remained statistically significant after adjustment for covariates. Despite the higher long-term mortality after surgery in the lower LVEF subgroups, surgery reduced mortality compared with medical therapy by ≈50%. Moreover, the benefit of surgery extended to all LVEF subgroups. Despite this encouraging finding, a limitation of the present study is that patients who were denied surgery may have had factors not captured in the comorbidity index (ie, frailty, cancer, severe dementia, etc) that may have precluded surgery and rendered their survival under medical therapy worse than expected. On the contrary, these findings are consistent with previous studies showing that mitral valve repair restores normal longevity. Recently, David et al reported the long-term results of mitral valve repair in 840 patients with degenerative MR. LVEF was ≥60% in 60% of patients, and lower LVEF was an independent predictor of all-cause mortality. Mitral valve repair was found to restore long-term survival to normal except when NYHA Class IV symptoms or LV dysfunction were present.

The findings of the present study confirm the guideline recommendations that surgery should be considered for asymptomatic patients before LVEF falls <60%. Of course, it is impossible to predict exactly when that is going to happen;

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Editorial

Left Ventricular Ejection Fraction in Mitral Regurgitation Because of Flail Leaflet

Paul A. Grayburn, MD; Robert L. Smith, II, MD
therefore, some advocate operating on patients with flail leaflet when the LVEF > 60%. An alternative strategy is to perform watchful waiting with careful and regular surveillance for onset of symptoms, decline in LVEF, atrial fibrillation, or pulmonary hypertension. The concept of early surgery versus watchful waiting has been a subject of controversy. However, a recent analysis of the MIDA registry with propensity matching demonstrated improved outcomes with a strategy of early surgery. Another factor that comes into play is the known propensity of patients with severe MR to sub-consciously reduce activities and avoid symptoms. Exercise testing in asymptomatic patients can often provoke previously unrecognized symptoms or induce pulmonary hypertension. The response to exercise testing in asymptomatic patients or patients with equivocal symptoms could make the decision for early surgery easier for the patient and the physician.

For decades, it has been recommended to repair asymptomatic patients with atrial septal defect to prevent the inevitable consequence of right ventricular (RV) failure and arrhythmias attributable to the chronic volume overload of a hemodynamically significant left-to-right shunt. A major justification for surgical intervention in such patients is the extremely low risk of atrial septal defect repair. A flail mitral leaflet represents an analogous situation in the left heart. Untreated, the chronic volume overload of MR on the left ventricle will eventually cause LV failure and atrial fibrillation. In the modern era, the surgical mortality of isolated mitral valve repair is close to zero in mitral valve centers of excellence, especially when LVEF is normal. In flail leaflet, repair rates are high with good durability, and surgical repairability can almost always be predicted from transesophageal echocardiography. Given the adverse prognosis now demonstrated to be associated with LVEF ≤ 60%, it would seem reasonable to perform early surgery in low-risk patients to avoid the inevitable consequence of declining LV function attributable to the LV volume overload associated with severe MR because of flail mitral leaflet.

Although Tribouilloy et al have convincingly shown that LVEF is a predictor of mortality in flail leaflet, it remains true that LVEF has limitations, is difficult to assess in atrial fibrillation, has broad limits of agreement, and does not directly measure myocardial function. The development of noninvasive measurement of myocardial strain and strain rate offers the potential for earlier detection of myocardial abnormalities associated with severe MR. Further studies are warranted to investigate this possibility in large randomized trials or registries like MIDA. Additionally, despite the limitations of LVEF, it is relatively easy to understand and communicate to patients, families, and other physicians. The results of this study may be useful to primary care physicians, as well as cardiac specialists. Detection of MR by auscultation in the primary care physician’s office should lead to echocardiographic evaluation in an accredited laboratory. Identification of flail leaflet should prompt referral to a cardiologist or cardiac surgeon with expertise in mitral valve disease. Such early recognition is vital in determining outcomes because only a quarter of these patients presented with significant symptoms.

Finally, despite broad criticism that Level C evidence is inadequate, it would seem that panels of experienced clinicians who write the guidelines may actually be pretty astute at predicting risks factors for poor outcomes and defining triggers for surgery. At least in the case of LVEF and MR, it seems that they got it exactly right.

Disclosures
Dr Grayburn is a consultant for Abbott Vascular and receives grant support from Abbott Vascular, Medtronic, and Edwards. He directs the echocardiography core laboratory for Guided Delivery Systems and ValTech Cardio. Dr Smith has no relevant disclosures.

References

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