Left ventricle geometry, atrial strain, ventricle strain, and hemodynamics across aortic valve before and after transcatheter aortic valve replacements

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ABSTRACT

Introduction: Transcatheter aortic valve replacements (TAVRs) has become widespread throughout the world. To date, there are no echocardiographic studies of TAVR patients from Southeast Asia (SEA). We sought to evaluate (1) changes in echocardiographic and strain values pre- and post-TAVR (2) relationship between aortic stenosis (AS) severity and strain values, (3) left ventricle geometry in severe AS, (4) relationship of flow rate to dimensionless index (DVI) and acceleration time (AT), and (5) effect of strains on the outcome.

Materials and methods: Retrospective study of 112 TAVR patients in our centre from 2009 to 2020. The echocardiographic and strain images pre (within 1 month), post (day after), and 6 months post-TAVR were analyzed by expert echocardiographer.

Results: The ejection fraction (EF) increased at 6 months (53.02 ± 12.12% to 56.35 ± 9.00%) (p=0.044). Interventricular septal thickness in diastole (IVSd) decreased (1.27 ± 0.21 cm to 1.21 ± 0.23 cm) (p=0.038) and left ventricle internal dimension in diastole (LVIDd) decreased from 4.77 ± 0.64 cm to 4.49 \pm 0.65 cm (p=0.001). No changes in stroke volume index (SVI pre vs 6 months p=0.187), but the flow rate increases (217.80 ± 57.61 mls/s to 251.94 ± 69.59 mls/s, p<0.001). Global longitudinal strain (GLS) improved from $-11.44 \pm 4.23\%$ to $-13.94 \pm 3.72\%$ (p<0.001), left atrial reservoir strain (Lar-S) increased from 17.44 ± 9.16% to 19.60 ± 8.77% (p=0.033). Eight patients (7.5%) had IVSd < 1.0 cm, and 4 patients (3.7%) had normal left ventricle (LV) geometry. There was linear relationship between IVSd and mean PG (r=0.208, p=0.031), between GLS to aortic valve area (AVA) and aortic valve area index (AVAi) (r = -0.305, p=0.001 and r = -0.316, p = 0.001). There was also relationship between AT (r=-0.20, p=0.04) and DVI (r=0.35, p<0.001) with flow rate. Patients who died late (after 6 months) had lower GLS at 6 months. (Alive; -13.94 ± 3.72% vs Died; -12.43 ± 4.19%, p=0.001).

Conclusion: At 6 months, TAVR cause reverse remodelling of the LV with the reduction in IVSd, LVIDd, and improvement in GLS and LAr-S. There is a linear relationship between GLS and AVA and between IVSd and AVA.

KEYWORDS:

Echocardiography, aortic stenosis, transcatheter aortic valve replacement, global longitudinal strain, Southeast Asia

INTRODUCTION

Since it was first performed in 2002 by Alan Cribier and his team, transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS) has become widespread worldwide.1 Its usage has expanded rapidly from the inoperable to intermediate and most recently to low-risk patients.²⁴ Echocardiography is one of the main tools for assessment of patients with severe AS either in general or pre and post TAVR. As far as we are aware, there is no published data from Southeast Asian (SEA) patients with most studies from this region coming from South Korea and Japan.⁵⁻⁷ With the advent of speckle tracking strain analysis, there were few publications from western countries looking at the changes in strain parameters pre- and post-TAVR and again there are no published data from SEA countries.⁸⁻¹⁰ In this study of multiracial patients in a single centre, Institut Jantung Negara (National Heart Institute), Kuala Lumpur, Malaysia, we sought to evaluate (1) immediate and 6 months changes in traditional echocardiographic and strain parameters, (2) relationship between these echocardiographic and strain parameters with AS severity, (3) pattern of left ventricle wall thickness and geometry pre-TAVR, (4) whether acceleration time (AT) and dimensionless index (DVI) is affected by flow rate, and finally (5) relationship of echocardiography and strain parameters to mortality.

MATERIALS AND METHODS

This is a single-centre retrospective study of patients with severe AS who underwent TAVR in our institution from 2009 to 2020.

Echocardiographic data

All the echocardiographic images from pre (up to 1-month pre-procedure), immediately (1-day post-procedure) and at 6 months post-procedure were analyzed. These duration for echocardiography is applied routinely for patients undergoing TAVR in our centre. We excluded those with incomplete images or those not suitable for interpretation

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(three patients excluded due to inadequate baseline images). For traditional echocardiographic parameters of left ventricle, we analyzed interventricular septal thickness at diastole (IVSd), left ventricle internal dimension at diastole (LVIDd), posterior wall thickness at diastole (PWTd), biplane Simpsons' ejection fraction (EF), and relative wall thickness (RWT). For aortic valve, we calculated aortic valve area (AVA), aortic valve area index (AVAi) from continuity equation, peak velocity (Vmax), mean gradient (meanPG), AT, AT/ejection time (AT/ET) and DVI across aortic valve. Lastly, we calculated the stroke volume index (SVi), flow rate (stroke volume/ET across left ventricular outflow tract), peak tricuspid regurgitation gradient (TRpeak PG), systolic pulmonary artery pressure (s-PAP), and left atrial volume index (LAVI).

Strain analysis

We analyzed strain by using Tom Tec software retrospectively by using apical four chamber view, apical three chamber view, apical two chamber view for global longitudinal strain (GLS), apical 4 chamber view for left atrial reservoir strain (LAr-S), left atrial conduit strain (LAc-S), and left atrial booster strain (LAbooster-S). For right ventricle free wall strain (RVFW-S), we used right ventricle focused apical four chamber views.

Statistical analysis

The categorical variables were presented as percentage and the continuous variables were presented in terms of mean and standard deviations. Repeated measures ANOVA were used to compare differences between groups at different time points with a Greehouse-Geisser correction and post hoc analysis of Bonferroni correction where applicable. The linear association between variables was determined using Pearson correlation coefficients. *p* values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS ver. 27.0 (SPSS, Chicago, IL, USA).

RESULTS

There was n=112 patients included in the study (female;57 and male; 55). The average age was 77.97 ± 5.01 years old. 45.5% (n=51) were Malay, 22.3% (n=25) were Chinese, 22% (n=19.6) were Indian, 5.4% (n=6) were of other races from Malaysia and 7.1% (n=8) were patients from other countries. The procedures were done with both self-expandable and balloon expandable TAVR valves. There are two procedure failures, and both are caused by left ventricle (LV) perforations. Overall, 6 (5.4%) patients died in the hospital and 7 (6.3%) patients died within 6 months of procedure (Total 6 months mortality was 13 patients, 11.6%). 34 (30.4%) patients died after 6 months, and 64 (57.1%) patients are still alive. One patient was lost to follow-up after the procedure. Therefore, they were 98 patients that have complete echocardiographic and strain data until 6 months postprocedure (34 who died after 6 months plus 64 that is still alive). 12 (10.7%) patients need pacemaker implantations. Pre-procedure, most patients are in NYHA II (48.2%) and III (28.6%), and at 1 month, majority of patients are in NYHA I (83.9%). Immediately post procedures majority of patients have mild paravalvular (83.9%) and mild transvalvular (86.6%) regurgitation (Table I).

At 6 months post-TAVR, AVA increased from 0.68 ± 0.19 cm² to 2.02 ± 0.73 cm² (p<0.001), peak aortic velocity went down from 4.45 ± 0.64 m/s to 2.06 ± 0.59 m/s (p<0.001), and mean PG came down from 49.94 ± 13.53 mmHg to 9.49 ± 6.09 mmHg (p<0.001). Interestingly, there were no significant changes in SVi (46.42 ± 13.71 mls/m2 to 49.00 ± 13.95 mls/m²; p=0.187) although the flow rate increased significantly to upper limit of normal (217.80 ± 57.61 mls/s to 251.94 ± 69.59 mls/s; p<0.001) (Table II)

For other echocardiographic parameters at 6 months, EF increased from $53.02 \pm 12.12\%$ to $56.35 \pm 9.00\%$ (p=0.004). Both IVSd and LVIDd reduced significantly (IVSd; 1.27 ± 0.21 cm to 1.21 ± 0.23 cm, p=0.022 and LVIDd; 4.77 ± 0.64 cm to 4.49 ± 0.65 cm, p<0.001). As expected, AT decreased from 120.00 ± 26.33 ms to 75.98 ± 16.82 ms (p<0.001) and DVI increased from 0.21 ± 0.06 to 0.60 ± 0.17 (p<0.001). There were no significant changes in PWTd (p=0.136), RWT (p=0.831), LAVI (p=0.183), and s-PAP (p=0.772) immediately and at 6 months (Table II).

From analysis of speckle tracking strain, both GLS and LAr-S had significant overall improvement at 6 months (GLS; from -11.44 ± 4.23% to -13.94 ± 3.72%, p<0.001 and LAr-S from $17.44 \pm 9.16\%$ to $19.60 \pm 8.77\%$, p=0.033). This was interesting as LAVI did not change significantly post-TAVR. There were no significant changes in left atrial conduit strain (LAc-S, p=0.326), left atrial booster strain (LA booster, p=0.562), and RVFW-S (p=0.543). There was a greater relative increase in GLS compared to EF (21.85% vs 6.28%) and relative increases in LAr-S were more than relative to decreases in LAVI (12.39% vs 5.38%). Patients who died after 6 months had lower GLS at 6 months (-12.43 \pm 4.19% vs - $13.94 \pm 3.72\%$, *p*=0.001) (Table II). We also analyzed the bull's eyes appearance of the GLS for apical sparing define by: (Average apical GLS/ (Average basal GLS + average mid GLS)> 1. However, none of our patients fulfilled those criteria.

We performed linear regression analysis to evaluate the relationship between pre-TAVR IVSd and strain with AS severity. IVSd had moderate but significant direct relationship with MeanPG (r=0.208, p=0.031) and AVA (r=0.239, p=0.013). GLS had stronger and significant inverse relationship with AVA (r=-0.305, p=0.001) and AVAi (r=-0.316, p=0.001) while RVFW-S had weak but significant inverse relationship with AVAi (r=-0.179, p=0.041) (Table III, Figure 1a to 1d). AT had significant inverse relationship with flow rate (r=-0.199, p=0.040) and DVI had significant direct relationship with flow rate (r=0.347, p<0.001) (Table III, Figure 1e). We also found 4 patients (3.74%) to have had normal LV geometry followed by eccentric hypertrophy, n=13 (12.15%) and concentric remodelling, n= 23 (21.5%). Majority had concentric hypertrophy=67 (62.62%) (Figure 2a). 8 patients (7.5%) had IVSd < 1.0cm while 13 patients (12.1%) had PWTd < 1.0cm (Figures 2b and 2c).

DISCUSSION

This study involved 112 severe AS patients from different ethnicities in Malaysia, a country in SEA where there is no existing published data about echocardiographic and strain parameters pre- and post-TAVR procedures. As expected, the

Variables		TAVR (N = 112)
	Demographics	
Age, mean ± SD	77.97 ± 5.01	
Female; N (%)	57 (50.9)	
Race group	Malay; N (%)	51 (45.5)
	Chinese; N (%)	25 (22.3)
	Indian; N (%)	22 (19.6)
	Other Malaysian; N (%)	6 (5.4)
	Foreigner; N (%)	8 (7.1)
	TAVR Patient Characteristics	
Valve type	Corevalve; N (%)	37 (33.0)
	Corevalve Evolut-R; N (%)	26 (23.2)
	Edwards Sapien; N (%)	13 (11.6)
	Edwards Sapien 3; N (%)	23 (20.5)
	Edwards Sapien XT; N (%)	10 (8.9)
	Myval; N (%)	3 (2.7)
	Outcomes	
In-hospital death; N (%)		6 (5.4)
Follow up	Death \leq 6 months; N (%)	7 (6.3)
	Death > 6 months; N (%)	34 (30.4)
	Lost to follow-up; N (%)	1 (0.9)
	Alive; N (%)	64 (57.1)
Pacemaker implantation; N (%)		12 (10.7)
NYHA pre-procedure	l; N (%)	17 (15.2)
	II; N (%)	54 (48.2)
	III; N (%)	32 (28.6)
	IV; N (%)	9 (8.0)
NYHA post-procedure at 1 months	I; N (%)	94 (83.9)
	ll; N (%)	7 (6.3)
	III; N (%)	1 (0.9)
	IV; N (%)	0 (0)
Post-procedure paravalvular regurgitation	None; N (%)	14 (12.5)
	Mild; N (%)	94 (83.9)
	Moderate; N (%)	3 (2.7)
	Severe; N (%)	1 (0.9)
Post-procedure transvalvular regurgitation	None; N (%)	14 (12.5)
	Mild; N (%)	97 (86.6)
	Moderate; N (%)	1 (0.9)
	Severe; N (%)	0 (0)

Table: I Demographics, TAVR patient characteristics, and outcomes

AVA increased while peak aortic velocity and meanPG decreased significantly, immediate and at 6 months post-TAVR. In term of EF, our patients showed significant improvements post-TAVR, like previous publications involving patients of different races¹¹⁻¹⁵. Next, we analyzed the changes in IVSd, LVIDd, and PWTd pre- and post-TAVR. Like TAVR, there are echocardiographic studies in surgical aortic valve replacement patients showing significant regression of these parameters.^{16,17} For TAVR patients, however, most of the studies utilize cardiac magnetic resonance imaging rather than echocardiography to demonstrate reverse remodeling¹⁸ ²⁰. In this study, there were significant reductions in IVSd and LVIDd at 6 months post-TAVR but there were no differences in PWTd and RWT. Flow (volume of blood ejected in a single heartbeat per body surface) and flow rate (volume of blood ejected per second) are different parameters. There is one prior study that illustrates how TAVR improves SVi21, but we could not find any publication looking at flow rate post-TAVR. In our study, we found that the SVi did not increase significantly but flow rate increased almost 16% from baseline.

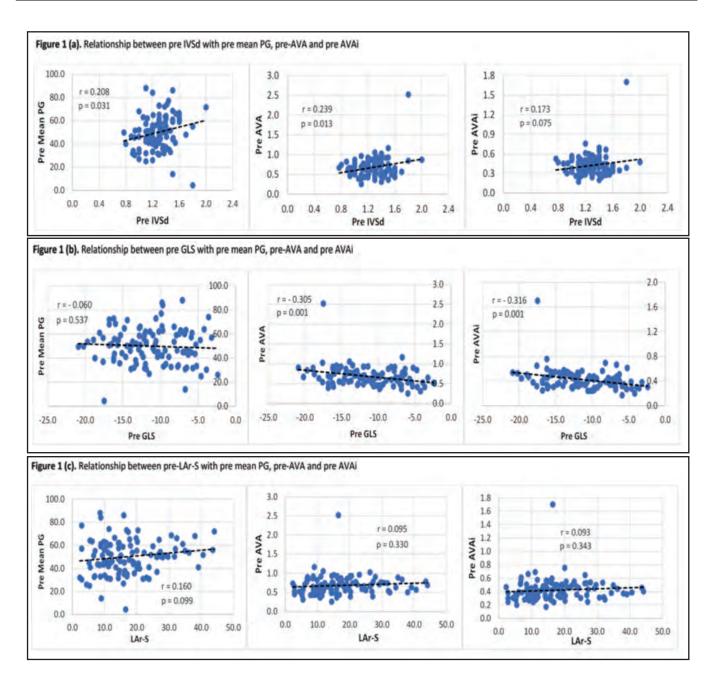
Prior studies tend to look at a single aspect of strain, but in this study, we analyzed almost all aspects of strain. There were many prior publications showing improvement in GLS after TAVR procedures, thus suggesting that baseline GLS can be predictive of outcome.8-10,22 Our study showed no improvement in GLS immediately post-TAVR, but significant improvement (21.9%) at 6 months post-AVR. The relative improvements in GLS were much higher than in EF (21.85% vs 6.28%). There was no difference in baseline GLS between those who died after 6 months versus those who did not, but patients who were still alive exhibited higher GLS at 6 months post-TAVR. Studies on LAr-S, LAc-S and LAbooster-S in TAVR are rare but published data did show improvement in LAr-S post-TAVR. $^{\scriptscriptstyle 23,\bar{2}4}$ In our study, LAr-S did not increase immediately but only improved at 6 months post-TAVR (relative increase of $12.\overline{4}\%$). There was no significant difference in LAc-S and LAbooster-S post-TAVR. Lastly, there are many different parameters of RV function, but RVFS-S has been suggested as single best parameter for right ventricle assessment and is predictive of mortality.^{25,26} However, there was no significant improvement and no difference in

Characteristics	Pre	Post Immediate	Post 6 months	Overall	p value	p value posts hoc analysis	sis	% Mean Difference
				p value	Pre-to-post Po	Post-to-6 month	Pre-to-6-month	(pre- to 6 months)
			Echocardio	Echocardiographic Parameters				
IVSd	1.27 ± 0.21	1.26 ± 0.19	1.21 ± 0.23	0.022	1.000	0.174	0.038	-4.72
PWTd	1.19 ± 0.24	1.17 ± 0.22	1.12 ± 0.20	0.136		-5.88		
LVIDd	4.77 ± 0.64	4.60 ± 0.58	4.49 ± 0.65	<0.001	0.044	0.288	0.001	-5.87
RWT	0.51 ± 0.14	0.52 ± 0.12	0.51 ± 0.11	0.831		0.00		
EF	53.02 ± 12.12	56.64 ± 11.31	56.35 ± 9.00	0.004	0.004	1.000	0.044	6.28
AVA	0.68 ± 0.19	2.07 ± 0.73	2.02 ± 0.73	<0.001	<0.001	1.000	<0.001	197.06
AVAi	0.42 ± 0.12	1.28 ± 0.44	1.25 ± 0.47	<0.001	<0.001	1.000	<0.001	197.62
Peak velocity	4.45 ± 0.64	1.98 ± 0.50	2.06 ± 0.59	<0.001	<0.001	0.463	<0.001	-53.71
Mean PG	49.94 ± 13.53	8.57 ± 4.51	9.49 ± 6.09	<0.001	<0.001	0.226	<0.001	-81.00
SVi	46.42 ± 13.71	46.34 ± 13.54	49.00 ± 13.95	0.187		5.56		
АТ	120.00 ± 26.33	73.74 ± 16.86	75.98 ± 16.82	<0.001	<0.001	1.000	<0.001	-36.68
AT/ET	0.35 ± 0.07	0.25 ± 0.05	0.24 ± 0.05	<0.001	<0.001	1.000	<0.001	-31.43
Flow rate	217.80 ± 57.61	249.32 ± 69.75	251.94 ± 69.59	<0.001	<0.001	1.000	<0.001	15.67
DVI	0.21 ± 0.06	0.62 ± 0.18	0.60 ± 0.17	<0.001	<0.001	0.851	<0.001	185.71
TR Peak PG	30.44 ± 14.34	29.59 ± 12.41	29.10 ± 10.62	0.806		-4.40		
s-PAP	34.96 ± 16.37	34.46 ± 14.42	33.29 ± 12.12	0.772		-4.78		
LAVI	52.96 ± 15.29	51.93 ± 16.74	50.11 ± 17.42	0.183		-5.38		
			Strair	Strain Parameters				
GLS	-11.44 ± 4.23	-11.65 ± 5.13	-13.94 ± 3.72	<0.001	1.000	0.003	<0.001	21.85%
LAr-S	17.44 ± 9.16	16.69 ± 7.98	19.60 ± 8.77	0.033	1.000	0.041	0.203	12.39%
LAc-S	10.17 ± 6.56	8.96 ± 5.26	10.07 ± 6.28	0.326		-0.98%		
LA booster	10.85 ± 5.90	11.24 ± 5.57	12.01 ± 6.02	0.562		10.69%		
RVFW-S	-19.01 ± 6.88	-18.26 ± 6.75	-19.27 ± 6.44	0.543		1.47%		
			Echocardiographic and Strain Parameters with mortality	Strain Parameters wi	th mortality			
Characteristics		Pre	Post	Post	% Mean Difference	e p value ¹	p value ²	p value ³
			immediate	6 months	(Pre- to-6-month)			
LAr-S	Overall	17.44 ± 9.16	16.69 ± 7.98	19.60 ± 8.77	12.39%	0.563		
	Alive	16.90 ± 8.12	16.93 ± 7.17	20.12 ± 7.51	19.00%		0.898	0.405
	Death	18.52 ± 11.07	16.21 ± 9.56	18.58 ± 10.98	0.31%			
GLS	Overall	-11.44 ± 4.23	-11.65 ± 5.13	-13.94 ± 3.72	21.80%	0.001		
	Alive	-11.53 ± 4.29	-11.84 ± 5.31	-14.69 ± 3.25	27.48%		0.206	0.246
	Death	-11.28 ± 4.19	-11.25 ± 4.84	-12.43 ± 4.19	10.19%			
RVFW-S	Overall	-19.01 ± 6.88	-18.26 ± 6.75	-19.29 ± 6.44	1.48%	1.000		
	Alive		+1	+I	10.09%		0.067	0.051
	Death	-19.06 ± 5.73	-17.06 ± 6.90	-16.07 ± 5.45	-15.68%			
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p value ¹ suggested any	statistically significance	p value' suggested any statistically significance of value differences at %	6 difference pre to post 6 months. p value ² suggested any statistically significance of value differences between groups regardless	nonths. <i>p</i> value ² suggeste	ed any statistically signi	ficance of value d	ifferences between	groups regardless
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	Relationship between IVSd, Strains with MeanPG, AVA and AVAi					
		MeanPG	AVA	AVAi		
IVSd	Correlation coefficient, r	0.208	0.239	0.173		
	p value	0.031	0.013	0.075		
GLS	Correlation coefficient, r	- 0.060	- 0.305	- 0.316		
	p value	0.537	0.001	0.001		
Lar-S	Correlation coefficient, r	0.160	0.095	0.093		
	p value	0.099	0.330	0.343		
RVFW-S	Correlation coefficient, r	- 0.172	- 0.151	- 0.197		
	p value	0.076	0.122	0.041		
	Relationship be	tween DVI/AT and Flow R	late	·		
		AT	DVI			
Flow rate	Correlation coefficient, r	- 0.199	0.347			
	p value	0.040	<0.001			

Table III: Relationship between IVSd, strains with meanPG, AVA and AVAi and relationship between DVI/AT and flow rate. N = 112 Relationship between IVSd. Strains with MeanPG, AVA and AVAi



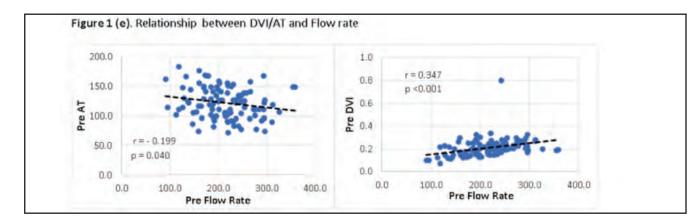
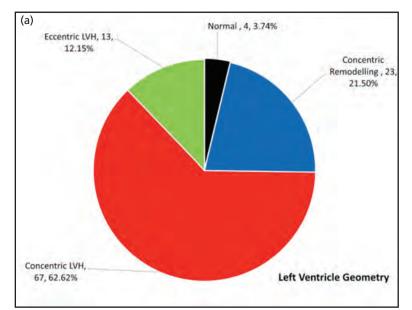


Fig. 1: (a) Relationship between pre IVSd with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, IVSd have a moderate but significant direct relationship with meanPG and AVA but not AVAi. (b) Relationship between pre-GLS with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, GLS have a strong and significant inverse relationship with AVA and AVAi but not meanPG. (c) Relationship between pre-LAr-S with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, LAr-S have no significant relationship with AS severity. (d) Relationship between pre RVFW-S with pre-mean PG, pre-AVA, and pre AVAi. In pre-TAVR patients, RVFW-S have a weak but significant inverse relationship with AVAi only. (e) Relationship between DVI/AT and flow rate. Both AT and DVI have a significant linear relationship with flow rate. The relationship is stronger between DVI and flow rate.



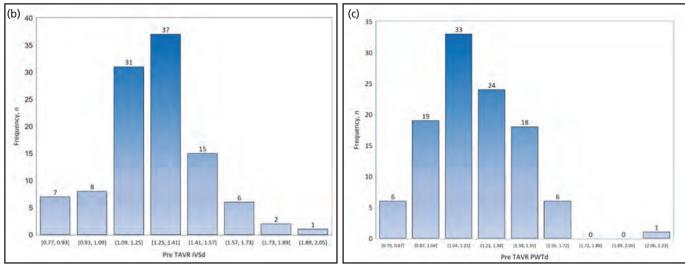


Fig. 2: (a) Left Ventricle Geometry. (b) Pre-TAVR IVSd. (c) Pre-TAVR PWTd.

baseline RVFW-S between those who were alive and those who died in our study at 6 months post-TAVR.

AS causes increase in afterload and therefore increase in LV wall thickness. There were studies previously showing that it was possible to have normal LV wall thickness and normal LV geometry in severe AS.^{6,18} This was seen in small group of our patients who have normal LV geometry (n=4; 3.74%) and wall thickness < 1.0 cm (IVSd n=8;7.5% and PWTd n=13;12.1%). There are not many studies looking at relationship between IVSd, PWTd, strain parameters, and AS severity.^{5,27} There is moderate direct relationship between IVSd and AS severity (meanPG and AVA), moderate inverse relationship between GLS and AS severity (AVA and AVAi) and finally weak inverse relationship between RVFW-S and AS severity (AVAi).

AT and DVI are echocardiographic parameters that was initially utilized for prosthetic aortic valve dysfunction assessment but recently has also been studied in native aortic valve patients.^{69,10,21} In this study, we wanted to see whether these parameters were related to flow rate, and indeed, we found that AT had moderate but inverse relationship with flow rate whereas DVI had stronger and direct relationship with flow rate. Therefore, flow rate should be considered when using these parameters.

CONCLUSION

Our study of multiracial patients in a single centre showed that TAVR improved EF, IVSd, LVIDd, GLS, and LAr-S at 6 months. Both IVSd and GLS have a linear relationship with AS severity and the AT and DVI were significantly affected by flow rate.

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