Survival after intervention in patients with low gradient severe aortic stenosis and preserved left ventricular function

Avishay Grupper, MD, Roy Beigel, MD, Elad Maor, MD, PhD, Rafael Kuperstein, MD, Ilan Hai, MD, Olga Perelshtein, MD, Ilan Goldenberg, MD, Micha Feinberg, MD, and Sagit Ben Zekry, MD

Objective: The outcome of aortic valve replacement for patients with low gradient severe aortic stenosis and preserved ejection fraction has been debated. The aim of the present study was to evaluate the effect of aortic valve intervention on survival in that group.

Methods: A cohort of 416 consecutive patients with low gradient severe aortic stenosis (aortic valve area, $\leq$1 cm^2; mean pressure gradient, <40 mm Hg) and preserved ejection fraction ($\geq$50%) were identified from the Sheba Medical Center echocardiography database. Clinical data, aortic valve intervention, and death were recorded.

Results: During an average follow-up of 28 months, of 416 study patients (mean age, 76 $\pm$ 14 years, 42% men), 97 (23%) underwent aortic valve intervention and 140 (32%) died. Mantel-Byar analysis showed that the cumulative probability of survival was significantly greater after aortic valve intervention. Multivariate analysis revealed a 49% reduction in the risk of death after surgery ($P < .05$). The survival benefit of aortic valve intervention was comparable with adjustment to older age, aortic valve area $\leq$ 0.8 cm^2, and a low ($\leq$35 cm^2/m^2) or normal (>35 cm^2/m^2) stroke volume index.

Conclusions: Our findings suggest that aortic valve intervention is associated with improved survival among patients with low gradient severe aortic stenosis and preserved left ventricular function. The presence of either a low or normal stroke volume index did not affect the mortality benefit. (J Thorac Cardiovasc Surg 2014;148:2823-8)

See related commentary on pages 2828-9.

Severe aortic stenosis (AS) is a common valvular disease defined as a calculated aortic valve area (AVA) $\leq$1 cm^2 and a mean pressure gradient of $\geq$40 mm Hg.[1,2] However, $\leq$30% of patients with AS and a preserved ($\geq$50%) ejection fraction (EF) might have the inconsistent results of a reduced AVA ($\leq$1.0 cm^2) and a lower than expected transvalvular gradient (<40 mm Hg).[3-5] Previous studies have differentiated these patient populations into those with either a low transvalvular flow (define as a stroke volume index [SVI] of $\leq$35 mL/m^2) or normal flow (NF). Accordingly, 4 groups of patients with severe AS and preserved EF were described: patients with NF and a high gradient (NF/HG), patients with NF and a low gradient (NF/LG), patients with low flow and a HG (LF/HG), and patients with LF and a LG (LF/LG).[6] Agreement has been reached on the survival benefit of aortic valve replacement (AVR) for symptomatic patients with HG (LF or HF) severe AS. Nevertheless, data have been conflicting regarding the effect of aortic intervention for patients with LG severe AS and preserved EF.[3,7-13] Studies have mostly shown that patients with LF/LG severe AS and preserved EF will fare better when referred for AVR.[3,6-8,10-12] However, the results from 1 study suggested that patients with LG/LF severe AS and a normal EF will have outcomes similar to those of patients with moderate AS and that AVR had no significant prognostic effect among these patients.[9] The aim of the present study was to evaluate the effect of aortic valve intervention (either surgical or transcatheter aortic valve placement) on survival among patients with LG severe AS and a preserved EF, and whether this was influenced by the presence of either a normal or decreased SVI (NF/LF).

From the Noninvasive Cardiology Unit, Leviev Heart Center, Sheba Medical Center, Tel HaShomer, Israel, and Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Drs A.G., R.B., and E.M. contributed equally to the present study.

Received for publication Dec 12, 2013; revisions received March 15, 2014; accepted for publication March 21, 2014; available ahead of print April 27, 2014.

Address for reprints: Sagit Ben Zekry, MD, Noninvasive Cardiology Unit, Leviev Heart Center, Sheba Medical Center, Tel HaShomer 52621, Israel (E-mail: sagit.benzekry@sheba.health.gov.il).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.03.039

METHODS

Patient Population

Echocardiographic and Doppler studies of patients with severe AS and preserved LVEF were retrospectively reviewed from the Sheba Medical Center echocardiography database from 2004 to 2012. The inclusion criteria were AVA $\leq$ 1 cm^2, mean aortic valve pressure gradient < 40 mm Hg, and EF $\geq$ 50% (ie, patients with LG severe AS with NF or LF). The exclusion criterion was any other significant valvular disease, defined as any moderate or moderate to severe valvular disease. The institutional review board approved the present study.

ACD

Abbreviations and Acronyms

- AS = aortic stenosis
- AVA = aortic valve area
- AVR = aortic valve replacement
- BSA = body surface area
- CI = confidence interval
- EF = ejection fraction
- HG = high gradient
- HR = hazard ratio
- LF = low flow
- LG = low gradient
- LV = left ventricular
- LVOT = left ventricular outflow tract
- NF = normal flow
- SVI = stroke volume index

Standard Echocardiographic and Doppler Measurements

Two-dimensional transthoracic echocardiographic and Doppler studies were obtained with clinical ultrasound machines equipped with 3.5-MHz transducers using standard views. The studies were digitally stored (McKesson's Horizon Cardiology Medical Software, Tel Aviv, Israel). The parasternal long-axis view was used to measure the aortic annulus diameter in early systole. Pulsed Doppler in the left ventricular (LV) outflow tract (LVOT) from the apical window allowed us to evaluate the flow. A continuous wave Doppler recording of the flow through the aortic valve was performed from the apical, right parasternal, suprasternal, and subcostal windows to minimize the effect of Doppler angulation with flow. The LV stroke volume was derived using the time velocity interval of the LVOT, assuming a circular geometry of the LVOT. The indexed stroke volume was calculated as the stroke volume divided by the body surface area (BSA). Multiplying the heart rate by the stroke volume allowed us to calculate the cardiac output; the cardiac output indexed to the BSA was also calculated. The AVA was derived from the continuity equation. The indexed AVA to BSA was calculated as the AVA divided by the BSA. Using the continuous wave jet recording, the peak and mean velocity were measured. The peak velocity was derived from the Bernoulli equation, and the mean gradient represents the integral of the maximal velocities acquired throughout all of systole. The LVEF was estimated by the reader.

ACD

Clinical Data

The clinical data were obtained from the Sheba Medical Center computerized patient records. The data included age, gender, BSA, body mass index, a history of smoking, hypertension, hyperlipidemia, diabetes mellitus, renal failure, coronary heart disease, and cerebrovascular disease. Complete clinical data were available for 87% of the study population. Intervention was defined as either surgical or transcatheter AVR. The decision regarding the choice of aortic valve intervention was made by the treating cardiologist. The decision of transcatheter aortic valve intervention was made by a heart team for patients with prohibitive risk. Mortality was evaluated using the Israeli Ministry of Interior National Registry and was confirmed in all patients; the cause of death was not available.

Statistical Analysis

The study population was divided into 2 groups (intervention vs medical treatment). The Student *t* test was used to compare continuous variables, and Fischer's exact test was used to compare dichotomous variables between the 2 groups. The benefit of aortic intervention on the estimated survival was compared, as previously described by Mantel and Byar.[14] In brief, all subjects began treatment in the conservative treatment group. The subjects who underwent aortic valve intervention were entered into the intervention group on the day of surgery and remained in the intervention group until death or censoring. The patients in the conservative treatment group remained in the no intervention group during the follow-up period. Univariate and multivariate Cox proportional hazards models were used to calculate the hazard ratio (HR) for the time-dependent surgical intervention for survival. The multivariate model included adjustment for age, gender, ischemic heart disease, body mass index, AVA ($\leq$0.8 cm^2), and aortic valve intervention as a time-dependent covariate. In addition, a propensity score model for the decision to perform aortic valve intervention was calculated for all subjects with available clinical data. The model included age gender, body mass index, mean aortic valve gradient, peak aortic valve velocity, AVA, LVEF, ischemic heart disease, and diabetes mellitus. The propensity score was then entered into the Cox regression analysis of long-term survival. Statistical significance was accepted for a 2-sided $P < .05$. The statistical analyses were performed using IBM SPSS, version 20.0 (IBM, Armonk, NY).

RESULTS

A total of 416 patients were identified (age, 76 ± 14 years; 42% men; Table 1) with LG severe AS and a preserved EF. The study population was divided into those with (91 surgical AVR, 6 transcatheter aortic valve placement) and without aortic valve intervention. The baseline characteristics of the study population are listed in Table 1; the groups were similar, although the patients referred for aortic valve intervention were significantly younger. The patients' echocardiographic parameters are listed in Table 2. LV function was comparable in both groups. In contrast to the medical group, the intervention group was characterized by a larger LV mass, higher gradients, a higher SVI, and a reduced AVA. Of the 416 patients, 303 had NF and 113 had LF. The LF group had a significantly greater BSA (1.9 ± 0.2 vs 1.8 ± 0.2 m^2) and body mass index (30 ± 6 vs 27 ± 6 kg/m^2). The LV dimensions and mass were comparable between the 2 groups, and the Doppler parameters revealed a significantly lower peak velocity (3.4 ± 0.4 vs 3.67 m/s), mean gradient (27 ± 7.5 vs 31.4 ± 0.6 mm Hg), stroke volume (57.6 vs 74.1 mL), cardiac index (2.5 vs 3.1 L/min/m^2), and EF (58.8% vs 60.1%) in the LF group.

Aortic Intervention and Survival

During the follow-up period (28 ± 25 months), 143 patients (32%) died. The 30-day mortality rate for the patients who underwent surgical or transcatheter aortic intervention was 16% (n = 15). The average follow-up period until aortic valve intervention was 11.3 ± 16.4 months. Mantel-Byar curve analysis revealed a significantly greater cumulative probability of survival after AVR (P = .001; Figure 1). Consistently, multivariate analysis showed that time-dependent AVR was associated with a 49% reduction in the risk of death ($P < .05$; Table 3). A similar reduction in the risk of death was obtained when a propensity score for the decision to perform aortic