Journal of the American College of Cardiology Vol. 60, No. 22, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.08.988

Asymptomatic Left Ventricular Systolic Dysfunction in Patients With Severe Aortic Stenosis

Characteristics and Outcomes

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Objectives This study sought to determine the prevalence, characteristics, and outcomes of asymptomatic left ventricular (LV) systolic dysfunction in patients with severe aortic stenosis (AS).

Background Management of asymptomatic patients with severe AS remains controversial. In these patients, LV systolic dysfunction, defined in the guidelines as ejection fraction <50%, is a Class I(C) indication for aortic valve replacement (AVR), but its prevalence is unknown.

Methods A retrospective study of adults ≥40 years of age with severe valvular AS (peak velocity ≥4 m/s, mean gradient >40 mm Hg, aortic valve area [AVA] <1 cm^2, or AVA index <0.6 cm^2/m^2) from 1984 to 2010 was undertaken. Patients with prior cardiac surgery, severe coronary artery disease, or greater than moderate aortic regurgitation were excluded.

Results Of 9,940 patients with severe AS, 43 (0.4%) patients had asymptomatic LV dysfunction. Age was 73 ± 14 years and 70% were male. Hypertension (78%) and LV hypertrophy (LV mass index 143 ± 36 g/m^2) were characteristic. Fifty-three percent of these patients developed symptoms at 21 ± 19 months after diagnosis. During 7.5 ± 6.7-year follow-up, 5-year mortality was 48%. After multivariable adjustment, there was no survival advantage with AVR in asymptomatic, severe AS with LV dysfunction ($p = 0.51$).

Conclusions In severe AS, the prevalence of asymptomatic LV systolic dysfunction is 0.4%. Despite an asymptomatic clinical status, patients with severe AS and LV ejection fraction <50% have a poor prognosis, with or without AVR.
(J Am Coll Cardiol 2012;60:2325–9) © 2012 by the American College of Cardiology Foundation

Management of the asymptomatic patient with severe aortic stenosis (AS) remains controversial. Patients who receive an aortic valve replacement (AVR) may have a better outcome (1–3), though this may be impacted by the selection of healthier patients for surgery. There is only 1 prospective study of early versus late surgical intervention in asymptomatic, severe AS (4) and there are no randomized controlled trials defining the optimal treatment strategy (5). According to American College of Cardiology/American Heart Association (ACC/AHA) guidelines, left ventricular (LV) systolic dysfunction, defined as LV ejection fraction (LVEF) <50%, is a Class I(C) indication for AVR in severe, asymptomatic AS (6,7). This recommendation is based on very limited evidence.

It is unknown how often LV dysfunction develops in the absence of symptoms in patients with severe AS. This study was undertaken to determine the prevalence, clinical characteristics, and outcomes of asymptomatic LV dysfunction in patients with severe AS.

Methods

Study patients. A retrospective study of all adults ≥40 years of age with severe valvular AS by a comprehensive 2-dimensional and Doppler transthoracic echocardiogram (TTE) from 1984 to 2010 was performed after Institutional Review Board approval. Severe AS was defined as a peak systolic velocity ≥4 m/s, mean gradient >40 mm Hg, aortic valve area (AVA) <1.0 cm^2, or AVA index of <0.6 cm^2/m^2

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Manuscript received March 27, 2012; revised manuscript received August 23, 2012, accepted August 30, 2012.

Abbreviations and acronyms

ACC = American College of Cardiology
AHA = American Heart Association
AS = aortic stenosis
AV = aortic valve
AVA = aortic valve area
AVR = aortic valve replacement
LV = left ventricle
LVEF = left ventricular ejection fraction
TTE = transthoracic echocardiogram

by Doppler echocardiography in combination with 2-dimensional echocardiographic appearance of severe valvular AS (7). Only one of these Doppler criteria of severe AS was required for study inclusion, thus ensuring that patients with low-output, low-gradient severe AS were included. Those with LVEF <50% on an initial qualifying TTE or subsequent follow-up TTE in the absence of prior AVR were reviewed for study inclusion.

Exclusion criteria included: 1) prior cardiac surgery; 2) multivalvular heart disease or greater than moderate aortic regurgitation; 3) prior valvuloplasty; 4) severe coronary artery disease by angiography (≥70% stenosis in ≥2 vessels); 5) prior myocardial infarction; 6) congenital heart disease other than bicuspid AV; 7) cardiomyopathy; and 8) cardiac symptoms (pre-syncope, syncope, angina, exertional dyspnea, heart failure, or resuscitated sudden cardiac death), with or without stress testing. Stress testing was not routinely performed.

Control patients. Following identification of asymptomatic patients with severe AS and LVEF <50%, a 3:1 age/gender/date matched–control group of asymptomatic patients with severe AS meeting the same criteria except having LVEF ≥50% was performed.

Statistical analysis. Nominal variables are presented as absolute count and percentage of cohort. Continuous variables are presented as mean ± SD. Categorical variables were compared between those with low LVEF and those with normal LVEF using chi-square tests. Continuous variables were compared between the groups using 2 sample *t* tests or nonparametric Wilcoxon rank sum tests. Paired *t* tests were used to compare changes in echo parameters over time. The Kaplan-Meier method was used to construct survival curves using time of death as event time and last known follow-up as censoring time. A time-dependent analysis was conducted to determine the effect of AVR on survival. Cox proportional hazards regression modeling was used to determine multivariate associations with survival and estimate hazard ratios.

Results

Prevalence of asymptomatic LV dysfunction in severe AS. From 1984 to 2010, 9,940 patients undergoing TTE and clinical evaluation at our institution had severe valvular AS; 1,960 (20%) presented with LVEF <50% and 7,980 (80%) had LVEF ≥50%. Excluding those who underwent AVR prior to follow-up TTE (n = 2,225), 59% (3,388 of 5,755) of patients had 1 or more follow-up TTEs performed: 14% (486 of 3,388) of these patients developed LV dysfunction. Thus, a total of 2,446 (24.6%) patients presented with (n = 1,960) or developed (n = 486) LV systolic dysfunction. Only 43 (1.8%) of the 2,446 patients had isolated severe AS and were asymptomatic, constituting 0.4% of all patients with severe AS.

The 43 patients included 38 patients with asymptomatic, severe AS and reduced LV function at the time of diagnosis, and 5 patients who developed asymptomatic LV dysfunction on follow-up TTE (range 6 to 44 months after presenting TTE).

Characteristics of asymptomatic patients with severe AS and LVEF <50%. Of the 43 asymptomatic patients with reduced LV function, severe AS was identified in 40 (98%) by AVA index, 34 (79%) by AV peak velocity, 31 (76%) by AVA, and 25 (64%) by AV gradient. Four patients met severe AS criteria solely by AVA index. The clinical and TTE characteristics of the 43 patients compared with the age/gender/date matched–control group of asymptomatic patients with severe AS and preserved LV function are shown in Tables 1 and 2, respectively.

Symptoms and survival during follow-up. Figure 1 illustrates onset of symptoms and/or treatment with AVR in the 43 patients during 7.5 ± 6.7 years of follow-up. Eighteen patients developed cardiac symptoms, 12 remained asymptomatic until death, and 4 had indeterminate clinical status. Of those who developed symptoms, the average time from qualifying TTE to onset of symptoms was 21 ± 19 months (range 1 month to 5.6 years). Echocardiographic differences before and after onset of symptoms included AVA index (0.47 ± 0.13 cm^2/m^2 vs. 0.41 ± 0.12 cm^2/m^2, p = 0.05), AV mean gradient (43 ± 10 mm Hg vs. 56 ± 13 mm Hg, p = 0.02), and left atrial dimension (44 ± 7 mm vs. 48 ± 7 mm, p = 0.02).

Vital status could be determined in 42 patients (Fig. 1); 33 (79%) of 42 died. Five-year mortality in initially asymptomatic unoperated patients with severe AS and LV dysfunction was 48% (Fig. 2). The cause of death was determined in 16 patients: 2 had sustained sudden, unexplained deaths within 6 weeks of their last clinical encounter without documented symptoms, 9 had cardiac death (6 heart failure, 1 myocardial infarction, 1 post-AVR, and 1 during valvuloplasty), and 5 had noncardiac death.

AVR and outcomes. Aortic valve replacement was performed in 25 (64%) of 39 patients in whom follow-up for AVR was available (Fig. 1); concomitant coronary artery bypass grafting was performed in 13 (52%), involving a single vessel in 9 (70%). Seven asymptomatic patients underwent AVR <3 months after their qualifying TTE, 13 developed symptoms prior to AVR and 5 asymptomatic patients underwent late AVR.

Post-operative survival is presented in Figure 2. There was a trend toward improved survival in patients undergoing AVR (hazard ratio: 0.46, 95% confidence interval: 0.18 to 1.16, p = 0.10), which was not present after adjustment for age, sex, and time of diagnosis (1984 to 1995 vs. 1996 to 2010) (hazard ratio: 0.77, 95% confidence interval: 0.36 to 1.67, p = 0.51).

Table 1 Baseline Characteristics of Asymptomatic Patients With Severe AS and LVEF <50% Versus Asymptomatic Patients With Severe AS and LVEF ≥50%

Baseline and Clinical Characteristics	Asymptomatic, Severe AS With LVEF <50% (n = 43)	Asymptomatic, Severe AS With LVEF ≥50% (n = 122)	p Value
Demographic characteristics			
Age, yrs	73 ± 14	73 ± 13	0.941
Male	30 (70%)	86 (70%)	0.929
Body mass index, kg/m^2	26.4 ± 3.9	27.7 ± 5.4	0.241
Assisted living	2 (4%)	8 (7%)	0.644
Historical medical comorbidities			
Systemic hypertension	33 (78%)	74 (61%)	0.05
Smoking history	20 (47%)	52 (43%)	0.659
Atrial fibrillation	12 (28%)	20 (16%)	0.111
Hyperlipidemia	9 (21%)	41 (34%)	0.105
Diabetes mellitus	5 (12%)	14 (11%)	0.979
Cardiac procedures			
Percutaneous coronary intervention	1 (2%)	6 (5%)	0.441
Medical therapy			
Antiplatelet	16 (37%)	49 (40%)	0.733
Diuretic*	15 (35%)	40 (33%)	0.802
Digoxin†	10 (23%)	22 (18%)	0.463
Angiotensin-converting enzyme inhibitor or receptor blocker*	10 (23%)	24 (20%)	0.621
Calcium-channel blocker*	9 (21%)	20 (16%)	0.508
Beta-blocker*	7 (16%)	22 (18%)	0.709
Coumadin	6 (14%)	7 (6%)	0.103
Statin	4 (9%)	21 (17%)	0.194
Nitrate	0 (0%)	5 (4%)	0.08
Electrocardiographic findings			
LV hypertrophy	14 (37%)	29 (24%)	0.120
Left bundle branch block	4 (11%)	2 (2%)	0.02
Laboratory values			
Hemoglobin, g/dl	13 ± 2	14 ± 2	0.768
Creatinine clearance, ml/min	61 ± 28	54 ± 10	0.288

Values are mean ± SD or n (%). *For treatment of hypertension. †For treatment of atrial fibrillation or flutter.
AS = aortic stenosis; LV = left ventricular; LVEF = left ventricular ejection fraction.

Of the 25 patients who underwent AVR, LVEF improved in 17 (81%) of the 21 with post-AVR TTEs.

Among the 14 patients who did not undergo AVR, 7 refused AVR despite physician recommendations, 4 were advised against AVR by their physician due to comorbidities or discordant clinical and echocardiographic interpretations of AS severity, and 3 died while waiting for planned AVR.

Discussion

Prevalence and incidence of asymptomatic LVEF <50% in severe AS. In this retrospective study of 9,940 adults with severe AS, 2,403 (24%) patients had symptomatic LV dysfunction. Asymptomatic LV dysfunction was present in only 43 (0.4%) patients, including 38 who had LV dysfunction on presentation with severe AS, and 5 who developed it during follow-up.

Current ACC/AHA guidelines recommend annual TTE for patients with severe AS (7), allowing recognition of an asymptomatic decline in LV systolic function. Herein we show that although it is uncommon, patients can develop progressive decline in LV function despite remaining symptom-free.

Characteristics of patients with asymptomatic, severe AS and LVEF <50%. AVA index <0.6 cm^2/m^2 was present in 98% of our cohort. While parameters of AV mean gradient and maximal velocity are impacted by LV function and may create confusion in grading AS severity, the AVA index establishes AS severity relatively independent of flow (8).

Compared to asymptomatic adults with severe AS and LVEF ≥50%, those with reduced LV function were more likely to have a history of hypertension and echocardiographic evidence of eccentric LV hypertrophic remodeling. While our study was not powered to evaluate predictors of LV systolic dysfunction, hypertension may be a poor prognostic factor in severe AS. Pellikka et al. (9) and Hachicha et al. (10), in independent studies of asymptomatic patients with severe AS and normal LV function, showed LV hypertrophy and increased valvuloarterial impedance, respectively, to be independent predictors of mortality.

Table 2 Echocardiographic Characteristics of Asymptomatic Patients With Severe AS and LVEF <50% Versus Asymptomatic Patients With Severe AS and LVEF ≥50%

Echocardiographic Parameter	Asymptomatic, Severe AS With LVEF <50% (n = 43)	Asymptomatic, Severe AS With LVEF ≥50% (n = 122)	p Value
Systolic blood pressure, mm Hg	135 ± 20	140 ± 21	0.441
LVEDD, mm	54 ± 7	47 ± 6	<0.001
LV mass index, g/m^2	145 ± 37	117 ± 40	0.0008
Relative wall thickness	0.46 ± 0.1	0.55 ± 0.12	0.003
LVEF, %	43 ± 6	64 ± 7	<0.001
Stroke volume index, ml/m^2	43 ± 11	48 ± 10	0.402
Cardiac index, l/min/m^2	3.1 ± 0.9	3.3 ± 0.7	0.258
AVA by continuity equation, cm^2	0.8 ± 0.2	0.8 ± 0.2	0.911
AVA index, cm^2/m^2	0.43 ± 0.1	0.44 ± 0.1	0.389
AV peak systolic velocity, m/s	4.1 ± 0.7	4.4 ± 0.7	0.02
AV mean gradient, mm Hg	43 ± 14	48 ± 16	0.192
LA end systolic dimension, mm	44 ± 7	46 ± 8	0.957
E/e' ratio	18 ± 8	16 ± 7	0.504
Mitral deceleration time, ms	212 ± 88	256 ± 73	<0.001
Right ventricular systolic pressure, mm Hg	42 ± 13	42 ± 29	0.179
Valvuloarterial impedance, mm Hg·min/ml	4.6 ± 1.3	4.0 ± 0.9	0.137

Values are mean ± SD.
AV = aortic valve; AVA = aortic valve area; LA = left atrial; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction.

Outcomes with asymptomatic LV dysfunction and severe AS. The compensated clinical status and independent functional status of asymptomatic patients with severe AS and decreased LV systolic function provide false reassurance for the underlying risk of morbidity and mortality. Within our study group, 53% (18 of 34) of unoperated patients developed symptoms within 2 years of their qualifying TTE; this rate was higher that reported by Pellikka et al. (9) in patients with asymptomatic AS and any LVEF where 33% developed symptoms at 2 years.

The 5-year mortality rate for our asymptomatic adults with severe AS and LV systolic dysfunction was substantial at 48%. While AVR has previously been shown to be beneficial in low-risk elderly patients with severe AS and in symptomatic patients with LV dysfunction (11–13), our study isolates, for the first time, asymptomatic patients with reduced LV function. Although LVEF improved after AVR

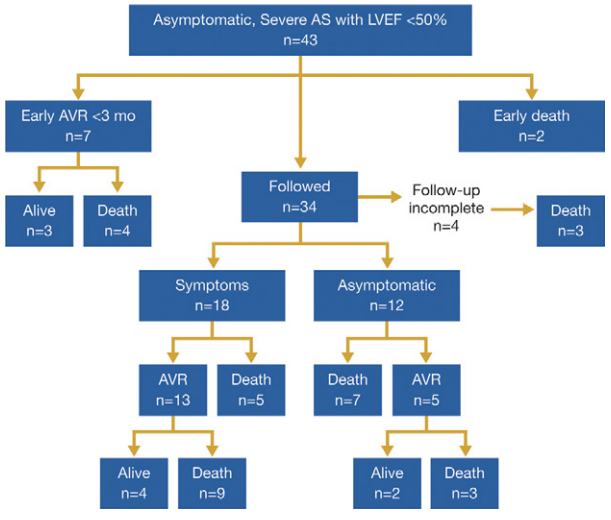

Figure 1 Asymptomatic Adults With Severe AS and LVEF <50% (n = 43)

During follow-up of 7.5 ± 6.7 years, 7 patients underwent early AVR and 2 of 43 patients died before scheduled follow-up. Of the remaining 34 patients, 18 developed symptoms, 12 remained asymptomatic, and 4 had indeterminate symptom and surgical status. AS = aortic stenosis; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction.

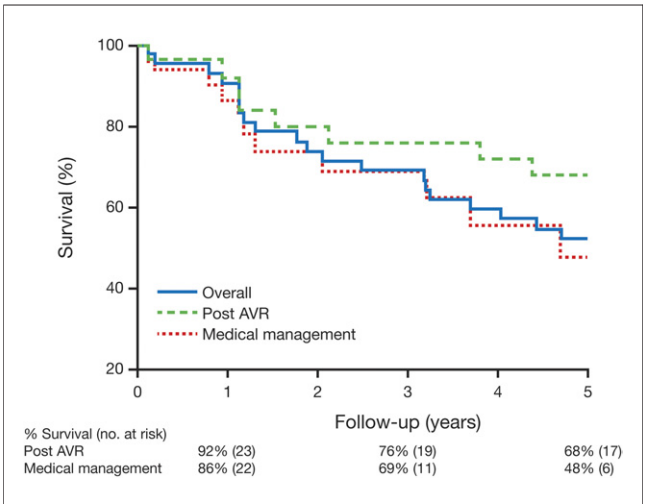

Figure 2 Unadjusted Survival in Asymptomatic Adults With Severe AS and LVEF <50%

During a median of 5.6 years follow-up, 33 of 42 patients died. After adjustment for age, sex, and time period (1984 to 1995 vs. 1996 to 2010) of diagnosis, there was no survival benefit with AVR (p = 0.51). Abbreviations as in Figure 1.

in these patients, survival was similar in patients with and without AVR after adjustment for age, sex, and study date. **Study limitations.** Given the retrospective method and small sample size, caution must be exercised in the conclusions drawn. Patients were deemed asymptomatic by review of medical history alone; exercise testing was not required. Coronary angiography was not performed in all patients and 52% who underwent AVR had concomitant coronary artery bypass. Similarly, hypertension was a frequent comorbidity and the combination of hypertension with severe AS may have adversely impacted outcome. Serial TTEs were not performed in all asymptomatic patients during follow-up. Newer methods for detecting LV dysfunction, including strain rate imaging (14), were not available.

Novel Study Conclusions

LV dysfunction may occur in patients with severe AS in the absence of symptoms. However, it is uncommon: our study defines the prevalence of asymptomatic LV dysfunction occurring in patients with severe valvular AS at 0.4%. Although 20% of patients with severe AS had LV dysfunction at presentation, the majority were symptomatic. While infrequently encountered, the asymptomatic patient with severe AS and LV dysfunction has a high risk of mortality, even with AVR.

Current ACC/AHA guidelines offer limited recommendations regarding management of asymptomatic patients with severe AS. We show that the Class I(c) indication for AVR in asymptomatic, severe AS, namely development of LVEF <50%, is rarely applicable. However, mortality for these patients is high—regardless of whether medical or surgical management is employed. Further efforts are needed to define the optimal time for AVR.

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Key Words: aortic stenosis ■ echocardiography ■ heart failure ■ valves ■ valve surgery.