Right Ventricular Function and Prognosis in Patients with Low-Flow, Low-Gradient Severe Aortic Stenosis

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Background: Patients with low left ventricular ejection fractions and low-flow, low-gradient aortic stenosis (AS) represent a challenging cohort with high morbidity and mortality. The prevalence and clinical impact of right ventricular dysfunction (RVD) on risk stratification and prognosis in these patients is unknown.

Methods: A retrospective analysis was performed of 65 patients with low-flow, low-gradient AS who underwent low-dose dobutamine stress echocardiography to determine AS severity and to ascertain flow reserve status (≥20% stroke volume increase). Clinical, demographic, and imaging data were prospectively collected. Per guidelines, RVD was defined as tricuspid annular plane systolic excursion < 16 mm in the apical four-chamber view and measured at baseline. Cox proportional hazards modeling was used to risk-adjust comparisons for the end point of all-cause mortality.

Results: The mean age was 74 ± 9 years, the mean left ventricular ejection fraction was 29 ± 10%, the mean indexed aortic valve (AV) area was 0.49 ± 0.1 cm^2/m^2, and the mean AV gradient 22 ± 7 mm Hg. RVD was present in 37 patients (57% of the study cohort). After a median follow-up period of 13 months (interquartile range, 5–30 months), there were 29 AV replacements and 30 deaths. The presence of RVD (hazard ratio, 2.86; 95% CI, 1.21−6.75; $P = .02$) was an independent risk factor associated with all-cause mortality despite many adjustments for potential clinical and echocardiographic confounders such as AV replacement, Society of Thoracic Surgeons Predicted Risk of Mortality score, severity of tricuspid regurgitation, and left ventricular global longitudinal strain.

Conclusions: Baseline RVD is prevalent in patients with low-flow, low-gradient AS undergoing dobutamine stress echocardiography. Quantification of right ventricular systolic function in these complex patients provides important prognostic value and risk stratification adjunctive to Society of Thoracic Surgeons Predicted Risk of Mortality score and should be incorporated into the decision-making process. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Right ventricular function, Prognosis, Low-flow, low-gradient aortic stenosis

Assessment of aortic stenosis (AS) severity is critical for treatment decisions but difficult in patients with left ventricular (LV) systolic dysfunction (i.e., LV ejection fraction [LVEF] < 50%) and low-flow, low-gradient (LFLG) physiology. Although this is an uncommon group (≤10% of the AS population),[1] these patients generally have a poor prognosis with conservative medical therapy and high operative morbidity and mortality if treated surgically.[2,3] Traditionally, risk stratification with low-dose dobutamine during cardiac catheterization[4] or more commonly with dobutamine stress echocardiography (DSE) is recommended to (1) verify true AS severity[5] and (2) risk-stratify patients for the presence of flow reserve (FR), which represents an enhancement of LV contractile function during dobutamine infusion (≥20% increase in stroke volume). FR has been traditionally associated with better outcomes after surgical aortic valve (AV) replacement (SAVR)[2,6,7] and more recently after transcatheter AV replacement (TAVR).[8]

Results from the multicenter True or Pseudo-Severe Aortic Stenosis (TOPAS) study have recently shown that (1) measurement of LV global longitudinal strain (GLS) adds incremental value to the risk stratification of these complex patients[9] and (2) the identification of moderate to severe tricuspid regurgitation is highly predictive of mortality in a prospective cohort of patients with LFLG AS.[10] However, a stated limitation of this latter study was that the objective quantification of right ventricular (RV) systolic function using parameters such as tricuspid annular plane systolic excursion (TAPSE) was not feasible, and therefore it is unknown whether the presence of baseline RV dysfunction (RVD) is in fact the main culprit and

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Abbreviations

AS = Aortic stenosis

AV = Aortic valve

AVR = Aortic valve replacement

DSE = Dobutamine stress echocardiography

FR = Flow reserve

GLS = Global longitudinal strain

HR = Hazard ratio

LFLG = Low-flow, low-gradient

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVOT = Left ventricular outflow tract

RV = Right ventricular

RVD = Right ventricular dysfunction

SAVR = Surgical aortic valve replacement

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TAPSE = Tricuspid annular plane systolic excursion

TAVR = Transcatheter aortic valve replacement

TOPAS = True or Pseudo-Severe Aortic Stenosis

associated with worse outcomes in these patients. We wanted to test the hypothesis that presence of RVD is an independent predictor of all-cause mortality in patients with LFLG AS, independent of established risk stratification schemes and novel parameters such as GLS.

METHODS

A retrospective review was performed of all a priori patients with severe AS and reduced LVEFs who had undergone DSE for the assessment of FR and AS severity at our institution from 2004 through 2013. Patients with LFLG AS were identified as having low stroke volume index values (<35 mL/m^2) and low mean AV gradients (<40 mm Hg). Clinical, demographic, and imaging data were prospectively collected. As recommended by guidelines, the decision to pursue low-dose DSE for these patients with symptomatic LFLG AS was driven predominantly by the need to confirm the severity of AS and evaluate for the presence of FR. Coronary artery disease was defined as the presence of >70% luminal stenosis on coronary angiography. The presence of hypertension, diabetes, dyslipidemia, and prior myocardial infarction was verified according to the information recorded in the electronic medical records and/or specific medication documentation. The study was approved by the University of Pittsburgh Institutional Review Board Committee.

Transthoracic echocardiography was performed using several systems (Siemens Acuson/Sequoia [Siemens Medical Solutions USA, Mountain View, CA], GE Vivid 7 [GE Medical Systems, Milwaukee, WI], HP Sonos 5500 [Hewlett-Packard, Palo Alto, CA], and Philips iE33 [Philips Medical Systems, Andover, MA]). Low-dose DSE was performed according to institutional protocol with continuous clinical, hemodynamic, and 12 lead electrocardiographic monitoring. Testing was begun at 5 μg/kg/min dobutamine, which was gradually increased in 5 μg/kg/min increments (i.e., 5, 10, 15, and 20 μg/kg/min) to the next rate every 3 min until the maximal dose of 20 μg/kg/min was achieved and/or until classification of low-gradient severe AS was established (i.e., increased AV mean gradient ≥ 40 mm Hg and AV area ≤ 1.0 cm^2).[4,11] All individual echocardiographic images and Doppler data were reviewed independently by a single level III trained cardiologist with 5 years of experience (J.L.C.), who was blinded to the clinical information. All measurements were performed at each dose of dobutamine for quantification of aortic velocity, mean pressure gradient and valve area, and LVEF per guidelines.[11-14] Spectral Doppler of the LV outflow tract (LVOT) (pulsed wave) and AV (continuous wave) were measured at each stage using the best baseline view determined for Doppler assessment. For each Doppler measurement, three cycles were averaged, and post–premature ventricular contraction beats were discarded (five cycles were averaged for patients with atrial fibrillation). LVOT diameter was assumed to have remained constant during the stress test protocol. FR was defined as an increase in stroke volume of ≥20% with dobutamine infusion[7,11,13] using the pulsed-wave spectral Doppler tracing of the velocity-time integral at baseline and at peak dobutamine dose. AV area was calculated using the continuity equation formula: AV area = (LVOT area × LVOT velocity-time integral)/AV velocity-time integral.[12]

TAPSE was measured only at baseline in the apical four-chamber view as the longitudinal systolic excursion of the tricuspid annulus.[15] Three consecutive heart cycles were recorded and averaged for patients in sinus rhythm, whereas five cardiac cycles were averaged for those in atrial fibrillation (Figure 1). RVD was defined as TAPSE < 16 mm per guideline recommendations.[15]

LV GLS analysis was performed offline using commercially available software (2D Cardiac Performance Analysis version 4.3.2.5; TomTec, Munich, Germany), averaging the peak longitudinal strain of the three apical views at rest. GLS analysis was feasible in 59 of 65 patients (91%), while six had suboptimal image quality for analysis. GLS data are expressed as absolute values. For patients in atrial fibrillation, the single-index-beat method has been validated for GLS evaluation.[16] In short, it establishes that if the R-R interval ratio of the two preceding beats equals 1, then the third beat can be used as the representation of average LV contractility. Therefore, in these patients, we chose the index cardiac cycle just after two cardiac cycles of similar length and/or with a maximal R-R interval difference of <60 msec.[16]

The optimal cutoff for GLS in our Cox modeling was assessed using Harrell's C index. A cut point of GLS < |9.0|% showed strong predictive value (Harrell's C = 0.821) in our models; moving the GLS threshold in either direction produced very similar results for the C index that eventually started to decline as we moved away from 9% (i.e., a threshold of 8.7% yielded a C index of 0.8; a threshold of 9.3% yielded a C index of 0.811). Therefore, we used the cutoff of GLS < |9.0|% in our analysis, which is similar to the one recently identified by Dahou *et al.*[9] in a prospective cohort of patients with LFLG AS.

The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score was calculated for each patient according to the planned treatment (i.e., SAVR with or without coronary artery bypass grafting) using the Society of Thoracic Surgeons online calculator (version 2.73), a well-validated composite score composed of >40 clinical parameters and risk factors.[17] Notably, the current STS-PROM score does not account for the presence or absence of RVD. All-cause mortality was assessed by reviewing electronic medical records and confirmed by the Social Security Death Index.

Statistical Analysis

Continuous variables are expressed as mean ± SD and were analyzed using Student's *t* test. Categorical variables are presented as frequency (percentage) and were compared using the Pearson χ^2 test or the Fisher exact test. One-way analysis of variance was used to compare characteristics according to the treatment assignment received. Survival curves were constructed using Kaplan-Meier estimates. AV replacement (AVR) was considered a time-dependent