Aortic Valve Replacement for the Asymptomatic Patient With Aortic Regurgitation
A New Piece of the Strategic Puzzle

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For patients with hemodynamically severe aortic regurgitation (AR), the primary remedial therapy is surgical aortic valve replacement (AVR). Timing of surgery, however, is a moving target. Techniques and prosthetic devices continually improve, justifying AVR progressively earlier in the natural history of the disease. Indeed, there is currently a general consensus that surgery for AR is appropriate when congestive symptoms first appear, even if they are mild. This philosophy represents a distinct departure from the accepted standard of a generation ago, when the symptomatic indication for AVR was New York Heart Association functional class III. For asymptomatic patients, AVR remains controversial, except when left ventricular (LV) systolic performance is subnormal at rest as judged from ejection fraction (EF, or the parallel echocardiographic measure of fractional shortening [FS]). This standard was first suggested by Henry et al, who began a prospective echocardiographic and clinical assessment of patients with AR in 1972. Henry et al tested two hypotheses: first, that outcome after AVR is dependent on LV systolic performance, and second, that progression to symptoms is predictable when performance is subnormal in asymptomatic patients.

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The patients of Henry et al underwent AVR only when symptoms developed. If, by that time, FS at rest was subnormal, long-term postoperative survival averaged approximately 45% at 4 years after operation, compared with 90% if FS was normal pre-AVR. Although the point estimates were confounded in some of their 49 patients by concomitant mild aortic stenosis or by coronary artery bypass grafting, the importance of LV performance in predicting outcome was clear, as was the sharp outcome dichotomization associated with normal versus subnormal LV performance. The data of Henry et al soon were supported by those of Cunha et al, Forman et al, and Greves et al. In the retrospective evaluation of 86 patients by Cunha et al, those patients with pre-AVR echocardiographic left ventricular ejection fraction at rest (LVEFrest) ≥60% or FS >35% suffered no deaths during approximately 21/2 years follow-up; survival fell to approximately 80% if LVEF was <60% or if FS was ≤30%. Although not reaching statistical significance, there was a tendency toward more early (<1 year) postoperative deaths among those with “low normal” FS (31% to 35%) than in patients with better-preserved LV performance (a tendency also inferable from the data of Henry et al). The analysis of Forman et al, like that of Cunha et al, was retrospective, included 90 patients with AR, and reported relatively similar findings: 3 years after AVR, survival was 93% among those with normal preoperative LVEFrest versus 64% if LVEF was subnormal. The retrospective findings of Greves et al in 39 patients also were similar: 5-year postoperative survival was 87% for those with normal preoperative LVEFrest versus 54% if LVEF was subnormal. In total, Henry et al, Cunha et al, Forman et al, and Greves et al evaluated pre-AVR prediction of post-operative survival in 265 patients, reported consistent findings and provided compelling evidence (and a reasonably stable relative risk point estimate) for substantially lower mortality up to 5 years after AVR among those with normal versus subnormal LV systolic performance.

Among Henry et al’s asymptomatic (and, hence, unoperated) patients, subnormal LVFSrest indicated 80% likelihood of symptom onset during an interval averaging slightly more than 3 years. Several months after the publication of the data of Henry et al, McDonald et al reported parallel findings. Approximately two-thirds of the patients of McDonald et al developed symptoms or died during a 4-year interval. In 1991, Bonow combined the data from these two series and demonstrated a 25%/y progression to symptoms (or, rarely, death) among unoperated initially asymptomatic patients with AR whose LVEF was subnormal or whose fractional shortening was <29%. Reassuringly, progression rate was remarkably similar in the two component series. In total, however, only 27 patients were appropriate for analysis; these 27 patients provide all published data currently available to rigorously define the progression rate to symptoms in patients with subnormal LV performance at rest. Several patients entered these studies with subnormal LV performance and were followed until symptoms developed; therefore, the data may, to some extent, overestimate the rate of progression to symptoms. The latter possibility is supported by the lower annualized event rate of 5.8% more recently defined retrospectively by Dujardin et al among unoperated asymptomatic patients with LVEFrest <55%. Though these data are not strictly comparable with those of Henry et al and McDonald...
et al because of differences in definition of events and patient selection, the data of Dujardin et al add importantly by demonstrating that, in the absence of symptoms, event rate in unoperated patients with subnormal LVEFrest is greater than that in patients whose LVEF is normal (annualized event rate 2.0%).

Recognizing that a controlled trial to resolve the issue of relative risk is highly unlikely (such a study never has been performed), physicians have used these data as the basis for recommending AVR to asymptomatic patients with subnormal LVEFrest to prolong survival. The logic underlying this strategy is as follows. If operation is withheld when LV performance is subnormal in the asymptomatic patient, and if symptoms develop predictably at a rate of 25%/y, then when the inevitable symptoms occur, the patient’s long-term postoperative survival will be even more compromised than it would have been if operation had been performed when LVEF was first found to be subnormal. As a corollary, it is assumed that LVEF will continue to worsen during the interval before development of symptoms and that prognosis after AVR will deteriorate progressively as preoperative LVEF declines.

Intuitively, this logic is reasonable, but requires assumptions that never have been assessed rigorously. Specifically, it must be assumed that, in the absence of symptoms, LV performance is subnormal. This is true unless symptoms had developed with subnormal LVEF; also, it must be assumed that LV performance deteriorates over time and that postoperative prognosis worsens related to this deterioration. If these conditions are not met, then there is little advantage to placing the asymptomatic patient at risk with an operation, especially when better surgical methods can be expected if operation is delayed (until symptom development).

Though the current strategy and its supporting assumptions are reasonable, the paucity of supporting data and the progressive improvement in surgical results suggest that periodic review is necessary to assure continued viability of inferences drawn from small cohorts a quarter century ago. The data of Chaliki et al10 reported in this issue of Circulation provide important support for the logic of current decision-making. Among 490 patients, 177 of whom had subnormal LVEFrest immediately before AVR, these authors definitively demonstrated that postoperative prognosis deteriorates as a function of the extent to which LVEF is subnormal. The patients from whom these data were drawn underwent operation between 1980 and 1995, substantially later (in terms of surgical methods) than those who comprised the earlier series. When combined with the data of Bonow et al11 and of my own group,12 which demonstrate gradual deterioration in LVEF at rest among asymptomatic patients with severe AR (particularly among those with compromised LV contractility), the findings of Chaliki et al strongly reinforce the practice of “prophylactic” operation in the asymptomatic patient with subnormal LVEFrest.

Chaliki et al also provide useful information about the modulating effect of symptoms on prediction from LVEF alone. Previously, this relation had not been rigorously defined. Intrinsically, the assessment is confounded by difficulty in quantifying debility based on patients’ descriptions of exercise capacity. Consequently, many investigators have grouped those with clearly established, relatively severe symptoms (functional classes III and IV) and those with absent or milder symptoms (functional classes I and II). As noted, the patients of Henry et al underwent operation only when symptoms had developed. Some unequivocally asymptomatic (functional class I) patients underwent operation in the series of Cunha et al, Forman et al, and Greves et al, but only Greves et al evaluated the impact of symptoms, suggesting that escalating symptoms were associated with progressively poorer postoperative prognosis in both normal and subnormal LVEF subgroups. These data did not resolve the issue, however: patients and events were far too few to provide power needed for statistically reliable conclusions; indeed, no asymptomatic patient was included in the normal LVEF subgroup. In the much larger data set of Chaliki et al, approximately one-third of patients in each LVEF-defined subgroup were in functional class I at AVR; multivariate analytic methods (little used in 1980) were applied to assess independent effects of multiple predictors, enabling Chaliki et al to demonstrate statistically that symptoms are independently associated with outcome, even as LVEF progressively falls, and, concomitantly, that LVEF provides independent predictive value even when symptoms already have been considered. Although additional statistical assessments could be performed to isolate the impact of LVEF, specifically in the asymptomatic subsets, the data of Chaliki et al strongly support the conclusion that postoperative outcome in the asymptomatic patient with subnormal LVEF is worse than in the asymptomatic patient with normal LVEF, while confirming that outcome in the symptomatic patient with normal LVEF is worse than in the asymptomatic patient with normal LVEF.

Though the study by Chaliki et al was not “prospective,” in that it was not based on a predetermined hypothesis, the results are nonetheless compelling because the cohort included almost all potentially eligible patients at the Mayo Clinic during the evaluation interval, ie, there were relatively few dropouts for lack of data, and considerable descriptive data were available for each patient.

The work of Chaliki et al provides important support for currently accepted strategy. However, current surgical results justify the search for predictors of prognostically important cardiac alterations in asymptomatic patients that appear earlier than normal LVEFrest. These should enable refinement of AVR indications to further maximize long-term survival. Several such predictors have been apparent for many years, though the strength of supporting evidence varies. These include LV systolic dimension >55 mm, another systolic phase descriptor first highlighted in the original study of Henry et al, which (rarely) is apparent in patients with normal FS/LVEF and seems to carry independent prognostic information. Although the value of this predictor has been debated,4 the recent demonstration by Dujardin et al of the prognostic utility of systolic dimension adjusted for body surface area (>25 mm²/m²) supports its use clinically. Similarly, though supporting evidence is more
modest, marked LV diastolic dilatation (>80 mm)\textsuperscript{11,13} is also occasionally seen when LVEF is normal, is associated with relatively compromised outcome on univariate analysis, and may carry independent prognostic information, though here, too, conflicting analyses exist.\textsuperscript{12,14} Recently, data from the long-term, prospectively designed assessment of natural history of AR and its predictors by my own group\textsuperscript{14} indicated that intrinsic contractility, measured as the change in LVEF from rest to exercise adjusted for the change in end-systolic stress from rest to exercise, is particularly useful in patients with normal LVEF\textsubscript{rest} and no symptoms. When this parameter was applied, neither LVEF nor end-systolic dimension or end-diastolic dimension added independently to prediction of subsequent heart failure, subnormal LVEF\textsubscript{rest}, or sudden death.

Like LVEF\textsubscript{rest}, none of these other descriptors is supported by randomized trial data as a basis for AVR. Additional work, like that of Chaliki et al, must determine their proper place in developing management strategy for the asymptomatic patient. However, gradual unraveling of the fundamental cellular and molecular pathophysiology underlying debility and death in AR\textsuperscript{15,16} suggests that we must begin to turn toward direct interrogation of myocardial biology to refine prognostication and, simultaneously, to define the basis for novel therapies to retard disease progression and to optimize outcome when AVR is performed. These are the directions of the future.

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References

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