JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 5, NO. 5, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2012.04.005

EDITORIAL COMMENT

Low-Gradient, Low-Ejection Fraction Aortic Stenosis

What We Know and What We Do Not Know*

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What We Know

It is generally held that outcome for patients with valvular heart disease is largely determined by the contractility of the left and/or right ventricles. This innate force generation capability might become compromised when chronic severe hemodynamic overload injures the myocardium, impairing function and prognosis. In aortic stenosis (AS), impaired left ventricular (LV) ejection is in part predicated on reduced contractility and also upon excess afterload imposed by the stenotic valve as it causes obstruction to outflow (1–4). The property that dominates—excess afterload versus reduced contractility—in a given patient determines prognosis (2).

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When afterload excess attended by a large transvalvular gradient is dominant, ejection fraction (EF) can return completely to normal after aortic valve replacement, and improvement in symptoms is striking (2,5). It is fair to add that many patients with a normal EF still have modest systolic dysfunction at the sarcomere level (6). This occurs as LV hypertrophy, by adding sarcomeres in parallel, allows normal LV systolic thickening despite reduced systolic sarcomere shortening. Still, aortic valve replacement (AVR) causes a large decrease in afterload, and impaired ejection improves almost immediately in the AS patient with a large gradient and a large preoperative afterload (5).

However, when impaired contractility is the major cause of impaired LV ejection, the prognosis is much worse (2,7–10). In such cases, the weakened ventricle produces a small stroke volume, which in turn produces a low transvalvular gradient. Operative mortality is high in such patients, approaching 35% in some series. Prognosis is improved if patients show a substantial (at least 20%) increase in stroke volume during infusion of a positive inotrope such as dobutamine (11,12). By contrast, patients with ultra-low mean gradients (<20 mm Hg) have a very poor prognosis, especially when impaired LV function is due to coronary disease and extensive myocardial infarction (9,10). We also know that operative outcome is reduced if the inserted prosthesis has a substantial residual gradient (8). The aforementioned findings are intuitive and logical. If the LV is extensively scarred by coronary disease, aortic valve replacement would be expected to be ineffective. Likewise, patients with the lowest gradients likely have the most impaired ventricles, and any residual gradient after AVR would detract from the hemodynamic benefit of the valve replacement. Or looking at the problem from another angle, a very low pre-operative gradient offers little chance for reduction in total LV pressure demand postoperatively, and improvement in symptoms and LV function is likely to be curtailed.

What We Do Not Know

Thus we have learned much about the low-EF, low-gradient patient, but much is left unknown. As noted in the preceding text, detection of inotropic reserve is very useful in assessing the risk of AVR. Operative risk is approximately 10% for those with inotropic reserve versus over 30% for those patients without inotropic reserve (12). Remarkably however, for those inotropic-negative patients who survive AVR, improvement in EF can be as robust as for patients that did have inotropic reserve (13). A reasonable hypothesis that follows is that inotropic reserve helps get the patient through the surgical stress of AVR, but once that hurdle is successfully overcome, other myocardial changes allow for improved LV function after a relatively non-stenotic valve is implanted. How and why the LV without inotropic reserve recovers after AVR will be crucial in determining which inotropic reserve-negative patients will and will not benefit from AVR.

For those patients who have inotropic reserve, 2 different responses have been observed. In some patients, increased stroke volume increases the gradient, and valve area remains small, as would be expected from a fixed obstruction to outflow. In others, the increase in stroke volume causes little increase in transvalvular gradient, and calculated valve area increases substantially. Such patients are believed to have aortic "pseudo" stenosis, wherein a LV weakened by an independent cardiomyopathy is unable to generate enough force to open a relatively pliable and only moderately stenotic valve (14,15). When increased inotropy is applied, the valve opens more widely, and calculated valve area increases. It has generally been assumed that AVR would

*Editorials published in the *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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not benefit such patients, because AS was not the major cause of patient heart failure to begin with. Accordingly, few such patients receive an AVR. Of interest are data (few as they might be) from the TOPAS (True or Pseudo-Severe Aortic Stenosis) registry where 4 of 5 patients with pseudo stenosis had a good outcome with AVR (16,17). It is possible that in such patients, the removal of only mild-to-moderate obstruction to outflow is beneficial to such severely compromised ventricles. Obviously, far more data are required to address this issue before AVR for pseudo AS could be realistically considered.

The Current Study

From the foregoing, the possible utility of avoiding standard open heart surgery in such ill patients—especially inotropic-negative low-EF, low-gradient patients—and replacing it with a transcatheter approach (transcatheter aortic valve replacement [TAVR]) has obvious appeal. That the currently available transcatheter valves have an excellent hemodynamic profile enhances the possibility of success. Comparison with other reports is fraught with difficulty, but such comparisons are inevitable. Thus, the paper by Lauten et al. (18) in this issue of *JACC: Cardiovascular Interventions* is of special interest. In their report of data from the German Transcatheter Aortic Valve Interventions Registry, the outcome of 149 patients undergoing TAVR with low-gradient, low-EF (mean gradient <40 mm Hg, EF <0.40). AS was compared with 1,153 patients with better LV function. The 1-year mortality in the current study, was 37% for the low-gradient, low-EF group, compared with 18% for patients with better LV function. The low EF group compared favorably with the 30% 1-year mortality in the TAVR arm of the PARTNER Cohort B (Placement of AoRTic TraNscathetER Valve—Cohort B) study of inoperable AS patients (19). Although PARTNER patients had serious comorbidities that rendered them inoperable, average EF was 0.54 compared with 0.38 in the current study; the mean gradient in the PARTNER study was greater—45 mm Hg versus 31 mm Hg in the current study. By contrast, in the study by Monin et al. (12) of low-gradient, low-EF patients, EF was 0.30 and mean gradient was 29 mm Hg. One-year mortality was approximately 15% for patients with inotropic reserve and approximately double that in the absence of inotropic reserve. In the current study, inotropic reserve was evaluated but not reported so that comparison is difficult. Thus the major question of whether TAVR is superior to standard AVR or even to "medical" therapy in low-gradient, low-EF AS patients cannot be answered from the current data, although the study is encouraging. Especially left in question are patients with the worst prognosis, those with mean gradients of <20 mm Hg and EF of <0.30. Cleary a randomized trial in this group of patients will be needed to see whether TAVR is superior to either "medical" therapy or standard surgery in this group.

Conclusions

Since its description over 30 years ago, we have learned much about the syndrome of low-EF, low-gradient AS. We know that the presence of a relatively high mean gradient, >20 mm Hg, combined with a positive inotropic response portends a relatively good prognosis, whereas the presence of postoperative patient-prosthetic mismatch indicates a poorer prognosis. We still don't know why some patients without inotropic reserve improve anyway or whether some patients with pseudo AS might also benefit and whether TAVR might be superior to standard AVR for such patients. The study by Lauten et al. (18) clearly demonstrates that TAVR is feasible in such patients and paves the way for a randomized clinical trial of TAVR versus medical therapy or TAVR versus surgical therapy.

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Key Words: aortic stenosis ■ aortic valve replacement ■ ejection fraction ■ valvular heart disease.