Right ventricular adaptation to chronic abnormal loading

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Cardiac magnetic resonance left ventricular strain-rate predicts ventricular tachycardia but not deterioration of ventricular function in patients with repaired tetralogy of Fallot

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ABSTRACT

Background: Myocardial strain has been shown to predict outcome in various cardiovascular diseases, including congenital heart diseases. The aim of this study was to evaluate the predictive value of cardiac magnetic resonance (CMR) feature-tracking derived strain parameters in repaired tetralogy of Fallot (TOF) patients for developing ventricular tachycardia (VT) and deterioration of ventricular function.

Methods: Patients with repaired TOF who underwent CMR investigation were included. Strain and strain-rate of both ventricles were assessed using CMR feature tracking. The primary outcome was a composite of the occurrence of sustained VT or non-sustained VT requiring invasive therapy. The secondary outcome was analyzed in patients that underwent a second CMR after 1.5 to 3.5 years. Deterioration was defined as reduction (≥10%) in right ventricular (RV) ejection fraction, reduction (≥10%) in left ventricular (LV) ejection fraction or increase (≥30mL/m^2) in indexed RV end-diastolic volume compared to baseline.

Results: 172 patients (median age 24.3 years, 54 patients <18 years) were included. Throughout a median follow-up of 7.4 years, 9 patients (4.5%) experienced the primary endpoint of VT. Multivariate Cox-regression analysis showed that LV systolic circumferential strain-rate was independently predictive of primary outcome (p = 0.023). 70 patients underwent a serial CMR, of whom 14 patients (20%) showed ventricular deterioration. Logistic regression showed no predictive value of strain and strain-rate parameters.

Conclusions: In repaired TOF patients, LV systolic circumferential strain-rate is an independent predictor for the development of VT. Ventricular strain parameters did not predict deterioration of ventricular function in the studied population.

BACKGROUND

Tetralogy of Fallot (TOF) is one of the most prevalent types of congenital heart diseases, with excellent survival into adulthood when surgical repair is performed in early childhood. However, the high prevalence of residual lesions, mostly pulmonary regurgitation (PR), and late complications, including right ventricular (RV) dysfunction, often require re-intervention. Previous surgery and progressive RV and left ventricular (LV) dilatation in combination with ventricular dysfunction are believed to form a substrate for electrical instability, resulting in both atrial- and ventricular tachyarrhythmias and sudden cardiac death (SCD) [1–3]. Exercise intolerance, signs of heart failure, QRS prolongation, and RV dilatation form the cornerstone in the risk stratification of patients with repaired TOF (rTOF) [2,4,5]. Cardiac magnetic resonance (CMR) imaging is the imaging modality of choice for measuring ventricular morphology, function, and quantification of PR [6,7]. To identify patients at risk for SCD and aiming at primary prevention, research has focused on identifying parameters predictive of malignant ventricular arrhythmias [8].

Myocardial deformation (strain), measured using cardiac magnetic resonance feature tracking, has shown to contain additive value in predicting outcome, when compared to conventional measurements of ventricular function and volume in various cardiovascular diseases [9,10]. Even in the absence of impaired ejection fraction (EF), strain variables are affected in heart failure, indicating that strain could be a more sensitive marker of myocardial dysfunction than EF [11]. Several studies have shown that in patients with rTOF, both RV and LV deformation, measured as strain using either echocardiography or CMR, are decreased when compared to healthy controls [12–14]. In addition, deformation parameters of both ventricles have been reported to predict quality of life, exercise capacity and SCD and/or ventricular tachycardia (VT) in patients with rTOF [15–18]. Furthermore, in patients with rTOF, RV longitudinal strain, LV circumferential strain, and LV longitudinal strain were also associated with deterioration of ventricular function and dilatation over time, when combined with conventional parameters of ventricular function, surgical history and QRS duration [19]. In this and other studies, deterioration of ventricular function is commonly defined as a composite of either decreased RV EF, decreased LV EF or increased indexed RV end-diastolic volume (EDVi) [19–21].

Ventricular strain is a measure of relative deformation in a certain direction, with the unit percentage. In contrast, strain-rate measures the rate of this deformation, and therefore provides conceptually different information regarding myocardial performance. Furthermore, strain-rate can be measured during both contraction phase and relaxation phase, providing information on systolic and diastolic function. The predictive value of CMR derived strain-rate parameters has not been reported previously in patients with rTOF. Thus, it remains unknown

whether the conceptual differences between strain and strain-rate translate into different prognostic potential. The aim of this study was to investigate the value of both CMR-feature tracking derived strain and strain-rate as predictors for VT, and additionally as a predictor for deterioration of ventricular function on CMR in patients with rTOF.

METHODS

Consecutive patients with rTOF, both adults and children, who underwent routine CMR between January 2007 and March 2016 at the University Medical Center Groningen were identified. Patients with pulmonary atresia, absent pulmonary valve, and partial anomalous pulmonary venous return were excluded. The first CMR within the inclusion period was used for mass and volume, pulmonary artery (PA) flow and myocardial deformation, as described below. CMR studies with significant artifacts limiting study quality were excluded. Patient characteristics at the time of CMR, including age, sex, and surgical history were collected from medical records. QRS duration was extracted from the standard 12-lead electrocardiogram (ECG) obtained <4 months from CMR. Pulmonary valve (PV) peak gradient was obtained from echocardiography performed within 6 months from CMR.

Furthermore, a subset of patients who underwent a second CMR study, performed between 1.5 and 3.5 years after the first CMR, was identified. From this second CMR, mass and volume measurements were performed and used to categorize patients into 'deterioration' or 'no deterioration', as described below. Patients with secondary CMR were excluded from this analysis if a valvular intervention (i.e. valve replacement, valvuloplasty) was performed between both CMRs. This study conforms to the Declaration of Helsinki. The need for individual informed consent for this study was waived by the institutional Medical Ethical Review Board.

CMR imaging protocol

CMR scans were performed using a 1.5 T scanner (Siemens, Erlangen, Germany), using a retrospectively gated steady-state free- precession (SSFP) sequence, ECG-gated cine loop images with breath holding at end-expiration were acquired. The four-chamber and two-chamber views were used for long-axis slices. Short-axis slices were subsequently acquired covering both ventricles from base to apex. Two-dimensional velocity encoded CMR flow measurements, perpendicular and 1.5 cm cranial to the PV, were performed using 2-D gradient echo Fast Low Angle SHot (FLASH), acquired during normal respiration with retrospective cardiac gating.

CMR analysis

All assessments of mass, volume, function and PA-flow were performed by two independent observers (Q.A.J.H. and T.M.G.), blinded for patient's history. Ventricular mass, volume, and function were analyzed using QMass 7.6 (Medis Medical Imaging, Leiden, The Netherlands) according to guidelines of the Society for Cardiovascular Magnetic Resonance. Good intra- and inter-observer variability analyses in our group have been reported previously [4]. Based on previous experience, the papillary muscle and trabeculae were excluded from ventricular volumes by using MassK Mode® (semi-automatic threshold-based segmentation software) [4,22].

PA-flow was analyzed using QFlow 5.6 (Medis Medical Imaging, Leiden, The Netherlands). PA-contours were semi-automatically generated, and thereafter manually adjusted. Automated background offset correction was performed, based on previous experience [7]. Pulmonary regurgitant fraction (PRF) was calculated.

Strain and strain-rate analyses were performed using QStrain 2.0 (Medis Medical Imaging, Leiden, The Netherlands) by one observer (J.D.L.V.). In all analyses, strain was defined as the peak of the global strain curve, systolic strain-rate the peak of the global strain-rate curve in systole, and diastolic strain-rate the peak in diastole. RV and LV longitudinal strain analyses were performed in the 4-chamber view, RV and LV circumferential strain at mid-papillary level using the short-axis view. Endocardial borders were manually traced in end-systole and end-diastole. Feature tracking was visually reviewed, and border tracing was manually adjusted if necessary. RV longitudinal strain was defined as longitudinal strain in the RV free wall. RV delay was defined as the time difference in time to peak global circumferential strain between RV and LV. If feature tracking in more than one of the views failed, strain analyses of this patient were not included.

Patient height and weight were extracted from the original CMR report to calculate body surface area (BSA) using Haycock's formula [23]. All volumes and masses were indexed for BSA.

Outcomes

The primary endpoint was a combined endpoint of the occurrence of SCD, sudden cardiac arrest with successful resuscitation, VT (defined as documented episode of sustained VT lasting ≥30 seconds), an appropriate implantable cardioverter defibrillator (ICD) shock or non-sustained VT (NSVT) requiring invasive therapy (i.e. ICD implantation, VT ablation). Follow-up time was defined as the time from the baseline CMR to the primary endpoint, or, in the absence of an endpoint, time to the last recorded patient contact.

The secondary endpoint was defined as deterioration of ventricular function or dimensions, based on any of the three criteria: a decrease in RV EF of ≥10% (absolute percent change), a

decrease in LV EF of ≥10% (absolute percent change) or an increase in RV EDVi of 30ml/m^2, in line with previous studies [19–21].

Statistics

Statistical analyses were performed using SPSS (version 23, 2015). A p-value below 0.05 was considered statistically significant. Data are displayed as mean ± standard deviation (SD) or number (percentage). Continuous variables were compared using independent samples t-test and categorical variables using Chi-squared test. Univariate Cox-regression analysis was performed to assess the predictive value of baseline characteristics, mass and volume measures, PRF, and strain for the primary endpoint. Parameters with p<0.05 were included in the multivariate stepwise backward Cox-regression analysis, using p>0.1 as criterion for removal. For all parameters with a univariate p<0.05, a receiver operator characteristic (ROC) curve was plotted with the corresponding area under the curve (AUC) calculations. For the independent parameter in the multivariate analysis, the optimal cut-off value was chosen according to the ROC curve. A Kaplan-Meier VT-free survival plot was made for the patient group above this cut-off value, compared with the group below this cut-off value. Associations between CMR parameters and the secondary outcome of deterioration were assessed using logistic regression. For intra-observer analyses, ten CMR studies were randomly selected and analyzed by J.D.L.V., at least two months after the original analysis. Even though all deformation analyses in this study were performed by one observer, inter-observer variability was assessed to provide reproducibility of these measures. Therefore, two blinded observers (J.D.L.V. and S.L.M.) performed deformation analyses in ten randomly selected CMR studies. Two-way mixed intra-class correlation coefficient was used, and mean bias ±SD was calculated. One-sample t-test was used to assess whether bias was significantly different from zero.

RESULTS

In total, 172 patients were included in this study, with a median age at the time of CMR examination of 24.3 years (interquartile range (IQR) 15.9 – 35.4). Due to significant artifacts, 11 patients were excluded. Of the included patients, 54 patients (31%) were pediatric (<18 years). Mass and volume measurements could be performed in 169 patients (98%), pulmonary flow measurements could be performed in 166 patients (97%), and strain measurements could be performed in 166 patients (97%). Within the predefined timeframe, a baseline echocardiographic examination was available for 143 patients (83%), and a baseline ECG examination was available for 162 patients (94%). Baseline characteristics are displayed in table 1. Intra- and inter-observer variability analysis showed good reproducibility and precision of strain and strain-rate measures (supplementary table 1).

Table 1 | Baseline characteristics (n=172).

Male sex	91 (53%)
Age (years)	24.3 (15.9 - 35.4)
Age at TOF repair (years)	1.6 (1.1 - 5.2)
Body mass index (kg/m^2)	22.4 ±4.7
Cardiac magnetic resonance	
RV EDVi (mL/m^2)	125 ±38
RV ESVi (mL/m^2)	62 ±23
RV mass index (g/m^2)	42 ±11
RV EF (%)	51 ±8
LV EDVi (mL/m^2)	80 ±17
LV ESVi (mL/m^2)	34 ±11
LV mass index (g/m^2)	55 ±16
LV EF (%)	58 ±8
PRF (%)	26 ±17
Echo PV peak gradient (mmHg)	24 ±15
QRS duration on ECG (ms)	136 ±27

Values are mean ± standard deviation or median (interquartile range). BMI body mass index, LV left ventricular, EDVi indexed end-diastolic volume, ESVi indexed end-systolic volume, EF ejection fraction, RV right ventricular, PRF pulmonary regurgitant fraction, PV pulmonary valve, ECG electrocardiography.

Primary endpoint: ventricular tachyarrhythmias

During a median follow-up time of 7.4 years (IQR 4.6 - 9.4 years), 9 patients (4.5%) experienced the primary outcome, of whom 6 patients experienced documented sustained VT, 1 patient experienced an appropriate ICD shock due to sustained VT in a symptomatic patient, 1 patient underwent VT ablation for recurrent NSVTs and 1 patient underwent ICD implantation for recurrent NSVTs. There were no SCDs or cardiac arrest survivors. Table 2 shows baseline deformation measures for the groups with or without the primary endpoint, figure 1 displays representative examples of feature tracking analyses from either group. When compared with normal values, measured using the same software vendor (Medis) in a cohort of healthy volunteers, the measured strain and strain-rate values in the cohort described in this study are all substantially lower [24]. Univariate Cox-regression analysis showed no significant associations between RV-strain variables and primary outcome (table 2). However, a significant association of both systolic and diastolic LV circumferential strain-rate with primary outcome was demonstrated. From patient characteristics, ECG, PV peak gradient, masses, volumes and pulmonary flow, age (p=0.015), RV mass index (p=0.022) and QRS duration (p=0.023) were identified as predictors of the primary endpoint of VT (supplementary table 2). A multivariate Cox-regression model, including these variables, revealed systolic LV circumferential strain-rate as an independent predictor of the primary outcome events (p=0.023, table 2).

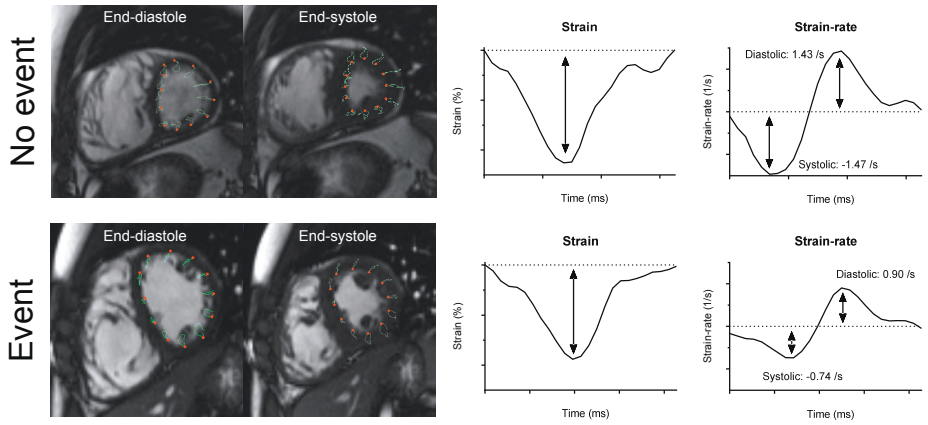

Figure 1 | Strain and strain-rate analysis. Representative examples of feature-tracking strain and strain-rate analysis in a patientwithout the primary outcome (no event) and a patientwith a primary outcome (event).

Table 2 | Cox-regression analysis for prediction of VT.

	No event	Event		Cox-regression	
RV longitudinal	**mean ±SD**	**mean ±SD**	**Step size**	**p-value**	**HR (95% CI)**
Strain (%)	-25.1 ±5.4	-24.3 ±3.3	per Δ5	0.592	1.19 (0.62 - 2.29)
Strain-rate systole (1/s)	-1.21 ±0.32	-1.14 ±0.19	per Δ0.25	0.495	1.22 (0.69 - 2.18)
Strain-rate diastole (1/s)	1.21 ±0.41	1.09 ±0.52	per Δ-0.25	0.458	1.19 (0.75 - 1.89)
RV circumferential					
Strain (%)	-19.9 ±4.7	-17.2 ±4.7	per Δ5	0.138	1.83 (0.82 - 4.07)
Strain-rate systole (1/s)	-0.81 ±0.24	-0.69 ±0.27	per Δ0.25	0.158	1.73 (0.81 - 3.71)
Strain-rate diastole (1/s)	0.88 ±0.30	0.73 ±0.40	per Δ-0.25	0.185	1.54 (0.81 - 2.96)
LV longitudinal					
Strain (%)	-19.5 ±4.0	-18.0 ±5.4	per Δ5	0.436	1.48 (0.55 - 3.95)
Strain-rate systole (1/s)	-1.01 ±0.28	-0.95 ±0.33	per Δ0.25	0.747	1.11 (0.58 - 2.11)
Strain-rate diastole (1/s)	1.06 ±0.37	1.02 ±0.32	per Δ-0.25	0.988	1.00 (0.61 - 1.66)
LV circumferential					
Strain (%)	-25.6 ±5.3	-23.2 ±4.0	per Δ5	0.094	1.35 (0.95 - 1.93)
Strain-rate systole (1/s)	-1.23 ±0.25	-0.98 ±0.28	per Δ0.25	**0.002**	3.15 (1.53 - 6.46)
Strain-rate diastole (1/s)	1.26 ±0.3	1.01 ±0.42	per Δ-0.25	**0.021**	2.06 (1.12 - 3.76)
RV delay (ms)	31.3 ±35.6	47.9 ±35.6	per Δ25	0.298	1.31 (0.78 - 2.25)

Multivariate Cox-regression analysis					
		Univariate		**Multivariate**	
	Step size	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**
Age (years)	per Δ10	**0.002**	1.71 (1.12 - 2.62)	0.090	1.68 (0.92 -3.02)
RV mass index (g/m²)	per Δ5	**0.021**	1.38 (1.05 - 1.73)	0.083	1.36 (0.97 - 1.83)
QRS duration (ms)	per Δ10	**0.002**	1.45 (1.05 - 2.00)	0.114	1.33 (0.93 - 1.91)
LV circ. strain-rate syst. (1/s)	per Δ0.25	**0.002**	3.15 (1.53 - 6.46)	**0.023**	4.30 (1.22 - 15.20)
LV circ. strain-rate diast. (1/s)	per Δ-0.25	**0.021**	2.06 (1.12 - 3.76)	0.168	0.47 (0.16 - 1.37)

VT ventricular tachycardia, RV right ventricular, HR hazard ratio, CI confidence interval, LV left ventricular, Circ. Circumferential. Significant p-values (<0.05) are bold.

Also when RV EF and LV EF, which are known predictors in previous studies, were added to this model or when analyzing RV EF and LV EF, together with LV systolic and diastolic circumferential strain-rate in a multivariate model, LV systolic circumferential strain-rate remained significantly associated with primary outcome (p=0.007 and p=0.002, respectively). In ROC analysis, the predictors which were significantly associated with outcome in univariate analysis showed the following AUC: LV systolic circumferential strain-rate 0.792 (95% CI 0.605 – 0.979, p=0.005), LV diastolic circumferential strain-rate 0.780 (95% CI 0.572 – 0.989, p=0.008), age 0.713 (95% CI 0.525 – 0.901, p=0.043), RV mass 0.696 (95% CI 0.496 – 0.896, p=0.062) and QRS duration 0.761 (95% CI 0.590 – 0.933, p=0.013), displayed in figure 2a. The ROC-analysis identified a systolic LV circumferential strain-rate of -1.05 as the optimal cut-off value, resulting in 75% sensitivity and 82% specificity. As the normal-value for LV circumferential strain-rate is -1.81 ±0.43, the cut-off value of -1.05 is substantially lower than normal [24]. Using this cut-off value, a Kaplan-Meier curve was plotted for VT-free survival of patients with either above or below the identified cut-off value of LV circumferential strain-rate (figure 2b). Log Rank analysis showed that using this cut-off point, survival was significantly different between groups (p<0.001).

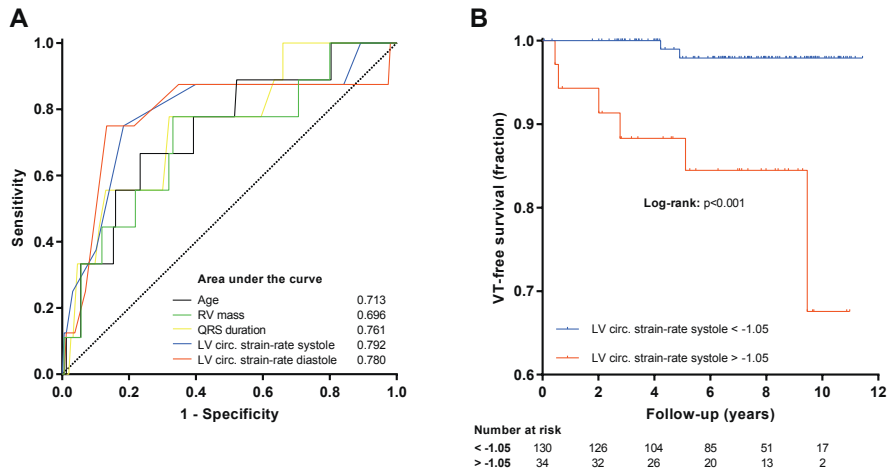

Figure 2 | Predictors of VT. a: Receiver-operator characteristic (ROC) curve for prediction of VT. VT ventricular tachycardia, RV right ventricle, LV left ventricle, circ. circumferential. b: Kaplan-Meier VT-free survival curve according to LV circumferential systolic strain rate.

Secondary endpoint: ventricular deterioration

For the secondary outcome of ventricular deterioration, 82 patients were identified who had a second CMR examination available within the predefined timeframe. Of these, 12 underwent pulmonary valve replacement (PVR) between both CMRs and were thus excluded from this analysis, leaving 70 patients included for secondary endpoint analysis. Of these, 14

patients were classified as deteriorated and 56 as not deteriorated. At baseline, RV EDVi and RV mass index were significantly different between the deteriorated and not-deteriorated group (145.7±29.3 vs. 121.1±32.4mL/m^2, p=0.012 and 47.0±8.1 vs. 41.5±9.3g/m^2, p=0.048 respectively). Using logistic regression, only RV EDVi at baseline appeared significantly associated with deterioration (p=0.018, odds ratio 1.26, 95% CI 1.04 - 1.51 per 10mL/m^2 increase) whereas for RV mass index, there was a borderline significant association (p=0.055, odds ratio 1.37, 95% CI 1.00 - 1.88 per 5g/m^2 increase). None of the strain or strain-rate variables were associated with deterioration (supplementary table 3).

DISCUSSION

This study describes the value of CMR-feature tracking derived measures of myocardial deformation for the prediction of VT or deterioration of ventricular function in patients with rTOF. LV systolic and diastolic circumferential strain-rate are identified as strong predictors of VT, of which LV systolic circumferential strain-rate was an independent predictor. In contrast, no association could be demonstrated between strain and strain-rate parameters and deterioration of ventricular function. The AUC values of LV circumferential strain-rate in the primary endpoint ROC-analysis were higher than the previously reported predictor QRS duration, illustrating the strong predictive value of these parameters.

Two studies that have previously examined the prognostic value of CMR-feature tracking derived strain parameters for VT and SCD in rTOF patients. Moon *et al.* in a case-control cohort including 16 cases of mainly SCD, showed that both RV and LV longitudinal strain and circumferential strain were predictors of VT and SCD [16]. Orwat *et al.* examined a large, prospective cohort, in which the authors describe a significantly decreased LV circumferential strain and RV longitudinal strain in the event group when compared with the no-event group [17]. This is in contrast with the current study, as the studied cohort did not show decreased strain measures in the VT group when compared with the no event group. Several factors may account for this difference. At first, both previous studies reported a significantly lower LV EF in the SCD/VT groups, whereas in the current cohort, LV EF was not associated with VT. As strain parameters are known to be correlated with EF, the preserved LV function might have also resulted in preserved strain. The current study shows that even in the absence of impaired ventricular function, deformation variables predict clinically relevant VT, therefore demonstrates the incremental value of deformation analyses next to conventional CMR variables. Secondly, the cohort described by Moon *et al.* experienced mainly SCD as outcome, and the cohort described by Orwat *et al.* experienced mainly either NSVT or SCD, but not sustained VT. In contrast, the latter was the predominant outcome event in the current study.

The finding that strain-rate variables are prognosticators of VT, even in the absence of affected strain parameters, highlights the relevance of strain-rate parameters in addition to strain. Systolic strain-rate is a conceptually different parameter of myocardial contractility than EF or strain, as it reflects the rate at which the myocardium deforms, rather than absolute proportion of deformation (strain) or volume change (EF). Diastolic strain-rate could potentially be a new approximation of assessment of diastolic function using CMR. The conceptual difference between strain and strain-rate parameters can explain why in the present study, strain-rate but not strain parameters proved to be predictive of VT. The message that the data of the current manuscript contains is therefore twofold. At first, it provides confirmation of results of previous studies, namely that deformation variables can predict outcome in patients with rTOF. Secondly, the current manuscript is the first to establish that strain-rate can predict outcome, in a population in which more conventional functional variables, such as strain and EF, could not. The authors advocate for future studies to include strain-rate parameters in their analyses.

In contrast to RV deformation variables, LV strain-rate emerged as a prognosticator of VT in the present cohort. Despite the perception of many that TOF is a mainly right-sided heart disease, various LV parameters have been associated with outcome. For example, LV end-diastolic pressure is prognostic for appropriate ICD discharge, LV dimensions and function are associated with SCD or VT, and LV strain is associated with SCD and VT [2,3,16,17,25]. This has also been described in other heart diseases with altered RV loading conditions, for example pulmonary arterial hypertension (PAH) where LV dimensions correlate with hemodynamics and survival, and LV strain predicts early mortality [26–28]. It thus appears that in right-sided heart diseases, monitoring the LV is of increasing importance [29]. Mechanical interventricular coupling could potentially play a role in the affected LV systolic function, as RV dilatation or RV pressure load leads to decreased LV function [30–32]. Furthermore, in rTOF patients, reduced RV dilatation after valve replacement resulted in improved LV strain, whereas RV strain was unaltered [33]. The present study supports the increasing attention for the LV in right-sided heart diseases.

In the described cohort, deterioration of ventricular function was associated with higher RV EDVi and RV mass index at baseline. The higher RV EDVi in the deterioration group is in accordance with the cohort described by Jing *et al.*, but not with the cohort described by Wald *et al.*, in which RV EDVi did not differ between the deteriorated group and not deteriorated group. Tretter *et al.* questioned in a recently published editorial whether RV volumes should be excluded from of decision making in rTOF patients, partly based on data of the INDICATOR cohort, where no association of pre-operative RV EDVi with all-cause mortality, aborted SCD or sustained VT after PVR could be demonstrated [34]. However, as the decision for PVR and therefore enrollment in the study was presumably partly based on RV EDV, this result should be interpreted with caution. The present study shows that RV EDVi is associated

with deterioration of ventricular function during follow-up without valvular interventions or replacements, and remains, therefore, a useful biomarker for clinical follow-up of rTOF patients.

The present study supports the association between RV mass and disease progression in rTOF patients. However, none of the studied CMR-strain variables differed significantly between both groups. This implies no additive value of strain and strain-rate parameters to conventional mass and volume measures for predicting ventricular deterioration. This finding is in line with the study of Jing *et al.*, although a later study of this same group suggested an additional prognostic value of LV circumferential, LV longitudinal and RV longitudinal strain parameters when combined in a model with conventional CMR measures using machine learning [19]. In summary, secondary endpoint analysis shows that increased RV EDVi and mass precede ventricular deterioration, but no additional value for strain parameters in the prediction of ventricular deterioration could be demonstrated.

Study limitations

This retrospective study inevitably comes with limitations. Although all patients, according to institutional protocol, undergo standardized follow-up, including CMR examination regularly, patients with contraindications, such as pacemaker implantation, did not undergo CMR, and were excluded for this study which might have resulted in some selection bias. The total number of primary endpoint events was only nine, limiting the statistical power of multivariate analyses. Also, only a subgroup of patients that underwent a second CMR examination within the defined timeframe was included for ventricular deterioration analysis, also having the potential for selection bias, and the number of patients in this subgroup limits the statistical power of deterioration analyses. Whether the conclusions drawn from these data hold for the general rTOF population should be addressed by prospective longitudinal studies.

CONCLUSION

The present study shows that systolic LV circumferential strain-rate is a strong predictor for the primary endpoint of VT, independent of conventional variables in a population of both children and adults with rTOF. Furthermore, RV EDVi was associated with deterioration of ventricular function. On the contrary, no association could be demonstrated between strain and strain-rate parameters and deterioration of ventricular function. As surveillance for potentially life-threatening arrhythmias and ventricular deterioration is key in the long-term clinical follow-up of rTOF, the current study suggests that strain-rate parameters may improve risk stratification in these patients.

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SUPPLEMENTARY DATA

Supplementary table 1 | Inter- and intra-observer variability analyses.

	Inter-observer		Intra-observer	
RV longitudinal	**ICC (95% CI)**	**Mean bias ±SD**	**ICC (95% CI)**	**Mean bias ±SD**
Strain	0.76 (-0.05 - 0.94)	-0.26 ±3.61	0.87 (0.47 - 0.97)	-0.75 ±3.40
Strain-rate systole	0.94 (0.76 - 0.99)	0.01 ±0.18	0.90 (0.61 - 0.98)	-0.04 ±0.19
Strain-rate diastole	0.88 (0.56 - 0.97)	0.10 ±0.31	0.98 (0.90 - 0.99)	-0.01 ±0.17
RV circumferential				
Strain	0.92 (0.70- 0.98)	0.26 ±2.14	0.83 (0.30 - 0.96)	-0.45 ±2.73
Strain-rate systole	0.94 (0.74 - 0.98)	0.01 ±0.12	0.80 (0.18 - 0.95)	-0.03 ±0.16
Strain-rate diastole	0.98 (0.91 - 0.99)	0.00 ±0.09	0.92 (0.70 - 0.98)	0.07 ±0.14
LV longitudinal				
Strain	0.80 (0.26 - 0.95)	-1.74 ±3.46	0.62 (-0.643- 0.91)	-0.50 ±2.69
Strain-rate systole	0.90 (0.63 - 0.98)	-0.08 ±0.20	0.93 (0.73 - 0.98)	0.01 ±0.14
Strain-rate diastole	0.74 (0.01 - 0.94)	0.09 ±0.31	0.99 (0.96 - 1.00)	0.00 ±0.08
LV circumferential				
Strain	0.78 (0.14 - 0.95)	-1.83 ±2.58	0.91 (0.61 - 0.98)	0.94 ±1.56
Strain-rate systole	0.77 (0.14 - 0.94)	-0.11 ±0.16	0.91 (0.66 - 0.98)	0.06 ±0.16
Strain-rate diastole	0.93 (0.51 - 0.99)	0.11 ±0.12*	0.98 (0.94 - 1.00)	-0.02 ±0.10
RV delay	0.89 (0.53 - 0.97)	1.90 ±18.85	0.71 (-0.29 - 0.93)	-0.30 ±17.92

RV right ventricular, ICC intraclass correlation coefficient, CI confidence interval, SD standard deviation, LV left ventricular, * means bias is significantly different from zero (p<0.05).

Supplementary table 2 | Cox-regression analysis for prediction of VT.

	No event	Event		Cox-regression	
	mean ±SD	**mean ±SD**	**Step size**	**p-value**	**HR (95% CI)**
Age (years)	26.2 ±13.3	38.4 ±15.3	per Δ10	**0.015**	1.71 (1.12 - 2.62)
Age at TOF repair (years)	3.6 ±5.1	7.4 ±6.4	per Δ5	0.094	1.79 (0.9 - 3.56)
Body mass index (kg/m^2)	22.3 ±4.6	24.9 ±6	per Δ1	0.057	1.07 (1 - 1.14)
Cardiac magnetic resonance					
RV EDVi (mL/m^2)	124.7 ±38.4	127.6 ±28.9	per Δ10	0.931	1.01 (0.84 - 1.2)
RV ESVi (mL/m^2)	61.2 ±23.6	68.4 ±14.5	per Δ10	0.462	1.1 (0.85 - 1.44)
RV mass index (g/m^2)	41.7 ±11.2	50.8 ±14.1	per Δ5	**0.022**	1.38 (1.05 - 1.73)
RV EF (%)	51.5 ±7.7	46 ±6.5	per Δ-10	0.055	2.48 (0.98 - 6.29)
LV EDVi (mL/m^2)	79.2 ±16.6	90.4 ±23.3	per Δ10	0.052	1.49 (1 - 2.22)
LV ESVi (mL/m^2)	33.2 ±10.8	39.5 ±12.5	per Δ10	0.127	1.51 (0.9 - 2.55)
LV mass index (g/m^2)	54.8 ±16	65.2 ±22.5	per Δ5	0.075	1.14 (0.99 - 1.33)
LV EF (%)	58.3 ±8.4	56.4 ±7.7	per Δ-10	0.649	1.2 (0.56 - 2.57)
PRF (%)	25.5 ±17	27.2 ±16.2	per Δ0.5	0.673	1.11 (0.68 - 1.82)
Echocardiography					
PV peak gradient (mmHg)	24.1 ±15.6	21 ±14.4	per Δ10	0.574	0.86 (0.51 - 1.45)
Electrocardiography					
QRS duration (ms)	134.8 ±26.8	158 ±20.5	per Δ10	**0.023**	1.45 (1.05 - 2)

VT ventricular tachycardia, HR hazard ratio, CI confidence interval, TOF tetralogy of Fallot, RV right ventricular, EDVi indexed end-diastolic volume, ESVi indexed end-systolic volume, EF ejection fraction, LV left ventricular, PRF pulmonary regurgitant fraction, PV pulmonary valve

Supplementary table 3 | Logistic regression for associations with deterioration.

		p	OR (95% CI)
Sex, male vs. female		0.472	1.56 (0.46 - 5.24)
Age (years)	per Δ10	0.694	1.09 (0.69 - 1.72)
BMI (kg/m^2)	per Δ5	0.245	0.63 (0.29 - 1.37)
Correction age (years)	per Δ1	0.708	0.98 (0.86 - 1.11)
RV EDVi (mL/m^2)	per Δ10	**0.018**	1.26 (1.04 - 1.51)
RV ESVi (mL/m^2)	per Δ10	0.097	1.26 (0.96 - 1.63)
RV mass index (g/m^2)	per Δ5	0.055	1.37 (1.00 - 1.88)
RV EF (%)	per Δ-10	0.968	0.98 (0.46 - 2.11)
LV EDVi (mL/m^2)	per Δ10	0.536	1.13 (0.78 - 1.63)
LV ESVi (mL/m^2)	per Δ10	0.758	0.91 (0.50 - 1.64)
LV mass index (g/m^2)	per Δ5	0.754	1.03 (0.88 - 1.20)
LV EF (%)	per Δ-10	0.263	0.66 (0.31 - 1.37)
Cardiac index (L/min/m^2)	per Δ0.5	0.069	1.63 (0.96 - 2.77)
PRF (%)	per Δ10	0.215	1.32 (0.85 - 2.02)
PV peak gradient (echo, mmHg)	per Δ10	0.232	0.72 (0.42 - 1.24)
QRS duration (ms)	per Δ10	0.117	1.28 (0.94 - 1.74)
RV longitudinal			
Strain (%)	per Δ5	0.337	0.75 (0.42 - 1.34)
Strain-rate systole (1/s)	per Δ0.25	0.073	0.62 (0.37 - 1.05)
Strain-rate diastole (1/s)	per Δ-0.25	0.506	0.87 (0.57 - 1.32)
RV circumferential			
Strain (%)	per Δ5	0.747	1.10 (0.60 - 2.02)
Strain-rate systole (1/s)	per Δ0.25	0.522	1.21 (0.68 - 2.16)
Strain-rate diastole (1/s)	per Δ-0.25	0.651	1.12 (0.69 - 1.81)
LV longitudinal			
Strain (%)	per Δ5	0.818	0.90 (0.38 - 2.16)
Strain-rate systole (1/s)	per Δ0.25	0.230	0.65 (0.32 - 1.31)
Strain-rate diastole (1/s)	per Δ-0.25	0.172	0.70 (0.42 - 1.17)
LV circumferential			
Strain (%)	per Δ5	0.207	1.75 (0.73 - 4.16)
Strain-rate systole (1/s)	per Δ0.25	0.588	1.21 (0.61 - 2.38)
Strain-rate diastole (1/s)	per Δ-0.25	0.564	1.17 (0.69 - 1.97)
RV delay (ms)	per Δ25	0.480	0.84 (0.53 - 1.35)

OR odds ratio, CI confidence interval, BMI body mass index, RV right ventricular, EDVi indexed end-diastolic volume, ESVi indexed end-systolic volume, EF ejection fraction, LV left ventricular, PRF pulmonary regurgitant fraction, PV pulmpnary valve