Impact of Metabolic Syndrome and/or Diabetes Mellitus on Left Ventricular Mass and Remodeling in Patients With Aortic Stenosis Before and After Aortic Valve Replacement

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In aortic stenosis (AS), metabolic syndrome (MetS), and diabetes mellitus (DM) are associated with more pronounced left ventricular (LV) hypertrophy and more concentric remodeling. We aimed to assess the impact of MetS and DM on LV mass, remodeling, and LV mass regression after aortic valve replacement (AVR) in patients with severe AS. We included 177 patients with severe AS and preserved LV ejection fraction (>50%). All patients underwent a complete echocardiogram before and 1 year after AVR. Forty-seven (27%) patients had MetS, 37 (21%) DM, and 93 (52%) neither MetS nor DM (No MetS-DM). Before AVR, indexed LV mass was higher in MetS and DM groups compared with No MetS-DM group (56.1 ± 14.2, 56.2 ± 18.2 vs 49.2 ± 14.1 g/m$^{2.7}$, respectively; p < 0.01). Prevalence of LV hypertrophy was higher in MetS and DM than in No MetS-DM patients (66%, 65% vs 44%, p < 0.01) as well as LV mass to end-diastolic volume ratio (2.10 ± 0.44 and 2.21 ± 0.63 vs 1.96 ± 0.41 g/ml, respectively, p = 0.03). After multivariate analysis, DM and MetS were independently associated with higher baseline LV mass (p < 0.05). One year after AVR, decrease in LV mass was significant (p < 0.001) in all 3 groups. MetS was independently associated with less LV mass regression and higher LV mass 1 year after AVR. Therefore, MetS and DM patients showed more residual LV hypertrophy than those with No MetS-DM (57%, 38%, and 17%, p < 0.01). In conclusion, MetS and DM were associated with higher preoperative LV mass, more LV hypertrophy, and more concentric remodeling. One year after AVR, MetS showed less significant LV mass regression and both DM and MetS persisted with more residual LV hypertrophy.
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Aortic stenosis (AS) is the most prevalent valvular disease in high-income countries, and it represents a major healthcare problem.[1] It is characterized by progressive narrowing of the aortic valve area, which generates an increased afterload on the left ventricle (LV). The hypertrophy that develops in response to afterload augmentation initially restores wall stress but ultimately becomes maladaptive[1] and is associated with increased mortality.[2,3] Metabolic syndrome (MetS), a cluster of metabolic abnormalities related with visceral obesity, is linked with faster progression of valve disease,[4] increased LV mass[5,6] and more pronounced impairment of LV geometry and function.[7] Diabetes mellitus (DM) is associated with clinical and subclinical myocardial impairment and increased LV hypertrophy. Besides, in patients with AS it has been shown to have an adverse effect on LV hypertrophy and remodeling.[8] Aortic valve replacement (AVR) is the only effective treatment for severe symptomatic AS and is associated with LV mass regression.[9] There is evidence that concentric LV remodeling increases early mortality after AVR[2] and concentric hypertrophy worsens prognosis in patients with AS.[10] Little is known about the association between MetS and the degree of LV mass regression after AVR. Therefore, this study examines the impact of MetS and DM on the extent of LV mass regression and reverse remodeling after AVR in patients with severe AS.

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See page 130 for disclosure information.

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Methods

We retrospectively analyzed prospectively acquired clinical and Doppler echocardiographic data of patients with severe AS who underwent isolated surgical AVR. Exclusion criteria were (1) LV ejection fraction $<50\%$, (2) greater than moderate aortic regurgitation, (3) previous valve intervention, (4) incomplete echocardiographic or clinical data. The study was approved by the Ethics Committee of the Quebec Heart and Lung Institute, and written informed consent was waived due to the retrospective nature of the analysis.

Clinical data were prospectively collected. Co-morbidities were documented by review of medical charts and included hypertension (patients receiving antihypertensive medications or having known but untreated hypertension [blood pressure $\geq 140/90$ mm Hg]), DM (patients receiving oral hypoglycemic drugs or insulin, or, in the absence of such medications, having a fasting glucose ≥ 7 mmol/L), coronary artery disease (history of myocardial infarction, significant coronary artery stenosis [i.e., $>50\%$] on coronary angiography, and/or regional wall motion abnormality on echocardiogram), long-term obstructive pulmonary disease and long-term kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m^2). Fasting blood samples were collected at baseline (before surgery) to obtain plasma levels of glucose and complete lipid profile using automated techniques standardized with the Canadian reference laboratory.

Patients were assigned to 1 of 3 metabolic groups: MetS (≥ 3 MetS criteria without overt DM), DM (clinical diagnosis of DM, even if concomitant MetS), and No MetS/DM (neither MetS nor DM). Clinical identification of patients with MetS was based on the criteria proposed by the National Cholesterol Education Program-Adult Treatment Panel III[11] modified in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute.[12] Patients were considered to have MetS when at least 3 of the following 5 criteria were present: elevated waist circumference (>88 cm in women and >102 cm in men); elevated triglycerides (≥ 1.7 mmol/L or pharmacologic treatment for hypertriglyceridemia); low High-density lipoprotein (HDL) cholesterol (men <1.0 mmol/L and women <1.3 mmol/L); elevated blood pressure ($\geq 130/85$ mm Hg or use of antihypertensive medication); and elevated fasting glucose (≥ 5.6 mmol/L). Diagnosis of DM was determined from the clinical record. Patients with definite diagnosis of DM were not included in the MetS group, even if they fulfilled 3 of the 5 criteria.

All patients underwent a comprehensive transthoracic echocardiographic examination after guideline recommendations.[13,14] Stroke volume was calculated by multiplying the flow velocity-time integral by the LV outflow tract area. The echocardiographic indexes of AS severity included peak aortic jet velocity, mean transvalvular pressure gradient, and aortic valve area calculated by continuity equation.[10] To overcome the potential underestimation related to indexing to body surface area in obese patients, stroke volume and aortic valve area were indexed to a 2.04 power of height as previously described.[7,15] At 1-year follow-up echocardiograms, prosthetic aortic valve area was evaluated by continuity equation and indexed to body surface area and to a 2.04 power of height. Severe patient-prosthesis mismatch was defined as the normal reference value of aortic valve area (for the model and size of the implanted prosthesis) indexed for patient's body surface area <0.65 cm/m^2 [16] and <0.55 cm^2/m^2 in obese patients (body mass index >30 kg/m^2).[17] Left ventricular mass was calculated using the modified cube formula[13] and indexed to body surface area and to a 2.7 power of height.[7,18–21] Left ventricular hypertrophy was defined as an indexed LV mass >49 $g/m^{2.7}$ in men and >47 $g/m^{2.7}$ in women.[7,18–21] Relative wall thickness ratio was calculated as the ratio of 2 times the posterior wall thickness to LV internal diameter in diastole.[13] By taking into account both values of LV mass and relative wall thickness ratio, patients were classified into 4 different patterns[13]: (1) Normal pattern: absence of LV hypertrophy and ratio ≤ 0.42, (2) Eccentric hypertrophy: presence of LV hypertrophy and ratio ≤ 0.42, (3) Concentric remodeling: absence of LV hypertrophy and ratio >0.42, and (4) Concentric hypertrophy: presence of LV hypertrophy and ratio >0.42. Left ventricular mass regression was calculated by subtracting preoperative from postoperative indexed LV mass. The index of LV mass to end-diastolic volume (mass-to-volume ratio), an alternative index of LV remodeling,[22] was measured before and after AVR. As a measure of global LV hemodynamic load, we calculated the valvulo-arterial impedance before and after AVR.[7,18,23]

The study end points were LV mass and remodeling pattern at baseline and 1 year after AVR and the degree of LV mass regression.

Continuous data were expressed as mean $\pm$ standard deviation and tested for normality of distribution and homogeneity of variances with the Shapiro-Wilk and Levene tests. They were compared using 1-way ANOVA, 2-way ANOVA (with post hoc Holm-Sidak test) or Kruskal-Wallis tests when appropriate. Categorical data were expressed as percentage and compared with the chi-square test, Fisher's exact test or McNemar's test when appropriate. Before and after AVR comparisons were made using paired statistical tests. Multivariate linear regression analysis was performed to identify the variables independently associated with baseline and postoperative LV mass and LV mass regression. The variables that were entered in these models were those with clinical relevance and/or a p value <0.1 after univariate analysis. A p value <0.05 was considered statistically significant. Statistical analyses were performed with STATA 15.1 (StataCorp LLC, Texas).

Results

A total of 177 patients were included in the analysis: 47 (27%) had MetS (without overt DM), 37 (21%) had DM (28 [74%] of whom also fulfilled ≥ 3 MetS criteria) and 93 (52%) had neither MetS nor DM (No MetS/DM). Patients with MetS or DM had larger body weight, body surface area, body mass index, and waist circumference compared with No MetS/DM patients (Table 1). There were no significant between-group differences in age, gender, or height. Hypertension, obesity, and dyslipidemia were more prevalent in patients with MetS and DM than in patients with No

Table 1
Baseline clinical and laboratory data

Variable	No MetS/DM (n = 93, 52%)	MetS (n = 47, 27%)	DM (n = 37, 21%)	p value
Age (years)	68 ± 11	67 ± 12	69 ± 9	0.87
Men	50 (54%)	27 (57%)	17 (46%)	0.57
Body Surface Area (m^2)	1.77 ± 0.19$^{*\#}$	1.89 ± 0.23	1.89 ± 0.19	< 0.01
Body Mass Index (kg/m^2)	26.7 ± 4.4$^{*\#}$	30.1 ± 4.6	30.8 ± 5.4	< 0.01
Height (cm)	164 ± 10	165 ± 11	164 ± 9	0.93
Weight (kg)	72 ± 14$^{*\#}$	82 ± 17	83 ± 15	< 0.01
Waist circumference (cm)	95 ± 12$^{*\#}$	106 ± 10	107 ± 12	< 0.01
SBP (mm Hg)	125 ± 18*	137 ± 18$^{\#}$	128 ± 21*	0.02
DBP (mm Hg)	72 ± 11*	77 ± 10$^{\#}$	71 ± 12*	0.03
Obesity[1]	16 (17%) $^{*\#}$	18 (38%)	19 (51%)	< 0.01
Symptomatic	89 (96%)	45 (96%)	35 (95%)	0.93
Hypertension[1]	61 (66%) $^{*\#}$	42 (89%)	32 (87%)	< 0.01
Dyslipidemia[1]	58 (62%) $^{*\#}$	42 (89%)	31 (84%)	< 0.01
CAD[1]	36 (39%)	24 (51%)	21 (57%)	0.13
Atrial fibrillation[1]	4 (4%)	4 (9%)	2 (5%)	0.28
COPD	11 (12%)	3 (6%)	3 (8%)	0.55
Smoker	40 (43%)	14 (30%)	17 (46%)	0.23
CKD	1 (1%)	1 (2%)	0	0.29
Antihypertensives	46 (49%) $^{\#}$	29 (62%)	30 (81%) ¶	< 0.01
ACEI/ARB	30 (38%) $^{\#}$	22 (47%) $^{\#}$	27 (73%) ¶*	< 0.01
Statins	42 (46%) $^{\#}$	26 (58%) $^{\#}$	31 (84%) ¶*	< 0.01
Total cholesterol (mmol/L) [mg/dl]	4.62 ± 1.03$^{\#}$ [178.4 ± 39.8]	4.52 ± 0.98 [174.5 ± 37.8]	4.00 ± 0.93¶ [154.4 ± 35.9]	0.01
Triglycerides (mmol/L) [mg/dl]	1.21 ± 0.47$^{*\#}$ [46.7 ± 18.1]	1.82 ± 0.96¶ [70.3 ± 37.1]	2.04 ± 1.42¶ [78.8 ± 54.8]	< 0.01
LDL cholesterol (mmol/L) [mg/dl]	2.61 ± 0.84$^{\#}$ [100.8 ± 32.4]	2.38 ± 0.79$^{\#}$ [91.9±30.5]	1.88 ± 0.67¶* [72.6 ± 25.9]	< 0.01
HDL cholesterol (mmol/L) [mg/dl]	2.03 ± 0.99 [78.4 ± 38.2]	2.52 ± 1.49 [97.3±57.5]	1.91 ± 1.10 [73.7±42.5]	0.08
Fasting plasma glucose (mmol/L) [mg/dl]	5.4 ± 0.6$^{*\#}$ [97 ± 11]	6.2 ± 1.2$^{¶\#}$ [112 ± 22]	6.6 ± 1.3¶* [119 ± 23]	< 0.01

Data are given as mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CAD = coronary artery disease; CKD = long-term kidney disease; COPD = long-term obstructive pulmonary disease; DBP = diastolic blood pressure; DM = Diabetes Mellitus; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MetS = metabolic syndrome (without overt diabetes); SBP = systolic blood pressure.

¶ $p < 0.05$ with No MetS/DM, *$p < 0.05$ with MetS, #$p < 0.05$ with DM.

[1] Obesity: BMI ≥ 30 kg/m^2; hypertension: blood pressure $\geq 130/85$ mm Hg or use of antihypertensive medication; dyslipidemia: total cholesterol > 5.0 mmol/L or HDL cholesterol < 1.0 mmol/L or TG > 1.7 mmol/L or under pharmacologic treatment for dyslipidemia; CAD: history of myocardial infarction, significant coronary artery stenosis on coronary angiography and/or regional wall motion abnormality on echocardiogram; atrial fibrillation: permanent, persistent or paroxysmal atrial fibrillation.

MetS/DM (Table 1). However, mean systolic and diastolic blood pressure were significantly higher in patients with MetS. There were no significant differences in other comorbidities, presence of symptoms or smoking status. Total and low-density lipoprotein cholesterol plasma levels were lower, and fasting glycemia was higher in the DM group. Patients with DM were more frequently treated with antihypertensive medication, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and statins.

There were no between-group differences regarding preoperative valve stenosis severity (Table 2). Indexed LV mass was higher in MetS and DM groups compared with No MetS/DM group, as was the prevalence of LV hypertrophy (Table 2 and Figure 1). There were no significant differences in preoperative LV diameters, ejection fraction, and diastolic dysfunction grade (Table 2). Preoperative distribution of LV remodeling patterns differed significantly between groups ($p = 0.045$, Figure 2). Before AVR, 60% of MetS patients and 54% of DM patients had concentric hypertrophy compared with 31% of No MetS/DM patients ($p < 0.01$). Mass-to-volume ratio was highest in patients with DM, intermediate in patients with MetS, and lowest in No MetS/DM (Table 2 and Figure 3).

One year after AVR, valvulo-arterial impedance and transvalvular gradients were similar between all groups, with comparable prevalence of severe patient-prosthesis mismatch (Table 2). Left ventricular mass significantly decreased compared with baseline in all 3 groups (Table 2 and Figure 1). Postoperative distribution of LV remodeling patterns differed significantly between groups ($p < 0.01$, Figure 2). After AVR, 19 (40%) of MetS patients had concentric hypertrophy compared with 8 (22%) of DM patients and 10 (11%) of No MetS/DM patients ($p < 0.001$). In the whole cohort, relative wall thickness ratio decreased significantly (before AVR: 0.48 ± 0.01 and 1-year post-AVR: 0.45 ± 0.01, $p = 0.003$), without significant difference between groups ($p = 0.60$). The mass-to-volume ratio decreased significantly at 1 year after AVR in all 3 groups ($p < 0.01$), without between-groups differences (p for interaction: 0.50; Figure 3).

One year after AVR, LV mass regression was significant in all 3 groups with no significant differences between groups (p for interaction: 0.65; Table 2 and Figure 1). Therefore, LV mass remained significantly higher in MetS and DM groups compared with No MetS/DM group at 1-year post-AVR (Figure 1). Overall, 1 year after AVR, a

Table 2
Baseline and 1-year post-AVR Doppler echocardiographic data

Variable	No MetS/DM (n = 93, 52%)	MetS (n = 47, 27%)	DM (n = 37, 21%)	p value
Preoperative Doppler Echocardiographic Data				
Aortic valve area (cm^2)	0.71 ± 0.15	0.74 ± 0.20	0.73 ± 0.14	0.65
Aortic valve area indexed by BSA (cm^2/m^2)	0.40 ± 0.08	0.39 ± 0.10	0.38 ± 0.07	0.75
Aortic valve area indexed by height ($cm^2/m^{2.04}$)	0.26 ± 0.06	0.27 ± 0.06	0.26 ± 0.05	0.68
Peak gradient (mm Hg)	74 ± 24	82 ± 27	74 ± 26	0.13
Mean gradient (mm Hg)	44 ± 16	50 ± 17	44 ± 17	0.10
Stroke volume index ($ml/m^{2.04}$)	25 ± 5	27 ± 6	26 ± 3	0.14
Valvuloarterial impedance (mm $Hg.ml^{-1}.m^{2.04}$)	6.9 ± 1.8	7.1 ± 1.6	6.9 ± 1.4	0.75
LV end-diastolic diameter (cm)	4.57 ± 0.56	4.69 ± 0.55	4.59 ± 0.49	0.34
LV end-systolic diameter (cm)	2.72 ± 0.58	2.74 ± 0.61	2.63 ± 0.50	0.65
Interventricular septum thickness (cm)	1.17 ± 0.19*#	1.26 ± 0.19	1.31 ± 0.26	< 0.01
Posterior wall thickness (cm)	1.05 ± 0.17*	1.13 ± 0.20 ¶	1.12 ± 0.24	0.05
LV mass (g)	188 ± 54*#	216 ± 63 ¶	217 ± 76 ¶	0.02
LV mass indexed by height ($g/m^{2.7}$)	49.2 ± 14.1*#	56.1 ± 14.2 ¶	56.2 ± 18.2	< 0.01
LV hypertrophy	41 (44%) *#	31 (66%) ¶	24 (65%) ¶	0.02
Relative wall thickness ratio	0.46±0.09	0.49±0.09	0.49±0.11	0.18
LVM/LVEDV (g/ml)	1.96 ± 0.41#	2.10 ± 0.44	2.21 ± 0.63 ¶	0.03
LV ejection fraction (%)	66 ± 7	65 ± 7	67 ± 9	0.80
Moderate AR	4 (4%) *	9 (19%) ¶	3 (8%)	0.02
Moderate/severe MR	6 (6%)	4 (9%)	0	0.22
Diastolic dysfunction grade				0.32
Mild	57 (65%)	35 (74%)	26 (76%)	
Moderate	31 (35%)	12 (26%)	8 (24%)	
Severe	0	0	0	
1-year postoperative Doppler Echocardiographic Data				
Aortic valve area (cm^2)	1.28 ± 0.4	1.33 ± 0.3	1.38 ± 0.34	0.23
Aortic valve area indexed by BSA (cm^2/m^2)	0.72 ± 0.20	0.71 ± 0.18	0.73 ± 0.18	0.90
Aortic valve area indexed by height ($cm^2/m^{2.04}$)	0.46 ± 0.13	0.48 ± 0.12	0.50 ± 0.12	0.29
Severe patient-prosthesis mismatch[1]	4 (4%) *	1 (2%) ¶	2 (5%)	0.72
Peak gradient (mm Hg)	27 ± 11	26 ± 10	25 ± 9	0.60
Mean gradient (mm Hg)	15 ± 6	14 ± 5	14 ± 5	0.50
Stroke volume index ($ml/m^{2.04}$)	24 ± 6	25 ± 5	25 ± 4	0.14
Valvuloarterial impedance (mm $Hg.ml^{-1}.m^{2.04}$)	5.9 ± 2.3	6.0 ± 1.6	6.0 ± 1.8	0.90
LV end-diastolic diameter (cm)	4.4 ± 0.5*	4.6 ± 0.5 ¶	4.6 ± 0.5	0.02
LV end-systolic diameter (cm)	2.63 ± 0.56	2.7 ± 0.48	2.62 ± 0.57	0.65
Interventricular septum thickness (cm)	1.07 ± 0.2*	1.19 ± 0.2 ¶#	1.13 ± 0.2*	0.02
Posterior wall thickness (cm)	0.97 ± 0.2	1.02 ± 0.2	1.03 ± 0.2	0.24
LV mass (g)	155 ± 43*#	187 ± 56 ¶	178 ± 57 ¶	< 0.01
LV mass indexed by height ($g/m^{2.7}$)	40.9 ± 13.2*#	48.9 ± 13.9 ¶	46.4 ± 14.3 ¶	< 0.01
LV hypertrophy	16 (17%) *#	27 (57%) ¶	14 (38%) ¶	< 0.01
Relative wall thickness ratio	0.44±0.09	0.45±0.10	0.46±0.10	0.80
LVM/LVEDV (g/ml)	1.76 ± 0.43	1.93 ± 0.53	1.92 ± 0.52	0.26
LV ejection fraction (%)	65 ± 8	65 ± 7	65 ± 8	0.90
Moderate/severe AR	2 (2%)	1 (2%)	1 (3%)	0.90
Moderate/severe MR	8 (9%)	1 (2%)	2 (5%)	0.40
Diastolic dysfunction grade				0.76
Mild	51 (64%)	26 (58%)	22 (65%)	
Moderate	29 (36%)	19 (42%)	12 (35%)	
Severe	0	0	0	
Change from preoperative to 1 year after AVR				
Absolute LV mass regression (g)	-33 ± 48	-29 ± 62	-39 ± 45	0.46
Indexed LV mass regression ($g/m^{2.7}$)	-8.3 ± 12.7	-7.2 ± 14.6	-9.6 ± 10.9	0.50
Delta mean gradient (mm Hg)	-29 ± 15	-36 ± 18	-30 ± 16	0.09
Normalization of LV hypertrophy	28 (30%)	8 (17%)	12 (32%)	0.19

AR = aortic regurgitation; BSA = body surface area; LV = left ventricle; LVM/LVEDV = ratio of LV mass to end-diastolic volume; MR = mitral regurgitation.

¶p < 0.05 with No MetS/DM, *p < 0.05 with MetS, #p < 0.05 with DM.

[1] Severe patient-prosthesis mismatch: predicted indexed aortic valve area < 0.65 $cm^2.m^{-2}$ and < 0.55 $cm^2.m^{-2}$ in obese patients (body mass index > 30 $kg.m^{-2}$).

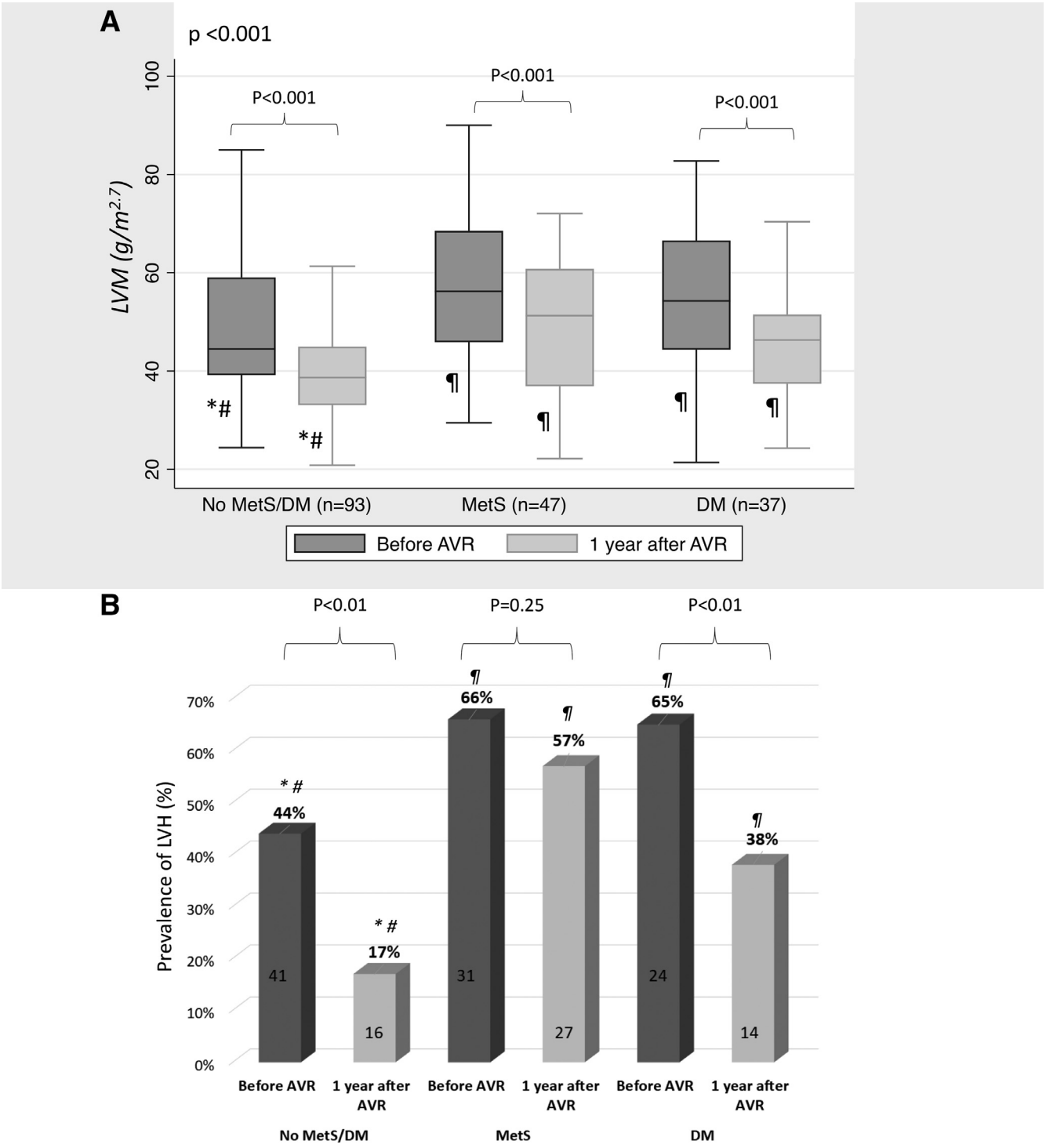

Figure 1. **(*A*) Left ventricular mass index before and 1 year after AVR according to metabolic group** This figure shows the boxplot of left ventricular mass indexed to a 2.7 power of height before (*dark gray*) and 1 year after (*light gray*) AVR and according to metabolic group. The boxes are presented with median (*central line*), percentiles 25 (*lower line*) and 75 (*upper line*). Whiskers represent the upper and lower adjacent values. p values represent the results of 2-way repeated measurements ANOVA. AVR = aortic valve replacement; DM = diabetes mellitus; LVM = left ventricular mass; MetS = metabolic syndrome. ¶p < 0.05 with No MetS/DM, *p < 0.05 with MetS, #p < 0.05 with DM. **(*B*) Prevalence of LV hypertrophy before and 1 year after AVR.** This figure shows a bar chart of the prevalence of LV hypertrophy ($LVMi^{2.7}$ > 49 g/$m^{2.7}$ in men and > 47 g/$m^{2.7}$ in women) for each metabolic group before (*dark gray*) and 1 year after (*light gray*) AVR. The height in the *Y* axis represents the prevalence in percentage for each metabolic group and time. The numbers inside the bar are the actual corresponding number of patients within each group and time. AVR = aortic valve replacement; DM = diabetes mellitus; LVH = left ventricular hypertrophy; MetS = metabolic syndrome. ¶p < 0.05 with No MetS/DM, *p < 0.05 with MetS, #p < 0.05 with DM.

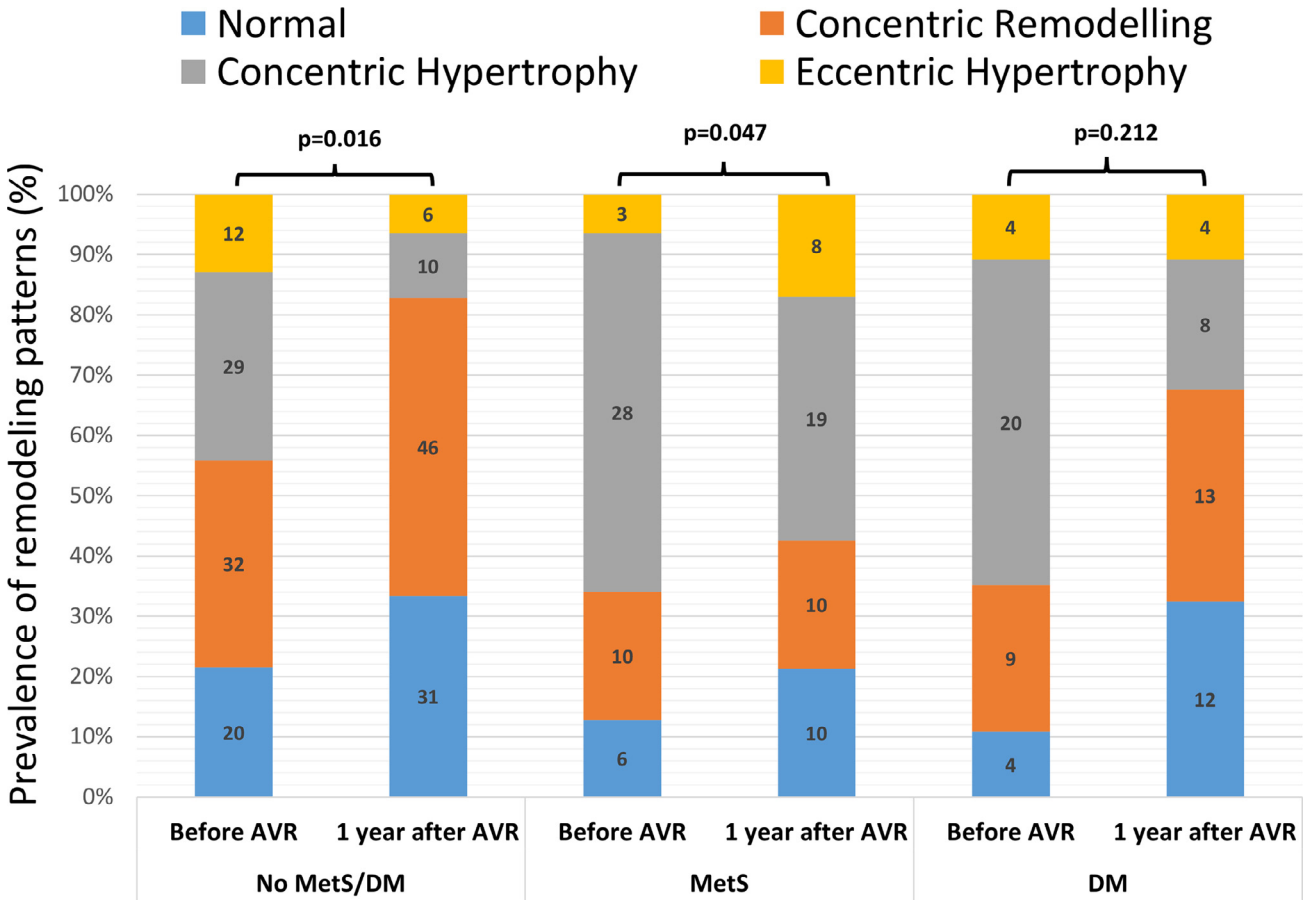

Figure 2. **LV remodeling patterns before and 1 year after AVR.** This figure shows a bar chart of the distribution of LV remodeling patterns (Normal, Concentric Remodeling, Concentric Hypertrophy, and Eccentric Hypertrophy) for each metabolic group before and 1 year after AVR. The height in the *Y* axis represents the percentage of each pattern for each metabolic group and time. The numbers inside the bar are the actual corresponding number of patients within each pattern, group and time. AVR = aortic valve replacement; DM = diabetes mellitus; MetS = metabolic syndrome; ¶p < 0.05 with No MetS/DM, *p < 0.05 with MetS, #p < 0.05 with DM.

total of 27% patients normalized their LV mass (i.e., from LV hypertrophy to normal LV mass), with no significant differences between groups (Table 2). Thus, patients with MetS or DM remained with more prevalence of LV hypertrophy (Figure 1) and worse LV remodeling (Figures 3 and 4) 1 year after AVR compared with No MetS-DM patients.

The number of positive MetS criteria (0-1, 2, 3 and 4-5 positive criteria) was significantly associated with higher LV mass both preoperative and 1-year post-AVR (both p < 0.01, Figure 4), as well as with higher preoperative mass-to-volume ratio (0-1 positive criterion: 1.88 ± 0.37, 2 positive criteria: 2.03 ± 0.44, 3 positive criteria: 2.13 ± 0.55, 4-5 positive criteria: 2.22 ± 0.49, p = 0.01). However, the degree of LV mass regression showed no significant association with the number of positive MetS criteria (p for interaction = 0.80). Therefore, the number of positive MetS criteria was significantly associated with prevalence of LV hypertrophy 1 year after AVR (0-1 positive criterion: 16%, 2 positive criteria: 19%, 3 positive criteria: 54%, 4-5 positive criteria: 48%, p < 0.01, Figure 4).

After adjustment for age, gender, coronary artery disease, systolic blood pressure, and mean pressure gradient, MetS and DM were both independently associated with a higher baseline LV mass, as did a higher preoperative transvalvular mean pressure gradient (Table 3). After adjustment for age, gender, coronary artery disease, preoperative LV mass, systolic blood pressure, and change in transvalvular mean pressure gradient, MetS (but not DM) was independently associated with less degree of LV mass regression 1 year after AVR (Table 3). A higher preoperative LV mass was independently associated with a greater degree of LV mass regression. Finally, after adjustment for age, gender, coronary artery disease, and hypertension, both MetS (standardized β 0.26 ± 2.5, p = 0.01) and DM (standardized β 0.16 ± 2.6, p = 0.036) were independently associated with a higher postoperative LV mass. However, after adding baseline LV mass to the model (Table 3), MetS (but not DM) remained independently associated with of a higher LV mass 1 year after AVR, as did a higher baseline LV mass (Table 3). In all models, inclusion of valvulo-arterial impedance as a marker of global afterload[24] had no impact on the results.

Discussion

The main findings of this study are that in patients with severe symptomatic AS and preserved LV ejection fraction underwent AVR (1) MetS and DM are associated with higher LV mass, higher mass-to-volume ratio, and higher

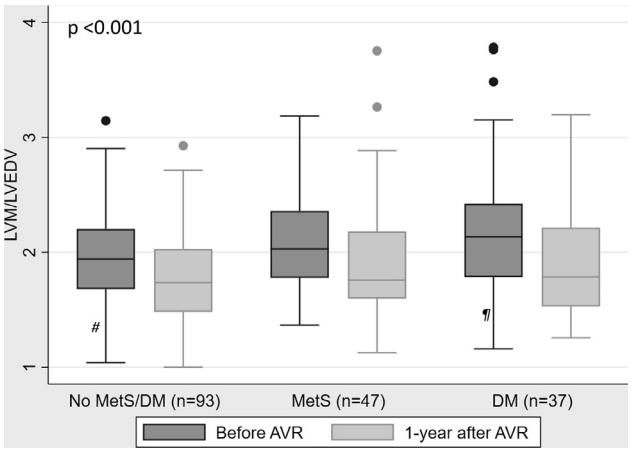

Figure 3. **Ratio of LV mass to end-diastolic volume before and 1 year after AVR.** This figure shows the boxplot of the ratio of LV mass to end-diastolic volume (an index of LV remodeling) according to metabolic group before (*dark gray*) and 1 year after (*light gray*) AVR. The boxes are presented with median (*central line*), percentiles 25 (*lower line*), and 75 (*upper line*). Whiskers represent the upper and lower adjacent values. p values represent the results of 2-way repeated measurements ANOVA. AVR = aortic valve replacement; DM = diabetes mellitus; LVM/LVEDV = ratio of left ventricular mass to end-diastolic volume; MetS = metabolic syndrome. ¶p < 0.05 with No MetS/DM, #p < 0.05 with DM.

prevalence of concentric LV hypertrophy before AVR; (2) One year after AVR, MetS (but not DM) was independently associated with less LV mass regression and higher LV mass; and (3) Patients with MetS or DM remained with higher prevalence of residual LV hypertrophy and concentric remodeling compared with patients with No MetS/DM.

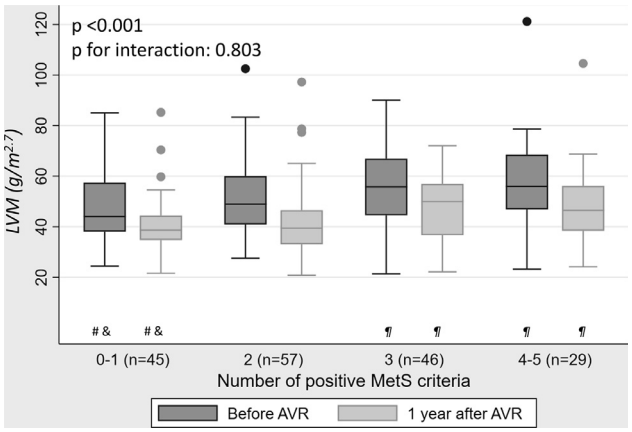

Figure 4. **LV mass regression according to the number of positive metabolic syndrome criteria.** This figure shows the boxplot of LV mass indexed to a 2.7 power of height (LVMi) before (*dark gray*) and 1 year after (*light gray*) AVR according to the number of positive metabolic syndrome criteria (0-1, 2, 3, or 4-5). The boxes are presented with median (*central line*), percentiles 25 (*lower line*), and 75 (*upper line*). Whiskers represent the upper and lower adjacent values. p values represent the results of 2-way repeated measurements ANOVA. AVR = aortic valve replacement; LVM = left ventricular mass; MetS = metabolic syndrome. ¶p < 0.05 with 0-1 criterion, #p < 0.05 with 3 criteria, and p < 0.05 with 4-5 criteria. ¶p < 0.05 with No MetS/DM, *p < 0.05 with MetS, #p < 0.05 with DM.

The hypertrophic response to AS is only weakly related to stenosis severity and appears to be more closely related to other factors, such as advanced age, male gender, and obesity.[1] Both MetS[6,7] and DM[8] are associated with increased LV hypertrophy. The potential mechanisms that link visceral obesity to LV hypertrophy are insulin resistance, activation of the renin-angiotensin system, a low-grade inflammatory state, and activation of the sympathetic nervous system, with induction of peripheral vasoconstriction and aortic stiffening. This ultimately leads to an increased vascular afterload that, added to the burden of AS, further increases the LV hypertrophic response.[7] However, in MetS, the myocardial hypertrophic response appears to be not only related to afterload, but also to excess epicardial fat and a dysregulation of the myocardial substrate oxidation from free fatty acids to carbohydrates.[7,23]

The results of this study emphasize the relation between MetS and/or DM with an exaggerated hypertrophic response to afterload in severe AS patients. There was a higher baseline LV mass, a greater prevalence of LV hypertrophy, and worse (more concentric) remodeling in MetS and DM patients than in No MetS/DM patients.

There is evidence that the degree of LV mass regression depends on several factors, such as gender,[25] patient-prosthesis mismatch[26] and type of aortic valve intervention (surgical vs transcatheter).[27,28] A study by Nakamura et al[29] showed a greater degree of LV mass regression in non-diabetics compared with diabetics. Age, female gender, and diabetes were all independently associated with less postoperative mass regression. We neither find gender nor diabetes to be associated with less LV mass regression might be explained by several differences between the cohort of Nakamura et al and ours: (1) forty-three percent of their patients underwent transcatheter aortic-valve replacement; (2) different baseline characteristics: inclusion of patients with LV dysfunction (15.9%, excluded from our study), more advanced age (median 79 vs 69 years), and markedly lower body mass index (median 22.5 vs 27.7 kg/m^2 respectively); and (3) different indexation methods (body surface area vs height using allometric scaling).

It is clear that MetS and DM are not 2 totally distinct entities but part of a clinical continuum where visceral obesity, insulin resistance, dyslipidemia, and hyperglycemia increase cardiovascular risk in a continuous fashion. However, it is well recognized that once the patient progressed to DM, cardiovascular risk is further increased, which justified our decision to separate MetS from DM patients.[12] Our results are consistent with previous studies showing that the number of positive MetS criteria are associated with more concentric remodeling and increased LV mass[7] before AVR. However, this is the first study to our knowledge that shows that MetS is associated with less degree of LV mass regression after AVR.

The fact that MetS (but not DM) was associated with less LV mass regression in a population of severe AS patients with preserved LV ejection fraction and absence of severe coronary artery disease (4.5% prevalence of previous myocardial infarction, concomitant coronary artery bypass-grafting excluded) is hypothesis generating. As the diagnosis of MetS was retrospective (as opposed to DM diagnosis which was based on clinical history), less

Table 3
Univariate and multivariate analyses of correlates with preoperative LV mass, LV mass regression, and LV mass 1 year after AVR

	Univariate		Multivariate	
Variable	Standardized β coefficient ± SE	p value	Standardized β coefficient ± SE	p value
LV mass (g/m$^{2.7}$) before AVR				
Metabolic syndrome	0.14±2.60	0.06	0.16±2.7	0.030
Diabetes mellitus	0.13±2.83	0.09	0.22±2.87	0.003
Mean gradient	0.24±0.07	<0.01	0.24±0.07	0.001
LV mass regression (g/m$^{2.7}$)				
Metabolic syndrome	-0.05±2.2	0.50	-0.16±2.12	0.030
Diabetes mellitus	0.05±2.37	0.47	-0.01±2.28	0.85
Preoperative LV mass	0.51±0.05	<0.01	0.52±0.06	<0.001
LV mass (g/m$^{2.7}$) after AVR				
Metabolic syndrome	0.13±2.06	0.055	0.13±2.10	0.045
Diabetes mellitus	0.03±2.18		0.02±2.29	0.79
Preoperative LV mass	0.62 ± 0.05	<0.01	0.60 ± 0.06	<0.001

β coefficients are standardized regression coefficient. The multivariable analysis for LV mass before AVR is adjusted for age, gender, coronary artery disease, and systolic blood pressure. The multivariable analysis for LV mass regression is adjusted for age, gender, coronary artery disease, preoperative LV mass, systolic blood pressure, and delta mean gradient. The multivariable analysis for LV mass after AVR is adjusted for age, gender, preoperative LV mass, systolic blood pressure, and CAD.

AVR = aortic valve replacement; LV = left ventricular; SE = standard error.

aggressive treatment of risk factors might have played a role. However, the relative importance of each individual effect of each MetS criteria (i.e., the known association between obesity and LV hypertrophy[30]) is difficult to ascertain and warrants further study. Finally, we found no correlation between the number of MetS criteria and the degree of LV mass regression after AVR.

Our study results should be viewed in the light of some inherent limitations. First, the relatively small number of patients and its retrospective nature limit the strength of the study. Second, LV mass was measured with the use of 2-dimensional echocardiography, which has been shown to be highly dependent to changes in LV diameters.[28] Another important inherent limitation is that MetS and DM are not 2 entirely distinct entities but part of a continuum of metabolic abnormalities (i.e., 74% of our DM cohort also fulfilled MetS criteria). However, we performed sensitivity analyses to evaluate independent interaction of DM, MetS and each individual MetS criteria which did not change the study conclusions.

In conclusion, in patients with symptomatic severe AS and preserved LV ejection fraction, MetS, and DM were independently associated with higher preoperative LV mass and more pronounced LV concentric remodeling. The relief of pressure overload by AVR results in less degree of LV mass regression in patients with MetS, but not in patients with DM. Patients with MetS and/or DM remained with higher LV mass and more residual LV hypertrophy, which may lead to worse outcomes. Clinical diagnosis of MetS should be considered in all AS patients and risk factors aggressively treated. Furthermore, an earlier intervention may be considered in severe AS patients with MetS/DM and excessive LV hypertrophy. However, further studies are needed to evaluate this option.

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Disclosures

The authors have no conflicts of interest to disclose.

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