

## EDITORIAL COMMENT

# Aortic Regurgitation: Time to Reassess Timing of Valve Replacement?\*

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Major advances in cardiac surgery and interventional cardiology over the past several decades have led to a gradual but substantial reduction in the threshold for cardiac valve replacement and repair. Whereas 30 to 40 years ago, surgery was indicated only when patients manifested severe symptoms, the field has progressed to the point at which current guidelines recommend intervening at the first onset of even mild symptoms and even in selected asymptomatic patients (1,2).

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Early referral for valve repair or replacement is justified when it is substantiated by the available natural history data and extensive clinical experience, and this is the case for many disorders of the aortic and mitral valves. However, the management of patients with aortic regurgitation (AR), in particular, remains problematic.

Percutaneous mitral balloon valvotomy offers a safe and effective treatment of mitral stenosis with excellent long-term results, and patients who are suitable candidates are recommended to undergo this intervention at an earlier stage of symptoms or pulmonary hypertension than are patients with severe valve deformities that require surgical valve replacement. Referral for mitral valve repair in asymptomatic patients with severe degenerative forms of mitral regurgitation (MR), the leading cause of MR in developed countries, is supported by natural history studies indicating a rapid progression toward symptoms, left ventricular (LV) dys-

function, atrial fibrillation, or pulmonary hypertension, and by studies indicating worse post-operative survival among patients with pre-operative symptoms compared to asymptomatic patients (3). Similarly, among patients with aortic stenosis (AS), the high likelihood that a patient with severe AS will require aortic valve replacement (AVR) within 5 years or less, coupled with concerns of sudden death, the difficulty in eliciting symptoms in sedentary patients, and the low operative risk in experienced centers, have led to consideration for early AVR in many patients (1–5). In contrast to this growing consensus regarding management of patients with mitral stenosis, MR, and AS, the timing of AVR in patients with AR continues to stand out as a subject of uncertainty and considerable controversy.

Optimal timing of AVR in patients with AR is problematic as they may remain asymptomatic with normal LV systolic function for many years despite the substantial LV volume load, yet by the time symptoms develop, a large number may have already developed myocardial dysfunction that may place them at high risk for post-operative heart failure and death. Unlike the trend for early surgery in asymptomatic patients with severe MR, the majority of whom are candidates for mitral valve repair, a higher threshold for surgery is set for patients with AR as they almost always face valve replacement. The time course toward development of symptoms and/or LV systolic dysfunction is gradual and protracted in younger patients with AR (1,6–8), although this appears to be a more rapid process in patients older than 50 years of age (9). Nonetheless, the average age of patients with severe AR is significantly less than that of patients undergoing surgery for severe AS, for whom the decision to replace the valve with a bioprosthesis is straightforward. In contrast, determining the optimum time for valve replacement in young asymptomatic

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patients with severe AR, and then selecting a mechanical prosthesis versus a bioprosthesis, present difficult, if not agonizing, decisions for the clinician.

Guideline recommendations for AVR in asymptomatic patients with AR have historically focused on LV ejection fraction and LV end-systolic dimension as measures of LV pump performance, and LV end-diastolic dimension as a measure of the severity of the volume overload (1,2). In addition to the inherent variability of these measurements, ejection fraction notoriously may fluctuate depending on blood pressure and other loading conditions, and LV short-axis diameters fail to adequately reflect the great individual variation in the 3-dimensional geometries of volume-loaded left ventricles. However, these simple measurements were those available to the investigators more than a decade ago who performed the long-term natural history and outcome studies that are the substrate for the current guidelines. In essence, the guidelines are based on 30-year-old technology. Although a more rigorous assessment of LV regional and global performance should be possible with our current imaging armamentarium, new evidence has yet to materialize to guide management decisions. Only recently have standardized criteria for LV volume measurements by echocardiography been established (9,10), and these have not been subjected to extensive long-term studies of sufficiently large numbers of patients. Newer methods to assess systolic and diastolic myocardial function with cardiac magnetic resonance or echocardiographic methods such as tissue Doppler imaging or speckle tracking are now available, but these too require careful prospective investigation to determine their potential role in clinical decision making.

In the current issue of *JACC*, Olsen et al. (11) have moved the field several steps forward by examining the potential of speckle-tracking echocardiography to predict clinical and functional changes over the course of time in asymptomatic patients with AR and normal LV systolic function and, in another group of patients undergoing AVR, to predict changes in LV function after surgery. In both groups of patients, reduced systolic strain, systolic strain rate, and diastolic strain were associated with worse outcome: more rapid progression of disease in the asymptomatic patients during conservative follow-up and worse functional outcome after AVR in the surgery group. These seminal findings and their intriguing implications regarding future clinical implementation need to be balanced against

several limitations, some of which are noted by the authors themselves.

First and foremost, Olsen et al. (11) studied only a small number of patients—35 in the serial follow-up group and 29 in the surgical group—which not only limited the ability to perform multivariate or subset analyses (as noted), but also required the use of composite end points, which comprised both clinical and LV function data. Changes in function represent only intermediate outcomes, and whether these translate into hard outcomes such as death, hospitalization, and quality of life is uncertain. The heterogeneous use of medications that might influence LV performance is an additional confounder. The number of patients in each of the 2 groups is too small, the follow-up periods too short, and the use of drugs too nonuniform to draw meaningful conclusions other than that this is a promising technique worthy of further investigation.

Second, the subgroup of surgical patients with the suboptimal outcome after AVR included many with such severe pre-operative LV dysfunction and/or LV dilation that it is not surprising that they also had other measures of impaired LV function that “predicted” the worse outcome. Whether speckle tracking adds incremental information to standard measures of LV volume and function in this situation is unclear; one would need to study a larger number of patients undergoing AVR with more normal ejection fraction and less severe dilation to determine if this technology is helpful in predicting post-operative outcome and, thus, in selecting patients for possible earlier surgery.

As the current data suggest a possible role of strain analysis in asymptomatic patients with preserved systolic function, it is noteworthy that a large number of patients in the conservative follow-up group reached an end point in a very short time: 25% of patients reached an end point during a mean follow-up period of only 19 months. This attrition rate is much more rapid than that reported in most natural history studies, in which the average is 4.3% per year (1,6–8), but is a similar pattern to that reported in the first paper published in the inaugural issue of *JACC* by Detaint et al. (9). The common thread may be the mean ages of the patients: 60 years in the Detaint report and 57 years in the current study, compared to 36, 41, and 46 years in the reports of Bonow et al. (6), Tornos et al. (7), and Borer et al. (8), respectively. The mean age of patients in the natural history series cited in the American College of Cardiology/American Heart

Association guidelines is 39 years. The implications are that older patients with asymptomatic AR have a much higher rate of development of symptoms and/or LV dysfunction than do younger patients, which may be related to effects of aging on vascular and myocardial stiffness that poorly tolerate a significant volume load. This observation suggests that the search for additional measures of LV performance beyond the standards of ejection fraction and volume is on the right track in older patients with AR, and that measures of both systolic and diastolic

strain may provide the key in such patients. Larger series with longer follow-up periods and rigorous control of medications are needed to determine whether this is the case and whether measures of myocardial strain have a place in the mainstream evaluation of patients with AR.

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