Left Ventricular Ejection Index as a Marker of Early Myocardial Dysfunction in Primary Mitral Regurgitation

Novel or Old in Disguise?

Francesca N. Delling, MD

Mitrval valve prolapse (MVP) is a common disorder affecting 2% to 5% of the general population (7.8 million individuals in the United States and 176 million individuals worldwide), and it is the most important cause of primary mitral regurgitation (MR) requiring surgery. In addition to progressive MR, MVP is associated with endocarditis, heart failure, and even sudden death. In the setting of severe primary MR, the left ventricle (LV) is affected by a significant volume load leading to compensatory adaptations that vary considerably depending on the prolonged clinical course of MR. In acute MR, late systolic volume is reduced and afterload is low, but as the ventricle enlarges and adapts to the chronic volume overload, afterload gradually increases. During the compensated stage of chronic MR, LV enlargement results from remodeling of the extracellular matrix with dissolution of collagen and rearrangement of myocardial fibers. Moreover, new sarcomeres are added in series, and at the ventricular level, eccentric hypertrophy develops. Consequently, preload (at the sarcomere level), afterload (at the ventricular level), and LV ejection fraction (LVEF) are normal, whereas total stroke volume is increased as a result of the large end-diastolic volume. The transition to decompensated chronic MR may occur as a consequence of a progressive increase in regurgitant volume, a decrease in LV contractile function, an increase in afterload, or a combination of these factors. During this stage, LVEF typically declines to 50% to 60%. Finally, decompensated MR is characterized by substantial and progressive LV dilation, elevated LV diastolic pressure, increased systolic wall stress, and an LVEF of <50%. The decline in LVEF is a consequence of depressed myocardial contractile state, LV afterload excess, or both. Although predominantly based on mitral valve replacement data, early echocardiographic studies have demonstrated a frequent decline in LVEF post surgery, even when MR was well compensated preoperatively. This was thought to be a consequence of an increase in LV afterload related to closure of the low-impedance left atrial leak, although others have postulated that the main culprit of LVEF decline postoperatively is the lack of preservation of the subvalvular apparatus in mitral valve replacement, as this leads to a more spherical LV and reduction of long-axis shortening. By contrast, valve repair or replacement with preservation of the subvalvular apparatus is less frequently associated with a significant fall in LVEF after surgery if MR is compensated preoperatively. The key is to identify, among patients who undergo mitral valve repair, the minority who will develop a reduction in postoperative LVEF (despite normal preoperative LVEF and LV cavity size) as a consequence of occult myocardial dysfunction.

See Article by Magne et al

On the basis of the 2014 American Heart Association/American College of Cardiology Valvular Heart Disease Guidelines, symptomatic patients with an LVEF of >30% or asymptomatic patients with an LVEF of ≤60% or LV end-systolic diameter (LVESD) of ≥40 mm should be treated surgically (class I). The optimal timing of surgery is less certain (class IIa) in asymptomatic patients with normal LV function (LVEF>60%) or normal LV end-systolic dimension (<40 mm). Some asymptomatic patients remain stable for years, but some develop irreversible LV systolic dysfunction. Surgical decisions in asymptomatic patients with preserved LV function often depend on associated factors, including patient preference, new onset atrial fibrillation, pulmonary hypertension, or high likelihood of successful mitral valve repair. Recently, physicians have debated whether the thresholds discussed above should be lowered, with proponents arguing that results are superior when there is earlier surgical intervention. The debate is further ignited by the lack of randomized trials evaluating the optimal management of asymptomatic patients with preserved LVEF and normal LV size, that is, whether early mitral valve repair is superior or comparable with conservative approach with expectant management. In this scenario, there is an emerging need to identify earlier markers of myocardial dysfunction able to identify, among asymptomatic patients with severe MVP-related MR and normal LV cavity size/function, those who might benefit the most from early mitral valve repair. This need was recently highlighted in the 2014 American Heart Association/American College of Cardiology Valvular Heart Disease Guidelines.

In a study in this issue of Circulation: Cardiovascular Imaging, Magne et al investigate the clinical and prognostic effect of a Doppler-based novel index of LV ejection index (LVEI) in primary MR due to MVP. The authors define LVEI
as the LVESD indexed to body size divided by the LV outflow tract (LVOT) time–velocity integral (TVI). As LVEI includes an estimate of LV contractility (LVOT TVI), the authors postulate it to be a better predictor of postrepair outcomes compared with classic parameters, such as LVEF and LVESD. Magne et al\textsuperscript{12} retrospectively examine 278 patients who underwent mitral valve repair for primary MR by comparing echocardiography-derived preoperative LV diameters, LV stroke volume, LVEF, and LVEI in patients with and without postoperative LV dysfunction. They demonstrate that a preoperative LVEI of >1.13 is an independent predictor of postoperative LV dysfunction and a determinant of postoperative survival and cardiovascular mortality, even in patients with a preserved LVEF of >60%. They conclude that LVEI index may be used as a complementary parameter to risk stratify and guide decision making in patients with primary MR.

Among the strengths of the investigation is first and foremost the novelty of the echocardiographic index proposed. Second, LVEI can be easily obtained in every day clinical practice by using measurements that are part of a standard examination and, with regard to LVESD, already recommended by current valvular guidelines.\textsuperscript{10} An imaging parameter that does not require additional acquisition or postprocessing time has the potential to be better accepted (and used) by both sonographers and cardiologists. In addition, the correlation of LVEI with clinical outcomes, specifically postoperative LV dysfunction, overall survival, and cardiac death–free survival further highlights its appeal in clinical practice. Importantly, because LVEI was found to be a powerful determinant of postoperative outcomes even in patients with a preoperative LVEF of >60%, it may be considered a potential marker of early myocardial dysfunction.

Other imaging modalities have played an important role in identifying early substrates of abnormal systolic function in primary MR. Specifically, patients with postoperative LV dysfunction have been shown to have greater alterations in preoperative LV global longitudinal strain than patients with normal postoperative LVEF, suggesting that global longitudinal strain may be more sensitive than LVEF for the detection of latent LV dysfunction in patients with severe MR.\textsuperscript{13} Although global longitudinal strain provides a more global assessment of geometric changes occurring with MR progression compared with LVEI (LVESD is measured at the base), it may be considered a potential marker of early myocardial dysfunction.

CMR has the potential to detect early myocardial dysfunction, although future studies are needed to link diffuse fibrosis with clinical outcomes in asymptomatic primary MR. Compared with CMR, echocardiographic LVEI is more readily available and has proven prognostic implications\textsuperscript{12} in MVP-related MR.

The work by Magne et al\textsuperscript{12} is not exempt from limitations. First, as the authors acknowledge, because of the retrospective nature of the data, LV volumes were only available in a small sample of the study population, precluding their inclusion in the analysis. Overall, the best predictors of postoperative LV systolic dysfunction should take into account geometric changes occurring with MR progression. As these changes are expected to be global rather than segmental, they would be better captured by LV volumes compared with a unidimensional measurement, such as LVESD. In addition, as the authors note, CMR data have recently shown that LV dilatation generally occurs in the mid apical section of the ventricle and only later, at an advanced stage of disease process, at the LV base.\textsuperscript{15} The use of LV diameters (typically measured at the base of the ventricle) may lead to underestimation of the effect of MR on LV size and consequently to delays in surgical referrals. This problem applies not only to LVESD in general but also to indexed LVESD used to calculate LVEI. Second, the authors examine the correlation of all other possible ratios and single variables, including nonindexed LVESD/TVI ratio, indexed LV stroke volume/TVI, LV stroke volume/TVI, LV stroke volume alone, and LVESD alone (indexed and nonindexed) with outcomes post surgery. Among these preoperative echocardiographic parameters, LVEI provided the best correlation with postoperative LV dysfunction in univariate analyses. Unfortunately, it is unclear whether LVESD indexed was included at all (only LVESD nonindexed is mentioned in the text and the tables) in the multivariate models for prediction of postoperative outcomes. This is problematic, as it is difficult to say whether the benefit of LVEI is driven only by indexing LVESD versus adding LVOT TVI to the denominator. Third, among the limitations of LVEI are the limitations related to its numerator LVESD. As for most LV size parameters, LVESD is load dependent. In addition, the authors use M-mode to quantify LVESD rather than 2-dimensional (2D) echocardiography. Single dimension may not be representative in distorted ventricles, and beam orientation is often off axis when using M-mode. Fourth, quantitative assessment of severity of MR using the proximal flow convergence method was not systematically performed in the current cohort (only in 59% of the whole cohort). The authors state that MR was quantified as grade 3+ or grade 4+ in all of the study patients using an echocardiographic multiparametric approach, although fail to describe which parameters were used. Fifth, the authors state that LVEF was estimated by the Simpson biplane method and only in a minority of cases (<5%), visually. This statement contradicts the fact that LV volumes were not available for analysis (as the Simpson biplane method is calculated from LV volumes). Sixth, 23 patients (8%) were reported to have recurrent grade 3+ or 4+ MR. Although there was no effect of residual or recurrent MR on postoperative LV dysfunction (P=0.152), the nonsignificance of this finding is difficult to interpret given the small sample size. In addition, the authors fail to clarify whether recurrent MR was associated with increased mortality (independently of the nonsignificant effect on postoperative LV dysfunction).
The various limitations of this article offer the opportunity for future research directions. A comparison of LVEI with other more global parameters of LV systolic function (eg, global longitudinal strain) is the obvious next step. Because the addition of a contractility measurement (LVOT TVI) seems to confer a prediction benefit to a unidimensional parameter, it is expected that a ratio of LV end-systolic volume/LVOT or 3D LV end-systolic volume/LVOT TVI will perform even better.

In conclusion, preoperative LVEI represents a novel and easy to obtain echocardiographic parameter able to predict post-operative LV dysfunction, overall survival, and cardiovascular mortality, at least in a preliminary retrospective analysis. The prognostic implications of LVEI remain strong even in patients with a preserved LVEF of >60%, indicating its potential to be used as a marker of early preoperative dysfunction. Nevertheless, LVEI is derived from LVESD (a unidimensional parameter) and cannot take into account the complex, global geometric changes that occur with progression of MR. Large prospective studies are needed to confirm the prognostic value of LVEI.

Sources of Funding
This work was supported by research grant K23HL116652.

Disclosures
None.

References

KEY WORDS: Editorials ■ echocardiography ■ mitral valve insufficiency ■ mitral valve prolapse ■ outcome assessment (health care)
Left Ventricular Ejection Index as a Marker of Early Myocardial Dysfunction in Primary Mitral Regurgitation: Novel or Old in Disguise?
Francesca N. Delling

Circ Cardiovasc Imaging. 2015;8:
doi: 10.1161/CIRCIMAGING.115.003995
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/9/e003995