Outstanding and Impact of Surgery in Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

A Cardiac Catheterization Study

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Background—The clinical relevance and management of paradoxical low-flow, low-gradient aortic stenosis (LFLG-AS) with preserved left ventricular ejection fraction remain debated. The aim of this study is to determine the features and outcome of LFLG-AS assessed using cardiac catheterization.

Methods and Results—Between 2000 and 2010, 768 patients with preserved left ventricular ejection fraction (>50%) and severe AS (valve area ≤1 cm²) without other valvular disease underwent cardiac catheterization. Mean age was 74±8 years, 42% were women, and 46% had associated coronary artery disease. The prevalence of LFLG (indexed left ventricular stroke volume <35 mL/m² and mean gradient <40 mmHg), normal flow high gradient, normal flow low gradient, and low flow high gradient were 13%, 50%, 22%, and 15%, respectively. Compared with patients with normal flow high gradient, those with LFLG were significantly older, with significantly reduced systemic arterial compliance and vascular resistances and increased valvulo-arterial impedance (all \( P < 0.05 \)). Ten-year survival was reduced in LFLG-AS (32±9%) compared with normal flow high gradient (66±4%; \( P = 0.0002 \)). After adjustment for other risk factors, LFLG-AS was independently associated with reduced long-term survival (hazard ratio, 1.85; 95% confidence interval, 1.08–3.07; \( P = 0.02 \)). However, despite higher operative mortality, patients with LFLG-AS undergoing aortic valve replacement seemed to have better long-term survival than those managed conservatively (5-year survival rate: 63±6% versus 38±15%; \( P = 0.007 \); hazard ratio, 0.23; 95% confidence interval, 0.09–0.59; \( P = 0.002 \)).

Conclusions—This large cardiac catheterization–based study reports that the LFLG-AS entity is not rare and is associated with worse outcome whether treated medically or surgically. However, these patients may have better long-term survival if treated surgically. Further prospective studies are needed to confirm this finding. (Circulation. 2013;128[suppl 1]:S235-S242.)

Key Words: aortic stenosis • catheterization • LV function • surgery • survival • valve

Calcific aortic stenosis (AS) is the most frequent valvular heart disease encountered in the Western countries. According to the current guidelines, two severe AS is defined as an aortic valve area (AVA) ≤1 cm² (AVA indexed ≤0.6 cm²/m²), a transaortic mean gradient (MG) ≥40 mmHg, or a peak velocity ≥4 m/s. However, in the presence of reduced left ventricular ejection fraction (LVEF), cardiac output, and indexed left ventricular (LV) stroke volume (SV), discrepancies between AVA and MG may occur, that is, the MG may be low (<40 mmHg), despite a small AVA (≤1 cm²). This entity of classical low-flow, low-gradient (LFLG) AS with reduced LVEF is well characterized and has previously been extensively studied. More recently, the presence of a new entity of paradoxical LFLG-AS with preserved LVEF (>50%) has been described. This condition was found to be associated with higher LV hemodynamic afterload, increased concentric remodeling, reduced LV longitudinal function, higher degree of LV myocardial fibrosis, and elevated brain natriuretic peptide level. However, the exact prevalence of this entity remains a source of debate.
because the vast majority of studies are based on echocardiographic data.7,9,11,12 Furthermore, conflicting data were published regarding the impact on outcome of LFLG-AS with preserved LVEF.7,11–15

Cardiac catheterization is an established method to assess aortic MG and AVA. After coronary angiography, these measurements are frequently performed to corroborate the echocardiographic findings, especially in case of discrepancies among gradients, AVA, LV function, and symptoms. In addition, the assessment of SV and AVA by cardiac catheterization may overcome the limitations of Doppler echocardiography (eg, angle dependency of the Doppler measures, pitfalls in the measurement of LV outflow tract diameter).2

The aims of this study are as follows: (1) to describe the prevalence and hemodynamic features of patients with paradoxic LFLG-AS exclusively using invasive data during cardiac catheterization, (2) to analyze short- and long-term prognosis of these patients, and (3) to compare outcome of patients according to the treatment received (ie, aortic valve replacement [AVR]±coronary artery bypass graft [CABG]) versus conservative management.

Methods

Study Population

From January 2000 to December 2010, demographic, clinical, and invasive hemodynamic data of all patients who underwent cardiac catheterization in a tertiary care center for evaluation of AS severity and identification of coronary artery disease (CAD) were collected. Clinical data included age, sex, body surface area, presence of atrial fibrillation, any related symptoms (chest pain, dyspnea, or syncope), history of hypertension, dyslipidemia, diabetes mellitus, or CAD defined by a previous history of CAD or any coronary artery stenosis >50% during coronary angiography. Only patients with AVA ≤1 cm² at the time of cardiac catheterization were included in the study. Exclusion criteria were LV systolic dysfunction defined by an angiographic LVEF ≤50%, any concomitant significant other valve disease, or any missing data of MG or SV.

The included patients with AVA ≤1 cm² and LVEF >50% were divided according to the invasive indexed LV SV (< versus ≥35 mL/m²) and aortic MG (< versus ≥40 mm Hg) as previously suggested,7,16 resulting in 4 groups:

- Normal-flow, high-gradient (NFHG) group
- Low-flow, low-gradient (LFLG) group
- Low-flow, high-gradient (LHFHG) group
- Normal-flow, low-gradient (NFLG) group

Cardiac Catheterization Data

Standard cardiac catheterization was performed in all patients (online-only Data Supplement). Briefly, pressures curves, cardiac output, MG, and the systolic ejection period were measured automatically by the device software of the cathlab system HORIZON 9000WS-MENNEN MEDICAL. The aortic valve pressure gradient was determined by catheter pullback into the aorta. The AVA was calculated using the Gorlin formula.17

The LVEF was assessed by LV angiography using the Simpson method with automatic edge detection and manual correction when necessary. Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, mean pulmonary arterial pressure, and the pulmonary capillary wedge pressure were obtained invasively during catheterization. The systemic arterial compliance, the valvulo-arterial impedance, and the systemic vascular resistance were calculated as appropriate (online-only Data Supplement).

Outcome Data

Survival data were obtained from death certificates or family physician phone contact or hospital records. To avoid misclassification of causes of death, all-cause mortality was selected as the outcome criteria. The primary outcome was long-term survival from the time of cardiac catheterization until the last available follow-up (in 98% of patients included) or until date of death. In patients who underwent AVR, operative mortality was defined as death occurring within 30 days after surgery or within any time interval if the patient was not discharged from the hospital.

In patients in the LFLG-AS group, the mortality rate after AVR was compared with those managed conservatively. To determine the prognostic impact of concomitant CABG, the same analysis was repeated after exclusion of those who had combined AVR+CABG surgery.

The study was approved by the local Ethics Committee of the CHU of Limoges, France, and written informed consent was waived because of the retrospective design of this study.

Statistical Analysis

Continuous data are expressed as mean±SD and compared using 1-way ANOVA and with a post hoc Tukey test. Categorical data are given as a percentage and compared with a χ² or Fisher exact test, as appropriate. The time of catheterization was used as baseline time for all patients included in the present study.

The cumulative probability of mortality was estimated by the Kaplan–Meier method, and survival rates are reported at 5 and 10 years. Log-rank tests were used to compare the 4 groups. Univariable Cox proportional-hazard models were used to test the association between survival and the most clinically relevant variables, including the 4 patient groups and the performance of AVR. We then performed a multivariable analysis including age and sex, as well as all the variables that had a P≤0.10 in univariable analysis, and taking the NFHG group (ie, the classical AS presentation) as the reference. The impact of AVR during follow-up was tested with AVR as a time-dependent covariate in the stratified Cox proportional-hazards model. A propensity score (PS) was obtained in the whole study group using an unconditional logistic regression that identified variables independently associated with AVR versus conservative treatment. This PS represented the probability of having AVR as opposed to conservative therapy. The calculated PS was then incorporated into subsequent proportional-hazards model. A new PS was built for the subanalysis performed in the subset of the LFLG-AS group. Results were reported as hazard ratios (HRs) with the 95% of confidence interval (95% CI) of probability values. For all statistical tests, a P≤0.05 was considered significant. All statistical analyses were performed with a commercially available software package JMP IN 8.1 (SAS, Institute, Cary, NC) and SPSS Inc (Chicago, IL).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Among the 1813 consecutive patients who underwent cardiac catheterization for AS assessment and coronary angiography during the inclusion period, 768 patients (mean age 74±8 years, 42% women) fulfilled inclusion criteria and were considered for the final analysis. In the whole cohort (Table 1), 89% (n=684) of patients were symptomatic, 62% (n=476) had hypertension, 50% (n=384) had dyslipidemia, 21% (n=161) had diabetes mellitus, 46% (n=353) had CAD, 90.7% (n=696) received AVR, and 32% (n=247) had associated CABG at the time of surgery. Angiographic LVEF was 72±10%, AVA was 0.69±0.17 cm², and mean aortic gradient was 48±17 mm Hg. The mean LV SV index was 40±9 mL/m². There were 386 (50%) patients in the NFHG group (reference group), 99 (13%) in the LFLG group, 111 (15%) in the LFHG group, and 172 (22%) in the NFLG group.
Comparison of Baseline Characteristics

Table 1 displays the comparison of baseline data among the 4 groups. Patients with LFLG were significantly older (P=0.002) compared with the 3 other groups, with higher rates of atrial fibrillation (P<0.0001), faster heart rate (P<0.0001), lower LVEF (P=0.01), and a trend (P=0.07) for higher rates of CAD.

By study design, peak-to-peak aortic gradient and MG, indexed LV SV, and cardiac output were significantly lower in the LFLG group compared with the referent NFHG group (P<0.0001 for all). Although the diastolic arterial pressure was significantly higher in the LFLG group than in the NFHG group, there was no significant difference regarding the systolic arterial pressure. In addition, compared with the 3 other groups, patients in the LFLG group had significantly higher systemic vascular resistance and valvulo-arterial impedance (both P<0.0001) but lower systemic arterial compliance (P<0.0001).

Clinical Outcome

Within the whole cohort, surgery was not performed in 72 (9.3%) patients (patient or surgical team refusal, or death before surgery). AVR was performed within 3 months after catheterization (58±25 days; median: 48 days; 25% and 75% percentiles: 36 and 65 days, respectively), and there was no significant (P=0.47) difference among the 4 groups regarding...
time between catheterization and AVR. AVR was significantly less frequent in patients with LFLG (n=83, 84%) compared with the 3 other groups (n=363, 94% in NFHG; n=150, 87% in NFLG; and n=101, 91% in LFHG; P=0.003 for all).

**Operative Mortality**

Among patients who received AVR with or without CABG, the overall operative mortality was 4.7% (n=33). The operative mortality rate tended (P=0.1) to be higher in the LFLG-AS group (9.8%) compared with the NFHG (3.8%), the NFLG (4.7%), and the LFHG (4%) groups.

**Long-Term Mortality**

The mean follow-up time was 4.6±3 years (maximum 12 years). The median follow-up time was 4.3 years, and 25% and 75% percentiles were 2.0 and 6.8 years, respectively. During this period, 27% of patients died. Overall, the 5- and 10-year survival rates were 75±2% and 56±3%, respectively. The long-term survival in each group is reported in Figure 1A. The survival curves of the 4 groups differed significantly (P=0.0002), with the most favorable outcome in the NFHG group (5-year survival: 81±2% and 10-year survival: 66±4%). In contrast, patients in the LFLG group exhibited the worst prognosis (5-year survival: 60±6% and 10-year survival: 32±9%) compared with the 3 other groups. In patients receiving AVR±CABG (ie, exclusion of those with conservative therapy, Figure 1B) or only AVR (ie, exclusion of those with conservative therapy or concomitant CABG, Figure 1C), long-term survival remained significantly lower in the LFLG group compared with the 3 other groups (P=0.001).

In univariable analysis (Table 2), using NFHG as the reference group, patients in LFLG and LFHG groups were at increased risk of long-term mortality (HR, 2.24; 95% CI, 1.5–3.27; P<0.0001 and HR, 1.64; 95% CI, 1.10–2.38; P=0.01, respectively). The other variables associated with an increased risk of long-term death are summarized in Table 2. The performance of AVR was also, as expected, a powerful univariable predictor of survival (P<0.0001). However, concomitant CABG was not significantly associated with better survival (P=0.72).

In multivariable analysis, after adjustment for univariate predictors of survival (model 1), the presence of LFLG-AS (HR=1.85; 95% CI, 1.08–3.07; P=0.02) remained significantly associated with increased risk of death compared with the NFHG group (Table 2). Furthermore, when we entered the MG and the SV in the multivariable model instead of the group classification, these variables were independent predictors of long-term outcome: MG (HR, 0.98; 95% CI, 0.97–0.99) per 1 mm Hg increase in MG (P=0.01) and SV (HR, 0.97; 95% CI, 0.95–0.99) per 1 mL/m² increase in SV (P=0.007).

**Impact of AVR on Survival**

In the multivariable model including AVR as a time-varying covariable (model 2, Table 2), LFLG remained an independent predictor of mortality (HR, 1.84; 95% CI, 1.13–2.99; P=0.014). When the PS was added to the latter model (model 3), AVR and LFLG remained powerful independent predictors of long-term outcome (HR, 0.25; 95% CI, 0.14–0.47; P<0.0001 and HR, 2.06; 95% CI, 1.26–3.38; P=0.004, respectively).

**AVR Versus Conservative Treatment in LFLG-AS Patients**

As shown in Figure 2, long-term survival of LFLG-AS was significantly (P=0.007) better in patients who received AVR compared with those with conservative management. As expected, patients who were treated conservatively were significantly older and had more comorbidities compared with those who...
underwent AVR (Table in the online-only Data Supplement). Another PS was obtained in the LFLG-AS group to adjust for the treatment selection bias. After adjustment for this PS, AVR was significantly associated with improved survival (HR, 0.23; 95% CI, 0.09–0.59; \(P = 0.002\)) in this subset of patients.

**Discussion**

The main findings of this study are that in patients with severe AS and preserved LVEF, both evaluated by cardiac catheterization (1) the prevalence of LFLG is 13%, consistent with recent studies using either Doppler echocardiography or cardiac catheterization; (2) LFLG is independently associated with increased long-term mortality; (3) when operated, patients with LFLG-AS had higher operative mortality; and (4) compared with conservative management, AVR may provide long-term survival advantage in the patients with LFLG-AS, despite the higher operative mortality observed in these patients.
Moderate AS. One possible explanation for this discrepancy may be related to the end point used that is at higher risk for prosthesis–patient mismatch after surgical AVR. Furthermore, patients with paradoxical LFLG-AS may be at higher risk for prosthesis–patient mismatch after surgical AVR. Further studies are needed to determine whether transcatheter AVR would contribute to reduce operative mortality in these patients.

Impact of AVR on the Outcome of Patients With Paradoxical LFLG-AS
We found that patients with LFLG were less often treated with AVR than other groups of severe AS and that, when operated, they had slightly higher operative mortality but, nevertheless, seemed to have long-term benefit with AVR compared with conservative therapy. The less frequent use of AVR observed in these patients may be related to their worse risk profile and the presence of a low gradient that may have yielded to the underestimation of stenosis severity. The potential benefit of surgery in patients with paradoxical LFLG-AS was observed even when limiting the analysis to those who underwent isolated AVR (ie, without concomitant CABG). Our data are consistent with those of a recent case-match study, as well as with those from smaller series.

The increased operative mortality observed in patients with paradoxical LFLG-AS compared with those with NFHG may be because of the more pronounced impairment of myocardial geometry and function. These patients indeed often have more myocardial fibrosis and worse LV longitudinal function, despite the presence of a preserved LVEF. Furthermore, patients with paradoxical LFLG-AS may be at higher risk for prosthesis–patient mismatch after surgical AVR. Further studies are needed to determine whether transcatheter AVR would contribute to reduce operative mortality in these patients.

Outcome of NFLG-AS
Besides LFLG, the NFLG entity also raises some challenges in terms of interpretation and clinical management. Indeed, these patients have a small AVA and a normal flow but a low gradient. Some studies suggest that this discordant grading of AS severity in the context of a normal flow may be related to an inherent inconsistency in the cut points of AVA (1.0 cm²) and MG (40 mmHg) proposed in the guidelines to define severe AS. Indeed, theoretical models have shown that a patient with normal transvalvular flow rate and an AVA of 1.0 cm² should be expected to have an MG =30 to 35 mmHg. In a recent study by Lancellotti et al, patients with NFLG had better prognosis compared with the 3 other flow-gradient groups, whereas in the present study, these patients tended to have similar worse outcome as compared to those with LFLG or with LFHG. These discrepancies in these 2 studies’ results may be related to the difference in the method used to classify the patients (catheter versus Doppler echocardiography) and to the fact that the patients in the study of Lancellotti et al were all asymptomatic at baseline, whereas in the present study the majority of patients were symptomatic. In addition, the discrepancies between the Lancellotti study and the present one may be related to the end point used that is
mainly driven by AVR while we analyzed postoperative overall survival. Further studies are needed to determine the most appropriate therapeutic management for these patients with NFLG-AS.

Limitations
This study was retrospective by design with some possible potential bias. This may include the mode of selection of patients because they were all referred to our department for coronary angiography and AS assessment after echocardiography performed elsewhere and possible exclusion of severe patients unsuitable for AVR. Thus, the exact prevalence of LFLG-AS may have been underestimated. However, our results are similar to those obtained in other centers using the same imaging modality and different inclusion modality. Importantly, our center is the unique cardiac catheterization laboratory in the area for this period study, limiting the referral bias.

The pullback method used in the present study to measure the transvalvular gradient may be less accurate than simultaneous measurement using a dual-lumen catheter. However, given that the same method (the only one available in our institution) was used in all patients, it did not probably affect the results of the intergroup comparisons.

The multivariable analysis comparing AVR versus conservative management in the LFLG-AS group is underpowered, and the PS adjustment may not compensate for all the factors that are potentially different between the 2 treatment subgroups. Further studies in larger series of patients are necessary to confirm these findings.

Given that this was a retrospective study, the exact cause of death was not always available so that we were unable to discriminate deaths due to cardiovascular from noncardiovascular causes. However, as emphasized by Lauer et al., retrospective studies should base their analyses on overall mortality rather than cardiac mortality to avoid bias related to the pitfalls in the identification of the cause of death.

Conclusions
This large cardiac catheterization–based study reports that the LFLG-AS entity is not rare and is associated with worse outcome. These patients may have better long-term survival with surgical AVR compared with conservative therapy, despite higher operative mortality. Further prospective studies are necessary to determine whether surgical or transcatheter AVR improves outcome in these patients with paradoxical LFLG-AS compared with medical management.

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Disclosures
None.

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