

# Doppler-derived strain and strain rate imaging assessment of right ventricular systolic function in adults late after tetralogy of Fallot repair: an observational study

*Yetişkinlerde tetraloji Fallot onarımından epey sonra sağ ventrikül sistolik fonksiyonunun Doppler kaynaklı strain ve strain rate görüntülemesi ile değerlendirilmesi: Gözlemsel bir çalışma*

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## ABSTRACT

**Objective:** Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. Today, we are faced with an increasing number of patients with residual pulmonary regurgitation (PR) late after TOF repair. The right ventricular (RV) volumes and function are among the most important factors influencing clinical decision-making. Cardiac magnetic resonance (CMR) is the gold standard method for the quantitative assessment of the RV function; it is, however, expensive for routine clinical follow-up and sometimes is contraindicated. We sought to evaluate the RV systolic function via CMR and compare it with Doppler-derived strain (S) and strain rate (SR) imaging in patients with repaired TOF.

**Methods:** In an observational cross-sectional study, 70 patients (22 women, mean age=22±4.9 years) late after TOF repair with severe PR were evaluated. Peak systolic strain and SR in the basal, mid, and apical segments of RV free wall (RVFW) were measured and compared with the RV function measured in the short-axis cine MR. Associations between RVEF and S/SR, investigated by ordinal logistic regression models.

**Results:** Significant association was observed between RV function and mean S of all the three segments of the RVFW segments [OR (CI95%): 1.17 (1.05-1.31)]. Association between RV function and mean SR of all the three segments of the RVFW segments was borderline significant [OR (CI95%): 1.7 (0.97-2.93)].

**Conclusion:** There was a significant correlation between the Doppler-derived mean strain of RVFW and the RV function measured by CMR in adults late after TOF repair. These quantitative methods improved the assessment of the RV function and served as an additional method to follow up patients with contraindications to CMR. (*Anadolu Kardiyol Derg 2013; 13: 536-42*)

**Key words:** Tetralogy of Fallot, right ventricle, cardiac magnetic resonance, strain, regression analysis, diagnostic value, sensitivity, specificity

## ÖZET

**Amaç:** Fallot tetralojisi (TOF) siyanotik konjenital kalp hastalığının en sık görülen şeklidir. Günümüzde, TOF onarımı sonrası rezidüel pulmoner yetersizliği (PR) olan hastaların sayılarında artış ile karşı karşıyayız. Sağ ventrikül (RV) hacim ve fonksiyonu klinik karar vermeyi etkileyen en önemli faktörler arasındadır. Kardiyak manyetik rezonans (CMR) RV fonksiyonunun nicel değerlendirilmesi için altın standart yöntemdir; ancak, rutin klinik takip için pahalıdır ve bazen kontrendikedir. Biz TOF onarımı yapılan hastalarda CMR ile RV sistolik fonksiyonu değerlendirmesini Doppler kaynaklı strain (S) ve strain rate (SR) görüntülemesi ile karşılaştırmaya çalıştık.

**Yöntemler:** Kesitsel bir çalışmada, TOF onarımından epey sonra şiddetli PR'li 70 hasta (22 kadın, ortalama yaş=22±4,9) değerlendirildi. RV serbest duvarının bazal, mid ve apikal segmentlerinde peak sistolik strain ve SR ölçülerek kısa-aks sine MR da ölçülen RV fonksiyonu ile karşılaştırıldı. RVEF ve S/SR arasındaki ilişkiler sıra lojistik regresyon modelleri ile incelendi.

**Bulgular:** RV fonksiyonu ve RVFW segmentlerinin üç segmentinin hepsinin S ortalaması arasında önemli bir ilişki gözlemlendi (OR [CI%95]: 1.17 [1,05-1,31]). RV fonksiyonu ve RVFW segmentlerinin her üç segmentinin SR ortalaması arasındaki bağlantı sınırdan önemliydi (OR [CI%95]: 1,7 [0,97-2,93]).

**Sonuç:** TOF onarımı görmüş yetişkinlerde Doppler kaynaklı RVFW ortalama strain ile CMR ile ölçülmüş RV fonksiyonu arasında önemli bir ilişki vardı. Bu nicel yöntemler RV fonksiyonunun değerlendirilmesini geliştirmiş ve CMR kontrendikasyonu olan hastaları takip etmek için ek bir yöntem olarak yer almıştır. (*Anadolu Kardiyol Derg 2013; 13: 536-42*)

**Anahtar kelimeler:** Tetraloji Fallot, sağ ventrikül, kardiyak manyetik rezonans, strain, regresyon analiz, tanısal değer, duyarlılık, özgüllük

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## Introduction

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease with a favorable outcome in most patients (1). During recent years, a rise in the number of patients with significant residual pulmonary regurgitation (PR) late after TOF repair has been witnessed (2-4). The deleterious effects of long-standing PR on the right ventricle (RV) size and function increase the risk of severe arrhythmias and sudden death (5-8). The timing of pulmonary valve replacement (PVR) in patients with repaired TOF and residual severe PR remains a major challenge. The RV volumes and function, as well as their changes over time, are among the most important factors influencing clinical decision-making. Published guidelines for adults with congenital heart disease recommend the qualitative assessment of the RV size and systolic function via two-dimensional echocardiographic (2D E) imaging in patients with repaired TOF (9). Nevertheless, the complex geometry of the RV renders the assessment of the RV size and function via standard 2D E difficult.

Cardiac magnetic resonance (CMR) imaging has become the reference method for the quantitative assessment of the RV volumes and systolic function (10-12). However, not only is it expensive for routine clinical follow-up but it is also unsuitable for patients with pacemakers, implantable defibrillators, and renal failure. An accurate, reliable, quantitative method in echocardiography would be of enormous clinical interest, therefore. Doppler-derived strain and strain rate (SR) imaging has been well established as a quantitative method for the regional myocardial function. Regional strain is a dimensionless measurement of deformation (percentage of the change from the original dimension), and SR denotes the speed at which deformation occurs.

We sought to evaluate the RV systolic function by CMR and compare it with Doppler-derived strain and SR imaging in patients with repaired TOF (13, 14).

## Methods

### Study design

This is an observational cross-sectional study.

### Study population

From January 2010 to April 2011, a total of 156 consecutive adult patients late after TOF repair were identified from our Adult Congenital Heart Disease Clinic. Adults patients (aged > 16 years old) with a history of TOF surgical repair (at least 10 years previously) with severe PR were included. Pulmonary regurgitation was considered severe if there was diastolic flow reversal in pulmonary artery branches and Pulmonary regurgitation pressure half time (PHT) was less than 100 msec. Patients with more than mild RV outflow tract obstruction, valvular or pulmonary artery (PA) branch stenosis, patients with pulmonary valve bio-

prostheses or RV-to-PA valve conduit, and patients with contraindications to CMR such as a history of pacemaker or ICD implantation were excluded.

This study was approved by the institutional Ethics Committee, and informed consent was obtained from all patients.

### Study protocol and variables

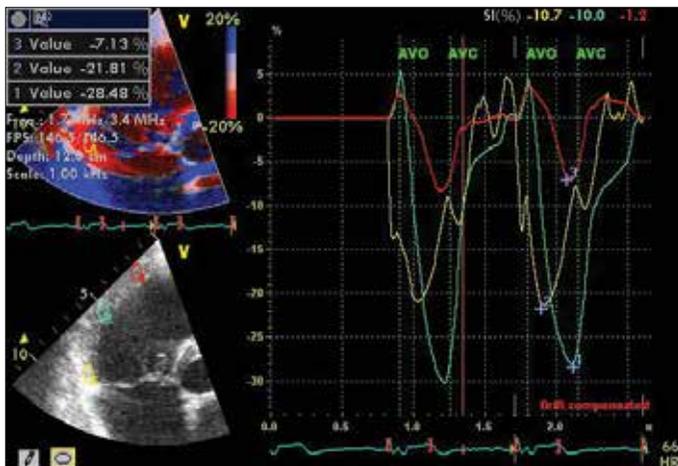
Seventy patients (22 women, mean age=22±4.9 years) with severe PR underwent both CMR and Doppler-derived strain and SR imaging less than one month apart. Peak systolic pulse wave tissue Doppler imaging (TDI) S velocity of the tricuspid annulus, tricuspid annular plane systolic excursion (TAPSE), strain, and SR in the basal, mid, and apical segments of the RV free wall (RVFW) were measured and compared with the RV ejection fraction (EF) measured in the end-systolic and end-diastolic phases in the short-axis cine MRI from the base to the apex sections.

### Echocardiographic evaluation of Doppler-derived strain and SR imaging

All the patients underwent a complete 2-D study and tissue Doppler study using Vivid 7 Digital Ultrasound System (GE Vingmed, Horten, Norway) with a 2.5-MHZ transducer. The studies were performed with the patients in the left lateral decubitus position in the apical four-chamber view. The digital data were transferred for offline analysis with the software incorporated in the Vivid Seven System to assess the regional systolic contraction in the three segments (base, mid, and apical segments) of the RVFW (Fig. 1 and 2). The images were acquired with a sweep speed of 100 cm/s, with gains and filters optimized. The pulsed wave TDI of the tricuspid annulus (Sm), TDI-derived strain, and SR measurements were sampled from the three cardiac cycles at each location with aligned Doppler beam to the RVFW. The results were thereafter averaged. All the data were obtained by a cardiologist expert in echocardiography.

### CMR

The CMR protocols and technical acquisition parameters used at our institution were identical in all the patients. The clinical studies were analyzed and interpreted by two experienced CMR readers using a 1.5 T machine (Siemens, Germany). The measurements of the RV systolic function were obtained on axial views from base to apex (12 slices, slice thickness= 7 mm; inter-slice space=0-2 mm) covering the entire length of the RV) with manual tracing of the endocardial contours at end -systole and end- diastole by including the papillary muscles and trabeculae in the blood pool. The RV volumes and function and LV function were measured by ECG-triggered, breath-hold cine steady-state free (SSFP) precession imaging sequences. Practically, the measurements of CMR-RVEF were categorized to four sub-groups: normal RV function (CMR-RVEF>50%), mild RV dysfunction (CMR-RVEF from 40% to 50%), moderate RV dysfunction (CMR-RVEF from 30% to 40%), and severe RV dysfunction (CMR-RVEF <30%), (15-17).



**Figure 1.** Demonstration of how to measure the peak systolic strain of the basal, mid, and apical segments of the right ventricular free wall

### Statistical analysis

SPSS 15 for Windows (SPSS Inc. Chicago, Illinois) was used for the statistical analyses. STATA 8 SE for Windows (STATA Corporation, Texas, USA) was also employed for statistical modeling.

The data are described as mean±standard deviation (SD) for the interval and count (%) for the categorical variables. Associations between these variables were investigated through simple linear regression models. Linear correlations between the interval variables were determined using the Pearson correlation coefficient ( $r$ ). Associations between the RV function as ordinal variable (as dependent variable) and echocardiographic parameters (as predictors) were investigated ordinal logistic regression models.  $P$  values  $< 0.05$  were considered statistically significant.

Considering CMR as gold standard for the determination of the RV function, the diagnostic accuracies of strain and SR were investigated by computing the area under the of Receiver Operative Characteristics (ROC) curve (AUC).

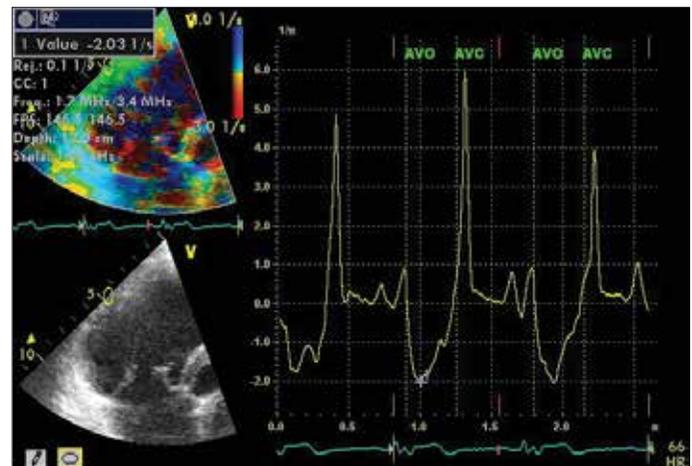
Interobserver variability for the RV systolic function was tested by re contouring the RV on 20 CMR studies. There was a high correlation between the two measurements (Pearson's  $r = 0.90$ ;  $p < 0.001$ ).

## Results

### Baseline characteristics

Seventy patients (22 women, mean age=22±4.9 years, range=15 to 42 years) late after TOF repair with severe PR were evaluated. The descriptive results of the CMR imaging and echocardiography are presented in Tables 1 and 2. LVEF by CMR was 48±5% and LVEF by echocardiography was about 47±5.1%.

The RV ejection fraction (RVEF), as an index of the RV function, was measured by CMR and its correlation with the strain and SR of the RVFW was determined (Table 3). The mean RV end-diastolic volume (RVEDV) corrected for the body surface area (RVEDVi) was 158±47.8 mL/m<sup>2</sup> and the mean of the RVEF by CMR was 37±8%. The mean of  $S_m$  at the TV annulus was 9±4.8m/sec. The mean of strain at the base of the RVFW was-



**Figure 2.** Demonstration of how to measure the peak systolic strain rate of the mid right ventricular free wall

**Table 1.** Descriptive results for cardiac magnetic resonance imaging (CMR) indices in the study participants (n=70)

| CMR Index                                                     | Mean±SD  |
|---------------------------------------------------------------|----------|
| Right ventricular ejection fraction, %                        | 37±8     |
| Right ventricle end-diastolic volume, mL                      | 267±81.2 |
| Right ventricle end-diastolic volume index, mL/m <sup>2</sup> | 158±47.8 |
| Right ventricular systolic pressure, mmHg                     | 41±14.1  |
| Pulmonary artery pressure, mmHg                               | 26±9     |
| Left ventricular ejection fraction, %                         | 48±5     |

**Table 2.** Descriptive results for echocardiography indices in the study participants (n=70)

| Echocardiography Index                         | Mean±SD  |
|------------------------------------------------|----------|
| Left ventricular ejection fraction, %          | 47±5.1   |
| Strain, %                                      |          |
| Base                                           | -21±7.3  |
| Mid                                            | -24±6.6  |
| Apex                                           | -13±5.2  |
| SR, s <sup>-1</sup>                            |          |
| Base                                           | -1.9±0.7 |
| Mid                                            | -1.7±0.6 |
| Apex                                           | -1.4±2.6 |
| Tricuspid annular plane systolic excursion, mm | 17±2.8   |
| S velocity, cm/s                               | 9±4.8    |

21±7.3% and the mean of SR was -1.9±0.7%. Additionally, the means of the strain and SR of the RVFW basal segment were reduced compared with their normal values.

### Assessment of right ventricle function by CMR compared to echocardiography

The strain and SR of the base, mid, and apical segments of the RVFW, with the exception of the SR of the apex, had linear correlation with the measurements of CMR- RVEF ( $p$  values

**Table 3. Correlations between right ventricular ejection fraction (RVEF) assessed by cardiac magnetic resonance imaging (CMR) and echocardiographic indices (n=70)**

| Echocardiographic Indexes                                                              | r *    | p      |
|----------------------------------------------------------------------------------------|--------|--------|
| S velocity, cm/s                                                                       | 0.093  | 0.297  |
| Strain, %                                                                              |        |        |
| Base                                                                                   | -0.388 | 0.002  |
| Mid                                                                                    | -0.321 | 0.013  |
| Apex                                                                                   | -0.397 | 0.002  |
| Average of segments                                                                    | -0.479 | <0.001 |
| SR, s <sup>-1</sup>                                                                    |        |        |
| Base                                                                                   | -0.337 | 0.009  |
| Mid                                                                                    | -0.357 | 0.006  |
| Apex                                                                                   | -0.117 | 0.376  |
| Average of segments                                                                    | -0.268 | 0.040  |
| Left ventricular ejection fraction, %                                                  | 0.218  | 0.029  |
| *linear correlation with RVEF assessed by CMR<br>r - Pearson's correlation coefficient |        |        |

<0.05). Quantitatively, the correlation between CMR-RVEF and average strain of the three cardiac segments was more than that of the other indices (Pearson's r=-0.479, p<0.001).

The associations between the categorized RVEF and echocardiographic parameters were investigated using several ordinal logistic regression models: there were significant associations between the RV function and average strain of the cardiac segments (Table 4). Adjustment having been made through multivariable models, direct significant associations were observed between the RV function and the average strain of the segments [OR (CI95%): 1.17 (1.05-1.31)]. Also, it was possible to predict the probability of the RV function state according to the statistical model. Association between average SR of cardiac segments and RVEF was on borderline significance [OR (CI95%): 1.7 (0.97-2.93)] and can be considered clinically important.

#### Diagnostic accuracy of strain and SR imaging

Considering CMR as the gold standard, RVEF <30% was defined as severe RV dysfunction. The accuracy of mean strain and SR imaging to diagnose severe RV dysfunction was investigated by ROC analysis. Area under the ROC curve (AUC) for mean strain was not desirable [AUC (CI95%): 0.50 (0.34-0.65, p value=0.9739)]. On the other hand, the accuracy of mean SR imaging was fair [AUC (CI95%): 0.72 (0.55-0.89, p value=0.017)] (Fig 3). Several cut-points and the relevant sensitivity and specificity were obtained. The optimal cut-off for the subjects with severe RV dysfunction was basal RVFW SR <-1.4 with sensitivity of 83% and specificity of 56%.

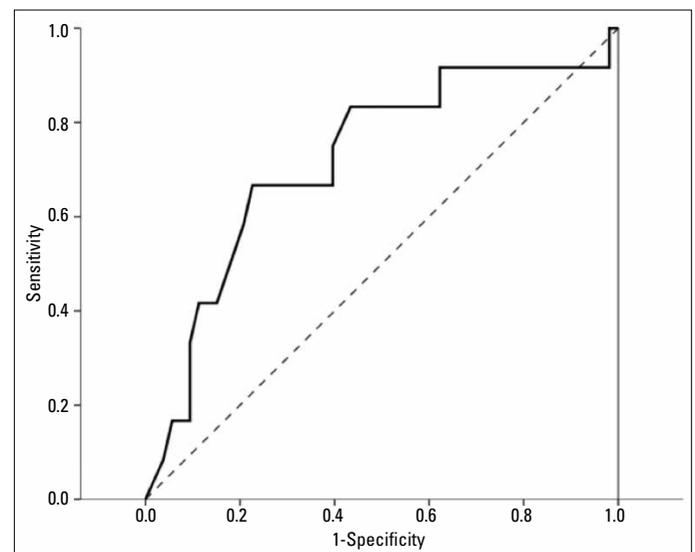
#### Discussion

The results of the present study demonstrated a significant association between the RV function measured by CMR and the

**Table 4. Ordinal logistic regression models for the association between the right ventricular ejection fraction (RVEF) assessed by cardiac magnetic resonance imaging (CMR) and strain/ strain rate assessed by echocardiography**

|         | Predictor*                                       | Coefficient ±SE | p     | Odds Ratio [CI 95%] |
|---------|--------------------------------------------------|-----------------|-------|---------------------|
| MODEL 1 | Average strain of segments, %                    | 0.16±0.06       | 0.006 | 1.17 [1.05-1.31]    |
| MODEL 2 | Average strain rate of segments, s <sup>-1</sup> | 0.52±0.28       | 0.065 | 1.7 [0.97-2.93]     |

\* Dependent variable was RVEF (expressed as normal RV function (CMR-RVEF>50%), mild RV dysfunction (CMR-RVEF from 40% to 50%), moderate RV dysfunction (CMR-RVEF from 30% to 40%), and severe RV dysfunction (CMR-RVEF <30%)  
RV - right ventricular



**Figure 3. Receiver Operating Characteristic (ROC) curve to show the accuracy of strain rate imaging to diagnose severe RV dysfunction in adults after repairing tetralogy of Fallot [AUC (CI95%): 0.72 (0.55-0.89), p=0.017]**

RV - right ventricular

Doppler-derived strain imaging of the RV in patients with repaired TOF and severe PR.

The assessment of the RV function remains a cornerstone of follow-up care in patients with repaired TOF; and in this regard, echocardiography and CMR provide complementary clinical information (18). CMR is the investigation of choice for the assessment of the RV function (19), but the echocardiographic markers of the RV function are helpful in the routine follow-up of such patients. Recently, Koestenberger et al. (20) found a positive correlation between TAPSE and RVEF measured by CMR. The RV stroke volume grossly depends on the longitudinal shortening (21). The deeper RV muscle fibers are predominantly arranged in a longitudinal fashion from the tricuspid valve annulus to the apex; consequently, other quantitative measurements of the RV longitudinal contractility such as M-mode tricuspid annular plane systolic excursion (TAPSE) and PW TDI Sm have

been proposed for the evaluation of the RV systolic function. Koestenberger et al. (20) concluded that TAPSE alone, albeit not suitable for the prediction of the RV systolic dysfunction in patients with TOF, was a useful tool in routine echocardiography for a speedy RV function assessment to indicate patients with clinically relevant RV systolic dysfunction.

Data on the use of strain and SR imaging for the evaluation of the RV function are relatively scarce. Our study is the first study of its kind to compare CMR and echocardiographic Doppler-derived strain and SR values in patients with repaired TOF. Compared to CMR, echocardiography is relatively inexpensive and could be a good method for the serial assessment of the RV function, not least in patients with contraindications to CMR, namely the growing number of patients with cardiac pacemakers or implantable defibrillators. It is deserving of note that echocardiography is deemed an inaccurate tool for the quantitative assessment of the RV function because of a lack of an ideal geometric model for the evaluation of ventricular volumes (22, 23). The major potential advantages of strain and SR imaging for the assessment of the RV function are the independence of geometric assumptions and endocardial border tracing. In addition, both strain and SR images are feasible in the majority of patients (even in the presence of low-quality 2-D imaging), reproducible, and relatively load and rate independent (24-26). Both techniques also permit the quantification of the longitudinal systolic function for each RV segment separately. Our results revealed a significant linear correlation between the RV function measured by CMR and mean systolic strain of all the three segments of the RVFW segments (base, mid, and apex). The SR of the basal RVFW  $< -1.4$  was 83% sensitive and 56% specific for severe RV dysfunction. It can, therefore, be concluded that echocardiography is a useful diagnostic method (especially for screening purposes) to detect severe RV dysfunction.

Our results also showed a significant reduction in the echocardiographic markers of the RV systolic function, by comparison with normal values, in our patients. Cut-off points of systolic strain and peak SR at the basal RVFW of 25% and  $-4 \text{ sec}^{-1}$  have been previously suggested for a preserved global RV systolic function ( $\text{RVEF} \geq 50\%$ ) with sensitivities of 81% and 85% and specificities of 82% and 88%, respectively (25, 26). In our study, the mean of the RVED index ( $158 \pm 47.8 \text{ cc/m}^2$ ) in CMR was also increased and the RVEF by CMR ( $38 \pm 8\%$ ) was reduced in most of our patients.

The mean of the PW-TDI of the tricuspid annular systolic velocity  $S_m$  was  $9 \pm 4.8 \text{ m/s}$ . There was no significant correlation between the RVEF in CMR and  $S_m$  in our study ( $p=0.297$ ). The TDI of the tricuspid annulus ( $S_m$ ) has also been suggested as a good quantitative parameter of the RV systolic function. The major limitation of  $S_m$  recording is that the measured velocity of an individual myocardial segment may be influenced by the motion of the adjacent muscle (tethering) or translational motion of the heart; as a result, velocities measured by TDI may overestimate or underestimate the active component or function of the tissue.

Harada et al. (27) reported that in patients with TOF after repair, the mean velocity during systolic ejection was lower than that of age-matched control subjects. Meluzin et al. (28) demonstrated that  $S_m < 11.5 \text{ cm/s}$  could predict the RV impairment. Others have suggested a direct and significant correlation between the RVEF derived from MRI and  $S_m$   $r = 0.64$ ;  $p < 0.001$  using a cut-off value of  $S_m < 9 \text{ cm/sec}$  to identify patients with a severely reduced RVEF ( $< 30\%$ ) with a 100% sensitivity and 92% specificity (17, 29, 30). No such correlation was observed in the present study. We assumed that  $S_m$  is load dependent and our patients suffered from pulmonary and tricuspid regurgitation. Furthermore,  $S_m$  may be influenced by the motion of the adjacent muscle (tethering) as was mentioned before. We utilized strain and SR imaging so as to overcome this limitation by measuring the actual extent of stretching or contraction. Mueller et al. (31) suggested that 2-D speckle tracking could provide information on the RV function but it required further investigation. More recently, in children, three-dimensional (3D) echocardiography has been found to have an excellent correlation with CMR in the assessment of the RV volumes and function. However, questions remain about the accuracy in adults because of inadequate windows and larger RV volumes (32-34). Evaluation of LV systolic function is critical for proper management of all patients with congenital heart disease. Severe pulmonary regurgitation and RV dysfunction are common after tetralogy of Fallot (TOF) repair and may also affect the shape and function of the left ventricle (LV). In our study we found that in adult patients late after TOF repair, despite abnormal LV geometry, visual assessment of LV systolic function by expert echocardiologist has a good correlation with quantitative measurement of LV systolic function by CMR. After repair of TOF, left and right ventricular ejection fraction are important markers of clinical status and outcome, but may not improve after pulmonary valve replacement. Strain is a sensitive marker of ventricular dysfunction and may yield incremental prognostic value beyond global RVEF assessment, however further study and new research is needed (35).

### Study limitations

Doppler-derived strain and SR imaging are angle-dependent; interpretations should, therefore, be made with caution if the tissue movement direction deviates from the direction of the beam. We did our utmost for the alignment not to exceed 20 degrees, which made the error negligible.

### Conclusion

In adult patients with repaired TOF, the assessment of the RV function via Doppler-derived strain imaging of the RVFW had a significant correlation with CMR. These quantitative methods improve the assessment of the RV function and serve as an additional method to assess and follow the RV systolic function in patients with contraindications to CMR. Doppler-derived

strain and SR imaging of the RVFW cannot be viewed as a surrogate for the RVEF measured by CMR, but they deserve further clinical investigation.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - A.S.; Design - A.S., M.K.; Supervision - M.K.; Resource - S.M., A.S.; Material - Z.A.S., Z.K.; Data collection&/or Processing - S.M., L.E., Z.K., Z.A.; Analysis &/or interpretation - A.S., L.E.; Literature search - A.S.; Writing - A.S.; Critical review - M.K.

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