Postoperative Reverse Remodeling and Symptomatic Improvement in Normal-Flow Low-Gradient Aortic Stenosis After Aortic Valve Replacement

Rasmus Carter-Storch, MD, PhD; Jacob E. Møller, MD, PhD, DMSci, PhD; Nicolaj L. Christensen, MD, PhD; Akhmadjon Irmukhadenov, MD; Lars M. Rasmussen, MD, PhD, DMSci; Redi Pecini, MD, PhD; Kristian A. Øvrehus, MD, PhD; Eva V. Søndergård, MD, PhD; Niels Marcussen, MD, PhD, DMSci; Jordi S. Dahl, MD, PhD

Background—Severe aortic stenosis (AS) most often presents with reduced aortic valve area (<1 cm^2), normal stroke volume index (≥35 mL/m^2), and either high mean gradient (≥40 mm Hg; normal-flow high-gradient AS) or low mean gradient (normal-flow low-gradient [NFLG] AS). The benefit of aortic valve replacement (AVR) among NFLG patients is controversial. We compared the impact of NFLG condition on preoperative left ventricular (LV) remodeling and myocardial fibrosis and postoperative remodeling and symptomatic benefit.

Methods and Results—Eighty-seven consecutive patients with reduced aortic valve area and normal stroke volume index undergoing AVR underwent echocardiography, magnetic resonance imaging, a 6-minute walk test, and measurement of natriuretic peptides before and 1 year after AVR. Myocardial fibrosis was assessed from magnetic resonance imaging. Patients were stratified as NFLG or normal-flow high-gradient. In total, 33 patients (38%) had NFLG. Before AVR, they were characterized by similar symptom burden but less severe AS measured by aortic valve area index (0.50±0.09 versus 0.40±0.08 cm^2/m^2; P<0.0001), lower LV mass index (74±18 versus 90±26 g/m^2; P=0.01), but the same degree of myocardial fibrosis. After AVR, NFLG had a smaller reduction in LV mass index (−3±10 versus −±18 g/m^2; P<0.0001) and a smaller reduction in natriuretic peptides. Both groups experienced similar symptomatic improvement. Normal-flow high-gradient condition independently predicted change in LV mass index.

Conclusions—Patients with NFLG had less severe AS and LV remodeling than patients with normal-flow high-gradient. Furthermore, NFLG patients experienced less reverse remodeling but the same symptomatic benefit.

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Key Words: aortic valve stenosis ■ heart valve prosthesis ■ magnetic resonance imaging ■ stroke volume ■ walk test

Aortic valve stenosis (AS) is the most common valvular disease in the Western world. With advancing AS severity, the left ventricle (LV) will be exposed to increased afterload and wall stress, causing LV hypertrophy, myocardial fibrosis, and eventually depressed LV function and development of symptoms where aortic valve replacement (AVR) is the standard of care.[1] There has been increasing recognition of different patterns of flow and transvalvular pressure gradients in patients with severe AS.[2] Thus, based on the transvalvular gradient and estimated stroke volume index (SVi), patients with severe AS can be subdivided. In the classic patient with AS, mean gradient is high and SVi is normal (normal-flow high-gradient [NFHG] AS). Not infrequently, however, patients present with apparently normal SVi, a morphologically severely stenotic valve, an estimated aortic valve area (AVA <1 cm^2), but only a moderately elevated mean gradient (<40 mm Hg). This condition termed normal-flow low-gradient (NFLG) AS is relatively common, with an estimated prevalence among patients with AS ranging from 13% to 31%[2–7] and associated with a favorable prognosis compared with other AS groups.[2,5,7,8] The benefit of AVR in these patients is controversial. Although a recent nonrandomized metastudy showed that AVR improved prognosis, other disagree.[7,9] We hypothesized that NFLG represents a subgroup of patients with milder degrees of AS and that these patients benefit less from AVR than patients with NFHG. Consequently, the aims of this study were to compare the extent of preoperative LV remodeling and myocardial fibrosis in a cohort of patients with NFHG and NFLG referred to AVR and to compare the effect of AVR in terms of symptom improvement and reverse remodeling.

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From the Departments of Cardiology (R.C.-S., J.E.M., N.L.C., R.P., K.A.Ø., E.V.S., J.E.M.), Thoracic Surgery (A.I.), Clinical Biochemistry (L.M.R.), and Pathology (N.M.), Odense University Hospital, Denmark; and OPEN Odense Patient data Explorative Network, Denmark (R.C.-S., J.E.M.).

Correspondence to Rasmus Carter-Storch, MD, PhD, Department of Cardiology, Odense University Hospital, Sdr. Blvd 29, 5000 Odense C, Denmark. E-mail rcarterstorch@gmail.com

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. This study was a single-center prospective study. Patients with severe AS (AVA <1 cm^2) who after heart team evaluation were scheduled for elective surgical AVR were eligible. Patients with concomitant coronary artery bypass graft surgery were enrolled only if AVR was considered the main reason for surgery. Patients with at least moderate concomitant valvular disease, chronic kidney disease (estimated glomerular filtration rate <40 mL/min per 1.73 m^2), chronic atrial fibrillation or flutter, pacemaker, or advanced cancer were excluded. Finally, patients with SVi <35 mL/m^2 determined by echocardiography were excluded (Figure 1).

The study was approved by the Danish Data Protection Agency and the Regional Scientific Ethical Committees for Southern Denmark (S-20130064) and was registered with ClinicalTrials.gov. All patients gave written informed consent. Study data were collected and managed using REDCap electronic data capture tools hosted at Odense Patient data Explorative Network.

All patients underwent a 6-minute walk test, answered a Duke Activity Status Index questionnaire,[10] comprehensive echocardiography, cardiac computed tomography (CT), and magnetic resonance imaging (MRI) scan before AVR and after 12 months. Echocardiography and functional testing were also performed after 6 months.

The primary end point was changes in MRI measured LV mass index (LVMi) 12 months after AVR. Secondary end points were changes in MRI measured left atrial volume index (LAVi) and in 6-minute walk test.

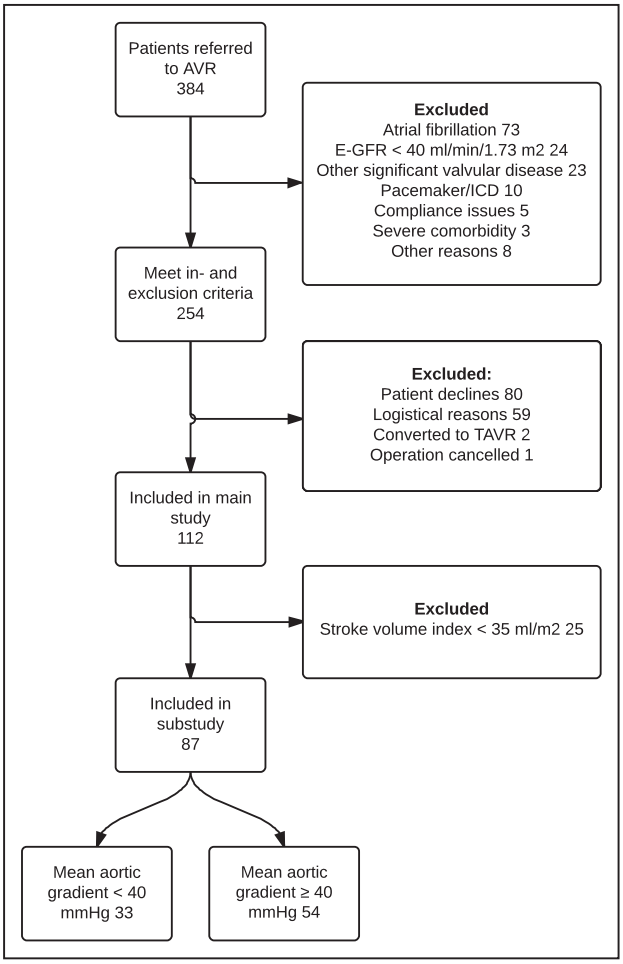

Figure 1. Consort diagram showing number of patient screened, excluded, and included. AVR indicates aortic valve replacement; E-GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; and TAVR, trans-aortic valve replacement.

Echocardiography

Echocardiograms were performed by the same experienced operator on a GE medical Vivid 9 ultrasound machine (GE Medical System, Horten, Norway). Images were analyzed offline on EchoPAC PC 08 (GE Medical system) in a blinded manner.

LV outflow tract diameter was measured in the parasternal long-axis view in early systole 5 mm from the aortic annulus. AVA index (AVAi), peak and mean flow velocities across the valve were measured as recommended by ESC guidelines.[11] A mean transvalvular aortic gradient ≥40 mm Hg was considered high. SVi was calculated using pulsed wave Doppler as the product of the estimated LV outflow tract area and time velocity integral. SVi ≥35 mL/m^2 was considered normal.[11] Valvuloarterial impedance, systemic arterial compliance, and systemic vascular resistance were calculated as previously described.[12]

Prosthesis–patient mismatch was calculated according to previous recommendations[13] with the use of patient's body surface area and the normal reference values of the effective orifice areas as reported by the manufacturer for Mitroflow (http://www.accessdata.fda.gov/cdrh_docs/pdf6/p060038c.pdf), Edwards-Carpentiers Magna Ease,[14] Medtronic ATS AP360 (http://www.accessdata.fda.gov/cdrh_docs/pdf/P990046c.pdf), and Carbomedics Top Hat valves.[15] An indexed effective orifice area <0.85 cm/m^2 was considered patient–prosthesis mismatch.

Mitral inflow was assessed in the apical 4-chamber view using pulsed-wave Doppler with the sample volume placed at the tips of mitral leaflets during diastole. Doppler tissue imaging was used to assess peak diastolic mitral annular motion as the average of septal and lateral valve annulus (e′).[16] Two-dimensional deformation was assessed with speckle tracking measuring global longitudinal strain as the maximal systolic deformation averaged from the 3 apical views.

Cardiac CT

Cardiac CT scans were performed before AVR on a Siemens Somatom Definition Flash 128 slice scanner (Siemens Healthcare Solutions, Forcheim, Germany). We performed a calcium score acquisition with prospective ECG-gated sequential scanning; tube voltage, 120 kV; tube current, 50 mA, with 3-mm slice thickness. Images were transferred to a workstation, and an Agatston score as well as an aortic valve calcification score were estimated.[17] Based on Clavel et al,[18] severe aortic valve calcification was defined as 1275 and 2065 arbitrary units for women and men, respectively.

Cardiac MRI

MRI was performed before AVR on a Phillips Ingenia 1.5-T scanner with Omega HP gradient system (Philips Electronics, Koninklijke, The Netherlands). Sequential short-axis cine slices (20–24) were performed during multiple breath hold sequences acquiring slices of 8-mm thickness.

Images were analyzed blinded for clinical and echocardiographic data by an experienced examiner on a dedicated work station with a Philips Workspace software package (2.6.3.5 2013).

In short axis and with minimal and maximal volumes, endo- and epicardial borders were manually traced. The difference in epicardial- and endocardial cross-sectional area multiplied by sum of slice thickness and gap multiplied by myocardial density (1.05 g/mL) was used to calculate LV mass.[19] Papillary muscles were considered as part of the LV cavity and excluded from calculation of LV mass. The left atrial (LA) appendage was excluded from the assessment of LA volume. Phase velocity flow mapping of flow volumes of the ascending aorta was used to assess forward and backward flows. SVi was calculated as forward flow divided by body surface area.

Late enhancement images were obtained 10 minutes after bolus injection of 0.1 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Aulnay-Bois, France). The inversion time was adjusted from visual inspection of a Look-Locker image to null the myocardium. Late enhancement pattern was reported as midwall or ischemic.

Table 1. Preoperative Characteristics According to Aortic Mean Gradient Group

	NFLG (n=33)	NFHG (n=54)	*P* Value
Baseline characteristics			
Age	71±10	69±7	0.36
Male gender	23 (70)	31 (57)	0.25
Body mass index, kg/m^2	26±4	27±4	0.18
Hypertension	23 (70)	29 (54)	0.14
Diabetes mellitus	5 (15)	11 (20)	0.54
Ischemic heart disease*	15 (45)	13 (24)	0.04
Stroke	9 (27)	5 (9)	0.03
Euroscore 2 (%)	1.9±1.5	1.7±1.5	0.58
Systolic blood pressure, mm Hg	142±16	145±16	0.27
Antihypertensive drugs (0/1/≥2)	6/14/13	21/10/23	0.03
NYHA class	2.2±0.6	2.1±0.7	0.19
Duke Activity score index questionnaire	27 (19–43)	37 (26–46)	0.20
6-minute walk test, m	492±99	474±100	0.44
Perioperative characteristics			
Prosthetic valve size, mm	23 (23–25)	23 (22–25)	0.65
Mechanical valve	7 (21)	10 (19)	0.80
Concomitant CABG	11 (33)	13 (24)	0.35
Moderate-severe PPM	5 (15)	8 (13)	0.77
Echocardiography			
E/e′	11±4	14±4	0.02
Global longitudinal strain (%)	–17.2	–16.8	0.56
Stroke volume index, mL/m^2	39 (37–45)	43 (39–49)	0.09
Aortic mean gradient, mm Hg	34 (30–38)	57 (47–73)	<0.0001
Aortic valve area index, cm^2/m^2	0.50±0.09	0.40±0.08	<0.0001
MRI			
LV ejection fraction (%)	62±9	62±9	0.88
LV end-diastolic volume index, mL/m^2	71±17	82±21	0.03
LV mass index, g/m^2	74±18	89±26	0.01
LA volume index, mL/m^2	49±13	58±12	0.007
Aortic regurgitation (%)	6 (3–11)	11 (5–19)	0.02
Midwall fibrosis	8 (31)	10 (30)	0.97
Ischemic fibrosis	6 (23)	6 (18)	0.64
All fibrosis	12 (46)	14 (42)	0.78
CT			
Coronary calcium score, AU	422 (83–572)	205 (11–889)	0.62
Aortic valve calcium score, AU	2620 (1655–3647)	2998 (2096–4625)	0.03

AU indicates arbitrary units; CABG, coronary artery bypass graft; CT, computed tomography; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; NFHG, normal-flow high gradient; NFLG, normal-flow low gradient; NYHA, New York Heart Association; and PPM, prosthesis–patient mismatch.

*Ischemic heart disease: history of coronary angioplasty, myocardial infarction, or significant lesions on coronary angiogram.

Biochemical Analyses

Venous blood was drawn from an antecubal vein after at least 10 minutes of rest and stored at −80°C for later analysis of brain natriuretic peptide (BNP) using an ARCHITECT BNP immunoassay (Abbott, Wiesbaden, Germany).

Statistics

Data are presented as mean±SD, median and (interquartile range), or number (percentages) as appropriate. Normality was assessed visually by q-q plots and histograms. Differences between groups were tested by Student *t* test; non-normally distributed data were log transformed and tested by Student *t* test if normally distributed, otherwise by Wilcoxons rank-sum test; categorical data were tested by the χ^2 test. Correlation between MRI and echocardiography SVi was assessed by Pearsons correlation. Uni- and multivariable linear regression analyses were performed to assess the relationship between AS group and changes in LVMi from baseline to 12 months after AVR, adjusting for potential confounders (age, sex, hypertension, number of antihypertensive drugs, and LVMi at baseline). A $P<0.05$ was considered significant. STATA/IC 14.1 (StataCorp LP, TX) software was used.

Results

A total of 87 patients with normal-flow severe AS undergoing AVR were included, 33 patients (38%) were classified as NFLG and 54 patients (62%) as NFHG (Table 1). Eighty-three patients underwent AVR because of valve-related symptoms (n=79 dyspnea or angina, n=4 syncope), 2 were operated before major noncardiac surgery, 1 experienced a significant blood pressure drop during exercise testing, and 1 patient was referred for AVR because of a high and rapidly rising peak jet velocity.

NFLG Versus NFHG Pre-Operatively

Clinical characteristics and functional status were similar between groups, except for a higher prevalence of ischemic heart disease and stroke among patients with NFLG, and fewer patients with NFHG taking ≥1 antihypertensive drugs (39% versus 18%; $P=0.03$). There was no difference in concomitant coronary artery bypass graft between groups (Table 1).

Table 2. Echocardiographic, MRI, and Biomarker Changes Among Patients Completing 12-Month Follow-Up

	NFLG (n=29)			NFHG (n=49)			*P* Value (Between Group Change)
	Pre-Operative	12 mo	Change	Pre-Operative	12 mo	Change	
Functional capacity							
NYHA class	2.2±0.6	1.5±0.6*	−0.7±0.6	2.0±0.7	1.3±0.5*	−0.7±0.7	0.54
Duke Activity score index questionnaire	27 (19 to 43)	46 (35 to 53)*	10 (−1 to 22)	38 (26 to 46)	46 (38 to 58)*	8 (0 to 16)	0.72
6-minute walk test, m	494±103	540±77*	45±55	484±97	550±80*	62±73	0.28
Echocardiography							
E/e′	12±4	11±4	0±3	13±4	13±7	0±4	0.84
Global longitudinal strain (%)	−17.1±2.8	−18.4±3.4†	−1.2±2.6	−16.7±3.4	−18.9±3.2*	−1.9±3.4	0.38
Aortic mean gradient, mm Hg	34 (30 to 38)	11 (10 to 16) *	−21±6	57 (47 to 73)‡	13 (11 to 16)*	−46±18	<0.0001
Aortic valve area index, cm^2/m^2	0.49±0.09	0.88±0.20*	0.39±0.19	0.40±0.08‡	0.90±0.21*	0.51±0.21	0.02
$Z_{VA,}$ mm Hg×mL/m^2	4.1±0.7	3.8±0.6†	−0.4±0.8	4.7±0.8‡	3.8±0.7*	−0.9±0.8	0.004
SAC mL/mm Hg per m^2	0.7±0.2	0.6±0.1	0±0.2	0.7±0.2	0.7±0.2	0±0.2	0.44
SVR dyne×s×cm^{-5}	1585±370	1586±458	1±478	1533±381	1537±378	4±433	0.98
MRI							
LV ejection fraction (%)	62±9	64±9	2±7	62±10	65±9†	3±8	0.5
LV end-diastolic volume index, mL/m^2	72±17	64±13†	−6±11	83±22§	65±16*	−19±17	0.004
LV mass index, g/m^2	75±19	72±14	−3±10	90±26§	70±17*	−21±18	0.0001
LA volume index, mL/m^2	49±14	49±12	0±8	58±12§	52±13*	−7±9	0.007
Stroke volume index, mL/m^2	41±9	39±7	−1±7	42±8	38±8*	−2±8	0.19
Aortic regurgitant fraction (%)	7 (3 to 12)	6 (3 to 10)	2 (−7 to 4)	10 (5 to 19)§	8 (3 to 15)†	−3 (−8 to 1)	0.12
Brain natriuretic peptide, pg/mL	37 (17 to 73)	40 (31 to 50)	4 (−21 to 22)	95 (33 to 142)‡	53 (30 to 86)*	−39 (−75 to 6)	0.003

LA indicates left atrium; LV, left ventricle; MRI, magnetic resonance imaging; NFHG, normal-flow high gradient; NFLG, normal-flow low gradient; NYHA, New York Heart Association; SAC, systemic arterial compliance; SVR, systemic vascular resistance; and ZVA, valvuloarterial impedance.

*P<0.005 different from baseline.

†P<0.05 different from baseline.

‡P<0.005 NFHG different than NFLG.

§P<0.05 NFHG different than NFLG.

Patients with NFLG presented with larger AVAi (0.50±0.09 versus 0.40±0.08 cm^2/m^2; P<0.0001) and lower valvuloarterial impedance (4.2±0.7 versus 4.7±0.8 mm Hg×mL per m^2; P=0.002) than patients with NFHG, mainly driven by their lower mean gradient. Systemic vascular resistance and systemic arterial compliance were similar between the 2 groups (Table 2). NFLG patients had more favorable diastolic function than patients with NFHG, but global longitudinal strain was similar (Table 1). MRI revealed that patients with NFLG had less severe LV remodeling both in terms of end-diastolic volume and mass (Table 1; Figure 2). Further, LAVi was smaller in the NFLG group. There were no differences in midwall or ischemic fibrosis between the 2 groups. SVi assessed by both echocardiography and MRI was similar between groups, but patients with NFLG had less aortic regurgitation (Tables 1 and 2). There was poor correlation between echocardiography and MRI assessment of SVi (Pearsons 0.25; P=0.07). Based on MRI assessment, 22% had SVi <35 mL/m^2, with similar distribution in the 2 groups (20% versus 24%; P=0.72). SVi measured by MRI was similar between the 2 groups. Cardiac CT showed no difference in coronary calcium score, but NFLG had significantly lower aortic valve calcium score, and fewer NFLG patients had severe aortic valve calcification than patients with NFHG (71% versus 91%; P=0.03). There was also a lower degree of aortic regurgitation in the NFLG group (6% [3%–11%] versus 11% [5%–19%]; P=0.02). Furthermore, the NFLG group had significantly lower BNP (43 pg/mL [19–79 pg/mL] versus 95 pg/mL [38–161 pg/mL]; P=0.005) at baseline (Table 2).

NFLG Versus NFHG After AVR

Serial changes in LV and LA structural parameters among patients completing 12-month follow-up after AVR are demonstrated in Table 2. Compared with NFHG, patients with NFLG experienced less extensive reverse LV and LA remodeling, with smaller decrease in LV end-diastolic volume index (−6±11 versus −19±17 mL/m^2; P=0.004), LVMi (−3±10 versus −21±18 g/m^2; P<0.0001), and LAVi (0±8 versus −7±9 mL/m^2; P=0.007; Figure 3). Differences in reverse remodeling between groups resulted in similar LVMi (70±17 versus 72±14, NFHG and NFLG, respectively, P=0.63) and LAVi (52±13 versus 49±12, NFHG and NFLG, respectively,

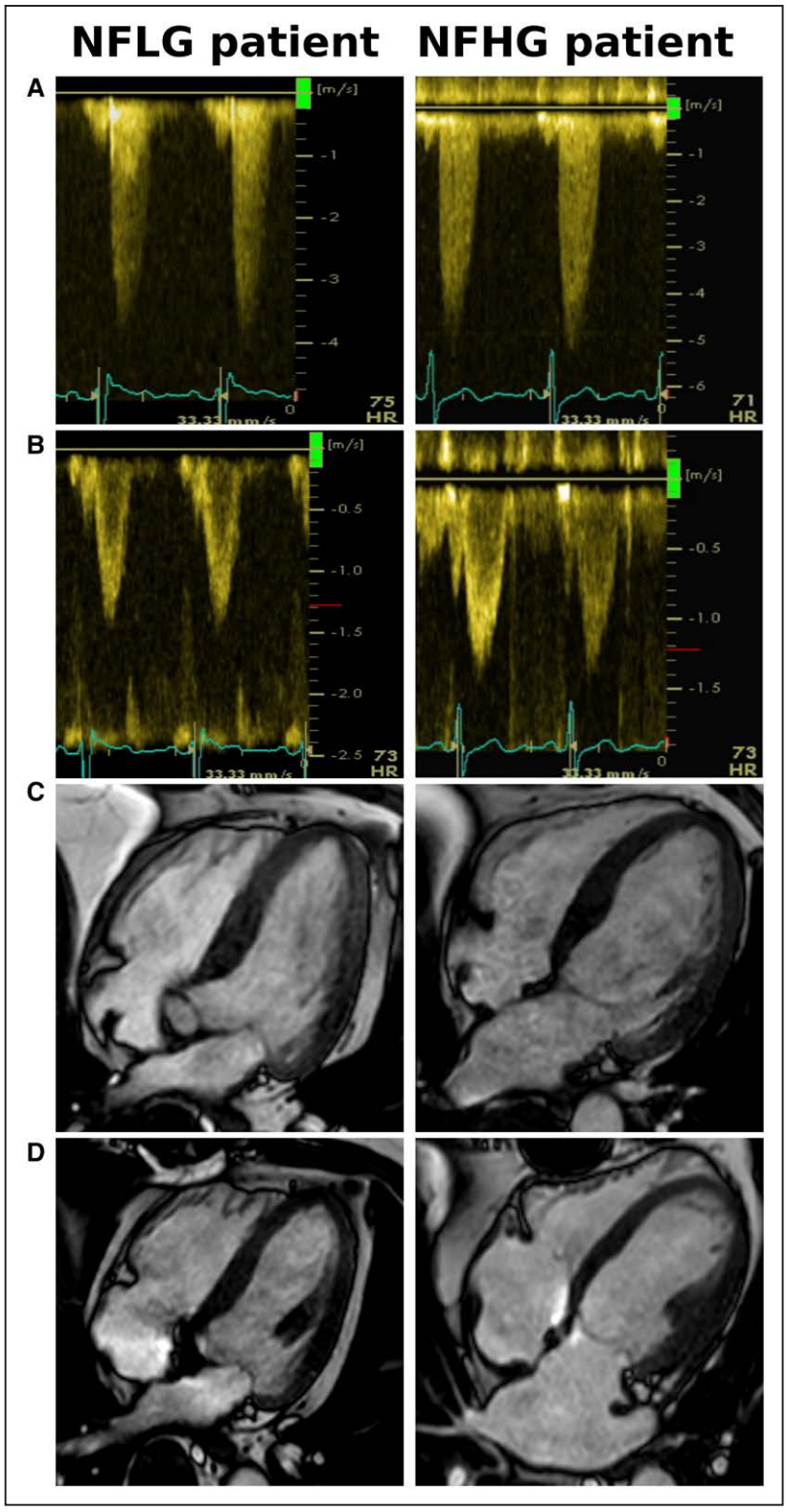

Figure 2. Two patients with normal-flow low-gradient (NFLG) aortic stenosis and normal-flow high-gradient (NFHG) aortic stenosis, respectively, displaying transvalvular gradient (**A**), left ventricular (LV) outflow tract flow (**B**), LV end-diastolic image preoperatively (**C**), and 12 mo post-operatively (**D**) on magnetic resonance imaging. The NFLG patient had mean gradient 37 mm Hg, stroke volume index (SVi) 37 mL/m^2, aortic valve area index (AVAi) 0.45 cm^2/m^2, and LV mass index (LVMi) 77 g/m^2 before surgery while the NFHG patient had mean gradient 70 mm Hg, SVi 51 mL/m^2, AVAi 0.40 cm^2/m^2, and LVMi 105 g/m^2 before surgery.

P=0.40) 12 months after surgery. Changes in MRI LVMi were still different between groups when excluding patients with a low aortic CT calcium score (−2±11 versus −22±18 g/m^2; *P*=0.0001). Both groups experienced similar improvements in global longitudinal strain (−1.2±2.6 versus −1.9±3.4; *P*=0.38) and MR LVEF (1.8±6.7 versus 3.3±8.0; *P*=0.50). Although SVi assessed by MRI was similar between groups after 12 months, there was a significant decrease in MRI SVi in the NFHG group (42±8 versus 38±8; *P*=0.002) but not in the NFLG group (41±9 versus 39±7 mL/m^2; *P*=0.33).

Both groups experienced a significant improvement in symptoms and 6-minute walk test (Figure 3; Table 2). At 6 months, the NFLG group had experienced a smaller improvement in the 6-minute walk test (31±38 versus 61±74 m;

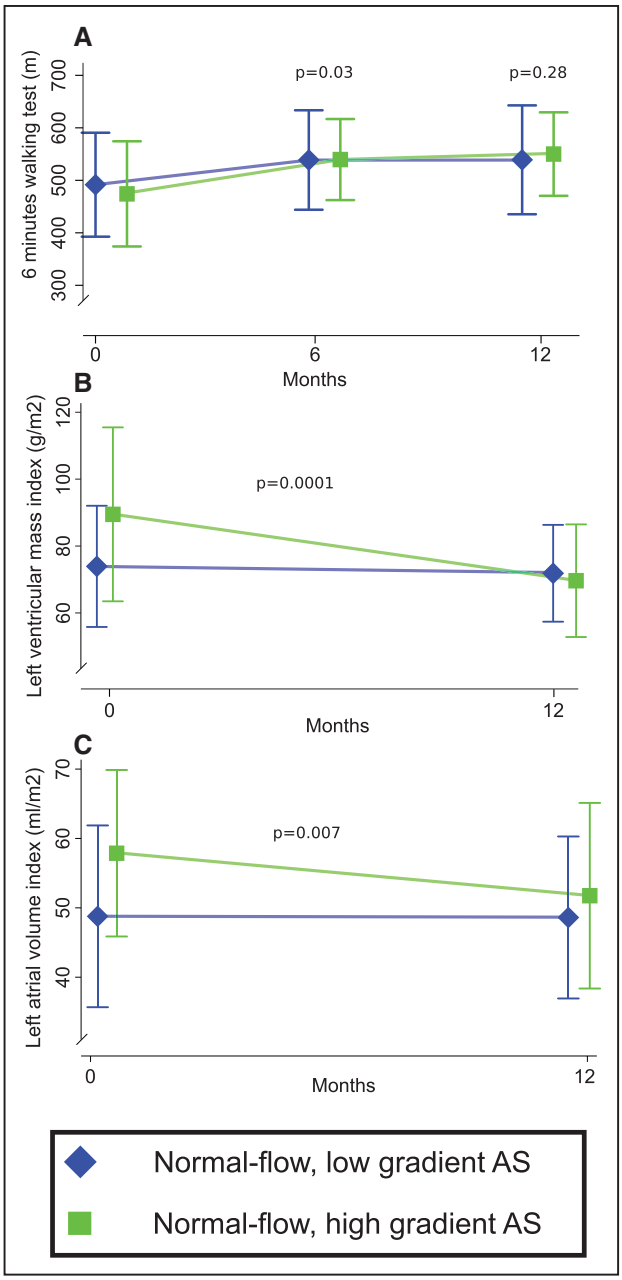

Figure 3. Changes after aortic valve replacement according to preoperative aortic mean gradient in 6-min walk test (**A**), left atrial volume index on magnetic resonance imaging (MRI; **B**), and left ventricular mass index on MRI (**C**). *P* value is difference in change from baseline between groups. AS indicates aortic stenosis.

P=0.03), but this difference did not persist at 12 months (Figure 3). These findings were consistent in the subset of 63 patients undergoing isolated AVR, where patients with NFLG experienced a smaller improvement in 6-minute walk test at 12 months as well (34±36 versus 68±78 m; *P*=0.03). BNP showed a significant decrease in the NFHG group (*P*=0.001) while it was unchanged in the NFLG group. There was a direct negative correlation between the preoperative aortic mean gradient and the postoperative changes in these measures (Figure 4).

In a univariable linear regression analysis NFHG condition, number of antihypertensive drugs, preoperative AVAi, aortic mean gradient, and LVMi at baseline as well as postoperative prosthesis–patient mismatch predicted postoperative changes in LVMi. In a multivariable analysis including the aforementioned variables, including age, sex, hypertension, number of antihypertensive drugs, and LVMi at baseline, only NFHG condition and baseline LVMi associated with changes in LVMi (Table 3). The same analyses were performed excluding patients with ischemic heart disease with consistent findings, except that prosthesis–patient mismatch no longer was a univariate predictor.

Discussion

The present study provides a meticulously examination of changes in LV morphology and functional capacity in patients with NFLG severe AS undergoing AVR. We demonstrate that, compared with NFHG, patients with NFLG are characterized by less severe remodeling and lower levels of circulating BNP before AVR but the same burden of myocardial fibrosis. After AVR, both groups experience a significant improvement in functional capacity and 6-minute walk test. Only patients with NFHG demonstrate significant reverse remodeling and reduction in BNP and patients with NFLG do not.

Although severe AS traditionally has been defined as an AVA <1 cm^2 with a mean gradient ≥40 mm Hg or a peak aortic velocity ≥4 m/s, in clinical practice, it is common for a patient to present with only 1 or 2 of these criteria. During the past decade, there has been great focus on the syndrome of low-gradient severe AS and preserved LVEF. Although low gradients may be the consequence of paradoxical reduced stroke volumes, a subgroup experience low gradients despite apparently preserved stroke volume. This condition (NFLG) has, by some, been proposed to be a condition in the transition from moderate to severe AS[20] and partially explained by inconsistencies in guidelines because an aortic mean gradient of 40 mm Hg better correlates with an AVA of 0.8 cm^2 among patients with normal stroke volume.[21] Consequently, this has led to a discussion of whether the cutoff for severe AS should be changed to AVA <0.8 cm^2.[22]

Consistent with this, we demonstrate that patients with NFLG present with less severe AS, measured by AVAi or aortic valve calcium score on CT, and have less LV hypertrophy and LA dilatation. In addition, we found that myocardial fibrosis assessed by MRI was common in the NFLG group although markers of filling pressure (E/e′ and BNP) were lower than in patients with high gradients. These findings corroborate data from previous studies[5–7] and further extend them because we found that despite differences in remodeling, patients with NFLG tend to have similar symptoms as NFHG patients. The less extensive valvular pathology with less LV/LA remodeling seen in NFLG and suggest that this phenotype of AS is a milder form than NFHG with the same symptom burden. With increased AS severity, valvular resistance leads to pressure overload and increased LV wall stress and consequently LV hypertrophy develops. In the absence of a high aortic mean gradient, it therefore seems reasonable that LV hypertrophy is less severe and consequently one might expect less LV remodeling in patients with NFLG. In line with this, we demonstrate that patients with NFLG present with lower valvuloarterial impedance. We could speculate that the high prevalence of LV

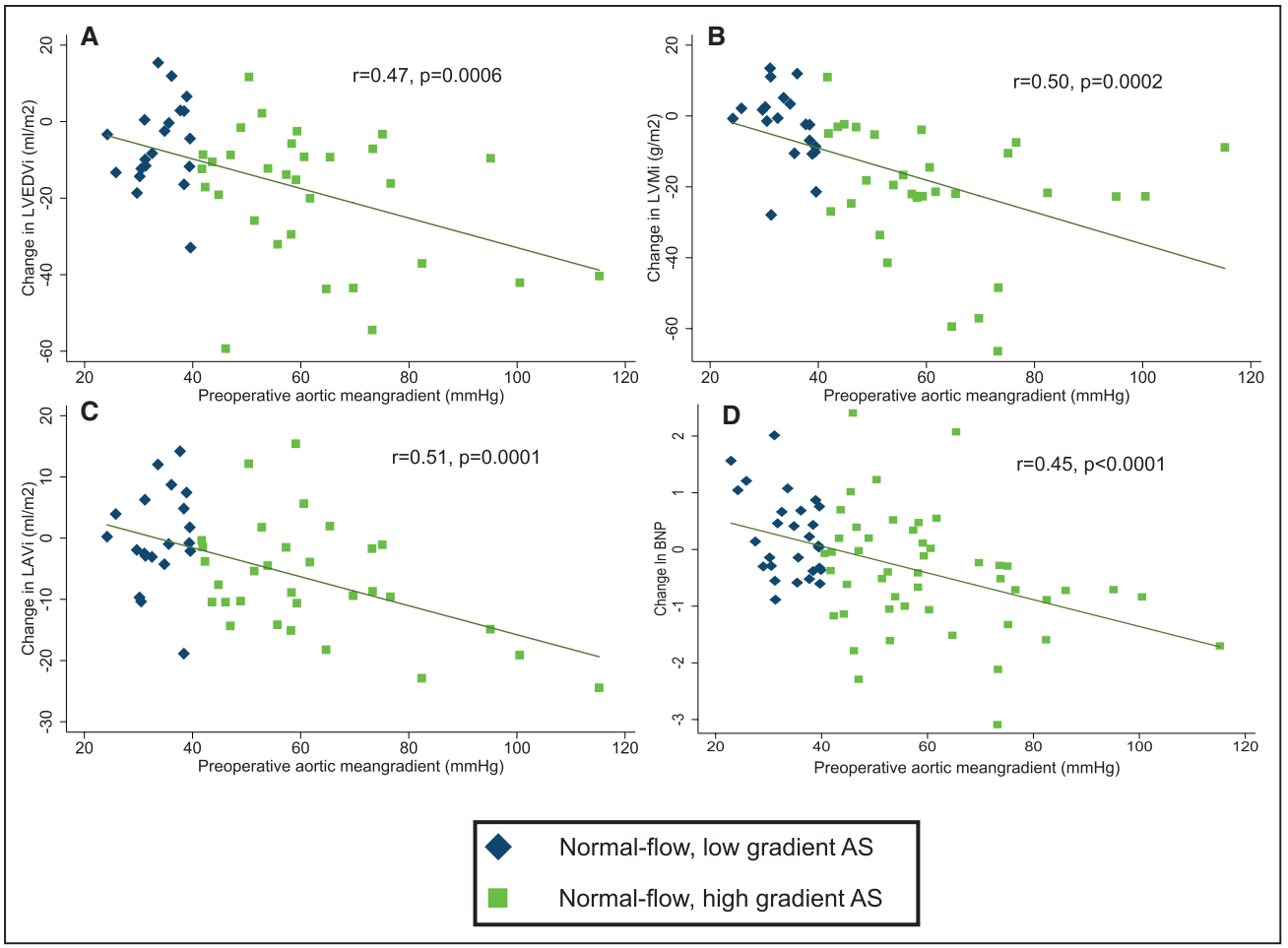

Figure 4. Changes after aortic valve replacement according to preoperative aortic mean gradient in magnetic resonance imaging (MRI) left ventricular end-diastolic volume index (LVEDVI; **A**), MRI left ventricular mass index (LVMI; **B**), MRI left atrial volume index (LAVI; **C**), and in brain natriuretic peptide (BNP; **D**). AS indicates aortic stenosis.

myocardial fibrosis may reflect existing comorbidities, such as hypertension and ischemic heart disease. A previous study found that up to 45% of patients with arterial hypertension have LGE fibrosis on MRI.[23]

In a recent observational study, Berthelot-Richer et al[24] suggested that patients with an AVA between 0.8 and 1.0 cm^2 still benefit from AVR compared with medical therapy and would thus imply that patients with NFLG would benefit from AVR. These assumptions have further been strengthened by a recent meta-analysis demonstrating that in patients with NFLG AS those referred for AVR had a better prognosis than patients treated conservatively.[8] It is thus interesting that we found that reverse remodeling after AVR was heavily influenced by the preoperative aortic mean gradient and that preoperative aortic mean gradient correlated strongly with both changes in LVMi, LAVi, LV end-diastolic volume index, and BNP. Consequently, patients with NFLG did not show the same benefit in terms of reduction in LVMi or LAVi as NFHG although baseline differences in LV remodeling between groups equipoised 12 months after surgery. This demonstrates that when LV remodeling is caused by a highly calcified aortic valve and resulting LV pressure overload, reduction of LV afterload by AVR will generate a significant postoperative reverse remodeling. We were unable to demonstrate an association between preoperative valvular gradients and symptom improvement after AVR. Although one could speculate that this improvement is driven by concomitant coronary revascularization, consistent findings were found in the subgroup of patients undergoing isolated AVR. The finding that patients demonstrate similar functional capacity and LV remodeling patterns 12 months after surgery may thus suggest that NFLG despite less severe than NFHG AS benefit equally from AVR.

The calculation of AVAi and SVi on echocardiography assumes that the LV outflow tract is circular in shape while it is often oval in real life. This can lead to underestimation of both true SVi and AVAi potentially explaining the mismatch between gradients and AVA. Accordingly, it has been suggested to measure the LVOT diameter at the level of the annulus.[25] Thus, this may have led to overestimation of severity of AS in some patients in the present study. Pulse wave spectra measured at the LV outflow tract may also be subject to error, if measured to close to the prestenotic flow acceleration, significant spectral broadening may be seen with overestimation of stroke volume. If measured too distant from the aortic valve underestimation of stroke volume may occur. Although we think the quality of echocardiograms in this study was

Table 3. Uni- and Multivariable Linear Regression Analysis for Predictors of Postoperative Change in Left Ventricular Mass Index From Baseline to 12 Months

	Univariate Analysis		Multivariate Analysis	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Age, y	0.0 (–0.7 to 0.8)	0.95	–0.3 (–0.7 to 0.2)	0.20
Male gender	–7 (–17 to 4)	0.21	–3 (–10 to 4)	0.37
Hypertension	10 (–1 to 20)	0.07	–7 (–18 to 4)	0.20
No. of hypertensive drugs	6 (0.5 to 12)	0.03	5 (–1 to 12)	0.10
Diabetes mellitus	–1 (–14 to 12)	0.88		
Ischemic heart disease*	0 (–11 to 11)	0.99		
Systolic blood pressure, mm Hg	–0.1 (–0.4 to 0.2)	0.55		
AVAi (per 0.01 cm/m^2)	1.0 (0.5 to 1.4)	<0.001	0.1 (–0.2 to 0.5)	0.49
Aortic mean gradient, mm Hg	–0.5 (–0.7 to –0.2)	0.002		
NFHG	–20 (–28 to –10)	<0.001	–5 (–9 to –2)	0.005
Moderate-severe PPM	16 (3 to 29)	0.02	6 (–3 to 14)	0.17
LVMi baseline	–0.6 (–0.7 to –0.4)	<0.001	–0.4 (–0.6 to –0.3)	<0.001

AVAi indicates aortic valve area index; CI, confidence interval; LVMi, left ventricular mass index; NFHG, normal-flow high-gradient aortic stenosis; and PPM, prosthesis–patient mismatch.

*Ischemic heart disease: history of coronary angioplasty, myocardial infarction, or significant lesions on coronary angiogram.

adequate, there may be cases where stroke volume estimation may have led to misclassification of patients. We found a weak association between SVi measured by echocardiography and MRI, similar to the findings of others,[26] and consequently some patients had low SVi according to our MRI assessment assuming that the cutoff is <35 mL/m^2. The weak association between the 2 modalities underlines the limitations of echocardiographic assessment of SVi. However, our MRI data show that there is no trend toward lower SVi in the NFLG groups compared with the NFHG group, and it is, therefore, unlikely that misclassification by echocardiography influenced one group more than the other.

Arterial hypertension is another issue that should be considered because increased arterial resistance may reduce and hence mask the aortic mean gradient. A study treated patients with low-gradient and severe arterial hypertension by infusion of sodium nitroprusside, causing an increase in both AVA and mean gradient, while reducing LV end-diastolic pressure and arterial blood pressure.[27] Conversely, in an animal study, increasing blood pressure reduced mean gradient.[28] Arterial hypertension should, therefore, be considered and possibly treated before reassessing the severity of AS. In our population, a larger proportion of patients with NFLG were being treated with ≥1 antihypertensive drugs, but neither hypertension nor number of antihypertensive drugs were independently associated with change in LVMi. Furthermore, because there was no difference in blood pressure between the 2 groups during echocardiography, we do not think hypertension has affected our echocardiographic measurements more in one group than the other.

Patients with NFLG are in the range between moderate and severe AS, and 50% percent of these may have hemodynamically severe stenosis.[18] Clavel et al[18] have shown that among patients with NFLG, CT calcium scoring of the aortic valve can help distinguish patients with true severe AS from patients with a less severe AS. It could thus be an option to recommend CT calcium scoring in patients with NFLG, especially when there seems to be incoherence between symptoms and severity of AS.

NFLG share some similarities with paradoxical low-flow low-gradient AS. The latter have a low gradient despite low AVA and share a high prevalence of ischemic heart disease, diabetes mellitus, and hypertension.[3,4,7] But it is crucial to distinguish between these 2 groups for several reasons. Patients with paradoxical low-flow low-gradient AS have a distinct pattern of concentric remodeling with high relative wall thickness, reducing LV intracavitary volume, and SVi[5,29] but also worse diastolic function and higher levels of BNP.[2,29] Importantly, low-flow low-gradient AS carry a much worse prognosis.[2,8,20]

Clinical Implications

The present study indicates that NFLG represent a milder phenotype of AS who are nonetheless equally symptomatic but gain less benefit of AVR in terms of reverse remodeling as patients with NFHG. Because they show the same degree of symptom improvement after surgery and LVMi in patients with NFHG and NFLG after 1 year is the same, our study suggests that they still benefit from AVR. If symptom status is unclear, cardiopulmonary exercise testing would be advisable,[30] and if they have insufficiently treated hypertension, optimal treatment of this could be considered before re-evaluation.

Limitations

A significant proportion of patients underwent concomitant coronary artery bypass graft alongside their AVR, and the risk that their operation was driven by the need for

revascularization instead of the need for a new valve exists. However, we only included patients where we assessed that the operation was driven by AVR. After the inclusion period had ended, preoperative data from all included patients with concomitant coronary artery bypass graft were re-evaluated by 2 independent investigators to make sure that this premise was still fulfilled. A larger proportion of patients in the NFLG group had a history of stroke. Although these were all minor strokes without significant disability, we cannot entirely exclude that prior stroke influenced functional improvement in this group.

Three patients died before follow-up (2 had NFHG, 1 NFLG), all within 30 days post-operatively. Furthermore, 8 patients survived but did not complete one or both follow-up visit, 5 had NFHG and 3 had NFLG. The reasons for not participating in follow-up visits were all noncardiac. Patients without complete data because of death or missing follow-up visits had a higher Euroscore 2 (1.6 [1.1–5.7] versus 1.2 [0.9–2.0]; P=0.03) than patients who completed all visits. Otherwise, the groups were similar with regards to echocardiography, CT, and MRI.

This study was performed on a relatively small cohort, and the risk of type 2 errors therefore exists. Furthermore, patients with atrial fibrillation were excluded, and our findings can, therefore, not be extended to these patients.

Conclusion

NFLG is common among patients being referred for AVR. This condition is associated with less LV hypertrophy despite similar myocardial fibrosis, smaller LA size, and less calcified aortic valves compared with patients with NFHG. After surgery, patients with NFLG experience less reverse remodeling but the same symptomatic benefit.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Although the severity of aortic stenosis (AS) patients with a low valve area (<1.0 cm^2) and moderately elevated mean gradient (20–40 mm Hg) despite normal stroke volume (≥35 mL/m^2; normal-flow low-gradient AS) is highly controversial, it is a common challenge in daily clinical practice. According to their valve area, they have severe AS, but according to their mean gradient, they only have moderate AS. This prospective study meticulously examines left ventricular remodeling and functional capacity among patients with normal-flow low-gradient aortic stenosis before and after aortic valve replacement. We find that these patients, despite being severely symptomatic, have clear indications of less severe aortic stenosis and left ventricular remodeling but with a high degree of myocardial fibrosis. After surgery, they show a clear symptomatic and functional benefit although they have less reverse remodeling than patients with high-gradient AS. Our study, therefore, supports aortic valve replacement in these patients when symptoms are evident.

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Postoperative Reverse Remodeling and Symptomatic Improvement in Normal-Flow Low-Gradient Aortic Stenosis After Aortic Valve Replacement

Rasmus Carter-Storch, Jacob E. Møller, Nicolaj L. Christensen, Akhmadjon Irmukhadenov, Lars M. Rasmussen, Redi Pecini, Kristian A. Øvrehus, Eva V. Søndergård, Niels Marcussen and Jordi S. Dahl

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