JMS 2018: 1(2):20-28
UDC: 613.25:616.132-007.271-089.843

Effect of overweight and obesity on left ventricular function recovery in patients with severe aortic stenosis after surgical aortic valve replacement

[1]Zafirovska Planinka, [2]Georgievska Ismail Lj, [3]Matveeva N, and [1]Mitrev Z
[1]Special Hospital for Surgical Diseases, "Zan Mitrev Clinic", Skopje, the Republic of Macedonia
[2]University Clinic of Cardiology, Skopje, the Republic of Macedonia
[3]Institute of Anatomy, University of Cyril and Methodius, Skopje, the Republic of Macedonia

Abstract

The aim of the study was to assess the effect of body mass index (BMI) on myocardial function and mechanics among patients with severe aortic stenosis (AS) admitted for surgical aortic valve replacement (SAVR).

The dramatic increase in the prevalence of obesity and its strong association with cardiovascular disease have resulted in growing interest in understanding the effects of obesity on the cardiovascular hemodynamics and mechanics especially in circumstances of valvular diseases.

A total of 51 consecutive patients (age: 65.8±9.6 y, 58.8% male,41.2% females) who underwent SAVR for severe AS were classified according to World Health Organization criteria such as normal weight, overweight, or obesity according to their BMI (18.5 to 24.9 kg/m2, 25.0 to 29.9 kg/m2, and ≥30.0 kg/m2, respectively).

Out of all, 31.4% were obese and 43.1% overweight, with more frequent history of atherosclerotic risk factors. Obese and overweight patients after SAVR showed in comparison to those with normal weight insignificantly smaller indexed aortic valve area (AVAi), higher indexed left atrial volume (LAVI) and left ventricular (LV) end-systolic dimension, lower LV ejection fraction (EF) as well as higher LV filling pressure (E/e`average) as a marker of diastolic dysfunction. In addition, obese patients showed significantly (p=0.008) the highest value of valvuloarterial impedance (Zva) and with borderline significance lowest GLS% (more positive value). Linear regression analysis showed that BMI adjusted to age, gender and history of hypertension appeared as independent significant predictor of higher Zva value (β=0.136; 95%CI 0.65 to 0.207; p=0.0001) and along with male gender of worse (more positive) LV GLS% values (β=0.314; 95%CI 0.098 to 0.531; p=0.005) after SAVR.

BMI appears as independent predictor of more extensive impairment of myocardial function and mechanics after SAVR that could contributed to more unfavorable long-term outcome in these patients.

Key words: body mass index, obesity, overweight, severe aortic stenosis, surgical aortic valve replacement, echocardiography, subclinical left ventricular function

Introduction

Aortic valve stenosis (AS) is one of the most common valvular heart disease with approximate prevalence of 2-4% in individuals over 65 years of age and almost 10% in those over 80 years [1]. The main treatment for AS is still surgical aortic valve replacement (SAVR) using more frequently bioprosthetic valve, thus it is very important to identify modifiable risk factors for outcome and later progression of disease including bioprothesis durability. Available evidence indicates possible links of disease progression with atherosclerotic risk factors, including smoking, hypertension, dyslipidemia, and diabetes mellitus [2-4]. However published data regarding the role of obesity in LV function recovery after SAVR as well as AS progression and structural valve degeneration especially taking into account some active mechanism potentially related to atherosclerotic pathways are inconclusive [4-8]. In addition, it is well-known that obesity is connected to LV hypertrophy and/or unhealthy metabolic profile that has strong influence on LV geometry and function as the AS itself [9- 12]. We assume that in overweight and/or obese patients after SAVR, such circumstances could have influence on less favorable outcome expressed as worse myocardial function and less amount of LV reverse remodeling which may, in turn, predispose them to the occurrence of adverse events.

Methods

Our study included 51 patients hospitalized in PZU "Zan Mitrev Clinic" in the period between November 2016 and June 2018 for surgical treatment of AS. Initial examination after having written consent for participation in the study from the patient included short interview for symptoms and comorbidities, physical examination, basic biochemical blood analysis and anthropometric measurements. Patients were classified according to World Health Organization criteria such as normal weight, overweight, or obesity according to their body mass index (BMI): 18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, and ≥30.0 kg/m^2, respectively. It is important to stress that weight didn't differ substantially in patients before and 4 months after surgery. Analysis of electrocardiogram and coronary angiography were done with evaluation of existing coronary artery disease (CAD) and its severity expressed by Syntax score.

Echocardiographic 2D examination was performed using Philips Epique 7 Cardiology Ultrasound Machine with recording of the views and later analyzing on the machine itself or on Philips IntelliSpace Cardiovascular portal before and around 4 months after SAVR. All measurements were performed according to guidelines suggested by professional echocardiographic societies [13, 14]. Standard measurements of LV systolic and diastolic function were done using 2D echocardiography and Tissue Doppler imaging (TDI) as well as LV mass indexed for body surface area (LVMi) and valvuloarterial impedance (Zva) were calculated [14-16]. Global peak systolic longitudinal strain (GLS) for LV using speckle tracking analysis was automatically provided as the average value of the three apical views by the software. Good quality ECG-gated images were obtained and recorded with frame rate >50 frames/s [17]. GLS values of -18.9 were used as a cut off value for normal longitudinal strain suggested by the vendor [13].

The study protocol was approved by the Medical Ethics Committee of Medical School, University "St.Cyril&Methodius), Skopje.

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as mean ±SD. Comparison among the groups was performed using ANOVA analysis of variance with Bonferroni post-hoc analysis for continuous parameters and Pearson's chi square test for categorical parameters. Assessment of correlation of overweight/obesity with various echocardiographic parameters was done using Pearson's correlation analysis. Multiple linear regression analysis was performed in stepwise order to determine independent predictors of echocardiographic LV changes after SAVR. All data analysis was performed using SPSS version 22.0 (IBM SPSS, Inc., Chicago, Illinois) and p value ≤ 0.05 was considered significant.

Results

Out of 51 patients who underwent SAVR (65.8±9.6 years, 30 to 80 years), obesity (BMI≥30.0 kg/m^2) was present in 16 (31.4%), overweight (BMI =25,0-29,9 kg/m^2) in 22 (43.1%) and 13 patients (25.5%) were with normal weight (BMI=18.5 to 24.9 kg/m^2). In comparison to patients with normal weight, those overweight and obese were younger (p=0.040), more often female (p=0.073), had more frequently history of hypertension (p=0.024) and insignificantly more frequently diabetes mellitus (p=0.449). Presence of other atherosclerotic risk factors as well as ECG signs of LV hypertrophy (LVH) and/or presence of CAD and its severity didn't show any significant difference among patients stratified according BMI (Table 1). NYHA class was with limited significance, the worst in patient with normal weight (p=0.073). There was lack of statistical significance in comparison of patients stratified according to the BMI regarding any of medications that were used.

Table 1. Baseline characteristics stratified according to the BMI categories

Parameter	Normal weight n=13	Overweight n=22	Obese n=16	p
Age (y)	69.7 ± 9.7	66.0 ± 8.4	62.3 ± 10.4	0.040
Gender (m/f %)	84.6/15.4	54.5/45.5	43.8/56.3	0.874
BMI (kg/m^2)	23.3 ± 1.3	27.4 ± 1.3	35.0 ± 3.4	0.073
Smoking (n/%)	3/23.1	4/18.2	1/6.3	0.424
Hypertension (n/%)	9/69.2	22/100	14/87.5	0.024
Dislipidemia (n/%)	7/53.8	14/63.6	7/56.3	0.580
Diabetes mellitus (n/%)	1/7.7	5/22.7	4/25.0	0.449
NYHA Class	2.3 ± 0.6	2.1 ± 0.3	2.0 ± 0	0.069
LVH on ECG (n/%)	5/38.5	5/26.3	6/40.0	0.652
CAD (n/%)	5/38.5	10/45.5	6/37.5	0.863
Syntax score	7.4 ± 11.2	6.4 ± 9.4	5.5 ± 11.8	0.893

BMI-body mass index; NYHA-New York Heart Association; LVH-left ventricular hypertrophy; CAD-coronary artery disease.
*p<0,05 for comparison between groups.

Out of 51 patient bioprothesis was implanted in 29 patients, 9/69.2% with normal weight, in 13/59.1% overweight and in 7/43.8% obese patients which didn't significantly differ among them (p=0.679). Also the distribution of other types of prothesis was almost identical in all three groups of patients: in those with normal weight (3/23.1% with reconstruction of aortic valve and 1/7.7% with artificial prothesis), in overweight (7/31.8% with reconstruction of aortic valve and 2/9.1% with artificial prothesis) and in obese patients (6/37.5% with reconstruction of aortic valve and 1/11.8% with artificial prothesis).

Echocardiographic data.

Indexed to BSA aortic valve area (AVAi) was insignificantly the smallest in obese patients before SAVR (p=0.192) and that remained the same after SAVR significantly different to those with normal weight (p=0.026) (Table 2). Change of the AVAi after SAVR was also the smallest in obese patients although without significance (p=0.160). As for pressure gradient before and after SAVR it showed insignificantly smallest values in patients with normal weight (Table 2).

Analysis of left atrial (LA) dimension indexed to BSA before and after SAVR in patients stratified according to BMI, showed significant difference in favor of highest, steel in reference limits, dimensions and volumes in those with normal weight (Table 2). LA dimensions insignificantly increased after SAVR in those with normal weight and overweight, respectively, insignificantly declining in obese (p=0.507). As for LA maximal volume (LAVI) before SAVR it showed insignificantly the highest increased value in obese patients and remained identically the highest in obese although they as well overweight patients showed its decrease after SAVR unlike those with normal weight who showed increase of LAVI (table 2). In addition, comparison of delta values of LAVI didn't showed statistical difference among three groups of patients (p=0.590). LV internal dimensions in systole and diastole showed the highest values in obese patients before as well after SAVR, but without significant difference among patients stratified according BMI (table 2). Analysis of systolic LV functional data showed that obese patients had insignificant lower LV ejection fraction (LVEF) and peak systolic mitral annular velocity assessed by TDI (TDIs') before SAVR which increased insignificantly in all patients no matter of BMI (p=0.399). LV filling pressure assessed by E/e' ratio as average value of two LV walls that was chosen along with LAVI as a marker of diastolic LV function, showed insignificantly the highest values in obese patients before and after SAVR, although postoperatively declined (Table 2). Interestingly indexed LV mass (LVMi) showed insignificantly the highest value in patients with normal weight before and after SAVR, although postoperatively declined (Table 2). Evaluation of valvuloarterial impedance (Zva) showed that all patient had abnormal high values (reference value: ≤3,5 3.5 mmHg/mL^{-1}/ m^2) before SAVR. Of note

is that Zva after SAVR in obese patient declined, but significantly remained high (p=0.008) in comparison to overweight who showed declined to medium value of Zva (p=0.037), and those with normal weight who obtained postoperatively normal Zva (p=0.012) (Table 2). Delta values of Zva as a change before and after SAVR was the lowest in obese patients, still insignificant (p=0.614). As for global longitudinal LV strain values (GLS%), obese patients with borderline significance had lowest GLS% (more positive value) before SAVR (p=0.093) and after SAVR (p=0.299), although showing slight improvement (less positive or increased negative value) after SAVR (Table 2). Delta values didn't achieved significant value (p=0.560).

Table 2. Echocardiographic data stratified according to the BMI categories in patients before and after SAVR

Parameter		Normal weight n=13	Overweight n=22	Obese n=16	p
AVAi (cm^2/m^2)	**Before SAVR**	0.44 ± 0.10	0.39 ± 0.10	0.38 ± 0.08	0.192
	After SAVR	1.13 ± 0.44	0.88 ± 0.37	0.83 ± 0.28	0.026
Pgr (mmHg)	**Before SAVR**	34.9 ± 12.8	45.5 ± 18.7	39.7 ± 12.1	0.144
	After SAVR	11.4 ± 4.7	15.9 ± 7.8	12.4 ± 6.0	0.108
LA/BSA (mm/m^2)	**Before SAVR**	23.7 ± 4.1	22.2 ± 2.2	20.9 ± 2.9	0.036
	After SAVR	24.1 ± 4.3	22.9 ± 2.5	20.8 ± 2.8	0.024
LAVI (ml/m^2)	**Before SAVR**	42.8 ± 14.8	42.4 ± 11.9	48.5 ± 15.1	0.361
	After SAVR	45.5 ± 19.6	40.9 ± 10.1	46.2 ± 18.8	0.535
LVEDd (mm)	**Before SAVR**	54.3 ± 10.4	51.0 ± 6.9	55.1 ± 8.8	0.304
	After SAVR	51.5 ± 5.6	51.0 ± 6.3	51.8 ± 5.7	0.514
LVEDs (mm)	**Before SAVR**	36.9 ± 11.8	31.6 ± 7.2	38.5 ± 9.7	0.071
	After SAVR	31.9 ± 8.2	29.9 ± 5.8	35.0 ± 5.4	0.067
E/e'average	**Before SAVR**	14.4 ± 5.7	14.1 ± 4.4	17.0 ± 6.9	0.271
	After SAVR	10.4 ± 3.9	12.3 ± 3.4	12.3 ± 5.3	0.330
TDIs' (cm/s)	**Before SAVR**	5.7 ± 1.1	5.9 ± 1.1	5.4 ± 1.2	0.475
	After SAVR	6.9 ± 1.4	7.2 ± 1.5	7.1 ± 1.7	0.801
LVEF (%)	**Before SAVR**	58.6 ± 11.8	62.5 ± 8.8	56.1 ± 13.5	0.179
	After SAVR	62.2 ± 12.0	64.1 ± 5.7	61.1 ± 6.9	0.504
LVMI (g/m^2)	**Before SAVR**	199.6 ± 67.1	177.4 ± 55.9	184.4 ± 51.2	0.550
	After SAVR	143.4 ± 31.6	138.4 ± 44.2	131.6 ± 18.7	0.656
Zva ($mmHg/ml^{-1}/m^2$)	**Before SAVR**	4.5 ± 1.1	5.0 ± 1.6	5.6 ± 1.6	0.174
	After SAVR	3.3 ± 0.7	3.6 ± 1.4	4.8 ± 1.4	0.008
LV GLS (%)	**Before SAVR**	-16.1 ± 3.9	-16.6 ± 4.0	-14.0 ± 4.3	0.093
	After SAVR	-19.1 ± 4.4	-18.6 ± 3.4	-16.9 ± 4.6	0.299

BSA-body surface area; AVAi-indexed aortic valve area; Pgr-pressure gradient; LA/BSA-indexed dimension of left atria; LAVI-eft atrial volume indexed to BSA; LVEDd-left ventricular dimension in diastole; LVEDs-left ventricular dimension in systole; E/e'-early mitral inflow velocity and early diastolic mitral annular tissue Doppler velocity ratio; s'TDI-peak systolic mitral annular velocity by TDI; LVEF-left ventricular ejection fraction; LVMI-indexed left ventricular mass; Zva-valvuloarterial impedance; GLS-LV global longitudinal strain.
*p<0,05 for comparison between groups.

Correlation analysis showed that higher BMI was significantly correlated with female gender (r=0.314, p=0.025), with smaller AVAi after SAVR (r=-0.278, p=0.048), higher LP/BSA dimension before SAVR (r=0.310, p=0.027), with borderline significance higher E/e' before (r=0.269, p=0.059)

and after SAVR (r=0.244, p=0.085), with borderline significance higher Zva before SAVR (r=0.252, p=0.075) and significantly higher after SAVR (r=0.482, p=0.0001) and with borderline significance worse value (more positive) of LV GLS% before (r=0.218, p=0.125) and after SAVR (r=0.240, p=0.090), (Figure 1).

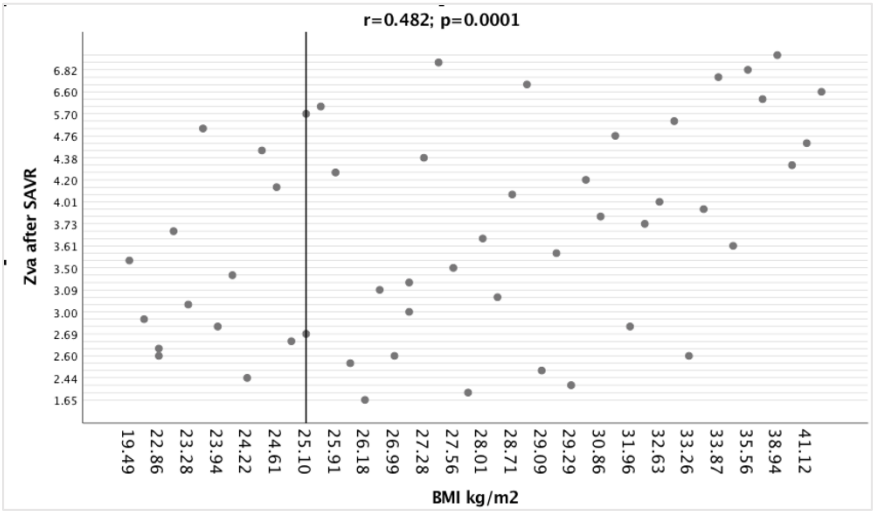

Figure 1. Positive correlation analysis between BMI presence and valvuloarterial impedance (Zva)

Linear regression analysis (Table 3) showed that BMI adjusted to age, gender and history of hypertension appeared as independent significant predictor of higher Zva value (β=0.136; 95%CI 0.65 to 0.207; p=0.0001) and along with male gender (β=-3.832; 95%CI -6.042 to -1.621; p=0.001) independent predictor of worse (more positive) LV GLS% values (β=0.314; 95%CI 0.098 to 0.531; p=0.005) after SAVR.

Table 3. Data on linear regression analysis with BMI as significant independent predictor of Zva and LV GLS% after SAVR

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	.030	1.033		.029	.977	-2.046	2.106
	BMI	.136	.035	.482	3.851	.000	.065	.207

a. Dependent Variable: Zva after SAVR

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	-14.276	1.676		-8.520	.000	-17.643	-10.909
	Male gender	-2.824	1.121	-.339	-2.520	.015	-5.076	-.572
2	(Constant)	-21.899	3.044		-7.194	.000	-28.020	-15.779
	Male gender	-3.832	1.099	-.460	-3.485	.001	-6.042	-1.621
	BMI	.314	.108	.385	2.917	.005	.098	.531

a. Dependent Variable: GLS after SAVR

Discussion

As demonstrated, increased BMI was common in patients with severe AS who have undergone SAVR: 43.1 % of the study population was overweight, while 25.5% of patients were

obese with average BMI of 35.0 kg/m^2 reflecting body stature for the general Macedonian population [18]. In the present study, obese patients were significantly younger than those with normal weight being overall on average over 60 years, and there was significant correlation with female gender. Hypertension was frequent in overweight (100%) and obese (88%) patients without confirming significant association with increased BMI along with more frequent diabetes presence (23%, 25%, respectively) in comparison to those with normal weight which was consistent with the published data confirming the parallel increase in prevalence of atherosclerotic risk factors with increasing BMI categories in patients with AS [2, 3, 7, 19, 20].

As for LV systolic function expressed by EF and/or TDIs' it had the lowest value, still normal for LVEF in obese patients before, and after SAVR when it insignificantly increased in all weight groups (p=0.399, p=0.815, respectively). Similarly, the LV inner dimensions in systole and diastole were insignificantly enlarged in obese patients before and after SAVR in comparison to those with overweight or normal weight, showing also insignificant decrease postoperatively. Turkbay et al. in the MESA study (Multi-Ethnic Study of Atherosclerosis) of overweight and obesity did not show significant association with low systolic LV function, suggesting that EF is an insensitive marker of myocardial changes in obesity [21]. However, findings of studies are quite variable showing depressed LVEF, normal EF and supernormal EF in obese subjects which mainly depend on population being evaluated as well as the effects of comorbidities such as hypertension, diabetes, coronary and/or vascular disease which often lead to cardiac enlargement and systolic dysfunction recognized as cardiomyopathy of obesity [11, 22]. Avelar et al. have speculated that even mild increases in blood pressure that still fall within the reference limit may have exaggerated effects on LV mass in obese subjects and consequently on the LV function [23]. However, it is important to stress that these findings are consistent with previous research on AS, describing reduced LV EF and cardiac output only in end-stage disease [24]. BMI in our study didn't appeared as independent predictor of LV systolic function.

As for the diastolic function, obese patients had insignificantly the highest enlargement of LAVI and highest value of E/e' ratio as marker of increased LV filling pressure before and after SAVR, but interestingly insignificant lower LVMi in comparison to patients with normal weight. BMI showed borderline positive correlation with postoperative E/e' which might have potentially detrimental effect on LV function after SAVR. We could not confirm the independent predictive role of BMI on the E/e' value, but only speculated that it might be due to significantly lower postoperative AVA/BSA (r=-0.285; p=0.043) in these obese patients along with influence of other risk factors. Numerous studies has been published on diastolic function either in obese population or patient with AS and almost in each study the close relationship of diastolic dysfunction with either obesity or AS was confirmed [11, 22, 24-26]. Russo et al. employed multivariable regression analysis to control for hypertension and diabetes mellitus in their study of diastolic filling in obesity [26]. They found that the relation between BMI and abnormalities of parameters of diastolic function was continuous and that even the overweight status was associated with diastolic dysfunction. Pascual et al. using Doppler echocardiographic indices of LV diastolic function showed that LV diastolic dysfunction occurred in 12% of class I, 35% of class II and 45% of class III obese patients [27]. Most studies demonstrating impaired LV diastolic function in obese patients have reported either a high prevalence of LV hypertrophy or an increased LV mass. However, several studies have identified impaired diastolic function in obese patients independent of LV mass identifying other mainly atherosclerotic factors responsible for it [22, 28]. As for diastolic function in AS, LV filling pressure is commonly increased in patients with severe disease mainly due to adaptive changes as response to increased pressure overload. Generally frequently accompanied with normal LV EF, diastolic dysfunction in AS exist and is confirmed factor of postoperative outcome [25, 29]. SAVR dramatically changes the clinical course of patients with AS by relieving the high pressure gradient and allowing the reversal of the LV hypertrophic process [29]. It is not clear whether the early reduction in afterload immediately after AVR (when hypertrophy is still present) also leads to improved diastolic function. In this context, Villari et al. concluded that it normalized late after SAVR [30].

Of note, patients with severe AS in process of progression are prone to extensive replacement fibrosis and reduced LV longitudinal shortening while LV EF is still normal, and at this point LV longitudinal strain could be assessed using speckle tracking echocardiography [25]. It is expected that

SAVR done on time, or before extensive myocardial impairment will obtained recovery of LV longitudinal shortening, reverse remodeling and improvement of a long-term outcome [31, 32]. Given that in our study patients were with severe AS it was not surprising to detect impaired GLS% at baseline, being more pronounced in obese patients. After SAVR, GLS% improved in all patients stratified according to BMI, but still remained rather low (more positive) in obese patients. Regression analysis revealed independent predictive value of BMI along with male gender for subnormal GLS% after SAVR, that was consistent with published data of several studies pointing that in obese subjects evidence of subclinical LV systolic dysfunction exist, even in the presence of normal LV EF [22, 24, 28, 33, 34]. The possible explanation for such result were: existence of systolic loads in obesity, even when hypertension is not present; evidence that LV geometric changes are associated with impaired mechanics; and presence of diastolic abnormality. In addition, existence of high valvulararterial impedance (Zva) could be further responsible for LV subclinical dysfunction taking into account that in patients with severe AS, LV is under double load of valvular and arterial load determined by a decrease in systemic arterial compliance [24, 35-37]. Hachicha et al. introduce this parameter as a marker of excessive LV hemodynamic load with goal to improve [36]. Assessement of stenosis severity beyond standard measurements. In addition, value of ≤ 3.5 mmHg/ ml^{-1} /m^2 was identified as cut-off value of normal impedance and according this value all patient in our study with severe AS showed highly increased Zva before SAVR, althoug without significant difference among them stratified according to BMI.

Zva after SAVR in obese patient declined, but significantly remained high in comparison to overweight who showed declined to medium value of Zva and those with normal weight who obtained postoperatively normal ZVA. In regression analysis, BMI appeared as independent significant predictor of higher Zva value which emphasize important role of this parameter in prediction of LV dysfunction and prognosis in patients postoperatively. Such results were in line with those who stressed that evaluation of Z_{va} seems to be a critical step in understanding the hemodynamics and mechanics of the heart in patients with AS, especially obese ones [38]. However, we could not find published data regarding relation between Zva and obesity, so far.

Study Limitations

The main limitation of our study is small number of patients. In addition, we assessed obesity only by BMI which might have its limitation regarding existence of other indices of fatness like waist circumference or waist-to-hip ratio who might better reflect presence and distribution of fat in the body and to identify central or visceral obesity, which is more closely associated with increased incidence of cardiovascular disease. Furthermore, patients were assessed 4 months after SAVR, thus it might be short period of time especially to assess diastolic function. Finally, present study didn't assessed whether weight loss will have positive impact on LV function after SAVR.

Conclusion

We could conclude that higher BMI is independent predictor of more extensive impairment of myocardial function and mechanics after SAVR for severe AS pointing that in obese subjects evidence of subclinical LV systolic dysfunction exist which along with more pronounced diastolic disfunction could contributed to more unfavorable long-term outcome.

References

1. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromso study. Heart 2013;99:396-400.
2. Yan AT, Koh M, Chan KK, et al. Association between cardiovascular risk factors and aortic stenosis: The CANHEART Aortic Stenosis Study. J Am Coll Cardiol 2017;69:1523-32.
3. Le Touneau T, Marechaux S, Vincentelli A, et al. Cardiovascular risk factors as predictors of early and late survival after bioprosthetic valve replacement for aortic stenosis. J Heart Valve Dis 2007; 16:483-8.
4. Ngo MV, Gottdiener JS, Fletcher RD, et al. Smoking and obesity are associated with the progression of aortic stenosis. Am J Geriatr Cardiol 2001;10:86-90.
5. Rodriguez-Gabella T, Voisine P, Puri R et al. Aortic bioprosthetic valve durability. Incidence, mechanisms, predictors, and management of surgical and transcatheter valve degeneration. J Am Coll Cardiol 2017;70:1013-28.

6. Rogge BP, Cramauric D, Lonnebakken MT, et al. Effect of overweight and obesity on cardiovascular events in asymptomatic aortic stenosis. A SEAS Substudy (Simvastatin Ezetimibe in Aortic Stenosis). J Am Coll Cardiol 2013; 62: 1683-90.
7. Smith II RL, Herbert MA, Dewey TM, et al. Does body mass index affect outcomes for aortic valve replacement surgery for aortic stenosis? Ann Thorac Surg 2012;93:742-7.
8. Daubert MA, Weissman NJ, Hahn RT, et al. Long-term valve performance of TAVR and SAVR. A Report From the PARTNER I Trial. J Am Coll Cardiol Img 2017;10:15-25.
9. Woodiwiss AJ, Libhaber CD, Majane OH, et al. Obesity promotes left ventricular concentric rather than eccentric geometric remodeling and hypertrophy independent of blood pressure. Am J Hypertens 2008;21:1144-51.
10. Pagé A, Dumesnil JG, Clavel MA, et al. Metabolic syndrome is associated with more pronounced impairement of left ventricular geometry and function in patients with calcific aortic stenosis. A substudy of the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin). J Am Coll Cardiol 2010; 55:1867-74.
11. Aurigemma GP, de Simone G, Fitzgibbons TP, et al. Cardiac remodeling in obesity. Circ Cardiovasc Imaging 2013;6:142-52.
12. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis. A disease of the valve and the myocardium. J Am Coll Cardiol 2012;60:1854-63.
13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-71.
14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277-314.
15. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:372-92.
16. Lancellotti P, Magne J. Valvuloarterial impedance in aortic stenosis: Look at the load, but do not forget the flow. Eur J Echocardiogr. 2011;12:354-357.
17. Voight JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J-Cardiovasc Img 2015; 16:1-11.
18. WHO Global Health Observatory Data Repository. Available at: http://apps.who.int/gho/data/node.main.A900?lang=en. Report of Instute for health of Former Yougoslav Republic of Macedonia, 2011.
19. Antonini-Canterin F, Hirsu M, Popescu BA, et al. Stage- related effect of statin treatment on the progression of aortic valve sclerosis and stenosis. Am J Cardiol 2008;102:738-42.
20. Capoulade R, Clavel MA, Dumesnil JG, et al. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. J Am Coll Cardiol 2012;60:216-23.
21. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC. Cardiovascular imaging 2010;3:266-74.
22. Abel ED, Litwin SE, and Sweeney G. Cardiac remodeling in obesity. Physiol Rev. 2008; 88: 389-419.
23. Avelar E, Cloward TV, Walker JM, et al. Left ventricular hypertrophy in severe obesity: interactions among blood pressure, nocturnal hypoxemia, and body mass. Hypertension 2007;49:34-9.
24. Calin A, Rosca M, beladan CC, et al. The left ventricle in aortic stenosis – imaging assessment and clinical implications. Cardiovasc Ultrasound 2015;13:22.
25. Chang SA, Park PW, Sung K, et al. Noninvasive estimate of left ventricular filling pressure correlated with early and midterm postoperative cardiovascular events after isolated aortic

valve replacement in patients with severe aortic stenosis. J Thorac Cardiovasc Surg 2010;140:1361-6.
26. Russo C, Jin Z, Homma S, et al. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. J Am Coll Cardiol 2011;57:1368-74.
27. Pascual M, Pascual DA, Soria F, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart. 2003;89:1152-1156.
28. Alpert MA, Omran J, Mehra A, Ardhanar S. Impact of obesity and weight loss on cardiac performance and morphology in adults. Prog Cardiovasc Dis 2014; 56: 391-400.
29. Elahi MM, Chuang A, Ewing MJ, et al. One problem two issues! Left ventricular systolic and diastolic dysfunction in aortic stenosis. Ann Transl Med 2014;2:10.
30. Villa E, Troise G, Cirillo M, et al.Factors affecting left ventricular remodeling after valve replacement for aortic stenosis. An overview. Cardiovascular Ustrasound 2006;4:25.
31. Dahl JS, Videbek L, Poulsen MK, et al. Global strain in severe aortic valve stenosis relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging. 2012;5:613-20.
32. Staron A, Bansal M, Kalakoti P, et al. Speckle tracking echocardiography derived 2-dimensional myocardial strain predicts left ventricular function and mass regression in aortic stenosis patients undergoing aortic valve replacement. Int J Cardiovasc Imaging 2013;29:797-808.
33. Iacobellis G, Ribaudo MC, Zappaterreno A, et al. Adapted changes in left ventricular structure and function in severe uncomplicated obesity. Obes Res 2004;12:1616-21.
34. Barbosa MM, Beleigoli AM, de Fatima Diniz M, et al. Strain imaging in morbid obesity: insights into subclinical ventricular dysfunction. Clin Cardiol. 2011;34:288-93.
35. Cramariuc D, Cioffi G, Rieck AE, et al. Low-flow aortic stenosis in asymptomatic patients: valvular arterial impedance and systolic func- tion from the SEAS substudy. J Am Coll Cardiol Img 2009;2:390 –9.
36. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol 2009;54:1003–11.
37. Jang JY, Seo JS, Joo Sun B, et al. Impact of valvuloarterial impedance on concentric remodeling in aortic stenosis and its regression after valve replacement. J Cardiovasc Ultrasound 2016;24:201-7.
38. Lancellotti P and Magne J. Valvuloarterial impedance in aortic stenosis: look at the load, but do not forget the flow. Eur J Echocardiog 2011;12:354-7.