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EDITORIAL COMMENT

A New Look to an Old Measurement*

Luc A. Pierard, MD, PHD, Julien Magne, PHD
Liege, Belgium

Valvular heart diseases often require intervention. In industrialized countries, the reduced incidence of rheumatic valve disease and the prolonged life expectancy account for a progressive increase in the incidence of degenerative valve disease. Their management remains difficult, despite the production of guidelines prepared by organizations (1,2). Because randomized clinical trials are particularly scarce in this setting, most recommendations are supported by only a Level of Evidence: C (consensus of opinion of experts established from small and retrospective studies). This can explain in part an inconsistent compliance with guidelines.

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In particular, the management of severe organic mitral regurgitation (MR) is controversial and the optimal timing of surgical intervention remains unclear. Mitral valve surgery is indicated in symptomatic patients with severe primary MR (class I) to prevent left ventricular (LV) dysfunction and improve outcome. In asymptomatic patients, indications for surgery should integrate the severity of MR, the probability of a durable valve repair and the consequences of MR on cardiac geometry and function, such as LV dilation, systolic dysfunction, atrial fibrillation, and/or pulmonary arterial hypertension. Indeed, surgery is recommended in the presence of LV impairment, defined as a LV ejection fraction ≤60% and/or a left ventricular end-systolic diameter (LVESD) ≥40 mm (in American College of Cardiology/American Heart Association guidelines) or >45 mm (in European Society of Cardiology guidelines). Severe, prolonged MR results in LV remodeling and initially normal forward stroke volume. The LV ejection fraction represents the sum of the forward LV ejection fraction and the regurgitant fraction. The evaluation of LV ejection fraction, thus, often leads in apparent preservation of LV function and may result in incorrect estimation of the real impact of MR on the ventricle. The use of LVESD could thus appear more appropriate, even if data on its prognostic importance and its association with postoperative outcome are limited, and despite guidelines' differences in the threshold that should be used (≥40 mm vs. >45 mm).

In this regard, the paper by Tribouilloy et al. (3) in this issue of the *Journal* provides an important contribution. A total of 861 patients with MR due to flail leaflets were enrolled between 1980 and 2004 in the MIDA (Mitral Regurgitation International Database) registry, a multicenter registry involving 4 European centers and 1 center in the U.S. Follow-up collection was completed in each center in >95% of their cohort. Only patients in whom LVESD was measured were included in the analysis. Among 739 patients, 74% had a LVESD <40 mm and 25% were managed only conservatively with a mean follow-up of 2.2 ± 3.1 years. In addition, the management of 75% of the whole cohort was medical followed by surgery and mean follow-up was 6.1 ± 3.7 years. Under conservative management, LVESD ≥40 mm was associated with approximately a 2- and 3-fold increase in overall and cardiac mortality risks, respectively. Interestingly, LVESD was also an independent determinant of lower survival even after surgical correction of MR. After adjusting for variables used as indication for surgery in guidelines (i.e., symptoms, ejection fraction, and atrial fibrillation), LVESD remained independently associated with poor outcome. When surgery was analyzed as a time-dependent variable in the multivariate model, the results showed that mitral valve surgery subsequently reduced the risk of mortality. The correction of LVESD to body surface area was used to avoid a misclassification of patients with large stature. Similar results were found using a cut-off of ≥22 mm/m^2.

The prognosis of patients with mitral flail leaflets was previously studied by Ling et al. (4). They already observed that MR due to flail leaflet, when treated conservatively, is associated with excess morbidity and mortality and that surgery allows an improvement of prognosis. Nonetheless, this "prophylactic and aggressive strategy" is based on the premise that the valve will be repairable (78% of the patients submitted to surgery in the present study), which is not always the case. The rate of mitral valve repair varies largely from institution to institution and from surgeon to surgeon. In the hands of experienced surgeons, >90% of the valves of patients with severe MR are repaired. However, the proportion was only 41% in a European Heart survey (5). By contrast, Rosenhek et al. (6) reported the results of a series of 56 patients with severe MR due to flail leaflets who underwent serial clinical and echocardiographic examinations and were only referred to surgery when a class I or IIa indication, according to the guidelines, was reached. This study revealed that asymptomatic patients with severe organic MR due to flail leaflet had similar survival rates compared with the general population and may be safely followed up using a "watchful waiting" strategy. However, the patients included in the study of Rosenhek et al. (6) were younger and had lower LV size, which suggests that these patients were probably less sick than those included by

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From the Department of Cardiology, University Hospital, Liege, Belgium.

Ling et al. (4). The results reported by Tribouilloy et al. (3), as well as those previously published by Grigioni et al. (7), confirm that severe MR due to flail leaflet is not a benign condition. The impact of LVESD on survival was not significantly affected by the origin of patients (Europe vs. U.S.; $p = 0.14$), suggesting that these results may be clinically applicable worldwide. Although the present study provides useful clinical information, only flail leaflets were included. The application of these results to other forms of severe organic MR should not be done automatically. Hence, organic MR tends to progress over time but the progression is variable. Higher rates of progression are mainly determined by the development of a new flail leaflet (8). In addition, sudden death is relatively common in patients with flail leaflet who are treated medically (9).

The echocardiographic measurement of LVESD should systematically be obtained. Although it seems relatively easy, some pitfalls exist. The ultrasonic beam should be directed between the mitral valve echoes and the papillary muscles echoes. Small differences in this direction can result in different measurements in the presence of a spherical LV dilation due to MR. It is recommended to use as end-systole peak downward motion of the septum (10), which usually occurs slightly before the peak upward motion of the posterior endocardium, but the difference can be greater in the presence of LV dyssynchrony. Importantly, the cursor should be perpendicular to the septum and the posterior wall. An oblique orientation would overestimate LV diameter, sometimes largely. In this case, it is preferable to use anatomic M-mode despite its much lower temporal resolution than conventional M-mode or to obtain the measurement from a stop-frame 2-dimensional echocardiogram despite the difficulty to precisely select the end-systolic frame. Therefore, when LVESD becomes close to the cut-off value of 40 mm, it is preferable to repeat the echocardiographic examination after a short period of time rather than taking an important decision based on this single parameter.

It is also necessary, when the patient is asymptomatic, to ensure that MR is really severe. In the study of Tribouilloy et al. (3), a flail leaflet was considered as a surrogate of severe MR, although any amount of flail does not necessarily imply severe MR. At the beginning of the registry, quantitative methods for grading MR were not yet developed. Since that time, it has been demonstrated that quantifying MR according to current guidelines provides powerful prediction of the clinical outcome of asymptomatic MR (11).

New echocardiographic tools could also enhance the management of patients with severe organic MR. Real-time 3-dimensional echocardiography allows accurate assessment of LV geometry and provides reproducible measurements of LV end-systolic and -diastolic volumes. The LV function could also be better estimated with new indices using tissue Doppler imaging and 2-dimensional speckle-tracking imaging. Measurements of longitudinal myocardial deformation improve the detection of subclinical LV dysfunction and were recently reported as an accurate predictor of postoperative LV dysfunction (12). The LV contractile reserve, assessed with exercise echocardiography could also play a role in the assessment of patients with valvular heart disease and this method should be investigated in the setting of severe organic MR. However, these new tools need to be evaluated in large multicenter registries with long-term follow-up. Meanwhile, the noteworthy study by Tribouilloy et al. (3) convincingly emphasizes that patients with severe primary MR, at least as a consequence of flail leaflets, who have LVESD $\geq$40 mm or $\geq$ 22 mm/m^2 should be promptly referred for surgical intervention.

Reprint requests and correspondence: Prof. Luc A. Pierard, Head of Department of Cardiology, University Hospital, CHU Sart Tilman, B-4000 Liege, Belgium. E-mail: lpierard@chu.ulg.ac.be.

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