

Multiparametric Assessment of Post-Transcatheter Aortic Valve Replacement Paravalvular Regurgitation Grading by Transthoracic Echocardiography and Cardiac Magnetic Resonance

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Abstract

Purpose: Paravalvular regurgitation post-transcatheter valve replacement is associated with poor outcomes. The Valve Academic Research Consortium has defined qualitative and quantitative criteria for assessing paravalvular leak severity by transthoracic echocardiography. Cardiac magnetic resonance imaging is highly accurate and reproducible in measuring aortic flow volumes, and has been used for further evaluation of paravalvular regurgitation. The agreement between the multiparametric grading of paravalvular regurgitation by transthoracic echocardiography and cardiac magnetic resonance imaging is unclear.

Methods: We retrospectively identified 18 patients who had undergone transcatheter aortic valve replacement and received both transthoracic echocardiography and cardiac magnetic resonance imaging. The following echocardiographic parameters were measured: regurgitant fraction, effective regurgitant orifice area, jet width diameter, circumferential extent of paravalvular leak. Regurgitant fraction was measured on cardiac magnetic resonance imaging using the phase-contrast technique. Paravalvular leak was graded according to the VARC-2 guidelines. A total of 21 paired imaging studies were compared.

Results: The interparametric agreement was poor, with a kappa statistic ranging between -0.02 to 0.21. Most notably, severity by echocardiographic circumferential extent was over-estimated in 85.7% of studies compared to cardiac magnetic resonance imaging.

Conclusions: The agreement between the different echocardiographic parameters, and between echocardiography and cardiac magnetic resonance in assessing paravalvular leak severity is poor. Cardiac magnetic resonance imaging should be considered in the evaluation of paravalvular severity when the echocardiographic assessment and clinical findings are incongruent. Larger, prospective studies comparing both modalities are needed to justify its routine use in the evaluation of paravalvular regurgitation post-transcatheter aortic valve replacement.

Keywords: Paravalvular regurgitation; Transcatheter aortic valve replacement; Echocardiography; CMR; TAVR; PVL

Abbreviations: CMR: Cardiac Magnetic Resonance; MDCT: Multi Detector Computed Tomography; PVL: Paravalvular leak; TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography

Background

Paravalvular Regurgitation or Leak (PVL) is common Post-Transcatheter Aortic Valve Replacement (TAVR), and has been consistently associated with increased short and long term mortality. Identifying and accurately characterizing paravalvular regurgitation in transcatheter heart valves is thus of paramount importance for both prognostication and potential intervention [1]. While multiple modalities such as angiography, computed tomography, as well as cardiac Magnetic Resonance Imaging (CMR) have been used to characterize PVL, echocardiography remains the least costly and most widely available. However, technical challenges relating to geometric assumptions, jet eccentricity, acoustic shadowing, shielding and reverberation of the valvular frame as well as the highly operator-dependent nature of echocardiography, preclude accurate and precise characterization of PVL severity. The Valve Academic Research Consortium (VARC) has defined qualitative and quantitative criteria for assessing PVL severity by echocardiography that emphasize describing the jet anatomy (i.e. location, circumferential extent and width, effective orifice area, pressure half-time), and estimating

regurgitant volume or fraction (Table 1). These criteria are derived from guidelines on measuring native aortic valve regurgitation [2]. They have not been universally adopted by the different studies, and it is still unclear which cut-offs or changes in echocardiographic parameters translate to changes in management, or correlate best with clinical outcomes.

CMR has been used as a supplement to echocardiography in the evaluation of PVL post-TAVR, especially when there is discordance in clinical findings and grading from different echocardiographic windows. Its advantages include improved endocardial definition, fewer geometric assumptions, and less angle dependence for flow measurements. By using phase-contrast velocity mapping, CMR allows for highly accurate and reproducible measurements of aortic flow, and subsequent quantification of regurgitant volumes, with significantly

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Parameter	Mild	Moderate	Severe
VARC-2			
Semi-quantitative parameters*			
Diastolic flow reversal in the descending aorta by pulsed wave	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of PVR (%)	<10%	10-29%	≥30%
Quantitative parameters*			
Regurgitant volume (ml/beat)	<30 ml	30-59 ml	≥60 ml
Regurgitant fraction (%)	<30%	30-50%	≥50%
EROA (cm ²)	<0.10 cm ²	0.1-0.29 cm ²	≥0.30 cm ²

*Adapted from the Valve Academic Research Consortium-2 [16]. EROA: Effective regurgitant orifice area; CW: Continuous wave Doppler; PW: Pulse wave Doppler.

Table 1: Echocardiographic Criteria for Grading PVL per VARC-2.

less intra and inter-observer variability [3-10]. High grade aortic regurgitation by CMR has also been associated with clinical outcomes in candidates for surgical aortic valve replacement [11]. PVL severity estimated by CMR has been shown to correlate well with severity assessment by angiography; considered the gold standard [12].

How well the multiple echocardiographic parameters correlate to each other and how parameters correlate to CMR in the determination of PVL severity is unknown. Given the prognostic and therapeutic implications of PVL severity, accurate determination of PVL grade is a necessity. In this retrospective study, we aimed to evaluate the agreement between PVL severity assessed by CMR, and that assessed

by the various echocardiographic parameters using the VARC-2 guidelines in patients who underwent TAVR with the Edwards Sapiens valve (Edwards Lifesciences, Irvine, CA).

Methods

Study design and population

Electronic medical charts of all patients who underwent TAVR at Emory University Hospital from January 2007 to May 2013 were reviewed. Those who received both TTE and CMR for the evaluation of PVL post-TAVR were identified retrospectively. Patients were included regardless of post-operative time of PVL evaluation. Patients who had undergone TTE and CMR more than 12 days apart were excluded. Studies were analyzed by two experienced and independent operators, one for each modality (CMR and TTE), who are blinded to the measurements of the other modality. Data collection and analysis was performed with approval of the Emory University institutional review board committee.

Echocardiography

Echocardiograms analyzed had been previously performed according to standard protocol. The following parameters were obtained by an experienced echocardiographer when possible: Regurgitant Fraction (RF), Effective Regurgitant Orifice Area (EROA), Jet Width Diameter (JW), Aortic Valve Pressure Half-Time (PHT), and Circumferential Extent of PVL (CIRC) (Figure 1). Severity of PVL

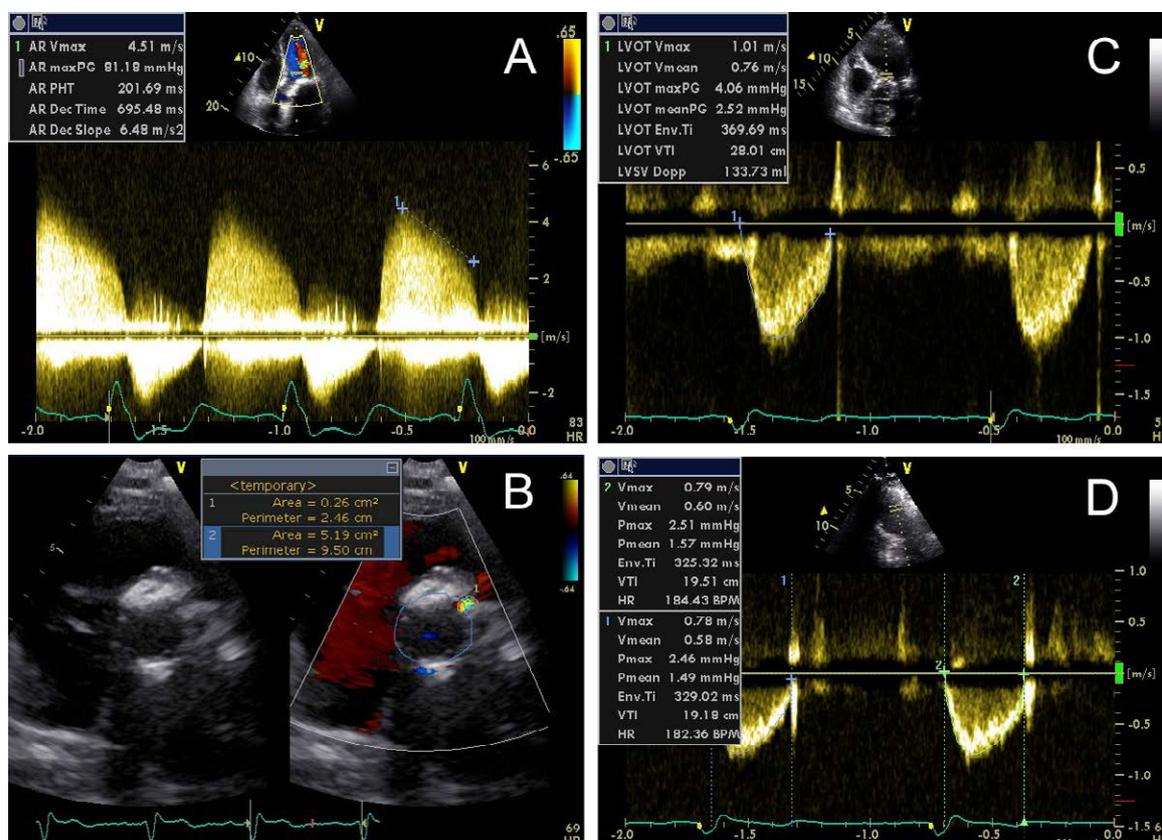


Figure 1: Echocardiographic Grading of Paravalvular Regurgitation. Panel A: Measurement of pressure half-time of aortic regurgitation off 5-chamber apical view. Panel B: Measurement of circumferential extent of aortic annulus and regurgitation in short axis view. Panel C: Measurement of velocity-time integral across the left ventricular outflow tract used to calculate left ventricular stroke volume. Panel D: Measurement of velocity-time integral across right ventricular outflow tract used to calculate right ventricular stroke volume.

was graded using each parameter according to the VARC-2 guidelines (Table 1). TTE measurements were made using Syngo Dynamics Workspace (V5.05, Siemens Medical Solutions, Malvern, PA).

CMR imaging

Cardiac magnetic resonance imaging had been performed in these patients for further evaluation of PVL, when discordance was noted between a patient's symptoms, BNP levels and echocardiogram findings. The following protocol was used for PVL measurement by CMR at our institution: images are acquired with a 1.5 Tesla MRI (Avanto, Siemens Medical Solutions, Erlangen, Germany). Post processing of images using the Argus software (Siemens Medical Solutions). Flow is measured with 2D, ECG-gated, segmented, turbo Flash Phase-Contrast Magnetic Resonance (PCMR) sequence. The velocity encoding basal value is set at 150 cm/sec and velocity was encoded in the through-plane direction. If aliasing is seen, the velocity encoding value is increased until no aliasing is noted. The image slice is positioned 5 mm above the aortic valve to ensure minimal impact of aortic compliance and metallic artifact on measurements. Coronal survey images are used to confirm that the slice is perpendicular to the aorta in two views. Image resolution is typically 1.6 x 1.3 x 6.0 mm, and

20 frames are reconstructed over the cardiac cycle using a retrospective ECG gating. A Region of Interest (ROI) is traced around the aorta on the magnitude images and this boundary is transferred to the phase images. The ROI's are adjusted in each cardiac phase to ensure the aorta was included, but not other vessels. The Argus program then automatically calculated an instantaneous flow rate for each cardiac cycle by integrating velocity values over the ROI's at each cardiac phase. The resulting curve reflects flow rate over the cardiac cycle (Figure 2). Integration of the flow rate curve gives the net, absolute forward and regurgitant flow volume. Regurgitant fraction (%) is calculated as the ratio of regurgitant volume in mL to the forward volume in mL. PVL is quantified as mild (RF <30% regurgitant fraction), moderate (RF 30-50%), or severe (RF >50%) based on established echocardiographic guidelines for regurgitant fraction in patients with PVL.

Statistical analysis

TTE and CMR studies were paired per patient and according to time proximity. Each pair was de-identified and assigned a study number. A total of 21 paired CMR-TTE evaluations were compared. The unweighted kappa statistic was used to describe agreement between PVL severity as classified by the different echocardiographic

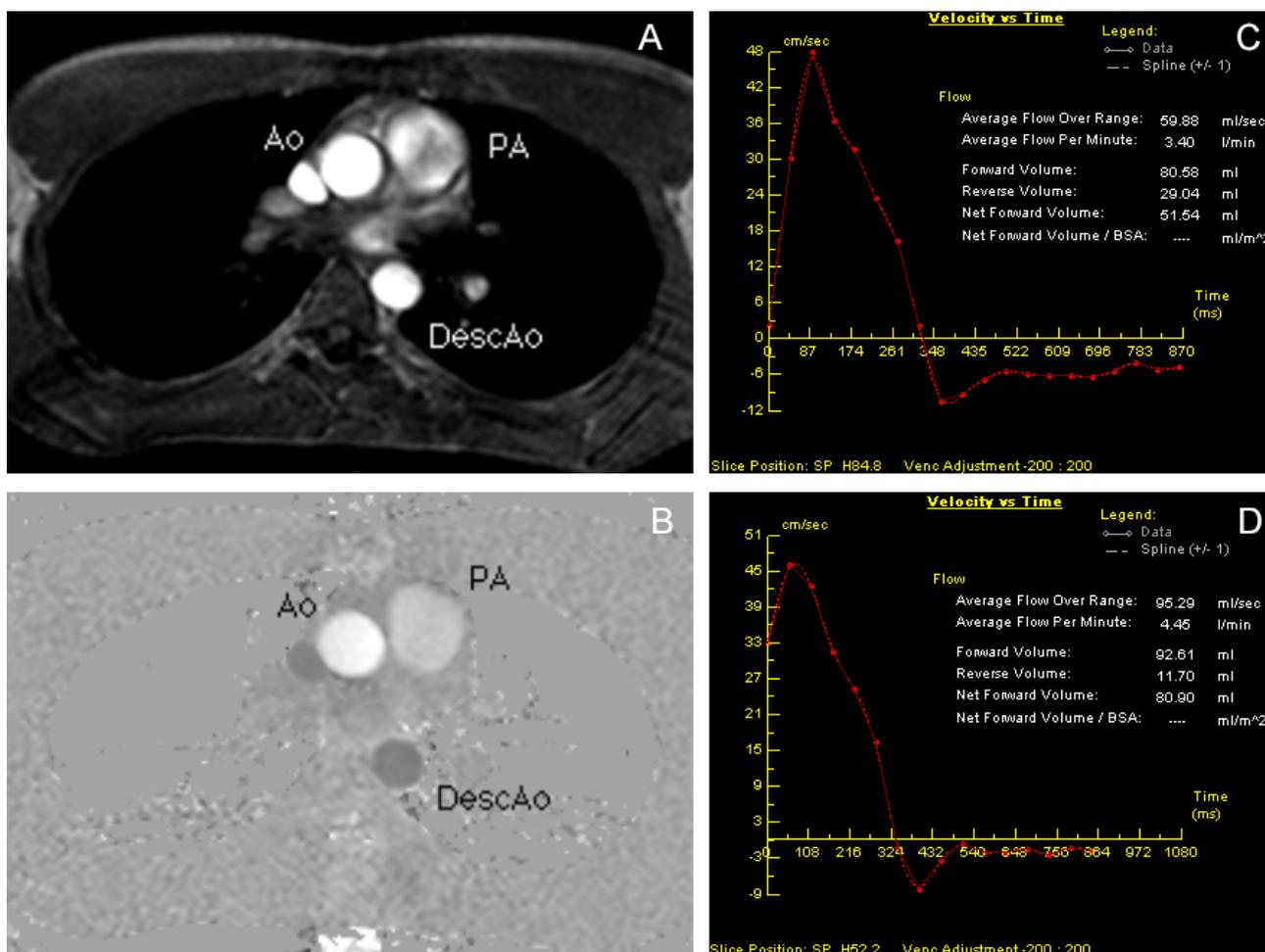


Figure 2: Measuring Regurgitation Fraction by Cardiac Magnetic Resonance Imaging. Panel A: Magnitude Image. Panel B: Through-plane phase contrast velocity mapping for flow quantification. Panel C: Velocity versus time curve depicting forward and reverse flow through aortic valve post-transcatheter valve replacement. Note significant regurgitation volume. Panel D: Velocity versus time curve of the same patient after undergoing valve-in-valve for significant paravalvular regurgitation. Note significant decrease in regurgitant volume.

parameters, as well as between echocardiographic parameters and CMR measured RF. The standards for strength of agreement for the kappa coefficient are as follows: ≤ 0 =poor, 0.01–.20=slight, 0.21–.40=fair, 0.41–0.60=moderate, 0.61–0.80=substantial, and 0.81–1=almost perfect [13]. Baseline characteristics of patients are reported as descriptive statistics with means, medians, SDs, and ranges. Categorical outcomes are presented as counts and percentages.

Results

Study population

A total of 18 patients underwent both TTE and CMR for the evaluation of PVL (Table 2). Three patients received two CMR and TTE studies each at different time intervals; pre and post procedural intervention for PVL repair. Included patients were mostly white (94.7%), male (63.2%), with a mean age of 85.0 ± 5.5 years, and BMI of 24 ± 2.2 kg/m². All patients received Edwards SAPIEN valves, with 7 (38.9%) receiving a 23 mm valve, 10 (55.5%) receiving a 26 mm valve, and one (5.5%) received a 29 mm valve. The average ejection fraction at PVL evaluation by TTE was $46 \pm 14.0\%$. The median time interval to PVL evaluation post-TAVR was 6 days, with a range of 1 to 1064 days. The median time between TTE and CMR was 1 day, with a range of 0 to 12 days (Table 1).

Paravalvular regurgitation by TTE

Severity of PVL was assessed using the different parameters indicated in the VARC-2 guidelines. Circumferential extent of PVL was obtained in all echocardiograms. PVL severity by circumferential extent was as follows: 14.3% of studies showed mild PVL, 19.0% moderate, and 66.7% severe. Regurgitant fraction was calculated in only 12 or 57.1% of echocardiograms. By TTE RF criteria, 41.3% of PVL would be classified as mild, 53.8% as moderate, and none as severe. Similarly, PVL severity by jet width was available in two thirds of studies, with 71.4% of studies classifying PVL as mild using this parameter, 28.6% as moderate and none as severe. Other measures of PVL such as effective regurgitant orifice area and pressure half-time were obtained in less than a third of the studies. Agreement between the different echocardiographic parameters was poor, with the kappa statistic ranging between -0.05 and 0.19 (Figure 3A and Table 3).

Paravalvular regurgitation by CMR

Paravalvular regurgitant fraction was calculated in all CMR studies. Using the aforementioned guidelines, 15 or 71.4% of studies classified PVL as mild, 6 or 28.6% moderate, and none as severe. The agreement between severity by CMR and the multiple echocardiographic parameters was poor, ranging from -0.02 to 0.21 (Table 3). Using the RF delimitations for PVL severity, 7 (58.3%) of 12 echocardiograms were in agreement with the respective CMR study, 4 (30%) over-estimated and only 1 underestimated PVL severity. By circumferential extent, only 3 of 21 studies which were in agreement between CMR and TTE, while TTE over-classified 18 or 85.7% of studies. CMR and TTE by jet width agreed in 9 or 60.0% of studies. Severity by jet width over-classified 2 or 13.3% of studies, under-classified 4 or 26.7% of studies compared to CMR (Figure 3B-D).

Outcomes

In this cohort of 18 patients, only 4 out of 13 (28.6%) patients whose PVL was classified as severe by circumferential extent underwent procedural repair; 1 received an Amplatzer plug, and 3 underwent valve-in valve implantation. On repeat imaging post-implantation, PVL was still graded as severe by TTE using circumferential extent,

while by CMR it was classified as mild. Fifteen (83.3%) of patients had follow-up at one year; 3 patients had died and one patient sustained a stroke. There was no statistically significant association between mortality and PVL severity by all parameters.

Discussion

The results of this small retrospective study comparing PVL grade by CMR and TTE highlight the significant disagreement in classification using VARC-2 criteria between the different echocardiographic parameters, as well as between those parameters and regurgitant fraction estimated by CMR.

Correlation between TTE and CMR

The poor correlation between TTE and CMR has been corroborated in previous studies [12,14]. Sherif et al. reported that jet width and area by TTE underestimated PVL severity when compared to CMR in a small prospective study of post-TAVR patients receiving a Medtronic CoreValve [12]. The challenge in using jet width as to grade PVL lies in its risk of both overestimating and underestimating severity of the regurgitant jet by color Doppler, as eccentric jets impinge on the wall of the left ventricular outflow tract and may appear less impressive, or cutting the jet obliquely when measuring risks overestimation [2]. In addition to examining the agreement with jet width, we show that circumferential extent of PVL, overestimated severity in all but 3 imaging studies when compared to CMR. Most importantly, two thirds of TTE studies classified PVL as severe based on circumferential extent. As for PVL grade by regurgitant fraction, the lack of agreement between

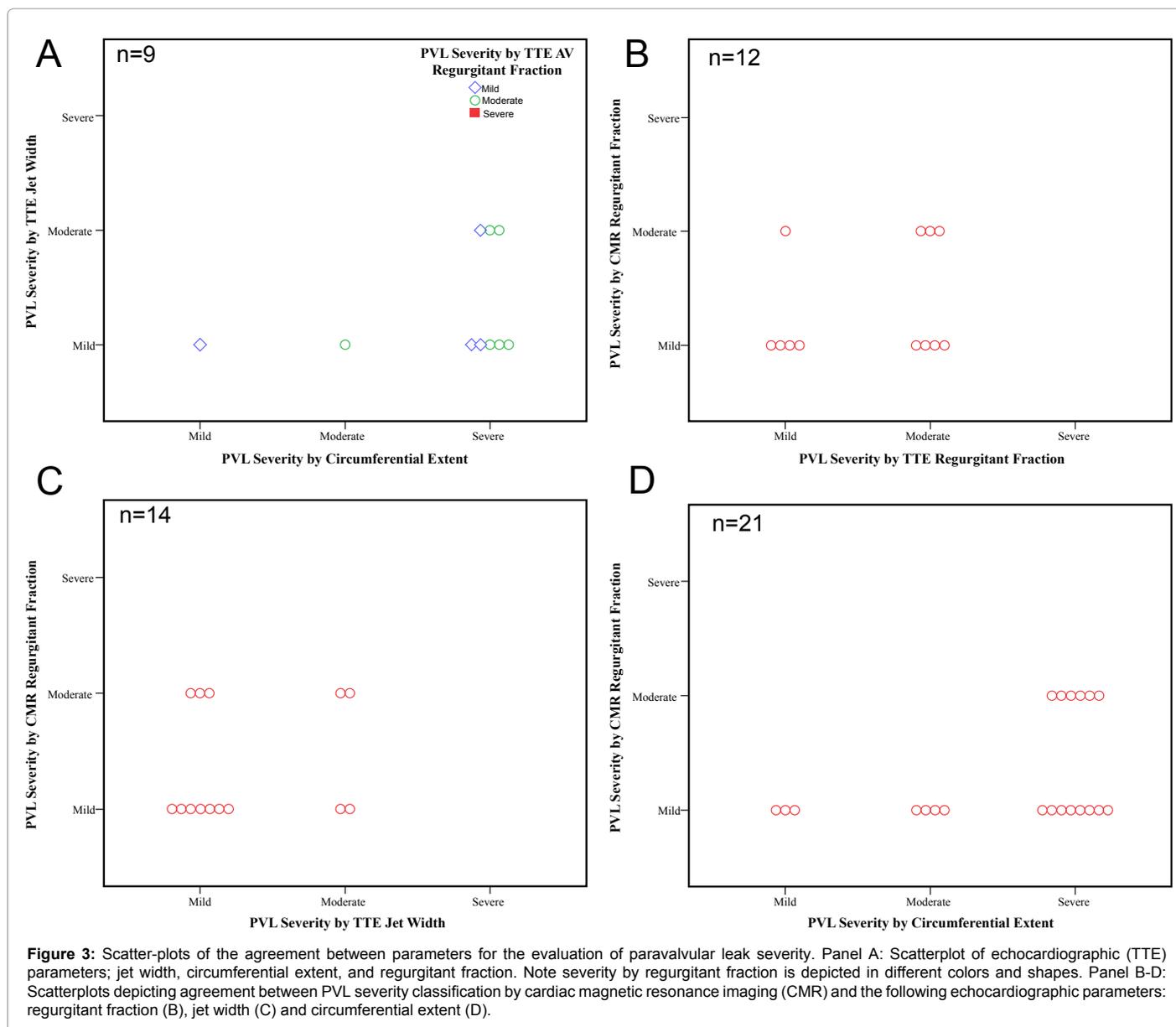
	N=18	Mean \pm SD or Median	Range
Demographics			
Age, y		85.0 \pm 5.5	
Male, %		66.7%	
White, %		88.9%	
BMI, kg/m ²		24.0 \pm 2.2	
Transcatheter Heart Valve			
Edwards SAPIEN, n (%)		15 (83.3%)	
Edwards SAPIEN-XT, n (%)		3 (16.7%)	
23 mm, n (%)		7 (38.9%)	
26 mm, n (%)		10 (55.6%)	
29 mm, n (%)		1 (5.6%)	
TAVR to CMR time, days		6	1-1064
TTE to CMR time, days		1	0-12
Outcomes			
Required PVL Intervention, n (%)		4 (22.2%)	
Mortality at 1 year, n (%)		3 (16.7%)	
Stroke at 1 year, n (%)		2 (11.1%)	

Table 2: Characteristics of Study Population.

Parameter	CMR Regurgitant Fraction	TTE Regurgitant Fraction	Jet Width	Circumferential Extent
CMR Regurgitant Fraction		0.21	0.19	-0.02
TTE Regurgitant Fraction	0.21		0.07	0.09
Jet Width	0.19	0.07		-0.05
Circumferential Extent	-0.02	0.09	-0.05	

*Kappa statistics for agreement in paravalvular regurgitation grading between Cardiac Magnetic Resonance Imaging (CMR) and Transthoracic Echocardiography (TTE) parameters. p-value > 0.05 for all Kappa statistics above.

Table 3: Multiparametric Agreement in Grading Paravalvular Regurgitation.



CMR and TTE is not unexpected. Determining regurgitant fraction is dependent on measuring flow across both the left and right ventricular outflow tract. Measuring Right Ventricular Outflow Tract (RVOT) and RV stroke volume by echocardiography is however limited by the retrosternal location of the right ventricle and its crescentic shape [15]. Any inaccuracy in measuring the RVOT will thus be compounded by squaring of the area when calculating RV stroke volume. Given the impact of PVL on outcomes post-TAVR, these findings might have translated to further intervention in order to address the PVL, had CMR not been performed.

Current criteria for PVL severity

The current guidelines adopted by VARC-2 are arbitrary, derived from the evaluation of aortic regurgitation in native valves, with certain adaptations emphasizing the description of jet anatomy [2,16]. The authors of the VARC-2 consensus document acknowledge that the evidence supporting the use of these parameters and their cut-offs is

limited [16]. In addition, these thresholds were established for use in echocardiography and are likely inappropriate for CMR. While studies are increasingly reporting an association between PVL and poor outcomes in patients undergoing TAVR, the multi-parametric nature of the guidelines and its inconsistent adoption in studies complicates the identification of appropriate cut-offs that correlate with outcomes, and that can be universally applied. A large, prospective cohort examining the association of the RF by CMR as a continuous variable with outcomes is necessary to determine clinically useful cut-offs.

PVL severity is not only of prognostic value, but may lead to therapeutic intervention. Given that patients undergoing TAVR are typically high risk, it is essential to accurately characterize the severity of PVL. Echocardiography should be the first step in a comprehensive and integrative evaluation of the post-TAVR patient. Unless multiple echocardiographic parameters confirm that PVL is severe, we advocate the use of CMR for accurate quantitation of regurgitant fraction prior to proceeding with therapeutic intervention.

Limitations

The retrospective nature of the study and the small number of patients preclude deriving definitive conclusions on recommending for the routine use of CMR in evaluating PVL. One major limitation relate to the fact that CMR in this study were performed at the clinician's behest for further characterization of PVL, which may have selected for TTE studies with discordant parameters. In addition, not all echocardiographic measures were obtained due to the inconsistency in quality of windows and images.

Conclusions

The agreement between the different echocardiographic parameters, and between echocardiography and CMR in assessing PVL severity is poor. Circumferential extent, the most commonly acquired echocardiographic parameter for PVL grading notably over-estimates PVL severity, and may lead to unnecessary intervention in the absence of a thorough assessment. CMR is safe, accurate, and reproducible and should be considered in the evaluation of PVL severity when the echocardiographic assessment and clinical findings are incongruent. Larger prospective studies comparing both modalities are needed to justify the routine use of CMR in the evaluation of PVL post-TAVR.

Author's Contributions

SH performed data collection, data analysis as well as drafted the manuscript. FS analyzed echocardiograms as well as participated in data collection. JO analyzed cardiac magnetic resonance images as well as provided input on data analysis and interpretation. SL conceived the study, participated in its design and coordination as well as helped draft the manuscript. All authors read and approved the final manuscript.

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