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Low-Gradient, Low-Flow Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction

Characteristics, Outcome, and Implications for Surgery

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ABSTRACT

BACKGROUND Severe low-gradient, low-flow (LG/LF) aortic stenosis with preserved left ventricular ejection fraction (EF) has been described as a more advanced form of aortic stenosis. However, the natural history and need for surgery in patients with LG/LF aortic stenosis remain subjects of intense debate.

OBJECTIVES We sought to investigate the outcome of LG/LF aortic stenosis in comparison with moderate aortic stenosis and with high-gradient (HG) aortic stenosis in a real-world study, in the context of routine practice.

METHODS This analysis included 809 patients (ages 75 $\pm$ 12 years) diagnosed with aortic stenosis and preserved EF ($\geq$50%). Patients were divided into 4 groups: mild-to-moderate aortic stenosis; HG aortic stenosis; LG/LF aortic stenosis; and low-gradient, normal-flow (LG/NF) aortic stenosis.

RESULTS Compared with mild-to-moderate aortic stenosis patients, LG/LF aortic stenosis patients had smaller valve areas and stroke volumes, higher mean gradients, and comparable degrees of ventricular hypertrophy. Under medical management (22.8 months; range 7 to 53 months), compared with mild-to-moderate aortic stenosis patients, HG aortic stenosis patients were at higher risk of death (adjusted hazard ratio [HR]: 1.47; 95% confidence interval [CI]: 1.03 to 2.07), whereas LG/LF aortic stenosis patients did not have an excess mortality risk (adjusted HR: 0.88; 95% CI: 0.53 to 1.48). During the entire (39.0 months; range 11 to 69 months) follow-up (with medical and surgical management), the mortality risk associated with LG/LF aortic stenosis was close to that of mild-to-moderate aortic stenosis (adjusted HR: 0.96; 95% CI: 0.58 to 1.53), whereas the excess risk of death associated with HG aortic stenosis was confirmed (adjusted HR: 1.74; 95% CI: 1.27 to 2.39). The benefit associated with aortic valve replacement was confined to the HG aortic stenosis group (adjusted HR: 0.29; 95% CI: 0.18 to 0.46) and was not observed for LG/LF aortic stenosis (adjusted HR: 0.75; 95% CI: 0.14 to 4.05).

CONCLUSIONS In this study, the outcome of severe LG/LF aortic stenosis with preserved EF was similar to that of mild-to-moderate aortic stenosis and was not favorably influenced by aortic surgery. Further research is needed to better understand the natural history and the progression of LG/LF aortic stenosis. (J Am Coll Cardiol 2015;65:55–66)
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A variable proportion of patients with aortic stenosis and preserved (>50%) left ventricular ejection fraction (EF) that are classified as "severe" by echocardiography (aortic valve area [AVA] <1 cm^2 or index AVA <0.6 cm^2/m^2) (1,2) have lower peak aortic velocity (<4 m/s) and/or a lower mean Doppler gradient (MDG) (<40 mm Hg) (3-7). Besides inconsistencies related to small body surface

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ABBREVIATIONS AND ACRONYMS

AVA = aortic valve area

AVR = aortic valve replacement

CAD = coronary artery disease

EF = ejection fraction

HG = high-gradient

LG/LF = low-gradient/low-flow

LG/NF = low-gradient/normal-flow

MDG = mean Doppler gradient

SV = stroke volume

area and errors in measurement of AVA or Doppler parameters, this discordance may reflect a low stroke volume (SV) index, despite a normal EF (paradoxical "low-flow") (8,9). Patients with low-gradient/low-flow (LG/LF) aortic stenosis have been reported to have small ventricular cavities (3,8), severe concentric hypertrophy (3,8), increased afterload (10,11), restrictive physiology (8), subtle systolic dysfunction (12), and increased subendocardial myocardial fibrosis (13). These features have been interpreted as markers of a more advanced disease, leading to poor prognosis under conservative therapy. Survival analyses of limited patient numbers suggest that LG/LF aortic stenosis is associated with greater mortality risk than high-gradient (HG) severe aortic stenosis (3–5,7,8), and that surgery might be beneficial in this subset of patients. Therefore, guidelines recommend (class IIa recommendation) aortic valve replacement (AVR) in symptomatic patients with LG/LF aortic stenosis when documented valvular obstruction is the most probable cause of symptoms (2).

SEE PAGE 67

The view that LG/LF aortic stenosis with preserved EF represents a more advanced form of the disease with pejorative outcome has been questioned by a subanalysis of the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial (14) and by a recent single-center European cohort study (15). Consistently, magnetic resonance data in LG aortic stenosis show larger AVAs, less hypertrophy, and similar focal fibrosis compared with HG aortic stenosis (16). These recent results raise doubts about whether LG/LF aortic stenosis with preserved EF truly represents a severe form of aortic stenosis with poor prognosis and increased risk of death when treated medically. Moreover, the impact of AVR in LG/LF aortic stenosis needs to be better defined to avoid unnecessary and potentially dangerous procedures.

The basis for the present study is the consecutive experience with aortic stenosis at the echocardiography laboratories of 2-F tertiary centers (Amiens and Lille) between 2000 and 2012. The aims of this analysis are 3-fold: 1) to establish the relation between LG/LF aortic stenosis and outcome, regardless of clinical management; 2) to compare the outcomes of LG aortic stenosis, HG aortic stenosis, and moderate aortic stenosis; and 3) to understand the impact of AVR in these subsets of patients.

METHODS

STUDY DESIGN. Consecutive patients ≥18 years of age diagnosed with mild or more than mild aortic stenosis (aortic valve calcification with reduction in systolic movements and AVA <2 cm^2) and an EF of ≥50% (1) who were managed medically for at least 3 months after diagnosis were prospectively identified and included in an electronic database. We excluded patients with the following: 1) more than mild aortic and/or mitral regurgitation; 2) prosthetic valves, congenital heart disease, supravalvular or subvalvular aortic stenosis, or dynamic left ventricular outflow tract obstruction; 3) an EF <50%; and 4) patients who denied authorization for research participation. We enrolled 898 patients. Subsequently, 89 were excluded because of missing data (n = 83) or absence of follow-up (n = 6). Patients were retrospectively classified into 3 groups: mild-to-moderate aortic stenosis (AVA ≥1 cm^2 or indexed AVA ≥0.6 cm^2, and MDG <40 mm Hg; n = 420); LG aortic stenosis (AVA <1 cm^2, indexed AVA <0.6 cm^2, and MDG <40 mm Hg; n = 142); and HG aortic stenosis (AVA <1 cm^2, indexed AVA <0.6 cm^2, and MDG ≥40 mm Hg, n = 247). LG aortic stenosis was further divided according to the SV index in LG/LF aortic stenosis (n = 57) when the index SV was <35 ml/m^2, and low-gradient, normal-flow (LG/NF) (n = 85) aortic stenosis when index SV was ≥35 ml/m^2 (3,4).

An index summating the patient's individual comorbidities was calculated (17). Coronary artery disease (CAD) was defined by the presence of a documented history of acute coronary syndromes, CAD previously confirmed by coronary angiography, or history of coronary revascularization.

We obtained institutional review board authorizations before conducting the study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive Doppler echocardiographic study, using commercially available ultrasound systems. Peak aortic velocity was recorded using continuous-wave Doppler in several acoustic windows (apical 5-chamber view, right parasternal, suprasternal, epigastric). AVA was calculated by the continuity equation and indexed for body surface area. SV was calculated by multiplying the area of the left ventricular outflow tract by the outflow tract time-velocity integral (3). When patients were in sinus rhythm, 3 cardiac cycles were averaged for all measures. For patients in atrial fibrillation, 5 cardiac cycles were averaged. EF was calculated using Simpson's biplane method. Left ventricular mass was estimated by the formula on the basis