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ORIGINAL PAPER

Right ventricular free wall strain predicts functional capacity in patients with repaired Tetralogy of Fallot

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Abstract

To investigate the role of right ventricular free wall strain (RVFWSL) to predict low functional capacity in repaired tetralogy of Fallot (rTOF). We prospectively enrolled 33 patients with rTOF with moderate to severe PR who underwent rest and peak exercise echocardiography on a semisupine cycloergometer. Conventional function and strain imaging parameters of both ventricles were measured. Patients performing < 7 METS were defined to have low functional capacity. Logistic regression was used to identify parameters associated with low functional capacity. Eleven patients (33.3%) had low functional capacity. These patients were shorter (height 155 ± 7 vs 163 ± 9 cm, p = 0.023), more frequently female (27.3 vs 72.7%, p = 0.024) and had history of Blalock–Taussig shunt (45.5 vs 9.1%, p = 0.027). On multivariate analysis RVFWSL was the only predictor of low functional capacity OR 1.39 (CI 95%, 1.06–1.83., p = 0.018) per % change. A RVFWSL < 17% (absolute value) had an AUC of 0.785, sensitivity of 81.8% and specificity of 77.3% to predict low functional capacity. Right ventricular free wall strain is an independent predictor of low functional capacity in repaired tetralogy of Fallot with moderate to severe PR. A value < 17% might be useful in deciding when to perform pulmonary valve replacement, when functional capacity cannot be objectively measured.

Keywords Tetralogy of Fallot · Pulmonary valve replacement · Echocardiography · Adult congenital heart disease · Global longitudinal strain · Stress echocardiography

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, occurring in approximately one in 3500 births [1]. Surgical repair has significantly changed the natural history of disease. However late after TOF repair significant comorbidities such as arrhythmias, sudden cardiac death, valvular heart disease and heart failure are common and contribute to adverse clinical outcomes [2]. Pulmonary regurgitation (PR) is the most common hemodynamic sequelae, and the main culprit for late complications [3]. NYHA functional class in patients with PR after TOF repair is a powerful predictor of hospitalization and death [4]. Accordingly guidelines give a Class I recommendation to perform pulmonary valve replacement (PVR) for patients with repaired TOF and moderate or greater PR with cardiovascular symptoms not otherwise explained (dyspnea, chest pain, and/or exercise

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intolerance). In the absence of symptoms, right ventricular dilation or dysfunction are considered reasonable triggers for PVR [2]

When measured objectively, more than 50% of patients who reported no symptoms have a reduced functional capacity [5, 6]. However stress testing is not always feasible. Therefore, we aimed to identify resting echocardiographic parameters that could predict low functional capacity.

Materials and methods

Study population

We prospectively enrolled asymptomatic patients (NYHA Class I) with repaired TOF and moderate to severe pulmonary regurgitation regularly evaluated in a dedicated adult congenital heart disease clinic, who were referred for echocardiographic examination to our department during the period March 2018–June 2019. To be eligible, patients had to be able to exercise on a semisupine cycle ergometer. Exclusion criteria included pregnancy, significant comorbidities limiting prognosis (life expectancy < 1 year) and associated major cardiac anomalies (atrioventricular canal, major aortopulmonary collateral arteries, pulmonary hypertension and Ebstein anomaly). All patients gave their informed consent prior to their inclusion in the study.

Echocardiographic examination

A complete baseline echocardiogram was performed before stress test, all measurements were performed according to current recommendations [7] using a Vivid-E9 machine (General Electric, Milwaukee, USA). Pulmonary regurgitation and stenosis were classified as mild, moderate or severe according to the recommendations of the American Society of Echocardiography [8–10]. Briefly, severity was visually assessed by an experienced echocardiographer, patients with more than mild pulmonary regurgitation were included in the study. Using color Doppler, and continuous wave Doppler, we evaluated jet width/annulus ratio, pulmonary regurgitation spectrum, pressure half time (PHT), early termination of the PR and diastolic flow reversal in the proximal branches. A PHT < 100 ms, PR index < 0.77, presence of diastolic flow reversal in the pulmonary branches and PR jet width/pulmonary annulus > 0.7, were the severity parameters used. Patients with the presence of 3 of this criteria, or 2 if PR index was < 0.77 and diastolic flow reversal in the pulmonary branches was present were classified as severe PR, while patients not satisfying these criteria were classified as moderate.

Exercise stress echocardiography

We performed exercise echocardiography (ESE) using semi supine cycle ergometry (Schiller CE 0124 Ergosana). With an Initial workload of 25 W, with 25 W increments every 2 min. Dedicated images for right free wall, left ventricular global longitudinal strain and three-dimensional volumes/ejection fraction were recorded at rest, peak stress and early recovery. All right function parameters were measured using a focused right ventricular view [11]. The following parameters were measured at rest and at peak exercise: tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RV FAC), tissue Doppler (TDI) tricuspid and mitral annular velocities, trans-tricuspid and transmitral inflow velocities, peak tricuspid regurgitation jet velocity, peak systolic transpulmonary gradient, peak protodiastolic pulmonary gradient (from pulmonary regurgitation continuous Doppler), end diastolic and end systolic left ventricular volumes as well as left ventricular ejection fraction. All images were stored for offline analysis.

Furthermore, we measured left ventricular contractile reserve (LVCR) defined as the stress/rest ratio of force, calculated as the ratio between systolic pressure (by automated cuff sphygmomanometer) and left ventricular end-systolic volume. End-systolic volume was obtained from the apical four- and two-chamber views using the biplane Simpson method [12, 13].

Right ventricular contractile reserve (RVCR) was defined as any increase in RV FAC between rest and peak exercise stress, calculated as [(RV FAC at peak exercise—RV FAC at rest)/RV FAC at rest] × 100 [14]. Right ventricular force (elastance) was calculated as the ratio between protodiastolic peak pulmonary gradient (as a surrogate of mean pulmonary artery pressure) [15] and right ventricular end-systolic area. The ratio of early trans-tricuspid flow velocity to annular velocity (E/e´) was considered an index of RV filling pressures. Lung ultrasound scanning was performed at rest and soon after exercise in the semisupine position using the simplified 4 region scan protocol [16].

Patients with < 7 metabolic equivalent of task (METs) were defined to have low functional capacity [17]. METs were calculated using the generated power (Watts) and the patient´s weight during cycle ergometry [18].

Strain analysis

Images were stored and analyzed offline in a dedicated workstation (EchoPAC GE v11.3). The images were analyzed by an experienced echocardiographer in strain imaging blinded to clinical data. For right ventricular

free-wall longitudinal strain (RVFWSL), the delineation started at the lateral tricuspid annulus level and stopped at the insertion of the RV free wall in the LV [19]. The endocardium was manually traced using the single wall tracking tool and adjusted to the wall thickness. RVFWSL was calculated from a focused right chamber view, by averaging the segmental maximum peak longitudinal strain of the RV free wall. For LV strain and LV mechanical dispersion, standard four, three and two chamber views were used, according to the EACVI/ ASE/Industry Task Force for 2D speckle tracking echocardiography [20]. Adequate tracking was visually assessed before acceptance. Inter-observer variability was assessed in 14 anonymized cases by using measures from two observers (ARC and HRZ). Intra-observer variability was assessed in the same cases measured by the same with a 2 weeks difference period.

Three-dimensional (3D) analysis

Dataset acquisition for 3DE images was performed using second harmonic imaging from the apical approach. During acquisition, we used the multi-slice display to ensure that the entire LV or RV cavity was included in the dataset. Four to six consecutive electrocardiography-gated sub-volumes were acquired during breath holding to generate full-volume datasets with a minimum volume rate of 20 vps [21]. Datasets were stored digitally in raw-data format and exported to a separate workstation. Measurements of 3DE LV volumes and LVEF were performed using a commercially available software package (4D AutoLVQ, GE Vingmed Ultrasound, Horten, Norway). Briefly, initialization of LV endocardial border tracing was manually performed by identifying two points on the 4-chamber view image at end-diastole and at end-systole (1 point in the middle of the mitral annulus and a second point at the LV apex). Manual editing of the semi-automatically generated endocardial contours was routinely applied to include the LV outflow tract, as well as papillary muscles and trabeculae within the LV cavity [22]. Measurements of the 3D RV volumes and RVEF were performed using the analysis by TomTec software (TomTec Imaging Systems, Unterschleissheim, Germany). Three orthogonal planes and various landmarks were selected to define the end-diastolic and end-systolic frames. The program automatically supplies 4-chamber, sagittal, and coronal RV views on the basis of the initial view adjustment. Right ventricular end diastolic volume (RVEDV) and right ventricular end systolic volume (RVESV) were calculated from 3D echocardiographic data sets. RVEF was determined as follows: RVEF = [(RVEDV-RVESV)/RVEDV] × 100.

Statistical analysis

Statistical analysis was performed using Stata V12.1. Shapiro–Wilk test was used to study the distribution of numerical variables. Parametric variables are expressed as mean ± standard deviation, comparison between groups was done with Student's *t* test. Non parametric variables are expressed as median and interquartile ranges, comparison between groups was performed using Wilcoxon sum rank test. Categorical variables are summarized as percentage, comparison between groups was done with Xi^2. To identify which parameters were independently associated with low functional capacity, multivariate logistic regression was performed including significant variables on univariate analysis. ROC curves were plotted to identify the cut-off value of RVFWSL to predict low functional capacity. Sensitivity, specificity and likelihood ratios were calculated using this cut-off value assuming the best case scenario. Two tailed *P* values with an α error less than 0.05 were considered statistically significant. RVFWSL variability was assessed by analyzing intra-class correlation (ICC) in 14 randomly selected cases.

Results

Forty-two patients met the inclusion criteria, eight were excluded (two patients were not able to exercise, one because of osteo-muscular disease and the other with Down syndrome without the ability to follow the instructions for exercise, one patient was pregnant, one patient had an unstable stent in a pulmonary branch and four patients had associated major cardiac anomalies.)

A total of thirty-four patients were enrolled, one was eliminated due to non-interpretable functional capacity (development of an anxiety crisis at the beginning of exercise n = 1) (Fig. 1).

Thirty-three patients with repaired Tetralogy of Fallot and moderate to severe PR (42% women; mean age 26.3 ± 6.7) were enrolled. Demographic and clinical data are summarized in Table 1. ESE was feasible in all patients. Eleven patients (33.3%) were found to have low functional capacity (achieved < 7 MET). Patients with low functional capacity were shorter (height 155 ± 7 vs 163 ± 9 cm, p = 0.023), more frequently female (27.3 vs 72.7%, p = 0.024) and had more common history of Blalock–Taussig shunt (45.5 vs 9.1%, p = 0.027). Additionally, the period of time from repair surgery to ESE was longer in those with low functional capacity (21.3 ± 6.5 vs 17.5 ± 4.9 years, *p* = 0.07). Importantly, the prevalence of severe pulmonary regurgitation and RVCR was comparable among groups (63.6 vs 72.7%, p = 0.709) and (72.7 vs 81.8%, p = 0.687) respectively.

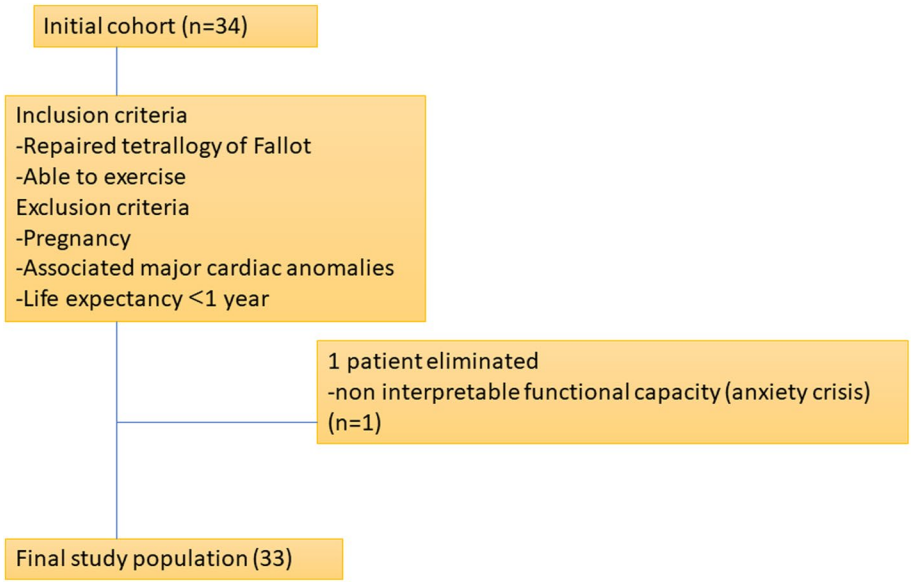

Fig. 1 Detailed graphical description of patient enrollment

Table 1 Clinical and demographic data according to functional capacity. N = 33

	Normal functional capacity (n = 22)	Low functional capacity (n = 11)	*p*
Age (years)	24.6 ± 6.6	28.6 ± 5.7	0.104
Female gender (%)	6 (27.3)	8 (72.7)	0.024
Weight (Kg)	58.8 ± 14	69.1 ± 32.7	0.218
Height (cm)	163 ± 9	155 ± 7	0.023
BMI (Kg/m^2)	21.7 ± 3.7	23.6 ± 5	0.212
BSA (m^2)	1.6 ± 0.2	1.55 ± 0.17	0.309
Age at primary repair (years)	5.5 (2–10)	5 (3–13)	0.729
Follow up from correction (years)	17.5 ± 4.9	21.3 ± 6.5	0.07
Type of primary repair			0.861
Total correction	14 (63.6)	6 (27.3)	
Total correction + pulmonary valve replacement	6 (27.3)	7 (63.6)	
Rastelli operation	1 (4.5)	3 (27.3)	
Total correction + surgical repair of pulmonary artery branches	1 (4.5)	1 (9.1)	
Previous shunt palliation	2 (9.1)	5 (45.5)	0.027
Re-operated patients (%)	8 (36.4)	2 (18.2)	0.43
Systolic pulmonary artery pressure (mmHg)	32 ± 10.8	25 ± 11.7	0.86
Peak trans-pulmonary gradient (mmHg)	22.5 (13–62)	24 (10–48)	0.553
Severe pulmonary valve stenosis	4 (18.2)	2 (18.2)	0.999
Severe pulmonary valve regurgitation	14 (63.6)	8 (72.7)	0.709
QRS (ms)	142 ± 26	135 ± 36	0.539
QRS ≥ 180 ms (%)	3 (13.6)	1 (9.1)	0.706
Arrhythmias[a]	4 (18.2)	3 (27.3)	0.661

Values presented as mean ± SD or median (25% and 75% percentile)

MS milliseconds

[a]Arrhythmias included atrial Flutter, ventricular bigeminy and frequent atrial premature beats

None of the resting LV systolic or diastolic echocardiographic parameters were related to low functional capacity. Both LV GLS and contractile reserve were impaired in both groups, whereas patients with low functional capacity had lower values of LV contractile reserve (1.4 ± 0.37 vs 1.7 ± 0.48, $p = 0.048$), (Table 2). Right ventricular ejection

Table 2 Echocardiographic and exercise stress test analysis

	Normal functional capacity (n = 22)	Low functional capacity (n = 11)	*p*
METs	7.55 (7.2–8.75)	6.2 (5.7–6.7)	< 0.001
Watts	116.7 ± 29.5	79 ± 19	0.0005
Maximal reached heart rate from predicted (%)	69.3 ± 12.6	69.8 ± 7.1	0.899
2D LVEF, baseline (%)	56.8 ± 6.4	55.8 ± 7.1	0.678
LV end diastolic volume (ml)	90 (80–97)	93 (68–96)	0.605
LV end systolic volume (ml)	39 (32–46)	40 (26–49)	0.842
2D LVEF, stress (%)	62.5 ± 6.2	59.6 ± 7.8	0.263
3D LVEF, baseline (%)	56.8 ± 5.2	57.2 ± 4.9	0.853
3D LVEF, early recovery (%)	58.9 ± 5.9	61.6 ± 5.9	0.281
LV GLS, baseline (%)	14.4 ± 3.2	14.1 ± 2	0.773
LV GLS, early recovery (%)	15.4 ± 3.2	15.8 ± 3.4	0.962
LV MD	57.3 ± 23.2	63.1 ± 21.1	0.488
LV contractile reserve	1.7 ± 0.48	1.4 ± 0.37	0.048
LV E/e', baseline	5.4 ± 1.9	5.6 ± 1.7	0.754
LV E/e', stress	5.4 (4.9–7.9)	5.2 (4.6–8.3)	0.803
RVEF, baseline (%)	56.8 ± 5.2	57.2 ± 4.9	0.853
RV end diastolic volume (ml)	159 (134–214)	156 (118–232)	0.641
RV end systolic volume (ml)	68 (66–118)	82 (53–105)	0.944
RVEF, early recovery (%)	58.9 ± 5.9	61.6 ± 5.9	0.281
TAPSE, baseline (mm)	18.1 ± 3.2	16.1 ± 2.3	0.075
TAPSE, stress (mm)	19.7 ± 3.9	18.2 ± 1.8	0.242
RVFAC, baseline (%)	43.1 ± 8.4	38.3 ± 7.7	0.116
RVFAC, stress (%)	47.8 ± 9.6	41.2 ± 10.8	0.089
RV contractile reserve[a]	16 (72.7)	9 (81.8)	0.687
RVFWSL, baseline (%)	20.2 ± 3.6	14.4 ± 4.8	0.0005
3DRVEF	50.5 ± 6.5	48.3 ± 7.7	0.505
RV elastance, baseline	1.0 ± 0.046	0.88 ± 4.5	0.453
RV E/e', baseline	4.9 (3.9–6.8)	5.5 (3.8–6.7)	0.954
RV E/e', stress	5.7 ± 2.6	5.7 ± 2.1	0.985
Dynamic pulmonary B lines	0	0	1

Values presented as mean ± SD or median (25% and 75% percentile)

MET metabolic equivalent of task, *2D LVEF* two dimensional left ventricular ejection fraction, *3D LVEF* three dimensional left ventricular ejection fraction, *LV MD* left ventricular mechanical dispersion, *LV* left ventricle, *LV GLS* left ventricular global longitudinal strain. *RVEF* right ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *RVFAC* right ventricular fractional area change, *RV* right ventricle, *RVFWSL* right ventricular free wall longitudinal strain, *3DRVEF* three dimensional right ventricular ejection fraction

[a]Patients showing any increase of RVFAC

fraction was comparable in both groups (50.5 ± 6.5 vs 48.3 ± 7.7, p = 0.505) but only feasible in 67% of patients. RVFWSL (14.4 ± 4.8 vs 20.2 ± 3.6, $p = 0.0005$) was the only resting echocardiographic parameter related to low functional capacity. In multivariate analysis including gender, height, RVFWSL and previous shunt palliation, RVFWSL remained the only predictor of low functional capacity (OR 1.39 CI 95%, 1.06–1.83., $p = 0.018$ per % change). Table 3. A RVFWSL < 17% (absolute value) had an AUC of 0.785 to predict low functional capacity (Fig. 2). In the best case scenario (since there was no validation in an independent cohort) this cut off value had a sensitivity of 81.8% and specificity of 77.3% to predict low functional capacity. A representative example of a patient with low functional capacity and normal functional capacity and their correspondent RVFWSL values is shown in Fig. 3.

We performed a second multivariate analysis including LV GLS, although it was not statistically significant in univariate analysis. In this model RVFWSL remained the only

Table 3 Univariate and multivariate analysis for predicting low functional class

R2 = 0.399	Bivariate analysis			Multivariate analysis		
	OR	95% confidence interval	*p* value	OR	95% confidence interval	*p* value
Female gender	7.1	1.4–36.1	0.018	5.9	0.65–54.1	0.113
Height (cm)	0.89	0.81–0.98	0.035	0.95	0.81–1.11	0.533
Blalock-Taussig shunt	8.3	1.2–54.4	0.027	3.2	0.23–44.2	0.383
RVFWSL	1.28	1.05–1.57	0.014	1.28	1.04–1.59	0.02

OR odds ratio, *RVFWSL* right ventricular free wall longitudinal strain

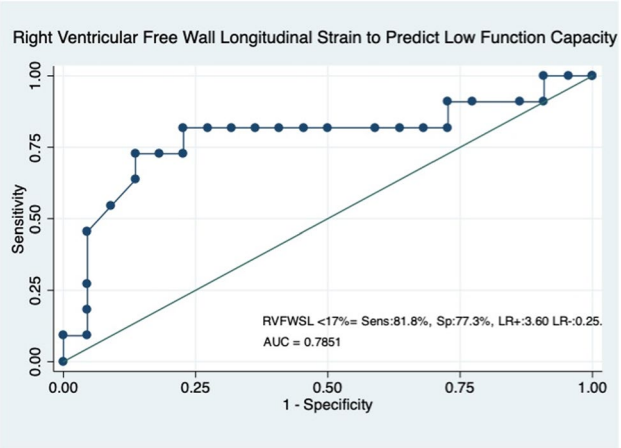

Fig. 2 ROC curve analysis. Receiver-operating characteristic (ROC) curves demonstrating diagnostic accuracy of right ventricular free wall longitudinal strain (RVFWSL) to predict low functional capacity. *Sens* sensitivity, *Sp* specificity, *LR* likelihood ratio, *AUC* area under the receiver-operating characteristic curve

independent predictor of low functional capacity (OR 1.3, CI 95% 1.03–1.63, p = 0.027 per % change) (Table 4.)

A good inter-observer agreement was found in the measurement of RVFWSL, ICC 0.95 (0.85–0.98, 95%CI).

Discussion

This study provides new evidence about the feasibility of ESE and clinical value of RVFWSL in patients with repaired tetralogy of Fallot (rTOF) and moderate to severe PR.

Our main findings can be summarized as follows: (1) right ventricular function quantification using TAPSE, FAC and right ventricular free wall strain is highly feasible in patients with rTOF and moderate to severe PR during exercise (2) in patients with rTOF and moderate to severe PR, subclinical left ventricular dysfunction is common (low GLS values and LVCR), however resting diastolic and systolic function parameters are not related to functional capacity. (3) low rest RVFWSL is an independent predictor of low functional capacity.

Surgical repair has improved survival in patients with tetralogy of Fallot, leading to an exponential growth of this population. Nonetheless late after repair complications are common and contribute to adverse clinical outcomes [2]. Severe pulmonary regurgitation is common (consistently 67% of our study population had severe PR), and contributes to adverse outcomes [3]. The presence of symptoms in patients with severe PR is currently a trigger for PVR according to the latest guidelines [2] aiming to improve symptoms and avoid ventricular function deterioration, although a significant benefit in mortality has yet to be demonstrated [23–25]. However the presence of symptoms can be underestimated, since patients with rTOF are in general younger than other patients with cardiovascular disease (i.e. HF, CAD, etc.) and have a long standing disease adapting their daily activities to their performance. Over 50% of patients with adult congenital heart disease (ACHD) in NYHA class 1 who underwent cardiopulmonary exercise testing, have been previously shown to have a peak VO2 below 80% of predicted for age and gender and thus, have an impaired functional capacity despite the lack of symptoms [5, 6]. In our study 33.3% of the patients were found to be symptomatic during ESE, most of which had severe PR, uncovering the need for PVR according to current guideline recommendations [2]. This finding highlights clinical assessment in the outpatient setting might not be sensitive enough and ESE may have important additional prognostic value in patients with rTOF. Furthermore, reclassification of NYHA with an objective test has prognostic implications as it has been shown that adult congenital heart disease patients with NYHA class II have a 2.5 fold increased risk of death. (5) With the increasing number of patients with ACHD, it might not be always feasible to perform cardiopulmonary exercise testing (CPET) or ESE, furthermore ACHD patients may not be able to exercise. Accordingly, the value of resting imaging variables as surrogate of low functional class might be useful for clinical decision making.

Although left ventricular dysfunction is common (reduced LVEF and/or GLS) in patients with rTOF, and its

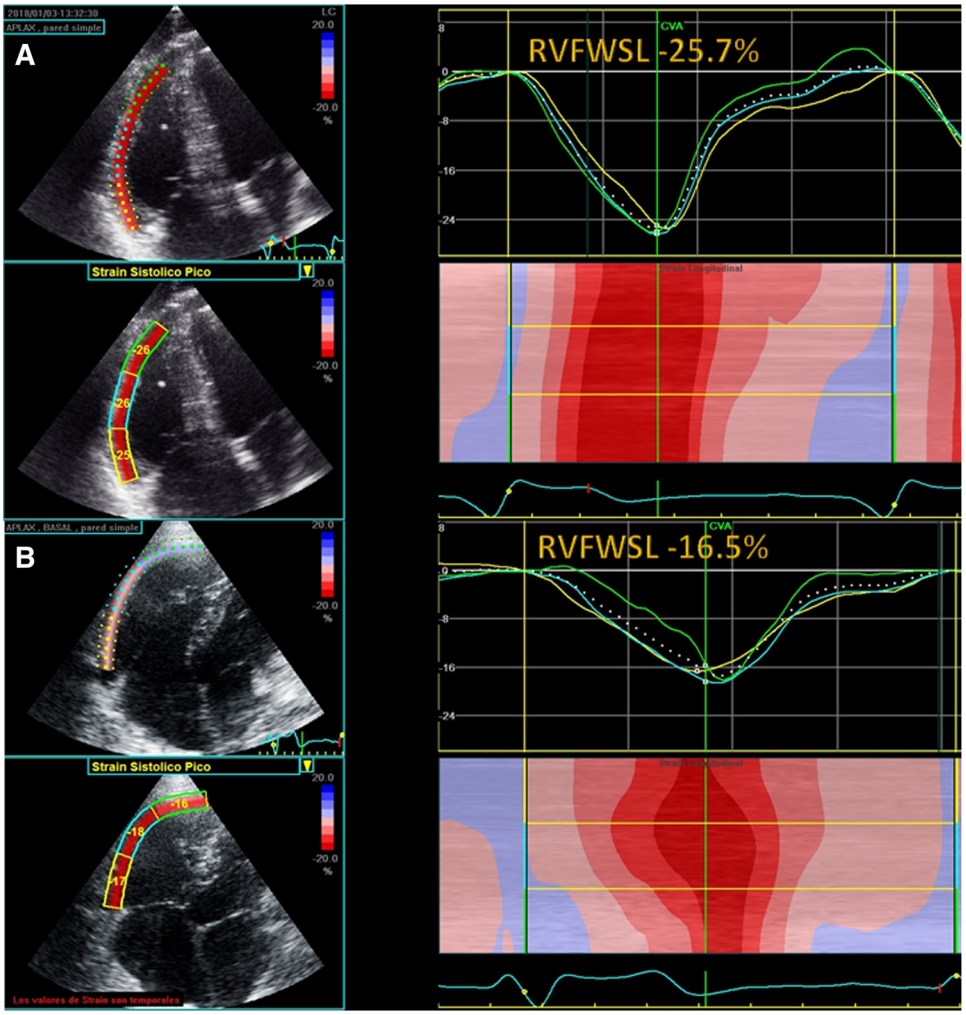

Fig. 3 Right ventricular free wall strain analysis showing a normal RVFWSL in a patient with normal functional capacity (**a**) and a reduced RVFWSL in a patient with low functional capacity (**b**). *RVFWSL* right ventricular free wall strain longitudinal

Table 4 Univariate and Multivariate analysis for predicting low functional class with LV GLS forced in the model

R2 = 0.424	Bivariate analysis			Multivariate analysis		
	OR	95% confidence interval	*p*	OR	95% confidence interval	*p*
Female gender	7.1	1.4–36.1	0.018	10.7	0.66–172.2	0.095
Height (cm)	0.89	0.81–0.98	0.035	0.92	0.77–1.11	0.398
Blalock-Taussig shunt	8.3	1.2–54.4	0.027	2.1	0.11–41.1	0.613
RVFWSL	1.28	1.05–1.57	0.014	1.29	1.02–1.63	0.027
LV GLS	1.03	0.85–1.34	0.765	1.26	0.78–2.03	0.333

LVGLS left ventricular global longitudinal strain. Other abbreviations as in Table 3

presence carries increased risk of mortality [26], we found none of these parameters were useful to predict a low functional capacity. Importantly RVFWSL was the only resting echocardiographic parameter capable to predict low functional capacity. Alghamdi et al. reported that RVFWSL was the best predictor of functional capacity, even superior to RVEF measured with cardiac MRI [27]. Also the most recent guidelines on multimodality imaging in ACHD support the use of RVFWSL in the follow up of ACHD patients [28]. Our study supports these findings and adds to literature a RVFWSL cut off value of < 17% (absolute value) during rest echocardiography which strongly correlates to low functional capacity.

Although the precise mechanism by which RVFWSL predicts low functional capacity is not clear, several theories might account for this finding. First, RVFWSL strongly correlates with the degree of histological fibrosis (R = 0.8, p < 0.0001), and was found to be markedly superior to

TAPSE (r = 0.34, 0.05) [29]. Therefore the degree of right ventricular fibrosis resulting in lower RVFWSL might contribute to abnormal exercise capacity. Second, patients with rTOF have been shown to have reduced right ventricular contractile reserve (RVCR) during stress compared to healthy subjects [30, 31]. Up to 40% of patients with rTOF do not have an increase in right ventricular function parameters during stress, supporting the notion of subclinical right ventricular dysfunction [14, 30]. Furthermore late after rTOF in a small subset during a 4.2 years follow up small increases in end systolic and diastolic volumes below guideline recommended thresholds were found, however a significant change in RVFWSL occurred [32]. These findings suggests RVFWSL might be able to detect patients with right ventricular dysfunction at an earlier stage, just as global longitudinal strain of the left ventricle has been shown to be useful to refine prognostic stratification [33–35].

The study of RVFWSL in patients with rTOF is particularly important as it carries incremental prognostic value as it has been related to poor quality of life, and adverse events (composite of death or heart failure), and in the present study with impaired functional class [36].

Study limitations

Small sample from a single institution is a limitation that needs to be acknowledged. However, our results add to the reported prognostic value of RVFWSL and for the first time (to the best of our knowledge) we present a cut off value of RVFWSL to predict low functional capacity in patients with repaired tetralogy of Fallot and moderate to severe PR. Our laboratory lacks the capacity of measuring expired gases and thus, the performance of a complete CPET, however the evaluation of NYHA functional class has been shown to be prognostically important in patients with ACHD. Although functional capacity was measured with the calculation of METs during semi supine cycloergometer, there is plenty of scientific evidence supporting the measurement of functional capacity with the calculation of METs and its strong predictive value for mortality [37, 38].

Moreover, previously reported mean peak VO2 values among rTOF individuals with mean age of 29–32 years are 24.2–25.2 ml/kg/min (corresponding to mean 71% of predicted) [39]. The threshold to define low functional capacity in our study was 7 METs which corresponds to an estimated VO_2 of 24.5 ml/min/kg. Hence in our cohort, individuals of similar age within the low functional capacity group achieved a median of 6.2 METs which likely represents true impaired exercise capacity.

Cardiac magnetic resonance (CMR) was not available within an acceptable time limit in most of our patients and therefore CMR data is not reported. However, the objective of this study was not to investigate a correlation between RVFWSL and RVEF measured with MRI and 3D echocardiogram which has been previously reported [27, 32], but to identify resting echocardiographic predictors of low functional capacity. Despite the fact that 3D and MRI RVED and volumes have a good correlation (r = 0.73), [40] in our study less than a 50% of the acquisitions were considered optimal (most of our patients had severe pulmonary regurgitation and important RV dilation which limits the acquisition quality) and was only feasible in 67% of the patients.

Quantification of pulmonary regurgitation in our study was performed by integrating multiple parameters as recommended by the American Society of Echocardiography guidelines. Although CMR was not performed to quantitate PR, echocardiography can reliable detect severe PR with multi parametric assessment compared to CMR. It has been shown in patients with rTOF that combining multiple 2D and Doppler echocardiography parameters; specifically, if diastolic flow reversal in branch pulmonary arteries and PR index < 0.77 were both present, the probability of having severe pulmonary valve regurgitation was 100% as compared with CMR (defined as the presence of ≥ 40% regurgitant volume) [41]. Furthermore, echocardiography can reliably distinguish mild pulmonary regurgitation, and has been shown to have a sensitivity of 97% to identify more than moderate PR compared to CMR [42]. Quantitative assessment of PR with echocardiography is challenging and lacks validation, and therefore was not used in this study. In our study ten patients had a CMR available with quantitation of pulmonary regurgitation severity with a time limit of 6 months. Agreement between CMR and echocardiography for classifying PR was 90% with a kappa coefficient of 0.62, p = 0.01 in this patient subset.

Conclusions

Right ventricular free wall strain is an independent predictor of low functional capacity in repaired tetralogy of Fallot patients with moderate to severe pulmonary regurgitation. A value < 17% might be useful in deciding when to perform pulmonary valve replacement, especially in those in which functional capacity cannot be objectively measured.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval This study has been approved by the ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All patients gave their informed consent prior to their inclusion in the study.

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