

The role of echocardiography for quantitative assessment of right ventricular size and function in adults with repaired tetralogy of Fallot

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Abstract

Background: Quantitative assessment of right ventricular (RV) systolic function by echocardiography is challenging in patients with congenital heart disease because of the complex geometry of the RV and the iatrogenic structural abnormalities resulting from prior cardiac surgeries. The purpose of this study was to determine the correlation between echocardiographic indices of RV systolic function and cardiac magnetic resonance imaging (CMRI) derived RV ejection fraction (RVEF) in adults with repaired tetralogy of Fallot (TOF).

Methods: Quantitative assessment of RV function was performed with RV tissue Doppler systolic velocity (RV s'), tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC). These echocardiographic indices were compared to RVEF from CMRI performed on the same day as echocardiogram.

Results: Of 209 patients, the mean RV FAC was $39 \pm 9\%$, TAPSE was 18 ± 4 mm, RV s' was 10 ± 2 cm/s, and RVEF was $40 \pm 10\%$. There was a good correlation between TAPSE and RVEF ($r = 0.79$, $P < .001$), good correlation between RV s' and RVEF ($r = 0.71$, $P < .001$), and modest correlation between FAC and RVEF ($r = 0.66$, $P < .001$). TAPSE < 17 mm effectively discriminated between patients with RV systolic dysfunction defined as RVEF $< 47\%$ (sensitivity 81%, specificity 79%, area under the curve [AUC] 0.805). FAC $< 40\%$ was associated with RVEF $< 47\%$ (sensitivity 72%, specificity 63%, AUC 0.719). RV s' < 11 cm was associated with RVEF $< 47\%$ (sensitivity 83%, specificity 68%, AUC 0.798).

Conclusion: Despite the structural and functional abnormalities of the RV in patients with repaired TOF, quantitative assessment of RV systolic function by echocardiography is feasible and had good correlation with CMRI-derived RVEF.

KEYWORDS

magnetic resonance imaging; echocardiography, right ventricular systolic function, tetralogy of Fallot

Abbreviations: AUC, area under the curve; CMRI, cardiac magnetic resonance imaging; FAC, fractional area change; RV s', RV tissue Doppler systolic velocity; RVEDV, RV end-diastolic volume; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESA, RV end-systolic area; RVESV, RV end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.

1 | INTRODUCTION

Surgical repair of tetralogy of Fallot (TOF) may result in pulmonary regurgitation which can lead to right ventricular (RV) dilation and systolic dysfunction over time.¹⁻³ The RV has a complex geometry, which makes the assessment of RV volumes very challenging by echocardiography.⁴ Similarly quantitative assessment of RV systolic function by echocardiography is also challenging in patients with TOF because of regional wall motion abnormalities from prosthetic materials used for patching of ventricular septal defect and RV outflow tract.^{4,5} As a result, echocardiography is predominantly used for qualitative assessment of RV size and systolic function. Cardiac magnetic resonance imaging (CMRI) provides quantitative and reproducible assessment of RV volume and systolic function, and is currently the gold standard for RV volumetric and systolic function assessment in patients with TOF.^{6,7}

The American Society of Echocardiography endorses the use of fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV tissue Doppler systolic velocity for quantitative assessment of RV systolic function.^{4,8} There are limited data about the use of these indices in the TOF population. The purpose of this study was to determine the correlation between echocardiographic indices of RV systolic function and CMRI-derived RV ejection fraction (RVEF).

2 | METHODS

2.1 | Patient selection

This a retrospective study of patients (age ≥ 18 years) with repaired TOF that underwent CMRI at Mayo Clinic Rochester, Minnesota from January 1, 2002 to December 31, 2015. We identified patients that underwent CMRI and transthoracic echocardiograms on the same day for inclusion in this study. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization.

2.2 | Study endpoints and definitions

The primary study objective was to determine the correlation between quantitative echocardiographic indices of RV systolic function and CMRI-derived RVEF. Quantitative echocardiographic indices of RV function were defined as RV s', TAPSE, and FAC. The secondary study objective was to determine the correlation between qualitative echocardiographic assessment of RV function and CMRI-derived RVEF. We used the visual assessment of RV function reported in the echocardiography report as a measure of qualitative RV function (for the secondary study objective) because this is a reflection of "real-world" assessment of RV function. Exploratory analysis was performed to assess the correlation between quantitative echocardiographic assessment of RV size and CMRI-derived RV volumes. RV end-diastolic area and end-systolic area were used for the assessment of RV size in this study.

2.2.1 | RV function assessment

Two-dimensional, M-mode and Doppler echocardiography were performed according to standard American Society of Echocardiography guidelines.⁸ Offline measurements of RV end-diastolic area (RVEDA) and end-systolic area (RVESA) were performed from the apical four-chamber window in all patients by an experienced sonographer (R.P) using the image that provided the most adequate visualization of RV walls.⁸ RVEDA was obtained by endocardial border tracing in end-diastole (beginning of QRS complex) and RVESA was obtained by endocardial border tracing in end-systole (end of T wave). FAC was calculated as $(RVEDA - RVESA) / RVEDA$. In order to assess intraobserver correlation, the same sonographer (R.P, blinded to previous measure) repeated RVEDA/RVESA tracings and FAC calculations in random sample of 20 patients. Similarly, to assess interobserver and test-retest correlation, one of the investigators (ACE blinded to previous measure) repeated RVEDA/RVESA tracings and FAC calculations in another random sample of 20 patients. Intraobserver and interobserver correlations were expressed as intraclass correlation (ICC) and 95% confidence interval (95% CI). TAPSE and RV s' values were abstracted from digital echocardiographic images and offline measurements performed as needed. Intraobserver and interobserver ICC were assessed for TAPSE and RV s' using the same methods as described for FAC.

Based on the qualitative assessment of RV function in echocardiography report, we categorized patients into two groups: normal function (normal or borderline function) or abnormal function ($\geq$ mild dysfunction). These reports were generated by six different cardiologists. In order to assess for the variability in the qualitative assessment of RV function due to multiple readers, a random sample of 20 studies were independently reviewed by R.P and ACE, and the RV function coded as normal vs abnormal. The interobserver agreement was assessed using kappa statistics. LV systolic indices (LVEDD, LVESD, and LVEF) were obtained using two-dimensional echocardiogram with images from the parasternal long-axis window.⁸ The severity of pulmonary regurgitation was determined by qualitative assessment using Doppler echocardiography (based on color and spectral Doppler).⁹

The protocol for volumetric assessment using CMRI at this institution has been previously described.¹⁰ All CMRI studies were performed on a 1.5-T system (Signa; GE Healthcare, Waukesha, WI) using an eight-element phased-array cardiac coil. RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV) were obtained by manual tracing of endocardial borders from axial images at end-diastole and end-systole respective, and RVEF was calculated from these volumes.

2.3 | Statistical analysis

Data were presented as mean $\pm$ standard deviation, median (interquartile range), or number (%). Linear regression was used to assess the correlation between echocardiographic indices of RV function (FAC, TAPSE, RV s') and CMRI-derived RVEF. Linear regression was also used to assess the correlation between echocardiographic indices of

RV size (RVEDA and RVESA) and CMRI-derived RVEDV and RVESV, respectively. Receiver operator characteristic curve was used to determine the optimal cutoff point for echocardiographic indices of RV function that predicted RV systolic dysfunction which was defined as $RVEF < 47\%$ for the purpose of this study. The decision to use " $RVEF < 47\%$ " was based on the criteria used in our institution, and values associated with meaningful clinical endpoints based on previous studies.^{11,12} We then compared the ability of qualitative and quantitative RV function to discriminate between normal vs abnormal RV systolic function using the area under the curve (AUC). A $P < .050$ was considered statistically significant. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC).

3 | RESULTS

3.1 | Baseline characteristics

Out of 218 TOF patients with CMRI data, we excluded patients that did not undergo echocardiogram on the same day ($n = 9$). Among the 209 patients in the study, the mean age at the time imaging was 33 ± 13 years; median age at the time of TOF repair was 4 (2-7) years and 42 (20%) patients had TOF with pulmonary atresia. Tables 1 and 2 show the baseline clinical and hemodynamic characteristics of the cohort.

3.2 | RV size and function assessment

Table 3 shows reproducibility of echocardiographic indices of quantitative RV systolic function. There was a good interobserver

TABLE 1 Baseline characteristics

	N = 209
Age at beginning of study, years	33 ± 13
Male	88 (42%)
Body mass index, kg/m ²	26 ± 6
Body surface area, m ²	1.8 ± 0.3
Age at TOF repair, years	4 (2-7)
Prior palliative shunt	86 (41%)
TOF-pulmonary atresia	42 (20%)
Comorbidities	
Atrial fibrillation	32 (15%)
Atrial flutter/tachycardia	27 (13%)
Hypertension	33 (16%)
Hyperlipidemia	65 (31%)
Coronary artery disease	9 (4%)
Current or prior smoker	39 (19%)
Diabetes mellitus	27 (13%)
Sleep apnea	36 (17%)
Prior stroke	15 (7%)
NYHA III/IV	28 (13%)

Abbreviations: NYHA, New York heart Association; TOF, tetralogy of Fallot.

TABLE 2 Noninvasive hemodynamic data

Echocardiography	N = 209
$\geq$ Moderate RV enlargement ^a	155 (74%)
$\geq$ Moderate RV systolic dysfunction ^a	52 (25%)
$\geq$ Moderate tricuspid regurgitation ^a	32 (219%)
$\geq$ Moderate pulmonary regurgitation ^a	157 (75%)
Severe pulmonary regurgitation ^a	129 (63%)
Tricuspid regurgitation velocity, m/s	3.1 ± 0.7
Pulmonary valve peak velocity, m/s	2.4 ± 0.9
$\geq$ Moderate RA enlargement ^a	81 (39%)
LA volume index, ml/m ²	30 ± 12
RA pressure, mmHg	8 ± 4
TAPSE, mm	18 ± 4
RV s', cm/s	10 ± 2
RV end-diastolic area, cm ²	42 ± 13
RV end-systolic area, cm ²	25 ± 8
Fractional area change, %	39 ± 9
Medial E, cm/s	10 ± 4
Lateral E, cm/s	15 ± 5
Medial E/e'	11 ± 4
Lateral E/e'	8 ± 3
LV end-diastolic dimension, mm	46 ± 8
LV end-systolic dimension, mm	30 ± 6
LV ejection fraction, %	58 ± 9
LV mass index, mg/m ²	84 ± 27
Relative wall thickness	0.39 ± 0.08
CMRI	
RVEDV index, ml/m ²	141 ± 43
RVESV index, ml/m ²	79 ± 38
RV stroke volume index, ml/m ²	59 ± 20
RV ejection fraction, %	44 ± 10
PR regurgitant volume index, ml/m ²	18 ± 6
PR regurgitant fraction, %	31 ± 7
LV stroke volume index, ml/m ²	41 ± 11
LV ejection fraction, %	58 ± 8

Abbreviations: E, mitral inflow early velocity; e', tissue Doppler early velocity; LA, left atrium; LV, left ventricle; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; s', tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

^aQualitative echocardiographic assessment.

agreement for qualitative RV systolic function assessment (kappa 0.93, 95% CI 0.89-0.98). RVESA and RVEDA were successfully performed in 204 of 209 patients. The mean RV FAC was $39 \pm 9\%$, TAPSE was 18 ± 4 mm, RV s' was 10 ± 2 cm/s, and RVEF was $40 \pm 10\%$. There was a good correlation between TAPSE and RVEF (adjusted $R^2 = 0.62$, $r = 0.79$, $P < .001$), good correlation between RV s' and RVEF (adjusted $R^2 = 0.52$, $r = 0.71$, $P < .001$), and modest

TABLE 3 Reproducibility of quantitative RV function indices

	Intraobserver ICC	95% CI	Interobserver ICC	95% CI
RVEDA	0.82	0.74-0.91	0.78	0.70-0.86
RVESA	0.83	0.73-0.92	0.79	0.68-0.91
FAC	0.88	0.82-0.94	0.83	0.75-0.90
TAPSE	0.92	0.89-0.96	0.87	0.82-0.91
RV s'	0.94	0.92-0.96	0.86	0.81-0.92

Abbreviations: CI, confidence interval; FAC, fractional area change; ICC, intraclass correlation; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; s', tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

correlation between FAC and RVEF (adjusted $R^2 = 0.45$, $r = 0.66$, $P < .001$), Figure 1. There was poor correlation between RVEDA and RVEDV (adjusted $R^2 = 0.11$, $r = 0.035$, $P = .032$), and no correlation between RVESA and RVESV (adjusted $R^2 = 0.002$, $r = 0.05$, $P = .831$).

TAPSE < 17 mm was associated with RVEF $< 47\%$, with sensitivity of 81%, specificity of 79%, and AUC 0.805. FAC $< 40\%$ was associated with RVEF $< 47\%$, with sensitivity of 72%, specificity of 63%, and AUC 0.719. RV s' < 11 cm/s was associated with RVEF $< 47\%$, with sensitivity of 83%, specificity of 68%, and AUC 0.798. Qualitative assessment of "abnormal" RV function was associated with RVEF $< 47\%$, with sensitivity of 83%, specificity of 55%, and AUC 0.676.

4 | DISCUSSION

In this study, we demonstrated a good correlation between echocardiographic indices of RV systolic function and CMRI-derived RVEF. Of the three echocardiographic indices analyzed, TAPSE and RV s' had better correlation with CMRI-derived RVEF compared to FAC. These indices were superior to qualitative (visual) assessment of RV function in predicting RV systolic dysfunction as defined by RVEF. The complex geometry of the RV makes quantitative assessment of RV size and function very challenging.^{4,8} Additionally, TOF patients sometime have regional wall motion abnormalities due to prior surgical repair.⁶ The current study demonstrates that quantitative assessment of RV systolic function in TOF patients was feasible and had good correlation with CMRI-derived RVEF.

A number of studies have evaluated the role of echocardiography for quantitative assessment of RV size and function.¹³⁻¹⁸ Selly et al studied the correlation between 3D-echocardiographic indices and CMR-derived indices of RV function, and reported a good correlation between RV volumes by 3D-echocardiogram and CMRI.¹³ Among the 2D-echocardiographic indices assessed in that study, only FAC correlated with RVEF.¹³ We did not observe a correlation between RV size by echocardiogram and CMRI-derived RV volumes in the current study, and we speculate that the differences between our results and that of Selly et al¹³ may be due to the differences in imaging technique (3D-echocardiogram-derived RV volume vs 2D-echocardiograph-derived RV surface areas). Additionally, the Selly et al¹³ study did not identify a correlation between TAPSE and RV s', and CMRI-derived RVEF, but we suspect that this may be related to a small sample size because that study was based on a cohort of 26 patients. Since 3D-echocardiogram is still not routinely used for the assessment of RV function in clinical practice in this population, the 2D-echocardiographic indices reported in our study may have a wider application in clinical practice.

In a different study, Mercer-Rosa et al¹⁵ demonstrated the feasibility of echocardiography for quantitative assessment of pulmonary regurgitation and RV systolic function in TOF. In that study, they reported a good correlation between Doppler-derived myocardial performance index and CMRI-derived RVEF.¹⁵ Our findings complement the results of that study by providing a broader range of echocardiographic indices that can be used for the quantification of RV systolic function. Considering the complex RV geometry and technically

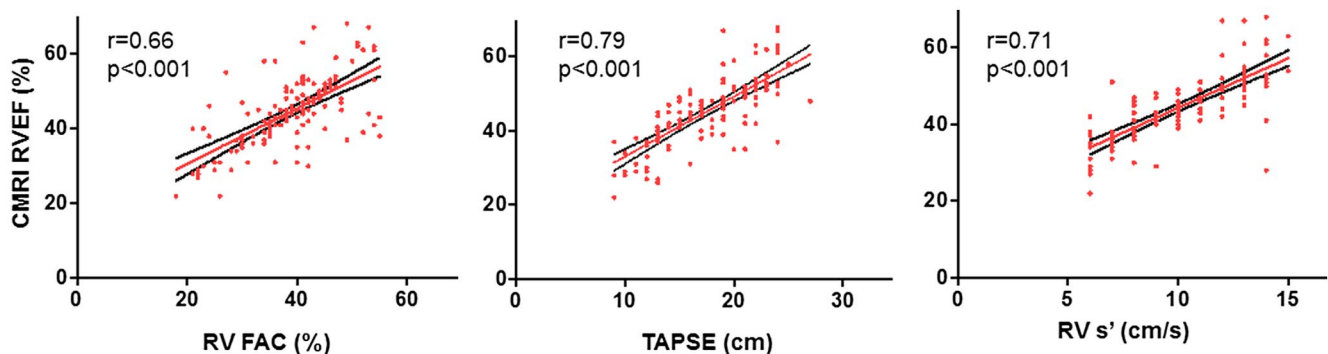


FIGURE 1 Linear regression of cardiac magnetic resonance imaging (CMRI) derived right ventricular ejection fraction (RVEF) and fractional area change (FAC) (left); tricuspid annular plane systolic excursion (TAPSE) (Middle); and right ventricular tissue Doppler systolic velocity (s') (right)

challenging image quality in this population, having more options of potential echocardiographic indices will be very important in clinical practice. Our study adds to the body of evidence supporting the use of echocardiography for quantitation of RV systolic function in routine clinical practice. This is important because although CMRI is available in most academic congenital heart disease centers, it is not always readily accessible. Moreover more than 10% of the adult TOF population have relative contraindications for CMRI because of cardiac implantable electronic devices.¹⁹

Patient with congenital heart disease such as TOF have several sternotomies during palliation and correction of their structural heart disease.^{3,20} Pericardial manipulation during cardiac surgery and the regional wall motion abnormalities that can result from myocardial injury or use of prosthetic material can also affect echocardiographic indices RV function.^{3,6,7,20} These are some of the concerns about quantitative assessment of RV systolic function in patients with TOF. The current study shows that quantitative RV systolic function by echocardiography is feasible and reliable in spite of these potential concerns.

Qualitative (visual) assessment of RV function is common practice in the congenital heart disease population, and some of the practice guideline recommendations are based on qualitative visual assessment of RV size and function.^{5,21,22} In this study, we showed that quantitative assessment (especially using TAPSE and RV s') had a better correlation with RV systolic dysfunction compared to visual assessment. On the other hand, quantitative assessment of RV size using RV end-diastolic and end-systolic surface areas did not correlate with CMR-derived RV volumes. We speculate that this may be related to difficulty in obtaining a "true RV-focused" apical four-chamber view which can result in a significant variability in the measurement of RVEDA and RVESA depending on the imaging window. However, this is not much of a problem for FAC calculation since FAC is not an absolute measure of a dimension but rather a change in dimension based on RVEDA and RVESA obtained from the same window.

4.1 | Limitations

This was a retrospective study of patients that underwent CMRI at a tertiary care center is therefore prone to selection bias. The quantitative indices used in this study were obtained by careful offline measurements by a single observer. The precision that results from a single-observer assessment may account for some of the correlation observed in the study. Another limitation of the study is that we did not analyze strain-imaging data in this study.

4.2 | Conclusions

The current study demonstrates good correlation between echocardiographic indices of RV systolic function assessment and the gold standard of CMRI-derived RVEF. Despite the structural and functional abnormalities of the RV in the patients with repaired TOF, quantitative analysis of RV systolic function by echocardiography is feasible and reliable. Further studies are required to assess the prognostic role of quantitative echocardiography in this population.

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CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

Conception and design, data collection, data analysis, manuscript drafting, critical revision, final review: Egbe

manuscript drafting, critical revision, final review: Kothapalli, Jadav, Masood, Angirekula, Pislaru, Pellikka

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