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Multi-parametric quantification of tricuspid regurgitation using cardiovascular magnetic resonance: A comparison to echocardiography

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Abstract

Background—Velocity-encoding is used to quantify tricuspid regurgitation (TR) by cardiovascular magnetic resonance (CMR), but requires additional dedicated imaging. We hypothesized that size and signal intensity (SI) of the cross-sectional TR jet area in the right atrium in short-axis steady-state free-precession images could be used to assess TR severity.

Methods—We studied 61 patients with TR, who underwent CMR and echocardiography within 24 h. TR severity was determined by vena contracta: severe (N = 20), moderate or mild (N = 41). CMR TR jet area and normalized SI were measured in the plane and frame that depicted maximum area. ROC analysis was performed in 21/61 patients to determine diagnostic accuracy of differentiating degrees of TR. Optimal cutoffs were independently tested in the remaining 40 patients.

Results—Measurable regions of signal loss depicting TR jets were noted in 51/61 patients, while 9/10 remaining patients had mild TR by echocardiography. With increasing TR severity, jet area significantly increased (15 ± 14 to 38 ± 20 mm²), while normalized SI decreased (57 ± 27 to 23 ± 11). ROC analysis showed high AUC values in the derivation group and good accuracy in the test group.

Conclusion—TR can be quantified from short-axis CMR images in agreement with echocardiography, while circumventing additional image acquisition.

Keywords

Tricuspid regurgitation; Quantification; Cardiac magnetic resonance imaging; Cardiac imaging; Valvular heart disease

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Disclosures

None of the authors have any potential conflicts of interest to disclose.

1. Introduction

Tricuspid regurgitation (TR) is increasingly being recognized as an important independent predictor of prognosis in various cardiovascular conditions [1–4]. Today, two-dimensional (2D) echocardiography is the reference standard for the assessment of severity of TR. Although cardiovascular magnetic resonance (CMR) imaging is an important tool for the assessment of most types of heart disease, little attention has been given to the evaluation of TR using CMR. Although velocity-encoded phase-contrast imaging is a well-validated CMR method for quantifying left-sided regurgitant valvular lesions [5,6], it has not been as extensively validated with TR, and the level of agreement with echocardiography has yet to be established. This approach requires the acquisition of additional images to measure right ventricular stroke volume and determine pulmonary flow using velocity-encoded phase-contrast images. Acquisition of these images is not routinely performed in clinical exams and requires specialized CMR sequences, which are associated with additional costs. Furthermore, this technique is subject to different sources of errors. Although TR is often qualitatively assessed in the long-axis view, its severity may be underestimated because the jet may be incompletely visualized in planes that do not cut through the center of the jet. However, in short-axis views, TR jets are readily visualized as regions of signal loss in the right atrium (RA) due to the outflow of excited spins from the imaging plane with the regurgitant jet and dephasing by turbulent flow.

We aimed at studying the agreement between echocardiography and the above described CMR methodology for the evaluation of TR severity and testing an alternative approach that might be less prone to errors. Accordingly, we hypothesized that measuring the size and signal intensity of the cross-sectional jet area in the short-axis view on cine CMR could provide quantitative information on TR severity. This pilot study was designed to test this hypothesis by comparing these two quantitative TR severity indices to those determined by standard echocardiographic methodology.

2. Methods

2.1. Population and study design

We studied 61 adult patients (12 males; age 51 ± 16 years; BSA 1.84 ± 0.26 m²) who underwent CMR and transthoracic 2D echocardiography on the same day to minimize the changes in loading conditions, and were diagnosed with more than trace TR. Of these patients, 47 (77%) had pulmonary hypertension, 12 (20%) cardiomyopathy and 2 (3%) no known cardiac pathology. The study was approved by the Institutional Review Board with a waiver of consent.

Echocardiographic color Doppler images were used to measure TR vena contracta (VC) and classify TR as mild or moderate versus severe. In a subgroup of 46/61 patients, in whom velocity-encoded phase-contrast images were available, we evaluated TR severity using the current CMR methodology [7–9], and compared the results to echocardiography. Additionally, short-axis CMR images were used to measure cross-sectional TR jet area and signal intensity. These novel CMR indices were also compared to echocardiographic VC measurements. Subsequently, receiver-operating characteristics (ROC) analysis was

performed in a derivation group of 21 patients (including randomly selected 7 patients from the severe TR group and 14 from the non-severe TR group) for each CMR parameter, in order to determine its diagnostic accuracy for discriminating severe from non-severe TR and identify the optimal cutoff. These optimal cutoffs were tested prospectively in the remaining 40 patients (test group) to determine their sensitivity, specificity and accuracy in an independent group of patients.

2.2. 2D echocardiography

2D and Doppler echocardiographic images were acquired using iE33 imaging system (Philips, Andover, MA). Presence of TR was initially determined qualitatively using color Doppler images and patients with no or trivial TR were excluded. Then TR severity was quantified by the highest VC value measured in the four-chamber and right ventricular (RV) inflow views. Patients were classified into two groups according to TR severity: mild or moderate for $VC < 7$ mm, and severe for $VC \geq 7$ mm.

2.3. CMR imaging

CMR imaging was performed on a 1.5T scanner (Philips, Best, Netherlands) with a 5-channel cardiac coil. Steady-state free-precession short-axis cine images (~30 phases per cardiac cycle) were obtained from the apex to above the ventricular base. Imaging parameters were: echo time: 1.25msec, repetition time: 2.5msec, flip angle: 60°, slice thickness: 6 mm with 4 mm gaps, resolution varying from 1.25×1.25 to 1.79×1.79 mm. Velocity-encoded phase-contrast images were acquired in the pulmonic valve plane (Fig. 1, left) using the following settings: retrospective ECG gating; slice thickness 10 mm; flip-angle 15°; in-plane resolution 1.2×1.2 mm; repetition/echo time (TR/TE) 4.28/2.63 ms; phase-encoding velocity 200 cm/s; temporal resolution 28 ms.

2.4. Standard CMR analysis of TR

Short-axis images were analyzed to obtain RV stroke volume using the method of disks. Velocity-encoded phase-contrast images were analyzed using commercial software (Medis, Leiden, Netherlands) to measure absolute forward flow volume through the pulmonic valve (Fig. 1, left), which was then subtracted from the RV stroke volume, in order to obtain TR volume (TRV). Patients were classified into two groups according to the severity of TR: severe (TRV either ≥ 30 ml, or in a separate analysis, ≥ 40 ml), moderate or mild (TRV $<$ the above threshold).

2.5. New CMR analysis of TR

The new CMR analysis included: (1) identification of the plane and frame where TR jet area was maximal; (2) counting the number of slices where TR jet was seen; and (3) manual delineation of region of interest of the visualized jet cross-section to measure jet area and mean signal intensity (SI) within the jet, which was normalized to SI measured in the RA cavity away from the jet in the same plane.

2.6. Statistical analysis

Inter-technique comparison between CMR-derived TRV and echocardiographic VC included linear regression with Pearson's correlation. Inter-technique agreement for TR severity classification was performed using kappa (κ) statistics. The calculated kappa coefficients were judged as: 0–0.20 low, 0.20–0.40 fair, 0.40–0.60 moderate, 0.60–0.80 good, and >0.80 excellent.

The TR jet area (JA) and normalized signal intensity (NSI) were first compared between the two groups of patients with different TR degrees using unpaired student's t -tests. P-values <0.05 were considered significant. Similar to CMR-derived TRV, inter-technique comparisons for JA and NSI against VC also included linear regression (in the entire study group) and κ -statistics for TR severity (in 46 patients with velocity-encoded images to facilitate inter-technique comparisons).

ROC analysis in the derivation group of 21 patients was performed for each parameter (JA and NSI), for the differentiation of severe from mild/moderate TR. For this differentiation, larger JA and smaller NSI indicated more severe TR. ROC curves were generated and used to calculate the area under curve (AUC), a standard measure of diagnostic performance independent of specific cutoff values. An optimal cutoff value was then identified for each parameter as the one that maximized the sum of sensitivity and specificity.

The optimal cutoff values derived from the derivation group were tested in the independent test group of 40 patients, by calculating the sensitivity, specificity, positive and negative predictive value (PPV, NPV) and overall accuracy. Finally, we tested a combination of the two CMR indices using the aforementioned optimal cutoffs: to be classified into a certain category, the jet had to simultaneously satisfy both severity criteria. Thus, only jets with area above the cutoff for "severe" and SI below the cutoff for "severe" were classified as severe.

2.7. Reproducibility analysis

CMR measurements were repeated in randomly selected 30 patients, including measurements by the same observer, at least one month later, and by a second observer, both blinded to all prior measurements. Intra- and inter-observer variability was assessed by calculating intraclass correlation (ICC) coefficients and the absolute difference between the corresponding pair of repeated measurements as % of their mean.

3. Results

Inter-modality comparison showed moderate correlation ($r = 0.66$) between echocardiographic VC and CMR-derived TRV (Fig. 1, right). Inter-modality agreement in TR classification was only fair (Table 1, top), when 40 ml cutoff for severe TR was used ($\kappa = 0.28$), and TR was classified differently in 12/46 patients (26%). Using the 30 ml cutoff improved the inter-modality agreement to moderate (Table 1, bottom, $\kappa = 0.55$) with disparate classification in 9/46 patients (20%).

Of the entire study group, 51/61 (84%) had regions of signal loss in the RA cavity depicting TR jets that were suitable for measurements. In the remaining 10/61 patients (16%), TR jets

were not traced. For statistical analyses, these 10 patients were set to have $JA = 0 \text{ mm}^2$ and $NSI = 100\%$. These 10 patients had mild or moderate TR by echocardiography.

Figs. 2–4 show images obtained in 3 patients with different TR severity. As TR severity increased, JA increased and NSI decreased progressively. Some of the TR jets appeared not only as a dark area but also had an adjacent white “halo” (Fig. 2), which was noted in 17/20 patients (85%) with severe TR, 11/21 (52%) with moderate TR, and in none with mild TR. Our measurements of TR jets did not include this white “halo”.

Table 2 shows the results of CMR analysis in the two groups of patients with different TR degrees by echocardiography. As expected, RV volumes were enlarged and ejection fraction reduced in patients with severe TR. With increasing TR, JA increased from 15 ± 14 to $38 \pm 20 \text{ mm}^2$, while NSI decreased from 57 ± 27 to $23 \pm 11\%$ (Fig. 5; all $p < 0.05$). The number of slices where TR was seen increased from 1.6 ± 1.1 to 3.6 ± 1.2 (all $p < 0.05$). Linear regression in the entire study group showed moderate inter-technique correlations between VC and CMR parameters of TR severity: $r = 0.57$ for JA, and $r = 0.68$ for NSI (Fig. 6). Inter-modality agreement in TR classification was moderate for both JA (Table 3, top; $k = 0.54$) and NSI (Table 3, center; $k = 0.59$), and was further improved to good agreement by combining these indices (Table 3, bottom; $k = 0.69$).

Table 4 shows the results of reproducibility analysis for the conventional measurement of TR volume, JA and NSI. Variability of the conventional TR volume measurements was very high in patients with mild TR, because these measurements sometimes resulted in negative values and the mean of the repeated measurements in these patients was near zero, resulting in turn in extremely high percent variability. In contrast, the new TR indices were considerably more reproducible, because these indices never measured below zero.

Fig. 7 and Table 5 (middle) show the results of ROC analysis in the derivation group. The diagnosis of severe TR was highly accurate for NSI ($AUC = 0.93$), but less accurate for JA ($AUC = 0.69$). Optimal cutoff values of these parameters are also listed in Table 5.

Testing these cutoff values prospectively resulted in good accuracy of diagnosis of severe TR (Table 5, right), as reflected by overall accuracy of 0.83 for both parameters, but with variable levels of sensitivity, specificity, PPV and NPV, with the lowest being $PPV = 0.65$ by NSI. Combining the 2 parameters together resulted in an improvement in specificity, PPV and overall accuracy.

4. Discussion

Accurate detection and quantification of valve regurgitation is crucial for optimal management of patients with valvular heart disease [10]. Although echocardiographic assessment of TR is the current standard of care, it is known to have limitations including operator dependence and limited use in patients with poor acoustic windows. Nevertheless, the decision about the optimal timing for valvular surgical intervention heavily depends on quantitative parameters that reflect the severity of valvular regurgitation [11,12]. CMR is increasingly used as an initial test for comprehensive evaluation of patients with valvular disease. CMR techniques have ranged from qualitative assessment of aortic or mitral

regurgitation to quantitative measurements, such as jet length or area that were compared against color Doppler echocardiography or angiography [13,14] and also mitral or aortic regurgitant volume and fraction [15]. However, CMR assessment of TR remains largely unexplored, despite the intrinsic strengths of this modality [13,16]. These include dedicated sequences with high blood-to-myocardium contrast, high signal-to-noise ratios, and high temporal resolution that allow robust quantification of RV stroke volume, and velocity-encoded phase-contrast images that allow quantification of flow volume through the pulmonic valve [5,6]. Current guidelines of valvular heart disease made recommendations for TR assessment using CMR [17,18], when available, even as the preferred method for evaluation of RV volumes and function in patients with severe TR, especially with suboptimal echocardiograms.

However, such an assessment only provides information about the effects of TR on RV size and function, but does not allow quantitative assessment of TR severity, which requires special acquisition, that is often not part of routine imaging protocols, and is only occasionally performed after valve regurgitation is already identified. Furthermore, the accuracy of measuring TRV is limited by compounded measurement errors inherent to the different imaging techniques. First, TRV calculation requires measuring total RV stroke volume, which relies on tracing endocardial boundaries at different phases of the cardiac cycle in multiple slices, where endocardial visualization may not be optimal. Secondly, it requires measuring the flow through the pulmonic valve instead of direct flow measurement through the tricuspid valve. This is done because the tricuspid annulus is less planar (more saddle-shaped) and more mobile than the pulmonic valve, making it difficult to image in a fixed plane throughout the cardiac cycle.

In this study, these errors resulted in moderate agreement between echocardiography and the conventional CMR methodology. This finding underscores the need for alternative approaches, which would potentially be more accurate and reproducible, and allow quantification of TR without the use of specialized pulse sequences, that require advance planning and are associated with additional costs. This study was designed to test the feasibility of such an alternative approach.

It is known that regurgitant jets can be visualized on short-axis cine images acquired in every CMR study [19–22]. This is because excited spins are ejected from the imaging plane due to rapid regurgitant flow and also undergo accelerated dephasing in turbulent flow areas, resulting in reduced SI [23], manifesting as dark jets projecting into the RA [12,24,25]. To our knowledge, quantitative assessment of TR severity from these images has not been described. Accordingly, we hypothesized that jet size and SI loss would correlate with TR severity and thus could be used for quantitative evaluation from images included in routine CMR studies.

Based on previous studies of mitral and aortic regurgitation, which evaluated jet characteristics in the 4-chamber or sagittal views [13,14], evaluation of regurgitant severity based on jet area or length is not recommended, because this method is unreliable in these views, as they are prone to missing the center of the jet and, as a result, underestimating its severity. As an alternative, quantification of TR severity is primarily focused today on

proximal jet geometry by echocardiography, including VC width and regurgitant orifice area. We sought to test the feasibility of evaluating TR severity by quantitative analysis of jet characteristics from short-axis images. Unlike echocardiography, where the sonographer is able to search in real time for the best view to identify and determine the severity of TR, CMR has its pre-specified views acquired in optimal imaging planes rather than accurate location of a regurgitant jet. However, short-axis cine views very often depict TR jets on cross section, irrespective of the direction of the jet, lending themselves to quantitative analysis of TR severity.

Because there is no well-established CMR threshold for TR volume, we tested two potential thresholds (30 and 40 ml) in order to assess the agreement between the conventional CMR methodology and echocardiography. Our results showed that the agreement was considerably better with the 30 ml threshold (see kappa-values in Table 1). This finding may contribute towards better understanding of the relationship between TR volume and severity.

By comparing subgroups of patients with different degrees of TR on echocardiography, we found significant differences in JA and NSI. JA was larger and the NSI smaller in patients with severe TR. The white “halo” adjacent to the area of signal loss was seen more frequently with severe TR, and was probably a result of aliasing due to high velocities of the TR jet. The number of slices depicting the jet was also larger with severe TR, as one would expect a larger jet to traverse a bigger number of short-axis slices in the RA. These two additional parameters may also be used to confirm the presence of significant TR. We also found that right ventricular volumes were larger and ejection fraction lower in patients with severe TR. While these indices are known to have prognostic value, they cannot be used to reflect the severity of TR, because TR can be present in both enlarged and normal sized ventricles with either reduced or normal function.

The correlations between CMR-derived quantitative indices and echocardiographic VC measurements were moderate, indicating that these indices provide meaningful information on TR severity. Moreover, the high AUC values measured in the derivation group, as well as the sensitivity, specificity, PPV, NPV and accuracy in the independent test group further reinforce the notion that these novel CMR indices may be useful.

An inherent limitation of the measurement technique we tested is that in different clinical protocols, short-axis slices and the gaps between them have different thickness, and the echo-time may vary causing differences in how TR jets are visualized. As a result, our cutoff values may not be directly extrapolated to protocols that use different imaging settings. Also, maximal cross-sectional jet area could theoretically appear in the gap between slices, and thus JA would be underestimated. Similarly, higher echo-times would likely increase the JA and reduce the SI. However, despite these limitations, our new indices were found to have good diagnostic accuracy in determining TR severity, and confirmed the concept that cross-sectional JA and NSI are useful parameters. It is likely that imaging without gaps would only further improve our results. Furthermore, one might argue that JA measurements performed in short-axis slices optimized to be perpendicular to the long axis of the left ventricle, rather than the more relevant right ventricle, could also be affected. However, TR jets are usually

not central and/or perpendicular to the tricuspid annular plane, and would still be oblique in short-axis slices perpendicular to the RV long axis.

A limitation of our study is the relatively small number of patients, especially in the derivation group. This reflects the pilot nature of the study, which was designed to validate CMR measurements against echocardiography, and thus mandated inclusion of patients with TR who had undergone echocardiography and CMR on the same day to minimize loading condition changes. However, the cutoff values derived in this study were tested in a larger independent group of patients and showed good diagnostic accuracy. Importantly, these cutoffs are not intended to be generalized for clinical use, but rather suggest that similar methodology could be used in larger patient populations to establish more statistically sound values. Such cutoff values could potentially allow quantitative differentiation of TR severity in individual patients in whom TR is newly diagnosed during the interpretation of a routine CMR study, and could trigger initiation of appropriate clinical management.

In summary, we found that in patients with TR, echocardiography and the conventional CMR methodology are not in good agreement with respect to TR severity. We also found that TR severity can be quantified on short-axis CMR images by measuring cross-sectional area and signal intensity of the jet, while avoiding the need for additional image acquisition using specialized pulse sequences. In this pilot study, this alternative CMR approach performed well and was more reproducible than the conventional CMR methodology. If further validated, this new approach may allow objective evaluation of TR severity, which may become part of the clinical CMR protocol.

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Fig. 1.

An example of a velocity-encoded phase contrast image of the pulmonic valve plane, shown with the tracing of the pulmonic valve (red line) used to calculate the absolute forward flow volume (left). The relationship between TR volume calculated by subtracting trans-pulmonic forward flow volume from right ventricular stroke volume and echocardiographic TR vena contracta (VC).

Fig. 2.

An example of a patient with severe TR assessed by both echocardiography (top) in RV inflow (top left) and apical 4-chamber (top right) and by CMR (bottom) in short-axis views, showing a signal loss in an area in the right atrium due to tricuspid regurgitation. This TR jet area is shown without (bottom left + zoomed insert) and with (bottom right) the manual tracing and measured values.

Fig. 3.
An example of a patient with moderate TR in the same format as Fig. 2.

Fig. 4.
An example of a patient with mild TR in the same format as Figs. 2 and 3.

Fig. 5. CMR-derived TR assessment by jet area and normalized signal intensity. With increasing severity of the TR, the area increased and the normalized signal intensity decreased (all $p < 0.05$).

Fig. 6. Results of linear regression analysis between echocardiographic vena contracta (VC) and CMR derived parameters of TR severity: jet area (left), and normalized signal intensity (right).

Fig. 7.

ROC curves obtained in a derivation group of 21 patients for the CMR-derived parameters of TR severity: jet area (top), and normalized signal intensity (bottom) for differentiating severe from non-severe TR.

Table 1

Contingency tables of agreement between echocardiographic and CMR velocity-encoding derived classification of TR severity using 2 different thresholds for separating between moderate and severe TR (see text for details).

		<u>Echocardiography</u>	
		Mild/Moderate	Severe
CMR	Mild/Moderate	30	11
cut-off 40 ml	Severe	1	4
Kappa 0.28—fair agreement			
		<u>Echocardiography</u>	
		Mild/Moderate	Severe
CMR	Mild/Moderate	27	5
cut-off 30 ml	Severe	4	10
Kappa 0.55—moderate agreement			

Table 2

Data are shown for 61 patients as well as for 2 subgroups according to severity of TR classified by echocardiography: RV volumes and EF, as well as the new indices of TR severity, derived from CMR images.

	Total N = 61	Severe N = 20	Mild/Moderate N = 41
RV EDV (ml)	240 ± 93	348 ± 135	203 ± 56 *
RV ESV (ml)	161 ± 88	262 ± 120	124 ± 56 *
RV EF (%)	36 ± 13	26 ± 6	41 ± 13 *
Patients with visible TR jets	51 (84%)	20 (100%)	31 (76%)
Patients with adjacent white “halo”	28 (46%)	17 (85%)	11 (27%) *
Number of slices with TR	2.3 ± 1.5	3.6 ± 1.2	1.6 ± 1.1 *
TR jet area	22.5 ± 19.4	37.9 ± 20.2	14.7 ± 13.7 *
Normalized signal intensity	45.3 ± 28.0	22.5 ± 11.2	56.7 ± 26.9 *

RV = right ventricular, EDV = end-diastolic volume, ESV = end-systolic volume, EF = ejection fraction, TR = tricuspid regurgitation, CMR = cardiovascular magnetic resonance.

* p-value <0.05 mild or moderate vs severe.

Table 3

Contingency tables of agreement between echocardiographic and new CMR derived classification of TR severity using TR jet area and normalized signal intensity, as well as their combination.

		<u>Echocardiography</u>	
		Mild/Moderate	Severe
TR jet area	Mild/Moderate	24	3
	Severe	7	12
Kappa 0.54—moderate agreement			
		<u>Echocardiography</u>	
		Mild/Moderate	Severe
Normalized signal intensity	Mild/Moderate	24	2
	Severe	7	13
Kappa 0.59—moderate agreement			
		<u>Echocardiography</u>	
		Mild/Moderate	Severe
Jet area AND signal intensity	Mild/Moderate	29	4
	Severe	2	11
Kappa 0.69—good agreement			

Table 4

Reproducibility of TR parameters by CMR.

	<u>Intra-observer</u>		<u>Inter-observer</u>	
	% variability	ICC	% variability	ICC
Conventional TR volume	40 ± 30	0.86	54 ± 68	0.81
TR Area	8 ± 6	0.97	13 ± 12	0.94
TR signal intensity	11 ± 9	0.99	16 ± 19	0.95

ICC = intraclass correlation, TR = tricuspid regurgitation, CMR = cardiovascular magnetic resonance imaging.

Table 5

Diagnostic accuracy of CMR-derived parameters of TR severity for differentiation between severe and mild/moderate TR: area under ROC curves (AUC) and optimal cutoff values obtained in a derivation group of 21 patients (middle section), and the sensitivity, specificity, positive and negative predictive values (PPV, NPV) obtained by prospectively testing these cutoffs in an independent test group of 40 patients (right-hand section, see text for details).

	<u>Derivation group (N = 21)</u>		<u>Test group (N = 40)</u>			
	AUC	Optimal cutoff	Sensitivity	Specificity	PPV	NPV
TR jet area	0.69	>20 mm ²	0.85	0.81	0.69	0.92
Normalized signal intensity	0.93	<36%	1.00	0.74	0.65	1.00
Jet Area AND Normalized signal intensity			0.85	0.93	0.85	0.93

AUC = area under the curve, TR = tricuspid regurgitation.