Symptomatic Low Gradient Severe Aortic Stenosis with Preserved Left Ventricular Ejection Fraction: Now Less of a Clinical Conundrum

Running title: Wiegers et al.; AVR for low gradient AS

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Accurate assessment of aortic stenosis (AS) severity is one of the more technically demanding studies in echocardiography. This is reflected in the Intersocietal Accreditation Commission for Echocardiography’s standards that specify that aortic stenosis gradients must be measured from at least 3 different transducer positions as well as with a non-imaging dedicated continuous wave Doppler transducer (Pedhoff). The standards do not specify the measurement of any other valvular lesion. Submission and review of aortic stenosis cases is required for lab accreditation by that body. Given the complexity in echocardiographic assessment, the determination that a patient has severe aortic stenosis (defined as a valve area \( \leq 1 \text{ cm}^2 \) or an indexed area \( \leq 0.6 \text{ cm}^2/\text{m}^2 \) but a mean gradient < 40 mm Hg despite a preserved LV ejection fraction (LVEF) is often met with skepticism by our interventional colleagues. Low gradient severe AS due to decreased LV systolic function can be assessed by dobutamine protocols intended to increased the flow across the valve and distinguish true from pseudo-AS.\(^1\) Such is usually not the case in patients with preserved LVEF.

Work by the group in Quebec has highlighted the existence of “paradoxical” low gradient severe AS (LGSAS) in patients with preserved EF but paradoxically low stroke volume.\(^2\) The low stroke volume is presumably due to a small LV cavity – infringed upon by left ventricular hypertrophy as well as decreased myocardial function that has not yet resulted in a decreased LVEF. Milano et al performed intraoperative myocardial biopsies on patients undergoing AVR for aortic stenosis and demonstrated that those patients with “moderate” fibrosis had much poorer long term outcome despite normal LVEF compared to the patients with no or mild fibrosis.\(^3\) Other groups have confirmed fibrosis and myocardial dysfunction in these patients with MRI to assess fibrosis and echocardiographic strain imaging to evaluate myocardial performance.\(^4,5\) In an important study published earlier this year, investigators confirmed that
low gradient severe AS with preserved LVEF was not due to systematic error in the echocardiographic assessment. They reviewed the echocardiographic and invasively obtained hemodynamic data on 58 patients at their institution with LGSAS and preserved LVEF and compared them to a group of 22 patients with “conventionally defined” AS (valve area $\leq 1$ cm$^2$, mean transvalvular gradient $\geq 40$ mm Hg). Invasive gradients were determined by pull back with manual tracing of the gradients and stroke volume was assessed by both oxymetry (using a nomogram for oxygen consumption) and thermodilution. Reclassification of patients with severe AS by echocardiography to moderate AS occurred in only 1 of 58 patients using thermodilution stroke volume and in just 10% of the patients using oxymetry. Reclassification occurred in 4% of patients with conventionally defined AS. Interestingly, while most of the LGSAS patients had an abnormally low stroke volume, 10% did not. Of the conventional AS group, 18 of 22 also had low stroke volume. This careful comparison of hemodynamic and echocardiographic data confirms that LGSAS with preserved LVEF and low or normal stroke volume is not a figment of the echocardiographer’s imagination but an important clinical entity.

An understanding of this controversy highlights the importance of the paper in this issue of Circulation by Ozkan et al which makes the strong case that LGSAS with preserved LVEF is best treated by aortic valve replacement (AVR). Since the gradients across a bioprosthetic valve may approach the level of gradients seen in patients with LGSAS, there is often hesitancy to offer this group surgery or transcatheter replacement. In the study under discussion, the investigators identified 260 patients by retrospective review of the echocardiographic database, with preserved LVEF and LGSAS. All the patients were symptomatic. This is an observational study and the treatment was decided upon by the treating team. If the patient underwent surgery, the type of surgery - conventional surgical AVR or transcatheter AVR was determined by the
same team. There was complete follow-up of both groups for all-cause mortality with follow-up over an average of 28 months ± 24 months. The authors used propensity score (PS) analysis to determine the possible benefit of AVR. PS is an attempt to account for baseline differences between treated and untreated subjects to estimate the treatment effect (see below). Their results demonstrate that the medically treated group had 2-fold increased risk of mortality compared to those who underwent AVR of either type.

The study group included patients with both low stroke volume indexes (SVI) (< 35 ml/m²) and those with normal stroke volume indexes. In the entire group there were 125 patients with normal SVI and 135 with low SVI. The low SVI patients had slightly lower LVEF while still in the normal range, lower mid-wall fractional shortening (a measure of myocardial function) and smaller aortic valve areas along with higher LV afterload. Surgical patients had a higher stroke volume on average and there were more low SVI patients in the medically treated group. After the PS analysis, it was shown that both low flow and normal flow patients treated medically had a 2-fold greater all-cause mortality compared to the AVR group. This is a very important finding. While other studies have generally found a mortality benefit in AVR in patients with LGSAS with preserved LVEF, none of them accounted as carefully for the significant differences in baseline characteristic between the two groups. It is well known that medical therapy for symptomatic severe aortic stenosis carries a terrible prognosis. The group of patients with LGSAS with preserved LVEF may have an even worse prognosis since the low gradient in general appears to reflect sub-clinical myocardial dysfunction. It is gratifying that this group can be offered AVR with an expectation of improvement in mortality. In this study, there was no difference in mortality for the medically treated patients with low or normal SVI. The recently released European guidelines rate AVR in the LGSAS group as a IIa indication, (level
of evidence C). They caution that the diagnosis of severe AS should be “carefully” confirmed. Each lab is of course responsible for the quality of their assessments. Although catheterization is considered a class III indication (should not be performed) for the assessment of AVA in patients with severe AS by echocardiography, this group of patients represents an exception to that rule.

Propensity scores have been increasingly used to analyze observational data in an attempt to approximate a randomized trial. In the paper under question, the differences between the surgical and medically treated groups were substantial. The surgical group was demonstrably healthier with less diabetes, better renal function, less hypotension and less diuretic use. Since the healthier group of patients underwent surgery, on the face of it, it is not surprising that AVR was associated with lower mortality. Although there are several methods for PS, in a relatively small group with marked differences in characteristics, the usual way to determine the PS is to perform a logistic regression with the treatment, in this case AVR, as the dependent variable. Since many of the clinical factors influence both treatment assignment and outcome, these clinical factors are all included in the logistic regression. The PS is then the likelihood of treatment assignment conditional on the baseline characteristics. The PS is entered into Cox multivariate models along with other clinical variable to estimate the treatment effect. As with all logistic regressions, there must be no “unmeasured confounders” or the results will not be accurate. The authors rightly note that such unmeasured characteristics such as frailty, severe COPD or dementia may have played a role in treatment selection and outcome.

How reliable is the method in general? In a recent analysis by Dahabreh et al the results of observational studies using PS and randomized clinical trials (RCT) were compared in the studies of treatments in patients with acute coronary syndromes. They found that the estimate of treatment effect on mortality were consistent between RCT and PS studies. In only 2 of the 17 studies of treatments in patients with acute coronary syndromes. They found that the estimate of treatment effect on mortality were consistent between RCT and PS studies. In only 2 of the 17
separate comparisons was there a statistically significant difference in treatment effect. However, the PS studies systematically over-estimated the magnitude of the treatment effect found in the RCT of the same therapy. So it must be cautioned that the finding that AVR substantially reduces mortality in the current paper may be an overestimate of the true benefit.

In conclusion, the paper is an important contribution to our growing understanding of the group of patients with severe aortic stenosis and low transvalvular gradients despite preserved ejection fraction. It goes without saying that a randomized controlled trial in this group of largely elderly patients with multiple co-morbidities is unlikely to be conducted, particularly when medical therapy has been shown to have so dismal an outcome. Ozkam et al expand our understanding of the entity of LGSAS and makes a powerful case for surgical intervention for symptomatic patients.

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References:


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