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EDITORIAL COMMENT

Is it Time to Lower the Bar?*

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Aortic valve surgery accounts for the majority of heart valve operations in the United States and is usually performed according to official guidelines of the American College of Cardiology and American Heart Association (1). It has been long established that once aortic stenosis (AS) becomes severe, the majority of patients will develop symptoms (angina, syncope, congestive heart failure) within 5 years and thus require surgery (2,3). Without surgery their prognosis is dismal (4). But what about the asymptomatic patient? Should surgery be performed early to pre-empt adverse remodeling associated with AS and other comorbidities? Or should it be delayed to favor the use of a bioprosthetic, rather than mechanical valve, and possibly to avoid a subsequent repeat procedure? In the present study, Beach et al. argue for early evaluation of asymptomatic patients with severe AS and coronary artery disease (CAD) risk factors, followed by surgical aortic valve replacement (AVR) and revascularization prior to the development of ischemic myocardial damage if risk factors are present.

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Although aortic valve replacement is the only solution for the mechanical problem of severe stenosis, the disease of degenerative AS must be viewed as more than a simple mechanical problem. As a disease of the older patient—the average patient undergoing AVR is in their seventh or eighth decade—AS does not often occur in isolation. It is frequently accompanied by comorbidities such as hypertension, CAD, and peripheral vascular disease, all of which influence the course of the disease.

Many AS patients undergo coronary artery bypass graft surgery (CABG) at the time of AVR and have a higher operative mortality than those having AVR alone (5). Beach et al. examined the survival implications of CAD in patients with severe AS (6). They studied 3,923 patients all of whom received a single type of bovine AVR for severe AS; 1,637 isolated AS patients underwent AVR alone and 2,286 with severe AS and CAD underwent AVR and CABG. Patients were followed at 2 and 5 years. Using propensity scores, isolated AS patients were matched to AS+CAD patients (total 2,164 matched patients). Survival analysis was performed on all. Numerous sophisticated and novel statistical techniques and models were used to identify unique risk factors between the 2 groups (isolated AS and AS+CAD) and to study survival.

Not surprisingly, the AS patients on the whole were younger and enjoyed better outcomes than the AS+CAD patients who were older with more comorbidities. Patients with isolated AS had the best outcomes, patients with AS+CAD without evidence of ischemic myocardial damage had an intermediate prognosis, equivalent to patients with isolated AS with similar comorbidities, while patients with AS+CAD with ischemic damage and multiple comorbidities had the worst outcomes.

A key finding of this study is that the survival curves for the propensity matched AS and AS+CAD patients were similar. Roberts recently showed equal early and late mortality in 871 propensity matched patients undergoing AVR with and without CABG (7). De Waard et al. showed by multivariate analysis that concomitant CABG was not independently associated with increased mortality (8). Thus, it is the patient characteristics and comorbidities, not the procedure, that determine outcome.

AS patients were adversely affected by left ventricular hypertrophy (LVH) and diastolic dysfunction. In the matched group, the adverse effect of LVH in AS-only patients was equivalent to the effect of CAD in AS+CAD patients. A number of investigators have asked if outcomes might be improved by earlier valve replacement before a significant increase in left ventricular (LV) mass index occurs (9–12). Beach et al. add their voices to this consideration for preemptive surgery but fall short of suggesting specifics. Fuster et al. in 2003 called for a randomized trial, but to date none has been done (11).

AS+CAD patients' mortality in this study was associated with the effects of prior myocardial damage. Beach et al. therefore recommend that early diagnosis of CAD and, by implication, revascularization, may prevent ischemic damage in AS patients. Yet a large body of literature does not support preemptive revascularization for asymptomatic coronary disease. Such a strategy needs to be proven before surgery can be recommended in the asymptomatic patient.

The unmatched AVR+CAD group, the older, sicker patients with many comorbidities and worse LV function had the poorest survival. With the advent of transcatheter strategies for valve implantation one already sees a trend toward a "softening" of indications for AVR, though guidelines do not yet address transcatheter approaches in asymptomatic patients.

The elusive goal for decades has been to identify factors, which, if identified early, would improve surgical outcomes.

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Many investigators have studied the natural history of AS, and its consequences: LVH, myocardial fibrosis, and LV diastolic dysfunction (2,3,10–12). LV systolic dysfunction is often more subtle; it can be difficult to differentiate myocardial contractile failure from so-called afterload mismatch. Factors that correlate with poor prognosis include the degree of valve calcium, high gradient, LV mass index, and concentric remodeling (10–14). More recently the degree of LV longitudinal shortening, B-type natriuretic peptide levels, flow/gradient ratios, and myocardial fibrosis using magnetic resonance imaging have all been studied as prognostic indicators with the hope of better defining and refining surgical indications (14–19). Many physicians have erroneously equated normal left ventricular ejection fraction (LVEF) with normal output/flow. Hachicha et al. brought to attention the fact that patients with low gradients due to low flow (despite preserved LVEF) may not, because of their low gradients, be recognized as having severe AS (20). Pibarot and Dumesnil emphasized the interrelation between valvular, ventricular, and arterial variables in newer approaches to assessing disease severity (21).

The fact that LVH and diastolic dysfunction adversely influence outcome in isolated AS does not in itself support performing AVR prior to symptom onset, as Beach et al. suggest. A commonly held idea is that if LVH regresses, function will improve. But LVH alone does not account for diastolic dysfunction, fibrosis also plays a significant role (19). Myocardial fibrosis causes decreased LV longitudinal shortening, which in turn predicts lack of functional improvement. Weidemann, using intraoperative myocardial biopsy and pre- and post-operative CMR, showed that fibrosis did not resolve after AVR (18). Of 21 patients with severe fibrosis, 4 died during follow-up; none of the 37 with no or mild fibrosis did. Using CMR, Dweck et al. showed that the pattern of LV remodeling and degree of LVH varied considerably and did not closely correlate with the severity of stenosis (22). These studies among many others suggest we still have a lot to learn about this disease. At what stage are changes irreversible? What interplay of factors is associated with irreversibility? And what are those factors?

The guidelines are changing. LV systolic dysfunction with EF <50% portends a poor prognosis and is now a Class I indication in severe AS patients even if asymptomatic. Perhaps longitudinal shortening, more reflective of the effects of myocardial fibrosis, will one day be included as a better indication than LVEF of myocardial dysfunction. The growing practice of exercise testing to uncover symptoms is reflected in the new European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines; with a Class I indication, "AVR is indicated in asymptomatic patients with severe AS and abnormal exercise test. . ." (still a Class IIb American College of Cardiology/American Heart Association 2008 guideline indication). The European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines include as Class IIa asymptomatic patients with normal EF with peak transvalvular velocity >5.5 m/s or severe valve calcium and peak valve velocity progression of >0.3 m/s per year (5).

The large well-conducted study of Beach et al. provides a wealth of information on a carefully characterized group of patients undergoing AVR with and without CABG and emphasizes the role of risk factors and comorbidities in determining surgical and longer-term survival among the broad range of AS patients. It helps us focus on the as yet unanswered question: Which high-risk asymptomatic AS patients will benefit from surgery? Will earlier intervention make a difference? Only a randomized clinical trial will answer these questions. In the meantime, we must apply our knowledge of risk factors for morbidity and mortality, of surgical outcomes, of the systemic nature of the disease, and importantly knowledge of our patients themselves in order to make the best decisions. They look to us for guidance, not guidelines.

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