Impact of Obesity on Persistent Left Ventricular Hypertrophy After Aortic Valve Replacement for Aortic Stenosis

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Normalization of left ventricular (LV) hypertrophy is expected after successful aortic valve replacement (AVR) in patients with aortic valve stenosis (AS), but is not always observed. We tested the impact of body mass index (BMI) ≥30 kg/m^2 on persistent post-AVR LV hypertrophy. In the present subanalysis of Simvastatin Ezetimibe in Aortic Stenosis study, clinical and echocardiographic data of 399 patients with severe AS who underwent surgical AVR were analyzed. All patients had a standardized pre- and post-AVR echocardiogram. Patients were grouped by BMI categories into BMI <25 kg/m^2, BMI 25 to 29.9 kg/m^2, and BMI ≥30 kg/m^2. LV hypertrophy was defined as LV mass/height$^{2.7}$ >49.2 g/m$^{2.7}$ in men and >46.7 g/m$^{2.7}$ in women. Predictors of persistent LV hypertrophy after AVR were identified in logistic regression analysis. After a median follow-up of 196 days after AVR, LV hypertrophy was more prevalent in patients with BMI ≥30 kg/m^2 compared with those with BMI 25 to 29.9 kg/m^2 and those patients with BMI <25 kg/m^2 (71% vs 47% and 37%, p <0.01). BMI ≥30 kg/m^2 patients also remained with lower LV midwall shortening post-AVR compared with patients with normal weight (p <0.01), independent of patient prosthesis mismatch. In multivariable logistic regression analysis, the presence of BMI ≥30 kg/m^2 before AVR was associated with an almost fourfold higher prevalence of post-AVR LV hypertrophy independent of significant associations with higher systolic blood pressure and lower LV midwall shortening preoperatively (odds ratio 3.75 [95% confidence interval 2.04 to 6.91], p <0.001). In conclusion, the presence of BMI ≥30 kg/m^2 before AVR in patients with severe AS was strongly and independently associated with persistent post-AVR LV hypertrophy. **(Am J Cardiol 2019;123:942−947)**

Aortic valve stenosis (AS) is a progressive disease that causes chronic pressure overload on the left ventricle, and induces structural and functional changes in the left ventricular (LV) myocardium.[1,2] Concomitant hypertension, obesity, and metabolic syndrome have all been shown to increase myocardial fibrosis and LV hypertrophy during progression of AS.[3−6] LV hypertrophy has been documented as an independent risk factor for impaired prognosis both during AS progression and after aortic valve replacement (AVR) in AS patients.[7−9] Following a successful AVR in AS patients, regression of LV hypertrophy is expected but may not always occur. Systemic hypertension and male gender have both been associated with reduced post-AVR regression of LV hypertrophy in AS patients.[10−12] In smaller studies focusing on the association of preoperative myocardial gene expression with post-AVR regression of LV hypertrophy, a negative impact of higher preoperative body mass index (BMI) on the postoperative LV hypertrophy regression was noted.[13,14] However, the influence of BMI ≥30 kg/m^2 on postoperative LV hypertrophy regression in AS patients has not been reported from larger clinical studies. Thus, the aim of the present study was to assess the association of overweight (BMI 25 to 29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) with persistent post-AVR LV hypertrophy in symptomatic severe AS patients treated with surgical AVR.

Methods

The present post hoc substudy was based on clinical and echocardiographic data from patients enrolled in the large prospective Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study who developed severe symptomatic AS during the study follow-up period, and subsequently underwent surgical AVR. The SEAS study was a randomized clinical control trial investigating the effect of combined treatment with Simvastatin 40 mg and ezetimibe 10 mg/day on progression of AS and associated cardiovascular events in patients with initially mild-to-moderate AS. Patients with preexisting coronary heart disease, heart failure, diabetes mellitus, or other severe preexisting conditions were not

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included in the SEAS study.[15] Ethical committees in all participating countries approved the SEAS study protocol, and patients signed written informed consent.[16]

Of the 1,873 patients enrolled in the SEAS study in 173 study centers within Europe, 545 patients underwent surgical AVR. Among these, a post-AVR follow-up echocardiogram was sent for blinded expert analysis at the SEAS core echocardiography laboratory in Haukeland University Hospital, Bergen, Norway in 456 patients. In a total of 57 patients, LV mass could not be assessed both on the pre- and post-AVR echocardiograms due to poor image quality in parasternal views. The remaining 399 patients were included in the present analysis. Patients were grouped according to BMI values measured at the pre-AVR clinical visit into normal weight (BMI <25 kg/m^2), overweight (BMI ≥25 kg/m^2 and <30 kg/m^2) and obesity (BMI ≥30 kg/m^2). Hypertension was defined as a history of hypertension, use of antihypertensive treatment, or clinical brachial blood pressure ≥140/90 mm Hg measured at the baseline clinical SEAS study visit.[4]

All echocardiograms used in the present study were first read by the same junior investigator (EE), and later proofread by an experienced investigator (EG).[15,16] Quantitative assessment of LV structure and function and AS severity was performed in accordance with current guidelines.[1,17] LV hypertrophy was defined using the prognostically validated cut-off values LV mass/height$^{2.7}$ >49.2 g/m$^{2.7}$ in men and >46.7 g/m$^{2.7}$ in women.[7] LV relative wall thickness was calculated as posterior wall thickness × 2/LV internal diameter in end-diastole, and considered increased if ≥0.43. LV geometry was categorizing from LV relative wall thickness and LV hypertrophy in combination, identifying concentric remodeling as increased LV relative wall thickness in patients with normal LV mass, and patients with LV hypertrophy as having eccentric and concentric hypertrophic patterns, respectively, depending on normal or increased LV relative wall thickness. Severe patient prosthesis mismatch was defined as an indexed effective orifice area ≤0.65 cm^2/m^2.[18]

Statistical analysis was performed using IBM SPSS version 24.0 (IBM, Armonk, New York). Findings are reported as mean with standard deviation for continuous variables and as percentages for categorical variables. Analysis of variance (ANOVA) with Scheffe's post hoc test for continuous variables and Sidak post hoc test for categorical variables was used to compare BMI groups, as appropriate. Covariates of persistent LV hypertrophy at the post-AVR echocardiogram were identified in uni- and multivariable logistic regression analyses, and reported as odds ratio (OR) and 95% confidence interval. A 2-tailed p value <0.05 was considered statistically significant in all analyses.

Results

Mean age in the total study population was 66 ± 9 years and 64% were male. BMI groups did not differ in blood pressure, age, or gender, but prevalence of hypertension increased in parallel with BMI (Table 1). The post-AVR echocardiogram was taken after a median of 196 days (mean 208 ± standard deviation 157 days). The post-AVR follow-up time did not differ between BMI groups. The prevalence of LV hypertrophy decreased in all groups from the pre-AVR to the post-AVR echocardiogram, but remained significantly higher in patients with BMI ≥30 kg/m^2 (p <0.01; Figure 1). In particular, eccentric hypertrophy was more prevalent among patients with BMI ≥30 kg/m^2 at the post-AVR echocardiogram (Table 2). Both patients with BMI 25 to

Table 1
Pre-AVR clinical characteristics of the BMI <25, BMI 25 to 29.9, and BMI ≥30 groups

	Body mass index (kg/m^2)			
Variable	<25 (n = 163)	25–29.9 (n = 154)	≥30 (n = 82)	ANOVA p
Age (years)	67 ± 10	65 ± 9	65 ± 9	0.052
Women	40%	34%	35%	0.525
Systolic blood pressure (mm Hg)	139 ± 20	140 ± 18	141 ± 18	0.358
Diastolic blood pressure (mm Hg)	78 ± 10	80 ± 10	80 ± 10	0.141
Heart rate (beats/min)	69 ± 12	70 ± 12	71 ± 13	0.567
Body surface area (m^2)	1.78 ± 0.16	1.95 ± 0.18*	2.01 ±0.19*,†	<0.001
BMI (kg/m^2)	22.8 ± 1.6	27.4 ± 1.4*	33.3 ± 3.1*,†	<0.001
Height (meters)	1.71 ± 0.1	1.72 ± 0.1	1.70 ± 0.1	0.243
Weight (kg)	68 ± 10	81 ± 11	95 ± 14	<0.001
Hypertension	77%	84%	89%	0.043
Serum creatinine (mg/dl)	1.0 ± 0.2	1.04 ± 0.2	1.0 ± 0.2	0.308
Total cholesterol (mg/dl)	181 ± 54	185 ± 54	178 ± 46	0.586
HDL cholesterol (mg/dl)	66 ± 15	58 ± 15*	50 ± 15*,†	<0.001
LDL cholesterol (mg/dl)	101 ± 50	104 ± 50	101 ± 46	0.376
Triglycerides (mg/dl)	88 ± 35	106 ± 53*	133 ± 53*,†	<0.001
Concomitant CAD requiring CABG	37%	30%	26%	0.185
Smoking	26%	21%	11%*	0.038

AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

* p <0.01 vs normal weight group.

† p <0.05 vs overweight group.

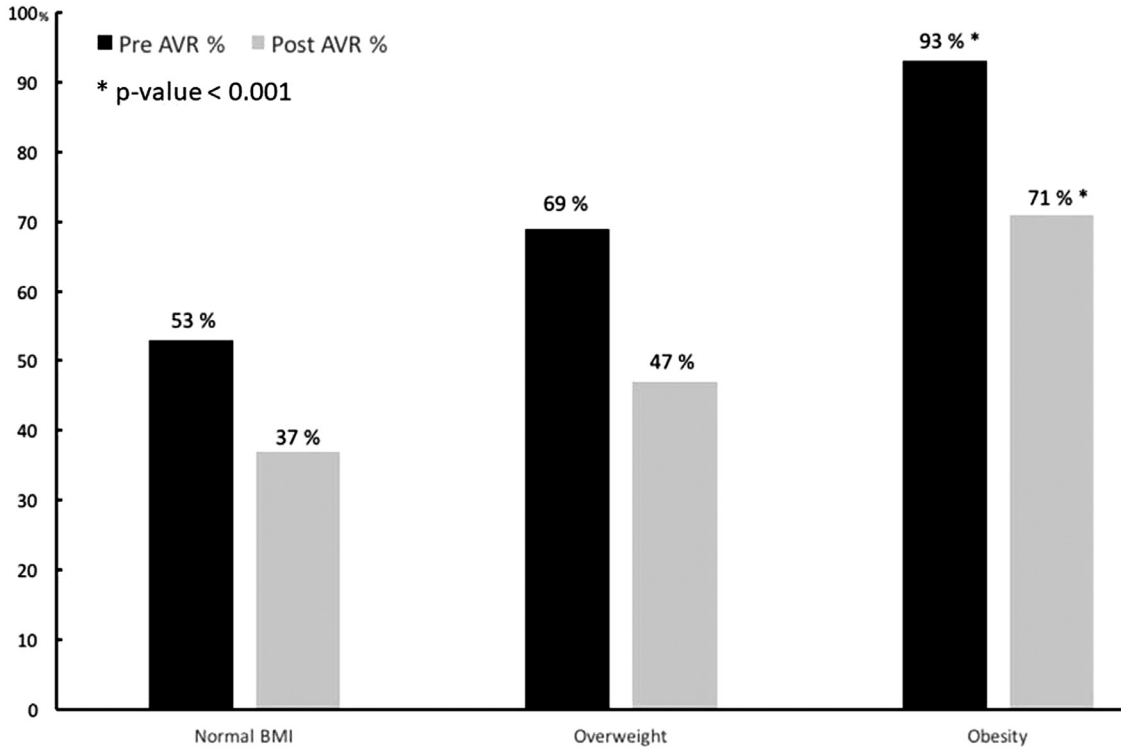

Figure 1. Prevalence of LV hypertrophy in obese, overweight, and normal weight groups at the pre- and post-AVR echocardiograms.

29.9 kg/m^2 and patients with BMI ≥30 kg/m^2 had significantly higher LV mass at the post-AVR echocardiogram compared with those with normal BMI. Patients with BMI ≥30 kg/m^2 also had significantly lower midwall shortening compared with patients with normal weight (Table 2). The mean change in LV mass after AVR did not differ between groups (11% reduction in the BMI ≥kg/m^2 30 group, 10% reduction in the BMI 25 to 29.9 kg/m^2 group and 10% reduction in the BMI <25 kg/m^2 group, p = 0.945). The prevalence of severe patient prosthesis mismatch did not differ between BMI groups (Table 2). The prevalence of persistent post-AVR LV hypertrophy did not differ by gender (46.2% for women and 48.8% for men, p = 0.67).

In univariable logistic regression analyses, persistent post-AVR LV hypertrophy was significantly associated with presence of BMI ≥30 kg/m^2, lower midwall shortening, and higher systolic blood pressure (all p <0.05), but not with gender, age, mean transprosthetic gradient, duration of days post-AVR follow-up echocardiography or presence of severe patient-prosthesis mismatch (all p >0.05; Table 3). In a multivariable logistic regression analysis, BMI ≥30 kg/m^2, but not BMI 25 to 29.9 kg/m^2, was associated with persistent post-AVR LV hypertrophy independent of significant associations with higher pre-AVR systolic blood pressure and lower midwall shortening (all p <0.05; Table 3). Multicolinearity was ruled out in a parallel linear regression model with post-AVR LV mass as a dependent variable and including the same independent variables. All variables had a high tolerance >0.96 and variance of inflation factor was <1.1 for all variables. Replacing pre-AVR with post-AVR BMI class in an alternative model yielded similar results (data not shown).

Discussion

The present post hoc substudy from the SEAS study focused on the impact of preoperative BMI ≥30 kg/m^2 on persistent LV hypertrophy after surgical AVR for severe AS. As demonstrated, BMI ≥30 kg/m^2 was strongly associated with LV hypertrophy and lower LV systolic myocardial function postoperatively, even after adjustment for important confounders including systolic blood pressure, and lower midwall shortening. These findings add to previous knowledge focusing on the impact of obesity on LV remodeling in preoperative studies in AS patients.[3,5,6,19]

Previous studies have documented the importance of LV hypertrophy regression for long-term postoperative prognosis.[9,20] The present study expands previous findings from smaller studies by documenting that BMI ≥30 kg/m^2 may independently impair normalization of LV mass during the first 6 months after surgical AVR for AS.[13,14] Biederman et al demonstrated using cardiac magnetic resonance imaging that although LV mass regression may continue up to 4 years after surgical AVR, it primarily may occur within the first 6 postoperative months.[21]

Obesity is associated with cardiac steatosis and induces LV hypertrophy through a number of hemodynamic and nonhemodynamic mechanisms.[22] In patients with AS, obesity has been shown to increase myocardial fibrosis and lead to more pathological remodeling during progression of AS.[3,6] The extent of myocardial fibrosis whether quantified

Table 2
Findings in BMI <25, BMI 25 to 29.9, and BMI ≥30 groups on the pre- and postaortic valve replacement echocardiogram

	Body mass index (kg/m^2)								
Pre-AVR variable	<25 (n = 163)	25-29.9 (n = 154)	≥30 (n = 82)	ANOVA p	Post-AVR variable	<25 (n = 163)	25-29.9 (n = 154)	≥30 (n = 82)	ANOVA p
Aortic annulus (cm)	2.26 ± 0.30	2.32 ± 0.30	2.33 ± 0.27	0.087	Aortic annulus (cm)	2.17 ± 0.25	2.21 ± 0.28	2.21 ± 0.24	0.241
LV end-diastolic diameter (cm)	4.72 ± 0.68	4.87 ± 0.71*	4.88 ± 0.69*	0.094	LV end-diastolic diameter (cm)	4.64 ± 0.58	4.90 ± 0.63*	4.95 ± 0.67*	<0.001
LV end-systolic diameter (cm)	3.11 ± 0.67	3.20 ± 0.68*	3.28 ± 0.72*	0.163	LV end-systolic diameter (cm)	3.08 ± 0.54	3.33 ± 0.59*	3.38 ± 0.64*	<0.001
Septal wall thickness (cm)	1.35 ± 0.28	1.43 ± 0.27	1.56 ± 0.30*,†	<0.001	Septal wall thickness (cm)	1.34 ± 0.28	1.36 ± 0.30	1.51 ± 0.35*,†	<0.001
Posterior wall thickness (cm)	1.07 ± 0.17	1.13 ± 0.20	1.21 ± 0.23*,†	<0.001	Posterior wall thickness (cm)	0.91 ± 0.20	0.95 ± 0.19	1.04 ± 0.22*,†	<0.001
LV mass index (g/m$^{2.7}$)	50.1 ± 13.5	57.6 ± 15.0*	67.1 ± 17.9*,†	<0.001	LV mass index (g/m$^{2.7}$)	44.8 ± 11.9	50.6 ± 14.2*	60.7 ± 18.3*,†	<0.001
Midwall LV shortening (%)	13.7 ± 2.9	13.5 ± 2.9	12.3 ± 2.4*,†	0.001	Midwall LV shortening (%)	12.5 ± 2.3	12.2 ± 2.2	11.5 ± 2.1*	0.003
Relative wall thickness	0.46 ± 0.10	0.48 ± 0.13	0.51 ± 0.14*	0.015	Relative wall thickness	0.40 ± 0.10	0.40 ± 0.10	0.43 ± 0.12	0.036
Ejection fraction (%)	63 ± 8	63 ± 8	62 ± 10	0.154	Ejection fraction (%)	61 ± 6	60 ± 6	60 ± 7	0.333
Peak aortic jet velocity (m/s)	4.20 ± 0.63	4.06 ± 0.62	4.13 ± 0.63	0.174	Peak aortic jet velocity (m/s)	2.23 ± 0.47	2.22 ± 0.52	2.28 ± 0.51	0.565
Mean transaortic gradient (mm Hg)	44 ± 13	41 ± 13	43 ± 13	0.066	Mean transaortic gradient (mm Hg)	10 ± 5	11 ± 5	11 ± 5	0.281
Aortic valve area (cm^2)	0.92 ± 0.37	1.04 ± 0.42*	0.99± 0.39	0.039	Aortic valve area (cm^2)	1.84 ± 0.91	1.87 ± 0.75	1.86 ± 0.66	0.949
Normal LV geometry	21%	14%	2%*	<0.001	Normal LV geometry	47%	40%	22*,†	0.001
Concentric remodeling	26%	17%	5%*,†	<0.001	Concentric remodeling	15%	13%	7%	0.232
Eccentric hypertrophy	22%	25%	34%	0.131	Eccentric hypertrophy	22%	29%	43%*	0.006
Concentric hypertrophy	31%	44%	59%*	<0.001	Concentric hypertrophy	16%	18%	28%	0.057
					Severe patient prosthesis mismatch	17%	20%	18%	0.599

AVR = aortic valve replacement; LV = left ventricular.
* p <0.01 vs normal weight group.
† p <0.05 vs overweight group.

Table 3
Impact of BMI ≥30 on persistent post-AVR LV hypertrophy, uni- and multivariable logistic regression analyses

	Univariable		Multivariable	
Variable	OR (95% CI)	p	OR (95% CI)	p
BMI ≥ 30	4.18 (2.32-7.52)	< 0.001	3.75 (2.04-6.91)	<0.001
BMI 25-29.9	1.48 (0.95-2.33)	0.086	1.47 (0.93-2.35)	0.102
Pre-AVR systolic blood pressure (mm Hg)	1.02 (1.01-1.03)	0.003	1.02 (1.01-1.03)	0.003
Pre-AVR midwall shortening	0.89 (0.83-0.96)	0.002	0.90 (0.83-0.97)	0.008
Baseline hypertension	1.47 (0.87-2.49)	0.149		
Post-AVR days	1.00 (0.99-1.00)	0.963		
Mean trans-prosthetic gradient (mm Hg)	1.02 (0.98-1.07)	0.256		
Age (years)	1.00 (0.98-1.02)	0.965		
Men	1.11 (0.74-0.68)	0.615		
Severe patient prosthesis mismatch	0.66 (0.38-1.14)	0.133		

BMI = body mass index.

by magnetic resonance imaging or histopathology has been associated with less LV functional improvement as well as increased late mortality after AVR for AS.[23] A nonlinear relation with BMI and 30-day and long-term mortality was reported by Roberts et al, demonstrating that patients treated with AVR for AS with BMI >40 kg/m^2 and in the mid-20s had significantly higher mortality rates compared with patients with BMI in the early 30s.[24] Recently, it was demonstrated by cardiac magnetic resonance spectroscopy also that severe AS is associated with myocardial steatosis.[25] This cardiac steatosis may saturate the beta-oxidative system, and fatty acids may by nonoxidative pathways lead to myocardial fibrosis and altered myocardial structure and function.[6] While post-AVR pressure-overload relief leads to reduction of the cardiomyocyte hypertrophy, nonmuscular myocardial components, including the obesity associated interstitial fat infiltration and accumulation of triglycerides in the contractile elements, will not be reduced, leading to persistent LV hypertrophy in these patients, as demonstrated by the present findings.[22] Our findings are in line with a recent report by Treibel et al demonstrating by cardiac magnetic resonance imaging that post-AVR regress of nonmuscular myocardial LVH in AS mainly took place after the first 6 postoperative months.[26]

In the SEAS-study, BMI ≥30 kg/m^2 was associated with higher LV mass, LV systolic dysfunction, and increased mortality during progression of AS.[3,19] The Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin study also linked obesity and metabolic syndrome with presence of impaired LV diastolic and systolic function, and reported that patients with obesity had significantly more concentric LV hypertrophy.[5] In contrast, BMI ≥30 kg/m^2 was particularly associated with persistent eccentric LV hypertrophy in the present post-AVR study. The contrasting findings may reflect that AVR effectively reduce pressure overload caused by the valvular obstruction in AS, whereas LV effects of concomitant obesity or hypertension are not influenced. Our findings expand previous knowledge by demonstrating the influence of BMI ≥30 on persistent LV hypertrophy and myocardial LV dysfunction after surgical AVR for severe AS.

Previous data from our group demonstrated that uncontrolled hypertension is associated with lack of improvement in postoperative exercise capacity in AS patients.[10] Imanaka et al also reported the importance of postoperative blood pressure control on regression of LV mass.[27] In the present study, no association between hypertension and post-AVR LV hypertrophy was found, but higher pre-AVR systolic blood pressure was associated with persistent post-AVR LV hypertrophy independent of presence of BMI ≥30 kg/m^2.

Prosthesis-patient mismatch is commonly found after surgical AVR for AS and associated with impaired post-AVR LV hypertrophy regression and prognosis, in particular in patients with impaired preoperative LV function.[18,28] In the present study, the prevalence severe prosthesis-patient mismatch did not differ between groups, and no significant association with persistent post-AVR LV hypertrophy was found.

Circulating female estrogens have been proposed to influence micro ribonucleic acid expression in collagens synthesis,[29] explaining the previous reported gender difference in LV remodeling during progression of AS.[2] In the present study, no association between gender and persistent post-AVR LV hypertrophy was observed, in line with previous findings by Dobson et al assessing LV structure by cardiac magnetic resonance imaging.[30] In contrast, among AS patients treated with transcatheter AVR (TAVR) in the PARTNER (Placement of Aortic Transcatheter Valves) study, women were reported to have significantly better post-TAVR reduction in LV mass compared with men which translated into lower incidence of rehospitalization for heart failure.[12] However, the majority of these patients had persistent LV hypertrophy at the 30-day post-TAVR echocardiogram.

In conclusion, the present findings expand current knowledge by demonstrating that preoperative BMI ≥30 in AS patients without known diabetes or cardiovascular disease is an independent and important contributor for persistent post-AVR LV hypertrophy.

Disclosures

JBC and EG were members of the scientific steering committee of the SEAS study and received honoraria for this work in the period 2002 to 2008. EE, DC, HM and SS have no conflicts of interest to disclose.

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